EuChemS CompChem 2023

European Conference on Computational & Theoretical Chemistry

"Exploring Molecular Space"

Presented by the
Division of Computational and Theoretical Chemistry

Thessaloniki, Greece
August 27-31, 2023

www.euchems-compchem.eu

Ένωση Ελλήνων Χημικών
Association of Greek Chemists

EuChemS
European Chemical Society

BOOK OF ABSTRACTS

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Welcome

Dear Colleagues and Friends,

It is a pleasure to welcome you to the EuChemS CompChem 2023, the flagship event of the European Chemical Society Division of Computational and Theoretical Chemistry (DCTC) from Sunday 27th August to Thursday 31st August, 2023, which takes place the Olympic Museum of Thessaloniki, Greece under the auspices of the Association of Greek Chemists.

EuChemS CompChem 2023 addresses key areas in computational and theoretical chemistry:
- Electronic Structure: Theory and Applications
- Artificial Intelligence in Chemical Research
- Materials Design
- Biomolecular Systems
- Computational Chemistry in Industry

Computational and theoretical chemistry have revolutionized the study of molecular events, the design and characterization of new materials, and the discovery of new drugs. The steady and consistent development of new theoretical methods and algorithms, access to massive compute resources, and breakthroughs in the processing of data using AI approaches allows the prediction of molecular properties at a level of accuracy required in industrial research, bringing computational chemistry to a new era.

We are particularly thrilled that the conference received an overwhelming response with over 300 participants from 33 countries, presenting 5 Keynote Lectures, 16 Invited Lectures, 40 Invited Contributions, 22 Short Communications, and 182 Poster Presentations contributing to a rich scientific program. The first day of the conference also features Opening Lectures by Prof. Michele Parrinello, Gold Medalist EuChemS 2020; Prof. Silvia Osuna, EuChemS Lecturer 2022, and our very own Chair of EuChemS-DCTC 2017-2022, Prof. Péter G. Szalay.

EuChemS CompChem 2023 presents the inaugural EuChemS Walter Thiel Award, an award recognizing biennially the outstanding scientific contributions of a young researcher based in a country affiliated to the EuChemS. The award is co-sponsored by Chemistry Europe, the German Chemical Society, the Swiss Chemcial Society, and the Max Planck Institut für Kohlenforschung. The inaugural award is presented to Dr. Felix Plasser of Loughborough University, UK. The Organizing Committee of EuChemS CompChem 2023 will also present a Lifetime Achievement Award to Prof. Hans Lischka. Moreover, three awards for outstanding poster presentations in each of the thematic sessions, as well as best contributed talk awards for outstanding contributed presentations will be given. Six fellowships to attend the EuChemS CompChem 2023 were granted as free registration fees to support students or early career scientists, kindly sponsored by CCP-BioSim.

Finally, I would like to extend our special thanks to the members of the organizing committee, who have worked tirelessly for the past year so that we can all be here today; to our scientific committee for ensuring the highest scientific standards; to our local organizing committee for tending to all meeting details; to EuChemS and the Association of Greek Chemists for providing the platform to organize this conference; to our DCTC delegates for engaging their local communities; to our sponsors for the financial assistance; to our media sponsors for disseminating the event; and last but not least to all of you for making this conference a success!

We are looking forward to an exciting EuChemS CompChem and wish you an enjoyable time at the historical and beautiful city of Thessaloniki.

Dr. Zoe Cournia
Chair, 2023 European Conference on Computational and Theoretical Chemistry
Treasurer, EuChemS DCTC
Senior Investigator, Biomedical Research Foundation Academy of Athens

Welcome

Dear colleagues,

On behalf of the European Chemical Society, I wish you a warm welcome to CompChem2023.

The European Chemical Society – in short EuChemS – is an overarching society at the European level with 50 national chemical societies and other organisations as members. Our mission is to nurture a platform for scientific discussion and provide an unbiased European voice on key policy issues in chemistry and related fields. In this way, EuChemS represents approximately 130,000 chemists from all over Europe.

Did you ever realize that by being a member of your national chemical society, you are a member of EuChemS too? If you are interested to learn more about EuChemS, feel free to sign up for our monthly newsletter EuChemS Magazine (www.magazine.euchems.eu), where we share information that is relevant for you.

The themes of this conference, ranging from Artificial Intelligence in Chemical Research to Computational Chemistry in Industry, are crucial in contemporary chemistry. In this field, it is especially important to remain on the cutting edge of innovative research – and occasions like this ensure the exchange of pioneering ideas. Therefore, I wish to express my gratitude to the EuChemS Division of Computational and Theoretical Chemistry for setting up such a wonderful conference.

While I have to remain in the Netherlands, I sincerely hope that you will participate in numerous exciting conversations, facilitate knowledge exchange, and make new connections with your colleagues in the field of computational chemistry and beyond in beautiful Thessaloniki.

I wish you a very enjoyable conference!

Floris Rutjes

Floris Rutjes
President of the European Chemical Society (EuChemS)

Dear colleagues,

On behalf of the Association of Greek Chemists, I welcome you to Thessaloniki and to the CompChem2023. The Association of Greek Chemists (AGC) is a scientific organization representing all Chemists in Greece and is member of the European Chemical Society and member of the chemical societies comprising Chemistry Europe.

AGC was founded in 1924 and since then has grown substantially, comprising at the moment of AGC has built a tradition in organizing international conferences, among which are the divisional conferences of EuChemS. In 2019, AGC has organized the 17th International Conference on chemistry and the Environment, which is the conference of the division of Chemistry and the Environment, in 2021 the conference on Green and Sustainable Chemistry, namely the conference of the Division of Green and Sustainable Chemistry, and this year the 14th European Conference on computational and theoretical chemistry.

We are therefore grateful to our members and delegates to the EuChemS divisions for taking such initiatives and organizing such high-profile events in our country.

This conference will serve as a platform for scientists to highlight their recent research findings in theoretical and computational chemistry, which certainly find applications to all other aspects of chemistry and other sciences as well. From this perspective, it will be a very stimulating conference for all chemists and I hope that several scientists from all over the world will attend. I wish to every participant an exciting and intriguing conference, full of interesting talks and fruitful discussions and I hope that you will find some time to discover the beauties and the history of Thessaloniki and Northern Greece.

Sincerely,

Ioannis Katsoyiannis
President of the Association of Greek Chemists

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Professor, University of Milano - Bicocca,
Italy

Conference Program

Sunday 27 August, 2023

14:00-16:00	**Registrations**	
16:00	**Opening Remarks** • **Zoe Cournia,** Chair EuChemS Comp Chem 2023; Treasurer of EuChemS DCTC; Senior Researcher Biomedical Research Foundation Academy of Athens, Greece • **Ioannis Katsoyannis,** President of the Association of Greek Chemists; Assoc. Professor, Laboratory of Chemical and Environmental Technology, Department of Chemistry, Aristotle University of Thessaloniki, Greece • **Hans Peter Lüthi,** co-Chair EuChemS Comp Chem 2023; Treasurer of EuChemS; Executive Board Member Swiss Chemical Society • **Tanja van Mourik,** President of EuChemS DCTC; Reader, School of Chemistry, University of St Andrews, UK • **Michail Sigalas,** Professor and Director, Laboratory of Quantum and Computational Chemistry, Department of Chemistry, Aristotle University of Thessaloniki	
16:30-18:15	**Opening Session** Chair: **Zoe Cournia**	
	16:30	**Opening Lecture: Michele Parrinello,** Italian Institute of Technology, Italy Gold Medalist EuChemS 2020 The physics of catalysis
	17:15	**Chemistry Europe Lectureship: Silvia Osuna,** University of Girona, Spain EuChemS Lectureship 2022 Computational enzyme design: Towards the development of fast yet accurate approaches
	17:45	**IL: Péter G. Szalay,** ELTE Eötvös Loránd University, Institute of Chemistry Immediate Past President EuChemS DCTC Ab initio fragment models for accurate excimer potential energy surfaces
18:15	**Coffee | Tea Break**	
18:35-19:30	**EuChemS Walter Thiel Award Ceremony & Award Lecture** Chair: **Hans Peter Lüthi**	
	18:35-18:45	**Walter Thiel Award Ceremony** **Hans Peter Lüthi,** EuChemS Treasurer, Swiss Chemical Society **Tanja van Mourik,** President EuChemS DCTC **Sarah-Lena Gombert,** MPI KoFo **Péter G. Szalay,** Immediate Past President EuChemS DCTC
	18:45-19:30	**Walter Thiel Award Lecture: Felix Plasser,** Loughborough University, UK New Analysis Tools for Excited-State Quantum Chemistry: From Numbers to Chemical Insight
19:30	**Welcome Apéro**	

Invited Contribution: **IC** | Invited Lecture: **IL** | Keynote Lecture: **KL** | Short Communication: **SC**

Conference Program

Monday August 28, 2023

08:45-10:30	**Electronic Structure: Theory and Applications** Chair: **Péter G. Szalay**	
	08:45	**KL: Katarzyna Pernal,** Lodz University of Technology, Poland Beyond-active-space electron correlation for molecules in excited states
	09:30	**IL: Sandra Luber,** University of Zürich, Switzerland Pushing the boundaries for computational spectroscopy and excited states in the condensed phase
	10:00	**IL: Marie-Liesse Doublet,** ICGM - CNRS, France Materials for Energy Storage: Challenges and Related Issues
10:30	**Coffee | Tea Break**	
11:00-13:10	**Electronic Structure: Theory and Applications** Chair: **Péter G. Szalay**	
	11:00	**IL: Sotiris Xantheas,** Pacific Northwest National Lab, USA The Many-Body Expansion in Chemistry
	11:30	**IL: Demeter Tzeli,** National and Kapodistrian University of Athens, Greece Electronic Structure and Chemical Bonding in systems containing of transition metals
	12:00	**IC: Jan Martin,** Weizmann Institute of Science, Israel Basis set convergence of post-CCSD(T) corrections to high-accuracy thermochemistry reconsidered: the power of lambda
	12:20	**IC: Herbert Fruchtl,** University of St Andrews, UK Flick the switch – a candidate molecule for molecular electronics
	12:40	**IL: Hans Lischka,** Texas Tech University, USA Solvent-enhanced symmetry-breaking induced by low-frequency vibrations in the covalently bound tetracene dimer leading to singlet-fission
13:10-14:30	**Lunch**	
14:30-16:25	**Materials Design** Chair: **Mercè Deumal**	
	14:30	**KL: Jacqueline Cole,** Department of Physics, University of Cambridge, UK Data-Driven Materials Discovery
	15:15	**IL: Benoît Champagne,** University of Namur, Belgium Predicting the Second-Order Nonlinear Optical Responses of Organic Materials in Complex Environments: The Role of Dynamics
	15:45	**IC: Cristina Trujillo,** University of Manchester, UK In Silico Design in Organocatalysis
	16:05	**IC: Carles Bo,** ICIQ, Spain New graph-based tools for taming complex reaction networks
16:25-17:00	**Coffee | Tea Break**	

Invited Contribution: **IC** | Invited Lecture: **IL** | Keynote Lecture: **KL** | Short Communication: **SC**

Conference Program

Monday August 28, 2023

17:00-17:50	**Materials Design** Chair: **Radu Silaghi-Dumitrescu**	
	17:00	**IL: Maria João Ramos,** University of Porto, Portugal Biodegrading Plastic
	17:30	**IC: Anton Stasyuk,** University of Girona, Spain Aromaticity controls the photoinduced electron transfer in host-guest complexes of nanohoops
18:00-18:50	**Short Communications** Chairs: **Peter Reinhardt, Radu Silaghi-Dumitrescu**	
	Electronic Structure: Theory and Applications	
	18:00	**SC: Eline Desmedt,** Vrije Universiteit Brussel, Belgium Designing Nonlinear Optical Redox Switches with Inverse Molecular Design: the Synergy between Core-modifications and Meso-substitutions
	18:05	**SC: Marco Mendolicchio,** Scuola Normale Superiore, Italy New Challenges in Computational Spectroscopy
	18:10	**SC: Josianne Owona,** Donostia International Physics Center, Spain Theoretical modelling of mechanoluminescent properties of pyridylvinylanthracene crystals
	18:15	**SC: Nora Gildemeister,** University of Cologne, Germany Modelling charge transport properties of dipolar self-assembly merocyanines: the role of static and dynamic disorder
	18:20	**SC: Jordan Rio,** Université Claude Bernard Lyon 1, France Unveiling the Dynamic Structure of Organozincs in THF: Elucidating solvent effects with Molecular Dynamics and X-Ray Absorption Spectroscopies
	Materials Design	
	18:25	**SC: Pierre Beaujean,** University of Namur, Belgium Ruthenium Complexes as a Test System to Unravel the Symmetry Effects on the Second-Order Nonlinear Optical Responses of Molecular Switches
	18:30	**SC: Manuel Pérez Escribano,** Universidad de Valencia, Spain Computational study into the formation of tin halide perovskite nanostructures
	18:35	**SC: Anthony Payne,** University of Surrey, UK Growth and reactivity of Hexagonal Boron Nitride
	18:40	**SC: Jakob Brauer,** University of Bremen, Germany Deducing desirable properties of porous materials for the adsorption of complex organic molecules by employing an efficient hierarchical screening approach
	18:45	**SC: Lyuben Borislavov,** Bulgarian Academy of Sciences, Institute of General and Inorganic Chemistry, Bulgaria Cheminformatics-Aided Prediction of Degradation Reaction Products in Energy Storage Materials
18:50-20:30	**Poster Session I**	

Invited Contribution: **IC** | Invited Lecture: **IL** | Keynote Lecture: **KL** | Short Communication: **SC**

Conference Program

Tuesday August 29, 2023

08:45-11:00	**Computational Chemistry in Industry** Chair: **Michael Edmund Beck**	
	08:45	**KL: Tobias Morawietz / Sadra Kashe Ol Gheta,** Bayer AG, Pharmaceuticals R&D, Computational Molecular Design, Germany AIQU: Bridging Artificial Intelligence and Quantum Chemistry for Improved Molecular Property Prediction in Industrial R&D
	09:30	**IL: Christoph Riplinger,** FAccTs GmbH, Germany Deciphering key interactions of ligand binding to biomolecular targets using high-level quantum mechanical methods
	10:00	**IC: Miles Pemberton,** AstraZeneca, UK Predicting the Future of our Medicines: Applying AI/ML to Investigate the Link Between Molecular Structures and their Transcriptomic Signatures
	10:20	**IC: Albert Sabadell-Rendón,** ICIQ – Institute of Chemical Research of Catalonia, Spain AMUSE - Automated MUltiscale Simulation Environment
	10:40	**IC: George Fanourgakis,** Aristotle University of Thessaloniki, Greece Machine Learning as a tool for predicting gas adsorption by Metal Organic Frameworks
11:00-11:20	**Coffee | Tea Break**	
11:20-13:00	**Computational Chemistry in Industry** Chair: **Michael Edmund Beck**	
	11:20	**IL: Maria Jose Aliaga Gosalvez,** Software for Chemistry & Materials BV (SCM), Netherlands Collaborating with SCM: (Horizon Europe) opportunities
	11:50	**IL: Matthew Bone,** Bristol Composites Institute, University of Bristol, University Walk, Bristol, UK High Throughput Modelling of Polymers with Molecular Dynamics and Machine Learning
	12:20	**IC: Froze Jameel,** Max Planck Institute for Dynamics of Complex Technical Systems, Germany Solvent Design for Green Homogeneous multi-phase Industrial Reactions
	12:40	**IC: Parvathi Krishnakumar,** University of Limerick, Ireland Predicting Thermodynamic Properties of Novel Compounds from their Starting Materials
13:00-14:30	**Poster Session II**	
13:00-14:30	**Lunch**	
14:30-16:30	**Discovering Thessaloniki** **Board Meeting, EuChemS Division of Computational and Theoretical Chemistry** (Seminar Hall, Olympic Museum of Thessaloniki)	
16:30 -17:50	**Materials Design** Chair: **Mercè Deumal**	
	16:30	**IC: Colm Burke,** University of Liverpool, UK High-throughput atomistic modelling of semiconducting polymers
	16:50	**IC: Irene Casademont Reig,** Vrije Universiteit Brussel, Belgium Manipulating Excited Estates using Inverse Design
	17:10	**IC: Julian Holland,** University of Southampton, UK Modelling LLZO: Limiting Structures in a Near-unlimited Configuration Space
	17:30	**IC: Ioannis Skarmoutsos,** University of Ioannina, Greece The unique structural features of water, ranging from ambient liquid up to supercritical, extreme-pressure conditions: Insights from classical and ab initio molecular dynamics simulations

Invited Contribution: **IC** | Invited Lecture: **IL** | Keynote Lecture: **KL** | Short Communication: **SC**

Conference Program

Tuesday August 29, 2023

17:50-18:00	**Short Break**	
	Short Communications Chair: **Stefan Kast**	
	Biomolecular Systems	
	18:00	**SC: Charlotte Bouquiaux,** University of Namur, Belgium Investigating the influence of the lipid structure on the global membrane organization: effect of the fatty acids
	18:05	**SC: Ho Ting Henry,** University of Oxford, UK Substrate Binding Dynamics of SARS-CoV-2 Cysteine Proteases
	18:10	**SC: Gianmarco Lazzeri,** Frankfurt Institute for Advanced Studies, Germany Reconstructing Rare Event Kinetics Using AI-enhanced Unbiased Molecular Dynamics Simulations
	18:15	**SC: Carlos Sequeiros-Borja,** Adam Mickiewicz University, Poland Water will find a way: transport through narrow tunnels and its significance in enzymes
	18:20	**SC: Andrea Levy,** École Polytechnique Fédérale de Lausanne (EPFL), Switzerland Addressing Challenges in Computational Simulations of Covalently Binding Transition Metal-Based Drugs
18:00-19:05	**Artificial Intelligence in Chemical Research**	
	18:25	**SC: Hannes Kneiding,** University of Oslo, Norway Machine Learning Quantum Properties of Transition Metal Complexes with Natural Quantum Graphs
	18:30	**SC: Elliot Farrar,** University of Bath, UK Machine learning and semi-empirical calculations: A synergistic approach to rapid, accurate, and mechanism-based reaction barrier prediction
	18:35	**SC: Edoardo Cignoni,** University of Pisa, Department of Chemistry and Industrial Chemistry, Italy Machine Learning Exciton Hamiltonians in Light-Harvesting Complexes
	18:40	**SC: Frédéric Celerse,** École Polytechnique Fédérale de Lausanne (EPFL), Switzerland Machine learning potentials for simulating solvent-assisted reactions
	18:45	**SC: Eugen Hruška,** Charles University, Czech Republic Bridging the explicit solvation experiment-calculation divide with machine learning and high-throughput simulation
	Materials Design	
	18:50	**SC: Edoardo Donadoni,** University of Milano-Bicocca, Italy Multi-scale modeling of folic acid-functionalized TiO_2 nanoparticles for active targeting of tumor cells
19:05-20:30	**Poster Session III**	

Invited Contribution: **IC** | Invited Lecture: **IL** | Keynote Lecture: **KL** | Short Communication: **SC**

Conference Program

Wednesday August 30, 2023

08:45-10:45	**Biomolecular Systems** Chair: **Michael Otyepka**	
	08:45	**KL: William Jorgensen,** Department of Chemistry, Yale University, USA Evolution of Free-Energy Calculations
	09:30	**IL: Kennie Merz,** Michigan State University, USA Molecular Gas Phase Conformational Ensembles
	10:00	**IC: Danai Maria Kotzampasi,** Biomedical Research Foundation Academy of Athens, Greece Insights into the mechanism of the C-terminal PIK3CA activating mutations
	10:15	**IL: Klaus Liedl,** University of Innsbruck, Austria Antibody Structure and Dynamics in Solution
10:45 - 11:15	**Coffee | Tea Break**	
11:15-13:15	**Biomolecular Systems** Chair: **Zoe Cournia**	
	11:15	**IL: Marco de Vivo,** Istituto Italiano di Tecnologia, Italy Function and inhibition of cation-coupled chloride cotransporters
	11:45	**IL: Chris Oostenbrink,** University of Natural Resources and Life Sciences, Vienna, Austria Free energies and enhanced sampling from accelerated enveloping distribution sampling
	12:15	**IC: Tobias Hüfner,** Max-Planck Institute for Biophysics, Germany Automated and Systematic Derivati on of Parameter Type Definitions for Molecular Mechanics Force Fields
	12:35	**IC: Katie Kuo,** Georgia Institute of Technology, USA From Closed to Open: Addressing the Role of the Efflux Pump AcrAB-TolC in Antibiotic Resistance
	12:55	**IC: Dan Major,** Bar-Ilan University, Israel Screening Enzyme Mechanisms using Multiscale Mechanistic Docking with EnzyDock
13:15-14:30	**Lunch**	
14:30-16:25	**Artificial Intelligence in Chemical Research** Chair: **Tanja Van Mourik**	
	14.30	**KL: Edward Pyzer-Knapp,** IBM Research-Europe, UK How AI accelerates the discovery of new molecules and materials
	15.15	**IL: Alexandre Tkatchenko,** University of Luxembourg, Luxembourg Fully Quantum (Bio)Molecular Simulations: Dream or Reality?
	15.45	**IC: Amol Thakkar,** IBM Research Europe, Switzerland Multi-Cloud Data Infrastructure for AI Foundation Models in Chemical Research
	16.05	**IC: Paul Katzberger,** ETH Zürich, Switzerland Graph Neural Networks as Implicit Solvents in MD Simulations
16:25-17:00	**Coffee | Tea Break**	

Invited Contribution: **IC** | Invited Lecture: **IL** | Keynote Lecture: **KL** | Short Communication: **SC**

Conference Program

Wednesday August 30, 2023

17:00-18:40	**Artificial Intelligence in Chemical Research** Chair: **Antti Poso**	
	17:00	**IC: Veronika Juraskova,** University of Oxford, UK Modelling Chemical Processes in Explicit Solvents with Machine Learning Potentials
	17:20	**IC: Elin Dypvik Sødahl,** Norwegian University of Life Sciences, Norway Investigating molecular rotations in ferroelectric plastic crystals using machine learned force fields
	17:40	**IC: Ganna Gryn'ova,** Heidelberg Institute for Theoretical Studies, Germany New representations for interpretable chemical machine learning
	18:00	**IC: Marco Bortoli,** University of Oslo, Norway Development of Machine Learning Potentials for Main Group Organometallic Reagents
	18:20	**IC: Massimo Delle Piane,** Politecnico di Torino, Italy Machine Learning Approaches to Unravel the Dynamic Behavior of Metal Surfaces and Nanoparticles
18:40-20:00	**Poster Session IV**	
20:00-21:00	**Break**	
21:00	**Conference Dinner**	

Invited Contribution: **IC** | Invited Lecture: **IL** | Keynote Lecture: **KL** | Short Communication: **SC**

Conference Program

Thursday August 31, 2023

08:40-10:20	**Biomolecular Systems** Chair: **Ivelina Georgieva**	
	08.40	**IC: Joep Wals,** University of Antwerp, Belgium Molecular Dynamics Simulations on UAMC-0001305 Warhead Derivatives to Theragnostically Target Fibroblast Activation Protein
	09.00	**IC: Stefano Serapian,** University of Pavia, Italy Learning the Languages of Allostery in K-Ras4B
	09.20	**IC: Dhiman Ray,** Italian Institute of Technology, Italy Data-Driven Classification of Ligand Unbinding Pathways and Kinetics
	09.40	**IC: Anastasia Rissanou,** National Hellenic Research Foundation, Greece A Computational Study of the Complexation of Single Stranded RNA with Lipid-based Agents
	10.00	**IC: Francesco Saverio di Leva,** University of Naples Federico II, Italy Free Energy Calculations in the Revival of Old-but-New Therapeutic Targets: Discovery and Development of RGD Integrin Peptides
10:20-10:50	**Coffee | Tea Break**	
10:50-12:10	**Biomolecular Systems** Chair: **Safiye Erdem**	
	10:50	**IC: Peter Starrs,** University of St Andrews, UK Molecular Dynamics Study of Arabinoxylan Polymer Flexibility with Forcefield Comparison
	11:10	**IC: Marketa Paloncyova,** Palacky University Olomouc, Czech Republic Lipid Nanoparticles: From Structure to Interactions with Cell Membranes
	11:30	**IC: Matteo Capone,** University of L'Aquila, Italy Alternative Fast and Slow Primary Charge-Separation Pathways in Photosystem II
	11:50	**IC: Vassilios Myrianthopoulos,** National and Kapodistrian University of Athens, Greece Right tools for the job. Simple and sophisticated approaches for enhancing performance of in silico methodologies in drug discovery
12:10-13:10	**Electronic Structure: Theory and Applications** Chair: **Peter Reinhardt**	
	12:10	**IC: Bernardo de Souza,** FAccTs GmbH, Germany On the importance of conformational Entropy when predicting Chemistry: results from the new Global Optimizer AlgoriThm (GOAT) implemented in ORCA
	12:30	**IC: Mario Piris,** DIPC & EHU/UPV & IKERBASQUE, Spain Time evolution of natural orbitals in ab initio molecular dynamics
	12:50	**IC: Adriana Pecoraro,** University of Naples Federico, Italy First-principles prediction of exotic hexagonal NaCl films on methylammonium lead iodide substrates, new hints for perovskite solar cells
13:10-14:30	**Lunch**	

Invited Contribution: **IC** | Invited Lecture: **IL** | Keynote Lecture: **KL** | Short Communication: **SC**

Conference Programme

Thursday August 31, 2023

14:30-15:50	**Electronic Structure: Theory and Applications** Chair: **Péter G. Szalay**	
	14:30	**IC: Yannik Schütze,** Helmholtz Zentrum Berlin für Materialien und Energie GmbH, Germany Multiscale modeling of conjugated organosulfur polymer cathodes for lithium-sulfur batteries
	14:50	**IC: Aslihan Sumer,** Saglik Bilimleri Universitesi, Turkey CO Oxidation on Molybdenum Oxide Clusters: Reaction Energetics and Mechanism
	15:10	**IC: Marc de Wergifosse,** Université Catholique de Louvain, Belgium The eXact integral simplified time-dependent density functional theory (XsTD-DFT)
	15:30	**IC: Örs Legeza,** Wigner Research Centre for Physics, Hungary Predicting the FCI energy of large systems to chemical accuracy from restricted active space density matrix renormalization group calculations via Hybrid CPU-GPU based architectures
15:50	**Awards | Farewell**	
16:30	**End of Conference**	
18:30-23:00	**Optional visit to the Museum of Byzantine Culture, Thessaloniki (free entrance)**	

Invited Contribution: **IC** | Invited Lecture: **IL** | Keynote Lecture: **KL** | Short Communication: **SC**

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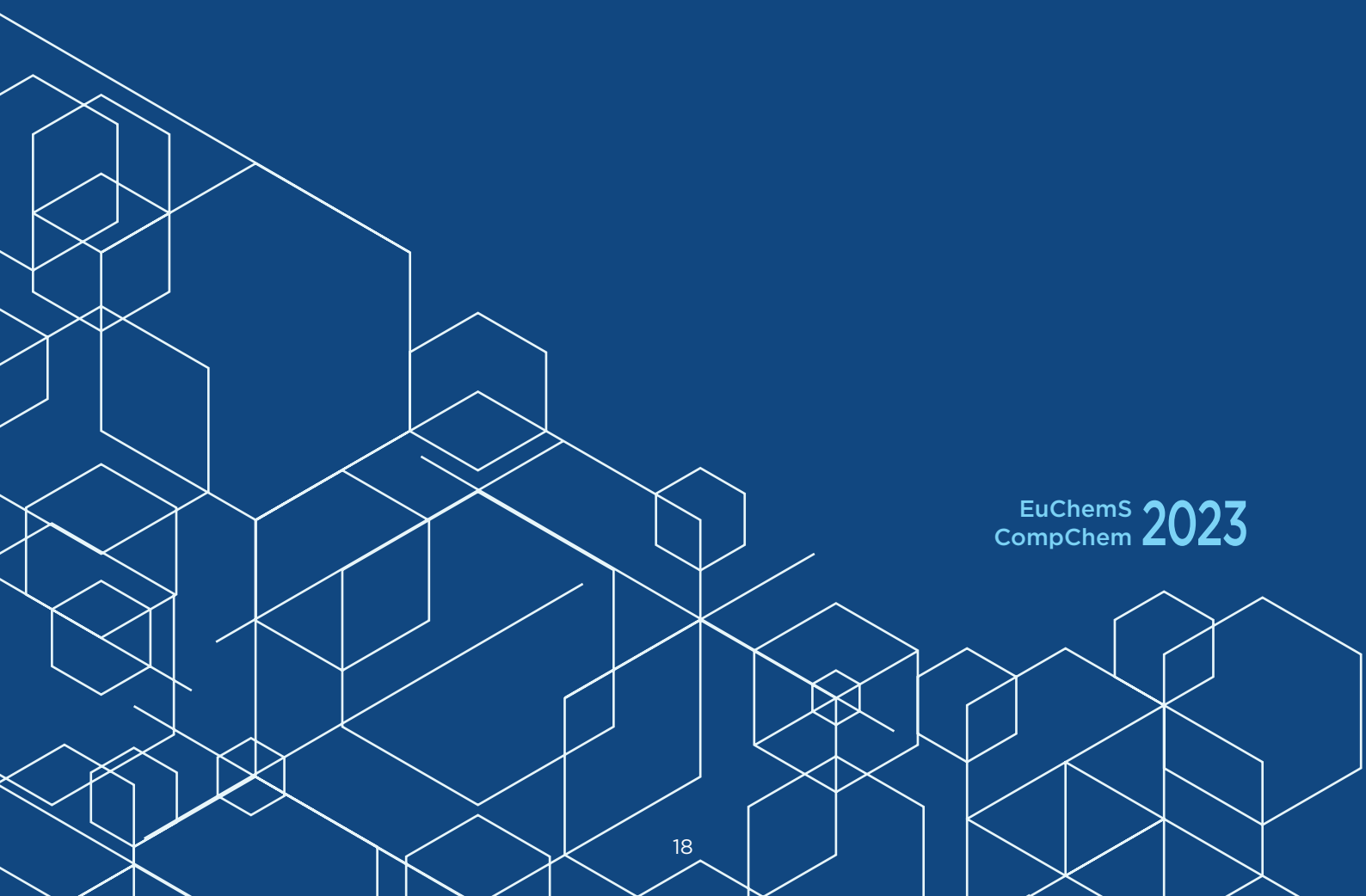
ABSTRACTS OF KEYNOTE TALKS



EuChemS CompChem 2023

The physics of catalysis

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The development of efficient catalysts is key to a green economy transition. In this respect, it suffices to mention the need to devise an energy-efficient production of hydrogen or an economical and environment friendly sequestration process.

However, the large-scale production of chemicals often takes place under extreme conditions of temperature and pressure, so extreme in fact that both simulations and experiment are difficult or outright impossible.

This challenges the conventional picture of catalysis in which a special static configuration of atoms is responsible for the catalytic activity.

Based on state-of-the-art simulations that take advantage of machine learning methodologies, we put forward a different picture, whose defining features are diffusion and disorder.

Namely, we associate the catalytic activity with a change in the physical state of the interface. Such a change can be induced for instance by the temperature or by the reactants themselves. We exemplify this behavior in the catalysis of ammonia by iron surfaces and the cracking of ammonia by the ionic compound.

The design of such a catalytic competent interfacial steady state is suggested as a strategy to design new, efficient and stable catalysts.

Computational enzyme design: Towards the development of fast yet accurate approaches

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Enzymes are essential for supporting life by accelerating chemical reactions in a biologically compatible timescale. These remarkable catalysts possess unique features like high specificity and selectivity, and they function under mild biological conditions. These extraordinary characteristics make the design of enzymes for industrially relevant targets highly appealing.

Enzymes exist as an ensemble of conformational states, and the populations of these states can be altered through substrate binding, allosteric interactions, and even by introducing mutations into their sequence. These conformational states can be altered through mutations, which facilitates the evolution of enzymes towards acquiring novel activities.[1] Interestingly, many laboratory-evolved enzymes exhibit a common pattern—a significant impact on the catalytic activity is often observed due to remote mutations located distal from the catalytic center.[2] Similar to allosterically regulated enzymes, distal mutations play a role in regulating enzyme activity by stabilizing pre-existing conformational states that are crucial for catalysis.

In this talk, the rational approaches we have developed for enzyme design along the years will be discussed. These approaches rely on inter-residue correlations derived from microsecond time-scale Molecular Dynamics (MD) simulations, enhanced sampling techniques, and more recently, the incorporation of AlphaFold2 predictions.[1-4] Over the years, our research on various enzyme systems has provided compelling evidence that the current challenge of predicting distal active sites to enhance functionality in computational enzyme design can ultimately be addressed.[3]

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Ab initio fragment models for accurate excimer potential energy surfaces

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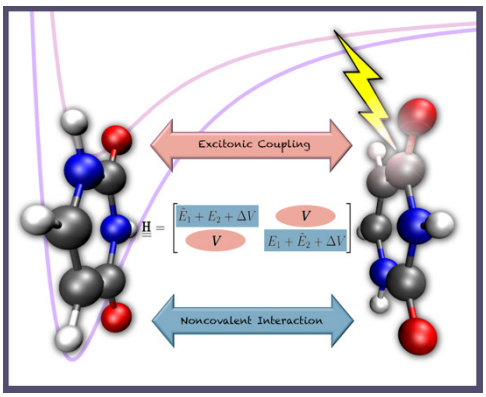
Electron transfer in electronically excited states plays an important role in biological processes and material science applications. While Coupled-Cluster methods have been proven to provide an accurate description of excited electronic states, the scaling of the computational costs with the system size limits the degree for which these methods can be applied.

In this work we evaluate fragment-based high-level quantum chemistry models which reduce the cost of the calculations while maintaining the accuracy. Such methods are preferred over other multiscale approaches due to the possibility to treat also multi-chromophore systems, such as the DNA molecule.

Several aspects of these models are considered:

- To describe the individual fragments including (some of) the interaction with the other fragments, we evaluate two approaches: QM/MM and Projection-based Embedding.
- The interaction energy predicted by fragment calculations has to be augmented with some missing contributions, like dispersion and Pauli (exchange) repulsion; several choices are considered and tested.
- The interaction of the chromophores localized on different fragments was estimated by an exciton scheme; multiple choices of the interaction matrix element have been compared.

Interaction curves for some N-containing heterocycle model systems are compared to those of dimer calculations. Various types of excited states (π - π*, n - π*, σ - π*, π - Rydberg) are investigated and the quality of the different approximations discussed. The results are promising, but further points of improvement are suggested.



Beyond-active-space electron correlation for molecules in excited states

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Single determinantal wavefunction is not adequate for molecules in excited states nor molecular complexes bounded by dispersion interaction. The major character of a state and a significant portion of electron correlation can be grasped by constructing a wavefunction from configurations living in the active space. Even then, out-of-active-space electron correlation is necessary to make accurate predictions for chemistry.

Recently, we have developed novel computational approaches to out-of-active-space electron correlation, by combining the adiabatic connection (AC) and random phase approximations[1]. Comparing with perturbation theory-based methods, these methods require only the one- and two-electron reduced density matrices and can be coupled with large active spaces - unavailable for perturbation approximations. The recent implementations scale only with the 5th power of the system size, thanks to using the Cholesky decomposition[2,3].

Two areas of applications will be presented. In the first one, energies of excited singlet and triplet states of organic chromophores are described and the mechanism of inverting the singlet-triplet energy gaps in the heptazine-based derivatives is investigated. The second scope of applicability includes dispersion energy calculations in molecular complexes with local excitation.

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Data-Driven Materials

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This talk will describe how one can combine the predictive power of artificial intelligence with data science and algorithms to discover new materials for the energy sector.

A 'design-to-device' pipeline for materials discovery will be demonstrated.

Thereby, large-scale data-mining workflows are fashioned to predict successfully new chemicals that possess a targeted functionality.

AIQU: Bridging Artificial Intelligence and Quantum Chemistry for Improved Molecular Property Prediction in Industrial R&D

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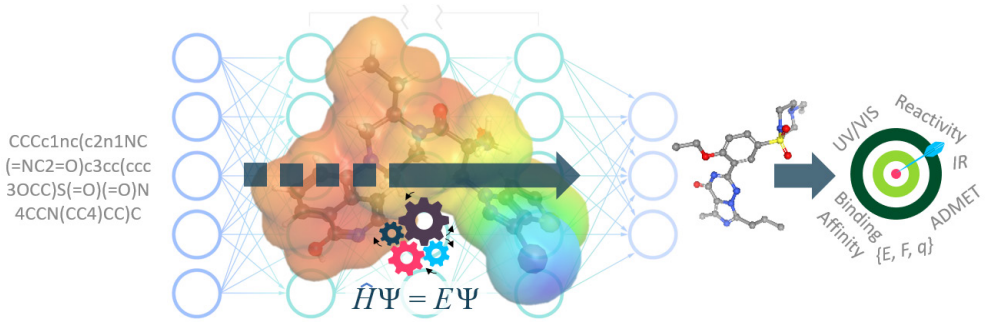
Machine learning models based on molecular fingerprints derived from 2D graphs are essential tools to predict a large range of properties relevant for industrial research projects[1]. Increase in data volume by multi-task or multi-partner approaches can improve predictive performance but only up to a certain limit[2]. An alternative is the *in-silico* prediction of properties by quantum chemical (QM) calculations, an approach which does not rely on experimental data but comes with high computational costs. The industry-academic collaboration "!AIQU"[3] explores ways to bridge AI/ML methods with QM calculations to accelerate and improve the prediction of molecular properties for industrial R&D processes.



A cornerstone of the project is the development of a database with QM properties of drug-like molecules based on rigorous QM workflows to identify relevant low-energy molecular conformers. Replacing the most time-consuming workflow steps by machine learning potentials (MLPs)[4-6] trained to high-level QM calculations can yield massive gains in speed and thereby a reduction in the overall compute costs. However, the construction of reliable MLPs requires training on large datasets that adequately cover the chemical space of the compounds of interest. Furthermore, the conformational space of the training data needs to be extensively sampled to account for the ensemble of relevant low-energy conformers.

Here, we present a series of approaches to (i) create a representative molecular subset covering drug-like chemical space; (ii) create and collect equilibrium as well as off-equilibrium structures from QM optimization trajectories and normal mode sampling; and (iii) develop robust MLPs to efficiently rank and optimize molecules beyond the learned chemical space.

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Evolution of Free-Energy Calculations

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Free-energy calculations have had a revolutionary effect on computational chemistry. In conjunction with molecular dynamics and Monte Carlo simulations, they have enabled the calculation of free energy changes for wide-ranging phenomena including fundamental solution thermodynamics, solvent effects on conformational equilibria, activation barriers for reactions in solution, host-guest binding, and drug lead optimization. An overview of our FEP efforts beginning with the ethane to methanol calculation in 1985 and leading to recent discoveries of extraordinarily potent inhibitors of the main protease of SARS-CoV-2 will be presented.

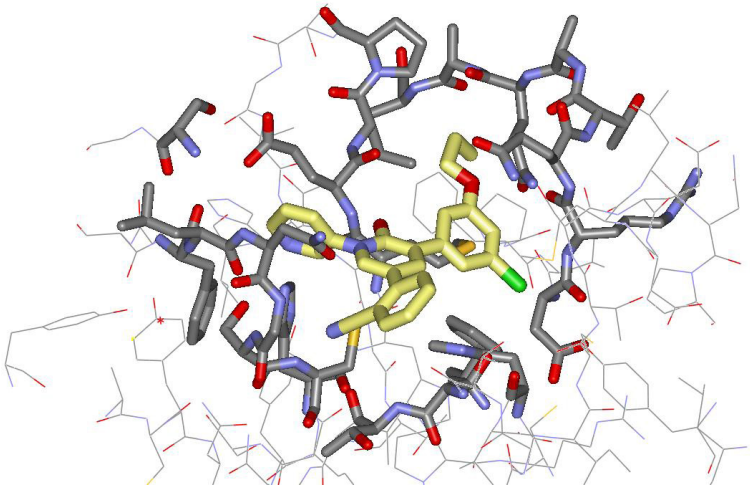

Figure 1. Rendering from a 1.8-Å crystal structure for a complex with the main protease of SARS-CoV-2 (PDB ID 7L11). Carbon atoms of the ligand are in yellow.

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How AI accelerates the discovery of new molecules and materials

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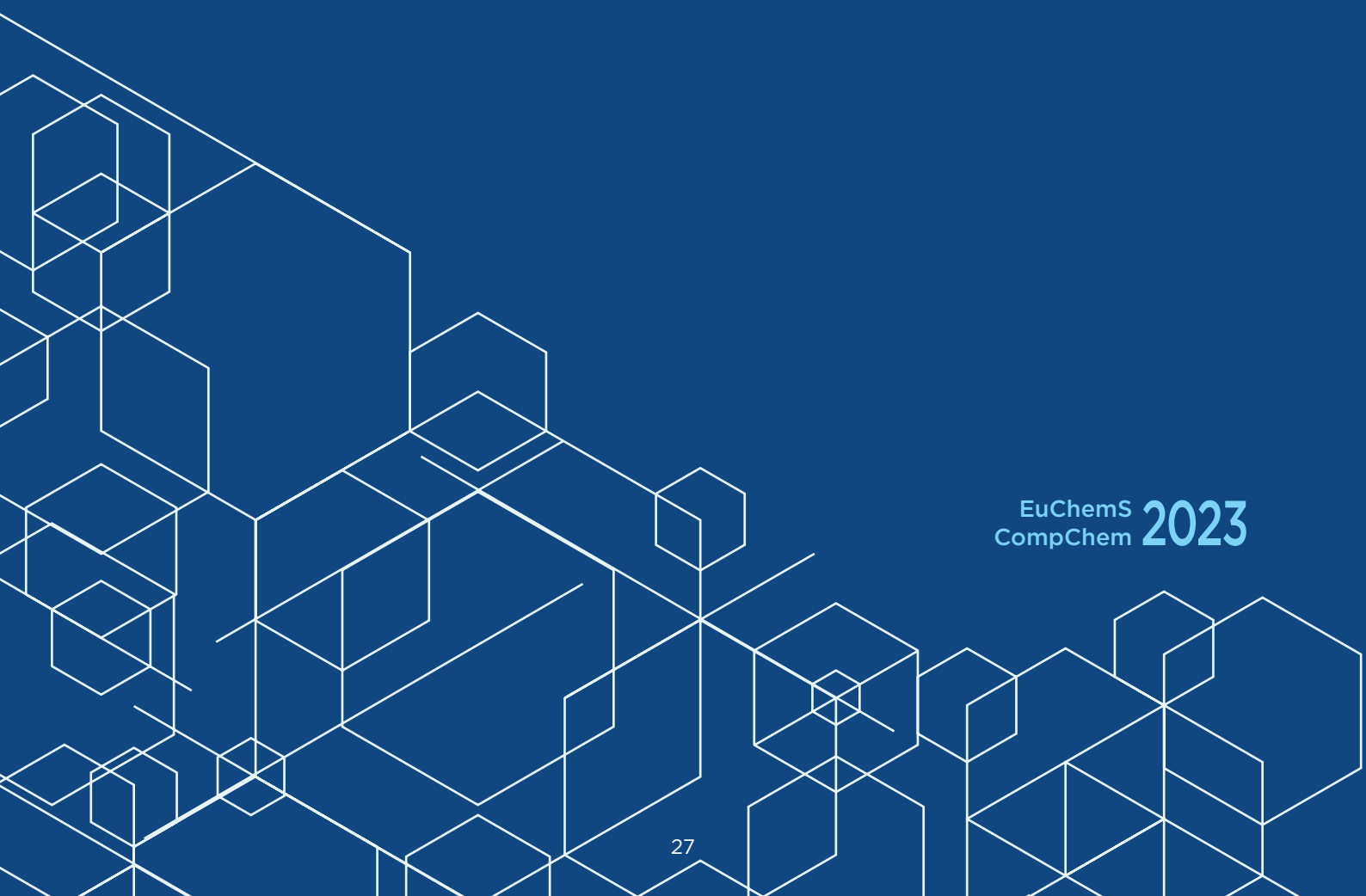
[1]IBM Research-Europe, UK

The history of chemical discovery has been punctuated by computational and theoretical developments. Evolving from empirical observation, increasingly systematised experimentation allowed for the development of theoretical underpinnings, which in turn afforded the paradigm shifting application of computational techniques, which has since co-evolved with the development of the technologies upon which they are run.

Recent years have seen the emergence of data-driven techniques and technologies for building powerful models, appearing to enable us to side-step the requirement for expensive experiments and physical simulations – replacing them with highly performant, but black-box alternatives.

In this talk I will highlight some of the key ways in which new methodologies in AI can drive us on to accelerate the discovery of new molecules and materials, whilst also talking about the importance of embracing these methods in a mindful manner through transparency and explainability.

EuChemS WALTER THIEL AWARD LECTURE



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New Analysis Tools for Excited-State Quantum Chemistry: From Numbers to Chemical Insight

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Excited electronic states are central to many areas of modern science and computational methods are becoming ever more accurate in their description. However, a new bottleneck is encountered in the analysis of the computations owing not only to the quantity of data produced but also because many of the phenomena studied are difficult to grasp within the standard molecular orbital (MO) picture at all. To remove this barrier an extended wavefunction analysis framework has been developed over the last years. I will illustrate how these tools can be used to (i) analyse excited state character in an automated and reproducible way[1], (ii) bridge between the MO, exciton, valence-bond and aromaticity pictures to gain comprehensive insight into excited state processes, (iii) provide new insight into excited state energetics beyond the MO picture[2], and (iv) use this information to develop new qualitative molecular design rules.

As a first example, we illustrate how excited-state localisation and charge transfer in transition metal complexes can be quantified in an automated way not requiring any visual inspection of orbitals[3]. Subsequently, we outline how the developed methods provide new insight into the energies of singlet and triplet excited states of conjugated hydrocarbons and push-pull systems via their transition densities (see Fig. 1)[4]. Finally, we present new qualitative design rules for developing molecules with maximised singlet triplet gaps.

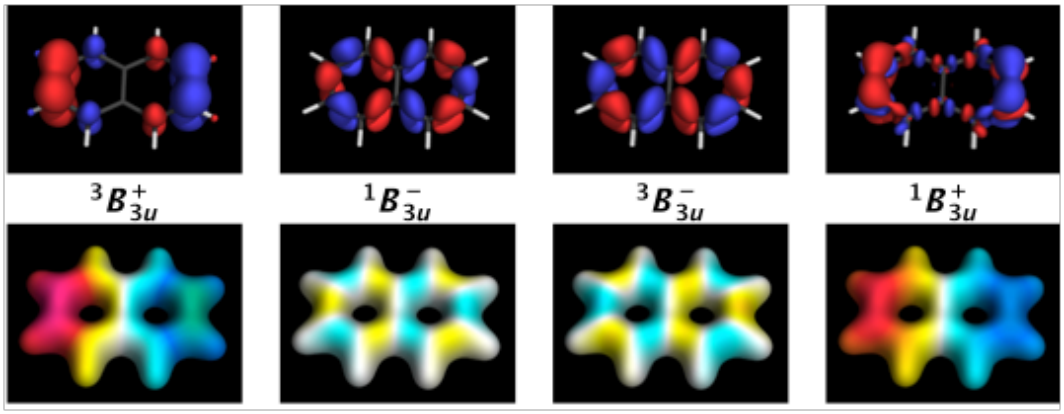

Figure 1: Transition densities and associated electrostatic potentials of the lowest singlet and triplet B_{3u} states of naphthalene.

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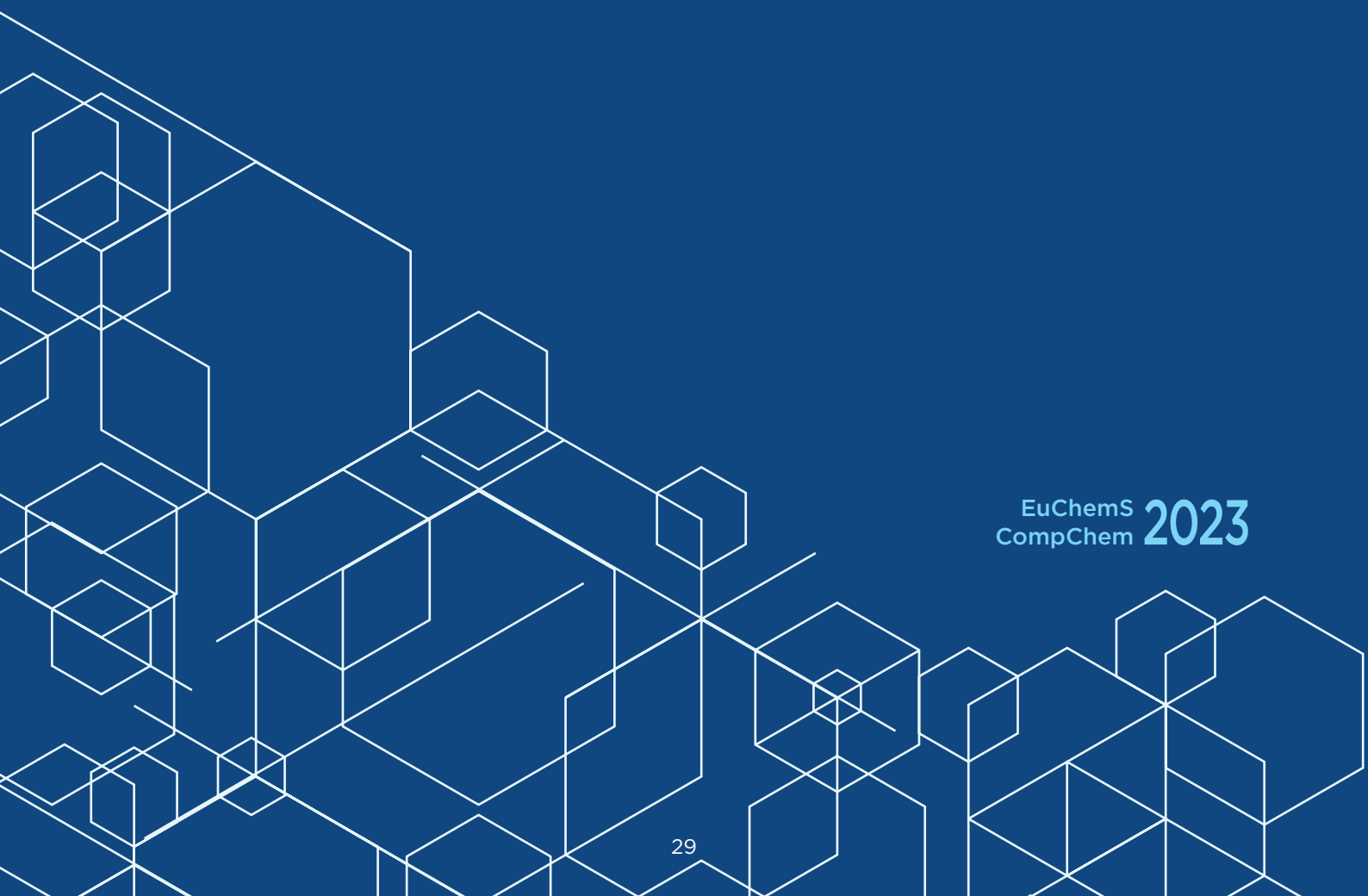
ABSTRACTS OF PRESENTATIONS



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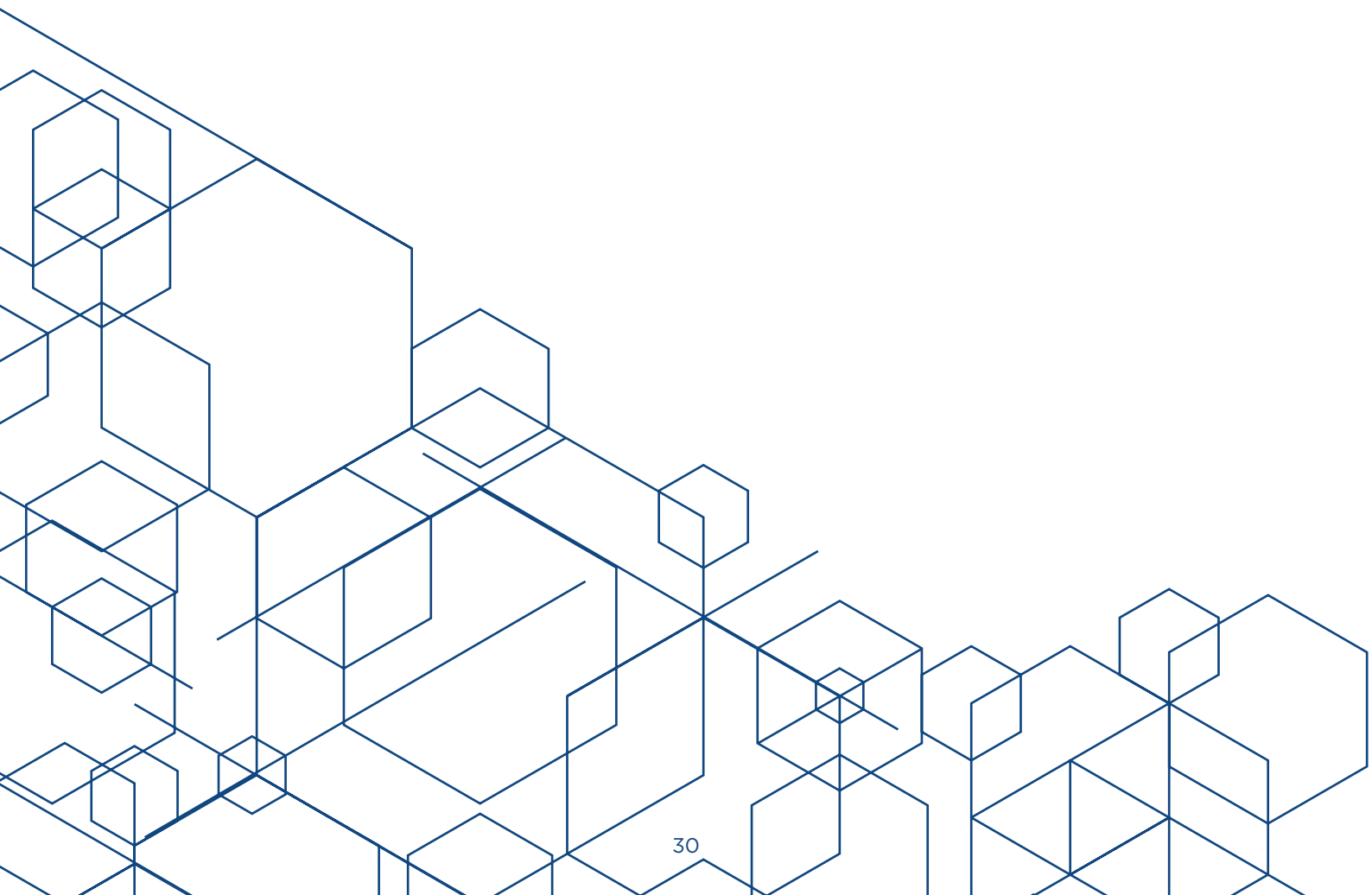
ELECTRONIC STRUCTURE: THEORY AND APPLICATIONS



Pushing the boundaries for computational spectroscopy and excited states in the condensed phase

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I will present our work on development of novel methods for spectroscopy and excited states with emphasis on dynamic methods for the condensed phase.

Besides periodic subsystem density functional theory (DFT) for efficient calculation and analysis of vibrational spectra [1], Raman [2], sum frequency generation [3], and pioneering Raman optical activity spectra [4] have been presented using high-performance DFT-based molecular dynamics [5] as well as an approach for vibrational circular dichroism [6].

I will also present real time propagation methods [7] for the study of absorption and vibrational spectra of (chiral) compounds in the gas and condensed phase, which have allowed a realistic description of (large) compounds including finite temperature and environmental effects as well as inclusion of pre- and on-resonance effects with electronically excited states.

Aside from that, we have advanced non-adiabatic dynamic approaches with emphasis on excited state dynamics in liquids [8] using robust ΔSCF methods in combination with explicit solvation and periodic boundary conditions (also using subsystem DFT).

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Materials for Energy Storage: Challenges and Related Issues

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To address the energy storage challenges in our society, it is crucial to enhance the autonomy and lifespan of batteries. This implies two key objectives: (i) improving the energy density of materials used in the positive electrode, and (ii) regulating the stability and reactivity of the electrode/electrolyte interfaces. Recent scientific advancements over the past decade have effectively doubled the storage capacity of Li-ion batteries, enabling remarkable progress [1-4]. However, these achievements have also unveiled new limitations pertaining to electrolyte stability and its interaction with electrodes. During battery operation, significant electric fields emerge at the electrode/electrolyte interfaces, leading to charge transfers and specific electrolyte reactivity. Understanding the microscopic mechanisms occurring at these interfaces requires a comprehensive modeling approach that accounts for the potential's impact. Thus, a general methodology capable of realistically describing electrochemical interfaces at the quantum level, while maintaining reasonable computational costs, becomes imperative. In this perspective, a grand canonical DFT approach has been developed and applied to several issues such as (i) the stability and the reactivity of electrolytes in the electrochemical double layer,[5] (ii) the impact of the electrolyte degradation on the formation of passivating layers (SEI) at the surface of the electrodes and (iii) the thermodynamic origin of the dendritic growth when batteries are deeply charged.[6] The perspective of this work on the development of new electrolytes for post-Li technologies and/or on the functionalization of electrode surfaces will be discussed. Moreover, we will highlight the impact of the dielectric constant and the composition of the electrolytes on the solvation and transport properties of the bulk electrolytes and discuss the perspectives it opens for future work. [7,8]

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The Many-Body Expansion in Chemistry

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The many-body expansion (MBE) has its origin in combinatorial mathematics and in particular the inclusion-exclusion principle, a counting technique used to obtain the number of elements in the union of finite sets. Its application in Chemistry consists of breaking up a chemical system into nonoverlapping fragments of *n* "bodies" of increasing size and casting the total energy as a sum of the energies of the constituent fragments up to rank *n*. The practical application of the MBE lies in cases where it converges at a low rank (typically the 3- or the 4-body term). Its introduction to the Chemical Physics community back in the 1970's[1,2] – and ever since – consisted of its application to the breaking of hydrogen bonds to define the "bodies" in the expansion.[3,4] We have in recent times revisited the MBE for water and ion-water systems,[5,6] including monatomic and polyatomic ions in the Hofmeister series,[7] confirmed its fast monotonic convergence at the 4-body term and established the theoretical requirements needed to accurately describe the terms of the expansion. Additionally, we have extended the MBE to account for the breaking of covalent[8] and metal-metal[9] bonds when defining the "bodies" of the expansion by introducing a new, novel implementation that is based on the *in situ* electronic structure of atoms in a larger system and finally extended it to light nuclear systems.[10] The recent extension of the MBE to periodic systems[11] offers the possibility to identify the factors stabilizing various forms of ice. I will discuss the implications of this new development in addressing modeling challenges in complex systems such as metal clusters, carbon materials and chemical transformations on metal and metal oxide surfaces in the context of structure and dynamics driven by the MBE.[12]

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Electronic Structure and Chemical Bonding in systems containing of transition metals

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Transition metal compounds attract considerable attention because of their widely recognized importance in many biological and industrial processes. [1] Their theoretical calculation can be quite complex due to the high density of states and high spin-space angular momentum of the constituent transition metal atom.[2] Since diatomic and triatomic molecules containing transition metals are part of these compounds, investigation of their electronic structure can provide valuable insights into properties of more complex transition metal systems.

In the first part of the presentation, the ground and low-lying excited states of selected diatomic and triatomic of molecules of transition metals will be presented. [3-5] Their bonding and their electronic structure will be analysed. There will be presented molecules that are part of the active site of enzymes or 2D materials or form multiple bonds up to sextuple.

In the second part of the presentation, how the electronic states of selected diatomic and triatomic molecules, that are model systems of complexes and 2D materials, are involved in them. Their bonding and their electronic structure will be discussed and analysed. [5-7]

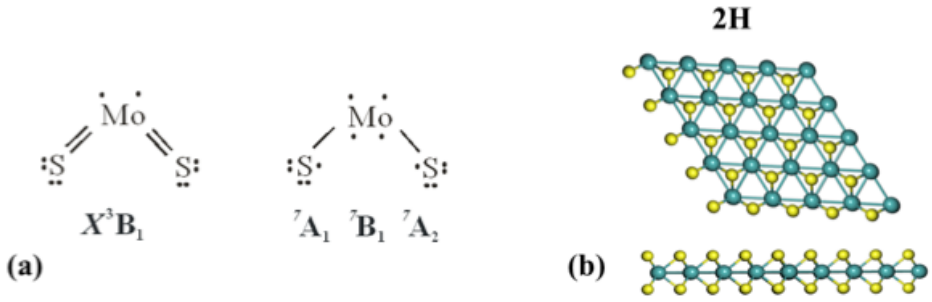

Figure 1: (a) Bonding in the MoS_2 triatomic molecule and (b) 2D-MoS_2 material.

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Basis set convergence of post-CCSDT) corrections to high-accuracy thermochemistry reconsidered: the power of lambda

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The main bottleneck in high-accuracy *ab initio* thermochemistry protocols based on coupled cluster theory, such as W4 theory [1,2] and HEAT [3], is the calculation of the post-CCSD(T) correction. By means of benchmark calculations up to cc-pV5Z basis sets on subsets of the W4-17 benchmark [4] we show that its evaluation can be sped up about an order of magnitude by means of the Lambda coupled cluster approach[5,6]. Specifically, the CCSDTQ-CCSDT(Q)$_\Lambda$ difference is both smaller and much less basis set-sensitive than CCSDTQ-CCSDT(Q), making it possible to break down the connected quadruples term can be evaluated much more economically by a composite of CCSDT(Q)/LARGE, CCSDT(Q)$_\Lambda$/MEDIUM, and CCSDTQ/SMALL, where SMALL can be as little as an unpolarized double-zeta basis set. (The latter is sufficient for the connected quintuples contribution, when evaluated as CCSDTQ(5)$_\Lambda$/SMALL.)

Combining this with updates in the other contributions (notably the use of F12 explicit correlation for the valence CCSD term, in conjunction with large *spdfgh* basis sets[7]), we are now able to revise the entire W4-17 benchmark of 200 molecules using new "W4neo" and "W4.3neo" ("new engine option") benchmark data, which should be accurate to much better than 1 kJ/mol. We also demonstrate the resilience of this approach with anharmonic force fields of "difficult" small molecules such as ozone.

As such calculations are still extremely resource-intensive, an inexpensive a priori diagnostic for their importance would be very valuable. We show that existing diagnostics for static correlation can be clustered statistically into 3-4 clear "classes", and propose two new such diagnostics, one[8] based on the difference between DFT and HF-DFT exchange energies, the other on the difference between CCSD(T) and CCSD+T(CCSD).

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Flick the switch – a candidate molecule for molecular electronics

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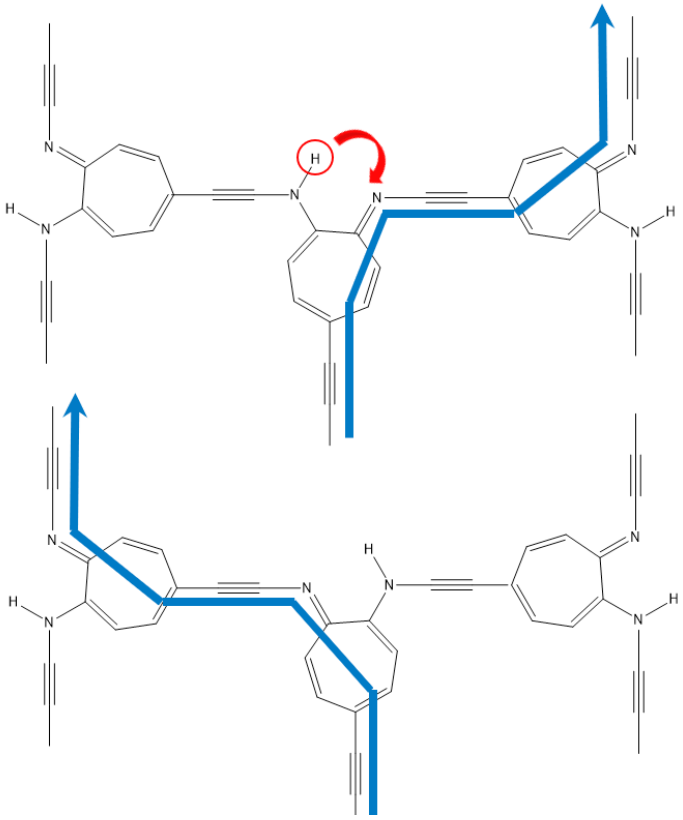
We present a molecule that promises to function as a single-molecule switch in molecular devices, allowing the direction of electric current to be changed by moving a single hydrogen atom across a small energy barrier and a distance of less than 1 Å, which may be triggered by an external electric field or a laser pulse, bringing rapid switching within experimental reach.



Using the rule that a sequence of conjugated double or triple bonds constitute a “molecular wire”, while consecutive single bonds disrupt electronic conductance, the tautomeric transfer of a proton from an amino to an adjacent imino group can change the direction of current through a molecule. Linking multiple switches via other molecular wires will allow the creation of more complex electronic devices and eventually the “molecular computer”. We will also discuss mechanisms of triggering the switch, including an external electric field or optical excitation.

Solvent-enhanced symmetry-breaking induced by low-frequency vibrations in the covalently bound tetracene dimer leading to singlet-fission

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Singlet fission (SF) has been extensively explored over recent years as a mechanism of carrier multiplication in organic photovoltaics, potentially increasing the photon-to-energy conversion efficiency above the Shockley-Queisser limit for p-n junction cells. In suitable SF materials, a photoexcited singlet exciton converts to a singlet-coupled triplet pair ^{1}(TT), which subsequently breaks up into independent, uncorrelated triplet excitons. In recent years, covalently bound dimers of chromophores have attracted significant interest because of better control of coupling of different electronic states to the gateway ^{1}(TT) by means of intramolecular vibrational modes. It has been shown that charge transfer (CT) play a crucial role in mediating the S_1-^{1}(TT) interaction and their influence can be conveniently tuned by solvent polarity.

Motivated by the experimental and theoretical work of Alvertis et al. [1], we have investigated the electronic states relevant to the SF for the covalently bound tetracene dimer with the goal to provide a broader picture of the occurring photodynamical processes. For that purpose, the second-order algebraic diagrammatic construction (ADC(2)) method has been used for the calculation of the singly excited states. Vertical excitations and potential energy curves for excitonic and CT states along low-frequency symmetric and antisymmetric normal modes have been computed for the gas phase using a polarizable continuum model in the form of the conductor-like screening model (COSMO). These results have been combined with those obtained by density functional theory/multireference configuration interaction (DFT/MRCI) calculations for the ^{1}(TT) state since its doubly-excited wavefunction is not accessible to the ADC(2) method.

The vertical excitation spectrum in the gas phase consists of a pair of delocalized resonant excitonic and two resonant CT states, plus the ^{1}(TT) state. COSMO solvation using solvents of different polarity do not change the spectrum much because of the zero net charge transfer occurring in the delocalized CT states. Three normal modes, consisting of a symmetric and an antisymmetric rotation around the CC linkage, and an antisymmetric mode comprising a bending of the tetracene planes have been chosen as models to investigate the evolution of local charge transfer character and the interaction with excitonic states. A localization of the two CT states, stabilizing one and destabilizing the other one, which is considered as a crucial step for the SF process, is found in the combination of state-specific solvation for one of the CT states and antisymmetric, symmetry breaking modes. The ^{1}(TT) state is near the energetically higher CT state. These results are used to analyze possible coherent and incoherent SF mechanisms.

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Designing Nonlinear Optical Redox Switches with Inverse Molecular Design: the Synergy between Core-modifications and *Meso*-substitutions

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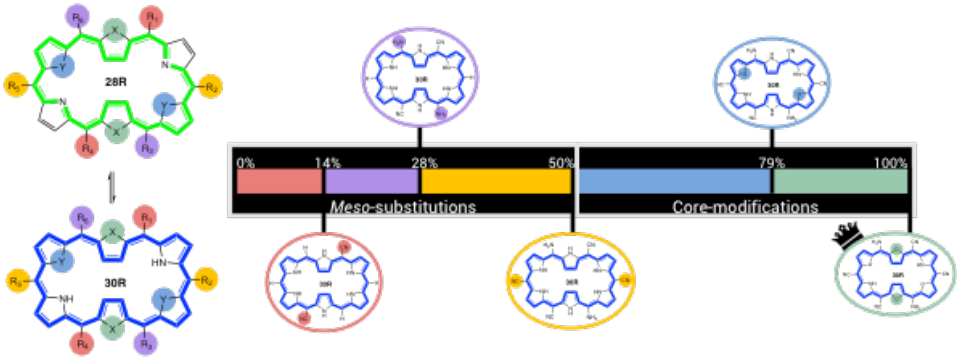
With traditional direct molecular design approaches, only small parts of the chemical compound space (CCS) are explored hampering the discovery for new functionalized molecules for potential nonlinear optical applications. Inverse molecular design aims to overcome this challenge by efficiently sampling larger regions of the CCS.[1] Recently, we took up the challenge to apply an inverse design algorithm, called the Best-First Search (BFS) algorithm, to discover promising modified hexaphyrins-based molecular switches with high nonlinear optical (NLO) contrasts based on the first hyperpolarizability related Hyper-Rayleigh Scattering phenomenon (β_{HRS}).[2,3]



First, we focused on understanding the influence of core-modifications and *meso*-substitutions on the NLO contrast of the **26R** ⇌ **28R** redox switch.[2] After applying the BFS procedure, several *meso*-substitutions patterns were obtained enhancing the NLO contrast up to 25 times, containing either a combination of two electron-donating groups (EDG) and one electron-withdrawing group (EWG) or only EDGs. Both the molecular symmetry as well as the electronic nature of the substituent are key players in tuning the β_{HRS} contrast. Next, we applied the BFS procedure on a more challenging switch, the **30R** ⇌ **28R** redox switch, that showed little to no improvement, when core-modified or fully substituted with a single type of *meso*-substituent.[3] In total, we collected 277 patterns and proposed design rules for functional NLO switches based on **30R** ⇌ **28R**. In contrast to the **26R** ⇌ **28R**, a combination of 2 EWGs and 1 EDG, together with a centrosymmetric OFF state is the ideal recipe to increase the NLO contrast. Adding core-modifications synergistically improves the NLO contrast. In a final step, we aim to optimize the three-state switch based on **26R** ⇌ **28R** ⇌ **30R**, where the individual contrasts are optimized at the same time.

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New Challenges in Computational Spectroscopy

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The quest for a reliable yet practical modelling of large molecular systems has always played a central role in the field of theoretical and computational chemistry. [1] In this framework, despite the undisputed effectiveness of static structure-property correlations and the fundamental rigid-rotor/harmonic-oscillator (RRHO) model, results that are directly comparable to experiment can only be achieved through more advanced models: (i) at the electronic level, employing highly correlated methods; (ii) at the nuclear level, by incorporating anharmonic effects in the description of the nuclear motions. Among the various methods for the inclusion of anharmonic effects, the vibrational second-order perturbation theory (VPT2), [2,3] allows the effective study of medium-to-large size molecular systems. At the VPT2 level, also the vibrational corrections to the rotational constants can be obtained, paving the way for the calculation of accurate molecular structures through the semi-experimental (SE) approach. [4]

While VPT2 can be successfully applied in many cases, it is also characterized by some intrinsic drawbacks that prevent its use in some situations, in particular when large amplitude motions (LAMs) are present. Unfortunately, variational approaches such as the vibrational configuration interaction (VCI) [5] become rapidly prohibitive as the size of the molecular systems increases. On the other hand, reduced-dimensionality methods tailored for describing one or a limited number of LAMs require an effective separation from the rest of vibrations, usually referred to as small amplitude motions (SAMs). As shown in a previous study, [6] the definition of a suitable set of internal coordinates able to decouple these two classes of vibrations allows to treat each normal mode through the most appropriate method. Based on this premise, a general and effective VPT2 framework in terms of curvilinear coordinates was developed. While for semi-rigid systems implementations employing Cartesian and Internal coordinates provide comparable results, in the case of flexible systems, internal coordinates lead to a very good decoupling of LAMs from SAMs.

In this presentation, the versatility of internal coordinates and their application in the fields of rotational and vibrational spectroscopy will be described, starting from the calculation of highly accurate extrapolated and SE molecular structures and proceeding up to reaction kinetics, extending in the latter case the vibrational treatment to different points along the minimum energy paths (MEPs) of bimolecular reactions. The performance of the new engine will be illustrated by its application to systems of biological and technological interest.

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Theoretical modelling of mechanoluminescent properties of pyridylvinylanthracene crystals

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Mechanoluminescent (ML), "smart" materials, which show color changes upon application of an external mechanical constraint, are of particular interest to the materials science community due to their vast potential in optical, electronic and medical applications. Luminescence properties of organic crystals are governed by the structure of the molecular units and their spatial arrangement. Application of pressure might trigger changes in the molecular conformation and packing that translate into changes in emission wavelength and intensity. The rational design of ML organic materials thus requires a detailed understanding of structural changes induced by pressure and of their subsequent impact on the nature and energy of the relevant excited states. In this context, computational techniques can be used to investigate the structural and electronic origins of ML in organic materials. However, very few theoretical studies have comprehensively assessed ML in organic materials, from the photophysical properties of individual molecules to their ML response of the solid state.

This work reports a computational study of the ML properties of recently synthesized 9,10-bis((E)-2-(pyrid-2-yl)vinyl)anthracene (BP2VA) crystals, whose powder luminescence response to hydrostatic pressure has been put in relation with the crystal's emissive properties of its three different polymoprhs.[1]

Firstly, BP2VA molecule for each crystalline polymorph were fully characterized at zero pressure (geometry, electronic structure, excited state nature). Secondly, the geometries of the three BP2VA crystal with and without pressure and their associated electronic and phonon structures were obtained using periodic DFT, allowing the control of their structure-property relationship. Optimized crystalline geometries were used for subsequent characterization of aggregates. Thirdly, finite-size aggregates extracted from the three polymorphs were fully characterized with and without pressure and changes in molecular arrangement and consequent intermolecular interactions were analyzed. The nature of the excited states was analysed using a diabatization scheme that allows to deconvolute the computed adiabatic states in terms of diabatic states with different nature (local excitation, charge transfer, etc.). Larger aggregates were considered and the level of theory employed was adjusted as necessary. This multiscale computational protocol provides a detailed mechanistic picture of ML at different scales of complexity.

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Modelling charge transport properties of dipolar self-assembly merocyanines: the role of static and dynamic disorder

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Merocyanines are highly dipolar pi-conjugated molecules, consisting of electronic donor (D) and acceptor (A) subunits connected via a methine bridge.[1] They have attracted special interest over the last decades due to their unique self-assembly and tuneable opto-electronic properties, making them optimal active materials for organic electronic applications, such as OFETs, OLEDs and solar cells.[2] Recent experiments on single-crystal OFETs of merocyanines revealed a hole mobility up to 2 $cm^2V^{-1}s^{-1}$, setting these D/A molecules on a competitive stage with respect to other organic semiconductors, such as acenes.[3] Via a bottom-up quantum-chemical and kinetic Monte-Carlo approach we modelled the structure vs. charge transport relationships for a comprehensive library of merocyanines, featuring various D/A units and side-chain groups (e.g., branched alkyl chains, rings, etc.).We studied both intra- and inter-molecular charge transport parameters, finally computing the Brownian and electric-field dependent charge (hole) mobilities. We analysed the impact of different side groups and D/A moieties affecting the supramolecular order and the (an)isotropy of the charge diffusion pathways, thus drawing clear structure-property relationships.[4] We extended our computational approach to include both static and dynamic disorder effects, revealing for the first time the impact of disorder for such class of organic functional materials. Results are here critically discussed with respect to state-of-the-art single crystal organic semiconductors.

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Unveiling the Dynamic Structure of Organozincs in THF: Elucidating solvent effects with Molecular Dynamics and X-Ray Absorption Spectroscopies

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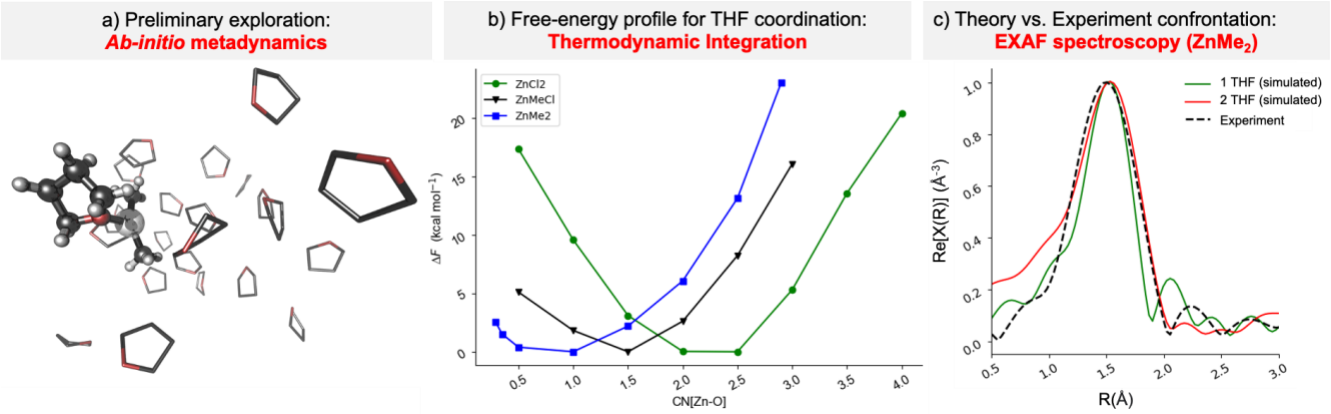
Over years, organozinc reagents have raised a considerable interest in synthesis to promote C–C bond formation under mild conditions, such as in carbozincation or Negishi reactions. In these reactions – and as it is often the case in organometallic chemistry, both the solvents and additivesare crucial, but their exact role at the molecular scale remains obscure. [1] These effects cannot be monitored by common experiments (NMR, …), but they are also not easily handled using DFT calculations due to the limitations of commonly used microsolvation models. Inspired by Cascellaand Eisenstein, [2] we have established a 3-step strategy based on *ab-initio* metadynamics (AIMD)using solvent cages to *i)* calculate accurate thermodynamics of the systems, *ii)* simulate EXAF spectra and *iii)* experimentally validate these predictions.



Using AIMD (Fig. a) combined with thermodynamic integration in Bluemoon ensemble (Fig. b), [3] we studied organozincs solvation states. For the first time, the solvation of $ZnMe_2$ was computedfavorable. This prediction was further validated by EXAFS (Fig. c). The strategy was then applied to transmetallation reactions of industrial interest. In particular, we studied how solvent dynamicscontrol these reactions.

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On the importance of conformational Entropy when predicting Chemistry: results from the new Global Optimizer AlgoriThm (GOAT) implemented in ORCA

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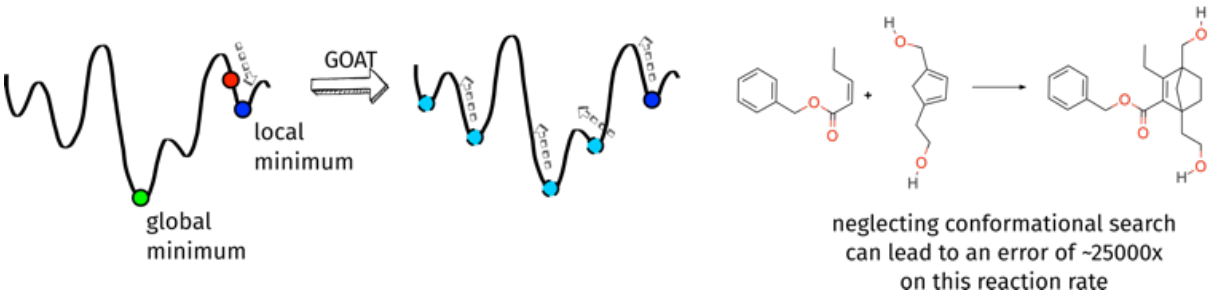
Although mostly neglected for a long time in Computational Chemistry, the conformational sampling of flexible molecules plays a major role in most real-life problems. The question of whether a certain guess conformer drawn, or automatically generated from a plain 2D Lewis structure, is the minimum on its PES is of no minor importance, because different conformers can have significantly different features. From the most complicated properties such as Circular Dichroism spectra to simpler ones as the molecule's dipole, there is always an effect from the geometry on the Hamiltonians, and having a full picture of the molecular ensemble in the gas phase or solution is of major importance for most of chemistry.

On top of that, the generation of complete (or nearly complete) ensembles allows one to compute rather abstract quantities such as the Conformational Entropy or Gibb's Free Energy, which are also still mostly neglected when computing reaction energies, binding constants, pKas and activation barriers – and comes with a price in accuracy as we want to show here.

In this work we will present the new Global Optimizer AlgoriThm (GOAT) implemented in the ORCA software, inspired by the classic work of D. Wales and S. Goedecker, and concrete examples of how one can be orders of magnitude wrong when predicting experimental rates and constants if these "conformational" or "ensemble" components of the thermodynamic functions are neglected. GOAT can be combined with everything that's already there in ORCA, including regular DFT, excited-states, broken-symmetry states and etc., when trying to find both the global minimum and/or molecular ensembles.



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Time evolution of natural orbitals in ab initio molecular dynamics

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One-particle reduced density matrix (1RDM) functional theory is an alternative formalism to both density functional and wavefunction based methods. A pragmatic approach results in approximate functionals of the 1RDM in its diagonal form, that is, the use of natural orbitals and its occupation numbers as the fundamental variables, which define a natural orbital functional (NOF).

In this talk, I will first introduce the recently proposed [1] global NOF (GNOF). The latter has shown a balanced treatment of electron correlation effects in molecular systems with different spins, including complete dissociation curves; as well as an adequate treatment of the strong electronic correlation regime in challenge systems [2,3]. The NOF theory is currently an active research field, which can already be applied to large molecular systems of general chemical interest [4,5] using open-source software like DoNOF [6].

Secondly, I will present a GNOF-based ab initio molecular dynamics (AIMD) within the Born-Oppenheimer approximation. The most prominent feature of GNOF-AIMD is the ability to display the real-time evolution of natural orbitals, providing detailed information on the time-dependent electronic structure of complex systems and processes, including reactive collisions. The quartet ground-state reaction N(4S) + H2(1Σ) → NH(3Σ) + H(2S) is taken as validation test. Collision energy influences on integral cross sections for different initial ro-vibrational states of H2 and rotational-state distributions of NH product are discussed, showing a good agreement with previous high-quality theoretical results.

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First-principles prediction of exotic hexagonal NaCl films on methylammonium lead iodide substrates, new hints for perovskite solar cells

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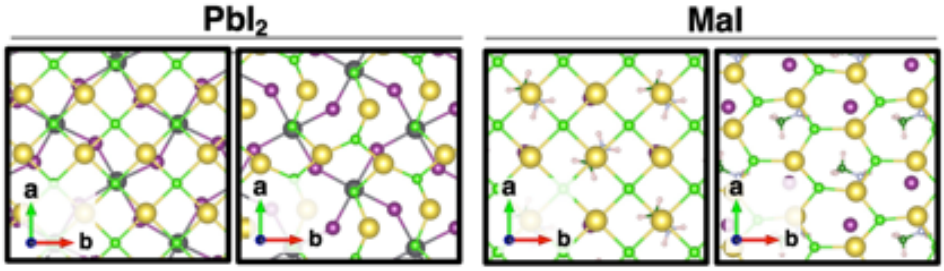
Sodium chloride is an ionic compound able to tune the electronic properties of the interface in heterogeneous junctions. It is often used in perovskite solar cells as interlayer between the photoactive material and the charge transport layers. Despite its simplicity, unexpected exotic NaCl interfacial structures can be found at high pressure or low dimension. [1,2] The (100) is the most stable surface facet, however recent experiments found different surface termination depending on the chemical nature and the structure of the substrate, for example an hexagonal surface of NaCl has been found on the diamond (110) surface.[3] Our study investigates the interface between NaCl and the archetypal lead halide perovskite (Methylammonium lead triiodide, MAPI) with first-principles calculations within the Density Functional Theory (DFT) framework.



Our results show different possible NaCl surface reconstructions depending on the MAPI terminations and the nature of the interactions at play.

Effects on MAPI electronic structure (work function, band edge potentials) are also discussed. We perform a thermodynamic investigation of I defects and assess their effects on the electronic structure. These findings can guide the design of new and high-performing perovskite solar cells.

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Combined first principles-statistical mechanics approach to sulfur structure in organic cathode hosts for polymer based lithium-sulfur (Li-S) batteries

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Polymer-based batteries that utilize organic electrode materials are considered viable candidates to overcome common drawbacks of lithium-sulfur (Li-S) batteries. A promising cathode is a conductive, flexible, and free-standing polymer poly(4-thiophen-3-yl)benzenethiol) (PTBT) as the sulfur host material. By a vulcanization process, sulfur is embedded into this polymer.

Here, we present a combination of electronic structure theory and statistical mechanics to characterize the structure of the initial state of the charged cathode on an atomic level. We perform a stability analysis of differently sulfurized TBT dimers as the basic polymer unit calculated within density-functional theory (DFT) and combine this with a statistical binding model for the binding probability distributions of the vulcanization process. From this, we deduce sulfur chain length ("rank") distributions and calculate the average sulfur rank in dependency of the sulfur concentration and temperature.

This multi-scale approach allows us to bridge the gap between the local description of the covalently bonding process and the derivation of macroscopic properties of the cathode. Our calculations show that the main reaction of the vulcanization process leads to high-probability states of sulfur chains cross-linking TBT units belonging to different polymer backbones, with a dominant rank around n=5. In contrast, the connection of adjacent TBT units of the same polymer backbone by a sulfur chain is the side reaction. These results are experimentally supported by Raman spectroscopy.

CO Oxidation on Molybdenum Oxide Clusters: Reaction Energetics and Mechanism

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Noble metal systems, both extended (surfaces) and nanosized (clusters), are among the most efficient catalysts for oxidation of CO. They, however, are costly, and finding alternative, cheaper ways for conversion of CO into CO_2 is a technologically important task. Here, we present results of a density functional theory (DFT) based computational study of the energetics and mechanism of CO oxidation on molybdenum oxide clusters with the latter serving as the source of the extra oxygen. The calculations were performed for CO interacting with Mo_3O_9 and Mo_3O_8 clusters used as paradigmatic cases. The neutral and the charged (anionic and cationic) states of the clusters were considered and the effects of the charge state of the cluster and the oxidation state of Mo in the molybdenum oxide were analyzed and characterized. Specifically, for each case ($CO + Mo_3O_n^{0/+1/-1} \rightarrow CO_2 + Mo_3O_{n-1}^{0/+1/-1}$, n=9 and 8) we mapped out the complete minimum energy path from the reactants to the products that includes all the intermediate steps (adsorption of CO on the cluster, transfer of oxygen from the cluster to CO, rearrangement of CO_2 on the cluster, desorption of CO_2) and the transition states (barriers) between them. The global findings are that the reaction is more facile on the cationic Mo_3O_9 and Mo_3O_8 than on their neutral and anionic counterparts, and on the stoichiometric Mo_3O_9 as compared to the sub-stoichiometric Mo_3O_8. The $CO + Mo_3O_9^+ \rightarrow CO_2 + Mo_3O_8^+$ reaction is exothermic while the other considered CO oxidation pathways are endothermic. Results on the effect of the degree of coverage of the clusters by CO on the energetics of CO oxidation will also be presented and discussed.

Acknowledgements. The work at Argonne was supported by the Office of Basic Energy Sciences, Division of Chemical Sciences, Geosciences and Biosciences, U.S. Department of Energy under Contract No. DE-AC02-06CH11357 (J.J.). This research used the resources of the National Energy Research Scientific Computing Center (NERSC) supported by the Office of Science of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231. We also gratefully acknowledge use of the Bebop cluster in the Laboratory Computing Resource Center (LCRC) at Argonne National Laboratory.

The eXact integral simplified time-dependent density functional theory (XsTD-DFT)

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In the framework of simplified quantum chemistry methods for large systems, we introduce the eXact integral simplified time-dependent density functional theory (XsTD-DFT). This method is based on the simplified time-dependent density functional theory (sTD-DFT)[1] where semi-empirical two-electron integrals are replaced by exact one- and two-center atomic orbital (AO) two-electron integrals. Other approximations in sTD-DFT are kept. The performances of this new parameter-free method were benchmarked to evaluate excited state and (non)linear response properties, including ultra-violet/visible absorption, circular dichroism, optical rotation, first hyperpolarizability, and two-photon absorption.

For a set of 77 molecules, the XsTDA approach was compared to TDA (TD-DFT considering the Tamm-Dancoff approximation) results. Our new implementation only deviates absolutely by 0.145 eV from excitation energies obtained with B3LYP exchange-correlation functional while drastically cutting computational costs. Comparing XsTDA and its predecessor sTDA, the new scheme globally improves excitation energies and oscillator strengths while absolute deviations with respect to the full scheme decreases when increasing the size of the system.

Furthermore, a noteworthy comparison between XsTD-DFT and TD-DFT shows that our new approach faithfully reproduced first hyperpolarizability frequency dispersions for a set of push-pull π-conjugated molecules. Excellent performances are also observed when computing 2PA cross-sections for a set of fluorescent protein chromophores, outperforming full TD-DFT results with respect to reference RI-CC2 values.

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Predicting the FCI energy of large systems to chemical accuracy from restricted active space density matrix renormalization group calculations via Hybrid CPU-GPU based architectures

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We theoretically derive and validate with large scale simulations a remarkably accurate power law scaling of errors for the restricted active space density matrix renormalization group (DMRG-RAS) method [1] in electronic structure calculations. This yields a new extrapolation method, DMRG-RAS-X, which reaches chemical accuracy for strongly correlated systems such as the Chromium dimer, dicarbon up to a large cc-pVQZ basis, and even a large chemical complex like the FeMoco with significantly lower computational demands than previous methods. The method is free of empirical parameters, performed robustly and reliably in all examples we tested, and has the potential to become a vital alternative method for electronic structure calculations in quantum chemistry, and more generally for the computation of strong correlations in nuclear and condensed matter physics [2]. Simulations have been performed via massively parallelized DMRG algorithm designed for high performance computing (HPC). We also discuss novel algorithmic solutions together with implementation details to extend current limits of DMRG algorithms on HPC infrastructure building on state-of-the-art hardware and software technologies. Benchmark results obtained via large-scale DMRG simulations are presented for selected strongly correlated molecular systems addressing problems on Hilbert space dimensions up to 2.88×10^{36}, i.e., for FeMoco in CAS(113,76) orbital space.

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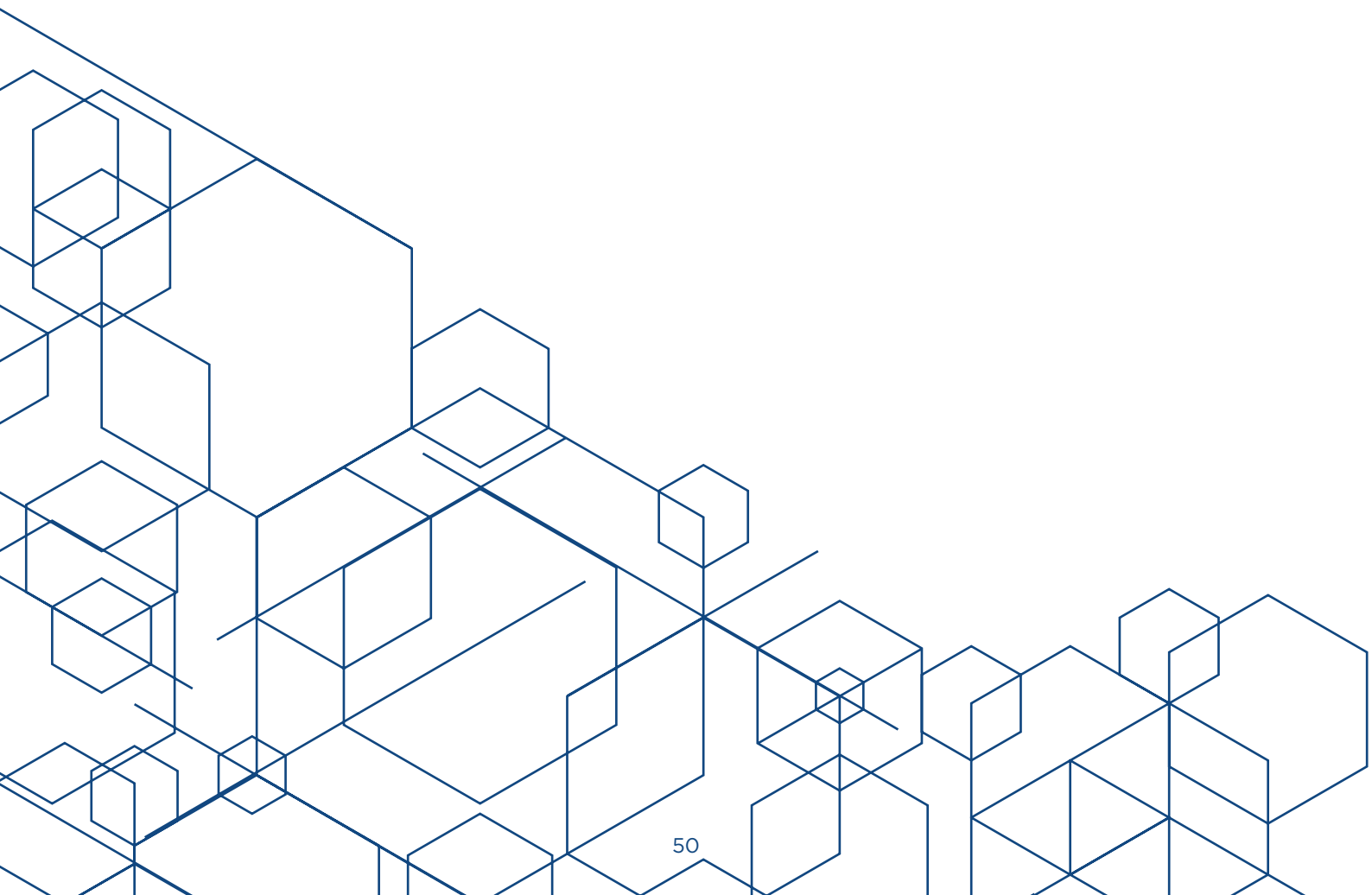
MATERIALS DESIGN



Predicting the Second-Order Nonlinear Optical Responses of Organic Materials in Complex Environments: The Role of Dynamics

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The last thirty years have witnessed an ever-growing application of computational chemistry for rationalizing the nonlinear optical (NLO) responses of organic chromophores. More specifically, quantum chemical calculations proved highly helpful in gaining fundamental insights on the factors governing the magnitude and character of molecular first hyperpolarizabilities (β), be they either intrinsic to the chromophore molecular structure and arising from symmetry, chemical substitution, or π-electron delocalization, or induced by external contributions such as the laser probe or solvation and polarization effects. Most theoretical reports assumed a rigid picture of the investigated systems, the NLO responses being computed solely at the most stable geometry of the chromophores. Yet, recent developments combining classical molecular dynamics (MD) simulations and DFT calculations have evidenced the significant role of structural fluctuations, which may induce broad distributions of NLO responses, and even generate them in some instances.

This talk focuses on recent case studies in which theoretical simulations have highlighted these effects. The selected examples include organic chromophores, photochromic systems, and ionic complexes in the liquid phase, for which the effects of explicit solvation, concentration and chromophore aggregation are emphasized, as well as large flexible systems such as peptide chains and pyrimidine-based helical polymers, in which the relative variations of the responses were shown to be several times larger than their average values. The impact of geometrical fluctuations is also illustrated for supramolecular architectures through the examples of nanoparticles formed by organic dipolar dyes in water solution, whose soft nature allows for large shape variations translating into huge fluctuations in time of their NLO response, and of self-assembled monolayers (SAMs) based on indolino-oxazolidine or azobenzene switches, in which the geometrical distortions of the photochromic molecules, as well as their orientational and positional disorder within the SAMs, again highly impact their NLO response and contrast upon switching. Finally, the effects of the rigidity and fluidity of the surrounding are evidenced for NLO dyes inserted in phospholipid bilayers.

In Silico Design in Organocatalysis

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Organocatalysis remains one of the most challenging topics in contemporary organic chemistry. While the symmetric and asymmetric organocatalysis fields are currently growing exponentially, an understanding of the mechanistic details involved in most of these reactions has often lagged far behind the pace of catalyst development, which retards catalyst design. However, over the last two decades, computational methods have become a cost-effective treatment of large chemical systems with reasonable accuracy not only to provide a rationale for the experimental outcome, but more importantly, to predict catalytic behaviour. Thus in silico catalyst design has become a "pot of gold" within the field of computational chemistry.

In this talk, a theoretical study on the computationally led design of catalysts in asymmetric organocatalysis will be presented. The delicate balance between steric and attractive Non-Covalent Interactions (NCIs), as the main controlling factors in organocatalysis, will be examined.

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New graph-based tools for taming complex reaction networks

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The development of new tools to properly manage research data is becoming more and more important. In the case of computational chemistry, the complexity of the reaction mechanisms that can be characterized by means of *in silico* methods is steadily increasing, through the synergistic combination of enhanced computing power and a larger degree of automation in the exploration of the chemical space. Our group has recently introduced new tools that enable the automatic construction of the complex chemical reaction networks (CRNs) involved in the growth of metal-oxo clusters in solution, [1] for instance, from DFT calculations directly. Using this method, which is called POMSimulator, we showed that the computed speciation phase diagrams (conc. vs pH) for Mo, W, V, Nb and Ta isopolyoxometalates perfectly agree with experimental data in a broad pH range.

To properly treat all the information associated to CRNs, we introduced OntoRXN,[2] a new ontology which allows the systematization of graphs-based analysis of reaction networks as knowledge graphs, by integrating data available in ioChem-BD[3]. Making use of all those tools, we recently reported multi-time scale kinetic simulations for the self-assembly processes of molecular metal-oxo clusters that comprise 22 orders of magnitude, from tens of femtoseconds to months of reaction time. Analysis of the kinetic data and of the CRN, which includes more than 200 single reactions, shed light onto the details of the main reaction mechanisms, and explains the origin of kinetic and thermodynamic control followed by the reaction.[4] In this talk, a summary all these recent advances will be given.

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Biodegrading Plastic

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This talk is concerned with the computational needs that we come across to figure out results within computational enzymology. Calculations devised to study protein interactions and circumvent problems in some relevant systems will be reported as well as recent developments in the establishment of some catalytic mechanisms. We have resorted to QM/MM methodologies[1,2,3] as well as other calculations[4], in order to analyse the energetics of processes related to the systems under study and evaluate their feasibility according to the available experimental data. We will look into more detail to biodegrading plastic[5].

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Aromaticity controls the photoinduced electron transfer in host-guest complexes of nanohoops

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Cycloparaphenylenes (CPPs) are one of the most extensively studied classes of curved nanostructures. Among the ways to modulate their properties are changing the size, substitution of benzene rings with electron-donating/withdrawing groups or introducing π-conjugated units. Majority of reported nanorings, consist of aromatic fragments. In turn, antiaromatic molecules can be promising modulators of the photophysical properties of nanorings. Recently, Esser and co-workers reported several nanohoops containing two and more antiaromatic pentalene units.[1,2] Some of them can efficiently accommodate C_{60} fullerene.

Computational modeling of excited state properties for a series of host-guest complexes of nanorings with aromatic/antiaromatic units (Figure 1) revealed their different behavior upon photoexcitation, depending on the degree of aromaticity.[3]

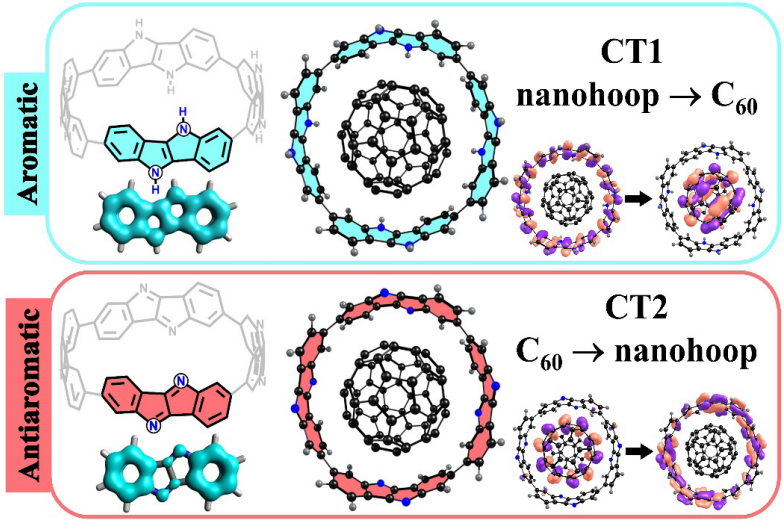

Figure 1. Charge ς (CT) in complexes of [4]cyclodibenzodihydropyrrolopyrrole (top) and [4] cyclodibenzopyrrolopyrrole (bottom) with C_{60} fullerene

In complexes with aromatic units, only electron transfer from the nanoring to C_{60} was found. In contrast, in complexes containing antiaromatic fragments, such direction of the electron transfer is unlikely. However, due to the significant lowering of the LUMO energies compared to the aromatic one, the electron transfer from C_{60} to nanohoop is almost barrierless and ultrafast.

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Ruthenium Complexes as a Test System to Unravel the Symmetry Effects on the Second-Order Nonlinear Optical Responses of Molecular Switches

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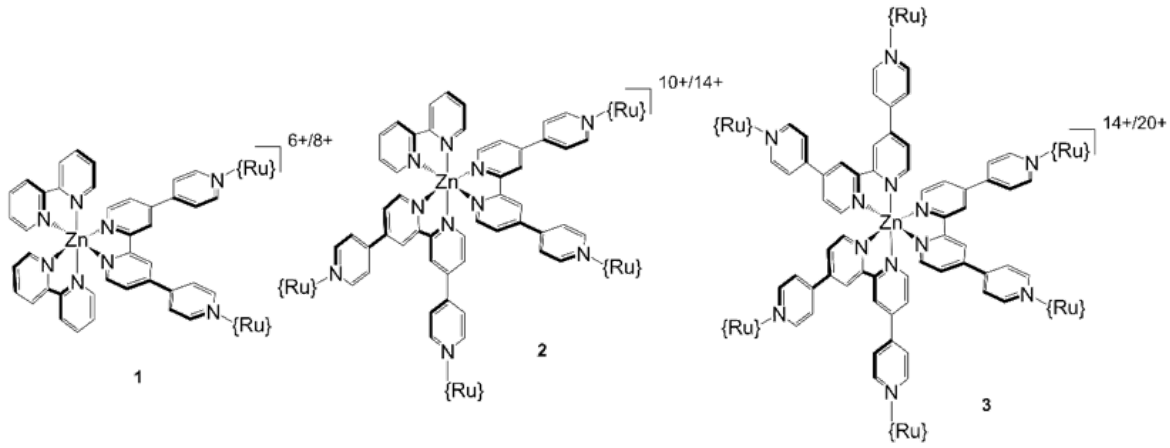
Molecular switches constitute a fascinating field, with applications in sensing and data storage/treatment. Our group has developed an expertise in those molecular switches displaying contrasts of their nonlinear optical (NLO) properties, which is useful for reading without erasing steps. Recently, we have been challenged by Benjamin COE [1], who was targeting the preparation and characterization of octupolar-like structures, like the one drawn below (**3**). This triggers a detailed quantum chemistry investigation that we will disclose in my talk. So, using (time-dependent) density functional theory we have characterized the second-order NLO properties (the hyper-Rayleigh scattering response, β_{HRS}, [2]) of **3**, in comparison to those of *pseudo* one-dimensional (**1**) and Λ-shape (**2**) analogs, as well as their contrasts upon oxidation (Ru^{II} to Ru^{III}).



It turns out that β_{HRS} of **1** and **2** are 3 times larger than the one of **3** and that this can be rationalized using few-state models [3]. Yet, **3** is more promising than **1** and **2**, provided electron-donor and -acceptor substituents are carefully chosen. The presentation will also present a new scheme to quantify the excitation-induced metal-to-ligand charge transfers. Finally, the redox-switching leads to a strong decrease of the response, which is linked to the loss of donor character of the Ru atoms.

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Computational study into the formation of tin halide perovskite nanostructures

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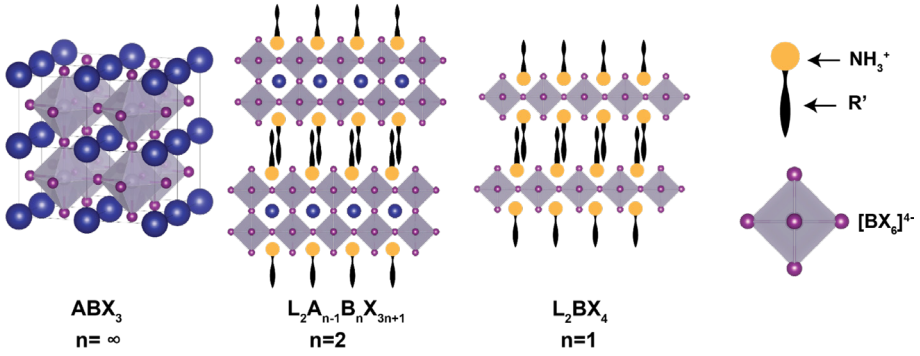
Metal halide perovskite nanocrystals have recently emerged as promising photoactive layers for solar cell devices with power conversion efficiencies up to the 25%.[1] Tin-based materials, with high charge carrier mobilities and optimal band gaps for photovoltaics, have been postulated as the most promising candidates to substitute the lead-based devices.[2] Interestingly, it has been recently shown that if tin halide salts are used as precursors, the simultaneous formation of 3D nanocrystals (ABX_3) and 2D nanosheets ($L_2A_{n-1}B_nX_{3n+1}$) can be induced.[3] This achievement opens the door for the synthesis and characterization of materials with tunable optical and electronic properties depending on the nanocrystal particle size and the nanosheet dimensionality. [4]



In this oral contribution, we present a theoretical and computational approach to unveil the mechanistic study and the formation driving forces of 2D nanosheets and 3D nanocrystals of tin halide perovskite nanostructures. Our protocol combines state-of-the-art density functional theory calculations with ab-initio molecular dynamics simulations. A special focus is given to the relationship between the dynamical disorder,[5] the chemical composition, the electronic properties and the formation energy of these materials.

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Growth and reactivity of Hexagonal Boron Nitride

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The properties of epitaxially grown 2D materials, such as hexagonal boron nitride (hBN) and graphene, depend on the growth mechanism and defects in the epitaxial layer. In our study, we employ Density Functional Theory (DFT) calculations to examine the epitaxial growth of hBN on a Ru(0001) surface; we aim to develop a detailed understanding of the formation of hBN from borazine. Our results predict the formation of a (3 × 3) meta-stable structure, consistent with results from helium atom scattering experiments.[1] Building on this finding, we have determined the behaviour of an isolated borazine molecule on a Ru(0001) surface and have investigated its polymerisation. We intend to use our findings to determine a detailed hexagonal boron nitride growth mechanism on Ru(0001). Our findings may have implications for CVD processes, the creation of defect sites and the design of new nanomaterials based on exploiting the growth phases of hBN.

We have also investigated the effect of defects on the catalytic activities of hBN. The many advantages of hBN for heterogeneous catalysis include high surface area, thermal stability, and durability. Furthermore, hBN is more sustainable than the ubiquitously employed precious and transition metal-based catalysts. Through DFT simulations, we have explored metal-free hBN as a valid alternative to precious metal catalysts for producing H_2 via the reaction of ammonia with a surface boron and nitrogen divacancy (VBN), achieving a decomposition barrier of 0.52 eV. For comparison, the reaction of ammonia with epitaxially grown hBN on a Ru(0001) substrate was investigated, and we observed similar NH_3 decomposition energy barriers (0.61 eV) but a much more facile H_2 desorption barrier (0.69 eV vs 5.89 eV).[2] We have continued to investigate how a hydrated vacancy can participate in the hydrogenation of NO_x to H_2O. Through completing this work, we hope to discover sustainable alternative catalysts.

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Deducing desirable properties of porous materials for the adsorption of complex organic molecules by employing an efficient hierarchical screening approach

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The rising contamination by pharmaceutical agents and ingredients of personal care products (PPCPs), which may enter the environment through various routes becomes an increasingly pressing issue [1]. Just last year the European Union has released a directive for stricter water legislation laying the basis for lowering pollution limits of water resources [2]. This is indispensable since a report of the German Environment Agency reviewing several thousand publications concluded that 37 pharmaceutically active substances or metabolites of these have been detected in surface, ground or drinking waters all around the world. A much larger number of PPCP pollutants have been found to occur in wastewaters, especially in industrial countries [3].

One approach for the selective removal of contaminants from water is the use of hydrophobic zeolites which profit from their defined pore structure. Carbon-based adsorbents, which are in principle suited to remove a broad range of PPCPs, may suffer from passivation by natural organic matter in waste waters [4, 5]. From an experimental point of view the adsorption of several PPCPs in hydrophobic zeolites has been investigated, but the required adsorption experiments are time-consuming and expensive. Simulation-based approaches are less frequently taken, although they could constitute a time-efficient, low-cost route to identify high-silica zeolites with promising properties for the adsorption of pharmaceutical agents [6].

In this work, we modelled the interaction of 14 all-silica zeolite frameworks with 53 PPCPs on the forcefield level, employing increasingly sophisticated methods to determine trends and assess criteria for a favourable interaction between the framework and the guest molecule. The PPCPs have been described with the OpenFF Sage force field [7] and parameters optimised by Emami *et al* were used to describe the zeolite framework atoms [8]. The molecular dynamics simulations were performed with the LAMMPS software package [9].

The first step in our hierarchical approach was to consider multiple conformers for each PPCP if they geometrically fit into the framework. Only the conformers that were predicted to fit into a pore were submitted to a random insertion into the framework. Afterwards a simulated annealing was performed to allow the guest molecule to access different adsorption sites. Subsequently, free energy simulations were performed for promising PPCP-zeolite combinations to evaluate if the adsorption is thermodynamically preferred over the aqueous phase.

By the information obtained from different adsorption geometries, deformation penalties and free energies of adsorption/hydration, an assessment can be made which zeolites have an enhanced ability to remove contaminants from aqueous solution. Based on the results, particular zeolite frameworks or combinations of framework types can be suggested for actual applications in PPCP removal. Also the findings allow the identification of ideal properties for the design of new framework types.

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Cheminformatics-Aided Prediction of Degradation Reaction Products in Energy Storage Materials

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The growing demand for sustainable energy storage devices requires fabrication of novel materials for rechargeable batteries. The stability of the materials incorporated in the electrochemical cells plays crucial role for the specific capacity and cycling stability of the energy storage devices. The processes that occur inside such systems are fairly complex and hence the identification of unwanted side reactions affecting the electrochemical stability is not trivial.

Classical cheminformatics approaches and machine learning, on the other hand, have proven their ability to determine possible products of chemical reactions. This kind of methods have successfully been utilized in synthesis planning [1], retrosynthetic analysis [2] and mass-spectroscopy fragmentation prediction [3]. In the present study different cheminformatics and machine learning approaches are deployed to create an algorithm that generates diverse feasible redox reactions given electrochemical system, e.g., cathode material, anode material, electrolyte, solvent, etc., can undergo. The results are validated using literature data about side reactions of well-studied electrochemical systems.

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High-throughput atomistic modelling of semiconducting polymers

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Background. Semiconducting polymers (SCPs) have a wide range of applications due to their ability to be used in low-cost, lightweight, and large-scale electronic devices. The physical properties of SCPs can be tailored by selecting a sequence of conjugated monomers and flexible side chains, which defines the chemistry. So far, materials development in the field has progressed largely by trial and error and a generic approach that provides the necessary design principles for the desired properties in SCPs is in extremely high demand. Atomistic-scale models are essential for relating microstructure to electronic structure properties. Existing computational methods are used to model SCPs, but there are several challenges that have inhibited the expected progress in the field thus far. Generating atomistic models through conventional MD approaches is a tedious and laborious task due to the lack of standard protocols in organic electronics. As such, compared to the volume of new materials introduced every year there is a very limited number of SCPs with reliable atomistic models since accurate simulations are reserved for just a few polymers per investigation.

We have developed a software package to generate an extensive library of existing and hypothetical SCPs. It: i) employs a multiscale resolution method (from sub-atomic to meso-scale), ii) enables speedy model generation, and iii) unlocks the composition-morphology-property relationship to inform the rational design of SCPs. The generation of hundreds of SCP models is foreseen, which informs the development of new generations of SCPs based on the desired electronic structure properties. This method includes:

1. **Development of an automatic workflow to define modular and transferable force fields for organic electronics**. An expandable library of building block parameters was constructed, associated with a protocol to determine the interaction parameters between blocks, and a tool to construct SCP topology of arbitrary size and complexity starting from their constituents.

2. **Single automated workflow for the generation of equilibrated SCP models**. A generic workflow was developed to automatically generate equilibrated models for any given SCP topology. Key parameters of the equilibration process are determined algorithmically by the protocol, rather than being arbitrarily chosen by the user.

3. **High-throughput microstructure analysis for equilibrated systems and development of design rules**. The analysis of the simulation was automated. It includes multiple morphological properties such as chain conformation, degree of phase separation, conjugated backbone connectivity, and chain ordering, all of which can be related to structural experimental data. The analysis also includes electronic properties via QM/MM schemes (density of states, localization length) and the modelling of charge transport for the given microstructure.

We will present the result of several benchmark SCPs generated by the method (e.g., IDT-BT polymer), and an in-depth verification for the model SCPs.

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Manipulating Excited Estates using Inverse Design

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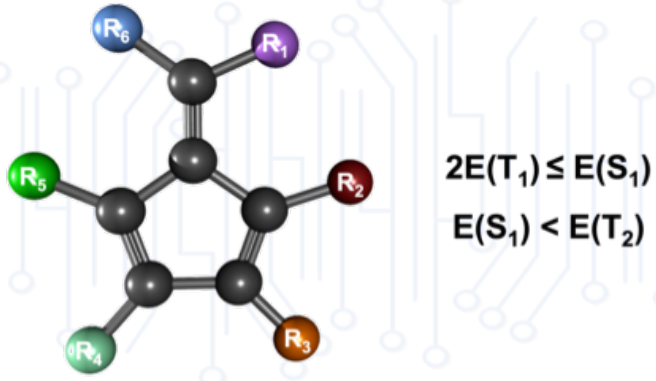
Electron excitation by photons is a key fundamental process to enhance the efficiency of photovoltaic devices.[1] Singlet-fission materials have the potential to surpass the efficiency of such devices as they can generate two excitons from a single photon, affording quantum efficiencies up to 200%.[2] A big challenge is to find chromophores that fulfil the strict energetic requirements for singlet fission with high photostability.

In this project, we will use fulvenes as a test bed to establish a robust inverse design[3] protocol that will be later applied to design new promising porphyrinoids as singlet-fission chromophores. A computational inverse design approach is highly desirable to reshape the landscape of structures available to singlet fission. The results will be compared to previous direct design strategies recently applied on fulvenes.[4] On the generated database, general design criteria spanning a wider chemical space will be devised, including the role of ground- and excited-state aromaticity and the diradical character.



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Modelling LLZO: Limiting Structures in a Near-unlimited Configuration Space

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With the promise of higher power density, increased safety, and reduced production costs,[1] solid electrolytes (SEs) appear to be the ideal next step in battery technology, especially for the automotive industry. One of the most promising candidates for SEs is $Li_7La_3Zr_2O_{12}$ (LLZO). It has the largest electrochemical stability window against Li metal,[2] the proposed anode for SEs. However, it is also subject to dendrite formation and shorting of the battery over repeated cycles. We aim to better understand the properties and stability of LLZO through computational modelling.

LLZO is a challenging system to model. It can adopt two phases: tetragonal (t-LLZO) and cubic (c-LLZO). The disordered c-LLZO is significantly more ionically conductive but is not stable at room temperature. c-LLZO can be stabilised at room temperature when doped with Al. However, even this artificial stability breaks down when in contact with the Li anode. This instability results in the formation of a t-LLZO-like interphase, around five-unit cells thick, at the Li|c-LLZO interface.[3] Our eventual scope is to investigate the full Li|t-LLZO|c-LLZO interphase using ONETEP, a linear-scaling DFT program capable of high-accuracy DFT calculations with thousands of atoms.[4] The development of such a model will enable us to search for causes and potential solutions to interfacial stability limiting ionic conductivity and causing dendrite growth. In pursuit of creating this model, we have

1. Developed a software tool to generate all possible structure models for sparsely occupied ionic conductors
   a. Applied this model to c-LLZO which, when combined with a machine learning-based clustering technique, allowed the isolation of motifs in the structures that lead to lower energy configurations
2. Applied the Fiorentini and Methfessel method for high accuracy insulator surface energies[5]
3. Began the development of a fully automated interface matching workflow using data pipelining

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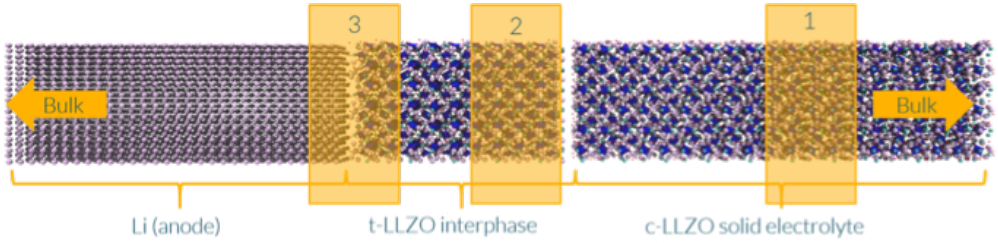

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The unique structural features of water, ranging from ambient liquid up to supercritical, extreme-pressure conditions: Insights from classical and ab initio molecular dynamics simulations

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The complex behaviour of water has motivated the scientific community to develop novel theories and methodologies to provide deeper insight into the molecular causes of its anomalies compared to most liquids. A molecular understanding of the water properties is crucial in numerous processes in chemistry, physics, geosciences, biology, and life evolution. Despite long-lasting research efforts, new intriguing properties are still being described and even the phase diagram of water, although systematically explored in the past, is far from being complete. From a theoretical point of view, the investigation of these characteristic structural features of water and the temperature and pressure effects upon them could be achieved by employing multi-scale modelling techniques, ranging from classical or ab initio molecular simulation techniques to coarse-graining methods. Our recent multi-scale simulation studies of water [1-7] at a very wide range of temperatures and pressures will be systematically presented, aiming to shed some light on the unique structural features of water at ambient liquid up to supercritical, extreme-pressure conditions.

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Multi-scale modeling of folic acid-functionalized TiO_2 nanoparticles for active targeting of tumor cells

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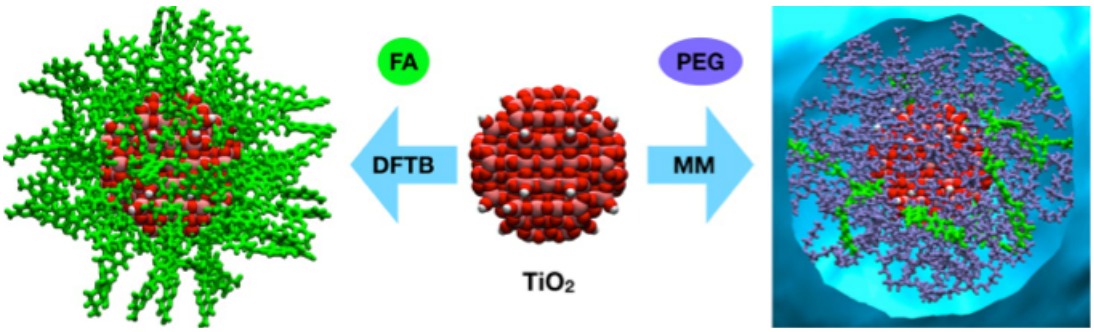
Strategies based on the active targeting of tumor cells are emerging as smart and efficient nanomedical procedures.[1] Folic acid (FA) is a vitamin and a well-established tumor targeting agent because of its strong affinity for the folate receptor (FR), which is an overexpressed protein on the cell membranes of the tumor cells.[2] FA can be successfully anchored to several nanocarriers, including inorganic nanoparticles (NPs) based on transition metal oxides.[3] Among them, TiO_2 is extremely interesting because of its excellent photoabsorption and photocatalytic properties, which can be exploited in photodynamic therapy.[4] However, it is not yet clear in which respects direct anchoring of FA to the NP or the use of spacers, based on polyethylene glycol (PEG) chains, are different and whether one approach is better than the other. In this work, we combine Quantum Mechanics (QM) and classical Molecular Dynamics (MD) to design and optimize the FA functionalization on bare and PEGylated TiO_2 models and to study the dynamical behavior of the resulting nanoconjugates in a pure water environment and in physiological conditions. We observe that they are chemically stable, even under the effect of increasing temperature (up to 500 K). Using the results from long MD simulations (100 ns) and from free energy calculations, we determine how the density of FA molecules on the TiO_2 NP and the presence of PEG spacers impact on the actual exposure of the ligands, especially by affecting the extent of FA–FA intermolecular interactions, which are detrimental for the targeting ability of FA towards the folate receptor. This analysis provides a solid and rational basis for experimentalists to define the optimal FA density and the more appropriate mode of anchoring to the carrier, according to the final purpose of the nanoconjugate.[5]



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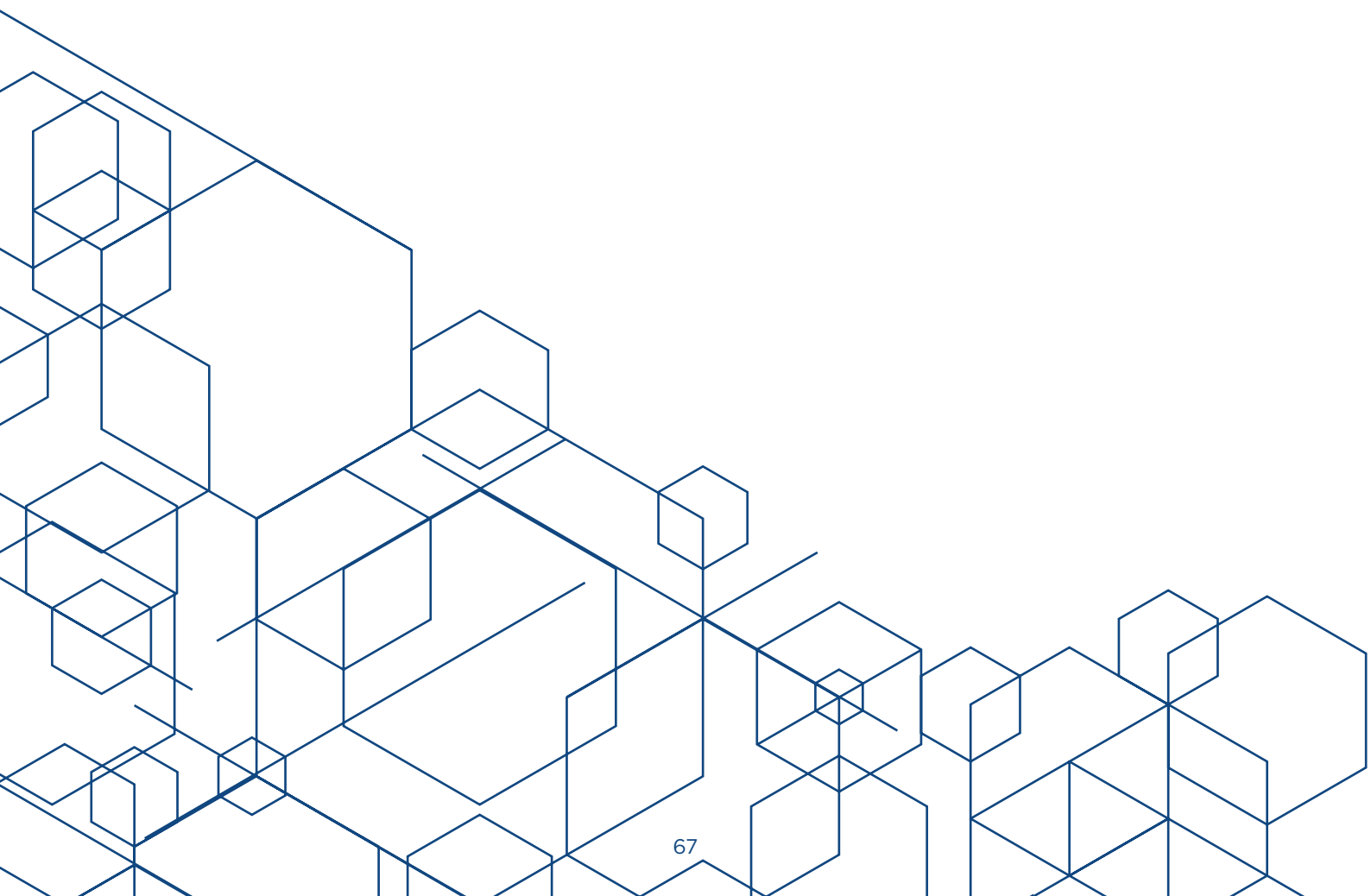
COMPUTATIONAL CHEMISTRY IN INDUSTRY



Deciphering key interactions of ligand binding to biomolecular targets using high-level quantum mechanical methods

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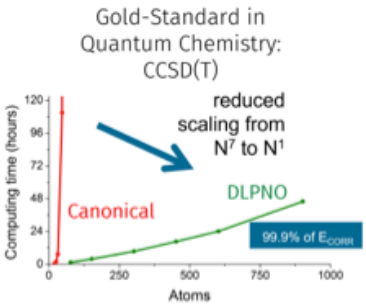
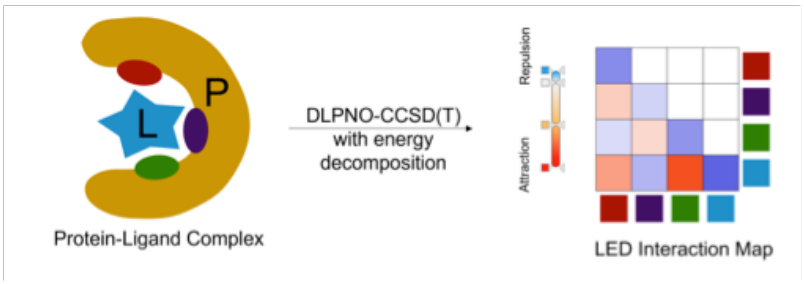
Most of the methods used in the modelling of biomolecular systems rely on empirical parametrization and thus - at least indirectly - on some sort of training, limiting insights as well as applicability domain. A significant part of potential targets for drug design, like RNA or metalloproteins, are outside their usual applicability domain and require significant efforts of parametrization.

CCSD(T) is a generally applicable method, which is known to provide highly accurate results for all types of organic, main-group and transition metal-containing systems. The recently developed DLPNO-CCSD(T) method is an approximation to CCSD(T), providing similar accuracy at a significantly lower cost and scaling, and it is nowadays applied in routine calculations on systems with dozens to hundreds of atoms.

In this talk we present recent advances in the DLPNO-CCSD(T) method, which significantly improve its performance and accuracy, including e.g. extrapolation to the complete PNO space limit. We provide best practices for its application in real-life (bio)chemical applications.

We show recent applications of the DLPNO-CCSD(T) method in biomolecular systems, including protein-ligand interactions as well RNA-ligand interactions. The computed accurate interaction energy can be decomposed into its components between different molecular fragments, and we show how this can be applied in deciphering key interactions between a ligand and its biomolecular target.





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Predicting the Future of our Medicines: Applying AI/ML to Investigate the Link Between Molecular Structures and their Transcriptomic Signatures

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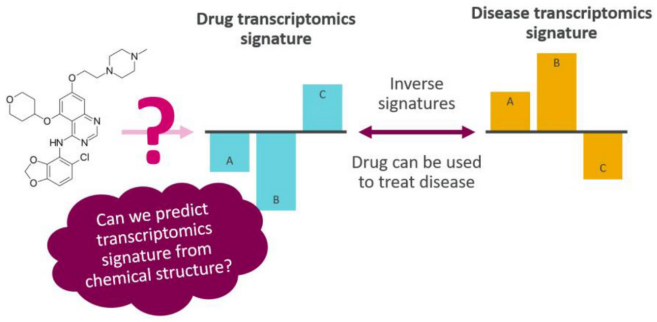
At AstraZeneca we recognise the importance of identifying multiple additional indications for our medicines, to increase their commercial potential and benefit more patients globally. To do this we are adopting innovative technologies to increase chances of success into a range of therapy areas; one such approach is the development of a chemotranscriptomics machine learning model.



Chemotranscriptomic signatures provide genome-wide information on the induced differential gene expression for a particular molecule. When paired with the corresponding disease transcriptomics signatures they can be leveraged to identify novel indications for that molecule.1,2 However, generating these signatures using experimental omics technologies can be limiting due to their expensive and relatively low-throughput nature.

Within the Indication Discovery team in Emerging Innovations, we have employed machine learning to exploit the vast amounts of gene expression data contained within the L1000 database.3 We have identified relationships between the structure of a molecule and the induced chemotranscriptomics signature. Owing to these relationships, a directed message passing neural network was trained and validated using the L1000 data and the Chemprop software package.4 Our initial model indicates that, given enough accurate and reliable experimental data, it is possible to predict the chemotranscriptomic signature for a given molecule and gain greater insight into the mechanism of action. This reduces the dependency on costly experimental screening, and allows us to quickly identify novel disease indications for our medicines.

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AMUSE: Automated MUltiscale Simulation Environment

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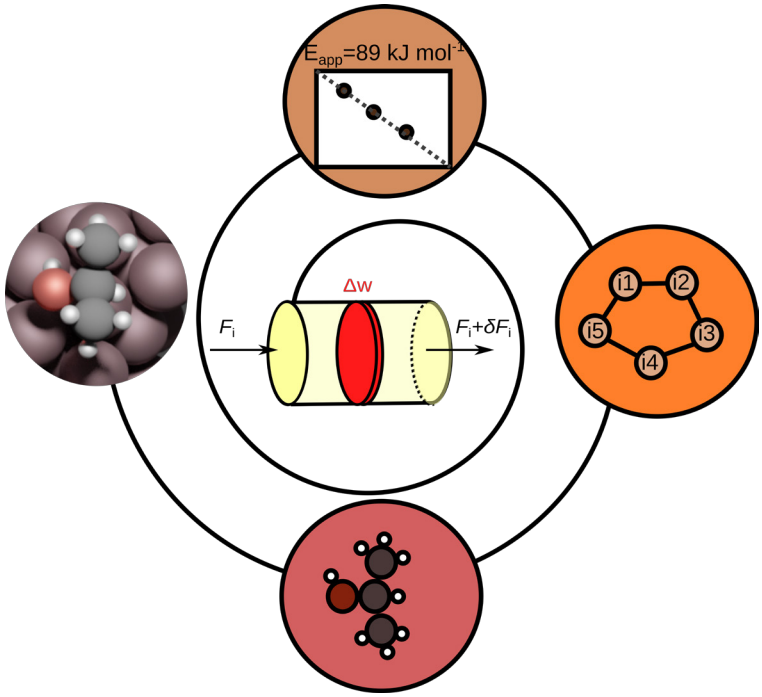
Multiscale modelling techniques are used to predict the catalysts' performance on full-scale reactors, starting from detailed atomistic information on materials and reactions[1]. Despite many reported attempts, it remains challenging to address properly the complexity of catalytic systems and integrate properly chemical and transport phenomena on different time and length scales[2,3].



Here, we present AMUSE (Automated MUltiscale Simulation Environment), which is a tool that enables a seamless multiscale modelling workflow [3]. It utilizes Density Functional Theory (DFT) calculation results as input data, automatically analyses the reaction networks through graph theory, performs microkinetic modelling, and integrates it's results into a standard open-source Computational Fluid Dynamics (CFD) code. The workflow was benchmarked on technologically relevant case studies, namely CO_2 hydrogenation on In_2O_3-based catalysts and isopropanol dehydrogenation on two Co facets [3].

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Machine Learning as a Tool for Predicting Gas Adsorption by Metal Organic Frameworks

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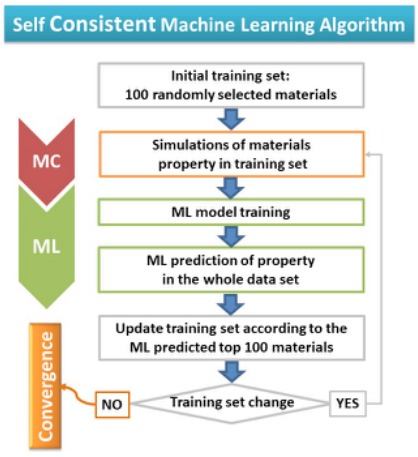
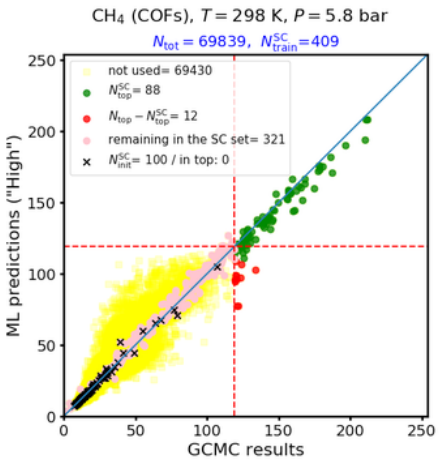
Due to their exceptional host-guest properties, nanoporous materials, such as Metal-Organic Frameworks (MOFs) are promising candidates for storage of various gases with environmental and technological interest. The discovery of new materials with desired properties may have an important impact in several scientific and technological fields. The number of MOFs that can be potentially synthesized by combining various structural building blocks is enormous, while their experimental synthesis and characterization is a time-consuming and expensive process. Despite the accuracy and efficiency of molecular simulations, the high-throughput screening of the enormous number of MOFs is also beyond present computer capabilities. Application of machine learning (ML) methods for the study of gas adsorption in nanoporous materials represents a promising and efficient alternative. In principle, a ML predictive model can almost instantly provide predictions for millions of these materials. During the presentation I will discuss a number of challenges that should be addressed before ML methodologies replace or significantly reduce the need of employing the previous traditional approaches. These challenges are related to the description of the system in a manner understandable by the ML algorithms (a.k.a. descriptors or futures), the data needed for the proper and efficient training of the ML algorithms, as well as the inherent limitation of ML methods to provide reliable predictions for cases far from the already known ones. Our recent efforts to address and overcome these challenges [1-5] will be presented.





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Collaborating with SCM: (Horizon Europe) opportunities

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Originating from an academic density functional development group in the 1970s, SCM is a well-established and steadily growing scientific software company, both in terms of (academic) developers and functionality. Academic connections have always been fostered by SCM, also in the frame of public-funded collaborations, and the company has ample experience applying to and participating in programs including H2020 and Horizon Europe. They have provided valuable funding for collaborations with academic (and industrial) partners, and Horizon Europe currently offers new funding opportunities for partners who wish to work with us to further develop our scientific software. Potential funding channels in Horizon Europe will be presented as well as what our friendly policies are for academic developers who are looking to contribute to our software.

The central framework in the Amsterdam Modeling Suite (AMS) enables the exploration of potential energy surfaces (PESs), mechanical, and electronic properties at several levels of theory. The unified AMS driver supports advanced PES explorations, molecular dynamics (MD) and Grand Canonical Monte Carlo (GCMC). Machine learned graph neural network potentials such as NEQUIP[1] and the universal model M3Gnet[2,3] can immediately be used for simulations of processes. The ParAMS module furthermore provides a comprehensive framework to build training data and optimize machine learned potentials (MLP), as well as ReaxFF and DFTB parameters. With different levels of electronic structure methods available in AMS, we are exploring ML methods to predict properties more efficiently for molecular materials. We welcome modelers and prospective developers from this computational chemistry community to discuss ideas and (funding) opportunities with us.

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High Throughput Modelling of Polymers with Molecular Dynamics and Machine Learning

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Traditional polymer discovery requires the use of long trial-and-error screening campaigns, carried out in the laboratory using great quantities of resources. Chemical simulation is a low cost/high speed alternative to laboratory testing that can provide valuable insight into material properties, whilst being far more sustainable: no disposable gloves or solvents are needed to simulate new materials. Pharmaceutical science has fully embraced molecular modelling for drug discovery, seeing the value in testing potential molecules virtually without expensive reagent costs. Despite a range of proven literature showcasing molecular dynamics (MD) in materials science [1, 2], both academia and industry have been slow to adopt the practice. It is believed that the high barrier to entry of MD and the high computational cost of simulation are inhibiting beginners to the field. This work has proven concepts that address these issues for polymer modelling applications.

This work focuses on two core areas: automating simulation setup, and surrogate modelling. Using the popular open-source package LAMMPS, an initial pre-processing workflow allows for the total automation of files required to run a simulation. This includes a novel atom type labelling system for the DREIDING forcefield [3] that has been built into the popular pre-processing tool Moltemplate [4]. Furthermore, it includes the rapid preparation of all files required to run the powerful REACTER polymerization algorithm implemented in LAMMPS with *fix bond/react* [5]. This has been published as AutoMapper [6] and is available open-source on GitHub. As seen in Fig. 1 combining these tools creates a workflow that computes all necessary files in moments, only requiring the user to submit molecular structures that can be easily drawn or found online.

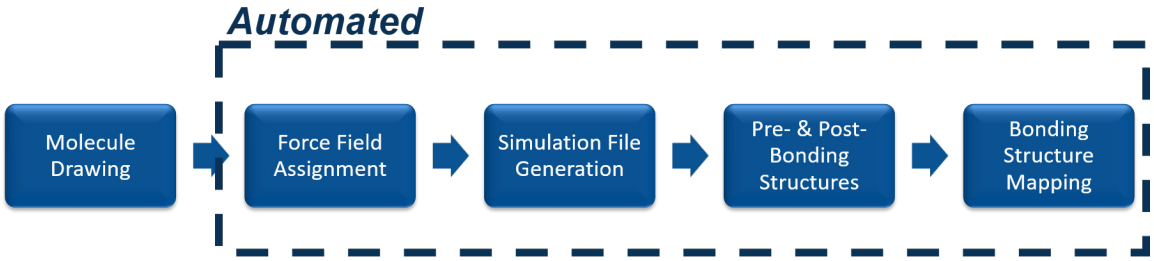

Fig. 1: An overview of the pre-processing automation achieved with Moltemplate and AutoMapper

The capability of this workflow for high throughput modelling is then demonstrated with the creation of a dataset of 96 cured polyurethane models. Further simulation was used to characterize the glass transition temperature (T_g) of each sample, which were then used as labels for a machine learned surrogate model. Using radial distribution functions, shown as capable features in literature [7], a simple feed-forward neural network was trained on the equilibrated polymer atomic topologies. Despite the simplicity of the network the learned representations of the model were able to predict the T_g within and error of 10-30 K on un-seen data. Whilst having clear room for improvement, application of the surrogate model reduced total simulation wall time by 75%. This clearly demonstrates the potential of surrogate models to enable high

throughput material simulation, accelerating research and reducing the need for computational resource.

This work represents the end of PhD project that has been undertaken at the University of Bristol. The output of this work has now been spun out to form Molydyn, a start-up company working to make computational chemistry more accessible to materials scientists.

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Solvent Design for Green Homogeneous multi-phase Industrial Reactions

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In homogeneously catalyzed complex reactions, finding green solvent alternatives instead of conventional industrial solvents, which ranks very low on environment, health and safety (EHS) index while ensuring optimal performance i.e. high rates and selectivity with least ecological impact is critical. Solvents perform a number of tasks in a chemical reaction. They dissolve reactants and catalysts to enable reactions, improve conversion, selectivity, and reaction rates by actively taking part in the reaction.

Here, we showcase rhodium-catalyzed reductive amination (RA) reaction as an example to analyze and quantify multiple roles that a solvent may play during the course of a multistep reaction.[1,2] Using quantum mechanical tools, physical solvent properties such as polarity and hydrogen-bond donating/accepting abilities of solvent molecules which have strong influence on the rate and reaction mechanism can be evaluated. Hydrogen bond donating polar solvents promote enamine formation by explicitly taking part the reaction. The sophisticated bidentate phosphine (SulfoXantPhos)RhH reducing catalyst controls the regioselectivity of the reaction by dedicated ligand-substrate interactions. Its activity is critically dependent on the strength of solvent coordination. The effect of solvent on the reaction rate becomes apparent from a solvent screening of the transition state of the rate-determining step and give a perspective on solvent control of rate constants in this complex multi-step reaction.

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Predicting Thermodynamic Properties of Novel Compounds from their Starting Materials

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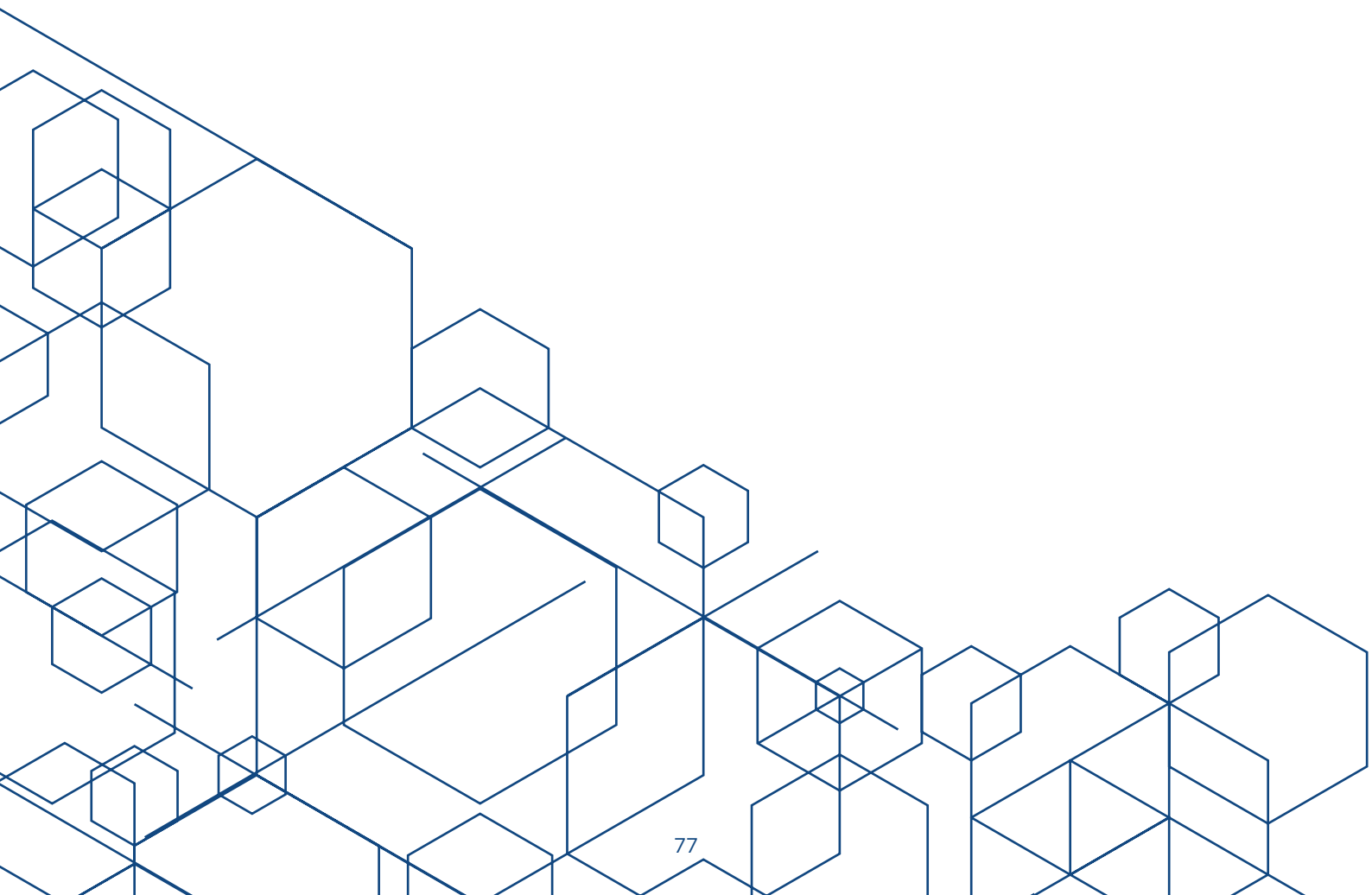
The physicochemical behavior of a material system is one of the most critical aspects to understand and characterize for the successful and safe manufacture of synthetic fine chemicals. Choosing a material system of optimal physicochemical behavior is the most impactful improvement to the design of a chemical train. Prediction of physicochemical properties has been a focus of research for decades leading to established methods, spanning from low to high computational complexity. Low complexity models are known to produce inaccurate predictions, unfit for process design. High complexity methods do not span all complex thermodynamic properties across phases and provide point predictions and not a continuum behavior with respect to variables like temperature, pressure, or composition.

The recently developed SAFT-gamma-mie methodology is an exciting new approach to the estimation of thermodynamic properties. This group-contribution methodology has proven to be successful in predicting a wide range of properties, including phase equilibrium, heat capacities, density, vapor pressures, solubilities, and chemical equilibrium using the same (Helmholtz energy centric) model. The key to the successful use of the methodology involves the ability to estimate the parameters of the contributing groups in a molecule. This remains a challenge given the immense diversity in chemistries found in these molecules.

One solution to this problem is to directly obtain the group parameters, by regression to easily obtainable experimental data of the product of interest. However, many of the newly synthesized chemicals are expensive, less pure, and limited by quantity. Here, we present a hybrid solution to the application of the SAFT-gamma-mie method for a new molecule. In this approach, parameters for available groups could be estimated from the starting materials; and the parameters for the groups that are not present in the starting material will be estimated from small molecules that contain those groups, for which experimental data are available, or from quantum mechanical methods. Obtaining parameters from starting materials is beneficial: (i) These parameters will incorporate neighboring group effects (cross-interactions); (ii) Starting materials are easily accessible, can be obtained in more quantity, and are purer and cheaper compared to the final product.

This method could be used in industrial R&D to create a powerful predictive platform that would enable making process-related decisions (solvent choices, reaction conditions, isolation strategies) in-silico early in the development timelines, and without the need to do any work with bulk amounts of materials.

BIOMOLECULAR SYSTEMS



Investigating the influence of the lipid structure on the global membrane organization: effect of the fatty acids

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Research on lipids is crucial in the fields of biology, bacteriology, ecology, and human health. This can be understood by the numerous and essential functions of lipids in cell membranes. The physicochemical properties of lipids rely on their chemical structure, explaining the vast diversity of lipid species. One factor contributing to this extensive collection is the number of distinct fatty acids (~ 8000 fatty acids are reported in the Lipid Maps structure). They differ in *(i)* their length (usually from 14 to 24 carbon atoms), and in *(ii)* the number and position of unsaturation(s) (from 0 to 6 double bond(s) (DB)), giving saturated (0 DB), mono-unsaturated (MUFA, 1 DB) or poly-unsaturated ((PUFA, 2DBs or more) fatty acids. The combination of those building blocks can yield either symmetrical or asymmetrical (or hybrid) lipids. As each structurally distinct lipid molecule contributes to the properties of cellular membranes and the biological processes taking place within them, we need a deeper understanding of the impact of varying the lipids hydrophobic region on the global membrane organization. So, in this work we investigate a collection of single-component glycerophospholipid (GPL) bilayers varying only in their fatty acids structures via Molecular Dynamics simulations. All systems are studied in the same "simulation" conditions to highlight the structural differences emanating from the diverse environments. Several properties of the bilayer are studied, namely the thickness, the area per lipid, the hydrocarbon parameter, and the orientation of the diverse molecules within the membranes. They allow us to go one step further than stating the obvious fact that the saturated lipids, with their straight chain, can create densely packed membrane, and the unsaturated ones, with their bent chain, cannot. For instance, the impact of the DB position or the presence of hybrid lipids are explored in detail.

To complement the study, the optical properties of an embedded di-8-ANEPPS probe are compared and put in relation with the structure of their host membrane. For this, the molecular nonlinear optical (NLO) responses, namely the first hyperpolarizabilities (β) of di-8-ANEPPS structures extracted from the MD trajectories are evaluated at the TDDFT/M06-2X/6-311+G* level. As this dye is embedded in the membranes, changes in the structural properties of the bilayers are transferred to the optical responses of the dye, and in particular the contribution to β parallel to the bilayer normal, β_{zzz}, which can be probed by NLO spectroscopies.

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Substrate Binding Dynamics of SARS-CoV-2 Cysteine Proteases

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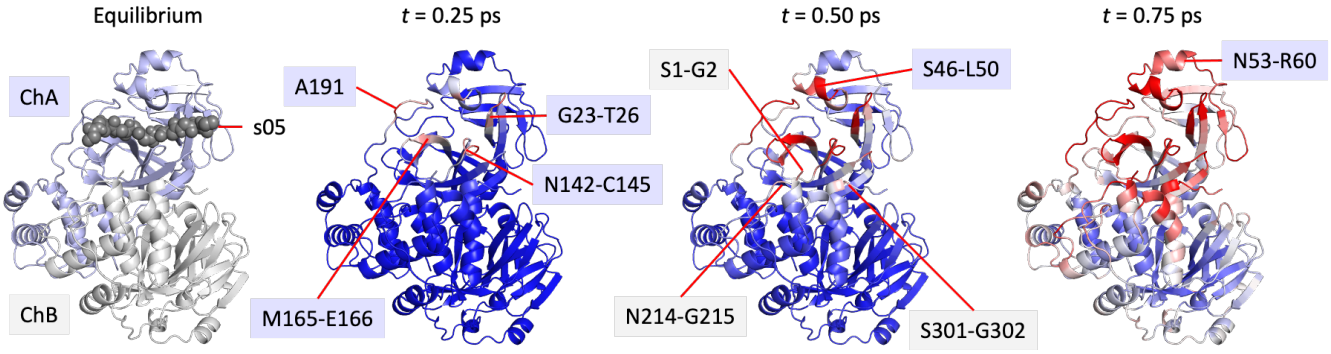
The coronavirus main protease (Mpro) and papain-like protease (PLpro) are essential cysteine proteases involved in viral polyprotein processing and thus attractive drug targets for diseases such as COVID-19. While a wealth of crystallographic data on SARS-CoV-2 Mpro is available, the exact mechanism of how the enzyme selectively hydrolyses the 11 cleavage sites in the polyproteins is unclear. By modelling Mpro complexed with each cleavage site substrate, and using a combination of equilibrium and nonequilibrium MD simulations analysed by the Kubo-Onsager method,[1] residues that play key roles in substrate binding were identified.[2] Dynamic communication pathways in Mpro upon substrate association were observed to extend well beyond the active site, and these networks provide insights into allosteric inhibition mechanisms and prediction of Mpro mutation sites relevant to nirmatrelvir resistance.[3]



Considering the threat of drug resistance, inhibition of PLpro, another cysteine protease with a structure and substrate profile distinct from Mpro and with additional deubiquitinating roles, may provide an alternative strategy.[4] Substrate-bound models of PLpro were predicted and studied using computational approaches including protein-peptide docking, protein-protein docking and MD, where the importance of enzyme loop dynamics in substrate recognition was identified. The results have guided experimental peptide screening to help understand substrate specificity and will aid the search of peptide and peptidomimetic protease inhibitors.

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Reconstructing Rare Event Kinetics Using AI-enhanced Unbiased Molecular Dynamics Simulations

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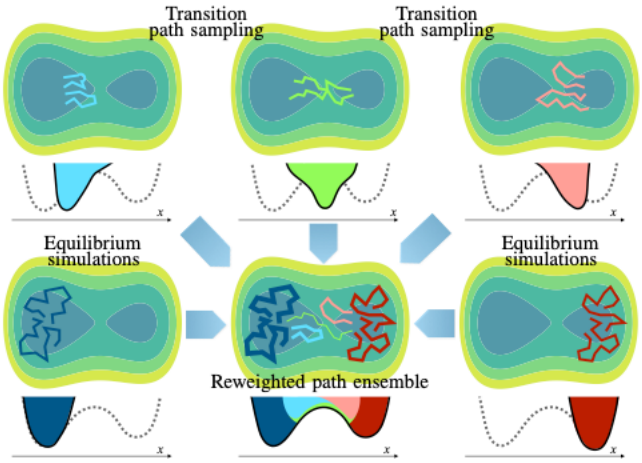
Equilibrium molecular dynamics (MD) simulations are powerful tools for studying biochemical systems at the atomic level. However, they face computational efficiency and interpretability issues. Rare events, such as conformational transitions, are particularly hard to characterize but are crucial for understanding biochemical pathways. To overcome these challenges, we use artificial intelligence (AI) to enhance transition path sampling (TPS) simulations [1]: we foster the production of reactive trajectories and learn the reaction properties in real time [2]. While the TPS simulations are all unbiased, their configurations do not follow the Boltzmann distribution. To address this issue, we repurpose the TPS trajectories to create the reweighted path ensemble (RPE) [3]. The RPE approximates indefinitely long equilibrium simulations and carries information about the free energy and reaction kinetics [4]. In our research, we leveraged the previously trained AI to develop a fast, efficient reweighting algorithm that performs well with limited data. Furthermore, we included short equilibrium simulations in metastable states to expand the RPE across the whole configuration space. In summary, the RPE combines equilibrium and TPS trajectories with optimal weights derived from the AI-learned model.



We tested this approach on the folding of the mini-protein chignolin and derived accurate free energy and transition rate estimates with significantly fewer resources than brute-force equilibrium simulations. The results showcase the potential of our technique and its applicability to a wide range of biochemical systems.

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Water will find a way: transport through narrow tunnels and its significance in enzymes

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An aqueous environment is necessary for life as we know it, and water is required for almost all biochemical processes at a molecular level. Enzymes employ water in different ways: as proton donors or receivers, molecular stabilizers, molecular lubricants, and as major contributors behind enthalpy-entropy compensation in protein-ligand binding. Even though water is an essential player in enzymatic activity and stability, its transport has been mostly neglected.

In this study, we focused on the transport of water molecules across three hydrolases: haloalkane dehalogenase from *Rhodococcus rhodochrous* (Hal), epoxide hydrolase 1 from *Solanum tuberosum* (Epx), and lipase from *Diutina rugosa* (Lip). The tunnel and water migration analysis of 5 µs adaptive molecular dynamics simulations per system with recently developed TransportTools [1] and the divide-and-conquer approach [2], showed that only a few tunnels were responsible for most water transport in Hal, contrasting with a higher tunnel diversity in Epx and Lip. Interestingly, water could also traverse narrow tunnels of subatomic radius, which is surprising given the accepted value of 1.4 Å as water molecule radius. Our analysis of the transport events in such narrow tunnels showed a significantly larger number of H-bonds formed between the water molecules and the protein, likely compensating for the steric penalty of the process. More, those H-bonds were frequently formed with protein backbone, indicating that such observation could be shared across at least the same protein fold. Our results reveal that commonly disregarded narrow tunnels account for ~20% of total water transport processes observed [3]. We show how the insights obtained could be applied to explain differences in a single-point mutation of the human soluble epoxide hydrolase, associated with a higher incidence of ischemic stroke. Here, we observed how a minimal change in the bottleneck of previously disregarded narrow tunnels could change their transport by up to three orders of magnitude. Finally, our results also highlight the importance of narrow tunnels as relevant targets for protein engineering [3].

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Addressing Challenges in Computational Simulations of Covalently Binding Transition Metal-Based Drugs

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Covalently binding transition metal-based drugs pose significant challenges for computational chemistry. This is mainly due to two factors: the low accuracy of classical force fields in treating transition metals and their inherent limitations in describing covalent bond formation and breaking. For such systems, hybrid quantum mechanics/molecular mechanics (QM/MM) molecular dynamics (MD) simulations are often the method of choice [1]. However, QM/MM MD simulations remain a computationally expensive technique, unfeasible to run in large numbers. Hence, it is of utmost importance to identify a limited number of putative binding sites, corresponding to likely starting points for QM/MM simulations. Additionally, it is essential to investigate these sites efficiently, as QM/MM remains the major computational bottleneck.

To address these challenges, we propose two complementary approaches. Firstly, we introduce Metal3D [2], a predictor based on 3D convolutional neural networks that accurately identifies the binding site location of metal ions. Although initially designed to predict binding sites of zinc, Metal3D demonstrates accurate prediction abilities for other transition metal ions and, more interestingly for drug design applications, for transition metal-based drugs as well. Metal3D can effectively reduce the number of binding sites to be investigated with more expensive techniques. Secondly, we present "multilevel thermodynamic integration", a multilevel approach combining classical (force field-based) and QM/MM constrained MD simulations. Classical MD is performed at large distances from the binding site, where extensive sampling is required, and the QM nature of the interaction between the drug and the binding site is negligible. QM/MM MD is employed only when the drug is in proximity to the binding site and covalent binding occurs. Thanks to this multilevel approach, we successfully obtained free energy profiles of binding for different metal-based drugs, from the bulk solvent to the binding site.

Both Metal3D and multilevel thermodynamic integration are robust methods independently. However, if used synergistically, they can combine the strengths of machine learning to provide likely starting points for QM/MM and an efficient approach to QM/MM MD to obtain free energy profiles. Consequently, the combination of these two approaches holds significant potential for drug design applications.

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Combining molecular dynamics simulations with machine learning driven analysis to study biomolecular interactions

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Enhanced sampling methods, multiscale approaches, and improved simulation models in combination with ever growing computational power have given us access to unprecedented system sizes and simulation times and have led to a massive increase in the amount of simulation data being produced. Thus, processing and analyzing exceedingly large high-dimensional data sets has become one of the major challenges. I will show how multiscale approaches in combination with advanced analysis methods can be used to investigate and characterize interactions in biomolecular systems, from protein conjugates to RNA riboswitches. Modern machine learning approaches are utilized to identify, compare, and classify relevant conformational states, to provide insights into the decisive features hidden in these high dimensional simulation data and to guide their interpretation with respect to experiments. Using efficient dimensionality reduction techniques we obtain low dimensional representations of the sampling which can be interpreted as conformational free energy landscapes. These low dimensional representations enable us to assess the consistency of the sampling in different models, to go back and forth between simulation scales or compare the conformational behavior of different systems.

Molecular Gas Phase Conformational Ensembles

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Validation of conformational search algorithms for small molecules involves the use of "bioactive" conformations from the PDB or X-ray structures from the CSD. However, conformational searches are almost exclusively carried out in the gas-phase suggesting that this approach for the validation of ubiquitous conformational search packages is less than optimal. Ion mobility coupled to mass spectrometry (IM-MS)

is a sophisticated, powerful and generally applicable experimental tool that can be used to identify the three dimensional structure of the global minimum of small-molecules in the gas-phase. However, the interpretation of IM-MS data is still a challenge and depends on accurate theoretical estimates of the

molecular ion collision cross section (CCS) against a buffer gas in a low pressure drift chamber. It is intrinsically challenging to CCS values using ab initio techniques when the conformational space of a metabolite is extensive. I will describe our workflow that generates ab initio derived, gas-phase small molecule ensembles that are validated by their ability to reproduce the experimentally observed CCS value.

Using these ensembles I will show how the derived gas-phase conformational ensembles can be used to validate a range of freely available conformational tools. The derived experimentally validated small molecule ensembles open up a new avenue to validate conformational search algorithms and the underlying potentials used to obtain them.

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Insights into the mechanism of the C-terminal PIK3CA activating mutations

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PI3Kα is the most frequently mutated kinase in human cancers with mutations often occurring at the C-terminus. The C-terminus has a dual function in regulating the kinase, playing an auto-inhibitory role for kinase activity and also mediating protein binding to the cell membrane. When PI3Kα attaches to the cell membrane, it phosphorylates its substrate PIP2 and converts it to PIP3, initiating a signaling cascade for cell proliferation.[1] Oncogenic mutations in the C-terminus of PI3Kα lead to overactivation of the kinase,[2,3] however, the molecular mechanisms by which these C-terminal oncogenic mutations cause PI3Kα overactivation remain unclear. H1047R, G1049R, and M1043L mutants increase ATPase activity compared to the WT, and H1047R, G1049R, and a frameshift mutation (N1068KLKR) increase membrane binding compared to the WT.[2,3] Moreover, after comparing available crystal structures of the WT and H1047R mutant, different conformations of the C-terminus are observed with the H1047R mutant structure displaying an open C-terminal conformation associated with PI3Kα activation (Figure 1).[4]

To understand how C-terminal mutations of PI3Kα alter kinase activity, we perform unbiased and biased Molecular Dynamics simulations of the above-mentioned mutants and report the free energy needed for the C-terminal “closed to open” transition and associated conformational changes. H1047R and G1049R mutants have the lowest free energy for the transition compared to the WT, M1043L and N1068KLKR mutants. In the open state of M1043L mutant, a different direction of the C-terminus is observed, which corroborates with experimental work showing that M1043L has a lower membrane-binding ability compared to the other mutants.[3] To validate our findings, we compare the results from Molecular Dynamics simulations with the existing HDX-MS experimental data,[3,5] calculating the solvent accessibility of the residues and their hydrogen bonding, and find that the results align. The differences in the free energy needed for the closed to open transition and the observed conformational changes across the different mutants provide valuable insights into the molecular mechanisms underlying the C-terminal activation in oncogenic and WT PI3Kα.

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Antibody Structure and Dynamics in Solution

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Even though the Ig fold itself is very stable and rigid, antibodies are highly flexible molecules. Two Fab units are linked to the Fc unit by flexible linkers allowing large scale rearrangements of the antibody's arms with respect to the Fc unit. This facilitates a wide range of possible orientations of the two paratopes and the Fc-receptor binding site. The Fab units and the Fc unit themselves can also kink allowing so-called elbow movements. The third level of flexibility originates from the rearrangements of the hydrophobic interface formed by pairs of Ig fold domains. Finally, even though the Ig fold itself is a very rigid beta-sandwich the loop regions can show considerable flexibility.

In the last years we have demonstrated that it is possible to sample possible loop rearrangements by modern computer simulation techniques. Thus, for the first time it is possible to characterise antibodies' paratopes as ensembles in solution. We consistently find, that the binding competent conformation is the dominant structure in solution. However, there is a large number of examples, where the crystal structure of the unbound Fab shows considerable loop rearrangements in comparison to the structures bound to the respective antigen. All these loop rearrangement seem to originate from crystal packing effects, which easily can distort these highly flexible systems. The crystal packing effects not only strongly influence the loop conformations, but also substantially distort the interdomain interface orientations and elbow angles.

Obviously these findings are challenging traditional antibody structure predictions. Historically antibody structure prediction has been considered a solved problem since three decades due to the seminal work of Chothia and Lesk on the "Canonical Structures for the Hypervariable Regions of Immunoglobulins" and its subsequent refinements, whereas protein structure prediction in general remained very demanding. Recent advances in protein structure prediction due to AI based techniques revived the interest in antibody structure prediction. Nevertheless, AI driven improvements of antibody structure prediction are impeded by three aspects: Predictions relying on canonical structures already achieve a rather high level of accuracy and reliability. Antibody loops have been shown to be considerably different to all other loops in known protein structure, i.e., they do not adhere to patterns found for other proteins. Finally, the number of learning templates for structures in solution not distorted by crystal packing effects is rather limited. Thus we believe that physics based antibody structure prediction is a more promising way towards a better understanding of antibody structure and properties.

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Function and inhibition of cation-coupled chloride cotransporters

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In our lab, we study pharmaceutically relevant proteins, with the aim to disclose mechanistic insights potentially useful for computer-aided drug discovery.

Here, I will present our work on the discovery of ARN23746 as the lead candidate of a novel class of selective inhibitors of NKCC1, which is an ion importer critically involved in the regulation of intracellular chloride concentration in neurons.

Importantly, NKCC1 is a promising target for many neurological disorders. I will present our efforts based on molecular modeling, medicinal chemistry, and *in vitro*/*in vivo* neuropharmacology for the discovery and extensive characterization of a new chemical class of selective NKCC1 inhibitors, with a focus on ARN23746 and other promising derivatives. In addition, I will also present our results on the mechanism for the NKCC1 function investigated via enhanced sampling simulations and mutagenesis experiments.

Free energies and enhanced sampling from accelerated enveloping distribution sampling

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Physically relevant free-energy differences can be calculated from simulations of unphysical reference states. Over the years, we have successfully applied the one-step perturbation method by the judicious design of reference states. To ensure overlap between the reference state and the end states enveloping distribution sampling (EDS) was developed over a decade ago [1]. Here, the reference state is constructed from the end states directly, potentially maximizing the overlap in sampling. By accelerating the EDS potential [2] improved sampling of the end-states becomes feasible. Various applications in drug-design settings [3] show that the accelerated EDS approach (A-EDS) can also enhance the sampling of orthogonal degrees of freedom [4] and may furthermore be used as a chemostat. This opens the way to applications in virtual screening or the sampling of water molecules in the active site of protein-ligand complexes.

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Automated and Systematic Derivation of Parameter Type Definitions for Molecular Mechanics Force Fields

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Molecular Mechanics force fields are of high relevance in various areas of chemistry, physics and biology. They require a large number of parameters, which are typically derived from quantum chemistry calculations and tuned to enable simulations to replicate experimental observables, e.g. properties of pure liquids, as well as quantum mechanical observables, e.g. energy profiles of rotatable bonds. In these force fields, a given parameter is always associated with a specific force type (e.g. bond stretching) and consists of (A) one or more numerical values specific for that force type and (B) a parameter type definition that enables the assignment of this parameter to specific atoms in the molecule via a chemical perception strategy (e.g. using atom types or SMARTS specifiers). While their numerical values can be straightforwardly optimized using numerical solvers, the parameter type definitions typically remain constant during the optimization process. For obvious reasons, force fields must contain as few parameters as possible while still accurately capturing the physics of the molecules. The choice as to which parameter type definition to include in the force field is usually made by a human with domain knowledge, however this limits the extensibility and transferability of the force field. Also, these choices are mostly made on an ad hoc basis since one can hardly evaluate the sensitivity of a force field with respect to each possible variation of parameter type definitions. For instance, it seems intuitively correct to assign distinct force field parameters to amide and ester structures, however it is not clear whether assigning them distinct parameters is actually justified by a reasonable improvement in force field accuracy with respect to high-level (or experimental) reference data.

In this contribution, we derive parameter type definitions alongside their parameter values from scratch using standard high-level reference data. Furthermore, we demonstrate how the posterior distribution of parameter type definitions can be sampled in an efficient way, thus allowing for the assessment of degeneracy and uncertainty in the space of parameter type definitions. Our approach does not require ad hoc human domain chemistry knowledge, like hand-drawn definitions of functional groups, thus enables a truly systematic and automated fitting of molecular mechanics force fields. In order to guide the search for parameter type definitions we leverage parameter gradients, which we currently limit to valence potential energy functions. We will demonstrate the validity of our approach using small molecule datasets of varying complexity and give an outlook for the derivation of force fields for drug-like molecules.

From Closed to Open: Addressing the Role of the Efflux Pump AcrAB-TolC in Antibiotic Resistance

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The emergence of antibiotic-resistant bacterial infections is an escalating public health challenge. In particular, Gram-negative bacteria are difficult to treat due to the additional outer membrane with embedded porins and efflux pumps that confer natural and acquired mechanisms of antibiotic resistance. AcrAB-TolC is a well-studied trans-envelope efflux pump in E. coli that expels toxic substrates and other small molecules. The complex is assembled from three main components: AcrA, AcrB, and TolC. AcrB in the inner membrane recognizes, binds, and extrudes a wide variety of substrates into the channel formed by AcrA-TolC using the proton-motive force. Due to the integral role of efflux pumps in expelling antibiotics, drugs targeting the pumps, which can inhibit efflux of existing antibiotics, have been investigated. Cryo-EM structures of the full protein have been solved in which both closed and open conformations of the AcrA-TolC channel are observed. In our present study, the conformational changes of the full protein complex, in going from the closed conformation to the open one, were resolved utilizing Targeted Molecular Dynamics. Both the original apo system and the system with a bound inhibitor, NSC 60339, were simulated, in order to quantify the effect of the compound on these conformational changes and to suggest possible mechanisms of action of the drug.

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Screening Enzyme Mechanisms using Multiscale Mechanistic Docking with EnzyDock

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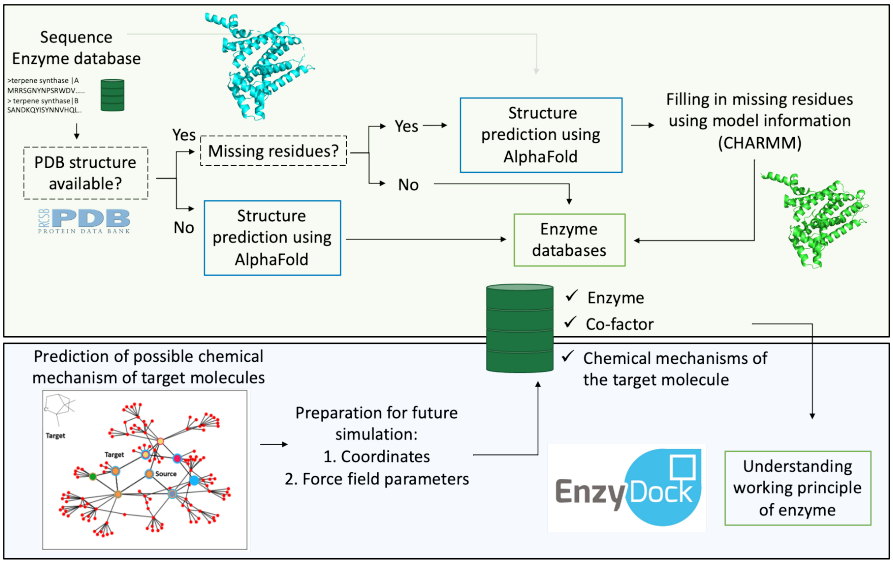
Predicting the correct, mechanistically appropriate binding modes in enzymes for substrate, product, as well as all reaction intermediates and transition states, along a reaction pathway is immensely challenging and remains an unsolved problem. Recently, we developed an effective methodology for identifying probable binding modes of multiple ligand states along a reaction coordinate in an enzyme active site. The program is called EnzyDock and is a CHARMM-based multiscale, multistate consensus docking program that can predict the chemically relevant orientation of substrate, reaction intermediates, transition states, product, and inhibitors [1]. Herein, we apply EnzyDock to several different kinds of problems. First, we study the terpene synthase reaction in the diterpene synthase CotB2. Second, we show how one can use EnzyDock to screen many plausible mechanisms in terpene synthases. Finally, we show how one can screen a mechanism against multiple enzyme targets.



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Molecular Dynamics Simulations on UAMC-0001305 Warhead Derivatives to Theragnostically Target Fibroblast Activation Protein

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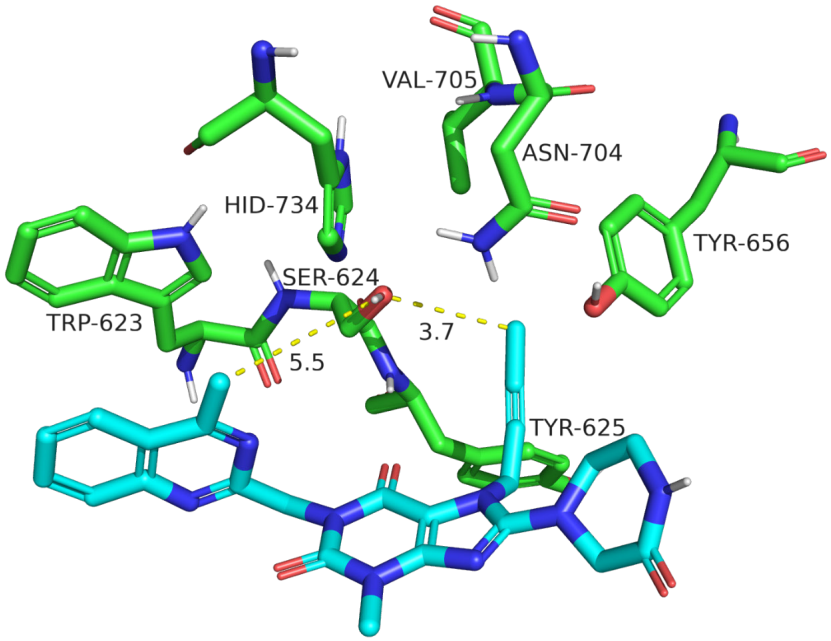
Fibroblast activation protein (FAP) is a type II transmembrane serine protease which is overexpressed in cancer-associated fibroblasts (CAFs). Currently, radiolabeled FAP inhibitors (FAPIs) using PET/CT are used for the diagnosis of tumors. A major drawback of these FAPIs are their relatively short tumor retention times. Radiolabeled FAPIs with a prolonged tumor retention time may be used in combination with external beam radiation therapy (EBRT) as a theragnostic treatment for cancer patients. Therefore, the scaffold of reversible inhibitor UAMC-0001305 (cyan structure in figure) will be scrutinized by addition of a warhead, which may result in covalent inhibition through binding with Ser-624 (see figure).



We performed MD simulations of UAMC-0001305 and designed UAMC-0001305 derivatives. The next step is to investigate the most promising compounds using QM/MM to determine the activation energy barrier of the different warheads. In the end, the tumor retention times of the adjusted inhibitors may be increased which will enable future theragnostic treatment of cancer patients.

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Learning the Languages of Allostery in *K-Ras4B*

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One of the bedrocks of protein function is allostery,[1] whereby binding of a ligand or complexation of a protein at a distal *allosteric* site triggers subtle conformational alterations that propagate to *orthosteric* sites or interfaces, and thus reshape reactivity, protein recognition, and cellular activities.[1] Atomistic molecular dynamics (MD) simulations have been widely employed to clarify allosteric mechanisms in contexts ranging from enzyme (re)design to regulation of pathogenic protein states.[2-7] Yet, though allostery often operates on longer timescales than those accessible by unbiased MD, numerous elegant solutions[2-6] devised to circumvent this problem tend, like languages, to be employed in isolation by different communities.

In this communication,[8] we report the application of four such allostery detection methods on µs-long unbiased MD simulations of membrane-embedded kinase *K-Ras4B*,[7] which widely studied mutations[9] are known to trap in an oncogenic GTP-bound active state in ways that are not always allosterically clear. Methods include: (1) detection of residues exhibiting coordinated *vs.* uncoordinated motions;[2] (2) instantly hydrolysing GTP at regular MD intervals and checking where differences accumulate;[3] (3) supercooling the kinase and re-heating GTP alone to check whereunto extra energy reverberates;[4] and (4) the *Shortest Path Map* approach by Osuna *et al.*[5,6]

Despite their different origins, chosen methods reach similar conclusions on allosteric pathways governing wild-type *K-Ras4B*, painting a unique chronological map in which key areas are affected *after* GTP hydrolysis, while others *control* hydrolysis; results are mutually consistent and add to current understanding of *K-Ras4B* mutations.[7,9] Our work highlights how, without resorting to biased MD, different methods can still work in synergy to capture details that they'd be unable to capture alone, making a strong case for scientists to learn more than one allosteric language.

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Data-Driven Classification of Ligand Unbinding Pathways and Kinetics

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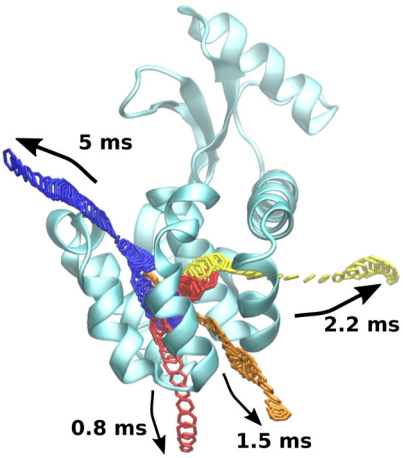
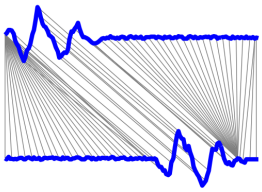
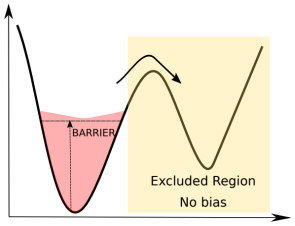
Protein-ligand interactions are pivotal to the action of therapeutic agents, and, therefore, of fundamental importance to computer-aided drug design. A wide range of enhanced sampling methods have been developed over the past few decades for calculating protein-ligand binding affinity. However, a key determinant of the in-vivo efficacy of a small molecule drug is the unbinding kinetics or residence time of the ligand in the binding pocket [1]. Unlike free energy, the kinetics of molecular processes depend strongly on transition paths; therefore, it is necessary to design efficient algorithms to sample possible drug unbinding pathways and the associated timescales. To address this challenge we developed the On-the-fly Probability Enhanced Sampling (OPES) flooding algorithm [2] where a bias potential is applied to the molecular system to accelerate transitions across the free energy barriers while keeping the transition state bias-free. This makes it possible to rigorously reconstruct unbiased kinetics. We also implement the multidimensional Dynamic Time Warping (DTW) algorithm [3], used in speech recognition and signal processing, to classify the ligand unbinding trajectories into different pathways in a data-driven and assumption-free manner.



Pathway dependent kinetics


Dynamic Time Warping



OPES Flooding

We tested our approach on the prototypical ligand-receptor complex of Benzene and T4 Lysozyme where multiple ligand dissociation pathways have been reported in the literature [4]. The combination of OPES flooding and DTW analysis led to (i) sampling of more than 100 different ligand unbinding trajectories, (ii) automated classification of the trajectories into different pathways with >90% accuracy, and (iii) calculation of the residence time associated with each pathway. The unbinding timescales are in excellent agreement with the millisecond range residence time observed in the experiment. The success and predictive power of our protocol make it a valuable tool in studying the mechanism of drug-receptor interaction in computational drug discovery.

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A Computational Study of the Complexation of Single Stranded RNA with Lipid-based Agents

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Complexation of a lipid-based ionizable cationic molecule (referred as DML) with RNA in an aqueous media, was examined in detail by means of fully atomistic molecular dynamics simulations.[1] The different stages of the DML-RNA association process were explored, while the structural characteristics of the final complex were described. The self-assembly process of the DML molecules was examined in the absence and in the presence of nucleotide sequences of different length. The formed DML clusters were described in detail in terms of their size and composition and were found to share common features in all the examined systems. Different timescales related to their self-assembly and their association with RNA were identified. It was found that beyond a time period of a few tens of ns, a conformationally stable DML-RNA complex was formed, characterized by DML clusters covering the entire contour of RNA. In a system with a 642-nucleotide sequence, the average size of the complex in the longest dimension was found to be close to 40nm. Apart from hydrophobic and electrostatic interactions, hydrogen bonding was found to play a key-role in the DML-DML and in the DML-RNA association.

In the following we examined two groups of lipid-based complexation agents, differing in the degree of hydrophobicity and in the overall charge.[2] The first group was comprised of cationic ionizable agents while the second included electrically neutral amphoteric phosphatidylcholine lipids. It was found that the overall charge of the complexation agents played the most decisive role in the energetics of the lipid/RNA association, while their degree of hydrophobicity affected their self-assembly and their complexation kinetics. The information obtained regarding the structural features of the final complex, the timescales and the driving forces associated with the complexation and the self-assembly processes, provide new insight towards a rational design of optimized lipid-based ionizable cationic gene delivery vectors.

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Free Energy Calculations in the Revival of Old-but-New Therapeutic Targets: Discovery and Development of RGD Integrin Peptides

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In recent years, the advancements in synthetic, delivery and bioimaging technologies, has led to a renaissance of peptide drug discovery and development.[1,2] In silico techniques are fundamental in peptide design, however they still face some challenges, including the complexity of the folding landscape and the presence of large peptide-receptor interacting surfaces. In this perspective, enhanced sampling methodologies are valuable tools to predict the bioactive conformation of peptides and to investigate their interaction with the desired macromolecule.[3] Here, we use metadynamics, in combination with other computational and experimental approaches, to design and develop peptides targeting RGD integrins.[4-7] These are transmembrane adhesion receptors that have been long investigated as therapeutic targets in cancer and in cardiovascular and chronic inflammatory diseases, leading to the approval of several drugs. The interest in RGD integrins has been renewed by to the identification of novel tumour-specific subtypes and their emerging role in cancer immunotherapy and diagnostics. In the presented case studies, we will particularly focus on the αvβ6 and αvβ5 receptors, for which a major involvement in many cancers and in infectious diseases has been widely demonstrated.

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Molecular Dynamics Study of Arabinoxylan Flexibility with Forcefield Comparison

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Arabinoxylan (AX) hydrogels hold potential in the food and drug delivery applications due to their physical properties.[1,2] AX found in the seed husk of certain species, such as *Plantago ovata*, forms gels via hydrogen bonding, with different extractable fractions producing gels with varying physical properties.[3] The specific structure and decoration pattern of side chains are believed to influence gel properties. We have used replica exchange molecular dynamics (REMD) simulations to study the effect of single-unit L-arabinose substitutions on xylan chain flexibility. We have conducted many simulations of small AX oligomers comprising different arabinose substitutions and used the results of these to statistically build large static chains in the unperturbed state. With these we can measure properties such as radius of gyration and persistence length as a function of any arbitrary arabinose substitution pattern. We find differences in results between the GLYCAM06 and CHARMM36 carbohydrate forcefields, with CHARMM36 generally indicating stiffer chains. Meanwhile, GLYCAM06 also predicts the inverted chair form of the xylopyranose units to be far too stable. Both models appear to overestimate persistence lengths relative to experiment, although there is disagreement amongst experimental results due to differing methodologies and assumptions.[4] We also make some limited comparison between both forcefields and density function theory (DFT) for the disaccharide xylobiose.

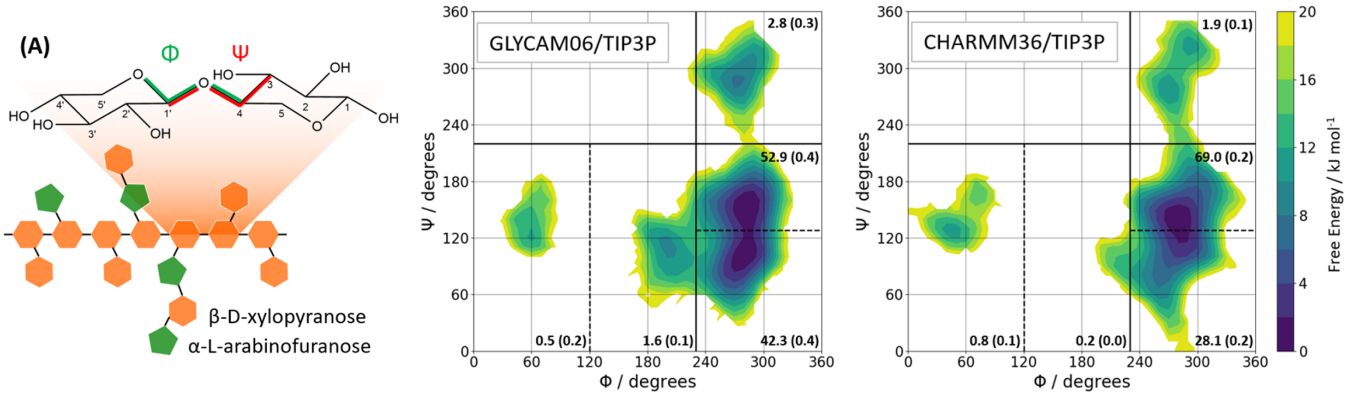

Figure 1: (A) Schematic of a generic AX structure with xylobiose highlighted as a simple model system for the backbone. (B) Free energy Ramachandran plot for the xylobiose β-1,4 glycosidic linkage obtained from REMD using GLYCAM06. (C) The same using CHARMM36m.

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Lipid Nanoparticles: From Structure to Interactions with Cell Membranes

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The RNA-based medicine became a breakthrough in vaccinations, rare diseases and anti-cancer therapy. Delivering of short-interfering or messenger RNA into cells is a very versatile strategy how to silence precisely defined genes, prepare vaccines against infectious diseases or personalized anti-cancer vaccines. However, the design of lipid nanoparticles (LNPs), non-viral vectors carrying the RNA, is hindered by a lack of knowledge of the roles of individual lipids in the structure and stability of LNP, interaction with encapsulated RNA or with the target cells.

Molecular dynamics (MD) simulations provide an insight into complex structures with atomic and femtosecond resolution. With current computational power and applying multiscale resolution, microseconds simulations of LNPs with diameters of several tens of nanometers are within reach. We investigated the behavior of lipid mixtures of LNPs with RNA in atomistic resolution [1] and described their preference for non-lamellar phases with high curvatures and separation of ionizable lipids (ILs) from other lipids in the mixture. Further, we moved to coarse-grained resolution, modelling the whole LNP and its pH dependent morphology [2]. In acidic pH, lipids assembled into rough LNP with lipids in a hexagonal phase, encapsulating RNA chains. Neutralizing the ILs led to spherical LNPs, releasing the majority of encapsulated RNA and formation of two lipid phases – bulk phase of uncharged ILs inside LNP and an ordered phase of phosphatidylcholine and cholesterol on LNP surface and interacting with resulting RNA molecules.

Here we present MD simulations of the LNP behavior in human body. We analyzed the interactions of LNPs with various phospholipids in atomistic resolution and described their pH dependent behavior. In neutral pH, the LNP lipids merged with cell membrane lipids, not affecting the membrane stability significantly. In acidic pH, LNPs made small blobs on the membrane surface, preferring high curvature and interacting with one membrane leaflet only. In order to evaluate this effect on cell membrane models in realistic spatial scale, we investigated the LNP-membrane interactions in coarse-grained resolution. In neutral pH, relevant to interactions with plasma membrane, we observed merging of LNP with the membrane model. In acidic pH, relevant to e.g. endosome maturation, positively charged LNPs interacted rapidly with negatively charged membrane models. After mixing of lipids from LNP and membrane, ILs induced a change in membrane phase increasing its curvature significantly. Such rapid changes in endosomal membrane stability can explain the mechanism of RNA release. The understanding of LNP behavior inside cells will be another step towards efficient in-silico design of LNP composition.

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Alternative Fast and Slow Primary Charge-Separation Pathways in Photosystem II

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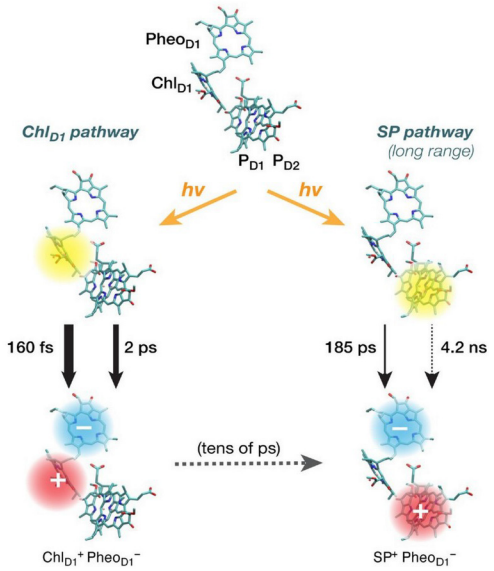
Photosystem-II (PSII) is a multi-subunit protein complex that harvests sunlight to perform oxygenic photosynthesis. Initial light-activated charge separation takes place at a reaction centre consisting of four chlorophylls and two pheophytins. Understanding the processes following light excitation remains elusive due to spectral congestion, the ultrafast nature, and multicomponent behaviour of the charge-separation (CS) process. Using advanced computational multiscale approaches, based on all-atom molecular dynamics simulations coupled with the Perturbed Matrix Method[2], we were able to achieve the first direct calculations of kinetics of charge separation pathways in the reaction center (RC) of PSII [1]. We also calculcualated the reduction potentials of the main actors in the RC, thus excluding the possibility of the formation of a Chl_{D1} - intermediate due to uberable free energy cost. Our results identify two primary radical-pair formation components that differ considerably in their respective time constants (see figure), with the slowly forming radical pair being created both by a primary and by a secondary electron transfer. The fast, dominant component is associated with formation of the Chl_{D1} +$Pheo_{D1}$ − charge-separated pair, where Chl_{D1}* functions as the primary donor, while the much slower component is associated with formation of the $SP^{+}Pheo_{D1}$ − pair by direct long-range electron transfer from the special pair to the unique electron acceptor $Pheo_{D1}$. The presence of a dominant and fast primary charge separation is fundamental for efficient light harvesting because it is crucial that excitation energy that reaches the RC is quickly quenched by electron transfer.



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Right tools for the job. Simple and sophisticated approaches for enhancing performance of *in silico* methodologies in drug discovery

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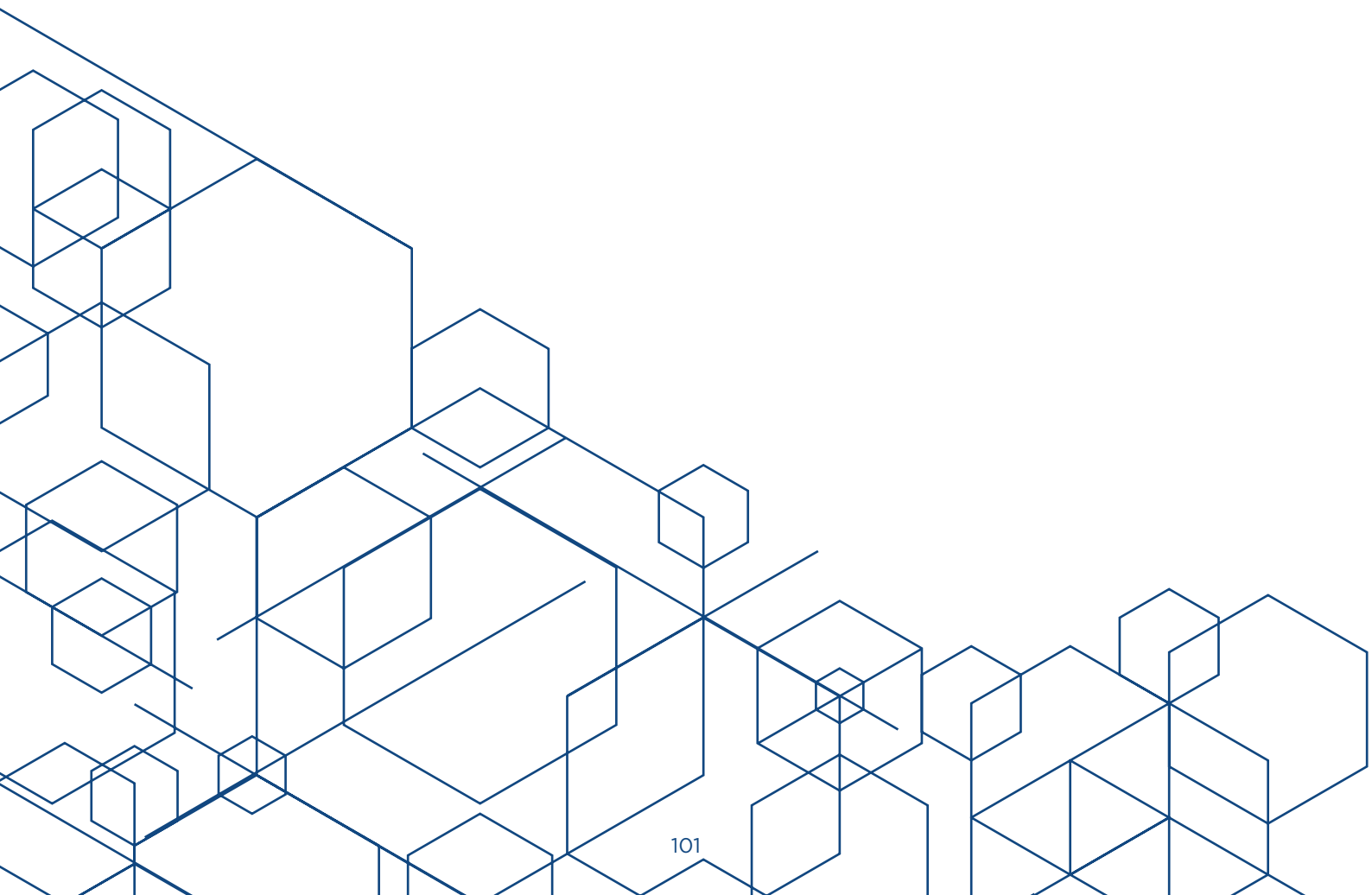
Nowadays, a multitude of computational methods are available for use in drug discovery endeavours. As to their complexity those techniques span an impressive range, from empirical scoring of binding interactions involving rigid molecules to thorough mapping of bimolecular conformational space and extraction of estimates for challenging thermodynamic properties. While not commonplace, custom optimization of those techniques, many of which are applied unaltered within the frameworks of particular software packages, is highly desired. In this presentation, three individual cases of applying targeted improvements in studies performed by ordinary molecular simulation machines are discussed. In the first case, a consensus ranking scheme combining virtual screening algorithms of varied orthogonality is discussed and its potential and limitations are evaluated. A second example deals with the incorporation of hydration effects derived by various methods, enabling rational optimization of a primary hit. In the third instance, the complex event of substrate binding, translocation and release and the simultaneous protein conformational change for a nucleobase transporter using path collective variables and funnel metadynamics is showcased. All paradigms discussed are fully supported by extensive biophysical and biochemical experiments, further strengthening the accuracy of each respective set of predictions.

ARTIFICIAL INTELLIGENCE IN CHEMICAL RESEARCH



Machine Learning Quantum Properties of Transition Metal Complexes with Natural Quantum Graphs

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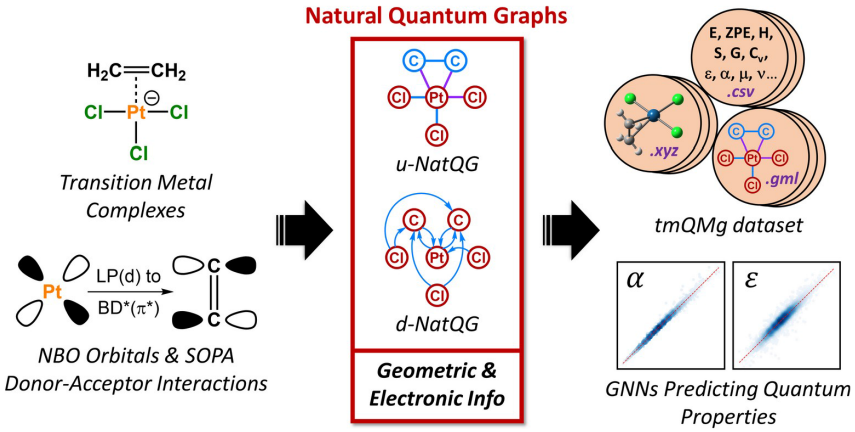
Graph-based learning methods for predicting molecular properties can make strong contributions to accelerate the discovery of new transition metal complexes (TMCs). Despite recent efforts most machine learning studies in chemistry focus on organic molecules (e.g. QM9 [1]) whereas approaches for TMCs remain challenged due to the more complex nature of the involved chemistry and lack of large datasets. In this work we present novel molecular representations for deep graph learning on TMCs – the natural quantum graphs (NatQGs). NatQG leverages the electronic structure information available from natural bond orbital (NBO) analysis data [2,3] and comes in two different flavours: an undirect and direct graph representation. Both graph representations were used to benchmark graph neural networks (GNNs) for the prediction of quantum properties such as the HOMO-LUMO gap and polarizability on a dataset of rougly 60k TMCs extracted from the Cambridge Structural Database. The experiments showed that the models based on NatQG surpass baseline models with traditional features and GNNs using radial cufoff graphs. Furthermore, the results showed that the electronic structure information encoded by the models has a stronger impact on their accuracy than the geometric information. The dataset including geometries, quantum properties and NatQG graphs as well as the code to build them are available online. [4]



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Machine learning and semi-empirical calculations: A synergistic approach to rapid, accurate, and mechanism-based reaction barrier prediction[1]

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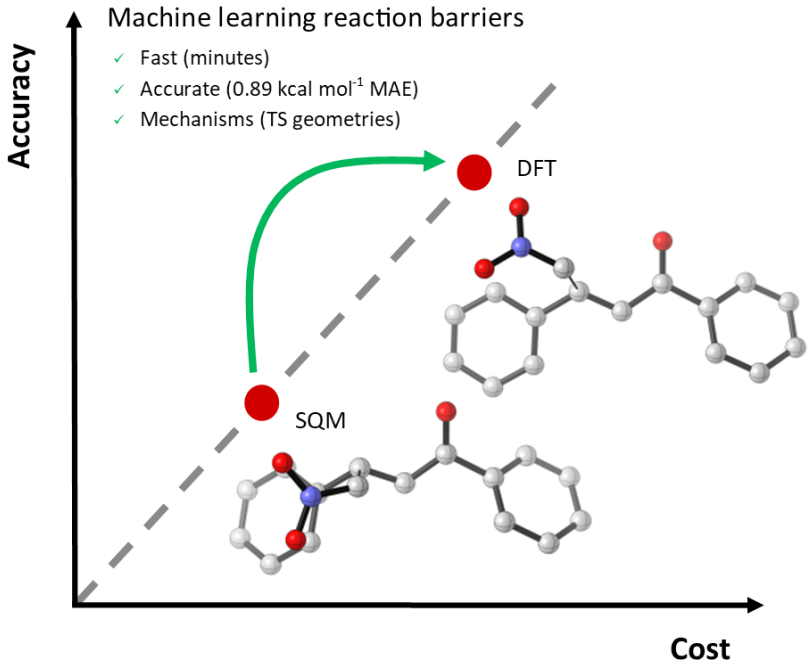
Modern quantum mechanical modelling methods, such as density functional theory (DFT), can provide detailed mechanistic insights into chemical reactions, but their computational cost can inhibit their ability to efficiently screen large numbers of reactions. We introduce a combined semi-empirical quantum mechanical (SQM) and machine learning (ML) approach to achieve the fast and accurate prediction of DFT-quality free energy activation barriers using purely SQM-derived data. Using this method, we achieve barrier predictions below the chemical accuracy threshold of below 1 kcal mol-1 on a dataset of 1000 unique Michael addition reactions with nitromethane. Additionally, we report a level of mechanistic insight that is unprecedented for ML models via the generation of SQM geometries which are found to be satisfactory approximations to the DFT geometries. We believe that the same principles could also be applied to achieve the rapid prediction of reaction barriers and mechanisms for other important classes of chemical reactions, paving the way for more efficient drug discovery and rational reaction design.



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Machine Learning Exciton Hamiltonians in Light-Harvesting Complexes

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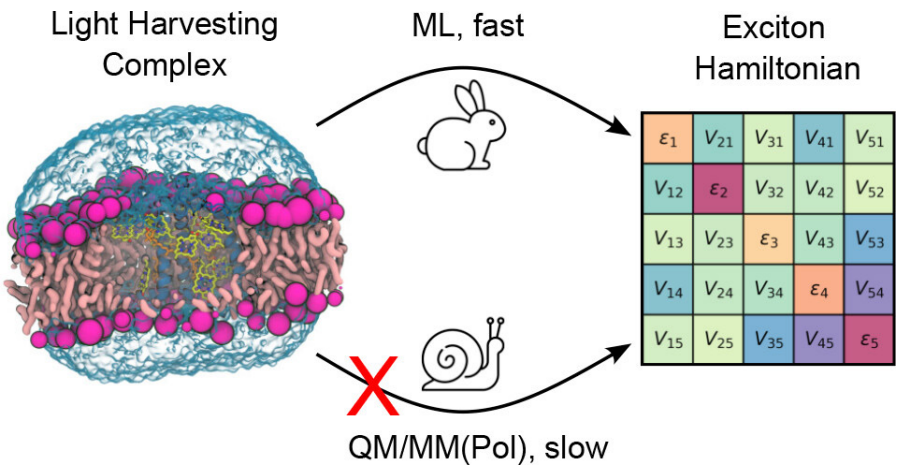
Light-harvesting complexes (LHCs) are of fundamental importance for carrying out photosynthesis [1]. Fine-tuning of their properties holds the promise of improving crop yields [2], stimulating researchers to investigate their excitation transport properties [3]. Still, the computational investigation of these complexes is considerably expensive, as many quantum mechanical (QM) calculations are needed to describe the excited states of the many pigments embedded in the LHCs [4]. We present a machine learning (ML)-based strategy for an inexpensive calculation of excitonic properties of LHCs [5, 6]. The strategy uses classical molecular dynamics simulations of LHCs in their natural environment combined with ML predictions of the excitonic Hamiltonian of the embedded aggregate of pigments. The proposed ML model can reproduce the effects of geometrical fluctuations together with those due to electrostatic and polarization interactions between the pigments and the protein. The training is performed on the chlorophylls of the major LHC of plants, but we demonstrate that the model is able to extrapolate well beyond the initial training set. Moreover, the accuracy in predicting the effects of the environment is tested on the simulation of the small changes observed in the absorption spectra of the wild-type and a mutant of a minor LHC.



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Machine learning potentials for simulating solvent-assisted reactions

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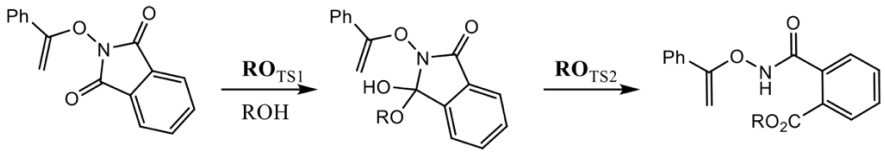
It is well-established that the solvent often plays a crucial role in the efficiency of organic reactions. Whereas chemically inert solvents influence reactivity only through relatively weak non-covalent solvent-solute interactions, protic solvents have the (potential) added complication of reacting directly with the solute. While experimental chemists can harness this reactivity to create new reactions, it also introduces a host of complications in unraveling the underlying reaction mechanism. Conventional approaches to consider solvent effects include implicit solvation and microsolvation, which are limited by the lack of explicit treatment of entropy effects and the absence of an explicit secondary solvation shell to stabilize reaction intermediate and transition state (TS) structures. While *ab initio* Molecular Dynamics (AIMD) is a robust tool that allows capturing the most detailed atomistic picture of the chemical processes in the condensed phase, the prohibitive computational cost restricts its use for simulating complex organic reactivity.

Machine Learning potentials (MLPs) trained with Density Functional Theory (DFT) data represent the best surrogate that can provide results with an accuracy comparable to *ab initio* methods but at a fractional cost of AIMD [1]. However, due to the highly complex intermediate and TS structures stabilized within the solvent networks featuring diverse intermolecular interactions, the construction of MLPs becomes very challenging.



Based on one of our previous works [2], we proposed an efficient pipeline for curating accurate databases for solvent-assisted reactions in condensed phases based on active and transfer learning strategies. From the structures stored in the database, we generate a MLP that can be used with molecular dynamics to simulate reactivity.

We applied our pipeline to a ring-opening reaction (see the scheme below) case using different protic solvents [3]. The results obtained with these MLPs were compared with the microsolvation approach [4,5]. It, thus, enables us to unravel mechanistic features and estimate the energetics accurately, which agrees with experimental observations [3] and serves as a proof of concept for establishing the validity of our pipeline.

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Bridging the explicit solvation experiment-calculation divide with machine learning and high-throughput simulation

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Many experiments are measured in water or other solvents, yet the quantum-accurate computational description of explicit solvation is challenging. The dynamic nature of the solvent at finite temperature requires accurately sampling the Boltzmann distribution of solvent conformations, significantly increasing the computational requirements for quantum calculations. Frequently, the parameters of the solute-solvent interface are a priori unknown, requiring extensive equilibration.

Here the open-source AutoSolvate package automates the setup of QM/MM, equilibration, and simulation of the explicitly solvated systems, resulting in ensembles of microsolvated clusters. Validation of multiple solvent shells for aspherical solute molecules was achieved with minimum distance distribution functions. The high-throughput simulation allowed to train a machine learning model to predict the solute-solvent closeness. For most of the solutes, multiple local minima were observed, highlighting the importance of accurately sampling the conformational landscape including the slower transitions between local minima.

To demonstrate the path for bridging the explicit solvation experiment-calculation divide, redox potentials were calculated for more than a hundred compounds and compared with experimental values. Here, applying a machine learning correction significantly improved the accuracy, reliability, and reduced bias. This machine learning correction approach extends to excited state solution-phase properties. Furthermore, with explainable machine learning, the calculated chemical properties can be attributed to individual atoms and bonds.

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Title of the Presentation Fully Quantum (Bio)Molecular Simulations: Dream or Reality?

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The convergence between accurate quantum-mechanical (QM) models (and codes) with efficient machine learning (ML) methods seem to promise a paradigm shift in molecular simulations.

Many challenging applications are now being tackled by increasingly powerful QM/ML methodologies. These include modelling covalent materials, molecules, molecular crystals, surfaces, and even whole proteins in explicit water [1]. In this talk, I attempt to provide a reality check on these recent advances and on the developments required to enable fully quantum dynamics of complex functional (bio)molecular systems. Multiple challenges are highlighted that should keep theorists in business for the foreseeable future:

(1) Ensuring the accuracy of high-level QM methods [2]

(2) Describing intricate QM long-range interactions [3, 4, 5]

(3) Treating quantum electrodynamic effects that become relevant for complex molecules [6, 7]

(4) Developing increasingly accurate, efficient, scalable, and transferable ML architectures for molecules and materials [8, 9, 10]

(5) Accounting for the quantum nature of the nuclei and the influence of external environments [11, 12]

I argue that only a conjunction of all these developments will enable the long-held dream of fully quantum (bio)molecular simulations.

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Multi-Cloud Data Infrastructure for AI Foundation Models in Chemical Reasearch

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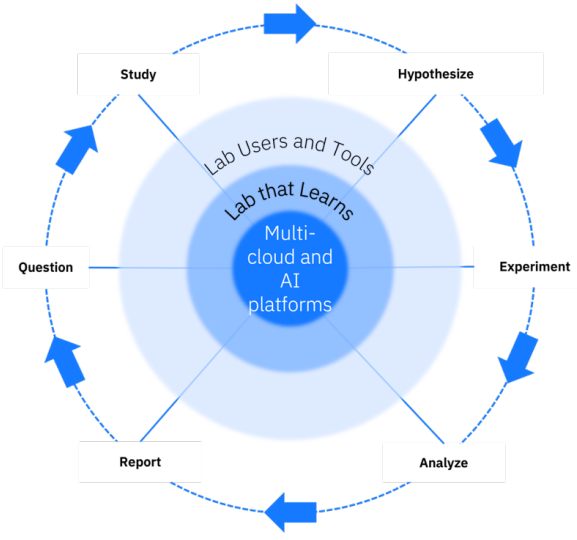
Learning from laboratory data at scale poses a bottleneck in the application of AI to research workflows. To overcome the bottleneck, we propose a framework driven by multi-cloud technologies and AI foundation models that enables collaborative experimentation and data-capture.

Whether for modelling chemical reactions, generating new molecules, or analyzing spectra, data capture forms the bedrock on which AI models are built. Unfortunately, up to 70 % of experimentation is not reproducible because of flawed experimental data or metadata [1]. One reason for the reproducibility problem is poor data capture.

We propose a data management infrastructure to capture a richer representation of experimental workflows to address the concerns. The infrastructure is divided into a primary component deployed in one or more cloud platforms and a minimal component installed on local laboratory instruments. Data generated during a workflow is automatically tied to the corresponding action, thereby improving the reproducibility of experiments, traceability, and automating data entry. Each experimental step, the related workflows, and data are readily accessible through cloud-based services. In turn, the infrastructure provides a framework for systematic and homogenous data collection to facilitate the application of machine learning (ML) on experimental data. This alleviates the burden of recording experimental data from the researcher while providing a framework for ML tools to gain a richer representation and understanding of the experiments carried out.



[1] Accenture Digital Transformation in the Lab (2020)

Graph Neural Networks as Implicit Solvents in MD Simulations

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Molecular dynamics simulations enable the study of the motion of small and large (bio)molecules and the estimation of their conformational ensembles. The description of the environment (solvent) has, therefore, a large impact. Implicit solvent representations are efficient but, in many cases, not accurate enough (especially for polar solvents, such as water). More accurate but also computationally more expensive is the explicit treatment of the solvent molecules. Recently, machine learning has been proposed to bridge the gap and simulate, in an implicit manner, explicit solvation effects [1]. However, the current approaches rely on prior knowledge of the entire conformational space, limiting their application in practice. Here, we introduce a graph neural network based implicit solvent that is capable of describing explicit solvent effects for peptides with different compositions than those contained in the training set [2].

The GNN, based on a Δ-machine-learning approach using the classical implicit solvent GBNeck2 [3], matches or surpasses the accuracy of explicit-solvent simulations with the simpler TIP3P water model. One example for the peptide KAYAE is shown in Figure 1. Key characteristics are high transferability and reproduction of crucial geometric features of TIP5P.

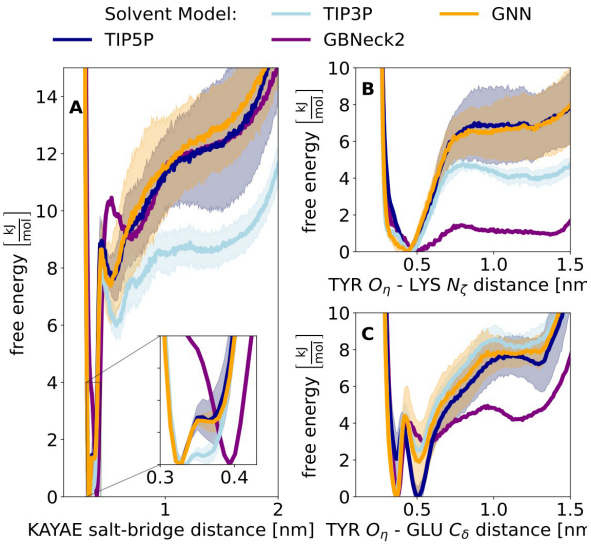

Figure 1 Comparison of the GNN implicit-solvent model (orange, 3 × 30 ns) with the explicit TIP5P (navy blue, 5 × 200 ns) and TIP3P (light blue, 5 × 200 ns) and the GB-Neck2 implicit solvent (purple, 5 × 200 ns). The results for KAYAE (split 3) are shown. (**A**) Free-energy profile of the salt bridge. (**B**) Distance TYR O_η–LYS N_ζ. (**C**) Distance TYR O_η–GLU C_δ. The shaded area indicates the standard deviation over the blocks or replicates of the corresponding solvent model (not shown for GB-Neck2 for clarity).

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Modelling Chemical Processes in Explicit Solvents with Machine Learning Potentials

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Solvent effects play a crucial role in chemical reactions. In addition to providing a medium for molecules to encounter each other, solvents significantly influence the relative stability of reaction intermediates and transition states and, consequently, reaction rate, selectivity, and even the reaction mechanism. However, the accurate computational modelling of these effects remains challenging, particularly when an explicit description of solute-solvent interactions is required.

State-of-the-art approaches for describing solvent effects on chemical reactivity often rely on expensive ab initio molecular dynamics (AIMD) simulations. In recent years, machine learning-based potentials (MLPs) have emerged as powerful surrogates for AIMD; however, their application in modelling chemical reactions in the condensed phase is still limited.

In this talk, I will discuss our ongoing efforts to develop general and efficient strategies for generating reactive MLPs to model chemical processes in diverse environments. [1,2,3] Our approach leverages the linear Atomic Cluster Expansion framework [4,5] and active learning, requiring only hundreds of energy and gradient evaluations in the training set. Furthermore, we combine active learning with enhanced sampling techniques (e.g., metadynamics) to efficiently sample the energy landscape. Our work demonstrates that reactive MLPs can achieve ab initio accuracy at a significantly lower cost than other strategies. I will present diverse examples for which extensive AIMD simulations would otherwise be needed.

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Investigating molecular rotations in plastic crystals using machine learned force fields

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Plastic crystals are characterized by a disordered mesophase where the molecular building blocks exhibit orientational disorder, while retaining lattice ordering. This gives rise to interesting properties, such as moldability and fusibility [1], as well as piezo- and ferroelectricity, where the underlying mechanisms are related to molecular rotations [2,3]. The materials can be built up of both neutral and charged species, and have broad range of intermolecular bonding, such as hydrogen bonding, charge transfer, van der Waals forces, and hybridization of intermolecular orbitals [4]. While the rotational nature of the molecules in plastic crystals are known, the mechanisms causing and allowing for molecular rotations in the solid crystals are not well established.

In this work, we use molecular dynamics (MD) simulations to investigate the nature of molecular rotation in plastic crystals. While complex intermolecular interactions, including dispersion forces, greatly benefit from ab-initio MD, the dynamical molecular rotations require large simulation cells and simulation times, which is not feasible for ab-initio computations. To overcome this challenge, the NeuralIL software [5,6] is used to train machine-learned force fields (MLFF) on atomic forces from ab-initio simulations. We find that careful selection of training data is central, and configurations with a range of intermolecular distances and molecular rotations should be included to represent less frequent occurring configurations. The configurations included in the training of the MLFF are chosen by an active learning procedure to achieve an MLFF that is suited to describe the intermolecular interactions in a plastic crystal material.

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New representations for interpretable chemical machine learning

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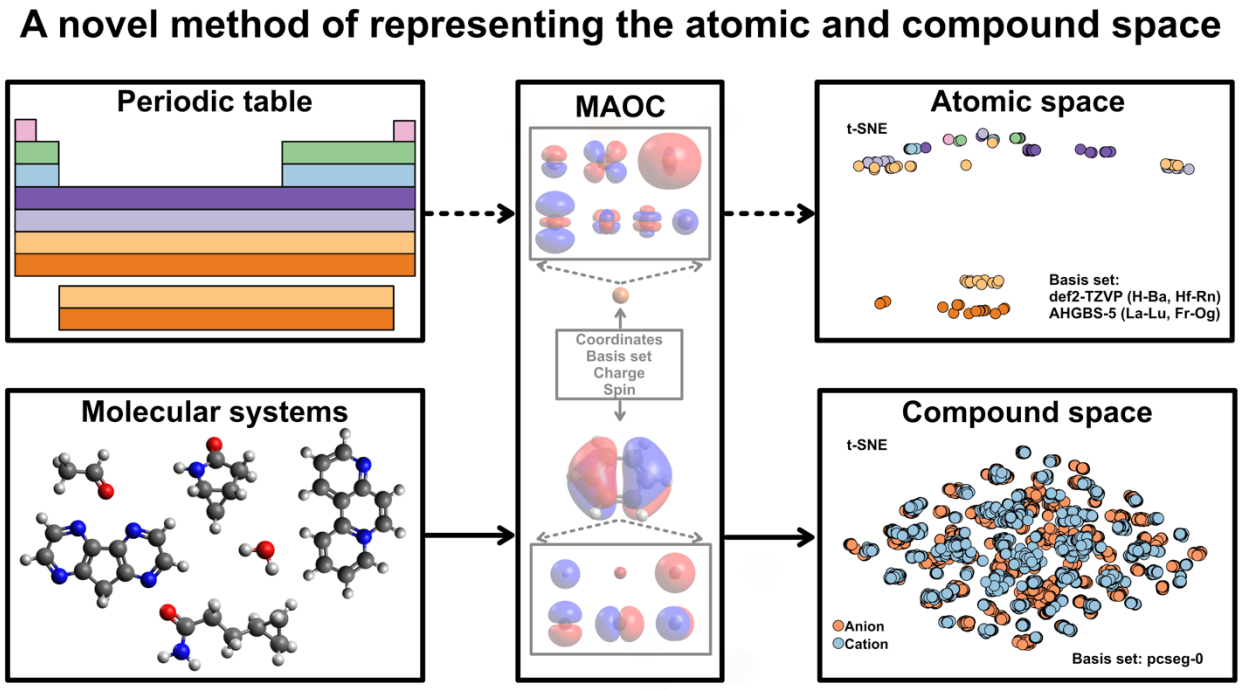
Chemical (molecular, quantum) machine learning relies on representing molecules in unique and informative ways. Here, we introduce two new representations – a quantum-inspired representation called matrix of orthogonalised atomic orbital coefficients (MAOC),[1] and a fragmentation-based technique called matrix of fragment similarity representation (MFSR). MAOC is based on a cost-effective localisation scheme that represents localised orbitals via a predefined set of atomic orbitals. The latter can be constructed from small atom-centred basis sets in conjunction with a guess electronic configuration of the molecule. Importantly, MAOC is uniquely suitable for representing monatomic, molecular, and periodic systems, and can distinguish compounds with identical compositions and geometries but distinct charges and spin multiplicities. MFSR is instead uniquely suited for mapping and exploring the chemical space of compounds composed of specific building blocks. Most industrially and biologically relevant macromolecules are formed as a combination of finite building blocks (e.g., all proteins are a combination of just 20 aminoacids), and MFSR can predict their properties in less than a fraction of a second and with the quantum-chemical accuracy. Moreover, MFSR allows even the most entangled deep learning models to be decodable in a chemically intuitive form.



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Development of Machine Learning Potentials for Main Group Organometallic Reagents in solvent

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Main group organometallic reagents have been used in synthetic chemistry since the early 1900s when V. Grignard discovered the eponymous reaction [1] and have recently been improved with the addition of lithium salts in the mixture, creating the so-called Turbo Grignard reagents [2]. The experimental study of these processes is challenging due to the difficulty to characterize the large array of fluxional species formed in solution, in which the solvent plays a key role [3].

Computational methods based on ab initio molecular (AIMD) dynamics represent the natural solution to this problem [4]. However, highly demanding DFT based trajectories are needed to describe these very complex free energy surfaces (FESs). Machine learned potentials (MLPs) have proved to be a valid and cheaper substitute for AIMD [5]. Here, I will present our results in the development of MLPs s through an active learning procedure for the simulation of Grignard and Turbo-Grignard reagents in THF. It takes advantage of the DeePMD potential [6] to train a deep neural network (DNN) on DFT data and on MLPs-driven enhanced sampling to extensively explore the PES. A query by committee protocol is used to add only relevant structures to the training set. We automated this procedure interfacing DeePMD (DNN training) with LAMMPS (MD enhanced sampling) and CP2K (periodic DFT calculations). After only a handful of sampling and training iterations this technique manages to capture the features of the free energy landscape. Moreover, the selection of suitable collective variables enabled us to model reactive pathways such as the Schlenk equilibrium.

Our goal is to create a library of accurate potentials for a large array of different reagents to unravel the structure-activity relationships to shift from a heuristic-based design, inferred from experimental results, to a rational-based designed, taken from first principles, which maximizes the effectiveness and efficiency of the reagent for a specific application.

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Machine Learning Approaches to Unravel the Dynamic Behavior of Metal Surfaces and Nanoparticles

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The detailed understanding of atomic-level dynamics in metal surfaces and nanoparticles (NPs) is a pivotal challenge in the field, with implications ranging from catalysis to energy conversion. In this presentation, we will discuss our recent studies that leverage machine learning techniques to achieve unprecedented atomistic-level understanding of these dynamics.

Our work initially focused on the complex dynamics of copper (Cu) surfaces, using deep neural network potentials in conjunction with molecular dynamics simulations.[1] This approach allowed us to observe and track the emergence and disappearance of atomic environments (AEs) at finite temperatures, revealing the dynamic and elusive nature of metal surfaces. We further extended this methodology to gold NPs, obtaining a level of detail rarely achieved in experimental studies due to the challenges associated with tracking individual atomic motions over time. By tracking the emergence, annihilation, lifetime, and dynamic interconversion of the AEs, we could estimate a "statistical equivalent identity" for these NPs, providing a comprehensive picture of their intrinsic atomic dynamics.[2] Our findings are complemented by the use of novel ML descriptors, which allow us to identify dynamic domains and detect local fluctuations and microscopic dynamical rearrangements in a variety of systems, including metals.[3-4]

Our work integrates experimental reconstruction, simulations, and ML to provide a comprehensive characterization of the dynamic behavior of metals with unprecedented resolution. This research opens new avenues for nanoparticle and metal surface manipulation and control across various applications and anticipates further exploration into the dynamic nature of other metallic systems.

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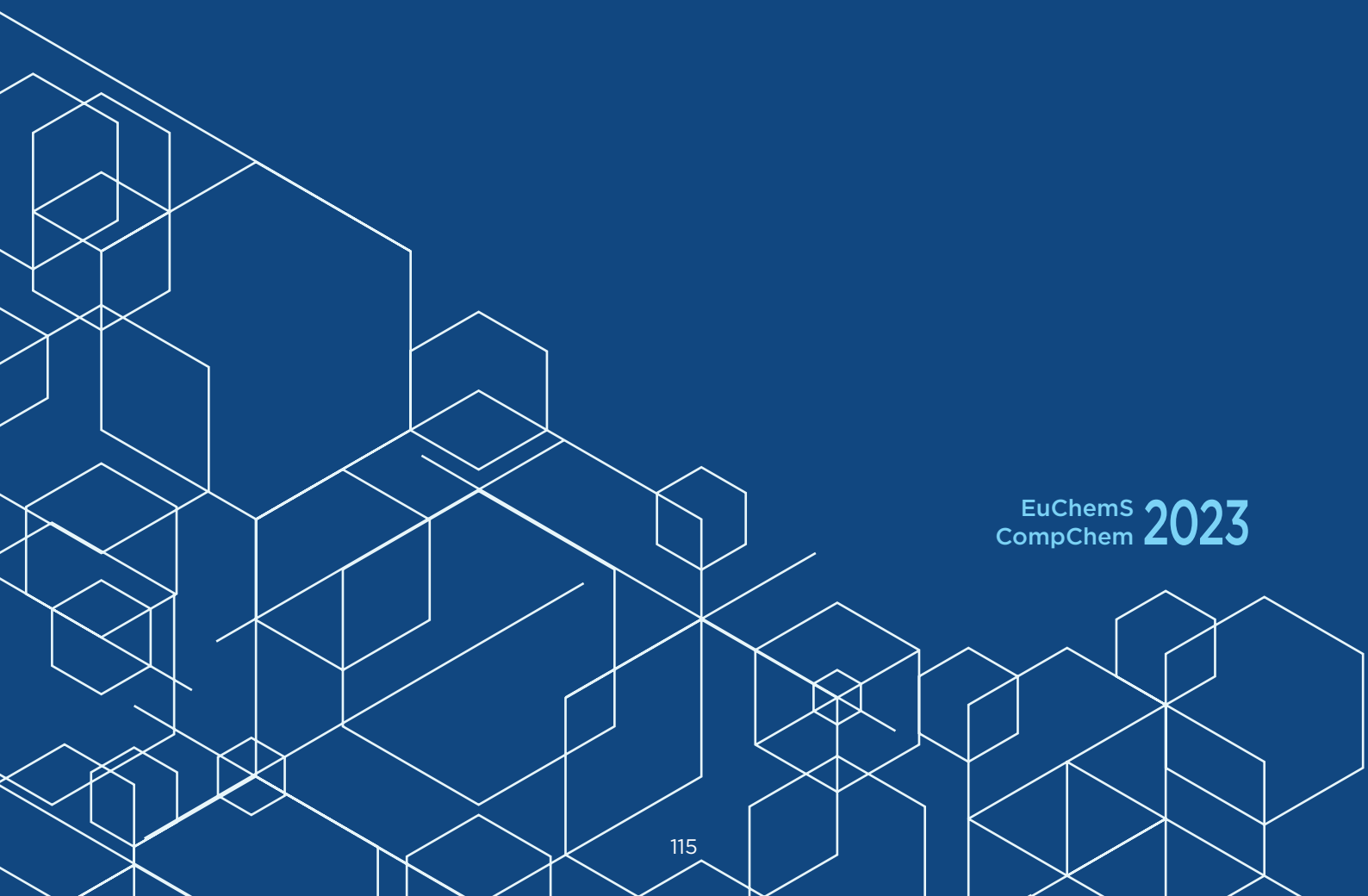
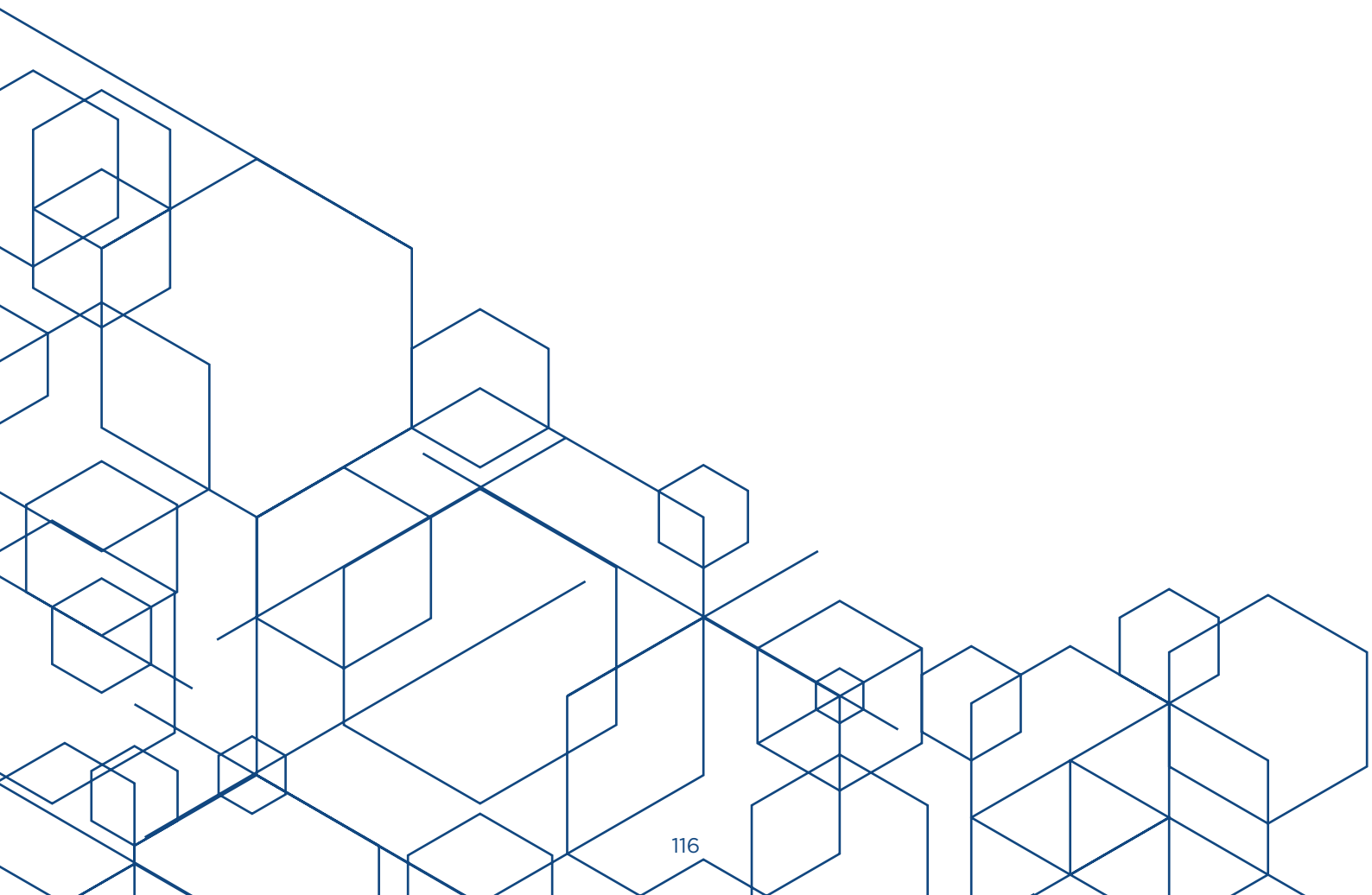
ABSTRACTS OF POSTERS



EuChemS CompChem 2023

ELECTRONIC STRUCTURE: THEORY AND APPLICATIONS



I-1

Halogen bonding with a flying molecule: the halogenabenzene bird

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Halogen-substituted benzenes have received ample attention in the literature. Conversely, benzene structures where a carbon is replaced by a halogen have received much less attention so far. Such structures, labelled halogenabenzenes, were first introduced by Glukhovtsev in 1991 [1]. Based on semiempirical calculations, he proposed a planar 8π-electron system. However with 8 π-electrons, this system is antiaromatic. Based on higher-level DFT and MP2 calculations, Rawashdeh et al. showed in 2017 that the planar iodabenzene structure is a transition state; the minima it is connected to are both an identical Cs-symmetric non-planar structure [2]. Rawashdeh et al. dubbed this structure "bird" because of the similarity with a flying bird (see Figure 1). The bird structure is unusual in the sense that the iodine is bonded to two carbon atoms. With the current interest in halogen bonds (X-bonds) in our group, we wondered how this topology would affect the halogen's ability to form X-bonds. To this aim, we investigated the ability of the bird-like halogenabenzene molecule, referred to as X-bird (X= Cl to At), to form halogen-bonded complexes with the nucleophiles H2O and NH3 using double-hybrid density functional theory and the aug-cc-pVTZ/aug-cc-pVTZ-PP basis set. The unusual structure of the X-bird results in two distinct σ-holes, roughly at the extension of the C-X bonds. Based on the behaviour of the interaction energy (which increases for heavier halogens) and van der Waals (vdW) ratio (which decreases for heavier halogens), it is concluded that the X-bird forms proper halogen bonds with H_2O and NH_3 [3].

Figure 1: The bird-like halogenabenzene molecule

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I-2

The electronic structure of actinides tailored by relativistic quantum chemistry approaches: applications to X-ray spectroscopies

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This talk will discuss the performance of relativistic quantum chemistry approaches in investigating the electronic structure of actinide-containing compounds, with a specific focus on the core-level spectroscopic observables of the uranyl moiety (UO_2^{2+}). The challenges associated with the handling of nuclear waste and the fate of fission products in the environment mean that research on efficient extraction and capture methods, as well as characterization methods of actinide-containing compounds, is of great societal importance. Regarding their characterization, compared to the rest of the periodic table, the electronic structure of these compounds is often still poorly understood. However, valence- and core-level spectroscopic techniques have been shown to shed light on this subject, whereas synchrotron-based X-ray spectroscopies have enabled the use of elemental and environmentally sensitive techniques to probe the electronic structure of such systems [1]. These experiments can be complemented and sometimes replaced by robust theoretical models capable of describing the electronic structure of complex systems in the ground and excited states.

We have investigated the X-ray absorption fine structure (XAFS) of uranyl compounds through 4-component damped-response time-dependent density functional theory (4c-DR-TD-DFT) simulations [2] and core-valence-separation equation-of-motion coupled-cluster method (CVS-EOM-CC) to investigate core-ionized states [3]. In addition to the 4c-DR-TD-DFT and CVS-EOM-CC simulations in the gas phase, we have also evaluated the performance of the frozen density embedding (FDE) method to account for environmental effects in these simulations, as previously done for valence-excited states [4]. Our 4c-DR-TD-DFT simulations for a representative system, the uranyl tetrachloride dianion ($UO_2Cl_4^{2-}$) in the $Cs_2UO_2Cl_4$ crystal, were found to be consistent with previously reported angle-resolved near-edge X-ray absorption spectroscopy (NEXAFS) at the oxygen K-edge and high-energy resolution fluorescence detected (HERFD) at the uranium M_4- and L_3-edges. Furthermore, CVS-EOM-IP results demonstrated qualitative agreement with previously reported X-ray photoemission spectroscopy (XPS) data for $Cs_2UO_2Cl_4$ in the soft X-ray range (0.1 – 1 keV). The FDE method allowed us to successfully address the role of electrostatic interactions in shifting binding energies in the soft X-ray range and the peak splittings observed in the emission spectra at the U M_4-edge, which has been a subject of debate in the literature [5]. Finally, we will discuss how these approaches can provide further insights into state-of-the-art experiments.

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I-3

An ETS-NOCV-based methodology to disclose molecular events in concerted transition states: applications to CO_2 capture and utilization

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Concerted transition states are quite common in reaction mechanisms, and their detailed characterization can be hampered by the interplay of different molecular events. Disclosing and quantitatively evaluating each one of them can be fruitful to deeply understand the reaction mechanism. With this aim we applied the Extended Transition State-Natural Orbitals for Chemical Valence analysis, combined with the Energy Decomposition Analysis,[1,2] to gain computational insights into processes involving carbon dioxide. Specifically, we focused on the reversible CO_2 capture by a sorbent;[3] ii) the iridium-catalyzed CO_2 reduction to formic acid;[2] and iii) the CO_2-catalyzed transamidation reaction.[2] The results allowed us to unravel the relative importance and asynchrony of all the concurrent molecular events. By extending this investigation to the potential energy surface around the transition states, we traced the evolution of molecular events guiding the reactivity, thus quantifying the relative importance of each interacting component. The outcomes of the different cases studies suggest the possible applicability to any concerted transition state.

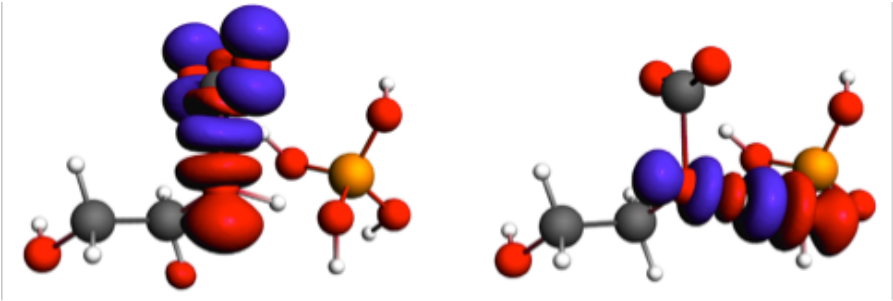

Figure 1. An example of two NOCVs for a concerted transition state from the CO_2 absorption process. The isodensity surfaces describe different simultaneous molecular events: the CO_2 binding to the substrate (on the left), and a proton transfer process (on the right). The charge flux is red → blue.

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I-4

Unveiling vinylene carbonate reactivity at Lithium metal anode interface via Density Functional Embedding Theory

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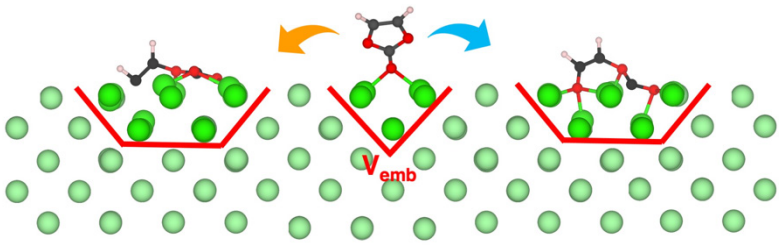
A strategy to achieve durable and effective anodes for Lithium metal batteries (LMB) is by engineering the solid-electrolyte interphase (SEI) with purposely designed molecules [1]. To this end, adding vinylene carbonate (VC) in conventional electrolytes promotes the formation of a stable and protective SEI between Li metal and electrolyte [2,3]. However, controlling the VC reactivity is not straightforward due to VC dissociation and polymerization at the electrode surface. To dissect such tangled VC reactivity, here we present new atomistic insights on VC-Lithium SEI formation via the Density Functional Embedding Theory (DFET) [4] by combining the best feasible approaches for molecular species (hybrid DFT for VC molecules and derivatives) and Li metal electrode (semi-local GGA density functional).



Our results highlight different VC dissociation pathways, with formation of reactive species and localized cluster of Li_2O and Li_2CO_3, in close agreement with experiments [3]. Our DFET investigation reveals the thermodynamically accessible mechanisms for the VC ring-opening reductive reaction on Li(001) feature energy barriers of about 0.3 eV. Plus, the energetics and structural features of VC open-ring intermediates improve the current understanding of SEI formation process and can be exploited to drive the reactions toward the desired interfacial properties [5]. Moreover, from a general perspective, our study highlights further the great potentialities of DFET for modelling complex reactions at hybrid interfaces in electrocatalysis.

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I-5

Small Molecule Activation at Biological Metal-Macrocycle Complexes: Contrasts between Heme and Vitamin B_{12}

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In heme-containing proteins, redox-active agents such as peroxides or oxyanions of halogens/sulfur/nitrogen offer a rich chemistry involving high-valent iron, free radical reactions and small molecule activation.[1,2]and serves for multi-electron reduction reactions. Clear explanations have not been demonstrated for the reasons behind the choice of siroheme (vs. other types of heme By contrast, until recently our knowledge of the reactivity of cobalamin with oxidizing agents has been confined to processes where, especially with strong oxidizing agents, the corrin ring is covalently modified by oxygenation or halogenation, or where Co(I) or Co(II) are oxidized to Co(III) in an outer-sphere manner (at times in pseudocatalytic cycles where reducing agents are also present) – but no complexes of Co(III) with oxidizing agents, and no ensuing high-valent Co centers.[3]

We have, however, recently reported that H_2O_2 does in fact form a stable and reversible complex with cobalamin, assigned as Co(III)-hydroperoxo based on UV-vis and NMR spectra complemented by density functional (DFT) calculations.[4] We describe here a combination of spectroscopic and computational results showing that m-chloroperoxobenzoic acid (MCPBA) at low concentrations yields a relatively stable complex with Co(III) cobalamin. Using the same experimental toolkit – centered mostly on 1H-NMR spectroscopy and DFT calculations – we then describe a stable adduct of Co(III) cobalamin with chlorite – which in contrast to the known instability of the putative heme-chlorite complex in the catalytic cycle of the enzyme chlorite dismutase.

Using the reactivity towards peroxides, halogen oxyanions and nitric oxide, we then employ computational approaches in order to rationalize the differences in reaction mechanisms between Fe(III) heme and and Co(III) cobalamin complexes.

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I-6

Intermolecular-type conical intersections in benzene and catechol dimers

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So far, the search for conical intersection (CI) type geometries in molecules has been almost exclusively limited to individual monomers analysis. Recently, in the case of catechol [1] and benzene [2] molecules, it has been shown that these CI geometries can be formed not only within monomers, but also in dimeric systems. Surprisingly, the resulting dimer-type CI geometries are energetically similar to, and perhaps even more favourable than, the monomer-type CIs known so far. However, to accurately identify these CI geometries, theoretical methods are needed that take into account not only static (or multireference) electron correlation effects, but also the higher-order correlation effects such as the dispersion interaction between monomers. Accordingly, the equilibrium geometries of the ground and first electronic excited states as well as the radiationless deactivation channels of catechol and benzene in their monomer and dimer configurations were investigated using the standard linear-response and the spin-flipped TDDFT together with the ωB97X-D3 exchange-correlation functional, as well as by the multireference CASSCF methods, considering the minimally augmented ma-def2-TZVPP and the 6-31G** basis sets. It was found that for the equilibrium geometry the stacking distance between the monomers decreases in the first electronic excited state, due to the stronger intermolecular interaction energy, bringing the two monomers closer together. Intermolecular-type CI geometries can be formed between the two monomers, where both aromatic rings show planar deformation and a weaker, approximately 1.6-1.8 Å long, C-C bonds are formed between the two monomers, with multiple orientation configurations of the monomers relative to each other. It was also shown that, these, intermolecular-type CIs are energetically more favourable than CIs containing only one deformed monomer. The validity of the dimer-type CI geometries obtained by SF-TDDFT was confirmed by the CASSCF method.

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I-7

Linear optimization of molecular vibrational states

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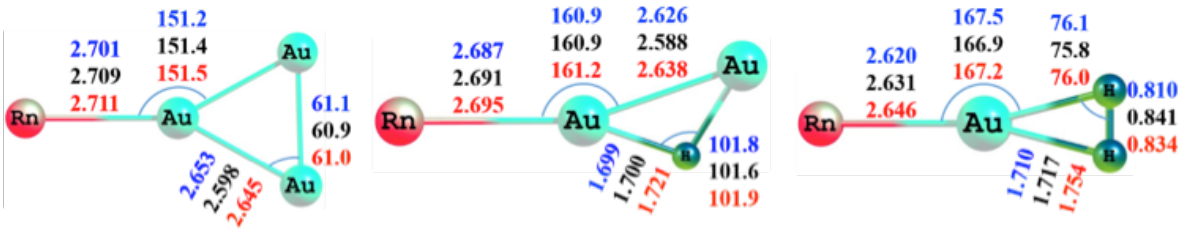
Highly accurate predictions of vibrational transition energies rely on the quantum-mechanical and anharmonic treatment of molecular vibrations. [1] We present - as an attractive alternative method to established mean-field and configuration-interaction-type approaches - the optimization of excited vibrational states based on the expansion of the vibrational wave function with respect to its variational parameters [2]. Our approach is a deterministic variant of the linear optimization method [3] and involves the



analytic computation of wave function derivatives. We illustrate the approach by computing the ground and excited vibrational states of a two-dimensional model Hamiltonian and of the formic acid monomer.

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I-8

Harnessing Non-covalent Interactions between Molecules for the Directed Evolution of Higher Component Co-crystals

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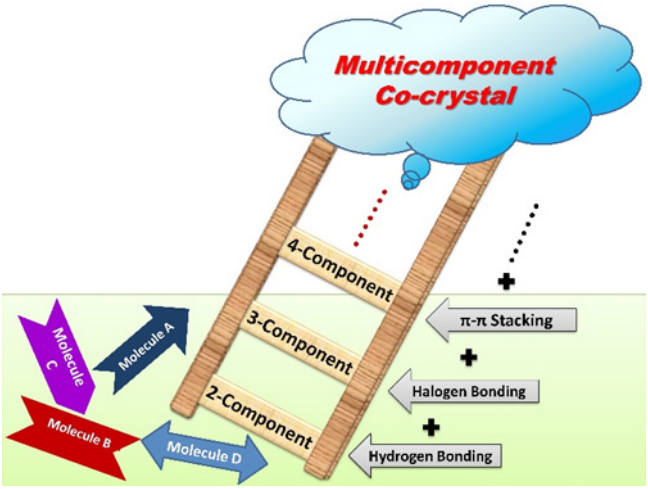
The formation of multicomponent co-crystal in preference over multi-bi-component ones has been reported for several systems recently. The factors that drive crystallization of such a multicomponent aggregate is elucidated based on density functional theory (DFT) and classical molecular dynamics (MD) simulations and tuned range-separated (RS)-DFT calculations are found to be capable in describing the ionic interactions in molecular solids. Estimating the stabilization energies between the three components of the ternary co-crystal of crown ether, thiourea and perfluoroarenes indicate a hierarchical preference of interactions namely, crown ether…thiourea (H-bonding) > thiourea…perfluoroarenes (halogen bonding). Generalizing the model further, it is shown that even higher order co-crystal or an ionic crystal can be envisioned by further harnessing the rich variety in non-covalent interactions.



Using a hybrid of strong and weak intermolecular interactions, one may generate exotic molecular complexity like n-component crystals.

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I-9

Design of blue fluorescent dyes with high-energy excited triplets for application in OLEDs

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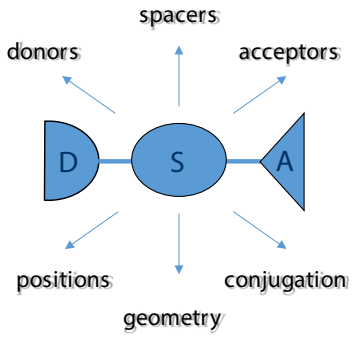
Organic light emitting diodes (OLEDs) are among the optoelectronic devices for which research is employed intensively to enhance their performance [1]. Blue OLEDs suffer from relatively short lifetimes and comparatively low lighting efficiency. One of the approaches to improve their characteristics is the development of luminophores with potential for thermally activated delayed fluorescence (TADF). These are compounds with high-energy excited triplet states and closely separated excited singlets. Therein, reverse intersystem crossing via thermal fluctuations might increase the overall luminescence quantum yield. In the current study, rational design is applied to predict new organic compounds, which emit blue light and have feasible TADF.



The structure and optical properties of a set of donor-spacer-acceptor molecules are computed with (TD)DFT [2] to reveal the relative importance of several molecular factors for accomplishing the desired luminescence characteristics. Size of the donor and acceptor and their binding position to the spacer, torsion angle between the donor and the spacer/acceptor, and variation of the donor-acceptor conjugation length turn out to be the crucial determinants. Meta-binding to the spacer is found essential for a high-energy triplet excited state. To ensure non-zero oscillator strength of the fluorescence transition, the donor and the acceptor should close an angle lower than 75° and their frontier orbitals should overlap partially on the spacer. The p-conjugation length of the chromophore should not exceed three cycles for blue fluorescence to take place.

Following the derived molecular guidelines, several compounds are put forward as promising blue emitters for organic light-emitting diodes.

The research is funded by the Bulgarian National Scientific Fund, Project № KP-06-N49/3 from 26. 11. 2020.

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I-10

QSPR models for efficient design of blue TADF emitters for OLEDs

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Organic light-emitting diodes (OLEDs) are found in most of the devices that require lighting nowadays. Unfortunately, the efficiency of blue light emission is not up to the standards of green and red OLEDs yet. A way to solve this problem is to design blue emitters, which fluoresce more intensively. One of the strategies to improve luminescence performance is to develop organic dyes, which have the potential for thermally activated delayed fluorescence (TADF) [1]. To observe this effect, compounds with energy difference between the lowest triplet (T_1) and the lowest singlet (S_1) excited states smaller than ca. 0.2 eV are sought.

The molecules of such compounds can be constructed by combining electron-donor and electron-acceptor fragments [2], which could be separated by a spacer [3]. However, the correlation between the optical properties of the composite emitter and those of the fragments it is built of is often not straightforward. The aim of the current work is to derive QSPR models to help understand the importance of different factors for the emission of the combined compounds and to search for a relation to characteristics of their building blocks. The structures and optical properties of a series of new organic TADF blue emitters are computed with (TD)DFT and the electron densities are post-processed in order to obtain descriptors for multiple linear regression models.

The generated models properly reflect the importance of charge transfer for suitable placement of the excited states in TADF materials. The amount of the electron located on the donor and the charge transfer from the acceptor to the spacer in particular are key properties for the excited states energies of the combined compounds. The S_1-T_1 energy separation turns out to depend critically also on the degree of overlap between the hole and the electron.

The developed models could be used to predict the energy gap between the T_1 and S_1 states without the sometimes computationally challenging task of optimizing the geometry of excited triplet states.

The research is funded by the Bulgarian National Scientific Fund, Project № KP-06-N49/3 from 26. 11. 2020.

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I-11

Simultaneous Hydrogen Bonds with Different Binding Modes: the Acceptor "Rules" but the Donor "Chooses"[1]

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Hydrogen bonds (HB) are one of the most important and abundant non-covalent interactions yet many aspects have still to be well described. Prevalent in the recognition of molecules be-tween a substrate and a corresponding enzyme making it a crucial step in many biological pro-cesses[2]. A multitude of life essential processes rely on site specific binding, proving the sig-nificance of molecular recognition, and are highly established in the immune system and DNA replication that depend on the recognition of antigen–antibody and DNA–protein, respective-ly[3]. Furthermore, pharmaceutical drugs help achieve therapeutic effects by having structural complementarities with specific biological targets[3]. With this in mind, squaramide, thiourea and guanidinium systems, well reported to be highly effective in HB formation having the capability to form two HB with a reactant and offers linearity facilitating HB[4], were chosen for a DFT investigation to elucidate and provide insight on the preferential binding mode in biological systems.

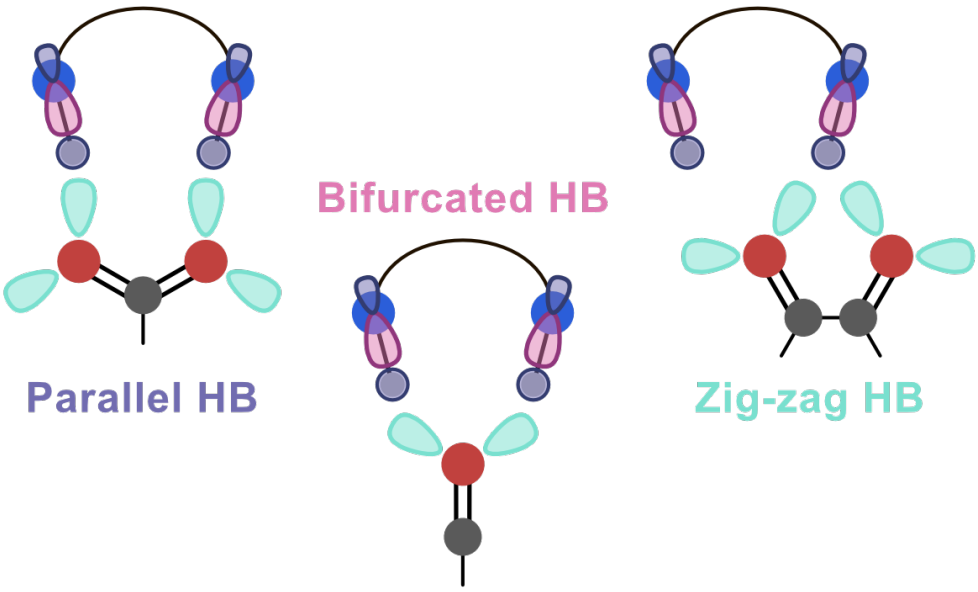

Figure 1. Three HB binding modes parallel (purple), bifurcated (pink) and zigzag (green)

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I-12

Enthalpies of formation obtained from atomization energies: experiment, theory or dice throwing? The case of fluorine containing organic and inorganic species

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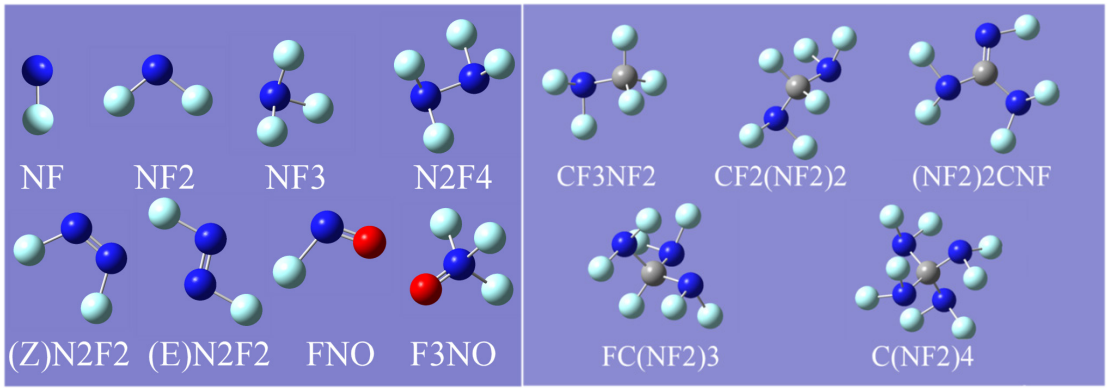
We present a benchmarking of the performance of the SVECV-f12[1] protocol for the calculation of the enthalpy of formation of fluorine-containing molecules derived from energies of atomization. We used the paper of Si et al[2] to benchmark the method, focusing on those species for which there are large discrepancies between the CCSD(T) calculations and the experimental results. CBS-QB3, G4, W1BD and SVECV-f12 methods were employed, as well as full CCSD(T)-F12/cc- pVNZ-F12 (N=D,T,Q) optimization and frequencies for the smaller molecules in the image at the left.



The SVECV-f12 protocol produced the smallest error compared to the experimental values available (both in terms of maximum and r.m.s. errors) for the trial molecules. Almost all the experimental values available lie in the range of the 95% confidence interval of the SVECV-f12 values. For the larger species, the W1BD method performed a bit better than the SVECV-f12 protocol, and this one, in turn, performed better than all the others, including CCSD(T)/CBS, both in terms of maximum and r.m.s values. Especially difficult cases, like fluorodinitromethane (CCSD(T) error of 14.8 kcal/mol) were improved but not completely by W1BD (error 5.8 kcal/mol) and SVECV-f12 (error 9.8 kcal/mol). We concluded that the use of atomization energies, a normally reliable procedure for other species, is inadequate in the case of species containing NF bonds.

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I-13

Excited state tautomerization of cytidine in water solution when exposed to UVC light

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The irradiation of water solution of cytidine with UVC light showed that the compound participates in tautomerism through a first order reaction with a rate constant of 34.26×10^{-3} min^{-1}. Once the UVC light source is removed, the compound undergoes a first order thermal reaction (in - dark) with a rate constant of 1.43×10^{-3} min^{-1} that recovers the original peak positions. According to the PIDA mechanism, which was explored at the TD DFT level, proton detachments in the cytidine tautomers occur through the $^1\pi\sigma^*$ excited states, leading to conical intersections S_0/S_1. The internal conversion of the $^1\pi\pi^*$ excited states through conical intersections S_0/S_1 to the ground states has been suggested as one of the excited state deactivation mechanisms[1-2]. The IRC mechanism, which follows the $^1\pi\pi^*$ excited-state reaction paths and explains the phototransformation of the amino oxo tautomer of cytidine into imino hydroxy one, is far more likely to take place. The GAUSSIAN 16 software package was used for all calculations (B3LYP and CASSCF) together with the aug-cc-pVDZ basis set[3].

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I-14

Quantum Mechanical Database Generation for Warhead-target reactions in Covalent Drug Design

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Covalent inhibitors (CIs) that can make covalent bonds with protein targets are gaining much attention lately due to their ability to target undruggable proteins. A main advantage of CIs over non-covalent inhibitors is their long-lasting pharmacological effects at low doses.[1] However, despite the emerging body of research devoting to develop covalent drugs, the lack of effective rational design strategies remains a current technical barrier to the extensive development of CIs. Herein, we aim to further develop the QM/MM-based EnzyDock[2] multistate docking approach and scoring of CIs in a mechanism-specific manner. We start off by creating a reaction database for relevant reactions with nucleophilic and electrophilic warheads based on ab-initio/DFT calculations and then develop a specific-reaction semi-empirical QM/MM Hamiltonians. One such reaction under study is the Michael addition, where we focus on Cys residues of proteins with several warheads. Using the Python programming language and RDKit library we create all possible combinations of reactants, intermediates, and products possible and their intrinsic reaction mechanisms at DFT and high-level ab initio QM level of theory. In this work, we focus on building a comprehensive database for warhead-targeted reactions and their underlying mechanisms. Apart from creating a covalent reaction database, our study sheds light on several important questions in covalent drug design, such as evaluating the factors that modulates the covalent interactions between warhead and target residues, understanding the kinetics of the processes and the means to distinguish between on and off-target binding.

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I-15

An *ab initio* charge transfer investigation of He^+ + CO system

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The charge transfer process is one of the often-seen events in high-energy (~ keV) collisions that correspond to typical solar wind conditions. The study of the collision of one of the most common molecules of outer space, CO, with the second most abundant singly charged species, He^+, has high astrophysical relevance. The high ionization potential of He (24.5 eV) allows a large number of the product channels to be accessible in the charge transfer (CT) reactions. An *ab initio* analysis has been carried out for the collision pair He^+ + CO. At the Multi-reference configuration interaction/*aug-cc-p*VQZ level of theory, an elaborate analysis involving the lowest nine electronic states for the system has been conducted to identify and investigate the involved potential energy surfaces for the charge transfer process. The nonadiabatic couplings and the associated quasi-diabatic surfaces have also been computed using *ab initio* procedure. The reaction is caused by non-adiabatic interactions (Landau-Zener and Demkov Coupling) among all the nine electronic states (as shown in Fig 1). The strength of the non-adiabatic couplings corroborates the experimental findings[1-3] on different probable charge transfer channels.

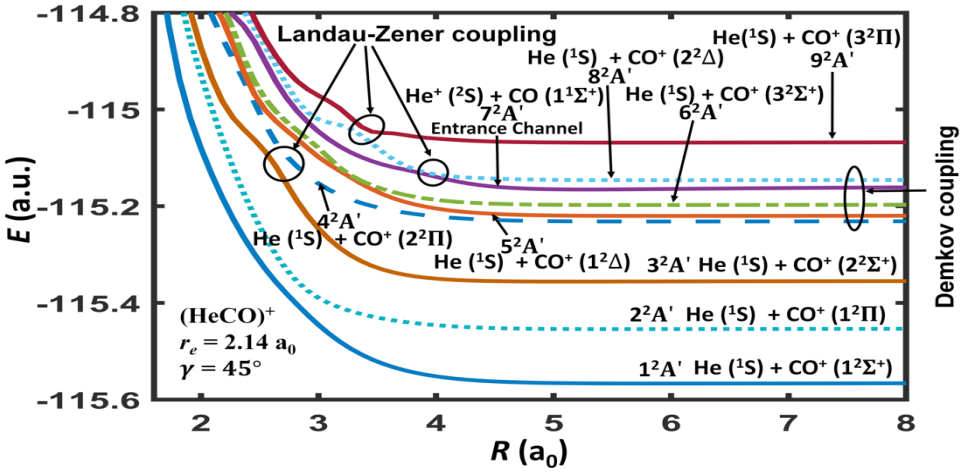

Fig 1: *Ab initio* adiabatic PECs of the $(HeCO)^+$ system as a function of *R* for γ = 45°, at r_e = 2.14 a_0.

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I-16

Significance of the Electronic "ladder of states" in the Entangled two-photon Absorption

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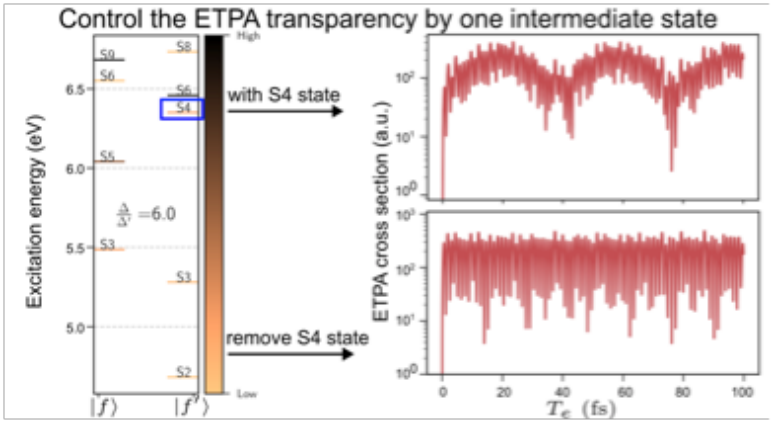
Entangled two-photon absorption (ETPA), presents a high efficiency compared with the classical two-photon absorption due to its quantum entanglement nature. Experiments observed ETPA cross sections for various chromophores may drop several order of magnitudes, sometimes leading to the ETPA transparency phenomenon [1]. In this work we attempt to explain the observed nonmonotonicity of ETPA cross-sections to the electronic structure of the chromophore.

Entangled and classical TPA cross-section are closely related. The classical TPA cross-section, on the other hand, is computationally challenging [2]. For large systems such as chromophores in the condense phase, the multi-scale approach is indispensable. In such a case, we will present benchmark TPA results obtained from Frozen Density Embedding Theory (FDET)[3]. FDET reducing N_{A+B} body to N_A electrons problem is both robust and practical, enabling us to accurately predict the impact of solvents on ETPA[4]. The detailed analysis of the sum-over-state formula for the ETPA transition moment shows that the magnitude of the ETPA cross-section is expected to vary significantly depending on the a)coherence time T_e and b) the relative position of just two electronic states of chromophores[5]. Moreover, the dependency on T_e is periodic. Furthermore, our quantum mechanical calculations demonstrate two possible ways to perturb the electronic structures of chromophores and consequently the ETPA properties. This could potentially tune or switch on/off the complex ETPA process by modifying only one-photon absorption properties.



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I-17

Unravelling the atmospheric degradation of pesticides using computational chemistry tools

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Pesticides (insecticides, fungicides, herbicides, rodents, and plant growth regulators) available in ambient air, water, and soil environments, cause adverse effects on the ecosystem as well as on human health. Understanding the decomposition and oxidation mechanisms of pesticides in environmental conditions is crucial for a better assessment of their toxicology and influence on the environment and human health.

Metazachlor is a chloroacetanilide class herbicide used to control the annual grass and broad-leaved weeds for different oil seed crops and inhibits the long-chain fatty acids formation that plays a key role in cell division and expansion processes. Quinmerac is one of the auxinic herbicides that are crucial active ingredients for the post-emergence control of cleavers, speedwells, and other broad-leaved weeds in cereals, oilseed rape, and sugar beet. Pentachlorophenol (PCP) C_6HCl_5O, is widespread contaminants in the environment and has been introduced as a wood preservative in industries, disinfectant, and as pesticide.

A careful study of the reaction mechanism and kinetics of selected pesticide molecules degradation pathways initiated by HO• is therefore necessary. It will provide essential information for further assessment of ecotoxicity risks and the influence on human health. Recently, the density functional theory (DFT) approach has been successfully applied to explore the mechanism and kinetics of different pesticides degradation reactions in in environmental conditions. This talk will summarize the results obtained for metazachlor, quinmerac and pentachlorophenol.

I-18

Probing the Second Harmonic Generation Responses at Liquid-Air Interfaces

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Dynamic processes at the interface between liquids and air have attracted significant attention due to their multidisciplinary aspects going from atmospheric, environmental, and synthetic organic chemistry. For instance, the reaction time at the interfacial water region is shorter than in the bulk phase, and the reasons remain unclear.[1] Thus, a detailed characterization of this region is crucial for exploiting its full capability of applications. The first hyperpolarizability (β) is particularly reliable to probe interfaces because the uppermost non-centrosymmetric layer dominates the β responses while the bulk contributions vanish.[2] In the present work, we report the calculated interfacial Second Harmonic Generation (SHG) responses of liquid water and methanol using a multiscale approach, following recent advances in the field.[3] Aggregates of molecules were extracted from different regions and treated at the QM level of calculation. Then, several approximations of the surrounding effects were probed, and we have shown that simplified models that do not account for polarizable point charges and effective fields lack an important part of these effects and cannot distinguish the bulk and interfacial β responses.[4] Our main observations, when going from the bulk to the interface, encompass i) an effective increase of between 10 and 20% on β_{HRS} (hyper-Hayleigh Scattering) and a slight increase of its depolarization ratio, and ii) a net increase on β_{ZZZ}, the β tensor component normal to the interface and dominant in the interfacial SHG response.[4] Also, the interfacial β at the methanol interface is weakly temperature dependent.

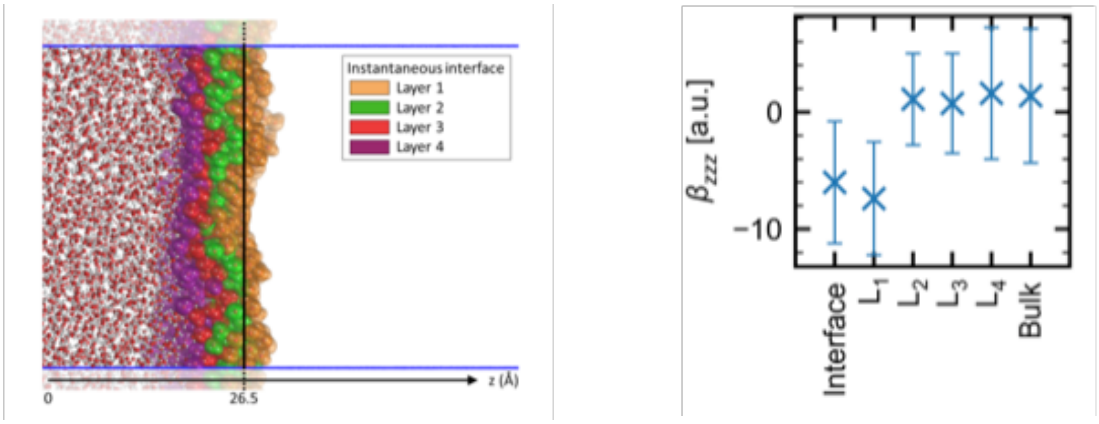

Figure 1. (left) Snapshot of an instantaneous water–vacuum interface. (right) β_{ZZZ} as a function of the molecular layer.

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I-19

Nonadiabatic dynamics in solution using linear vibronic coupling models

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In this contribution, we present a novel approach for the simulation of nonadiabatic dynamics in solution: the LVC/MM method. For this, we combined the linear vibronic coupling model (LVC) known from quantum dynamics studies[1] with electrostatic embedding quantum mechanical/molecular mechanical (QM/MM). This facilitates dynamics with multiple nonadiabatically coupled potential energy surfaces at a cost comparable to traditional force fields, enabling the study of photoinduced relaxation processes of extended systems.

The computational cost of the electronic structure is a key factor in nonadiabatic dynamics simulations with surface hopping including arbitrary couplings (SHARC),[2] since we need to compute energies, gradients, and couplings of multiple states at every time step of every trajectory. Hence, the efficiency of SHARC simulations with LVC in the gas phase[3] encouraged us to develop LVC/MM. The "glue" of the LVC/MM model—the electrostatic interaction between LVC and MM regions—is modeled using distributed multipole expansions (DMEs).[4] Each state and transition density in the diabatic basis is represented by an individual DME, which is fitted to accurately reproduce the respective electrostatic potential, rather than traditional partial charges.

We chose thioformaldehyde[5] in water as a test system. A 1 ns LVC/MM simulation uncovers the solvation shell of the S0 state with hydrogen bonds in the molecular plane towards the sulfur lone pair. We show how this solvation shell significantly affects the nonadiabatic dynamics after excitation, allowing for intersystem crossing, and how the relative motion between solute and solvent plays a decisive role in the relaxation of the solvation shell occurring within only 100 fs. The LVC/MM model allows us to study such solvent shell dynamics with sufficient statistics by enabling the simulation of thousands of trajectories propagated over multiple picoseconds. For thioformaldehyde, we simulated 9500 trajectories over 3 ps (totaling 28 ns), using potentials fitted to the CASPT2 level of theory. Our contribution highlights how LVC/MM enables access to comparably vast simulations, opening up a new avenue to study the excitedstates of extended molecular systems.

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II-1

Comparative Study of CO_2 Insertion into Pincer Supported Palladium Alkyl and Aryl Complexes

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Carbon Dioxide (CO_2) is an important synthon for organic molecule synthesis, and transition metal catalysts offer a promising approach to activate and functionalize CO_2. However, current catalysts have limited ability to produce products with C–C bonds, such as fuels. The insertion of CO_2 into metal alkyl bonds is crucial because it can lead to the formation of C–C bond-containing products.

Recently, our collaborative research associates have reported the insertion of CO_2 into palladium methyl complexes supported by ^{R}PBP pincer ligands, which contain a strongly donating central boryl donor. [1] Using the same metal complex, we have conducted a combined experimental and computational analysis, comparing the CO_2 insertion into a range of pincer-supported palladium complexes, featuring various alkyl and aryl bonds (Figure 1a).[2] Mechanistic insights obtained from DFT calculations indicate that CO_2 insertion can proceed via either an innersphere or outersphere pathway, with CO_2 interacting with the palladium metal in the former but not in the latter. Our results highlight the critical role of steric factors in determining the CO_2 insertion pathway. The observed rate acceleration of CO_2 insertion into the Pd-Ethyl bond relative to the Pd-Me bond can be rationalized by the presence of favorable interactions between ligand C-H bonds and the incipient acetate group in the rate determining TS of the former (Figure 1b). Our findings show correlation between CO_2 incorporation rates and structural characteristics of palladium alkyl and aryl complexes, relevant for catalytic reactions where CO_2 insertion is crucial.

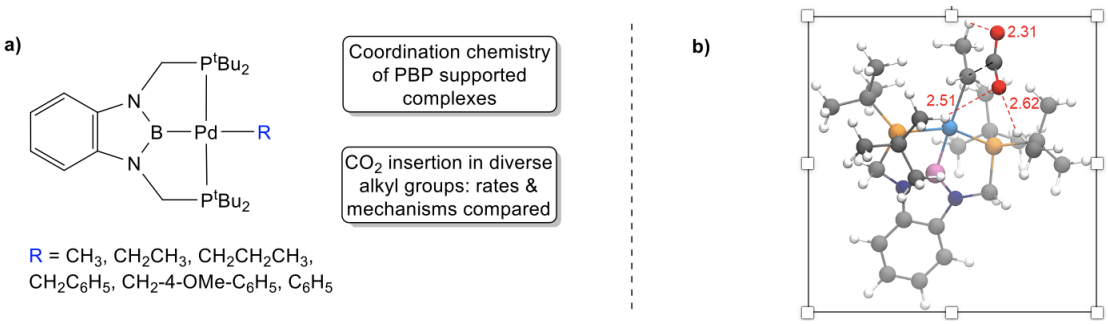

Figure 1: a) ^{tBu}PBP supported palladium complexes studied in this work, which reveal fundamental information about the novel coordination chemistry of the ^{tBu}PBP ligand and enable a comparison between the rates of CO_2 insertion as a function of the alkyl ligand.[2] **b)** Rate determining transition state for CO2 insertion into Pd-ethyl bond. Close contacts between ligand C–H bonds and the incipient acetate group are highlighted in red with distance shown in Å. The bond forming atoms are connected by a black line.

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II-2

Beyond Frontier Molecular Orbital Theory: Reactivity in Bioorthogonal Diels–Alder Cycloadditions

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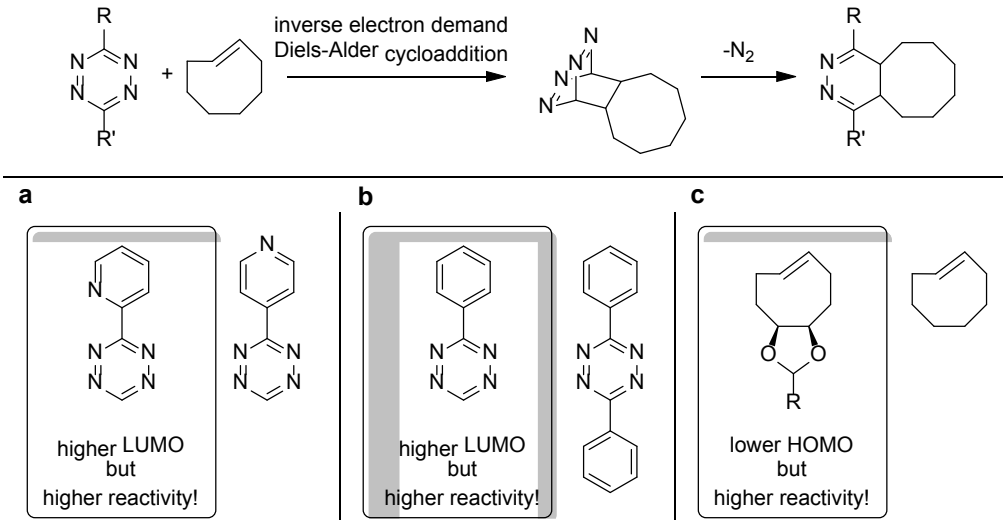
Understanding reactivity and selectivity in bioorthogonal cycloadditions is essential for improving these chemical tools. Our research focuses on cycloadditions of 1,2,4,5-tetrazines due to their high reaction rates. Typically, Frontier Molecular Orbital (FMO) theory is used to explain and predict such cycloaddition reactivity.

However, our studies show that FMO often fails to accurately describe the reactivity and selectivity of 1,2,4,5-tetrazine cycloadditions. We found that 4-Pyridyl-1,2,4,5-tetrazines, which have a lower LUMO than 2-pyridyl-1,2,4,5-tetrazine, should react faster according to FMO theory. Yet, 2-pyridyl-1,2,4,5-tetrazine shows higher reactivity (Figure **a**). Similarly, mono-substituted tetrazines react faster in Diels–Alder reactions than their disubstituted counterparts, even though they have higher LUMOs (Figure **b**). In another example, dioxolane substituted trans-cyclooctenes, despite having a lower LUMO than unsubstituted trans-cyclooctene, display greater reactivity (Figure **c**).



We use computational models, such as energy decomposition analysis, to unravel the origins of these non-FMO controlled cycloadditions. We also demonstrate how the insights gained from this process can be applied to improve bioorthogonal chemical tools.

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II-3

Developing a Predictive Model for Novel Biofuel Molecules

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The world's increasing demand for transportation fuels – road, railway, air and sea – greatly depended on derivatives of fossil fuel. This heavy reliance coupled with the limited rate of fuel production has resulted in high fuel price volatility. Economical and environmentally friendly options are required to address this problem. Bisabolane a novel biofuel molecules contains branched chain cycloalkane. The implications of branching in alkanes on reaction mechanisms differ depending on the phenomena (e.g. laminar flame speeds, ignition delay times) as reportedin several studies for mono-, di-, and tri-methylated alkanes. Because of its structural symmetry,and presence of branched alknaes, which are important components in conventional petroleum transportation fuels, present at a range of 40 – 60% in gasolin and approximately 40% in aviation fuel.[1-3] The degree of influence that alkane branching exerts on autoignition chemistry dependsstrongly on the temperature regime, which gives rise to distinct modes of chain-branching. In this work we will apply Component Centered (CC) approach and propose a surrogate biofuel moleculeto study the complex biofuel molecules Chemical kinetics of O2-addition to alkyl radicals (R), termed first O2-addition in the oxidation mechanism of alkanes, are of central importance to next-generation combustion strategies designed for operations in the low- to intermediate-temperatureregion (<1000 K). In this talk , stationary points on potential energy surfaces (PES), temperature-and pressure-dependent rate coefficients, and branching fractions of product formation from R +O2 reactions initiated by the addition of molecular oxygen (O2) to the different alkyl radicals of abranched alkane, 2,5-dimethylhexane, 2,6-dimethylheptane will be presented The stationary points were determined utilizing ab initio/DFT methods and the reaction energies coupled Rice– Ramsperger–Kassel–Marcus (RRKM)/master-equation (ME) calculations were employed to compute rate coefficients, from which branching fractions over the pressure range of 10-3 –20 atm and the temperature range of 400–900 K on different surfaces. The updated rate constants and branching ratios may also serve as general prototypes for low-temperature oxidation of branched alkanes of next-generation biofuels such as bisabolane.

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II-4

A Computational Adventure in POM Land: Where are the Electrons?

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Polyoxometalates (POMs) typically comprise group 5 and/or group 6 metals in their highest oxidation state and straddle the interface between solid-state metal oxides and oxoanions. With properties such as thermal and chemical stability, tuneable solubility and photosensitivity, coupled with the ability to undergo reversible multi-electron redox processes, POMs have found applications in a wide range of fields, e.g. catalysis, non-linear optics, energy storage, medicine and data processing. In recent years, covalent functionalisation of POMs with organic groups has emerged as a powerful tool for the modulation of their physical and electronic properties.

As part of a collaboration between the groups of Newton and Robinson, we have synthesised, investigated and characterised a range of different hybrid POMs (Figure 1), led by computational characterisation of their potential redox properties.[1-3] In this communication, we discuss aspects of these POMs, either capped or bridged, and the influence of their electronic properties on the redox properties of these photocatalysts.

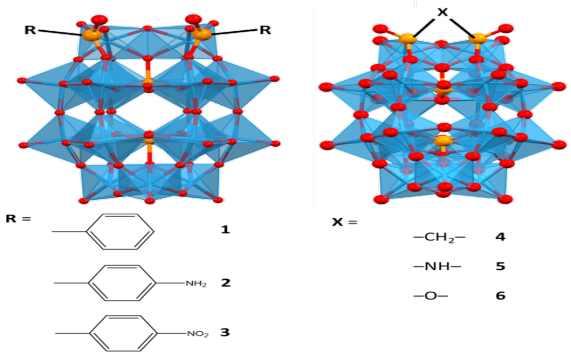

Figure 1. General structure of the POMs studied.

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II-5

Effective hamiltonian of crystal field method for periodic systems containing transition metals

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Effective Hamiltonian of Crystal Field (EHCF) is a hybrid quantum chemical method originally developed for an accurate treatment of highly correlated *d*-shells in molecular complexes of transition metals [1,2]. In the present work, we generalise the EHCF method to periodic systems containing transition metal atoms with isolated *d*-shells, either as a part of their crystal structure or as point defects. A general solution is achieved by expressing the effective resonance interactions of an isolated *d*-shell with the band structure of the crystal in terms of the Green's functions represented in the basis of local atomic orbitals [3,4]. Such representation can be obtained for perfect crystals and for periodic systems containing atomic scale defects.

Our test results for transition metal oxides (MnO, FeO, CoO, and NiO) and MgO periodic solid containing transition metal impurities demonstrate the ability of the EHCF method to accurately reproduce the spin multiplicity and spatial symmetry of the ground state [3]. For the studied materials, these results are in a good agreement with experimentally observed *d*-*d* transitions in optical spectra.

In addition, we apply the proposed method to carbodiimides and hydrocyanamides of various transition metals (Mn, Fe, Co and Ni), which, on the one hand, posses interesting magnetic properties and, on the other, are well studied experimentally [5] allowing detailed testing of theoretical predictions against experimental benchmarks.

Finally, periodic EHCF is successfully used to investigate electronic structure and magnetic properties of a series of metal-organic frameworks M-MOF-74 (M is Fe, Co or Ni), having relatively large unit-cells and, therefore, being challenging objects for computational study at the quantum level.

In conclusion, future perspectives of the EHCF and its place in the context of modern solid state quantum chemistry and physics are discussed.

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II-6

Mechanism of Sensitization of the S- and N-heteroligand Luminescent Sm^{3+} and Eu^{3+} Complexes Predicted by Theoretical and Experimental Studies

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The use of pyrrolidinedithiocarbamate (pdtc) and 1,10-phenantroline (phen) chromophores as antenna-ligands leads to better sensitization for Sm^{3+} and Pr^{3+} luminescence than that of Eu^{3+}, Tb^{3+} and Dy^{3+}. The operative mechanism, that modulates the luminescence efficiency of S- and N-heteroligand Ln(III) complexes is still not fully understood. The present study aims to highlight the energy conversion mechanism, from absorption to luminescence for two $Ln(pdtc)_3(phen)$ complexes (Ln ⍰ Sm^{3+}, Eu^{3+}) by means of spectroscopic measurements (UV-Vis, EPR, IR, PL, DRS, excitation) and quantum chemical calculations.

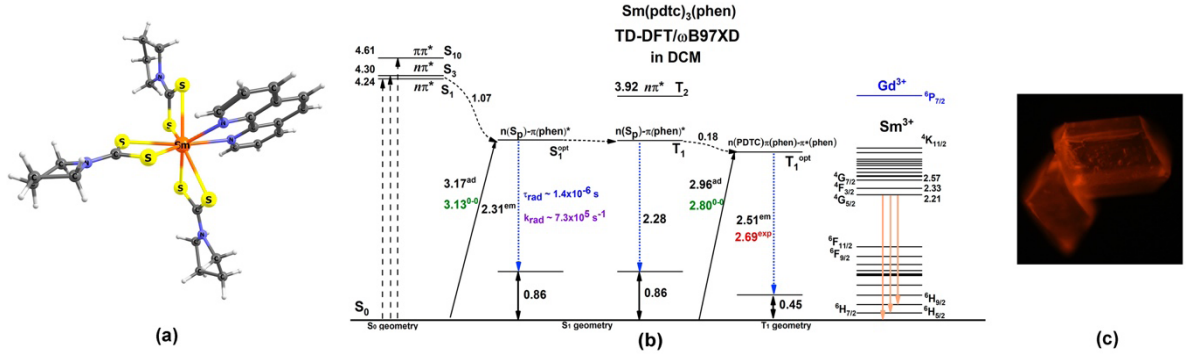

Fig. 1. Molecular structure of $Sm(pdtc)_3(phen)$ (**1**) (a), calculated Jablonski diagram of **1** in dichloromethane (b), luminescent monocrystalline sample **1** (c).

Electronic relaxation pathways within the ligand-centered excited state energy levels were reconstructed on the basis of DFT/TDDFT/ωB97xD calculations. Rates of radiative and non-radiative (internal conversion and intersystem crossing) deactivation of S_1 and T_1 states were evaluated. The theoretical framework, developed by Malta was further implemented to estimate the ligand-to-metal energy transfer rates for the Eu^{3+} complex. The software packages: Gaussian16Rev.C1, ORCA4.1.2, VASP5.4.4, MOMAP2012A and LUMPAC1.4.1 were used. The combined experimental and computational study allows to explain the role of the *pdtc* ligand in the sensitization process and to assess the UV-to-visible light converting efficiency for each of the two complexes.

Acknowledgements: The authors thank for the financial support the Bulgarian National Science Fund of Bulgarian Ministry of Education and Science, Grant КП-06-Н59/6 (2021), project (PhotoMetalMod).

II-7

A multiscale approach to coupled nuclear and electronic dynamics: quantum-stochastic Liouville equation

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Multiscale methods are based on a hierarchical partitioning of the degrees of freedom (d.o.f.) of the system, so that each set can be treated in the most computational efficient way. In the context of coupled nuclear and electronic dynamics, a multiscale approach can overcome current computational limits in fully treating complex systems at quantum mechanical level, such as biological macromolecules in explicit solvent. Based on the pioneering work of R. Kapral and G. Ciccotti [1], this presentation is intended to show a nonadiabatic theory that describes the evolution of electronic populations coupled with the dynamics of the nuclei under the basic approximations of the quantum-classical Liouville equation. The two elements of novelty that are here introduced are: i) the casting of the theory in the natural, internal coordinates, which recall chemists' description of molecular structure and dynamics; ii) the projection of the nuclear d.o.f. which can be treated as a thermal bath, leading to a quantum-stochastic Liouville equation (QSLE) [2,3]. Some tests on a simple 1D model are presented to demonstrate the main features of the method. Finally, the cis-trans photoisomerization of azobenzene (Figure 1) is shown as an example of a real system application of the QSLE.

Figure 1. A possible scheme for partitioning the coordinates to study the photoswitching properties of azobenzene with the QSLE. Here, the quantum degrees of freedom of the system (QS) are the electrons, especially those responsible for the HOMO and LUMO orbitals (for this picture, obtained at B3LYP/6-31G* level in the optimum geometry). The relevant classical internal coordinates (CS) are the rigid body roto-translations and the dihedral angle (φ) highlighted with a red arrow in the picture. All the other molecular internal degrees of freedom and the solvent coordinates (represented as a blue surface in the background) constitute the set of irrelevant bath coordinates (CB).

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II-8

Unraveling Ligand Effects on Mn-based Catalyst mediated CO_2 Reduction using DFT and AIMD Simulations

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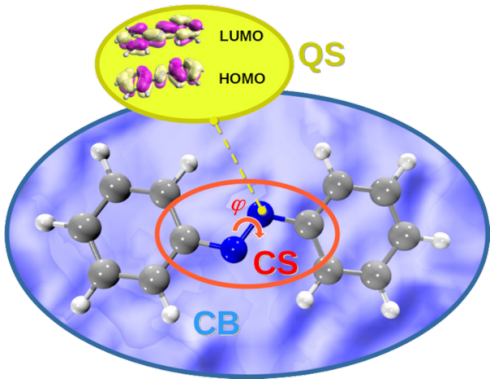
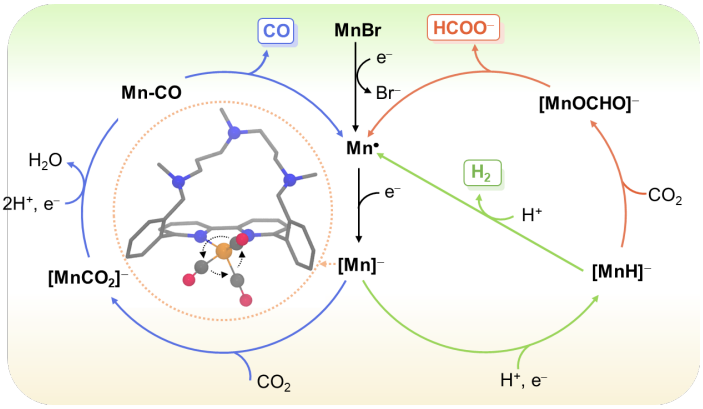
Selective reduction of CO_2 using molecular electrocatalysts is an active area of research to produce non-fossil-based chemical feedstocks and reduce greenhouse gas concentrations. However, achieving high selectivity remains challenging. In this study, [1] we use a combination of Static and Ab-initio Molecular Dynamics (AIMD) simulations to investigate the impact of ligand design on the product selectivity of a Manganese-based electrocatalyst for CO_2 reduction. In contrast to previous catalysts containing the pendant amines in the vicinity of the Br ligand,[2] here we report that locking these amines in a macrocyclic fashion at the side opposite to the Br ligand changes the product selectivity from HCOOH to H_2. AIMD



simulations of the active species revealed that free rotation of the $Mn(CO)_3$ moiety allows for the approach of the protonated amine to the reactive centre, yielding a Mn-hydride intermediate, which is the key to the formation of H_2 and HCOOH. Our DFT studies further support that the macrocyclic moiety impedes CO_2 insertion into the metal-hydride, favouring H_2 production. Our calculations also suggest that the experimentally observed minor CO product is formed when CO_2 adds to Mn on the side opposite the pendant amine before protonation. These findings provide detailed atomistic insights into the role of ligand design in modulating product selectivity in Mn-based catalysts and offer a roadmap towards developing fully selective systems.



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II-9

QM/Classical Modeling of Surface Enhanced Raman Scattering Based on Atomistic Electromagnetic Models

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Surface-enhanced Raman scattering (SERS) is a powerful sensing technique that exploits the significant enhancement of Raman scattering cross sections of target molecules when in close proximity to plasmonic nanostructured substrates. [1-2] With enhancement factors reaching values up to 10^{10} – 10^{11}, SERS has gained popularity enabling single molecule detection, [3] by addressing the limitations of classical Raman spectroscopy, which typically exhibits low scattering amplitudes.

In this contribution, we present two multiscale approaches, namely quantum mechanics/frequency-dependent fluctuating charge (QM/ωFQ) and fluctuating dipoles (QM/ωFQFμ), to model SERS spectra of molecular systems adsorbed on plasmonic nanostructures. [4] These methods employ a QM/Classical partitioning scheme, where the plasmonic substrate is treated using atomistic electromagnetic models such as ωFQ and ωFQFμ, [5,6] which are able to describe in a unique fashion and at the same level of accuracy the plasmonic properties of noble metal nanostructures and graphene-based materials.

QM/ωFQ and QM/ωFQFμ are validated through selected test cases for which computed results are compared with available experimental data.

This work has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No. 818064)

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II-10

The Role of the Triplet States in the Thermal *Z/E*-Isomerization of Arylazo-1,3,5-Trimethylpyrazole

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In this work, we computationally unravel the controversial thermal *Z/E*-isomerization of arylazo-1,3,5-trimethylpyrazole (see Figure), provide evidence for the involvement of a multistate rotational isomerization mechanism, and calculate the overall thermal half-life. Photoswitches, like arylazo-1,3,5-trimethylpyrazole, are molecules able to interconvert reversibly between two photoisomers upon light irradiation, which makes them sought after for applications, amongst others, in photopharmacology. Especially for applications, a clear understanding of the thermal isomerization mechanism to the stable isomer and the associated half-life is necessary. There are multiple different thermal isomerization mechanisms known for azobenzene derivatives.[1] Most notably: (i+ii) the in-plane inversions of one or the other aryl/heteroaryl moiety around its neighboring azo nitrogen (see angles α and α′ in the Figure) and (iii) the out-of-plane rotational mechanism around the azo-bond. However, for azobenzene a fourth mechanism (iv) involving intersystem crossing from S_0 to T_1 and back to S_0 can occur in a mechanism similar to the rotational transition mechanism.[1,2] We show that the latter mechanism not only occurs in arylazo-1,3,5-trimethylpyrazole, but also is the energetically lowest pathway dominating the overall half-life. These findings were validated by experiment and the experimental half-life is reproduced using conventional[3,4] and non-adiabatic[5] transition state theory.

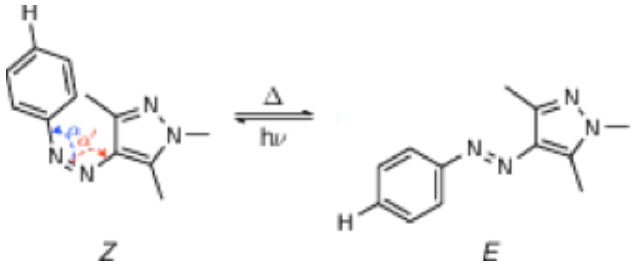

Figure: Schematic depiction of the thermal *Z/E*-isomerization of arylazo-1,3,5-trimethylpyrazole. The two angles (α, α′) involved in the inversion mechanisms are highlighted.

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II-11

Structural and NMR Properties of Ionic Liquid Systems Modelled by an Integrated MD-QM/MM Approach

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An integrated approach based on molecular dynamics (MD) simulations and combined quantum mechanics/molecular mechanics (QM/MM) models has proven to be a powerful technique for accurate predictions of electronic properties of extensive molecular systems. MD simulation protocols are employed to sample the phase space of molecular system of interest. Then, QM/MM calculations of electronic properties are performed where the central part of the system is described by an electronic structure method and the rest of the system is described by the static multipole distributions. In this presentation we will discuss our recent attempts to model structural and nuclear magnetic resonance (NMR) properties of ionic liquid (IL) systems using the MD-QM/MM scheme based on classical MD simulations and density functional theory.

In order to gain insight into ion pairing phenomenon, we have conducted classical MD simulations of the 1-decyl-3-methyl-imidazolium chloride contact ion pair as well as of free ions in water, acetonitrile, and dichloromethane [1]. The QM/MM model was used to predict NMR chemical shift for the so-called H2 proton in the imidazolium ring of the cation, which has displayed prominent sensitivity to the nature of the solvent. By comparing experimental and computational results, we were able to get quantitative information concerning chemical equilibrium between contact ion pairs and free ions established in each solvent.

We have also scrutinized the molecular mechanism behind the observed non-monotonic dependence of the ^{1}H NMR chemical shift of water on the composition of the aqueous mixtures of the 1-butyl-3-methylimidazolium chloride IL [2]. We have found that complex chemical equilibrium between various water-ionic aggregates is established in these mixtures. The experimentally observed strong dependence of the chemical shift of the H2 proton on the composition of the mixture was rationalized as well.

We will also discuss our very recent computational NMR studies of the molecular mechanism behind the increased solubility of drug molecules in aqueous solution of choline based ILs. In all cases, we will focus on the physical insight we have gained, but we will also highlight practical aspects and issues of applications of MD-QM/MM techniques for these complex materials.

Support from Lithuanian Science Council (grant no. S-MIP-22-74) is acknowledged.

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II-12

Efficient Computation of Interaction Energies of Very Large Noncovalently Bound Complexes

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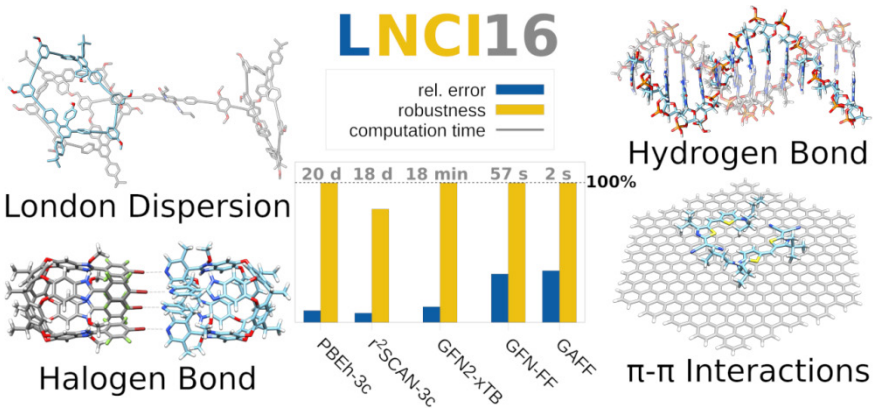
We present a new benchmark set consisting of 16 large noncovalently bound systems (LNCI16)[1] ranging from 380 up to 1988 atoms. They feature supramolecular and biochemical complexes with a great diversity in interaction motives. Gas-phase interaction energies are computed using various popular force field (FF), semi-empirical quantum mechanical (SQM), and composite density functional theory (DFT) methods. The robust and efficient ωB97X-3c[2] composite DFT method is used as reference since local coupled cluster or conventional (double) hybrid DFT methods with extended basis sets are computationally too demanding for the system sizes at hand.



The efficient ωB97X-3c method is based on the popular and accurate ωB97X-V range-separated hybrid density functional[3] together with the D4 dispersion correction[4], effective core potentials (ECP), and a new polarized valence double-zeta basis set (vDZP) which was specially optimized in molecular DFT calculations. Due to its particularly good performance for noncovalent interactions (NCIs), it provides suitable reference values for the complicated but chemically relevant systems contained in the presented benchmark set, at least for the rather approximate SQM and FF methods. The latter, however, represent the level of theory typically applied for modeling systems of this large size and hence, it is of great practical relevance to know, which of them perform well.

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II-13

On the automation of VRC-TST simulations: strategies to determine wave function guesses, exploration of black box methodologies, and application to test systems

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The accurate characterization of barrierless reactions is crucial for gaining further insights into an array of chemical phenomena in several research areas. In this work, we present an innovative methodology that improves two cornerstone theoretical kinetics statistical approaches—variable reaction coordinate transition state theory (VRC-TST) [1] and variational transition state theory (VTST)—offering a powerful platform placed at the frontier of the most refined theoretical investigations of barrierless reactions. Our VRC-TST enhancement seamlessly integrates density functional theory (DFT) with Monte Carlo (MC) sampling, resulting in a synergistic combination that optimizes reactive fluxes with computational efficiency, flexibility, and stability. We employ a black-box strategy to identify the optimal exchange-correlation functional with respect to a reference high-level potential, effectively addressing the active-space inconsistency issue commonly encountered during reduced-active-space MC sampling. Microcanonical VTST is improved by adopting distinct models to treat hindered rotations based on their corresponding frequency values along the reaction path. The effective implementation of these novel approaches significantly bolsters the predictive capabilities of our method. The performance of the strategy has been assessed by two prototypical reactions, exhibiting different multireference character: H_2S + Cl hydrogen abstraction and CH_3 + CH_3 association. The former reaction plays a significant role in atmospheric chemistry due to its relationship with acid rains, visibility reduction and climate change,[2] while the latter reaction is essential in combustion chemistry and as a termination reaction. The remarkable agreement between our predictions and the available experimental data underscores the reliability and versatility of our methodology, showcasing its potential as a powerful investigative tool for a wide range of barrierless reactions. Our method is rooted into recent advances, developments, and trends in theoretical and computational chemistry exploiting their full potential in barrierless reaction characterization. In particular, the improvement of the available TST procedures and the implementation of the whole strategy in a black-box user-friendly platform paves the way toward systematic investigations of gas-phase reaction mechanisms involving barrierless entrance channels, which play a key role in widely different areas ranging from astrochemistry to atmospheric chemistry and combustion.

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II-14

The Parameter-Free JunChS-F12 Model for Structural, Spectroscopic and Cost-Effective Thermochemical Characterization

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The coupled-cluster method including single and double excitations, augmented with perturbative triples correction [CCSD(T)], is considered the "gold standard" of quantum chemistry. Improved accuracy can be reached including complete basis set (CBS) extrapolation and core-valence (CV) correlation. Further refinements led to the development of several composite schemes, providing results with sub-chemical accuracy but troubled by a very unfavorable scaling with the size of molecular systems. To overcome this limitation, the so-called "cheap" composite schemes (ChS) [1] have been developed. It is based on frozen core (fc) CCSD(T) calculations in conjunction with a triple-zeta basis set, including the CBS and CV contributions using second-order Møller-Plesset perturbation theory (MP2). The ChS can be further improved by employing partially augmented (June) basis sets (junChS)[2] and replacing conventional CCSD(T) with the corresponding explicitly correlated (F12) approach leading to the junChS-F12 variant [3]. Thanks to its accuracy and favorable scaling, it is possible to characterize medium-sized systems with non-prohibitive computational costs. However, a limitation of the method is the lack of F12 terms in the triples contribution to CCSD(T)-F12. Recently, the new (T+) approach has been proposed[4]; It strongly reduces the basis set incompleteness error of the triple excitation contribution into CCSD(T)-F12 calculations, enforcing the exact size consistency. This new method has been introduced in the junChS-F12 model and validated in this work for the thermochemistry of molecules containing 2nd- and 3rd-row atoms. Moreover, with the (T+) approach is possible to extend the junChS-F12 to the study of larger systems, employing its reduced-cost version[5], permitting an accessible thermochemical characterization. A comprehensive benchmark showed that the junChS-F12, which employs revDSD-PBEP86-D3(BJ) geometries, is a very good compromise between accuracy and computational cost without any empirical parameter. To refine the geometrical structures, the most effective option is to add MP2-F12 CV corrections to fc-CCSD(T)-F12/jun-cc-pVTZ geometries without performing any extrapolation to the CBS limit. Within the same model, fc-CCSD(T)-F12/jun-cc-pVTZ harmonic frequencies are remarkably accurate without additional contributions.

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II-15

Deciphering the Multiple Roles of Li to Unlock the "Naphtalene Problem" in Nickel-Olefin-Catalyzed Cross-Coupling of Aryl Ethers: A Combined Theoretical and Experimental Mechanistic Study

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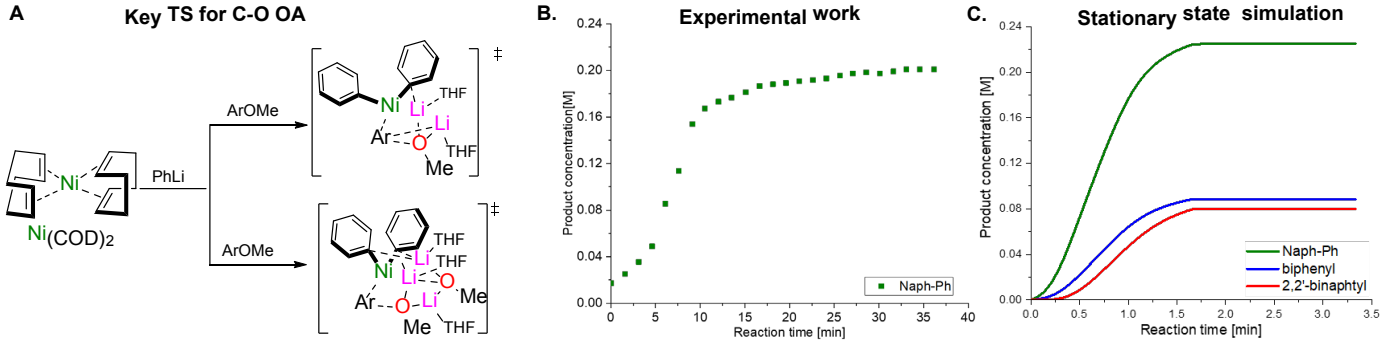
The selective cleavage of C–O bonds and subsequent functionalization by transition-metal-catalyzed cross-coupling reactions constitutes an attractive strategy for the direct valorization of widely available phenol derivates. Ethereal C–O bonds are unreactive however, and most of the well-established Pd-catalyzed cross-coupling methods are ineffective for these substrates. Ni-catalysis on the other hand has proven to be effective for many types of C–O bond cleavage in Kumada-Tamao-Corriu, Suzuki, Negishi and Murahashi cross-coupling reactions.

The conventional mechanism of cross-coupling reactions starts from a neutral Ni^0 complex has been shown to be inappropriate for aryl ethers due to the high bond dissociation enthalpy of the C_{aryl}–OMe bond. Wang and Uchiyama provided an alternative anionic pathway.[1] Nevertheless, the lack of experimental evidence, and the limited speciation of both nickelate complexes and polar organometallic aggregates temper the conclusions drawn.

More recently, Hevia's group provided an in-depth experimental mechanistic study into the cross-coupling reaction between 2-methoxynaphthalene and phenyl-lithium catalyzed by $Ni(COD)_2$.[2] This study supports the involvement of lithium nickelates, but precise details on how they facilitate the C–OMe bond cleavage remained unclear.



This has motivated a combined experimental and computational mechanistic investigation to address: i) the nature of the active lithium nickelate complexes formed (stoichiometry and ligands), ii) the crucial roles played by solvent molecules and Li^+ in enabling the reaction, iii) the promotion of unbiased aryl ethers cross-coupling under mild conditions beyond the naphthalene case.[3]

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II-16

Computational study on the Mechanism of Dual Ni(II)- and Photo-catalyzed sp^3-C-H Activation and Cross-coupling Reaction

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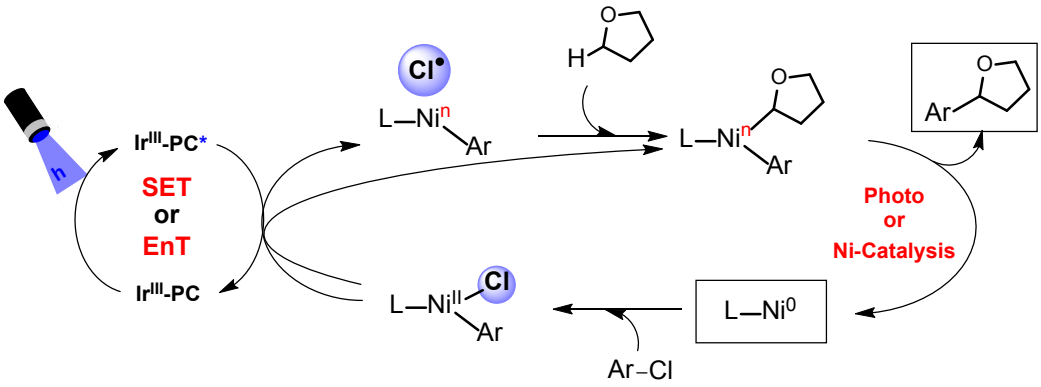
Photocatalysis has emerged as a pivotal tool for organic synthesis over the past two decades. [1] Combining photocatalysis with metal- or organo-catalysis (dual catalysis) has expanded the applicability of photocatalysis. It has helped to perform the challenging reactions, such as sp^3-C-H activation under milder reaction conditions. The mechanism of such dual-catalyzed reactions generally involves two cycles, light-driven (photocatalyzed) cycle and dark cycle facilitated by metal or organo-catalyst.[2] Recently, dual photo/Ni-catalyzed cross-coupling reactions between an aryl halide and ether have been reported (Scheme 1), which involve sp^3-C-H activation.[3] However, the mechanism of this reaction is contentious. The photocatalyzed cycle leading to Cl-radical may either involve energy transfer (EnT) or single electron transfer (SET) between excited Ir^{III} photocatalyst (PC) and Ni-complex. The C-H activation can also occur without halide-radical formation. In most of dual photocatalyzed reactions, single step of the catalytic cycle is photocatalyzed, but in this reaction the mechanism involving two photocatlyzed steps is also proposed. We studied the reaction through DFT (Density Functional Theory) methods and examined the different mechanistic proposals for the reaction.



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II-17

Strategy to Fix the Structure of Density Functional Approximations to Deal with Vibrational Properties

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Density functional theory is the most widely used method to calculate vibrational properties of medium and large sized molecules. Yet, as we have recently reported, the vast majority of the density functional approximations are unreliable for these calculations. [1] This unreliability manifests in spurious oscillations of the energy derivatives with respect to the normal modes. In turn, these can lead to errors in harmonic frequencies of tens of percent and errors in anharmonic corrections and vibrational intensities of hundreds and even thousands of percent. We show that this problem is caused by the unphysical oscillations of the local exchange-correlation energy density derivatives in real space. We further show that these local oscillations are an artifact of the underlying mathematical structure of the functionals. We developed a strategy for fixing the GGA-based density functionals and apply this strategy to the B97 functional. The resulting remedy is directly transferable to many best-performing density functionals, most notably the functionals of the ωB97 family.

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II-18

Dye-encapsulated zeolitic imidazolate framework (ZIF-71) for fluorochromic sensing, a novel theoretical insight

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Fluorchromic materials provide a photoluminescent response to an external physical or chemical stimuli, among them, Luminescent metal–organic frameworks (LMOFs) are an emerging class of these materials with high versatility and functionality [1]. In particular, Guest@MOF systems are considered as promising condidates for multimodal and ultrasensitive sensing of pressure [2,3]. Recently, LMOFs based on Rhodamine B (RhB) and Tetrapehnylethylene (TPE) incorporated in the zeolitic imidazolate framework (ZIF-71) were shown to exhibit ultra-sensitive sensing properties. In the case of mechanochromism, RhB@ZIF-71 and TPE@ZIF-71 displayed a linear relationship between the emission peak wavelength, and the applied pressure as well as emission intensity in the case of TPE@ZIF-71. However, the driving mechanisms of the fluorochromic sensing properties of Guest@MOF systems are not understood, and the theoretical background is lacking due to the complex environment of the Guest@MOF. Indeed, this environment is challenging for the available theoretical methods. In this study, we propose a computational approach relying on both Quantum calculations and classical molecular dynamics by developing an *ad hoc* force field [4]. This latter is derived from quantum calculations for the ground and excited states in the aim of addressing the effect of nanoconfinement on the optical properties of the guest fluorophore, as well as providing a theoretical understanding of the experimentally observed linear relationship between the emission spectra and the external mechanical stimuli.

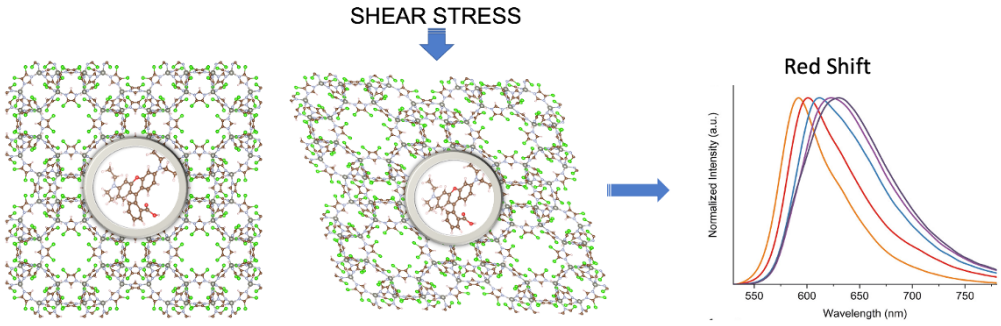

Figure 1: Schematic representation of the Mechanofluorochromic effect exhibited by RhB@ZIF-71, under shear stress the caging effect increases and the emission peak of the compound display a redshift in linear relationship with the applied stress

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II-19

DFT Simulation of Complex Reaction Networks: Aqueous speciation of Molybdenum Oxides and Formation of the Keggin anion

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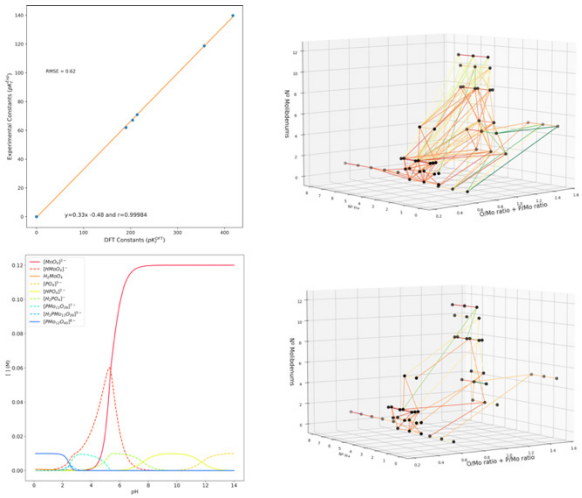
Our group introduced a new computational methodology, which we called POMSimulator,[1,2,3] to simulate the complex multi-species multi-equilibria taking place in the self-assembly processes leading to polyoxometalates. POMSimulator is an automated workflow that relies exclusively on DFT calculations, and has been successfully applied to isopolyoxometalates of Mo, W, V, Nb and Ta systems. It has been demonstrated to be in excellent agreement with experimental results, in the case of the complex speciation phase diagram for vanadates. Also, our method reproduced the significant differences in the behavior of those metal oxides in solution at different pH between the different metals. Additionally, we observed strong linear correlations between available experimental formation constants and our computed values, which were used to correct the DFT values.

To reduce the reliance of the POMSimulator on experimental formation constants, we seek to find a universal scaling method for the computed equilibrium constants of polyoxometalates. In this communication, we will discuss recent progress in this direction, and the dependence of the scaling constants on the DFT method. Also, statistical analysis of POMSimulator with massive amounts of data will be discussed. Although heteropolyoxometalates introduce more complexity, we will show how our method can be used to predict unreported formation constants for the phosphomolybdate Keggin system.



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III-1

Modeling isolated monomeric MoO_x and VO_x clusters on ZrO_2 support and their interaction with each other: A DFT+U Study

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Over consumption of fossil fuels in recent years has not only put an additional burden on the existing reserves but also raised environmental concerns [1]. One such concern is the continuous rise in the average global temperature, which is assumed to be responsible for climatic disturbances across the globe. There has been a continuous thrust in the recent years to shift to environmentally friendly and sustainable sources of energy [2,3]. Energy from biomass serves as one of the promising sustainable alternatives. The first step towards conversion of biomass to biofuels involves pyrolysis (thermal decomposition at high temperatures) to bioil (a complex mixture of several oxygenated compounds) [4]. The second step requires upgrading the bio-oil to conventional transportation fuel with improved combustion properties [5]. Hydrodeoxygenation is one of the key routes for upgrading bio-oil as it enhances the energy density of biofuels [6] by removing the oxygen containing compounds from bio-oil. Reduced MoO_x clusters dispersed on supports like ZrO_2 or TiO_2 or Al_2O_3 have proven to be excellent hydrodeoxygenation catalysts under low partial pressures of H_2 [7]. Despite significant progress, the structural aspects and the nature of catalytic sites are still elusive. In this work, we have used DFT+U calculations to investigate the structure of isolated monomeric MoO_x clusters supported on ZrO_2 (111) facet. MoO_x clusters are hypothesized to exist in a mono-oxo, di-oxo or a pero-oxo state. We have studied the formation of mono-oxo, di-oxo and pero-oxo under strictly dehydrated conditions. Our results show that the mono-oxo cluster of MoO_x moiety is the most stable as it has a lower formation energy. Our frequency calculations on the mono-oxo cluster, shown in Figure 1, reveals vibrational modes at 973 cm^{-1} and 849 cm^{-1}, which is attributed to Mo=O stretching and symmetric $O_{cluster}$–Mo–$O_{cluster}$ vibrations, respectively. Both these modes are in close agreement with previously reported experimental Raman frequencies [8]. We also perform ab initio thermodynamic calculations to examine the effect of hydroxyls on the support surface. Our findings confirm that at low partial pressure of water mono-oxo species continue to predominate over the di-oxo clusters. We also observe that adsorbing hydrogen on the support surface tends to localize the electrons on the Mo atom thereby making it active for oxygen uptake from bio-oil model compounds. In addition to studying isolated MoO_x clusters we also study the simultaneous presence of MoO_x and VO_x clusters on the support. We find that in the presence of VO_x cluster, the oxygen vacancy formation energy on MoO_x cluster reduces, suggesting a more active catalyst for the deoxygenation reaction.

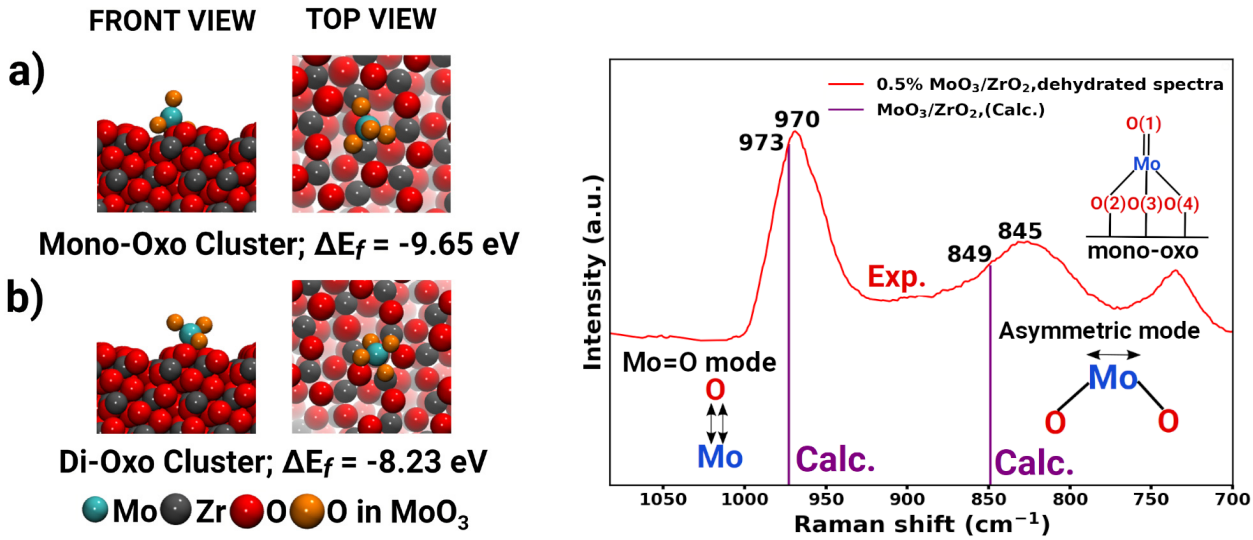

Figure 1. (i) Top and front views of optimized structure of mono-oxo and di-oxo clusters of MoO_x on ZrO_2 (ii) Vibrational modes of mono-oxo cluster. 970 and 945 cm^{-1} modes of vibration refer to experimental studies [8].

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III-2

Precision of Projector Augmented Wave Method for Non-covalent Interactions

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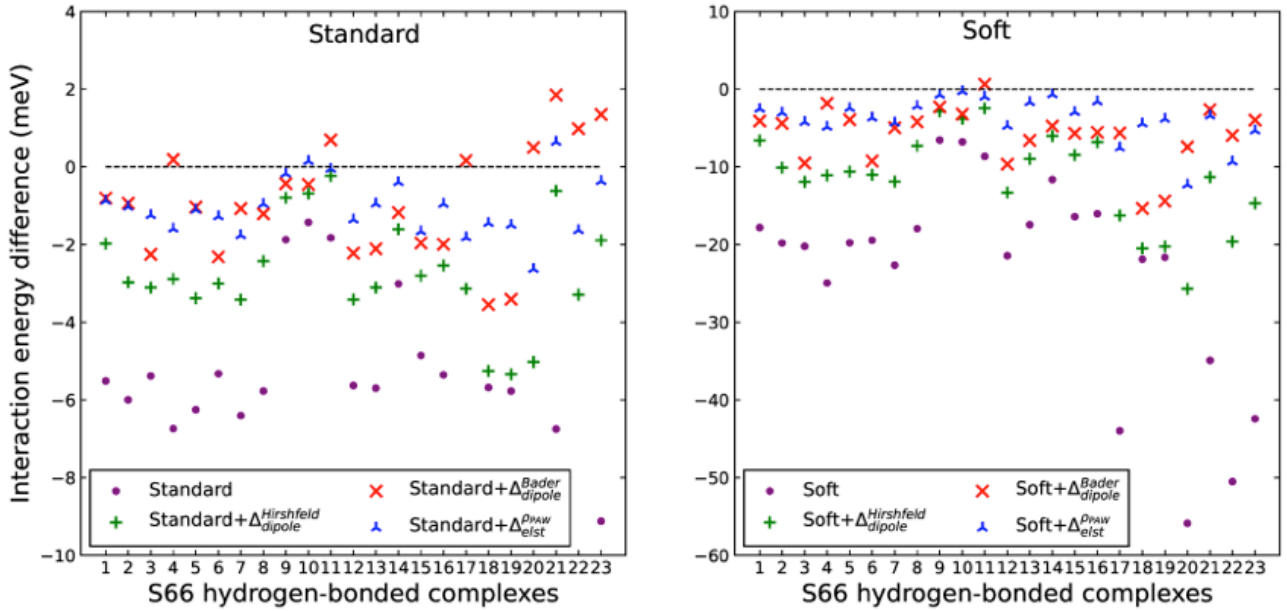
Projector augmented wave (PAW) method is a widely used scheme for an approximate treatment of the core electrons. While the PAW approximation is often used to obtain various properties of molecular solids, there is little to none analysis of how using PAW affects the precision of the results. Here, we perform such an analysis focusing on binding energies of molecular dimer as two-body energies usually dominate the binding energies of molecular solids.



We observe that the main cause of the errors is due to an inaccurate description of electron density in the investigated systems. The density error can be approximated by a set of local dipoles centered at electronegative atoms. Additionally, we propose a simple electrostatic correction to the intermolecular interaction energies which quenches the Soft potential error by up to 80\% for water dimer. For the hydrogen bonded systems for which the PAW errors are the largest, the proposed correction reduces the errors of the Soft potential to the level of Standard potential.

III-3

DFT Studies of phytyl chain in chlorophyll type molecules

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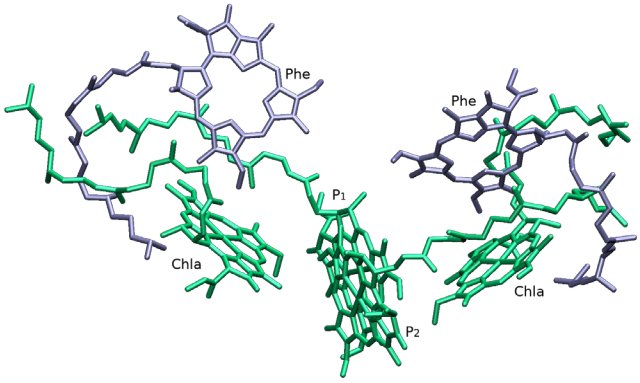
Plants contain chlorophyll-type molecules, which play a vital role in photosynthesis for several reasons. Among the numerous molecules involved, chlorophylls are particularly crucial. Photosynthesis, a well-known process, involves two distinct photosystems: Photosystem I (PSI) and Photosystem II (PSII). PSI acts as the catalyst in this reaction, utilizing light to transfer electrons from plastocyanin to ferredoxin.



This study represents the beginning of an ongoing research project. It comprises two parts: a dynamics12 component and an addition of a methanol molecule component. The dynamics aspect occurs in collaboration with experimental chemists who employ a mass spectrum to investigate on chlorophyll a. Our specific focus is to examine the behavior of the phytyl tail in the gas phase using a PM6-DH23 method. The flexibility of the phytyl chain posed challenges in achieving convergence, and we did not observe any significantly favored minima over others.

Within the same collaborative context, the second part focuses on the addition of methanol, which serves as a solvent in our coworker's electrospray. We utilized an ADFT4 (auxiliary density functional theory) method implemented in deMon2K5, employing the PBE6 (Perdew-Burke-Ernzerhof) functional, a gen-A2 auxiliary function, and a TZVP (Triple-Zeta Valence Polarization) basis to export attachment sites. Our analysis revealed the preferred site of MeO attachment on the phytyl chain. In addition, we investigate a proton migration that contributes to the stabilization of the system.

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III-4

Ab initio investigation of the effect of molecular vibrations on molecular electron transport

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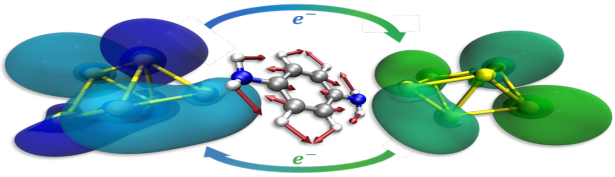
Quantum electron transport through molecules is in the interest of both experimental and theoretical studies for decades due to the potential use of molecular electronic devices in electronics and sensor applications. The most popular model platform in these investigations is the so-called Single-Molecule Junction (SMJ) which consists of two or more electrodes that connect a molecule to a circuit. The related theoretical studies are mainly based on the Landauer picture, describing the transport as the scattering of the electrons through the molecule. Within this theory, the electronic structure of the molecule is usually treated with the mean-field approximation using simple Tight-Binding models or Density Functional Theory. Although these methods are practically usable for a quantitative analysis of the conductivity properties of molecules, especially in those cases where the molecule is strongly coupled to the electrodes, the predicted molecular conductance can differ by several orders of magnitude.



In this work we investigated the effect of the molecular vibrations on the electron transport through SMJs using *ab initio* quantum chemistry to improve the description of the electronic structure. Two SMJ model systems were created from a conductor (benzene-1,4-diamine)[1] and an insulator molecule (1,4-diazabicyclo[2.2.2]octane) which are embedded between two gold clusters. The electron attached states, representing the excess electron arriving from the electrodes, were computed at the SOS-ADC(2) level and followed along the different normal modes of the isolated molecules. Analysing the change of the associated partial charge distribution facilitated the understanding of the relation between internal motions and electron transport, allowing for the identification of contributing normal modes. Even a quantity characterizing the transmission probability can be defined by quantifying the electron transport with which the conductor and insulator type systems can be distinguished from straightforward and cost-effective quantum chemical calculations.

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III-5

Investigating autoionizing Rydberg states using non-Hermitian methods

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Rydberg states are electronically excited states of atoms and molecules distinguished by an electron occupying a high-lying diffuse orbital. Their name is derived from the well-known Rydberg formula for hydrogen atoms since the behaviour of Rydberg states of other atoms and molecules mimics this equation. The Rydberg formula describes how a series of excited states converge to an ionization potential.

In this presentation we deal with Rydberg states above the first ionization potential which are not bound states but electronic resonances. They are thus associated with a finite lifetime and undergo electronic decay and are therefore said to be autoionizing. These autoionizing Rydberg states have been shown to be important in applications such as quantum information science [1], ultrafast spectroscopy [2], plasma environments [4] and radiation biology [5]. It would therefore be pertinent to take the autoionizing nature of Rydberg states into account to obtain a meaningful interpretation of these processes. However, our standard electronic structure methods are designed for bound states. Thus, to be able to describe electronic resonances, we must go beyond Hermitian quantum mechanics.

In this presentation, we will present how non-Hermitian methods in quantum chemistry can be used to describe autoionizing Rydberg states. Methods such as complex basis functions [6] and complex absorbing potentials [7] have been combined with equation of motion coupled cluster to describe Rydberg states of a series of organic molecules. This enables a computational protocol for future studies where applications involving autoionizing Rydberg states will become important.

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III-6

Interatomic and intermolecular Coulombic decay rates from equation-of-motion coupled-cluster theory with complex basis functions

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When a vacancy is created in an inner-valence orbital of a cluster of atoms or molecules, the system can undergo interatomic/intermolecular Coulombic decay (ICD)[1]: the hole is filled through a relaxation process that leads to a doubly ionized cluster with two positively charged atoms or molecules. This mechanism is allowed when the double ionization energy of the cluster is lower than the energy necessary to create a single vacancy in the valence shells. Typical ICD lifetimes are of the order of tens or hundreds of femtoseconds: it outperforms other decay pathways, like photon emission, and is competitive with nuclear dynamics, but it is slower than Auger decay.

Since they are subject to electronic decay, inner-valence ionized states are not bound states but electronic resonances[2] whose transient nature can only be described with special quantum-chemical methods. We explore the capacity of equation-of-motion coupled-cluster theory [3] combined with two methods from non-Hermitian quantum mechanics, complex basis functions [4] and Feshbach-Fano projection [5,6], to describe ICD. To this end, we compute decay rates of several dimers: Ne_2, NeAr, NeMg, and $(HF)_2$, among which the energy of the outgoing electron varies between 0.3 eV and 16 eV. We observe that both methods deliver better results when the outgoing electron is fast, whereas the characteristic R^{-6} distance dependence of the ICD width is captured much better with complex basis functions [7].

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III-7

Experimental and computational investigation of the cage effect's influence on photoinduced migration of cymantren

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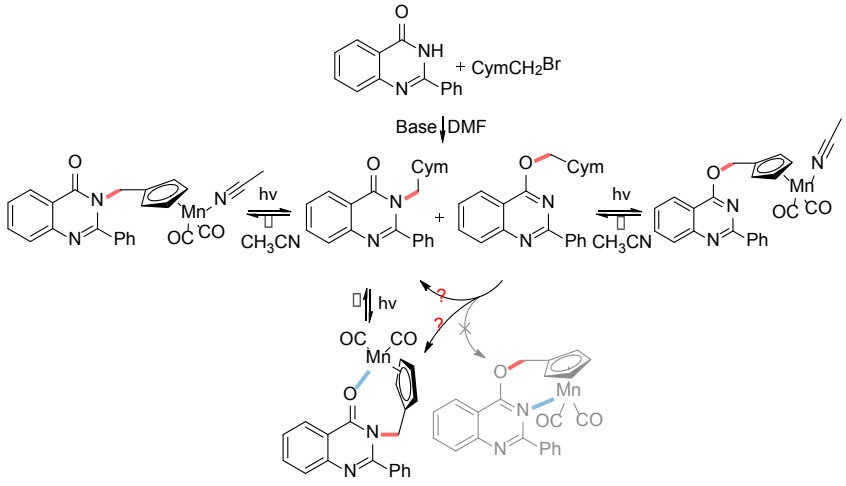
Cymantrene *modus operandi* upon excitation consists in releasing one carbonyl with the formation of a 16-electron Mn complex and then filling the emerged Mn valence with whatever is present nearby before proceeding to the thermodynamic sink [1]. We present [2] the first example of photochemical transfer of the cymantrenyl moiety where cymantrene does not release one of its carbonyls upon photoexcitation, which is proven by various spectral methods. A tandem experimental and computational investigation based on the DFT (density functional theory), allows us to explain this unexpected behavior: the rearrangement, indeed, begins with the dissociation of a single ligand, but the cage effect [3] traps CO molecule in the solvent cell allowing it to reattach after intramolecular rearrangement. We proved our hypothesis by quantum chemical modeling of the rearrangement mechanism and conducting an experiment in an ultrasonic bath.



This work was supported by the Russian Science Foundation (#22-73-10124)

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III-8

Theoretical quantification of molecular surfaces: new insights from quantum mechanics, importance and applications

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Molecular surfaces are fundamental concepts with a broad range of important applications in computational chemistry, e.g. in studying solvent effects based on implicit solvent approaches or investigating non-covalent interactions.

In theoretical chemistry, the quantification of molecular surfaces is primarily achieved through the quantum theory of Atoms In Molecules (AIM). One approach is the Bader definition, which identifies molecular surfaces as surfaces with specific electronic density [1]. This provides a direct theoretical estimation of molecular surfaces. An alternative approach is the estimation of van der Waals (vdW) radii of atoms in molecules based on the Tkatchenko-Scheffler method [2], which allows for an indirect construction of vdW surfaces.

There exist some ambiguities in defining and characterizing molecular surfaces via these methods, which have not yet been amenable to experimental verification due to lack of a precise and explicit experimental method for quantifying molecular surfaces. The recently introduced concept of thermodynamically effective molecular surfaces [3] can shed a new light on this long-standing problem via providing a thermodynamically consistent definition of the molecular surface, thereby improving on the heuristic based and parameter-heavy models that are widely employed in the current literature. In the present study, we employ this method for acquiring a precise experimental approximation of molecular surfaces for a dataset of 215 molecules. These obtained molecular surfaces, by serving as a reference to benchmark and fine-tune theoretical methods, can result in a more accurate theoretical estimation of molecular surfaces. We discuss the significance and demonstrate the usefulness of this improved estimation of molecular surfaces in a theoretical study of solvent effects using implicit solvent approaches, and in an investigation of non-bonded interactions in molecular systems.

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III-9

Role of the Chalcogen in the Reduction Mechanism of Chalcogenoxides by Thiols and Selenols

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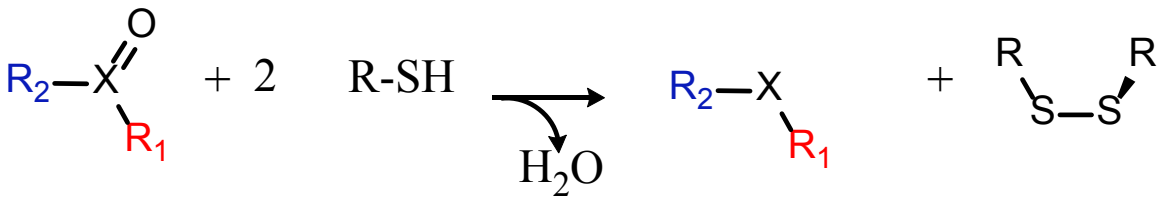
Sulfoxides and selenoxides are well-known mild oxidizing agents, capable of converting thiols to disulfides while being reduced back to sulfides and selenides. While the reaction of the latter is rather fast, occurring at room temperature, the former requires medium-high temperature to induce disulfide formation. (Scheme 1)



Scheme 1. Reaction of a general chalcogenoxide (X=S, Se) with two thiols.

Indeed, within mammals, the reduction of sulfoxides is catalyzed by the enzyme methionine sulfoxide reductase (Msr). Different classes of Msrs exist, and the most abundant in mammals is a selenoenzyme, which has got a catalytic selenocysteine residue. In this work, we employ benchmarked density functional theory (DFT) calculations to investigate the reduction mechanism of dimethyl selenoxide by two equivalents of methyl thiol. A comparison is made with the analogous reaction for dimethyl sulfoxide. Additionally, the potential of both chalcogenoxides to react with selenols, rather than thiols, to form selenyl – sulfide bridges is explored to gain insight into the role of selenocysteine in Msrs. Particular attention is devoted to the steps which are common to the molecular and the enzymatic mechanism, i.e., those leading to key sulfurane and selenurane intermediates. The Activation Strain Model of chemical reactivity is then employed as a chemically intuitive tool to pinpoint the factors which control the reactivity of the investigated systems, focusing on the chalcogen role of both the chalcogenoxide and the chalcogenol, thus providing a comprehensive picture of the reaction.[1]

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III-10

Radical scavenging potential of ginkgolides and bilobalide: insight from molecular modeling

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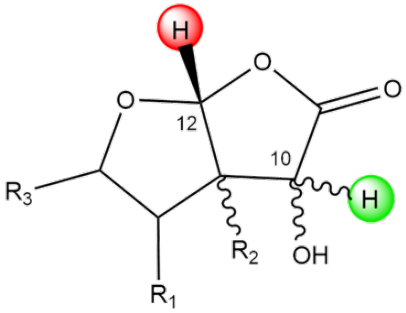
Ginkgolides are a family of C20 terpenic trilactones present in the leaves and root bark of *Ginkgo biloba*[1], whose extracts have been reported to possess radical scavenging activity towards superoxide, hydroperoxyl and hydroxyl radicals. However, it is not clear which components of the extracts are responsible for this activity [2], as mixtures of different ginkgolides, bilobalide and flavonoids are present. Ginkgolides and bilobalide are the peculiar constituents of *G. biloba*; they possess more than one hydroxyl group, but, unlike polyphenols, their structures are completely saturated, and this results in completely different reactivity profiles. The reactive oxygen species (ROS) scavenging capacity of five ginkgolides and bilobalide are investigated *in silico* (level of theory: (SMD)-M06-2X/6-311+G(d,p)//M06-2X/6-31G(d)). The high reactivity toward alkoxyl radicals via hydrogen-atom transfer (HAT) is assessed [3]; importantly, the scavenging of peroxyl radicals is also possible from a peculiar site, here labelled C10 both for ginkgolides and bilobalide. The energetics is described in detail, and the analysis discloses that the studied compounds are powerful scavengers, with thermodynamic and kinetic properties, similar to those of trolox and melatonin [4], and that, in addition, they display selectivity for peroxyl radicals. Finally, the comparison between ginkgolides and bilobalide leads to interesting aspects to establish general structure-reactivity relationships, highlighting the chemical scaffold of the sites associated to particularly favored (green H) and disfavored (red H) HAT reactions.



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III-11

Effect of Phosphorus and Nitrogen Heteroatoms on Pentahapto Coordination of Diazaphosphole Ligands in Binuclear Ruthenium and Iron Carbonyl Derivatives

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The significant discovery of ferrocene in 1951, which featured a new sandwich structure with an iron atom sandwiched between two planar cyclopentadienyl rings, showed for the first time that planar carbocyclic rings can serve as ligands in transition metal complexes in which all of the ring carbon atoms were within bonding distance of the central metal atom.[1,2] A question of interest is the extent to which some of the carbon atoms in the cyclopentadienyl ring could be replaced by heteroatoms and still maintain the pentahapto mode of bonding to transition metals.

Figure 1. The first and the second lowest energy $(CNPCN)_2Ru_2(CO)_4$ singlet structures.

Density functional theory has been used to examine the structures and energies of the $(Me_2C_2N_2P)_2Ru_2(CO)_n$ (n = 4, 3) complexes of the four isomeric diazaphospholyl ligands. One or both diazaphospholyl rings typically bridge a central Ru-Ru bond through Ru-N and/or Ru-P bonds in these systems' low-energy structures without the assistance of the other three ring atoms. There are a few higher energy structures in these systems that either have bridging pentahapto η^5,η^1-$Me_2C_2N_2P$ ligands or terminal pentahapto η^5-$Me_2C_2N_2P$ ligands that are connected to one ruthenium atom through a P→Ru or N→Ru dative bond and to the other ruthenium atom. Other triplet and even quintet structures with energies comparable to those of the low-energy ruthenium structures greatly complicate the potential surfaces of the related iron systems $(Me_2C_2N_2P)_2Fe_2(CO)_n$ (n = 4, 3). This is due to iron complexes having weaker ligand field strengths than their ruthenium equivalents.

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III-12

Dynamics and Microsolvation in a DNA-Protein Photo-Crosslinking Model System

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A molecular description of the interplay between nucleic acids and proteins is vital to understand the most basic processes of life, from DNA replication to protein expression and synthesis. Isolation of transient DNA-protein complexes in their biological conformation is a challenging task:
a promising technique for this goal is to induce in vivo DNA-protein crosslinking by femtosecond-stimulated UV laser pulses.[1] The photo-addiction of phenylalanine to thymine results an exemplificatory reaction of such a class of crosslinking and the photocyclization of 5-benzyluracil (5BU) to 1,2-indaneuracil has been proposed as a model reaction for studying the mechanism of DNA-protein photo-crosslinking.[2]

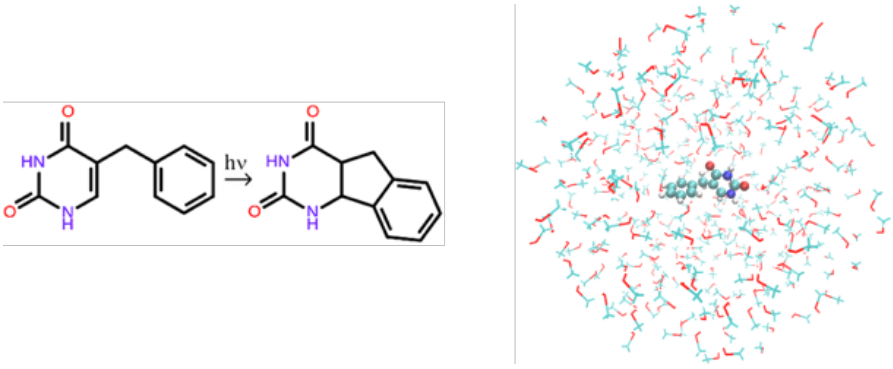

Fig.1 The photocyclization of 5BU (left) and A snapshot from the AIMD of 5BU in methanol (right).

In this context, we present a combined theoretical and computational study of the ground-state conformational equilibrium and the resulting photophysics of 5BU in methanol solution at room temperature,[3] exploiting the framework of the density functional theory (DFT) and its time-dependent version (TD-DFT)[4] combined with ab initio molecular dynamics (AIMD) simulations. For this aim, we collected a ground-state AIMD via ADMP[5] method, using the hybrid QM/MM ONIOM[6] partition scheme and non-periodic boundary conditions:[7] the solute, treated at DFT level, was embedded in a cluster of explicit MM solvent molecules, covering the first four solvation shells, to accurately reproduce the physical behaviour of the solvent. We computed the UV-Vis absorption spectra with a good agreement with experiments[8] and we found out that the first two excited states are the ones responsible for the absorption preceding the photoreaction. Additionally, from the atomistic simulations we unveil the brightness of such electronic transitions is strongly influenced by the accessible conformations for the 5BU at room temperature and the microsolvation of its heteroatoms (oxygen and nitrogen atoms). These results were not predicted

by previous works (using few representative structures)[9] and they suggest a dependence of DNA-protein photo-crosslinking on the surrounding environment, as well as the importance of MD and explicit solvation methods to model the photophysics of this model system.

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III-13

Quantum Mechanical Investigation on the Covalent Binding of Fullerene Derivatives to Glutathione for the Assessment of Potential Toxicity

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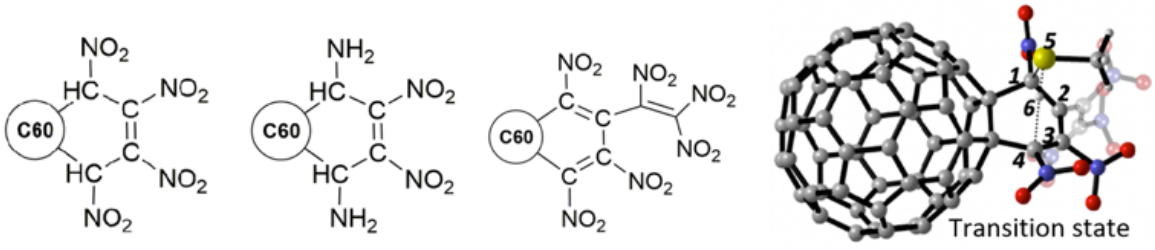
Fullerene derivatives (FDs) belong to the new family of nano-sized organic compounds used in various application in material science, biomedical applications as well as medicine. However, studies have shown evidence of toxicity to living organisms and potentially negative impact on environmental ecosystem. Since glutathione (GSH) reactivity is responsible for the detoxification, the depletion of GSH concentration is an indication of toxicity [1].

In this study, irreversible covalent bond formation (1,2 or 1,4-addition reaction) between GSH and various fullerene derivatives [2] having Michael acceptors were explored with DFT calculations to provide insights into the details of the reaction mechanism and to predict the potential toxicity. Methyl thiol was used as to represent GSH. Geometry optimizations were performed at the M06-2X/6-31+G(d,p)//M06-2X/6-31+G(d,p) level using PCM solvation model in water. Among several fullerene derivatives, the ones bearing strong electron-withdrawing groups (shown below) were found to exhibit small energy barrier for forward reaction but large barrier for the reverse reaction. Thus, such FDs are expected to decrease GSH concentration, through irreversible binding. Our results will assist the assessment of molecular initiating event leading to toxicity.



Acknowledgments: Authors thank the Scientific and Technological Research Council of Turkey (TÜBITAK; Grant Number 119N567) and the Slovenian Ministry of Higher Education, Science and Technology (ARRS Grant Number P1-017). Computing resources used in this work were partially provided by TÜBİTAK High Performance and Grid Computing Center-TRUBA resources.

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III-14

Accurate Prediction of Acidity Constants with an ONIOM Embedded Cluster RISM Approach

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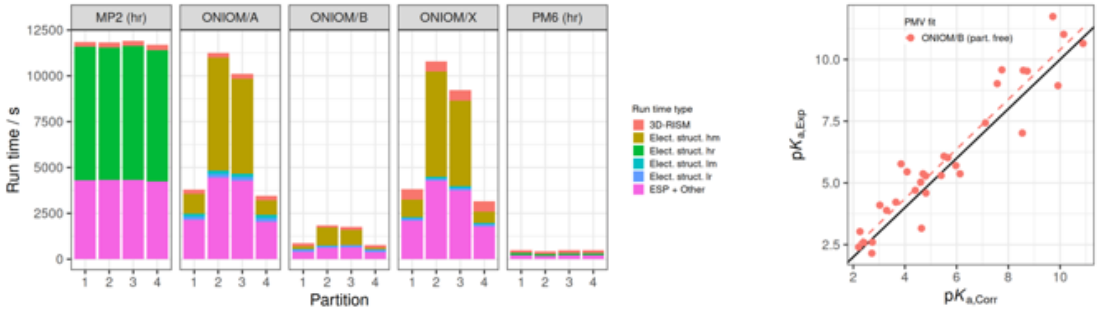
The accurate prediction of physicochemical properties such as acidity constants (pK_a) plays a decisive role for, e.g., modeling protein function or in the development of drug-like molecules. As cellular environments show a variety of different pH values, the pK_a of a titratable residue or drug therefore heavily influences the mode and strength with which it may bind to its target. Our previous strategy for predicting pK_a values for small molecules focused on modeling the compounds' thermodynamics in an aqueous environment by means of our "embedded cluster RISM" (EC-RISM) solvation model and first-principles quantum mechanical (QM) calculations.[1] However, the size of most biomolecular systems prevents the application of these QM methods and, thus, the accurate and granular modelling of the solvent environment with EC-RISM. Since the first suggestion by Warshel and Levitt[2] multiscale methods have emerged as an effective tool to model large-scale chemical processes in various environments, thus offering a route to expand the range of system sizes that can be modeled via EC-RISM theory.



Here, we present a novel multiscale solvation model which integrates a subtractive ONIOM(QM:SQM)[3] description of the solute into the EC-RISM formalism, combining established high-level QM methodology with EMPIRE[4] for the low-level semiempirical (SQM) component. We show how the set of equations used within this model can be derived, employing similar approximations as in the ONIOM-PCM solvation model.[5] Extending previous schemes,[1] we develop an empirical correction to the solute's Gibbs energy, which is free of any ONIOM partitioning error. The resulting model is then validated for the SAMPL6 pK_a challenge dataset[1,6] and additionally for biomolecular systems. Our promising results show that the novel ONIOM-EC-RISM approach ranks equal in prediction quality with our previous full-QM EC-RISM methodology, while simultaneously drastically reducing the required computational cost.

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III-15

The Accuracy Limit of Chemical Shift Predictions for Species in Aqueous Solution

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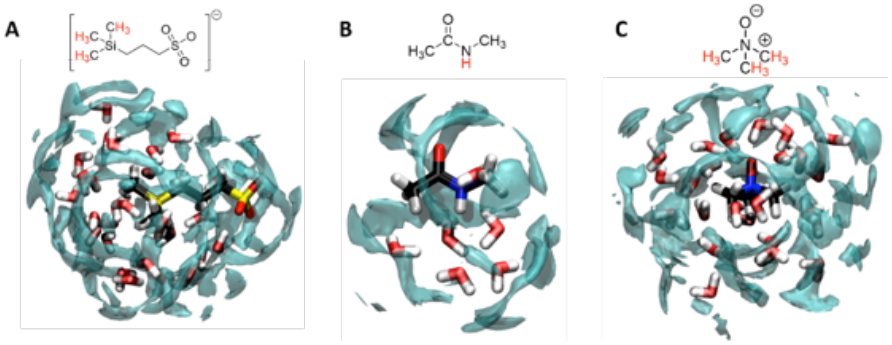
Nuclear magnetic resonance (NMR) spectroscopy is one of the main analytical techniques to investigate chemical systems. In addition to experiments, computational methods have been employed to calculate NMR parameters and gain insights on an atomistic level.[1] In this approach, accurate computational methods to predict NMR parameters regardless of the experimental conditions are a necessity. However, reaching quantitative agreement with experiments is still a challenging task even at ambient conditions due to the high structural sensitivity of NMR oberservables, especially with respect to the accurate description of the solvent influence.[2]

Here we show the first example of joining state-of-the-art computational methodologies, *ab initio* molecular dynamics simulations (AIMD) for generating microsolvated structural ensembles and "embedded cluster reference interaction site model" (EC-RISM[3]) calculations for predicting accurate NMR response parameters for species in aqueous solution, extending a previous approach for electron paramagnetic resonance (EPR) parameters.[4] Applied to the reference compound trimethylsilylpropanesulfonate (DSS) and target molecules *N*-methylacetamide (NMA) and trimethylamine *N*-oxide (TMAO), we demonstrate that a hybrid solvent system, consisting of a limited number of explicit water molecules in an EC-RISM background, achieves quantitative accuracy for chemical shifts and is considerably more efficient than previous approaches.[5]



Using the same hybrid solvent system in classical force field molecular dynamics simulations (FFMD) reveals that the general approach to hybrid solvent systems is transferable. However, inaccuracies in the predicted NMR parameters from FFMD-generated ensembles can be traced back to the inaccurate modelling of hydrogen bonds as well as intramolecular bond lengths.

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III-16

Localization and Decomposition of Free Energies in Solution

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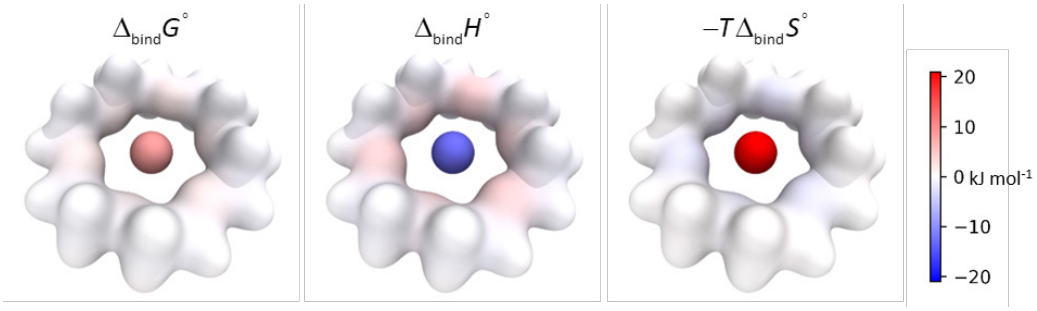
The Gibbs free energy is the relevant thermodynamic quantity to understand the direction and outcomes of chemical reactions or biophysical processes. It is directly associated with binding constants for e.g., host-guest and protein-ligand complexes. Thus, several experimental and computational methods are established to determine binding free energies. However, interpreting these macroscopic quantities can be especially challenging, for instance when the Gibbs energy is relatively small due to underlying counteracting processes.[1]

To get a better insight into the reaction thermodynamics we here present approaches to decompose and localize free energy contributions using classical and quantum mechanical methods. The three-dimensional reference interaction site model (3D RISM) is used to calculate local solvation free energies that can be mapped onto individual molecular sites.[2,3] Local energetic components are obtained using a force field approach, while local vibrational entropy contributions can be calculated via normal mode analysis or density of states integration.[4,5]



With these novel approaches we can combine both the decomposition and localization aspects, as atom-wise contributions are not only calculated for the binding free energy but also for its thermodynamic components. These atom-local values can be used to identify “hot spots” in terms of reaction sites or protein regions for e.g., ligand binding.[4] Furthermore, major energetic and entropic contributions to the driving force can be identified. Exemplary applications include crown ether complexes and solvent-controlled supramolecular cage formation.

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III-17

Characterization of Exciton and Charge-Transfer Excited States in Conformationally Restricted Arylene Cages by Spin-Component scaled ADC(2) methods

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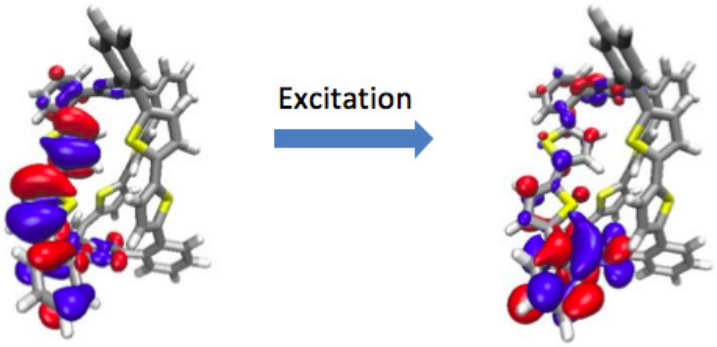
In this study, we model the electronic properties of two newly developed triple-stranded cage architectures that consist of bithiophene units and phenyl or triazine caps on the top and bottom of the cage.[1] These systems show different photochemical behaviour depending on the cap type, attributed to the presence of low-lying charge transfer (CT) excitations in the triazine variant.[1]

The SOS-ADC(2) electronic structure method, which represents a more accurate, yet cost- effective alternative to mean-field models,[2] is applied to the analysis of excited states, natural transition orbitals (NTOs), spectra, and charge transfer character to characterize the nature of excitations in the cage systems as well as in their monomers. The methods are validated against high-level ab initio results for the isolated subunits.

The results show that the low-energy vertical excitations of the phenyl cage are local excitations on the bithiophene and phenyl assemblies, with some minor delocalization on the bithiophene groups, while those of the triazine cage are localized on the bithiophene and triazine units and exhibit a significant charge transfer character between the two. This indicates that the CT natureof such an excited cage structure can be identified already at the equilibrium geometry If appropriate electronic structure methods and tools are applied.



Charge Transfer of the Triazine-Capped Thiophene Cage

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III-18

Computing RedOx Properties in Solution

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Solvation effects have a significant impact on chemical reactions, and many molecular properties are influenced by the choice of solvent. However, precise quantum chemistry (QM) calculations are most often done either in vacuum neglecting the role of the solvent or using continuum solvent model ignoring its molecular nature. We propose a new method coupling a quantum description of the solute using a selected configuration interaction (SCI) method with a classical grand-canonical treatment of the solvent using molecular density functional theory (MDFT).

We will study strongly correlated or open-shell molecules that require an accurate description of electronic structure, which can be achieved by the SCI method. Indeed, for a given orbital basis set, the SCI obtains a near exact description of the electronic correlation. Moreover, only the major determinants of the wave function are selected to compute the energy, and the remaining ones are treated as a perturbation. Thereby, this method reduces the numerical cost of the calculations while maintaining a very accurate description of the solute electronic structure.

On the other hand, in MDFT the solvent molecules are treated as rigid molecules represented by a density field that depends on both position and orientation. To account for the interaction experienced by the solvent due to the solute, the solute is represented by an external potential, which is treated as a perturbation. There exists a functional of the solvent density that reaches its minimum for the equilibrium density. At its minimum, the functional equals the solvation free energy (SFE). Thus, MDFT is particularly suitable for capturing solvent effects, as both the SFE and solvent structure can be calculated through numerically efficient functional minimization.

To assess our framework, we studied a water molecule solvated in water. This system is interesting because the polarization in the solute is the most challenging property for the method. We observed that the results are not yet fully quantitative compared to experimental data, but the most important features are qualitatively captured. Nevertheless, it is crucial to develop a better method to describe the repulsive solute-solvent interactions in order to investigate strong polarized systems.

III-19

Developing Theoretical Spectroscopy Protocols that are able to Tackle the Spectroscopic Response of Photoluminescence Materials with Extraordinary Properties

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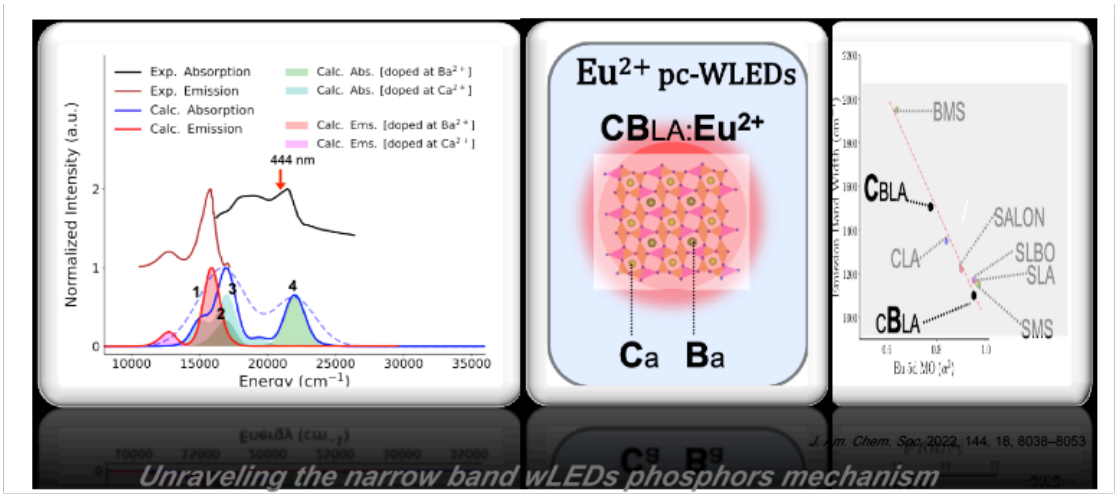
With the aim to uniquely correlate excited state dynamics spectroscopic properties to electronic structure and geometric properties of target phosphor and chiral photoluminescent materials, we employ in house developed theoretical spectroscopy protocols in an effort to evaluate unique spectroscopic signatures. This requires to use methods and protocols that do not belong in the standard arsenal of quantum chemistry. Over the last years we have developed numerous wavefunction as well as TDDFT based methods and protocols that are able to access a large variety of valence and core excited states in classes of chemical systems. Recently absorption (ABS), photoluminescent (PL) spectroscopy protocols, their circularly polarized counterparts (ECD, CPL), as well as MCD have been developed in the framework of excited state dynamics (ESD). This provides access to absorption and photoluminescent chemical problems that are dominated by vibronic and spin-vibronic coupling effects. The talk will provide an overview of all the above methods and protocols and will explore their abilities in representative examples with emphasis to next generation narrow band wLED phosphors.[1]



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IV-1

Theoretical assessment of the complexation ability of metal cations (mono-, di, and trivalent) to cucurbiturils

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Supramolecular chemistry is a field of enormous potential finding application in both scientific research and industry. A great variety of cavitands have been recognized and extensively studied, among which are cyclodextrins, calixarenes, crown-ethers, and the promising entrant to this class, the cucurbituril family. Due to their broad applications as drug delivery carriers, biological and chemical sensors, light-emitting materials, bioimaging agents, etc., and their high affinity for various guest molecules, cucurbiturils have attracted much attention recently. However, there is no systematic study on the key factors controlling the processes of metal coordination to these systems and not much is known about their metal-binding properties. Therefore, DFT molecular modeling has been employed in order to assess the complexation ability of mono- (Na^+), di- (Mg^{2+}) and some trivalent (La^{3+}, Lu^{3+}) metal cations to cucurbit[n]urils in the computational study presented herein. The thermodynamic descriptors (Gibbs energies in the gas phase and in a water medium) of the modeled reactions have been estimated and help evaluate the major determinants shaping the processes of complexation. The yielded results shed light on the host–guest recognition mechanism and disclose significant factors affecting the metal binding processes. [1,2]

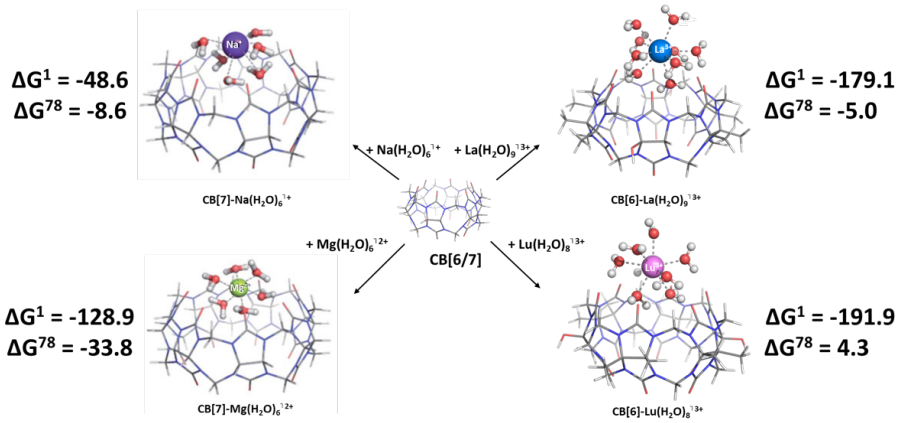

Figure 1. M062X/6-31G(d,p) optimized structures of CB[6/7]–M^{n+} complexes in the gas phase. Calculated Gibbs energies for CB[6/7]–M^{n+} complex formation in the gas phase, ΔG^1, and in aqueous medium, ΔG^{78}, in kcal mol^{-1}.

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IV-2

Computational Investigation of the 11*H*-Indeno[1,2-*b*]quinoxalin-11-one Oxime and Tryptanthrin-6-oxime isomerization

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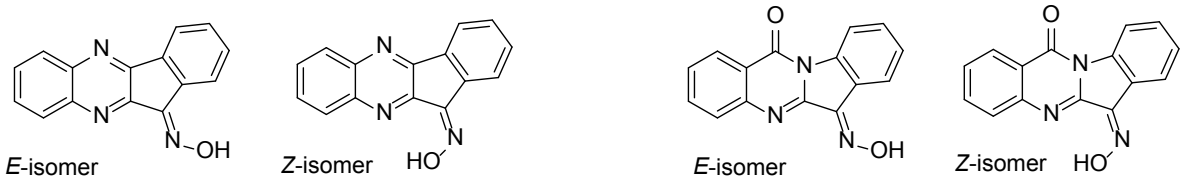
11*H*-Indeno[1,2-*b*]quinoxalin-11-one oxime (**IQ-1**) and tryptanthrin-6-oxime (**Trp-Ox**) can be considered as biologically active compounds. Despite a wide range of potential therapeutic activity, the stereochemistry of the oxime C=N double bond in **IQ-1** and **Trp-Ox** is still unknown; in some works, they were assigned as individual *Z*- or *E*-isomers, or considered as a mixture of dynamically interconverting isomers [1]. Using the five computational protocols known for their good accuracy in predicting ^{1}H and ^{13}C chemical shifts for organic compounds [2, 3], isotropic magnetic shielding constants for *E*- and *Z*-isomers of **IQ-1** and **Trp-Ox** were calculated, and the obtained values were converted to NMR chemical shifts in DMSO using the corresponding slope and intercept coefficients. A much better calculation–experiment correlations were observed for *E*-isomers of **IQ-1** and **Trp-Ox** for all computational models used. Therefore, a dominating isomer in solution of **IQ-1** as well as the only detected isomer of **Trp-Ox** should be identified as *E*-isomers.



The isomeric (*E*- and *Z*-) 11*H*-Indeno[1,2-*b*]quinoxalin-11-one oxime (IQ-1) and tryptanthrin-6-oxime (Trp-Ox).

DFT calculations were carried out for thermodynamic stability *E*- and *Z*-isomers of **IQ-1** and **Trp-Ox** (B3LYP/6-31+G(d), CPCM (DMSO)) and the transition state for *E/Z*-isomerization (NEB-CI). For both oximes, the *E*-isomer has a thermodynamically more stable "out" conformer, which is obviously explained by a steric repulsion between the hydrogen atoms of the oxime group and the heterocycle in the "in" conformers. *Z*-isomers of **IQ-1** and **Trp-Ox** are more stable in the form of "in"-conformers, probably due to the formation of an intramolecular hydrogen bond OH---N. The imaginary frequency for both transition states **IQ-1** and **Trp-Ox** corresponds to the in-plane inversion of the oxime nitrogen atom, i.e., the isomerization occurs without rotation around the C=N bond and is not accompanied by breaking of the bond. In this regard, the geometric structure of the found transition states is characterized by an approximately linear arrangement of the C=N–O atomic group. At room temperature in DMSO the interconversion of the isomers is extremely unlikely.

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IV-3

Key Factors Governing the Catalytic Activity of Cobalt and Iron Chalcogenide Clusters Coordinated by Carbonyl Ligands in Redox Reactions: Water Splitting and CO_2 Reduction

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Transition metal chalcogenide complexes $M_2X_2(CO)_4$, where M=Co, Fe and X=S, Se, are capable to redistribute electron density upon electron attachment [1,2]. Cobalt centres proved to be efficient in activating proton transfer to substrates [3]. Our density functional calculations reveal that the protons, attached to a chalcogenide centre (S, Se), can shift their position upon one-electron reduction and form bonds with the cobalt centres. In the $Co_2Se_2(CO)_4$ complexes, three sites lying close by energy are distinguished for hydrogen binding, whereas in $Co_2S_2(CO)_4$ two sites with larger energy gap are found. The reaction of CO_2 reduction requires multiple proton-electron transfers. For example, to produce methanol, the reduction involves six proton-electron couples. The reduction to either CO or formic acid (HCOOH) is a two-electron process: $CO_2 + 2H^+ + 2e^- \text{ Þ } CO + H_2O$; respectively $CO_2 + 2H^+ + 2e^- \text{ Þ } HCOOH$. The first step of water splitting is a dissociative adsorption of water, $H_2O \text{ Þ } H^+ + OH^-$, and it can provide protons, needed for other redox reactions, including CO_2 reduction. Another feature of the cobalt and iron selenide and sulphide carbonyl complexes is the availability of favourable light-absorption bands, which allow photo-excitation. These bands lie in the visible part of the spectrum for the iron-containing complexes, and in the near IR part for the cobalt-containing complexes.

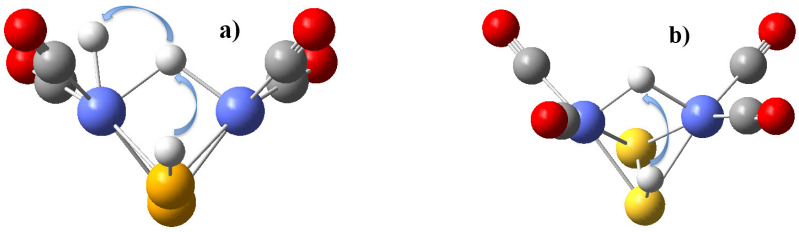

Figure 1. a) The three distinct positions of hydrogen in $Co_2Se_2(CO)_4$. b) The two distinct positions of hydrogen in $Co_2S_2(CO)_4$.

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IV-4

Understanding Electronic Properties of Pt(II) Complexes via ^{195}Pt NMR Chemical Shifts

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Nuclear Magnetic Resonance (NMR) is a powerful spectroscopic technique to determine the structure of transition-metal complexes. In addition to structural information, NMR also offers insights into the electronic structure of these complexes. The chemical shift is, in fact, directly linked to the frontier molecular orbitals and thus to reactivity.[1,2] Platinum complexes containingdiimine ancillary ligands are promising candidates for C-H bonding activation under direct oxidative conditions, leading to the production of valuable hydrocarbons.[3] Varying the substituents of the ancillary ligand directly influences the local environment of the Pt nucleus, which is evident from the broad range of ^{195}Pt NMR chemical shifts observed. Hence, a molecularapproach to the ^{195}Pt NMR chemical shift can help in rationalizing the observed NMR signatures and to establish correlations with descriptors such as the empirical Hammett's parameters.

In this study, we employ a computational protocol for modelling and analyzing the ^{195}Pt NMR chemical shifts in an extensive series of Pt(II) complexes bonded to diimine ancillary ligands (Figure 1). Our aim is to gain a deep understanding of how the ligands and other descriptors influence the NMR signature of the complexes. The modelling of structural parameters and ^{195}PtNMR chemical shifts was performed at the relativistic 2c-ZORA-PBE0/TZ2P level of theory, including the COSMO model for solvation in CH_2Cl_2. Our results confirm a linear correlation between the Hammett's parameters and the ^{195}Pt NMR chemical shift values. The NaturalChemical Shift (NCS) analysis, which provides the chemical shift tensor in terms of natural orbitals,[4] is used to identify the most important shielding contributions. These findings demonstrate the potential of ^{195}Pt NMR as a descriptor of stability and reactivity, enabling the exploration of new complexes and materials.

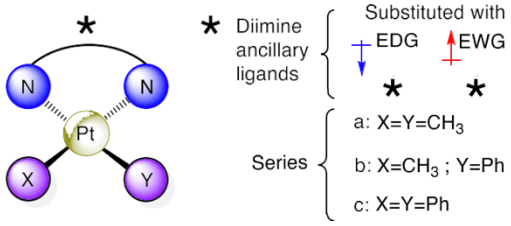

Figure 1. Series of selected Pt(II) complexes. Electron-donating (EDG) or -withdrawing groups (EWG).

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IV-5

Bandgap Engineering of Doped Oxide Solar Cell in Silico

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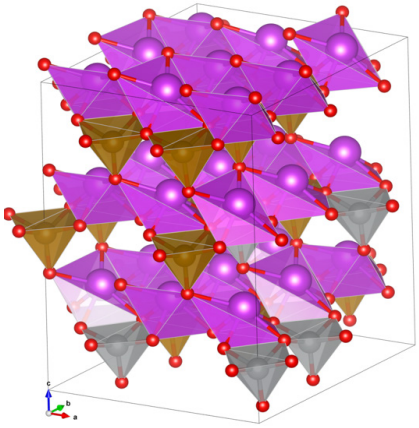
Photovoltaic is one of the widely accessible renewable energies with low infrastructures cost. The thin film halide perovskite solar cell is known for its high efficiency and defect tolerance but hindered by the long-term instability and contains toxic chemical (Pb). One of the alternative solutions is using oxide perovskite that have excellent stability and often ferroelectricity properties that can separate electron and hole on different channels and suppress electron-hole recombination rate. However, the bandgap of most oxide materials is typically more than 2 eV and ultimately not ideal as sun light absorber layer.



The goal of this work is to tune the bandgap of oxide perovskite via doping by replacing some of the sites in perovskite structures using density functional theory. We model the systems using conventional DFT (plane wave) and KKR-Green's Function DFT methods. [1,2]

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IV-6

A layered view on non-radiative photodeactivation

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Computational studies of ultrafast photoinduced processes give valuable insights into the photochemical mechanisms of a broad range of compounds. Various approaches exist to elucidate the non-radiative decay of excited molecules after photoexcitation, from detailed static studies to non-adiabatic molecular dynamics (NAMD) on long length- and timescales.

The topography around a conical intersection (CI) regulates the non-adiabatic transitions, thereby governing the deactivation pathway, products and lifetime of non-radiative decay processes.[1] A local diabatisation method to characterise CIs between two adiabatic electronic states will be presented, from which the non-adiabatic coupling vectors (NACs) can be calculated in a wave function-free, energy-based approach.[2] To prove the universality of the developed methodology, CIs between singlet states of formamide, cyclopropanone, benzene and thiophene were investigated using the state-averaged complete active space self-consistent field (SA-CASSCF), extended multi-state complete active space second-order perturbation theory (XMS-CASPT2) and time-dependent density functional theory (TDDFT) methods.

To accurately reproduce and predict experimental results, it is indispensable to include a condensed phase environment in the computational model. The ΔSCF electronic structure method with explicit quantum-mechanical solvation gives unique insights into the non-radiative decay of various systems in solution.[3-5] By applying subsystem density embedding, the simulation time can be reduced without significantly compromising the accuracy.[6] Moreover, new approaches to calculate the UV absorption spectrum with ΔSCF and pioneering inclusion of spin-orbit coupling into ΔSCF will be presented.[7]

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IV-7

A correlated potential surface for studying the collisions CO + O → CO_2 → CO + O

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During an atom-molecule collision with an intermediate CO_2 molecule a possible isotope exchange between the two oxygen atoms may take place, obeying the quantum-mechanical principle of indistinguishability of identical particles. For simulating this quantum effect, a potential surface is needed. We present a correlated (MRCI) ground-state surface $V(r_{C\text{-}O,1}, r_{C\text{-}O,2}, r_{O\text{-}O})$ developed into one-body, two-body and three-body contributions as

$$V(r_{C\text{-}O,1}, r_{C\text{-}O,2}, r_{O\text{-}O}) = E_C + 2\,E_O + V_{Morse,CO}(r_{C\text{-}O,1}) + V_{Morse,CO}(r_{C\text{-}O,2}) + V_{Morse,CO}(r_{O\text{-}O}) + V_{COO}(r_{C\text{-}O}, r_{O\text{-}O}, \phi_{COO}) + V_{OCO}(r_{C\text{-}O,1}, r_{C\text{-}O,2}, \phi_{OCO})$$

with $r_{C\text{-}O,1} \le r_{C\text{-}O,2}$. Potential points have been determined (using the code Molpro) on a grid (distances between 1.6 and 10 bohr, angles between 50 and 180 degrees), interpolated with 3D splines, and encoded with 1st-order derivatives in all variables (f, f_x, f_{xy}, f_{xyz} etc) for a rapid evaluation. Together with analytical extrapolation functions the surface reproduces characteristic points as well as the reaction barrier between the singlet CO_2 molecule and the triplet ensemble CO + O.

IV-8

Automating transition state search in metal catalysed C-H activation

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Direct functionalisation of C-H bonds using transition metal (TM) catalysts, such as Pd and Pt, has received significant interest in the past two decades, particularly in drug discovery, as it enables shorter and more efficient syntheses.[1] However, designing catalysts that promote regio- or stereo-selective activation has remained a challenge, often relying on trial-and-error approaches. In this scenario, computational chemistry plays a crucial role by facilitating *in silico* elucidation of reaction mechanisms, including the characterisation of transition states (TS) and intermediates. This understanding can aid in optimising catalysts for improved yield and selectivity. However, the complex nature of the potential energy surface (PES) of TM-complexes poses difficulties in automating such studies.

In this work, we present our efforts to introduce optimisation algorithms capable of elucidating reaction pathways involving TM-complexes. These efforts build on the software autodE[2] which has been developed in our group. Furthermore, we also compare the efficiency and accuracy of currently available approaches in representative systems. We demonstrate that even for simple reactions, such as benzene C-H activation with $Pd(OAc)_2$ catalyst, some methods fail to identify the correct TS. We hope that this study will contribute to the broader application of automated reaction path finding methods.

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IV-9

Synthesis, DFT and molecular docking study of the indenoquinoxaline-based oxime derivative

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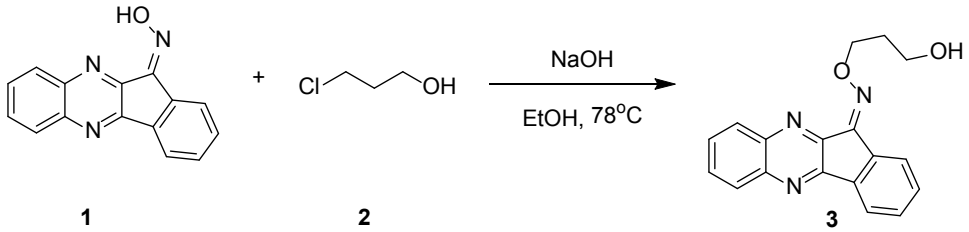
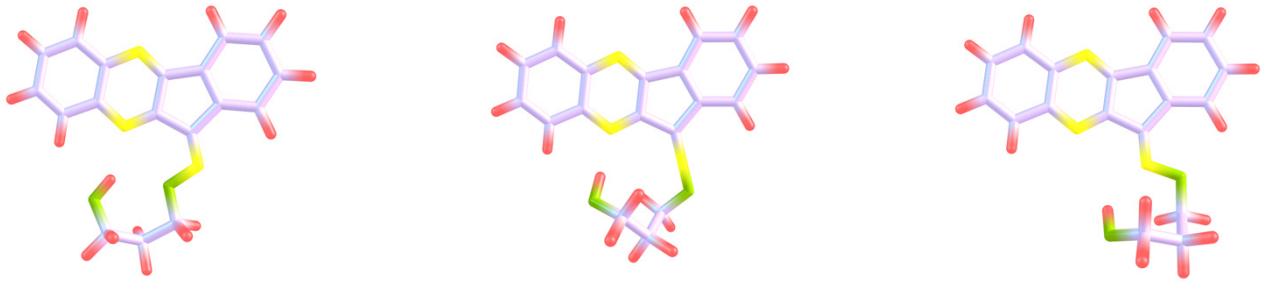
Indenoquinoxaline derivatives possess supreme pharmacological properties[1] which include anti-inflammatory[2], neuroprotective[3], antitumor[4] and other activities. During our synthesis of 11*H*-indeno[1,2-*b*]quinoxalin-11-one *O*-(3-hydroxypropyl)oxime (**3**), only one of the possible geometric isomers (presumably *Z*-product) was formed, according to the NMR data.



1 **2** **3**

We have evaluated relative thermodynamic stabilities of *Z*- and *E*-isomers of substituted oxime **3** by the DFT method. Preliminarily, a conformational search was performed for both isomers using VeraChem package. It was found that in the low-energy conformers, the terminal OH group forms intramolecular hydrogen bonds with heterocyclic and/or oxime nitrogen atoms. These conformers were further optimized using ORCA 5.0.3 software, and the Gibbs energy of *Z*→*E* isomerization was estimated as ΔG°=1.30 kcal/mol, i.e., the *Z*-isomer has a higher stability. With the application of NEB-TS methodology, we have found that the isomerization occurs by the in-plane inversion of the oxime nitrogen atom via the linear transition state, which corresponds to the energy barrier of about 46 kcal/mol.



Z-isomer Transition state *E*-isomer

The docking study of both *Z*- and *E*-isomers into the c-Jun-N-terminal kinase (JNK3) binding site was undertaken. The obtained docking scores show good perspectives of compound **3** as potential JNK3 inhibitor, similarly to the unsubstituted oxime. However, the synthesized substituted derivative **3** has a higher solubility in most of organic solvents.

The research was supported by the Tomsk Polytechnic University development program (project Priority-2030-NIP/IZ-009-375-2023).

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IV-10

Exploring ligand effects in Mn-catalysis with DFT and machine learning

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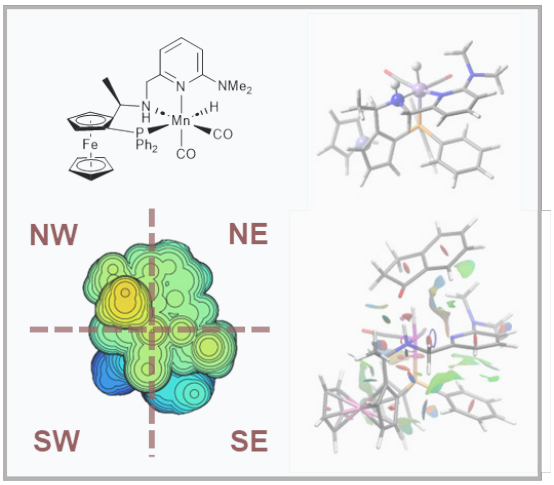
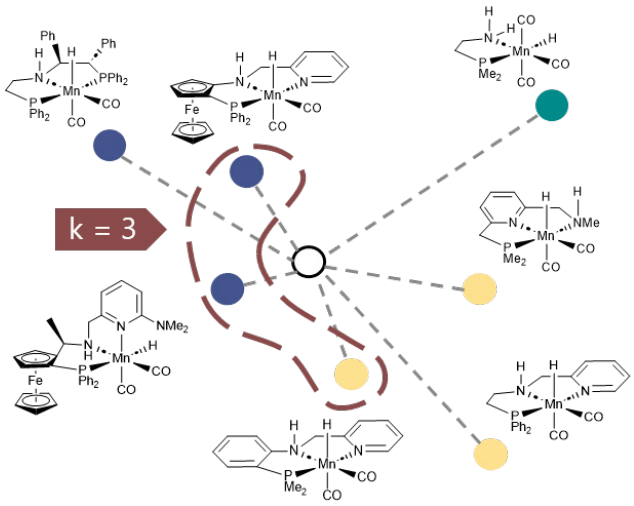
Catalytic reactions involving 3d metals are widespread in the literature and present a move away from the use of unsustainable, heavier metals. Manganese is active in homogeneous catalysis for transfer hydrogenation reactions involving a range of substrates, including a variety of aromatic ketones.[1] Further experimental work in this field has shown that these reactions can be performed with control over enantioselectivity using a chiral ligand system.[2]

In this work, we explore ligand effects across a variety of different systems, from a detailed DFT perspective and using Machine Learning algorithms such as *k*-nearest neighbours. With DFT (PBE0-D3$_{PCM}$/def2-TZVP//RI-BP86$_{PCM}$/def2-SVP)[3] we rationalise and predict enantiocontrol through either stabilising a favoured or destabilising a disfavoured diastereomeric transition state and examine the effect of electronics on reactivity. On a larger scale, by using semi-empirical GFN2-xTB derived descriptors, we can predict DFT barriers to within mean absolute error of <1 kcal/mol, allowing for a comparison of relative activity across a range of different ligand systems at a far lower cost than with DFT.





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IV-11

Multidentate halogen bond-based catalysis: A computational study

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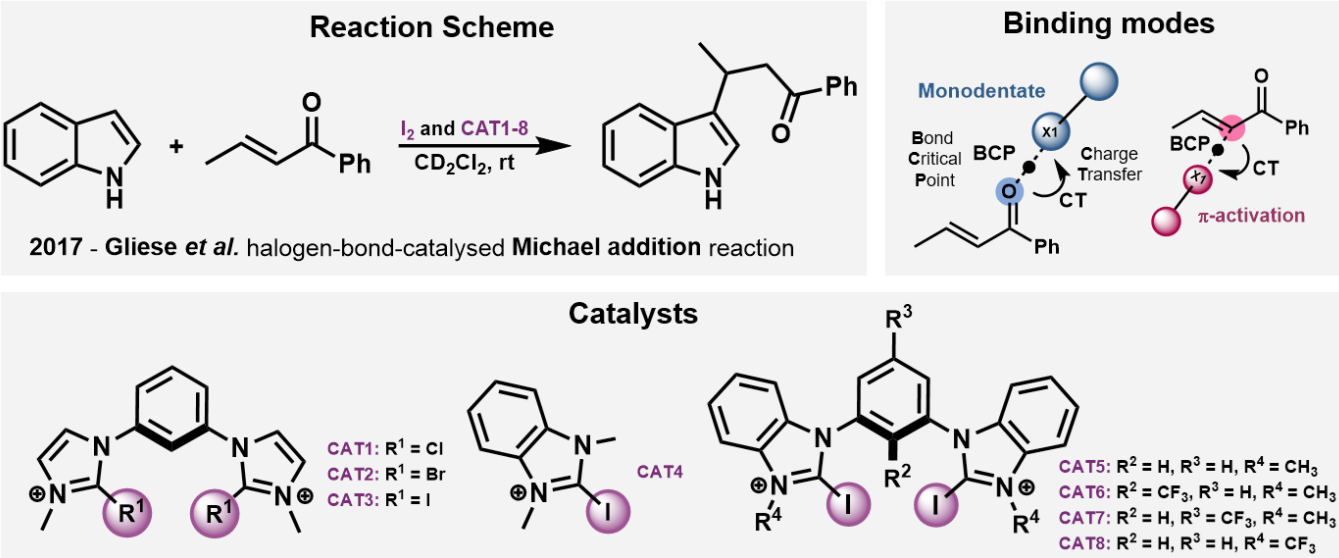
This research focuses on the investigation of σ-hole interactions in organocatalysis, which involves the use of small organic molecules to facilitate chemical transformations. σ-hole interactions, a term coined by Clark, Murray, and Politzer in 2006, refer to non-covalent forces resulting from the elongation of σ-bonds. These interactions offer unique features, including robust directionality, and are being explored as an alternative to the traditional hydrogen bonding.

The study specifically explores the impact of halogen bond (XB) donors and substituents in a series of achiral organocatalysts. By studying the Michael addition of indole to *trans*-crotonophenone, valuable insights into the structural and electronic characteristics of the σ-hole were revealed, as well as the mechanistic profiles, preferred binding modes, and XB interactions within complexation. This research sheds light on the potential of σ-hole interactions in organocatalysis and contributes to a deeper understanding of these intriguing non-covalent forces.



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IV-12

Grand canonical ensemble approaches for modeling electrochemistry in CP2K

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In many electrochemical experiments, the number of electrons of the electrode immersed in the electrolyte is variable, and the number of adsorbed substances on the surface of the electrode can also vary. However, treating electrochemical solid-liquid interfaces with the typical canonical DFT tends to be a challenge. This can be addressed by using grand canonical approaches. We present the implementation of two grand canonical approaches that go beyond the existing canonical ensemble paradigm in the open-source computational chemistry software CP2K. The first approach includes a number of recent developments: (a) grand canonical self-consistent field (GC-SCF) method[1]the number of electrons in the portion of the system treated quantum mechanically changes continuously, with a balancing charge appearing in the continuum electrolyte. A grand-canonical ensemble of electrons at a chemical potential set by the electrode potential is therefore the ideal description of such systems that directly mimics the experimental condition. We present two distinct algorithms: a self-consistent field method and a direct variational free energy minimization method using auxiliary Hamiltonians (GC-AuxH allowing the electron number of the system to fluctuate naturally and accordingly with the experimental electrode potential, (b) planar counter charge (PCC)[2,3] salt model completely screening the net charge of the electrode model, (c) the solvent-aware interfaces[4] between solute and solvent in continuum solvation for overcoming the unphysical isolated cavities or pockets of the dielectric function. In contrast with the previous studies, in our implementation, the work function (absolute electrode potential) is the constrained quantity during an SCF optimization instead of the Fermi energy. We derived the analytical expressions of the potential and force compatible with the Quickstep framework of the CP2K software package. The second approach (referred to as the two-surface method and the numerical litmus method)[5–7] is used to calculate the absolute electrode potential corresponding to an equilibrium electrochemical half-reaction ($M^{(n+m)+} + ne^- \rightarrow M^{m+}$) which involves DFT-MD and explicit modeling of the solvent molecules. The systematic tests have verified that the implementation of both two methods in CP2K is reliable. This opens the way for forefront electrochemical calculations in CP2K for a broad range of systems.

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IV-13

Exploring Cholinium-Based Catalysts for PET Recycling: Understanding the Role of Ethylene Glycol Solvent

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Polyethylene terephthalate (PET) is a fossil fuel-derived plastic found in fibres and many types of food packaging which in 2021 represented *ca.* 12% of global solid waste.[1] Thus, the study of how we can effectively break down this plastic is critical. The objective of this study is to understand the depolymerization of PET using cholinium-based, metal-free ionic liquid (IL)[2] catalysts; which offer considerable advantages in terms of environmental and toxicological concerns.[3] Although current mechanistic details suggest a bifunctional catalysis mode of action[4] which are chemically intuitive; there remain many unresolved questions concerning the competition between cholinium and the reaction solvent in facilitating the reaction. Understanding this competition has the potential to completely change our understanding of PET degradation.

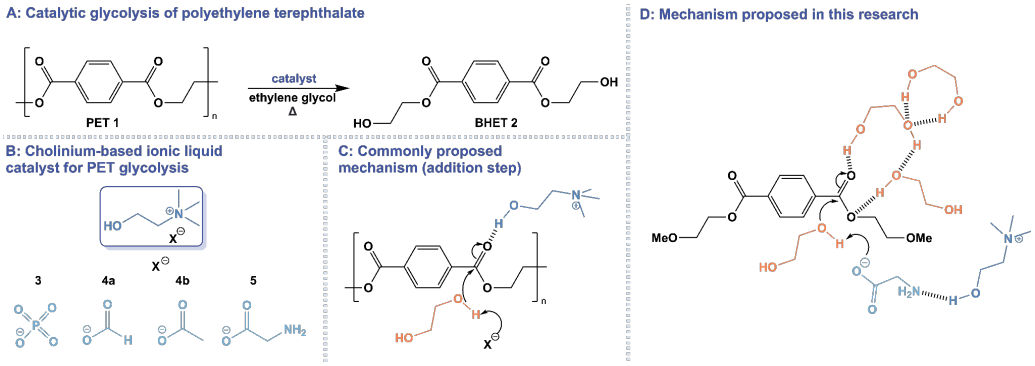

Fig. 1. Catalytic glycolysis of PET

A DFT computational study, alongside experimental studies, were conducted focusing on this new possible mechanism to gain full control over the reaction site encounter and maximise the reaction efficiency, ensuring complete degradation of the polymeric plastic as we strive to achieve designing the ultimate PET recycling process.

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IV-14

Ab initio study of the photophysical behaviour of the tautomers of 2-carboxamido-1,3,-indandione in the gas phase and in solution

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The 2-carboxamido-1,3-indandione (CAID) is an unique compound, where two tautomeric forms (CAID-A and CAID-B) coexist in various equilibrium depending on the environment (gas phase, solution, solid state and external electric field) [1-3]. Previous experimental and theoretical spectroscopic studies of CAID have shown that it is a suitable candidate as a fluorescent biomarker and sunscreen. The fluorescent properties of CAID are of particular interest, especially concerning their dependence on the type of solvent. Profound insights into the photophysical behaviour of the tautomeric forms and solvent effects on CAID, which highlight its potential for different applications, could be achieved by accurate *ab initio* calculations. A detailed description of the absorption and emission properties of CAID is performed in the present study by means of the MP2/RI-ADC(2)-def2-SVPD calculations (Turbomole software package). Jablonski diagrams for CAID-A and CAID-B have been established in the gas phase and in solution (acetonitrile (AN) and ethanol (EtOH)). The calculated vertical excitation energies (VEE) of the two tautomers in gas phase predict nπ* character for S_1 state (dark), while the higher-energy S_2 state is of ππ* character. However, in solution (simulating geometry in solution and nonequilibrium solvation contribution to VEE), the energies of S_1(nπ*) and S_2(ππ*) states become practically isoenergetic. At the same time, the experimental emission spectra in AN and EtOH suggest that the bright singlet excited state is active for radiative relaxation. Unlike the ground state, where CAID-A is more stable than CAID-B, in the S_1 state CAID-B becomes more stable, indicating a possibility of CAID-A conversion into CAID-B, with a low-energy barrier of 4.28 kcal mol^{-1}. The complicated excited state behavior of CAID-A and CAID-B in solution is discussed for the estimation of the possible mechanism of emission.

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IV-15

Theoretical Approach for Energy Transfer Assessment in Molecules of Optical Eu^{III} - Aromatic Phosphine oxide Based Complexes

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Eu^{III} compounds are some of the most-widely studied luminophores. Their unique emission spectra, long radiative lifetimes and the high yields of red light make these materials suitable for the development of lasers, screens, lighting, etc. The productivity of these applications is improved distinctively by the binding of the europium ion to a sensitizing chromophore. The latter absorbs UV light and transfers the energy to a 4f - excited state through non-radiative mechanism. Presently, a significant amount of experience has been accumulated in the design of such chromophores, particularly organic ligands. Bulky three dimensional structures based on aromatic phosphine oxides have drawn a specific attention, because of their notable absorption in the UV region of the spectrum anddue to their ability to prevent quenching of the luminescent emission by small molecules.

Three luminescent complexes of Eu^{III} with bidentate phosphine-oxide based ligands: Bis[2-(diphenylphosphino)phenyl] ether oxide (*DPEPO*), 1,1'-biphenyl-2,2'-diylbis(diphenyl phosphane oxide) (*BIPHEPO*) and Phenacyldiphenylphosphine oxide (*Phenac*) were modelled with the help of quantum chemical calculations. The computational protocol was developed and tested in our previous works [1-3]. DFT and TDDFT calculations were used to optimize the molecular geometry and electron density for the ground (S_0) state, first singlet excited (S_1) and first triplet excited state (T_1). Quasi-degenerate perturbation theory (QDPT) was employed to assess the spin-orbit coupling strength between excited singlet and triplet states. Based on the obtained results, calculations of the respective intersystem crossing rates and rates of radiative transitions are performed. A Judd-Ofelt analysis of the luminescence spectrum is implemented within the frame of the QDC model of Freire and co-workers. Energy transfer rates, quantum efficiencies and quantum yields are calculated with the formalism of Malta and co-workers. The theoretical estimates are validated through comparison with available experimental data. All major electronic relaxation and energy transfer pathways in the Eu^{III} complexes are defined.

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Acknowledgements: The authors thank for the financial support the Bulgarian National Science Fund of Bulgarian Ministry of Education and Science, Grant КП-06-Н59/6 (2021), project (PhotoMetalMod)". Ts.Z. and I.G. thank the project CoE "National center of mechatronics and clean technologies BG05M2OP001-1.001-0008-C01**.** The authors also acknowledge the provided access to the e-infrastructure of the NCHDC - part of the Bulgarian National Roadmap on RIs, with the financial support by the Grant No D01-168/28.07.2022.

IV-16

Compound: A powerful workflow solution for ORCA

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Compound is a form of sophisticated scripting language that can be used directly in the input of ORCA[1]. The designing target of it, is to combine all features of a normal programming language with direct knowledge of ORCA variables. In this respect the language is capable of all 'common' language structures, like 'if' statements, 'for' loops, different type of variables, the ability to handle scalars and arrays and also use system commands. At the same time 'Compound' can use, as variables, practically all of the calculated quantities of an ORCA calculation.

Using „Compound" :

- it is possible to save several protocols in a single file and subsequently execute them on different molecules.
- complex workflows can be automated.
- easily and straightforwardly perform a meta-analysis of ORCA results.
- it is possible to create a collection of protocols for a group, allowing everyone to utilize them.

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IV-17

Computational Study of Natural-Product-Like Macrocycles

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Macrocycles are promising candidates for therapy against previously undruggable targets.[1] However, their synthesis and diversification are often inefficient and expensive, mostly due to the risks associated with the final ring-closing step.[2] Computational tools offer promise to minimise such risks. Bogdan *et al.*[3] have explored a series of 9 cyclophane macrocycles and found a correlation between strain and product-to-dimer ratios. Colwell *et al.*[4] have also introduced StrainViz, a semi-automated tool for calculating the strain of π-conjugated macrocycles. Finally, Saha *et al*.[5] have reported an automated tool for the enumeration of building blocks to generate a library of more than 2 billion theoretically-accessible peptide-derived macrocyclic scaffolds. While useful, these tools remain limited to specific families of macrocycles.

Here, we discuss our ongoing computational efforts to guide the synthesis of macrocycles. Work is ongoing to include strain energy calculations in our tool AutodE[6], allowing for both thermodynamic and kinetic insight to be gained. We discuss current challenges, including conformational sampling and limitations of published data. Finally, we demonstrate the application of our current framework in a representative set of natural-product-like macrocycles.

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IV-18

Towards an understanding of Turbo Grignard reagents: structural information from AIMD studies

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Main group organometallic reagents constitute today a critical asset for the synthesis of a broad range of valuable compounds, and are used daily in academy and industry. In recent years, bimetallic formulations resulting from the association of Li salts with these compounds have attracted great attention, due to the improved performance offered to such a critical class of compounds. This association yields extremely powerful reagents, as illustrated by the Turbo Grignard, the enhanced version of one of most prominent functionalisation tools in organic synthesis [1]. Compared to pure Grignard reactants, the metallation promoted by Turbo Grignards (RMgX·LiCl) proceeds selectively, with high-group tolerance and in high-yields [2]. The enhancement provided by the association with LiCl awarded iPrMgCl·LiCl the Encyclopaedia of Reagents for Organic Chemistry (EROS) best reagent award in 2011. Despite the success of these bimetallic formulations, the current understanding of the origin of the beneficial association with Li salts remains rather unsatisfactory, so far attributed to unidentified synergistic effects between the two metals. In our group, we recently used ab initio molecular dynamics (AIMD) coupled to enhanced sampling techniques to determine the mechanism of the Grignard reaction at its molecular level in THF [3,4]. Here, we used the same approach to characterise the structure of LiCl in solution and its interaction with Grignard reagents. AIMD simulations reveal that the symmetric crystallographic $Li_4Cl_4(THF)_4$ structure observed when crystallising the compound at low temperature is not representative of the molecular moiety present in liquid THF at room conditions. This is instead a very dynamic, non-symmetrical species, where key is the role of the solvent, in agreement with our previous findings for Grignard reagents [3,4]. In particular, Li_4Cl_4 takes the form of a distorted cube where one of the twelve Li-Cl bonds is broken, in favour of the coordination of an additional THF molecule at the Li site. The intrinsic weakening of a Li-Cl interaction promotes the aggregation of the Li_4Cl_4 cluster with the Grignard species through the formation of a Li-Cl-Mg-Cl wire. The binding affinity between $LiCl_4$ and CH_3MgCl can control the distribution of the species present in solution by disturbing the Schlenk equilibrium, overall promoting the dissolution of smaller, more soluble, mixed Li:Mg:Cl clusters [5].

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IV-19

Stability of $Ru@Sn_9$ Zintl cluster on a CeO_2 (111) surface and its catalytic activity in Water-Gas-Shift (WGS) reaction

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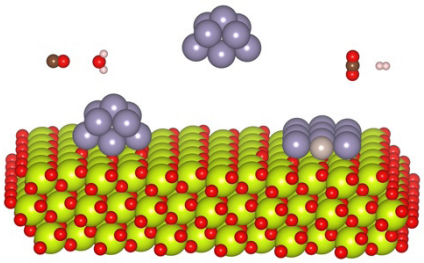
Cerium Oxide (CeO_2) is one of the most efficient compounds and supporting surface, because of the facile changes in oxidation state between Ce^{4+} to Ce^{3+}, and is widely used in high-performance oxygen storage applications and catalytic redox reactions, solid oxide fuel cells, water-gas shift reactions, etc. The use of Zintl clusters or metalloids rather than isolated noble metal atoms as a catalytic centre offers the potential to exploit the interactions between transition and main-group metal to achieve low-barrier reactions, and some recent works suggest that Zintl clusters are effective catalysts for some important reactions (e.g. WGS, r-WGS, methanation etc.). Recently, Sun et al. have reported the selective reduction of CO_2 over highly dispersed $RuSnO_x$ sites, derived from a $[Ru@Sn_9]^{6-}$ Zintl cluster but an atomic-level understanding of mechanism, and how it relates to the electronic properties of the cluster remain unclear.



In this work, we firstly investigate the stability of the $Ru@Sn_9$ Zintl cluster on the CeO_2(111) surface by comparing the optimised energy of the cluster on the surface with a dispersed structure where the Ru and Sn atoms are dispersed on the surface, using periodic Density Functional Theory (DFT). Interestingly, in many cases clusters prove not to be stable on surface, but rather are disrupted by strong metal-support interactions (SMSI).[2] An important first objective therefore is to establish the stability of the $Ru@Sn_9$ cluster on the surface under normal reaction conditions. It has been found that $Ru@Sn_9$ cluster will disperse over the surface and accumulate in a monolayer where Ru would prefer to stay at the edge. Later, we report some studies on the $RuSn_9/CeO_2$ (111) catalyst for WGS reaction where possible reaction mechanisms have been explored and activation energy barriers have been calculated. This catalyst shows a significantly lower energy barrier using different reaction path, compared to other reported heterogeneous catalysts such as Au, Pt, Cu nanoparticles on supported surfaces.

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IV-20

The Electronic Structure and Catalytic Activity of a Ru_3 Cluster Embedded on Nitrogen-doped Graphene

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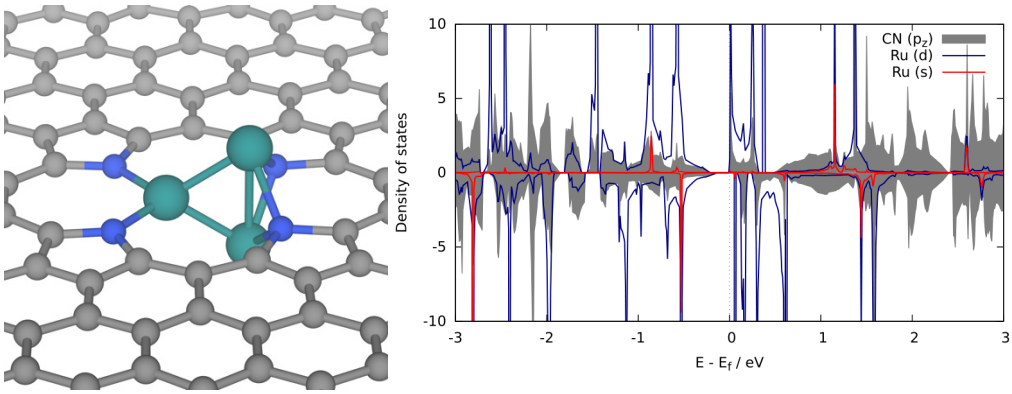
Pyrolysis has been a popular synthetic technique in producing single-atom catalysts (SACs) embedded on graphene-based materials. A slight variation, triple-atom catalysts composed of three Ru atoms embedded on N-doped graphene was synthesised in a confined pyrolysis of $Ru_3(CO)_{12}$ and reported to catalyse alcohol oxidation 10 times more efficiently compared to its SAC analogue.[1] Here, by employing both molecular and periodic DFT calculations, we build the models of Ru_3/N-graphene and analyse their electronic structures and orbital interactions between the cluster and N-graphene. The molecular model reveals that significant orbital interactions with localised p defect states on the N-graphene model led to the transfer of two electrons from the cluster to the conduction band of the surface. The surface therefore acts as a buffer, removing and restoring electrons to the active site during the catalytic cycle. Our initial exploration of the cycle indicates a potential role for Ru=O species in the C-H bond cleavage step of alcohol oxidation.



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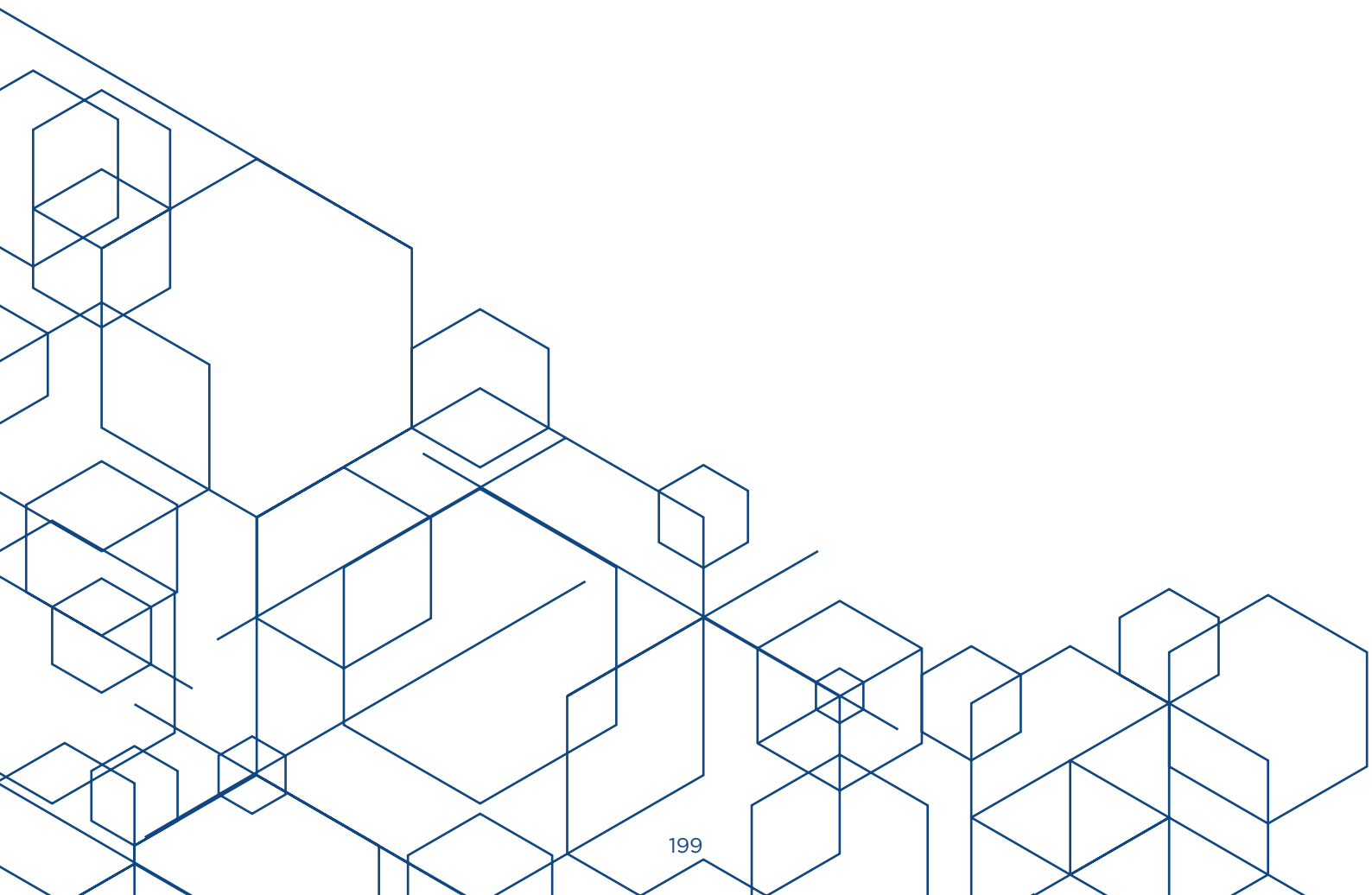
MATERIALS DESIGN



III-36

Computational Design of Frustrated Lewis Pair Catalysts for CO2 hydrogenation

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In 2006, Welch, G. et. al., reported the reversible splitting of H2 by a molecule containing a Lewis acid B center and a Lewis base P atom, namely p-(Mes_2P)C_6F_4($B(C_6F_5)_2$) (Figure 1).[1] One year later, the terminology "frustrated Lewis pair" was coined to describe such reactivity of transition metal free molecular catalysts,[2] and has extended over years to other combinations of acid and base partners, including B/N, Al/P, etc. This family of compounds represents a good transition metal free alternative to reduce CO_2 due to their ability to heterolytically split molecular H_2 into a hydride and a proton, which can be used for subsequent hydrogenation of CO_2 to formic acid. Although the physicochemical properties of the substituents of each of the FLP components is known to have an important impact on their reactivity and selectivity, still very little is known on how to tune the geometric and chemical structure of an FLP to target tailored catalytic properties.

Here, we aim to establish effective rules from fundamental molecular descriptors and multivariate regression techniques to design optimal FLP catalysts for CO_2 reduction to formic acid. To do so, we have fully characterized through DFT calculations (at the ωB97X-D/6-311G(d,p)/IEF-PCM level) the free-energy landscape of this reaction catalyzed by a series of more than B/N 100 FLPs, along which electronic and steric parameters are systematically tuned. The construction of multivariate regression models revealed that besides the B···N distance, the energy of p-type virtual orbital centered on the B center of the FLP is a key parameter. Specifically, the latter correlates with the individual barriers for H_2 splitting and CO_2 hydrogenation in an opposite manner, indicating that a moderate electron density is required to be supported by the B center to attain both H_2 splitting and CO_2 hydrogenation activity simultaneously. Also, the bulkiness of the substituents at the B center was found to have a significant impact on the H_2 splitting barrier via modulation of the directionality of the lobes of the aforementioned orbitals.

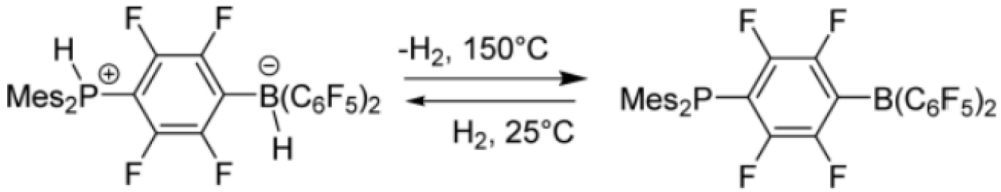

Figure 1: Reversible splitting of H2 by p-(Mes2P)C6F4(B(C6F5)2)

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III-37

Chemical space exploration towards novel and high-potential radical components for organic radical batteries

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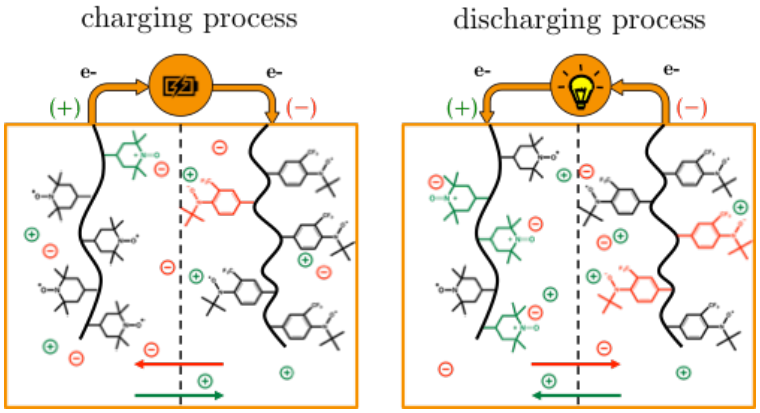
In this study, the chemical compound space is screened in search for stable, redox active radicals. The central idea is to extend the collection of radicals that are currently known to be promising components usable for industrial applications, particularly for organic radical batteries (ORBs).



A diversity-driven inverse design strategy is applied using the automated Property-Optimizing Algorithm for Chemical Space Exploration with Stochastic Search (PO-ACSESS) [1],[2] program. Two ORB design criteria are applied: generated radicals should be sufficiently thermodynamically stable and highly redox active. An intrinsic radical stability scale, developed by us in 2008, is the foundation from which new stable radicals are designed. [3] The redox activity of each radical is calculated via the well-established relationship between the reduction potential and the Gibbs free reaction energy for the reduction half reaction. Experimental circumstances are included into the theoretical calculations by simply rescaling computed reduction potentials via a theory-experiment correlation equation to afford redox potentials relative to the Ag/AgCl electrode. The study results in the proposal of conventional and rocking-chair-type organic radical batteries, with estimated theoretical cell voltages up to 2.1V.

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III-38

In Silico informed design of next generation sensors for rapid opioid detection

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In 2021, the US suffered over 80,000 overdose deaths involving an opioid.[1] In England and Wales, half of all drug poisoning deaths registered in 2021 involved an opiate.[2] The opioid family is structurally diverse and there are multiple existing and emerging classes of novel synthetic opioids (NSOs) with varying degrees of potency. NSOs, in particular synthetic fentanyls arguably pose a greater public health concern than heroin and other morphine derivatives, as a consequence of their increased potency. An ability to rapidly detect the classes of opioid present in mixtures has the potential to significantly reduce incidences of harm caused by NSO abuse.

Distinction between opioid class is rarely documented due to limitations in testing, therefore the development of the discriminative ability of detection methods for opioid types is essential to not only reduce harm, but to refine and improve the data reported on opioid overdoses and deaths.[3]

Molecular modelling techniques provide a credible starting point in aiding the rational design of molecular sensors for the purpose of opioid detection. This research utilizes pharmacophores to establish templates for synthesizable compounds that can selectively recognize one particular class of opioids over others.

A dataset of 437 of known prescription and illicit opioid compounds was identified from literature, guided by the current trends reported by drugs and drug crime monitoring bodies, including the European Monitoring Centre for Drugs and Drug Addicition (EMCDDA). Heirarchical clustering and similarity testing techniques were employed to divide the dataset into nineteen superclusters based on similiarities between chemical structures. Nineteen clusters of various sizes were generated, with three of these only containing two molecules, and five singletons.

Pharmacophore models were generated for seven clusters which contained at least six compunds. The pharmacophores were then used to screen the entire dataset and test the pharmacophores' ability to preferentially identify the compounds from the cluster used to generate them. Enrichment factors were calculated at 2, 5, and 10% of the virtual screen to provide objective measures of pharmacophore selectivity. The importance of each feature to the selectivity of the pharmacophore was evaluated using the 'Leave One Out' methodology in order to generate the most discriminitive pharmacophore with the fewest features for each cluster.

Seven distinctive pharmacophores which showed enrichment factors ranging between 0 and 7 were generated. These pharmacophore models may act as templates to inform the synthesis of a recognition element for class-specific molecular sensors, as they show selectivity for structurally similar opioid compounds over others. The discriminative power of these pharmacophores was evaluated by screening a larger database of novel psychoactive substances, seeded with the original opioid dataset.

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III-39

Modeling of Photoluminescent Carbon Dots

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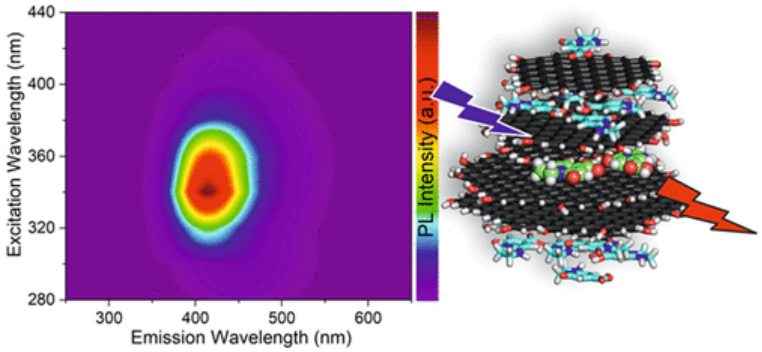
Carbon dots (CDs) represent an important class of carbon-based nanomaterials that has been extensively studied owing to a wide range of applications resulting from their bright, tunable photoluminescence (PL), high (photo-)stability, low toxicity, and excellent biocompatibility. However, due to complex structure and variability of the PL centers of CDs, our understanding of the PL mechanisms is still incomplete. To address this issue, we employed a combination of classical molecular dynamics (MD) simulations and quantum chemistry methods, relying predominantly on time-dependent density functional theory, to analyze the structure of CDs, the nature of their excited states and potential relaxation pathways. Our MD studies provided atomistic details on the dynamics and the structural organization of quasi-spherical CDs showing that the units of CDs spontaneously self-assemble and coexist in solution with molecular fluorophores. Furthermore, our quantum mechanical and hybrid quantum mechanics/molecular mechanics calculations explained how the optical characteristics of a prototypical molecular fluorophore are altered upon dimerization and/or confinement inside the CDs. The developed methodology provided valuable insights into the key photophysical processes accompanying PL od CDs and was successfully utilized to rationalize experimental observations of CDs.



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III-40

DEFECT ENGINEERING CREATION OF PHOTOCATALYST MOFs

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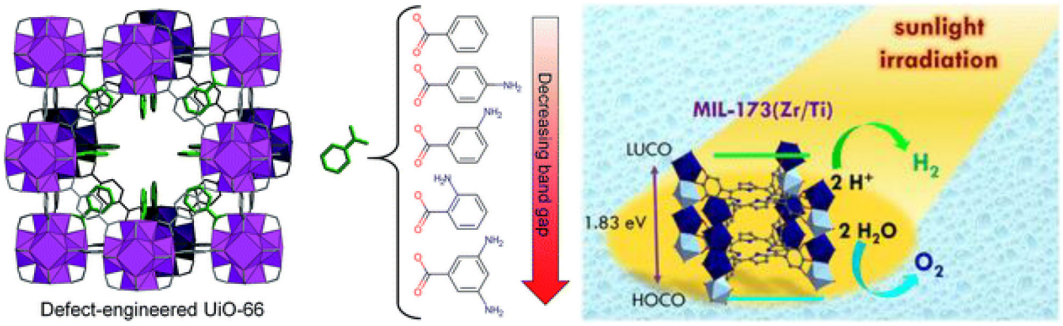
In the last decades MOFs have become an important area of research that goes beyond the simple gas-adsorption. Creating defects inside of the MOFs (eg doping of the metal node, missing linker, missing cluster) provides an extra degree of freedom that can be used for tuning the opto-electronic properties[1,2] of MOFs aiming to use them in catalysis. [3,4]

In the 1st part of the talk I will show how computational chemistry can be used to study MOFs, explaining their properties at atomistic level.[5,6] In the 2nd part I will show how, by combining simulations and experiments, we have been able to create two new photo-catalysts: one able to reduce CO_2 to CO, the other capable of producing hydrogen from water splitting without any sacrificial agent. [7]



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III-41

In-situ investigation of polymer autoxidation

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Oxidation of most polymers is an auto-accelerated process, attributed to a free-radical oxidation scheme[1]. Past theoretical studies that focused on the thermochemistry of key elementary reactions of the scheme, i.e., hydrogen abstraction by the peroxyl radical, resorted to gas- and solution-phase calculations after exhausting relaxation of the polymeric structures. However, this contradicts the nature of many dense polymeric solids, e.g., polymer glasses, that have their chains "trapped" in thermodynamically unfavourable configurations. In order to shed light on the thermochemistry of polymer autoxidation under realistically dense conditions, we present an in-situ approach that utilizes trustworthy glassy configurations, produced by consecutive Monte-Carlo (MC) and Molecular Dynamics (MD) equilibration steps, as sampling grounds of potential oxidation-initiation sites and their local reaction environment. A QM-cluster approach is employed to follow the crucial propagation reactions at each site. In this way we are able to properly capture the effect of the explicitly described environment on the reaction energies. Harmonic confinement of terminal carbons of the polymers backbones prevents the collapse of the active site during the DFT optimisations, while preserving correct physics for the energy calculations[2]. We prove that a cut-off radius is appropriate for converged energetics. And, we apply the approach to demonstrate the impact of the mobility of the radical on the reaction barriers by studying the oxidation pathways in two representative cases, where the radical centre is located away and near the chain end, respectively. By comparing our results with calculations of unconstrained chains we highlight the importance of proper representation of the dense environment in the computational investigation of reactions in amorphous solids.

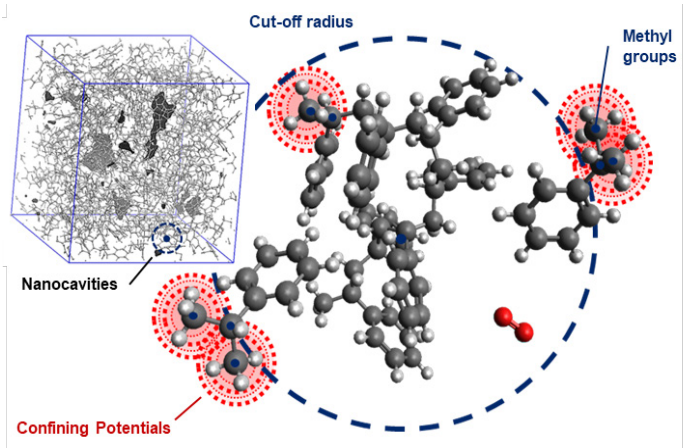

Figure 1: Schematic of the QM-cluster approach.

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III-42

Nitrogen-rich MN_8 compounds with 2D extended crown-like N nets

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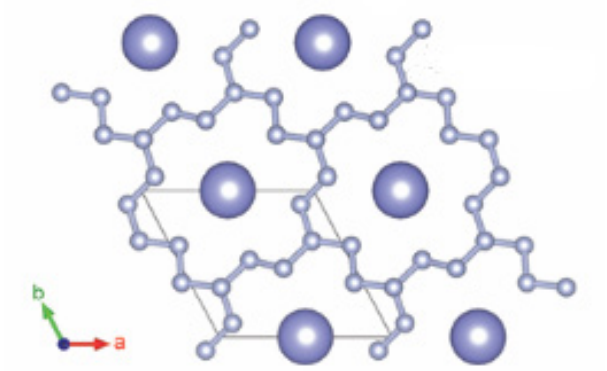
The application of polynitrogen as a high-energy density material (HEDM) is hampered because of the high reactivity of most predicted allotropic phases of nitrogen. However, mixing nitrogen with other elements M can help to overcome this kinetic instability. By modulating pressure, MN_x products can be stabilized and then quenched to obtain "polymerized nitrogen" and nitrogen-rich compounds. Our theoretical exploration of different M-N binary phase diagrams under pressure[1-3] has resulted in the emergence of appealing N-based molecular motifs like chains or layers. For instance, we predicted the isolation of a layered unsaturated 18-crown-like N_8 material[4]. We explored the possibility of predicting the emergence of novel and viable nitrogen-rich MN_8 compounds by mixing an electropositive metal with the unsaturated moieties. Our investigation involved a wide range of solid-state compounds MN_8 under pressure, with M supporting different oxidation numbers such as Na^+, Ag^+, Ca^{2+}, Pb^{2+}, Y^{3+}, and Hf^{4+}. By assessing dynamical (phonons), thermodynamic (enthalpies), and kinetic (AIMD) stabilities, we predicted over 14 viable compounds with different crystalline phases. To locate the different phases of the 2D 18-crown-6 MN_8, we used the evolutionary algorithm “USPEX”[5] combined with DFT calculations at various levels of theory (PBE, PBE-D3(BJ), R2SCAN, R2SCAN+rVV10, or HSE06) depending on the property being evaluated (structure, energy, phonons, AIMD, DOS, COHP, energy gap, bands, etc.). Our extensive exploration demonstrated that the extended crown-like N_8 net is a common and stable topological motif stabilized by cations through ionic interactions.



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III-43

Simulating Metal Interfaces Under Extreme Conditions

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We present a novel particle-based coarse-grain simulation technique that efficiently describes the complex response of energetic material composites at the microscale. We incorporate the Sutton-Chen (SC)[1] potential and the quasi-coarse-grained dynamics (QCGD)[2] into the generalized energy-conserving dissipative particle dynamics (GenDPDE)[3] to simulate metal-metal interfaces under extreme conditions. The SC potential is a relatively simple density-dependent potential based on the embedded atom model that has been widely used to study metals with face-centered crystal lattice, but we show that it is also suitable for other structures such as the hexagonal close-packed lattice. The QCGD scheme introduces efficient coarse-graining, enabling study of metalic materials at mesoscale, while GenDPDE is a method appropriate for the non-isothermal simulation of particle interaction force fields that are both density- and temperature-dependent. A GenDPDE particle is a material element embodying many physical constituent and, therefore, has internal degrees of freedom represented by internal energy. We validated the scheme by reproducing melting temperatures of pure metals, showing that more than a single set of SC parameters can be used for most metals. Then, we investigated metal-metal interfaces using the GenDPDE scheme, showing the coarse-graining scheme coupled with the GenDPDE is a powerful tool to investigate complex systems.

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III-44

Reactive force fields development for polyoxometalates in water solution

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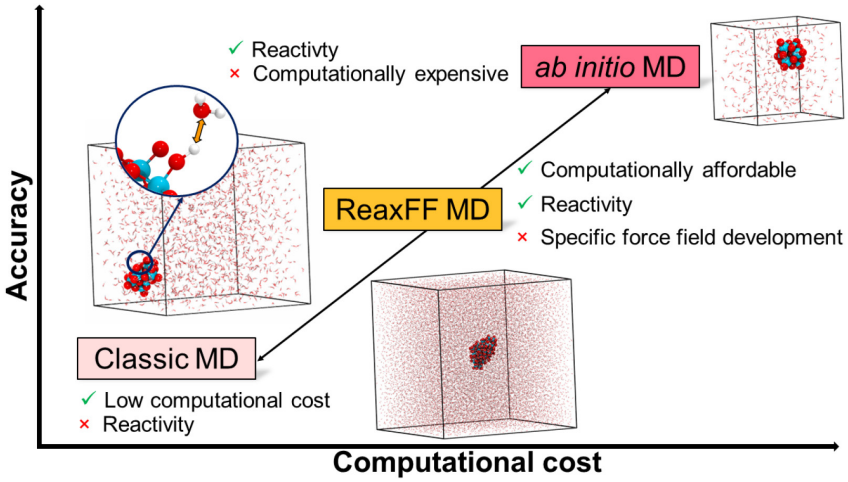
Polyoxometalates (POMs) are an emerging class of catalysts consisting in well-defined metal oxide clusters involving d^0 metal ions (as W(VI), Mo(VI), V(V), Nb(V) and Ta(V)). They can form different structure types (such as Lindqvist, Keggin, Well-Dawson) with their own features. To fully understand polyoxometalate (POM) chemistry in solution is essential to identify their individual speciation profiles, assessing their protonation state, composition, and active structures at the operating experimental conditions.[1] Atomistic modelling of these properties have relied on classical Molecular Dynamics (MD), which lack the ability to reproduce reactive events, or **ab initio** MD simulations, which are unpractical due to the high computational cost. Alternatively, reactive force fields methods such as ReaxFF, are able to simulate bond forming/breaking processes at a similar computational spence to classical MD simulations.[2] Musaev *et al.* have developed ReaxFF parameters for investigating the protonation state of niobates in water solution.[3] Here, we extend the development of ReaxFF parameters for molybdates and tungstates in water solution using conventional optimizers and an in-house implemented machine learning method, the Genetic Algorithm and Artificial Neural Network hybrid method (GA-ANN).[4] In this way, we have established a rigorous and multi-step procedure for the force field development. The resulting force field has been applied to a varied set of structures (Mo_6, Mo_7, Mo_{32}, Mo_{132}) allowing us to gain a comprehensive understanding of their properties at atomistic level.



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III-45

Graphene-based Electrodes for Lithium-Ion Batteries

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After their discovery, carbon nanomaterials have undergone extensive theoretical and empirical investigations for a broad range of applications. The distinctive properties exhibited by these substances offer significant prospects for electrochemical applications in lithium-ion battery (LIB) design. Based on this premise, the present study introduces and analyses various carbon-based materials as potential candidates for integration into LIBs, employing density functional theory (DFT) calculations.

The electronic properties of graphene, graphyne-1, and biphenylene, both with and without specific substituents, were computationally assessed to evaluate their suitability as electrodes for LIBs. Additionally, the optimal adsorption sites for Li atoms and Li ions, along with their corresponding electrode potentials, were determined. Furthermore, achieving a high charging/discharging rate is critical for the effective functioning of LIBs. This rate is influenced by the ease of migration of electrochemical species across the electrode surfaces. Consequently, we have characterized the energy profiles for the most probable pathways of Li and Li+ migration between two favourable adsorption sites on the surfaces.

The findings indicate that graphene and graphyne with nitro and carbonyl substituents exhibited the most promising characteristics as electrodes. In contrast, the introduction of fluorine and other ligands did not appear to enhance the electrode's potential.

III-46

Theoretical study of the early chiral organization of low dimensional hybrid perovskites

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In recent years, there has been a continuously growing interest in chiral low-dimensional hybrid perovskites (LDHPs) due to their remarkable optoelectronic properties and environmental stability. These materials consist of inorganic polyhedra encapsulating chiral organic ligands. Their optical and electronic properties rely on the inorganic sublattice and on the related non covalent interactions with the organic ligands. Very recently, the chirality generation into the inorganic sub-lattice of perovskites has emerged by incorporating chiral organic cations. In this context, chiral LDHPs embedding methylbenzhylammonium (MBA^+) as chiral organic ligand within $[PbI_4]^{2-}$ inorganic layers has shown a set of chiroptical properties as circular dichroism (CD) and circularly polarized photoluminescence (CPL). However, the thorough details of how chirality is imparted from the organic ligand to the inorganic framework remain unclear.

Motivated by the willing in understanding the fundamental principles behind the generation of chirality and to boost the design of chiral LDHPs, we investigated the details of the early chiral organization of 2D perovskite. *Ab initio* molecular dynamics (AIMD) simulations based on density functional theory (DFT) in conjunction with enhanced sampling methods have been performed on the crystallographic coordinates of the $(MBA^+)_2PbI_4$. The structure is reported by Jana et al. [1,2] and is available in the Cambridge Crystallographic Data Center (CCDC) database with the deposition number of 2015617. *Ab initio* steered molecular dynamics simulations were initially performed to induce increasing disorder in the considered chiral LDHPs, using as collective variable the root mean square deviation (RMSD) from the crystallographic coordinates. Then, in order to enhance the sampling and the efficiency in exploring and reconstructing the related free-energy profiles, independent *ab initio* metadynamics simulations were carried out spanning several configurations identified through different RMSD values extracted from the computed steered trajectory. The innovative mean force integration (MFI) [3] method was eventually applied to patch together the metadynamics trajectories and accurately reconstruct the free-energy profiles in the space of collective variables.

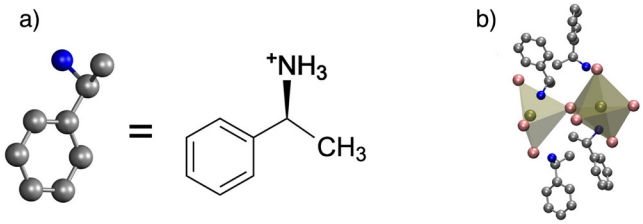

Figure 1. a) Molecular structure of the ligand S-MBA^+; b) Schematic crystal structure of $(S\text{-}MBA)_2PbI_4$ perovskite

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IV-35

Engineering new organic proton-transfer acid-base (anti-)ferroelectric cocrystals using crystal structure prediction

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Hydrogen-bonded organic molecular ferroelectrics are an attractive alternative to conventional inorganic ferroelectrics due to potentially low-cost environmentally friendly processing and flexibility. One such class of systems is the acid-base co-crystals, where ferroelectric switching is achieved through the transfer of protons between the acid and base molecules [1]. Furthermore, the typically low coercive fields exhibited by these materials make them suitable candidates for applications in low-voltage electronics. However, the occurrence of ferroelectric properties is limited to specific circumstances: the presence of a suitable protonation state and specific molecular packing arrangement. The "correct" packing would facilitate a proton transfer cascade that spans the whole unit cell. Currently, the polarization of acid-base ferroelectric is lower than comparable tautomers, in part due to the larger size of the molecules involved. The objective of this study is to design new acid-base ferroelectrics by systematically combining small acid and base molecules in order to achieve higher polarization. Crystal structure prediction for over 100 different acid-base combinations was performed, resulting in a few candidates with promising ferroelectric or anti-ferroelectric properties. Our study massively narrows down the scope of ongoing experimental efforts to realize novel organic ferroelectrics and anti-ferroelectrics.

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IV-36

Revealing the interplay between the structural complexity of triphenylamine redox derivatives and their charge transport processes via computational modeling

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Triphenylamine (**TPA**) derivatives are organic functional materials well known for their semiconducting hole transport properties. [1] These features characterize their applications in the field of organic electronics, for instance as hole transport layer for organic light emitting diodes (OLEDs) [2], and perovskite-based solar cells (PSCs) [3], as well as organic cathodes for electrochemical energy storage (EES) devices (e.g. organic batteries) [4]. Here, we explore through a bottom-up computational approach the molecular and solid state structures, as well as the charge transport processes in amorphous and single crystalline phases of four different redox active **TPA**s, characterized by increased molecular structure complexity. The **TPA**s considered feature different one-, two- or four redox centers, namely i) a single **TPA** unit, two **TPA**s linked via ii) a flexible diphenyl bridge (**TPD**) or iii) a rigid fluorene bridge (**FTPD**), and four **TPA**s connected via a spiro-center (***spiro*-OMeTAD**). A combination of density functional theory (DFT), semiempirical quantum mechanical (SQM) and molecular dynamics (MD) methods are used to generate amorphous morphologies, to analyse the crystalline phases and to calculate the charge transport parameters and mobility. Our results show that short- and long-range structural order in condensed phases are strongly influenced by the molecular architecture. Furthermore, charge transport parameters, such as site energies, reorganization energies and coupling integrals, are intimately coupled with the number of redox centers and the way they are connected. The charge transport is characterized differently depending on the degree of morphological disorder, i.e. reorganization energy-controlled transport in the crystalline phase and site-energy static-disorder controlled transport in the amorphous phase. The computed hole bulk mobilities are in good agreement with the experimental literature data.

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IV-37

N-doped Graphene-based Nickel(II) Single-Atom Catalyst for Hydrogen Borrowing: a DFT computational study

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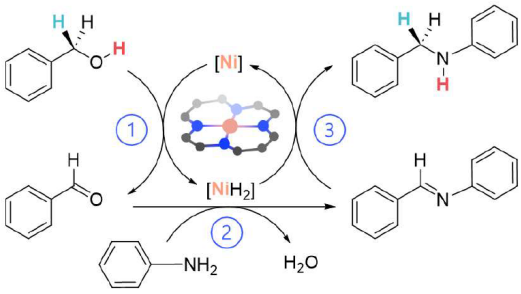
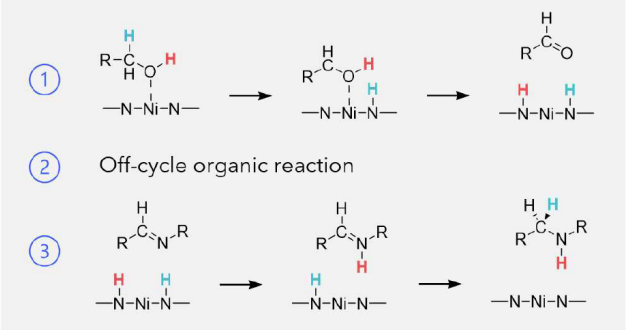
Graphene-based single atoms catalysts (SACs), which are expected to provide robust catalysts with well-defined reactive centers, are primarily used in electrochemistry.[1,2] Yet, thermal organic reactions like hydrogen borrowing (HB) are highly valuable for numerous synthetic processes. Examples of graphene-based SACs for HB are scarce, with only a few examples reported in the literature. Furthermore, the lack of computational studies has contributed to an insufficient understanding of the reactivity of these systems. To gain more insight into SACs for HB, a first study on a reported nickel N-doped graphene-based material converting aniline and benzyl alcohol into N-benzylaniline has been carried out at the DFT level, using cluster models.[3]





R: Aryl, ●: Ni, ●: N, ●: C

Our calculations revealed that, unlike typical homogeneous systems, and for all tested models, the H_2 dissociation step results in the formation of two protons, while the remaining electrons are transferred to the surface. The Ni-atom only acts as a spectator, challenging common expectations. Interestingly, the mechanism of the HB reaction is significantly different from that postulated for homogeneous catalysts, involving first the transfer of the carbon's hydrogen to the surface. Finally, our findings highlight the influence of the system charge on the reactivity and feasibility of the reaction. We believe that these results will contribute to the further development of more efficient catalysts.

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IV-38

Molecular dynamics simulations of cRGD-conjugated PEGylated TiO_2 nanoparticles for targeted photodynamic therapy

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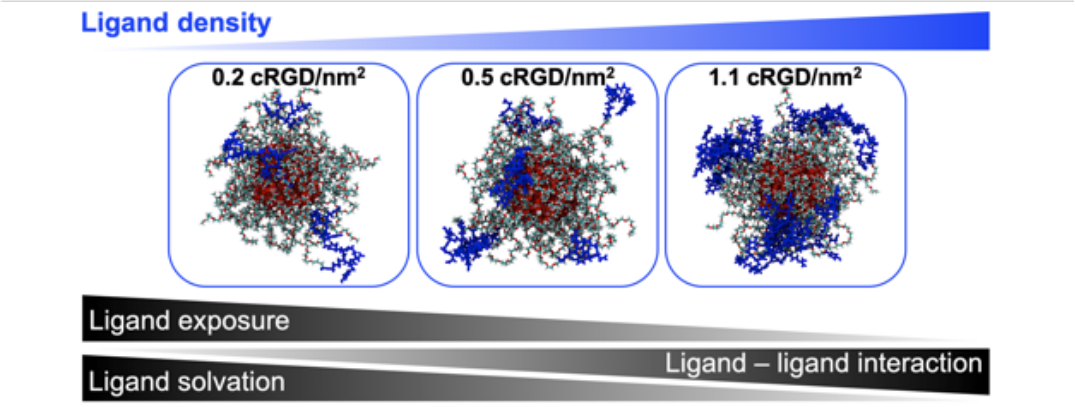
The conjugation of cyclic RGD (cRGD) peptides with a high affinity to $\alpha_V\beta_3$ integrins is a promising strategy in nanomedicine to efficiently reduce off-targeting effects of nanoparticles and enhance their cellular uptake by integrin-overexpressing tumor cells. [1] We used atomistic molecular dynamics simulations [2,3] to evaluate key structural–functional parameters of these targeting ligands for an effective binding activity towards $\alpha_V\beta_3$ integrins. An increasing number of cRGD ligands is conjugated to PEG chains grafted to highly curved TiO_2 nanoparticles [4] to unveil the impact of cRGD density on the ligand's presentation, stability, and conformation in an explicit aqueous environment.



We find that a low density leads to an optimal spatial presentation of cRGD ligands out of the ''stealth" PEGylated layer around the nanosystem, favoring a straight upward orientation and spaced distribution of the targeting ligands in the bulk-water phase. On the contrary, high densities favor over-clustering of cRGD ligands, driven by a concerted mechanism of enhanced ligand–ligand interactions and reduced water accessibility over the ligand's molecular surface. These findings strongly suggest that the ligand density modulation is a key factor in the design of cRGD-targeting nanodevices to maximize their binding efficiency into over-expressed $\alpha_V\beta_3$ integrin receptors. [5]

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IV-39

Solvent-dependent conformational diversity of polysaccharide-based chiral selectors

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Presently, around 60 % of newly commercialized drugs are chiral. In a racemic drug mixture, the enantiomer that does not cause the therapeutic effect may cause side effects or even be toxic. Therefore, the development of enantiopure drugs is strongly recommended by the regulatory authorities [1]. This generally imposes a need to separate the enantiomers in an analytical as well as in a preparative context. This is often accomplished by chiral chromatography – most frequently using polysaccharide-based chiral stationary phases. The present study is part of a broader effort to gain fundamental insights into the molecular mechanisms of separation on such polysaccharide-based chiral selectors. Critical to this endeavor is improving the available knowledge of the 3D structure and motion of these selectors in chromatographically relevant conditions. To this end, undecamers of amylose tris(3,5dimethylphenylcarbamate) and cellulose tris(3,5dimethylphenylcarbamate) chiral selectors were simulated on microsecond time scales in explicit acetonitrile/water mixtures with different compositions. Additionally, simulations in chloroform were performed for the purpose of validation against NMR data [2].

A thorough analysis of the simulation results in terms of local dihedral angles, helical twist angles as well as global undecamer conformation, reveals relatively large conformational fluctuations. In addition, qualitative differences were observed in the conformational sampling as a function of the composition of the acetonitrile/water mixture. The helix propensity of the polysaccharide selectors was found to differ depending on the solvent mixture. Overall, the results strongly imply that these types of chiral selectors should not be represented as rigid structures in future work, but as conformational ensembles that are highly dependent on the chromatographic conditions. In summary, the present observations not only provide guidance for the authors' future work, but also are relevant for the broader scientific community investigating separations on this class of chiral selectors.

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IV-40

Unlocking the Secrets of UiO-MOFs: Exploring Porosity, Confinement Effect and Catalyst Performance

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Metal-organic frameworks (MOFs), consisting of metal-ion-based centers and organic linkers, have gained increasing attention in recent decades. The frameworks exhibit high porosity, tunable pore size and a large surface area. These unique properties make them suitable for various applications including absorption, hydrogen storage, or heterogeneous catalysis. Among the well-known MOFs, the cubic Zr-based UiO frameworks, consisting of a metallic center and 12 linkers of tunable length, stand out due to their exceptional thermal and pressure stability, as well as solvent resistance.

In this work, we have constructed molecular models of catalytically active UiO frameworks with linkers of varying lengths. In detail monophenyl, biphenyl or triphenyl linkers with or without the organic catalyst proline were utilized to generate frameworks with different porosity and catalyst loading of 25, 50, 75 or 100 %. The systems are used to investigate adsorption in and diffusion through UiO-based MOFs using molecular dynamics (MD) simulations. Our goal is to unravel local diffusion and confinement effects of solvent, reactants and products and to predict maximal and optimal catalyst loadings for a specific combination of UiO-framework/catalyst/reaction kind.

Due to the large number of atoms and structural complexity of MOFs, coarse-grained (CG) MD simulations represent a meaningful simplification of the system. In CG representation atoms are bundled together into so-called beads with average properties of the atoms they represent. CG MD simulations require less computational power and are thus well-suited to study large and complex systems over long simulation times. Here, we parameterize the CG Martini3 force field for UiO-based MOFs. This process involves (i) establishment of the mapping strategy from AA to CG representation and (ii) fine-tuning the van der Waals properties of the CG beads through comparison with all-atom MD simulations. The CG parameters will boost our understanding and high-throughput characterization of MOFs.

IV-41

Polyhistidine-polyethylene glycol copolymers synthesized via solid-phase synthesis utilized for the self-assembling into pH-sensitive micelles for drug delivery applications

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pH-Responsive drug delivery systems hold significant importance for biomedical applications due to their ability to selectively release therapeutic agents in response to the specific pH conditions found in target tissues or cellular environments, thereby enhancing treatment efficacy while minimizing off-target effects. The present study investigated the efficacy of three different copolymer sequences consisting of poly (L-histidine) and polyethylene glycol (PEG) to self-assemble into micelles and subsequently utilized as pH-responsive drug delivery systems. The designed PEG unit length of co-polymer remained constant in all three sequences, with only the length of poly(L-histidine) varying. Synthesized sequences were assembled into micelles and loaded with precise amounts of doxorubicin (DOX). The pH-dependent disassembly owes to the amphiphilic character of the copolymer and the unsaturated imidazole groups of poly(L-histidine) that undergo a hydrophobic-to-hydrophilic transition in an acidic pH. The fluorescence-based pyrene method was employed to determine the critical micellar concentrations (CMC) of the three copolymer sequences in a pH 7.4 PBS buffer solution. The encapsulation efficiency and loading capacity of the micelles were assessed using spectrophotometric methods. Furthermore, the micelles' dimensions were characterized using dynamic light scattering (DLS) and scanning transmission electron microscopy (STEM). Finally, the DOX-loaded micelles were evaluated for their impact on cell viability using MDA-MB231 breast cancer cells.

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IV-42

cell2mol: Encoding Chemistry to Interpret Crystallographic Data

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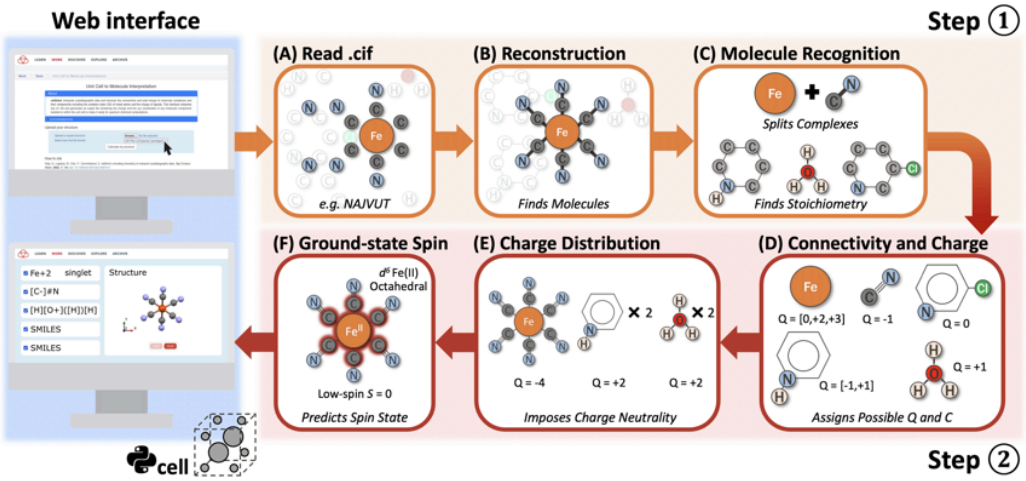
In data-driven computational chemistry, crystallographic data repositories (*e.g.* Cambridge Structural Database, CSD) can be an excellent source for building ideal datasets, given their database size, chemical diversity, and synthesizability. However, one major impediment to exploiting crystallographic data in computational chemistry, aside from experimental uncertainties, is that crystallographic data do not provide all the necessary information to run electronic structure computations. Basically, all quantum chemistry (QC) computations require the specification of atomic coordinates, total charge, and spin multiplicity of a molecular system. Determining these essential pieces of information from crystal structures is a demanding task, especially when dealing with molecular crystals containing transition metal (TM) complexes. This is because most TMs have multiple metal oxidation states (OS) that must be identified to determine the total charge of the molecular complex, and several TM ions even adopt different ground-state spin complexes depending on the coordination environment.

These challenges have prompted our development of *cell2mol*, a software that interprets the unit cell of molecular crystals, including those with TM complexes. *cell2mol* identifies all chemical species in a unit cell and retrieves the connectivity and total charge of molecular complexes and their components, including the OS of metal atoms and the charge of ligands. To demonstrate the performance of *cell2mol*, we construct datasets comprising 70,000 TM molecular crystals extracted from CSD, whose constituents include the largest variety of metals, ligands, solvents, and counterions, benefiting from decades of creativity in synthetic chemistry work. More than 1,000 different types of first coordination spheres and 8,000 unique ligands have been identified, and can be retrieved independently to generate a range of unprecedented combinations of species. Moreover, by leveraging these datasets, we develop an approach to predict ground-state spins of TM complexes. Lastly, we create a web interface for *cell2mol*, allowing users to upload a crystallography file and obtain output files containing all the essential information about the isolated molecular components or those within the unit cell, making them ready for QC computations.



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IV-43

Conformational Control of Thermally Activated Delayed Fluorescence (TADF) Molecules using Non-Covalent Interactions

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Thermally Activated Delayed Fluorescence (TADF) molecules have emerged as promising candidates for various applications, including organic light-emitting diodes (OLEDs), sensors, photocatalysts, imaging, and fluorescence labels. The molecular design of TADF emitters typically involves a Donor-Acceptor (D-A) framework, which necessitates a near 90° angle between the D and A units [1] to achieve a small spatial overlap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), leading to a small energy gap between low lying singlet and triplet states facilitating the use of thermal energy to up-convert non-emission triplet [2]. However, excessively rigid dihedral bonds can hinder the rotational and vibrational freedom necessary for the vibrational coupling mechanism [3], often leading to room temperature phosphorescence instead of TADF. Conversely, unconstrained motion around the D-A bond results in a dispersion of TADF rates, broad emission widths [4], and increased non-radiative decay rates. Introducing explicit chemical bonds to enhance rigidity often alters the electronic structure of TADF emitters significantly. Hence, achieving precise control over the molecular conformation of TADF emitters remains a critical challenge. One approach involves introducing steric hindrance between the D-A groups, e.g. methylation, but this can lead to conformational changes that restrict TADF. Another approach is to control the dynamics of D-A molecules through non-covalent interactions between the D and A groups which helps to reduce the conformational dynamics without restricting TADF. In this study, we explore the use of non-covalent interactions to exert conformational control over TADF molecules. We investigate the role of heteroatoms in controlling the orthogonal arrangement of the D-A groups in TADF molecules. Specifically, we explore weak interactions, such as B...O, B...S, or B...Se interactions, between the donor and acceptor groups. Additionally, we examine a D-A-D system where the central methyl substituents are replaced with methoxy, methylthio, and methylseleno groups to control motion around the D-A bond. Overall, this study highlights the importance of non-covalent interactions in controlling the conformational behaviour of TADF molecules and provides insights into the design principles for achieving efficient TADF materials.

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IV-44

Investigating the allosteric inhibition mechanism of I2 ligands in MAO-B using MD simulations with organic solvent/water mixtures

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The imidazoline receptors (IRs) are a group of pharmacologically characterized receptors involved in several physiological functions and are classified as I1-IRs, I2-IRs, or I3-IRs based on their affinity for different radioligands. I2-IRs are relevant in human brain disorders like depression, Alzheimer's[1], Parkinson's[2], and glial tumors. Highly affine and selective I_2-IR ligands have shown great potential as neuroprotective agents,[3] however, to date efforts aimed at identifying the molecular structure of I_2-IRs have been unsuccessful. Evidence suggests neuroprotective effects of I2-IR ligands may be linked to interactions with different proteins[4,5], particularly monoaminoxidase-B (MAO-B)[6], involved in dopamine deamination.

In this work, we employed molecular dynamics simulations using solvation boxes of water/organic solvent mixtures[7] to characterize putative I2-IR sites within the structure of several potential I2-IRs. Probes like ethanol, iso-propanol, pyridine, and water were utilized to reveal high-affinity interaction spots for I2-IR ligands. Density analysis of retained solvent molecules provided valuable insights into binding sites for I2-IR ligands. Among these proteins, our objective is initially to investigate the entrance and exit pathways of MAO-B substrate Dopamine and its aldehyde metabolite Dopal. By comparing these pathways with the interactions of 2-BFI I2 ligand, we aim to uncover the mechanism through which I2 ligands regulate MAO-B. We will investigate the regulation of MAOB by 2-BFI I2 ligand, which is likely achieved by disrupting the normal enzyme turnover and potentially competing for binding sites along the product pathways.

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IV-45

An exceptional reaction mechanism of a hydropyrene terpene synthase

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Terpene synthases are responsible for the biosynthesis of terpenes, the largest family of natural products. Hydropyrene synthase (HpS) generates hydropyrene and hydropyrenol as its main products along with two byproducts, isoelisabethatrienes A and B. Fascinatingly, a single active site mutation (M75L) diverts the product distribution towards isoelisabethatrienes A and B.

In the current work, we study the competing pathways leading to these products using quantum chemical calculations in the gas phase (M06-2X/6-31G+(d,p)) and in the enzyme using ligand-protein docking. From the gas-phase calculation, we show that there is a great thermodynamic preference for hydropyrene and hydropyrenol formation, and hence most likely in the synthesis of the isoelisabethatriene products kinetic control is at play. To further investigate the role of HpS in the biosynthesis of hydropyrene, hydropyrenol, isoelisabethatrienes A and isoelisabethatrienes B, we performed EnzyDock multiscale mechanistic docking. From these simulations, we demonstrate the working principle of this enzyme and the effect of the mutant. [1-2]

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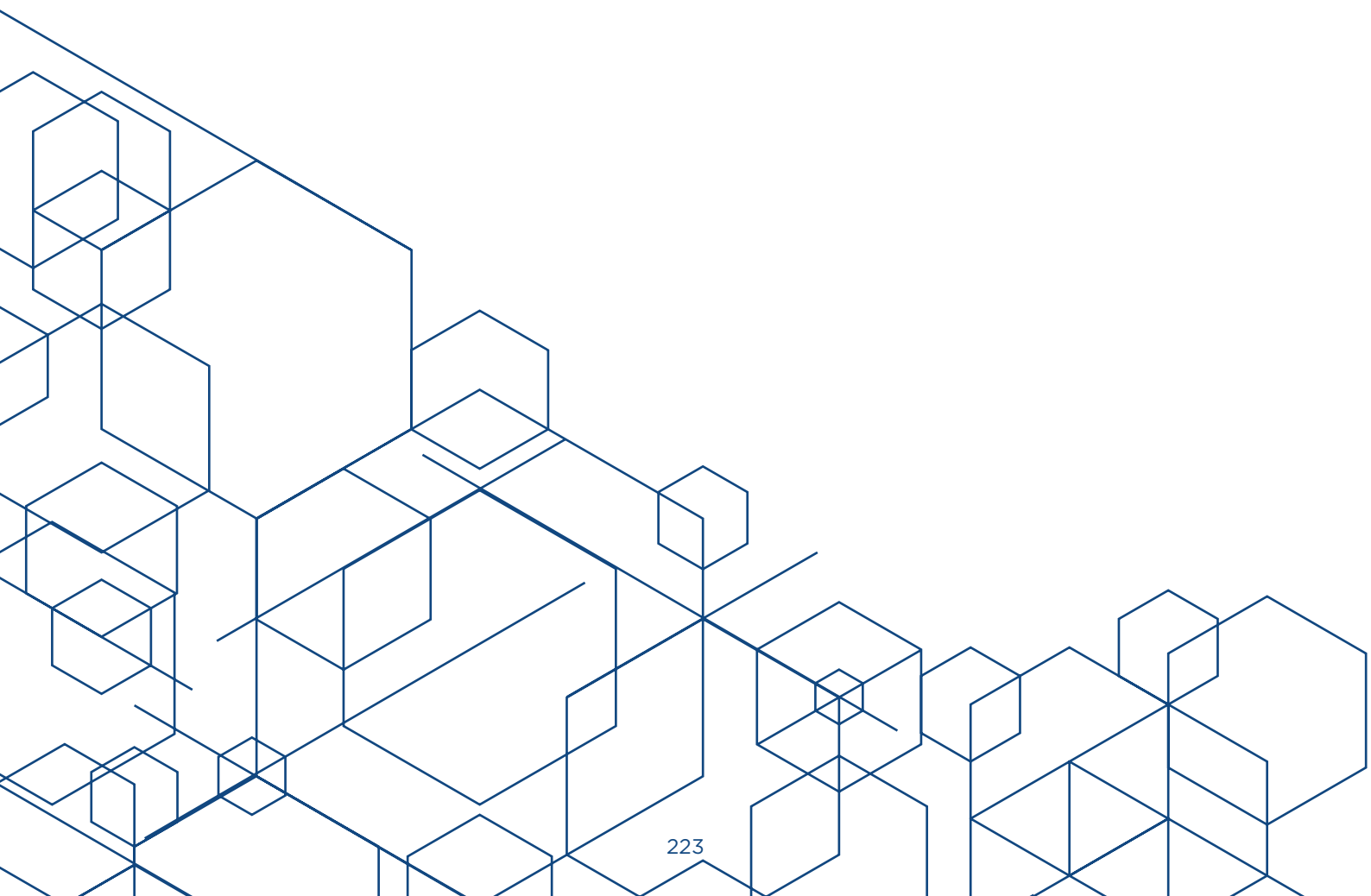
COMPUTATIONAL CHEMISTRY IN INDUSTRY



I-20

First-principles insights on solid-state transitions in layered oxides as high energy cathodes for Na-ion batteries: effects of sodiation/desodiation in Na_xMnO_2

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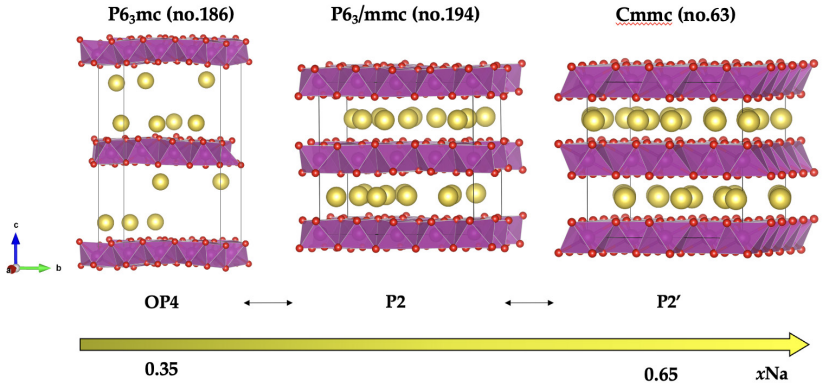
Layered Transition Metal Oxides (Na_xTMO_2) are a promising class of high-energy cathode materials for Na-ion batteries [1]. Their general structure consists of TMO_6-octahedra 2D slabs sandwiched between Na layers, the relative position among the slabs and the packing of oxide layers defines the material morphology, P2- and O3- structures are some examples [2]. While mixed transition metal oxides in this class of cathodes have shown promising performances and enhanced anion redox activity [3, 4], ongoing research aims at improving their long-term stability, which is often hampered by solid-state phase transitions occurring during Na^+ insertion and extraction cycles, with structural collapse and significant capacity loss. Understanding and controlling these structural transformations is therefore of outmost importance to boost the electrochemical performance of layered oxides. Using the solid state nudged elastic band (ss-NEB) method [5] combined with state-of-the-art density functional theory (DFT) calculations, here we address the prototypical case of P2 ↔ P2'/OP4 transitions in Na_xMnO_2 [6]. Thus, we provide an atomic-level perspective on the glide-driven processes in these compounds. In particular, our analysis confirms that the key role of Jahn-Teller effects and of Na^+ ordering at low state of charge as the driving forces for these phase transitions, also pointing out how the ss-NEB method can be useful to finely characterize these subtle processes. In conclusions, our new structural and electronic insights will provide a solid scientific framework for designing new layered transition-metal oxides with enhanced stability for long term battery operations.



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I-21

DFT study of the cyclohexane oxidation mechanism with a tridentate copper complex

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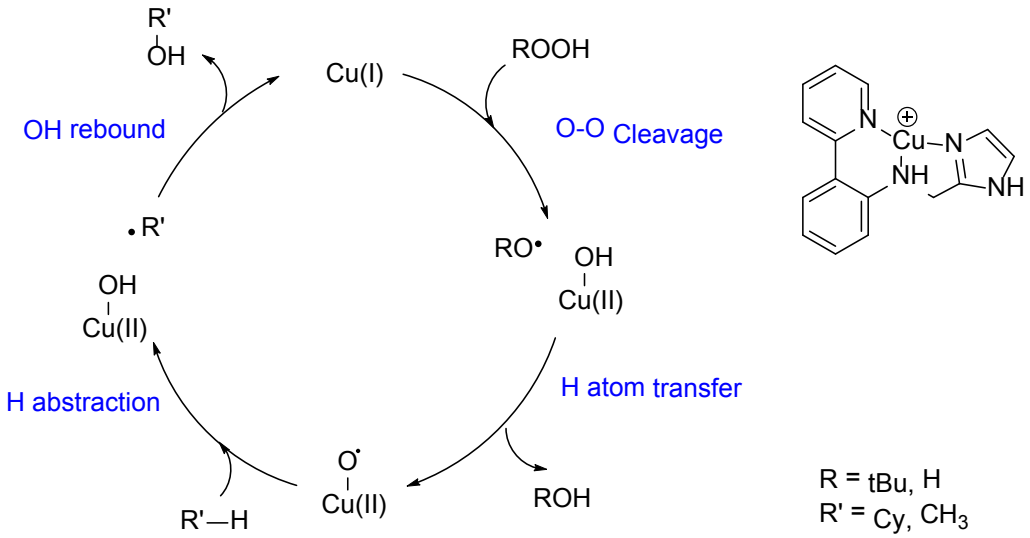
In Nature, monooxygenases (such as pMMOs and LPMOs) consisting of 'histidine brace' and copper species have shown promise in the selective cleavage of strong C-H bonds [1]. Our group have synthesized a tridentate copper complex, which includes the histidine brace, and tested it for cyclohexane oxidation [2]. However, the active species of copper remained unclear.



In this work, we investigated the reaction mechanism of the Cu(I) complex activated by H_2O_2 and the formation of Cu(II)-O• species using DFT calculations. We propose a catalytic cycle that begin with the homolytic cleavage of H_2O_2 on the copper site, leading to the formation of Cu(II)-O• species and eventually H_2O. The Cu(II)-O• species can then abstract hydrogen from cyclohexane, forming Cu(II)-OH species and cyclohexyl radicals. Finally, the rebound step occurs, resulting in the production of cyclohexanol and reduction of Cu(II) to Cu(I). The effect of the solvent and water on the formation of Cu(II)-O• species was also investigated using AIMD simulations. These findings shed light on the potential of the tridentate copper complex for selective C-H bond cleavage, and provide insights into the role of the solvent and water in this process.

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I-22

A Mechanistic view towards CO_2 reduction at Solvent-Metal interface by Ab-Initio Molecular Dynamics

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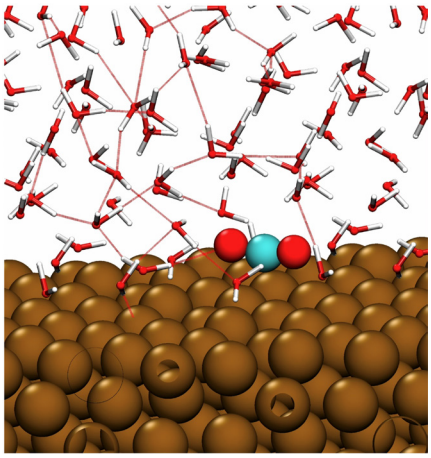
The considerable increase in carbon dioxide (CO_2) concentration in the atmosphere due to fossil fuel consumption could lead to irreversible climate changes. An effective way to reduce atmospheric CO_2 is electrochemical conversion of CO_2 to value-added chemicals and low carbon fuel. Copper (Cu) based electrodes are one of the extensively researched heterogeneous catalysts for this reaction. In this research, CO_2 reduction at the Metal-water interface is studied by first-principle molecular simulation with the aim to elucidate the reactions pathways and understand the role of solvent conditions and their interaction with the metal surface which has been shown to have an effect in the reaction process.



CO2 adsorbed on to Cu surface with explicit water molecules

We employ a realistic model based on density functional theory, that incorporates explicit water molecules and accounts for thermal fluctuations by molecular dynamics. This may provide guidelines for rational design for optimal Cu-based electrochemical devices for CO_2 conversion which will provide basis for exploring other (e.g. Pt-Pd) systems.

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I-23

Molecular Dynamics of Glyme-based Electrolytes in Battery Systems

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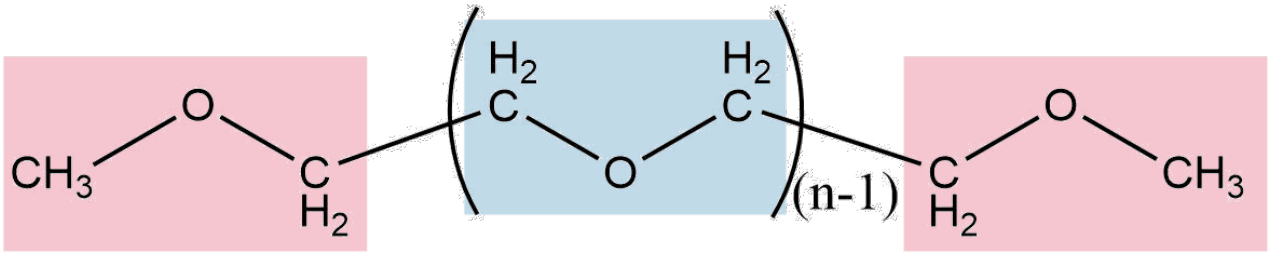
Glyme (glycol methyl ether)-based electrolytes are currently of interest for developing various alkaline and alkaline-earth ion battery technologies due to their higher stability with respect to carbonate-based electrolytes. Performance is crucial for the viability of these systems, and it is closely linked to atomic scale properties such as ionic conductivity and electrode-electrolyte interface (SEI) formation. Classical molecular dynamics (MD) is a powerful tool for gaining insight into such phenomena. Efficient and accurate simulations with the AMOEBA[1] polarizable force field are made possible with recent software such as Tinker-HP[2].



We first propose a procedure to parametrize a universal AMOEBA force field for all glymes[3] and assess the robustness of parameters with respect to experimental and computational results. A series of trajectories are then generated for different cation systems. In addition to conventional methods such as radial distribution functions, graph theory is employed to perform more thorough analyses of trajectories. We ultimately discuss the potential relations between the calculated local and bulk properties; and experimental observations.

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I-24

Effects of dispersion corrections on the temperature dependent structural properties of $SrZrS_3$ phases

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Chalcogenide perovskites can exist in multiple phases, each exhibiting distinct electronic properties. $SrZrS_3$ is the only ternary chalcogenide which can be experimentally synthesized in two separate crystal phases, NH_4CdCl_3 and $GdFeO_3$ structures, also commonly known as the needle (NL) and distorted perovskite (DP) phase respectively. Although the ground state energy differences of these phases is very small, the NL phase is favoured over DP phase at low temperatures. The prediction of accurate structure highly depends on the quality of description of long-range van der Waals interactions, which are neglected by conventional semi-local DFT functionals. Ergo, the performance of different dispersion correction methods have been tested at static level of theory, based on which, the DFT-D3 [1] and the Tkatchenko-Scheffler method with iterative Hirshfeld partitioning [2] (TS/HI) are found to achieve correct predictions of structural parameters. Temperature dependent structural properties for both the DP and NL phases have then been investigated for the DFT-D3 and TS/HI dispersion corrections, using ab-initio molecular dynamics accelerated by machine-learned force fields.[3,4] We infer that the TS/HI corrections yield predictions with significantly lower mean absolute errors as compared to DFT-D3 method. We also put forward some insights into the thermal stability of these phases at different temperatures.

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I-25

Role of Third Gas Species in CO_2-CH_4 Exchange in Natural Gas Hydrates

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In the modern era, population growth and shifting of lifestyle towards technology has led to an overgrowing requirement for energy and clean environment. One of the major energy resources are fossil fuels, however they are limited and also major reason for increasing environmental pollution. Hence, better alternatives for clean energy are needed and, in this direction, Natural Gas Hydrates (NGHs) are one of the most abundant and clean energy alternatives. The exchange of CH_4 with CO_2 in NGHs is one of the potential alternatives to recover clean energy and simultaneous sequestration of CO_2.[1-2] The radius of CO_2 molecule (2.56 Å) is large compare to CH_4 (2.18 Å), hence, ideally, 80% of CH_4 can be replaced with CO_2 in NGHs [3]. However, success upto 50% has been obtained at the laboratory scale for CH_4-CO_2 exchange. In swap method, a mixture of CO_2 and N_2 is used to replace CH_4 that showed methane recovery upto 84%.[4] However, currently there is limited understanding about the factors that control CO_2-CH_4 exchange in NGHs at molecular level in heterogeneous medium. In this work, we have studied the role of different gas species as a function of size and interaction strength to explore the role of factors that control CO_2-CH_4 exchange in NGHs using molecular dynamics simulation techniques. The results provide detailed insights into molecular factors and helped to predict novel alternatives that could enhance CO_2-CH_4 exchange in NGHs.

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I-26

Thermochemical conversion of CO_2 to C_1 & C_2 compounds: Perspectives from a combined density functional theory and microkinetic modelling approach

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Carbon dioxide (CO_2) is one of the key contributors of atmospheric pollution and plays a significant role in anthropogenic global warming. Therefore, scientists across the world are focused on CO_2 capture and utilization. In this regard, there have been tremendous efforts in reducing CO_2 primarily *via* electrochemical methods; however, most of the electrochemical CO_2 reduction reaction (CO_2RR) experiments are found to be selective to C_1-products, with trace or comparatively less amounts of $\geq C_2$-products.[1,2] Longer chain molecules are valuable as increasing carbon content in hydrocarbons increases their energy density.[2] The formation of less $\geq C_2$ products in electrochemical CO_2RR processes is majorly because of energy-intensive C-C coupling reactions, which are independent of the electrode potential. In this study, we extensively explore the mechanistic pathways of thermochemical CO_2 reduction, targeting all possible C_1 and C_2 compounds (Figure 1(a)) using density functional theory (DFT) and microkinetic modelling (MKM).

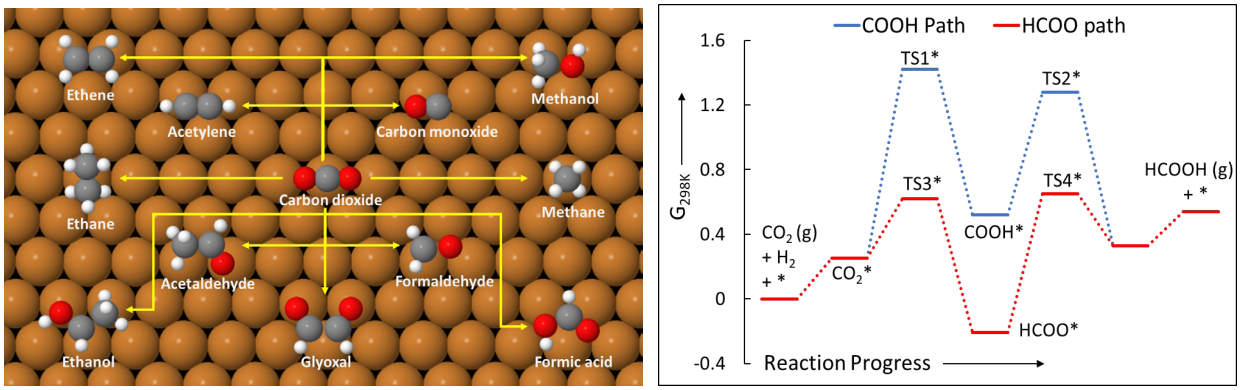

Figure 1. a) Graphical representation of CO_2RR producing all C_1 & C_2 products on the Cu(111) surface, b) CO_2 reduction reaction kinetics to produce formic acid via COOH and HCOO pathways.

We map a comprehensive CO_2RR reaction network with a total of 70 surface reactions on the Cu(111) catalyst surface. DFT was utilized to obtain the reaction thermodynamics and kinetics, and MKM was employed to predict the production rates by solving the reaction rate expressions. According to DFT, the elementary reaction steps in the most favourable pathway for the production of all C_2 compounds remain below 1 eV except for the rate-determining step (HCOOH ➠ CHO, $\Delta^{\ddagger}G_{298K}$ = 1.21 eV). Because of such a high activation barrier, our MKM study predicts major production of HCOOH, with C_2-products in comparatively less amounts. Nevertheless, the reaction conditions, e.g., temperature, pressure, and feed composition are shown to have considerably positive effect on the selectivity of C_2-products.

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I-27

Substituted Cu (100) stepped surfaces as potential sensors for volatile organic compounds: A first-principles outlook

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In this paper, first principles calculations based on the periodic density functional theory are used to investigate the adsorption and sensing performance of a Cu (100) stepped surface for thiophene (C4H4S) and pyridine (C5H5N) volatile organic compounds, with a vdW interaction scheme to account for dispersion effects.

Theoretical analysis of the adsorption configuration of both molecules with surface defects exhibit remarkable structural effects, the results for Cu (100) surface defects are higher than the adsorption behavior of thiophene and pyridine molecules on pure Cu (100) surface. This type of interaction between the hetero-molecules and metal atoms in typical stepped surfaces, allowed generating organic interaction with more realistic surfaces.

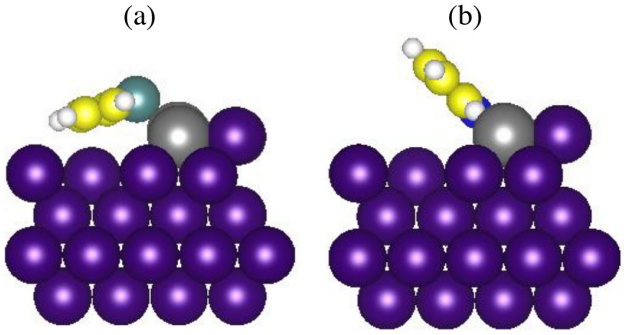

Figure 1. Adsorption of thiophene (a) and pyridine (b) molecules on substituted Pt-Cu (100) stepped surface.

In real applications, Cu (100) surface defects might be an efficient adsorbent and an appropriate sensing platform for VOCs molecules.

Keywords: Adsorption, DFT investigation, Cu (100) stepped surface, Thiophene, Pyridine, Volatile organic compounds.

I-28

From reference data to predictive models: modeling physicochemical properties of ionic solutes

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The accurate prediction of physicochemical properties of ionic solutes, e.g., solvation free energy, solubility, and lipophilicity, is crucial for designing and developing new materials, optimizing chemical processes, and modeling pharmacokinetics. However, the high uncertainty and limited availability of data pose a challenge in the development of computational prediction methods. To address the first issue, we created the DISSOLVE[1] database consisting of 330 data entries and achieving uncertainties of 1.5 kcal/mol for aqueous and 2.6 kcal/mol for non-aqueous absolute solvation free energies of ionic solutes. We further addressed the issue of data scarcity by extending DISSOLVE[1] to more than 10000 data entries, creating the DISSOLVE^{XT} database, which provides a robust foundation for future research in this field. To achieve this, we initially collected approximately 10000 pK_a values from the iBonD[2] database. Next, we calculated gas phase acidities, benchmarking various levels of quantum chemical theory to achieve an optimal balance of computational cost and accuracy. We determined the solvation free energies of neutral solutes and utilized previously published data on the solvation free energies of the proton. In this work, we further discuss how the data is leveraged to parameterize the openCOSMO-RS[3] solvation model and train a D-MPNN model for the accurate prediction of solvation free energies of ionic solutes. After evaluating the performance of these methods, we discuss the future research directions for modeling the complex chemistries of ionic solutes, highlighting the need for continued innovation and discovery in this rapidly evolving field.

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I-29

Bonding Interaction of NO and Fe^{2+}/Fe^{3+} for the Reversible Redox Reaction: Density Functional Theory Study

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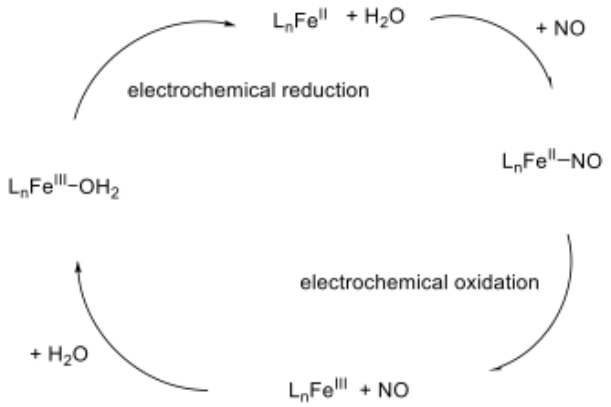
Combustion of fossil fuels generates nitrogen oxides (NOx), a combination of nitric oxide (NO) and nitrogen dioxide (NO_2), which have given harmful impact on human health and the environment. NOx is converted to nitrate particulates in the atmosphere. and these make up a large proportion of the fine particle pollution. To remove these contaminants to comply with the strict environmental emission standards, selective catalytic reduction (SCR) using ammonia at 300-500°C is currently widely used. The problems of catalyst poisoning by fly ash rich in arsenic or alkali, disposal of spent toxic catalysts, and the effects of ammonia by-products on plant components downstream, created needs for better systems.[1,2] Here we presents an alternative method of using metal complexes for absorbing NO at a certain oxidation state and removing it at a different oxidation state using electrochemical methods. To develop a better catalyst for the above role, we calculated interaction between NO and various metal complexes using density functional theory study.

Three different ligands shown in Figure 1 were studied for the catalytic cycle shown in Scheme 1. All Fe(II) complexes studied can combine one NO or two NO molecules. And all Fe(II) complexes releases one NO upon oxidation to Fe(III). Therefore, the proposed concept is proven.



Scheme 1. Proposed Catalytic Cycle

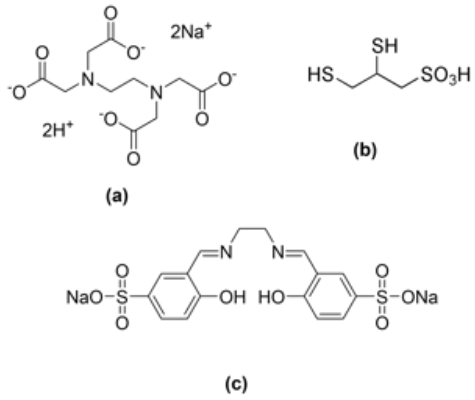


Figure 1. Ligands Studied.

(a) EDTA (b) DMPS (c) Salen

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I-30

Modelling Ion-Assisted CO_2 Electro-Conversion in Metal Porphyrin Cages

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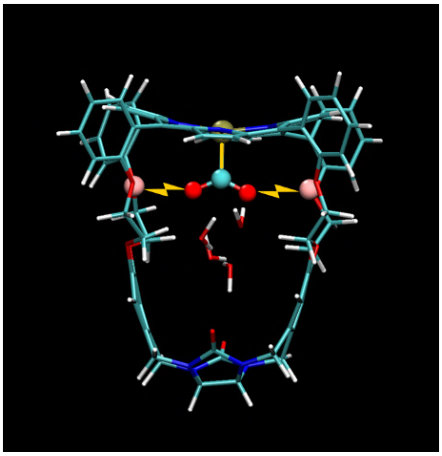
Using renewable electricity to convert greenhouse gas CO into commodity chemicals is promising. Alkali cations in the electrolyte have been proposed to regulate the reactivity of catalysts. While their impact in heterogeneous catalysis is demonstrated in detail, cations' role in homogeneous electrocatalysis remains underexplored. In this research, focusing on CO product, hosting of potassium or sodium ions in the metalloporphyrin cage assists in decreasing the overpotential of CO electroreduction with high selectivity. Ab initio molecular dynamics simulations (with the Born-Oppenheimer approach, implemented in CP2K) will be employed to probe the behaviour of K and Na in the system with an aqueous solution, ascertaining how numbers and types of alkali cations affect catalytic process.



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I-31

ONIOM meets *xtb: Efficient, Accurate, and Robust Multi-Layer Simulations Across The Periodic Table*

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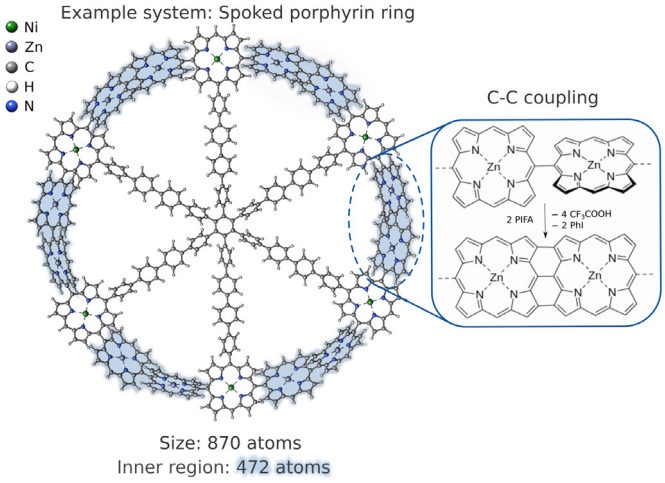
With the advancement of computational power, modern computational chemistry has gained resources to study increasingly complex molecular structures. To analyze such systems the development of well-balanced (in terms of speed and accuracy) computational methods is of great relevance. One prominent example is the "Our own N-layered Integrated molecular Orbital and molecular Mechanic" (ONIOM) [1] integration framework, which fragments the system into multiple layers each treated separately with the different levels of theory.

In our research, we have implemented the ONIOM framework in the *xtb* extended tight-binding program package [2] and applied it to several complex metal-organic systems. The calculations involved elucidation of electronic energies, geometry optimization, and accounting for explicit solvation effects in the transition-metal complexes containing several hundreds of atoms.



Our findings show that the ONIOM combination of density functional approximations, semi-empirical, and force-field methods drastically reduces the computational costs with minimal compromise in accuracy even for complicated electronic structures such as metal-organic frameworks (MOFs).

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I-32

A DFT Approach to Exploring Metal-Assisted Complexation of Dye Molecules by Cucurbiturils

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The discovery of host-guest systems has revolutionized the complexation chemistry, which led to their widespread application in industries like food, pharmacy, medicine, environmental protection, and cosmetics. Among the great variety of host systems, cucurbiturils (CB) have attracted substantial scientific interest due to their superior qualities as cavitands, surpassing the traditional cyclodextrins and calixarenes. Furthermore, metal cations have been explored as effective agents in order to enhance the complexation properties of CBs, exerting a unique dual effect on the recognition processes: they can either compete with another guest molecule for binding or associate to already formed CB@guest structures. Previous research has identified magnesium (Mg^{2+}) and gallium ions (Ga^{3+}) as the most potent cations to bind the studied CB molecules. The present study focuses on elucidating the role of these metal species in the complex formation of ternary complexes with three dye molecules: thiazole orange, neutral red, and thioflavin T. Various key factors influencing the process have been recognized, including pH and dielectric constant of the medium, cavity size of the host molecule, charge of the metal ion (M^{n+}), and the presence or absence of a hydration shell when modeling the metal cation. To investigate these aspects, a previously calibrated and further validated DFT methodology (in line with experimental data) is employed. The findings derived from this comprehensive investigation shed new light on several fundamental aspects of the cucurbituril complexation chemistry, thereby enriching our understanding of the intriguing host-guest recognition process.

[1] Kircheva, N.; Dobrev, S.; Dasheva, L.; Nikolova, V.; Angelova, S.; Dudev, T. *Molecules* **2023**, *28*, 1540–1555.

Funding This poster presentation is funded by the Bulgarian National Science Fund, grant number KP-06-N39/10 (project "BIRDCagE").

I-33

Computer-aided analysis for identification of novel analogues of ketoprofen based on molecular docking for the treatment of inflammation

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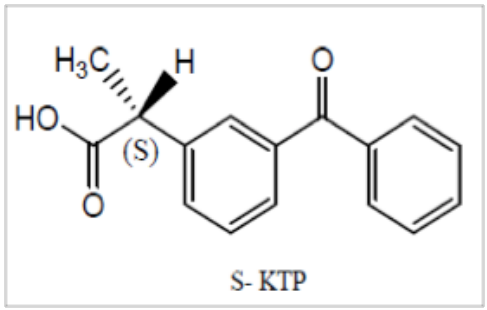
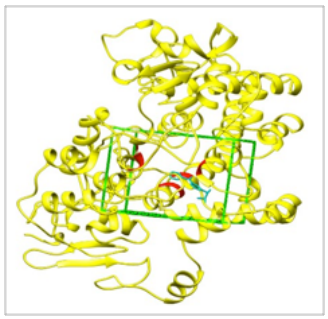
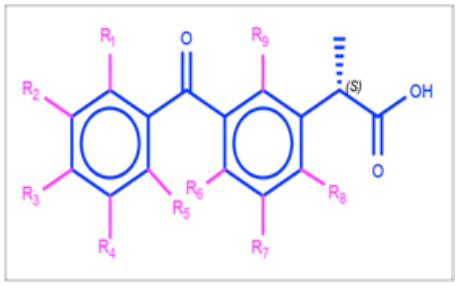
Computer-based drug design is increasingly used in strategies for discovering new molecules for therapeutic purposes. In silico drug design methods facilitate the search for bioactive molecules, make it possible to reduce costs, identify potentially therapeutic molecules more quickly and reduce in vivo / in vitro tests. The targeted drug is ketoprofen (KTP), which belongs to the family of non-steroidal anti-inflammatory drugs, which are widely used for the treatment of pain, fever, inflammation and certain types of cancers. To carry out this work we have rationalize 72 new potential anti-inflammatory compounds on the COX-2 enzyme, we carried out a theoretical study mainly based on molecular docking. It's an important tool in computational drug design by which one can predict the pharmacological activity and predominant binding mode(s) of a ligand with a target protein. For that, a molecular docking analysis was performed by using AutoDock Vina 1.1.2 program implemented in UCSF Chimera 1.15 software. The optimized analogues were subjected to a molecular docking study against human prostaglandin synthase protein 5F1A (chain A). We consider the protein as a macromolecule and the candidates as ligand where the KTP drug was considered as control and derivatives binding affinity was compared with the parent drug, which is a known COX-2 inhibitor. The 3D visualizations and 2D non-bond interactions of the complex receptor-ligand structure were performed using Discovery Studio 2020 software to analyse the docking result. Therefore, at the end of this study only 20 compounds were selected and predicted to be the most active systems since they are characterized by a lower binding energy compared to the starting compound S-KTP towards the COX-2 target.





(b)



(a)

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I-34

ChemTraYzer: A Novel Tool for Finding Reaction Pathways to support construction and refinement of Chemical Models

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Chemical models are an effective support for explorative research, and especially crucial in optimization of large scale technical applications, e.g. in chemical engineering, combustion, and (electro)-catalysis. The still most frequently used approach (the "conventional" approach) consists of creating a model from intuition, databases, reaction classes and analogies and then refining it based on experimental data. Especially for less common compounds, e.g. novel bio-hybrid fuels or not well-understood processes, the current model creation approach is time consuming and error prone. Therefore, researchers currently investigate different approaches to automate the model creation. One of these approaches is the Chemical Trajectory analYzer, ChemTraYzer or just CTY[1]. It analyses trajectories from reactive molecular simulations for reactive events, provides means for accelerating them (CTY-temperature accelerated dynamics[2] and metadynamics), and can schedule high-level quantum mechanical calculations if needed.

In this poster, we report on recent CTY developments and analyse the potential of acceleration techniques and transition state finding. We apply CTY to industrially relevant reactions, and soot precursor formation pathways and discuss the reactions found in relation to known reactions and reaction classes.

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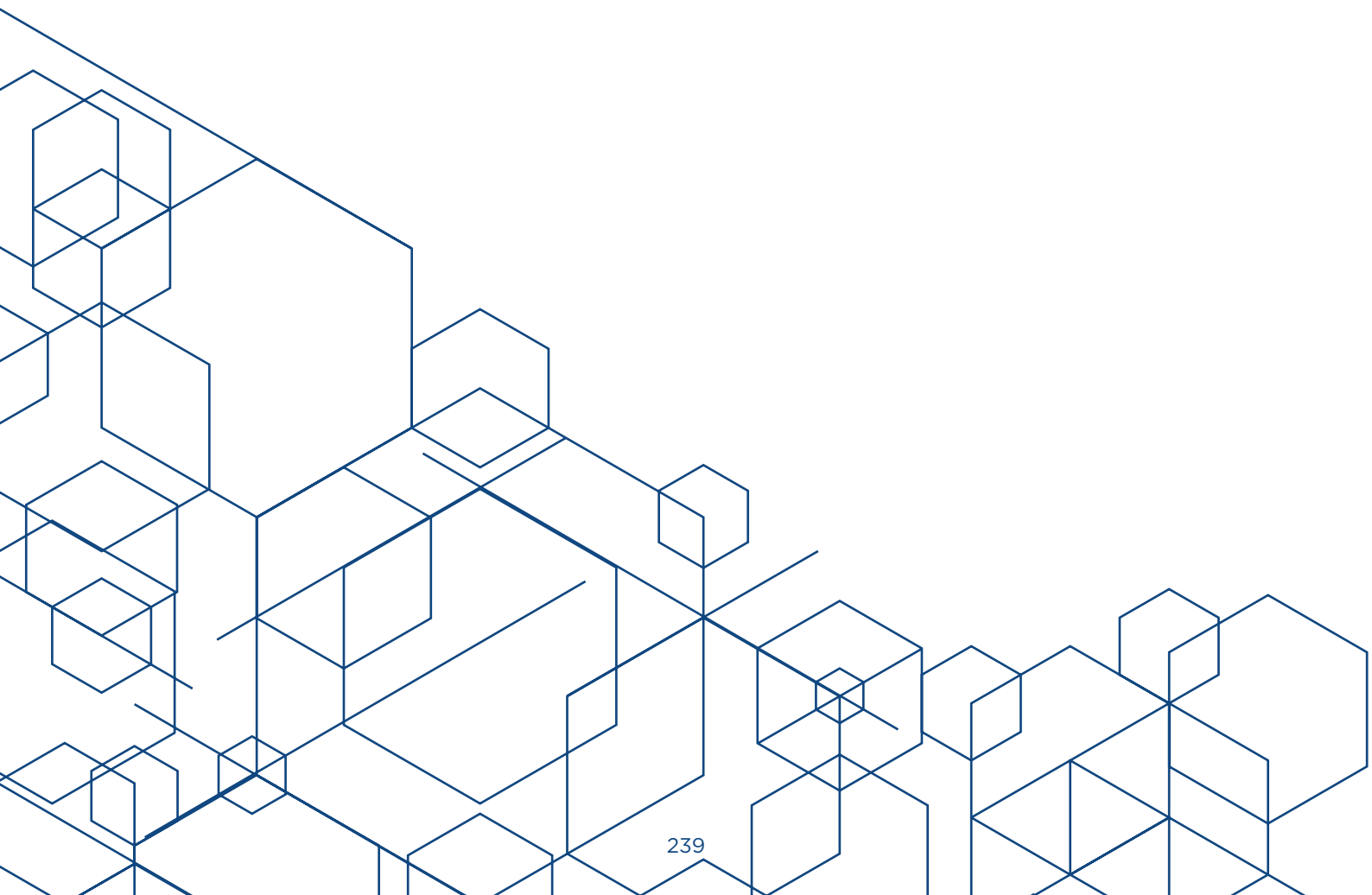
BIOMOLECULAR SYSTEMS



II-20

Gaseous Inhibition of the Transsulfuration Pathway by Cystathionine β-synthase: CO, or NO?

Neil R. McFarlane, Jiangli Gui, Jeremy N. Harvey, Julianna Oláh

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Human cystathionine β-synthase (CBS) plays a key role in the transsulfuration pathway,[1,2] in which the canonical reaction involves thiol transfer from homocysteine to cysteine, and side-reactions generate H_2S. The mechanism by which these reactions occur is relatively well-understood,[3,4] but the inhibitory role of a rather unusual 6-coordinate heme cofactor lying 20 Å from the active site and its pyridoxal 5'-phosphate cofactor (see ***Figure 1a***) is less well known and is the focus of this study.[5]

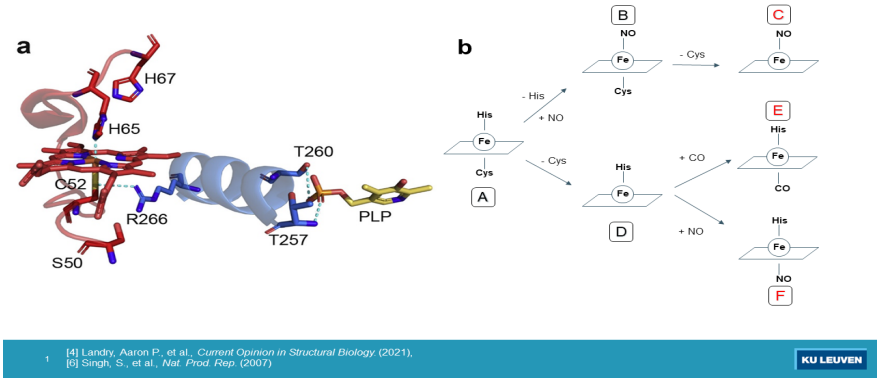

Figure 1: ***(a)*** Heme and PLP active site cofactors in human CBS. ***(b)*** Experimentally observed gaseous inhibitory pathways (A ➠ C and A ➠ E) and possible additional inhibitory pathway (A ➠ F).

Cysteine 52, which interacts with the heme group in the resting state, is expected to play a key role in inhibition.[6] In this study, we explore the structures that arise following coordination of small gaseous inhibitors CO or NO to the heme group, and which involve decoordination of Cysteine 52 (***Figure 1b***). Energetics of the coordination/decoordination steps are studied using a model system with DFT and DLPNO-CCSD(T_1) calculations, while MD simulations are used to explore the ensuing changes in structure in the active site. We consider these computations within a biological context, and highlight the emerging theme of the complex interplay between the gaseous signalling molecules CO, NO and H_2S.[7]

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II-21

Stopping metastasis through Cortactin-SH3 inhibitors

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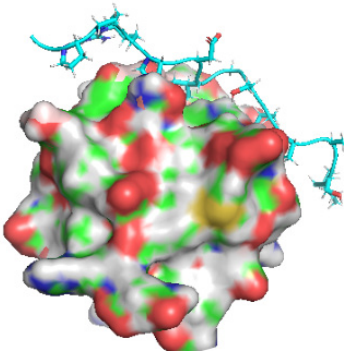
Cortactin is a protein located in the cytoplasm of cells that is important for the polymerization and rearrangement of the actin cytoskeleton. When activated, it stabilizes nucleation sites for actin branching. Cortactin SH3 domains bind peptides or segments of proteins that usually are rich in prolines with a "PXXP" motif, such as Pyk2 and WIP.

Our goal is to discover peptides that bind with high affinity to the SH3 domain of cortactin and thus function as regulators of its behavior. The current research is based on combined experimental and computational approaches. For the computational part, we use the HADDOCK docking program, as well as the docking program EnzyDock, which is a CHARMM-based program utilizing molecular dynamics and Monte Carlo simulated annealing, together with minimizations and chemical information. Using docking, we narrow down the number of promising peptides to a small number that can be tested experimentally. This small set of peptides is prepared experimentally and studied using NMR spectroscopy. We use HSQCs to determine affinities and ^{13}C-edited NOESY spectra to determine the structure of key complexes. So far, we have found a peptide that increases the affinity by 50-fold relative to the WT and we identified critical residues and their positions.



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II-22

Understanding Fe3+ Theft by *Neisseria Meningiditis*: A Comprehensive Computational Study

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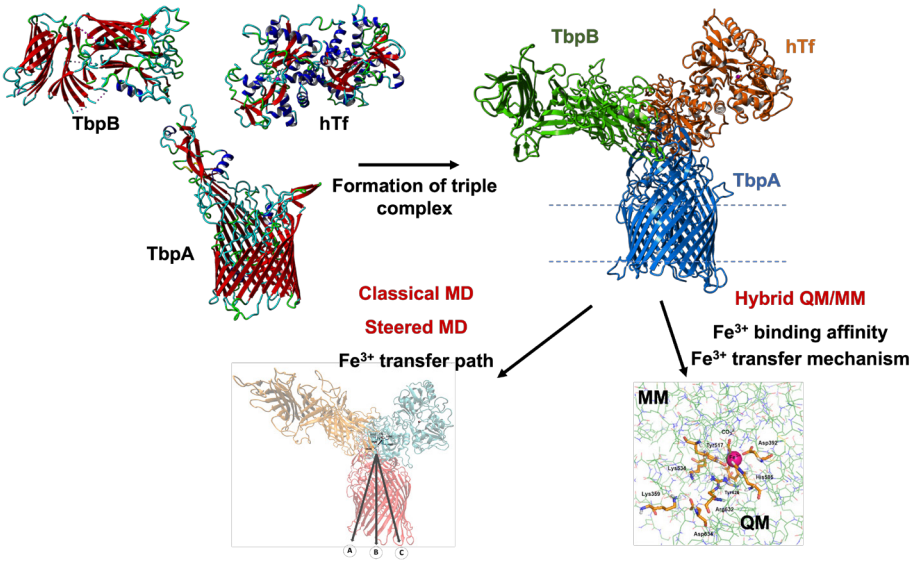
Ions such as sodium (Na^+), chloride (Cl^-), zinc (Zn^{2+}), and iron (Fe^{3+}) play vital roles in homeostasis, excitability, signal transduction, and enzymatic processes in cells. Among these ions Zn^{2+} and Fe^{3+} cannot penetrate the phospholipid cell membrane, thus they require transmembrane ion channels or complex protein complexes, which transport these ions in and out the cell. [1] The pathogen *Neisseria meningitidis*, that causes meningitis, needs iron for its virulence and life cycle. [2] It acquires Fe^{3+} ion by the help of TbpA-TbpB protein complex, binding to human Tf protein. 3-D structure for this triple protein complex hasn't been resolved, although there are double protein complex 3D structures available. [3-4] Thus, it is very important to model this triple protein complex at atomistic level of detail to understand the exact mechanism for this ion transfer, which will further allow researchers to design drug candidate molecules to stop this transfer from the human host to pathogen bacterium. There are several experimental and computational studies in the literature trying to elucidate this iron transfer mechanism. [5-9] However, they either lack atomistic detail or the triple protein complex formation. In this study, structure of triple TpbA-TbpB-hTf protein complex were built utilizing classical molecular dynamics (MD) simulations, protein-protein docking simulations and meticulous modelling, for the first time in the literature, revealing key amino acids at the protein interface. In addition to wild-type protein complex, TbpA protein Lys359Ala mutant triple



complex structure was also created to understand the role of Lys359 amino acid at the ion transfer. Hybrid quantum/molecular mechanics (QM/MM) calculations were utilized to understand the mechanism of Fe^{3+} abstraction from the coordination shell and hierarchy of events leading to the ion transfer at the atomistic level of detail. Upon studying both wild type and Lys359Ala mutant, it was clear that TbpA Lys359 amino

acid clearly plays a pivotal role in loosening of Fe^{3+} ion from the coordination shell through Lys-Asp-Arg-Tyr network, which forms the first step for the ion transfer. Following the abstraction, the most possible path that ion follows towards the bacterium interior through TbpA protein was studied utilizing steered MD (SMD) simulations. Various computational tools were utilized to understand the exact mechanism of Fe^{3+} ion transfer for the first time, which makes the current study unique. The outcomes of this project will lead the computational and experimental design of small molecules to inhibit this ion transfer, which in return might cure the meningitis.

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II-23

Computational and experimental insights of natural molecules from Indian traditional herbs in the treatment of p53-driven carcinogenesis

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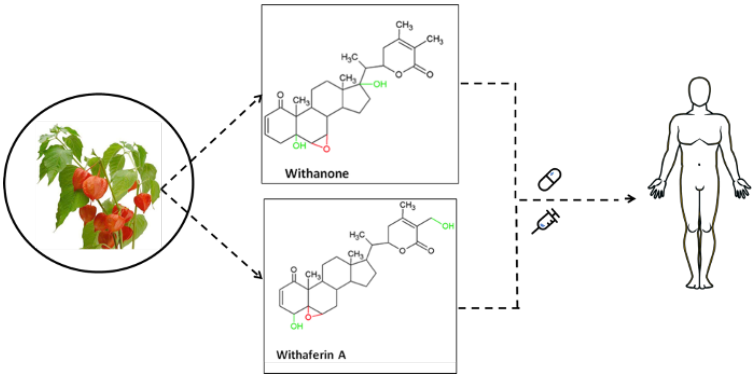
Natural resources have emerged as a crucial source of pharmaceutically relevant novel secondary metabolites, several of which are already approved, and many are under development or in clinical trials. The bioactivity of natural compounds like withaferin-A, caffeic acid phenethyl ester, and so on have been investigated for their anti-cancer potential. Our results from *in-silico* molecular modelling and simulation studies explained the molecular mechanism of these studied compounds. In our recent study, we have reported Withanone, Withaferin-a, and Cuc-B could able to restore p53-p62 interaction for phosphorylation-deficient p53 mutants. Our study suggested that the use of these natural compounds helps in the treatment of $p53^{Ser46}$ mutant harbouring cancers [1].



Further, we have also studied a derivative from the natural compound known as *Mortaparib*^{MILD} for the abrogation of Mortalin(HSP90) from p53 and preventing the cytoplasmic sequestration of p53 [2]. In a separate study, we also found the combination of these natural inhibitors like CAPE and Withaferin-a prevents the down regulators of p53 like PARP1 which in turn induce cell death in cancer cells using the synergetic effect [3]. The anti-cancer properties of these natural compounds were further validated using *In-vivo* and *In-vitro* experiments.

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II-24

Why does sulfite reductase employ siroheme?

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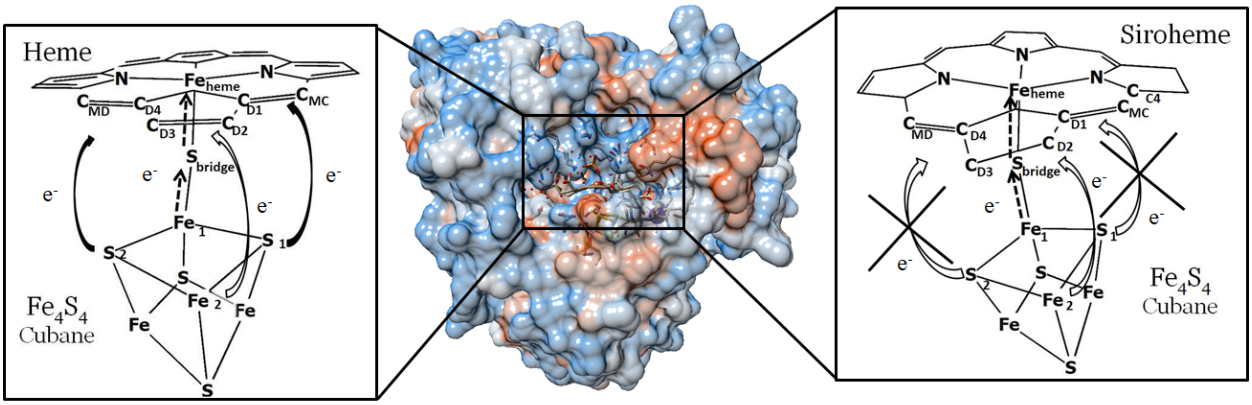
Sulfite reductase (SiR) contains in the active site a unique assembly of siroheme and a [4Fe4S] cluster, linked by a cysteine residue. Siroheme is a doubly reduced variant of heme that is not used for a catalytic function in any other enzyme. We have used[1] non-equilibrium Green's function methods coupled with density functional theory computations to explain why SiR employs siroheme rather than heme. The results show that direct, through vacuum, charge-transfer routes are inhibited when heme is replaced by siroheme. This ensures more efficient channelling of the electrons to the catalytic iron during the six-electron reduction of sulfite to sulfide, limiting potential side reactions that could occur if the incoming electrons were delocalized onto the macrocyclic ring.



Synthetic active site | Sulfite Reductase | Biological active site

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II-25

EnzyDock: Protein–Ligand Docking of Multiple Reactive States

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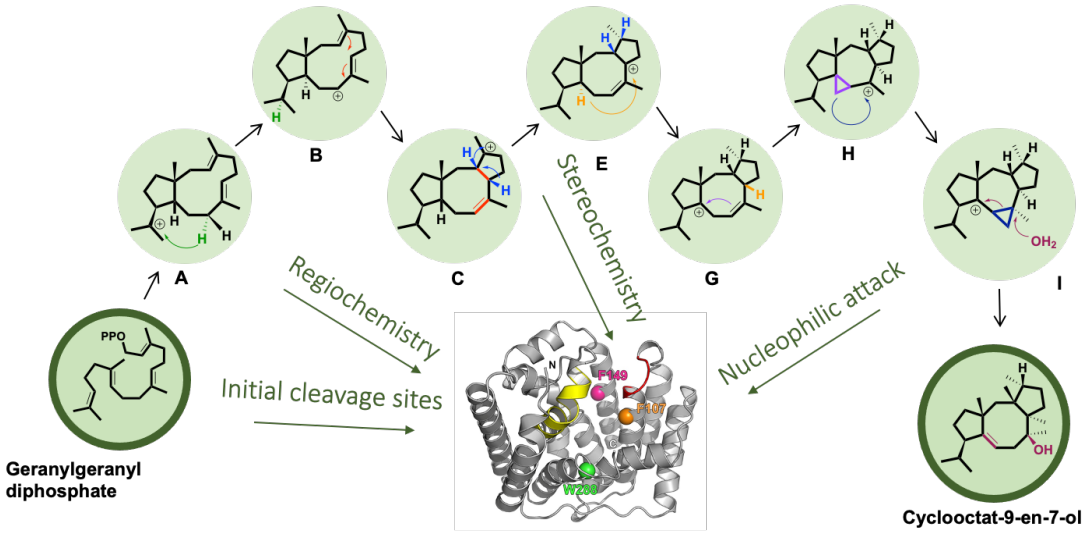
EnzyDock is a docking program with unique abilities to dock ligands to enzymes that catalyze complex, multistep reactions, allowing the presence of various cofactors and various solvation models. Employing the abilities of the CHARMM program, EnzyDock allows the user to incorporate their chemical intuition about the reaction in the docking process, by means of a variety of restraints. Here, I will present several complicated enzymatic systems, like terpene cyclases, where EnzyDock correctly predicts the ligand binding pose compared to crystal structures and produce a consistent set of docked poses for the substrate, intermediates, and product along the reaction path. In another case, we compared the ability of different



docking programs to reproduce and identify the correct binding pose of a set of ligands of the SARS-COV-19 Mpro. EnzyDock performed as good as commercially available Docking programs as Glide, both for covalent and non-covalent ligands.

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II-26

Design of selective Dipeptidyl Peptidase 8/9 inhibitors using cosolvent molecular dynamics-based pharmacophore models

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Dipeptidyl peptidase 8 (DPP8) and dipeptidyl peptidase 9 (DPP9) are highly similar cytosolic serine proteases. DPP9 is an interesting drug target as inhibition leads to inflammatory cell death [1]. The role of DPP8 is still under investigation, but the availability of selective inhibitors might accelerate this research. However, the high similarity between DPP8 and DPP9 renders the design of selective inhibitors a challenging task. Our approach to tackle this challenge is studying the preferred locations of several organic fragments using long-length cosolvent molecular dynamics. We subsequently use the calculated preferred locations of the fragments to build pharmacophore models. By comparing organic fragment locations between DPP8 and DPP9 we will search for pharmacophoric sites with selectivity potential.

The organic fragments used in the cosolvent molecular dynamics simulations are isopropanol, isopropylamine, acetate, acetamide, benzene and isobutane. Benzene and isobutane are insoluble hydrophobic fragments, while isopropanol, isopropylamine, acetate and acetamide are water soluble. The water soluble fragment locations were calculated from 18 µs of molecular dynamics simulation per protein system, with top fragment locations replicating pharmacophore features of known non-selective inhibitors. The hydrophobic fragments present an additional challenge, as aggregation leading to phase separation from water can be expected. To avoid aggregation, we are validating a flexible and easy-to-use intermolecular repulsion methodology using the same artificial potential as 'SILCS' [2]. We utilise this easy-to-use methodology to prevent hydrophobic fragment aggregation in our production runs for DPP8 and DPP9. We are generating 5 µs long molecular dynamics trajectories for the calculation of the preferred positions of the hydrophobic fragments. Using the fragment density maps we build the aforementioned pharmacophore models with potential for selectivity. The results of a pharmacophore screen using these pharmacophore models will be presented as final outcome of the study.

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II-27

Interaction Point Approach to Non-polar Interactions

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The Surface Site Interaction Points (SSIPs) were created to describe the non-covalent interactions of molecules in the solution phase [1-2]. The interaction parameters used to describe SSIPs are derived from the DFT (B3LYP/6-31G(d)) Molecular Electrostatic Potential at the van der Waals surface. Intermolecular interaction is signified by their overlap, and the free energy change of binding is a function of the SSIP values. The SSIMPLE model [3] provides a method for determining the effect of solvent on an SSIP, therefore enabling a direct comparison with experimental data in any solvent. The SSIPs have been found to describe solvation, phase transfer, and hydrogen bonding well [4-6]. This work shows how they can be used to accurately predict non-polar interactions found in aromatic stacking and edge-to-face complexes. The SSIP contacts were identified with a modified maximum bipartite algorithm. We have found the SSIP interaction energy to be a good predictor of the experimental free energy of binding, corresponding to the electrostatic and inductive effects altered with different ring substituents. The poster will introduce the intermolecular interface pairing algorithm and its application to aromatic interactions.

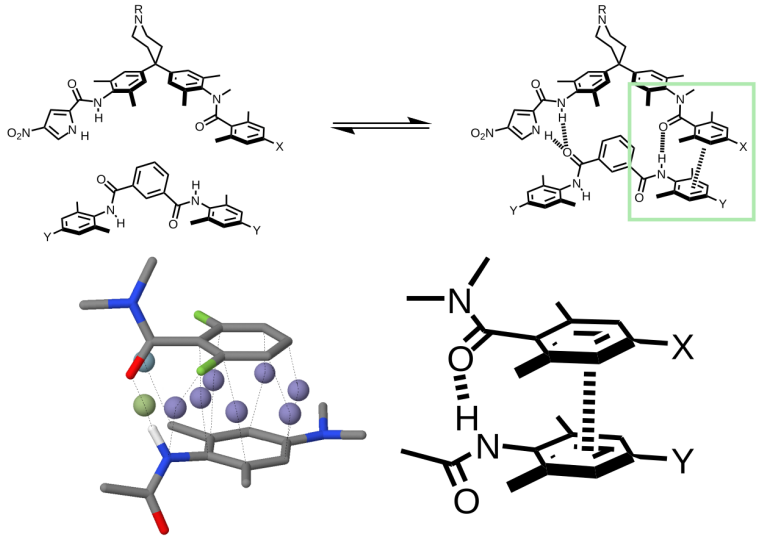

Figure 1. The hydrogen bond zipper complexes were used for the experimental double mutant cycle study of aromatic stacking energies. They were simplified to the amide fragments for calculation. The resultant intermolecular interactions for example complex are represented as spheres linked to interacting atoms; green is hydrogen bond, blue - attractive non-polar contact, violet - weakly repulsive non-polar contact.

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II-28

Tuning and tweaking of the state-of-the-art AMBER OL3 RNA force field

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Atomistic molecular dynamics (MD) simulations are being routinely applied in wide range of topics from medical, pharmaceutical and bio(nano)technological fields. However, the outcome of MD studies critically depends on the accuracy of the potential energy function and associated parameters (i.e., empirical potentials, force fields), which reproduce important structural features of biomolecular systems. On one hand, whole basic AMBER force-field form is already close to its limits of tuning capability and additional recalibrations of dihedral potentials has not lead to decisive improvements.[1] On the other hand, current AMBER RNA OL3 version, which remains the most widely used RNA force field, still has persisting limitations[1,2,3] Complex attempts to reparametrize the core AMBER RNA force field via refinement of nonbonded terms are a daunting task often resulting in improvements for certain systems and problems for others[2] Here, we present new avenues to improve (i.e., fine-tune) the AMBER OL3 force-field performance. Firstly, we increase flexibility of the core force field by external corrections and potentials. Such approach is extending the force-field parameter space and still results in generally applicable force-field versions. New terms (e.g., external potentials) should be orthogonal to the existing force-field terms and simple, in order to prevent overfitting. As an example, we recently developed the general H-bond fix (gHBfix), which allows well-controllable tuning of H-bond interactions, while the force field remains entirely general.[2,4,5] Another approach is the modification of the van der Waals combination rules for specific atom pairs via nonbonded fix (NBfix) approach. The gHBfix and NBfix can be effectively combined. The gHBfix excels for fine-tuning of H-bonds and NBfix is more suitable to eliminate excessive short-range repulsions or correct stacking interactions.[3,6,7,8] Next, we show examples of system- and objective-specific force-field adjustments for cases, where searching for the universal force field would be probably unrealistic task. Using goal-specific force-field modifications narrowing massive (under) over stabilizations of certain terms is straightforward (and fully justified) approach allowing to study specific topics.[8]

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II-29

Unraveling the Photoactivation of a Blue Light Using Flavin Photoreceptor through excited-state SCF dynamics

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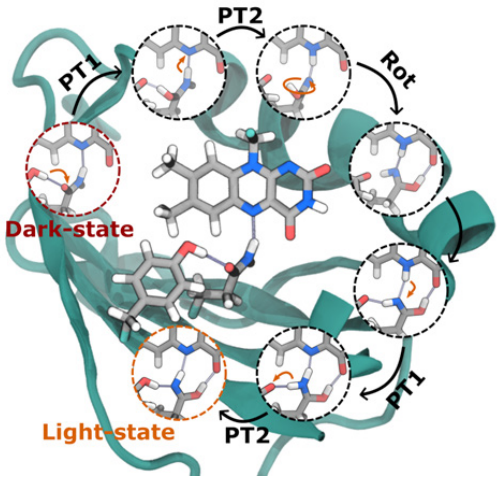
Blue-Light Using Flavin (BLUF) proteins are photoreceptors with an intriguing activation mechanism. Experiments and computational studies on BLUF proteins suggest a conserved proton-coupled electron transfer (PCET) mechanism [1,2,3] involving the flavin chromophore (FMN) and the conserved active-site tyrosine (Tyr) and glutamine (Gln) residues (see Figure) [4]. Upon blue-light absorption, excited FMN accepts an electron from the Tyr, followed by a double proton transfer from Tyr to FMN mediated by the Gln residue (*forward PCET*), resulting in a Gln imidic acid tautomer. The Gln side chain then rotates, and the diradical intermediate undergoes *reverse PCET*. This process consists of a back electron transfer from the FMN radical to the Tyr radical and of two subsequent proton transfers, ultimately leading to a stable Gln tautomer (see the circles in Figure) [2,5]. However, no direct spectroscopic evidence supports the PCET mechanism in the BLUF domain of the AppA protein from *Rb. sphaeroides.* Indeed, the radical PCET intermediates have not been detected [6], which led researchers to classify AppA as an exceptional case among BLUF domains. Alternative mechanisms were proposed, but none of them has found a robust demonstration [6,7].

Here, by exploiting a combination of a newly implemented method for excited state simulations (polarizable ΔSCF/AMOEBA dynamics) and closed-shell DFT/AMOEBA dynamics, we show that the PCET process is also valid for AppA, supporting Gln tautomer as the light-adapted characteristic feature [8].



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II-30

Dynamics and Allostery of Heat Shock Proteins

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Heat Shock Proteins (HSPs) such as HSP60, HSP90 and HSP70 are chaperones regulating the folding and activation of a great number of client proteins.[1] Their role in carcinogenesis is recognized but multifaceted and not fully understood;[2] moreover, mutations impairing the activity of HSP60 were directly related to neurological disorders.[3]

From a fundamental point of view, HSPs are a paradigmatic example of allosterically regulated proteins with nucleotide state coupled to activity on client protein folding[4,5] and an interesting playground for studying protein-protein interactions, being part of a complex network at the crossroad of several signalling pathways.[2]

In this context, MD simulations followed by analysis of protein internal dynamics and energetic footprint can give molecular-level mechanistic insights which can be translated into therapeutic applications aiming at manipulating protein-protein interfaces or enzymatic activity.[6,7] In particular, building on previous results[8,9] we show how a combination of knowledge on protein internal dynamics, docking and molecular dynamics guided the design of Trap1 allosteric ligands. Moreover, following a similar approach we were able to provide a rational background for the effects of the pathologic point mutation V98I on Hsp60 function while highlighting the complex interplay between protein structure, dynamics and energetics in protein functional states.

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II-31

MetalDock: an open software docking tool for easy and reproducible docking of metal-organic compounds

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Despite the proven potential of metal-organic compounds as therapeutics, the lack of computational tools available for high-throughput screening of their interaction with proteins is a limiting factor for their development to the clinics. To address this challenge, we introduce here MetalDock, an open software docking tool for docking metal-organic compounds. Our tool combines the AutoDock docking engine with three quantum software packages and automates the docking procedure of these compounds to proteins. We used a Monte Carlo sampling scheme to obtain the missing Lennard Jones parameters for 12 metal atom types, and exhibit that these parameters generalise exceptionally well. Our results show that the poses obtained by MetalDock are highly accurate and often surpass the experimental resolution of the crystallographic data. Three different compelling case studies are also presented which demonstrate the versatility of MetalDock in successfully docking any metal-organic compound to any biomolecule.

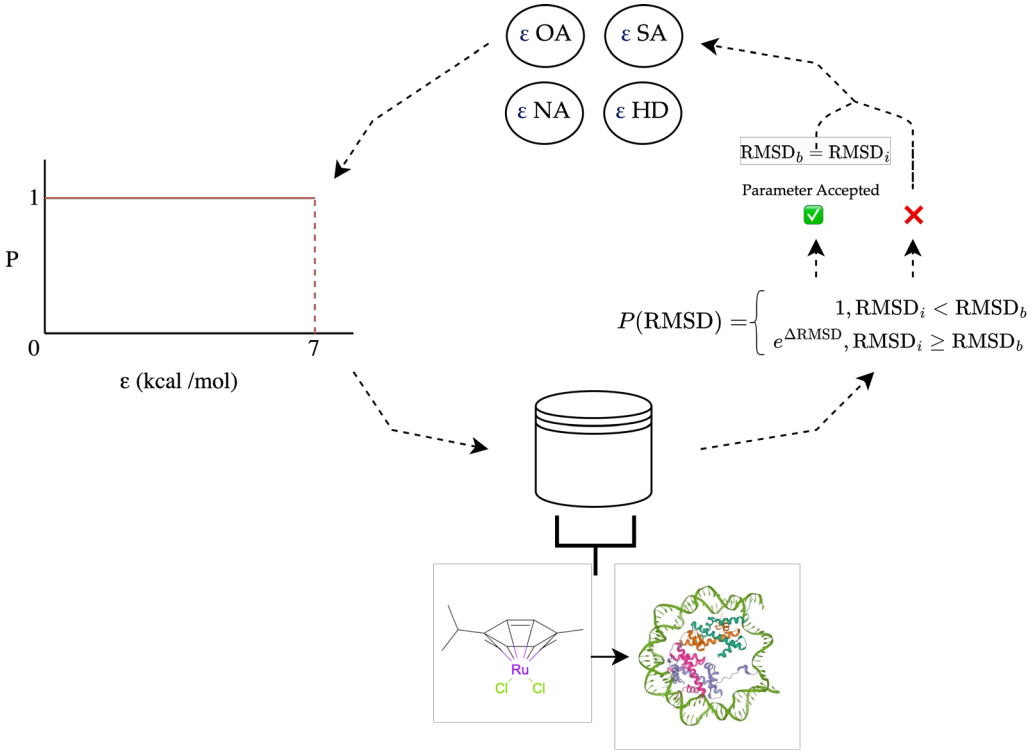

Figure 1. Schematic figure of the Monte Carlo scheme developed to optimize the Lennard Jones parameters.

II-32

Illuminating the Dark Side of COX-2: Insights from Computational Simulations and Fluorescent Probes in Cancer Research

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Cyclooxygenases are a family of enzymes that play a critical role in regulating inflammation, pain, and fever in the human body. There are two main isoforms of cyclooxygenases, COX-1 and COX- 2, with different roles and expression patterns in various tissues. COX-1 is constitutively expressed in most tissues and plays a crucial role in maintaining homeostasis, while constitutively expressed COX-2 is restricted to specific regions. In addition, COX-2 is an inducible enzyme, expressed at sites of inflammation and cancer.

Despite their essential functions in the body, cyclooxygenases are also associated with the development of various diseases, including cancer. It has been noted that in several types of tumours, such as colorectal, breast, and lung cancer, there is an increase in the expression of the COX-2 enzyme, which is associated with the development and progression of cancer. The overexpression of COX-2 leads to an increase in prostaglandin production, which promotes tumour growth and angiogenesis, making it an attractive target for cancer therapy.

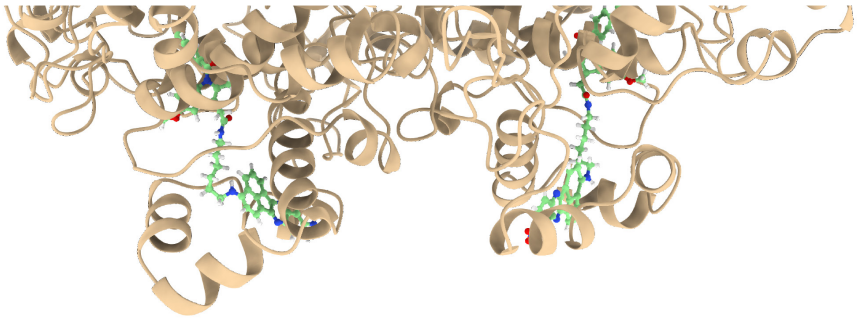

Figure 1. Dimer huCOX-2 enzyme accommodating the fluorogenic designed drugs inside its two monomers.

To study the behaviour of COX-2 in cancerous cells, researchers employed fluorescent compounds derived from known anti-inflammatory drugs. These compounds can differentiate between healthy cells undergoing a common inflammatory process and cancerous cells with an overexpression of the enzyme. Using these fluorescent probes, researchers can study the behaviour of the enzyme and its effect on the surrounding cellular environment.

Advanced computational tools, such as hybrid QM/MM molecular dynamics simulations, havebeen used to simulate the fluorescence spectra of COX-2-specific fluorogenic probe bound to huCOX-2 monomer and

dimer. This study aims to investigate the effect of the two types of systems on the fluorescence maxima of the modified drugs. By exploring the relationship between the formation of the huCOX-2 dimer and cancer in more depth, this research sheds light on the behaviour of the protein in cells that are not in homeostasis and present huCOX-2 overexpression. Furthermore, this study provides valuable insights into the design of specific drugs for cancertreatment, which could potentially improve patient outcomes and quality of life.

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II-33

One- and Two- Electron Reductions in MiniSOG and their Implication in Catalysis

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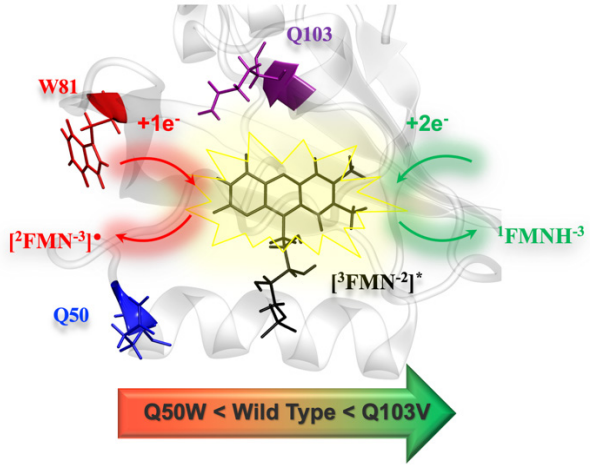
In the last years, the unconventional bioorthogonal catalytic activation of anticancer metal complexes by flavin and flavoproteins photocatalysis has been described[1]. The reactivity is based on a two-electron redox reaction of the photoactivated flavin. Furthermore, when it comes to flavoproteins, we recently reported that site mutagenesis can modulate and improve this catalytic activity in the mini Singlet Oxygen Generator protein (SOG)[2].



In this work[3], we analyze the reductive half-reaction in the different miniSOG environments by means of density functional theory. We report that the redox properties of the flavin and the resulting reactivity of miniSOG is modulated by specific mutations, in line with the experimental results in the literature. This modulation can be attributed to fundamental physicochemical properties of the system, specifically (i) the competition of single and double reduction of the flavin and (ii) the probability of electron transfer from the protein to the flavin. These factors are ultimately linked to the stability of the electron-accepting orbitals of the flavin in the different coordination modes.

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II-34

Targeting the Pro-oncogenic EphA2 Receptor with RNA Aptamers: From 2D Structure Prediction to Protein-Ligand Interaction Studies

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Ephrin tyrosine kinase receptors (Eph) are transmembrane receptors, which are involved in cell growth, differentiation, and signalling pathways. Upregulations in Eph expression are associated with human malignancies, like melanoma, breast cancer, and glioma. Specifically, Ephrin type-A receptor 2 (EphA2) is overexpressed in glioblastoma (GBM) stem cells promoting tumorigenesis. Therefore, blockage of EphA2 has been defined as a promising strategy to reduce overexpression and induce tumor suppression.[1] Several EphA2 targeting agents have been developed including small-molecule inhibitors, antibodies, peptide-drug conjugates, and siRNAs, with some of them reaching clinical trials.[2] On the other hand, inhibition of EphA2 using DNA/RNA aptamers has been so far inadequately explored. In this context, a 2-fluoropyrimidine 30-nt RNA aptamer, namely A40S, has been recently identified as an EphA2 binder by some of us, using systematic evolution of ligands by exponential enrichment (SELEX) procedure.[3] Here, the structure and dynamics as well as the EphA2 binding properties of A40S are investigated through computational and experimental studies. Initially, the secondary and tertiary structure of the aptamer are predicted starting from the 1D sequence using several online available prediction tools. Subsequently, μs-long all-atom Molecular Dynamics (MD) simulations are performed to examine the stability of the predicted 3D aptamer conformations in solution. Preliminary interaction studies of A40S to the different possible EphA2 states are also presented. Our results will provide hints for further improving its binding affinity and possibly its in vivo stability, with the final aim to allow its potential use as a therapeutic molecule.

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II-35

Looking for Echoes of the Past: Reconverting a Hydroxynitrile Lyase to an Arylesterase

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Arising from the same esterase ancestor, *Hevea brasiliensis* hydroxynitrile lyase (*Hb*HNL) and salicylic acid binding protein 2 (SABP2) have evolved to catalyze the cleavage of hydroxynitriles and the hydrolysis of esters, respectively. These two phylogenetically related enzymes belong to the α/β-fold hydrolase superfamily and share the same Ser-His-Asp catalytic triad, common in many hydrolases. However, interestingly they only share 45% of amino acid sequence identity. To understand the differences between the catalytic nature of these enzymes as a consequence of amino acid changes suffered along evolution, Prof. Kauskazlas and coworkers substituted the obvious active site catalytically-relevant amino acids of *Hb*HNL that are important for the catalytic mechanism into the corresponding SABP2 residues. An increase in esterase activity (EST) and a decrease in hydroxynitrile lyase activity (HNL) was expected, but unfortunately, pure EST activity was not achieved by the *Hb*HNL variant (*Hb*HNL-EST) [1].

In this work, we focus on the identification of the amino acids required for recovering the esterase activity of *Hb*HNL that was lost throughout evolution. We aim to design a new *Hb*HNL-EST variant by considering the amino acids of the first and second shell active site amino acids needed to reach a complete esterase activity.

To that end, we develop a specific computational protocol that allows us to locate promising candidates by means of molecular dynamics (MD). We simulated SABP2 and *Hb*HNL-EST enzymes in the *apo* state (*i.e.* without ligand), and with the correlation-based tool named Shortest Path Map[2] (SPM), we could identify promising positions that were non-conserved between enzymes. Combinations of these positions were used to create a new set of *Hb*HNL-EST variants with presumed EST activity improvements, which were modeled using Alphafold2[3] and the same MD protocol previously used, and finally experimentally validated. The MD simulations together with the kinetic values highlighted the importance of the oxyanion hole and catalytic triad preorganization to improve EST activity. Thanks to the developed methodology, we designed new variants with a k_{cat}/K_M fold increase of up to 1390 in esterase activity compared to the starting *Hb*HNL WT enzyme.

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III-20

Computational Study of the structure and transport mechanism of Cystine/Glutamate Antiporter System x_c^- (Sx_c^-)

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The cystine/glutamate antiporter system x_c^- (Sx_c^-) is a member of the SLC7 family, which comprises the main plasma transporters. It functions by exporting intracellular glutamate along the latter's concentration gradient to facilitate the uptake of extracellular cystine.[1] The imported cystine is primarily utilized in the synthesis of glutathione, a vital tripeptide thiol essential for the protection of cells against oxidative stress and drug resistance.[2] Overexpression of Sx_c^- has been found in several cancer cell lines, where enhanced cystine uptake is thought to counteract the increased oxidative stress commonly observed in cancer cells.[3] In addition, Sx_c^- is important in the Central Nervous System, playing a complex role in glutamate excitotoxicity.[4] Thus, this transporter is considered as a drug target for cancer treatment and neurological diseases.

In the present work, we performed elaborate multi-template homology modeling and Molecular Dynamics (MD), yielding four conformations of the apo state of Sx_c^- along its transport pathway. A comparison of our inward open conformation with a recently released Cryo-EM structure revealed an excellent agreement. In contrast to this inward-open model, there is no direct experimental counterpart for the other three conformations we obtained, although they are in fair agreement with the other stages of the transport mechanism seen in other SLC7 transporters.[5] For the Glutamate-bound state, conformational changes on the intracellular side and the corresponding free energy profiles are explored using MD and Adaptive Biasing Force simulations. These findings contribute to an understanding of the transport mechanism as well as opening the prospect for targeting alternative Sx_c^- conformations in structure-based drug design efforts.

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III-21

Theoretical Chemistry as a tool to investigate peptide-based ligands for Lanthanides

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The chemical similarity of lanthanides makes their separation a complex process.[1, 2] Recent studies have demonstrated that biopolymers such as proteins can have extremely high affinities for lanthanides.[3, 4, 5] In addition, some biopolymers have been shown to distinguish lighter and heavier lanthanides.[4, 5] Such promising candidates are the motivation for the PepTight project, which aims to identify new peptide structures for the purpose of lanthanide separation.

The ongoing experimental studies are supported by theoretical chemistry. Here, the focus is on two different aspects. On the one side, molecular dynamics simulations of the structures of lanthanide complexes are performed to obtain a deeper understanding of differences with respect to thermodynamic stability. On the other hand, computational methods are used for screening randomly generated peptide sequences for their affinity to lanthanides. In this semi-automated way, unusual ligands can be identified from thousands of structures, for which experimental techniques are not suitable.

The presentation will focus on the screening method, which is based on a combination of density functional theory and molecular mechanics. Force field calculations are carried out with frozen coordinates of the atoms directly binding to the metal centre. Those Coordinates are set at the position of each atom determined by a density functional theory calculation. This allows the screening of thousands of different peptides based on how well each of them satisfies the optimal coordination geometry.

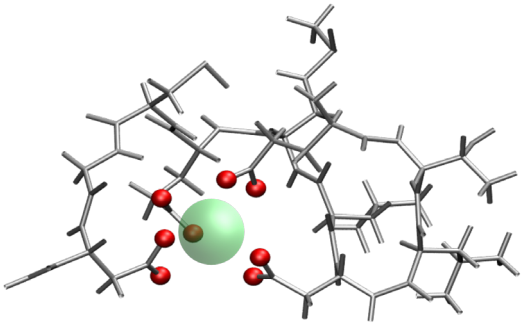

Figure 1: Example complex of a peptide coordinating with a lanthanide; grey: MM optimized system, colorful: DFT supported coordinates.

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III-22

Computational Modelling of the DNA-dependent redox activity of the BER enzyme MutY

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Base excision repair (BER) is one of several DNA repair pathways. It deals with the mutagenic effects of damage that occurs continuously to the DNA bases. The BER pathway is initiated by DNA glycosylases. These enzymes remove damaged bases in DNA. In particular, MutY is involved in the repair of the insidious oxoG:A mismatches. Commonly considered a cofactor, $[4Fe\text{-}4S]^{2+}$ are ubiquitous to BER enzymes. Electrochemistry on DNA-modified electrodes showed a potential characteristic of high potential iron proteins (HiPIPs) for MutY. Recently, electrochemical studies reported a negative shift of the reduction potential of this enzyme when bound to a DNA molecule [1]. Here, we propose a computational study to investigate the DNA-dependent redox activity of MutY. We applied the PMM-MD procedure, a QM/MM method particularly suitable for the study of processes occurring in biological systems [2]. We considered the oxidation of one of iron atoms of the $[4Fe\text{-}4S]^{2+}$ cofactor (see Fig. 1a) in both unbound and in complex with an undamaged DNA (see Fig. 1b) [3]. In our procedure, $[Fe_4S_4(SCH_3)_4]^{2-/1}$ was considered as the quantum centre (QC) (see Fig. 1c), whereas the remaining part of the system, acting as perturbation, was taken into account through MD simulations. According to the experimental findings [1], our data shows a negative shift of the reduction potential of the couple $[Fe_4S_4(SCH_3)_4]^{2-/1}$ in MutY when it is complexed with the DNA. Moreover, we explain such an effect considering the different solvent dynamics in the complexed and uncomplexed enzyme.

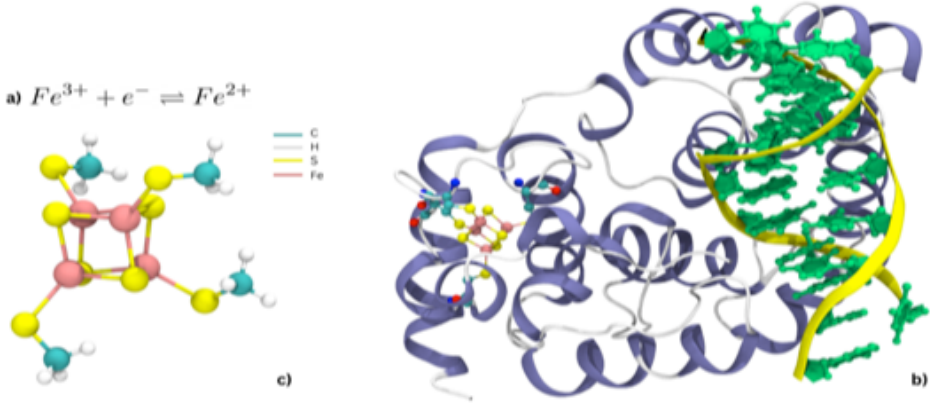

Figure 1: a) Reduction half reaction of the redox couple Fe^{3+}/Fe^{2+}; b) Crystallographic structure of the MutY N-terminal domain in complex with undamaged DNA (PDB: 5KN8) [3]; c) Model cluster $[Fe_4S_4(SCH_3)_4]^{2-/1-}$ taken as QC in our work.

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III-23

Deciphering the various reactivities of acetylcholinesterase by combining QM/MM and MD

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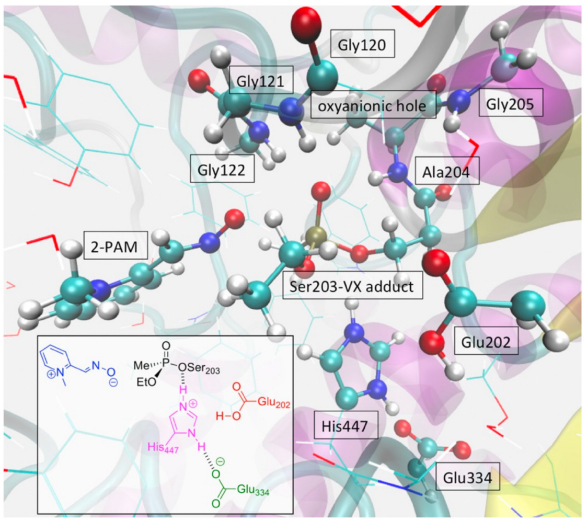
Acetylcholinesterase (AChE) is an enzyme from the family of serine hydrolase which is involved in the transmission of nervous signal at cholinergic synapses. It is key to breathe, move and think.

But unfortunately, this enzyme is subject to inhibition by organophosphates (OPs), including but not limited to nerve agents such as Sarin, VX, Tabun and Soman. The crystal structure of electric ray AChE, and subsequently of human AChE, has revealed that the catalytic site is a triad constituted by Ser203/His447/Glu334 (Figure below) and is located at the bottom of a 20Å deep narrow gorge lined by aromatic residues.



View of the active site of AChE, inhibited by VX and in presence of a reactivator (2-PAM).

Since more than ten years, our group has performed QM, QM/MM and MD simulations to decipher all the mechanisms related to the reactivity of AChE. What we discovered can be quickly summarized by: biochemistry textbooks are wrong. I will show that the normal mechanism for acetylcholine hydrolysis is regulated by a single water molecule present in the aromatic gorge, that the inhibition by nerve agents is not a classical nucleophilic substitution and that reactivation of AChE involves the protonation of a usually unprotonated amino-acid (Glu202).

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III-24

Six- and two-electron oxidation products of 2'-deoxyguanosine. The influence of oxidized iminoalantoin on ds-DNA electronic properties in the presence of ^{oxo}dG.

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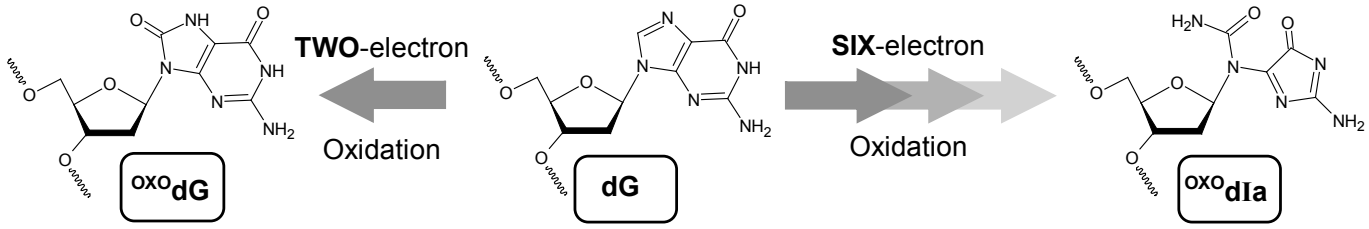
The genetic information stored in the nucleobase sequence is continuously exposed to harmful extra- and intra-cellular factors, which can lead to different types of DNA damage, with more than 70 lesion types identified so far [1]. Here, the influence of a multi-damage site containing oxidized 2'-deoxyiminoalantoin (^{oxo}dIa) and 7,8-dihydro-8-oxo-2′-deoxyguanosine (^{oxo}dG) on charge transfer through ds-DNA was taken into consideration [2,3]. The spatial geometries of oligo-^{oxo}Ia: d[A_1 ^{oxo}Ia$_2$$A_3$ ^{oxo}$G_4$$A_5$]*d[$T_5$$C_4$$T_3$$C_2$$T_1$] was optimized at the M06-2X/6-D95**//M06-2X/sto-3G level of theory in the aqueous phase using ONIOM methodology [4]. For all the electronic property energies under discussion, the M06-2X/6-31++G** level of theory was used. Additionally, the non-equilibrated and equilibrated solvent-solute interactions were into consideration.



The obtained results confirm the predisposition of ^{oxo}dG to radical cation formation regardless of the presence of other lesions in a ds-DNA structure. In the case of electron transfer, however, the situation is different ie.: the excess electron migration towards ^{oxo}dIa was found to be preferred. The above observation was confirmed by the charge transfer rate constant, vertical/adiabatic ionization potential, and electron affinity energy values, as well as the charge and spin distribution analysis. The obtained results indicate that oxidized 2'-deoxyiminoalantoin, can significantly influence the electron migration process through the double helix. The above can be manifested by the slowdown of DNA lesion recognition and removal processes, which can increase the probability of mutagenesis and subsequent pathological processes.

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III-25

Rational engineering of binding pocket's structure and dynamics in penicillin G acylase for selective degradation of bacterial signaling molecules

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Rapidly increasing bacterial resistance to antibiotics is a global health problem prioritized by the World Health Organization. As antibiotics are mostly lethal to the microbiota, they exert strong selective pressure and promote the development of resistance mechanisms that are difficult to overcome by conventional treatments. Thus efficient alternatives to combat resistant species are urgently needed. One of these alternatives focuses on quorum sensing - bacterial communication induced by organic compounds. Its disruption, known as quorum quenching (QQ), can be achieved by enzymatic cleavage of these molecules. QQ has been demonstrated to inhibit the expression of genes responsible for virulence factors and biofilm formation.

Therefore, we first performed extensive molecular modelling, including hybrid quantum mechanics/ molecular dynamics simulations, of a biotechnologically well-optimized enzyme, *E. coli* penicillin G acylase (ecPGA), discovering and validating its QQ activity [1] which enables bacteria to sense the surrounding bacterial cell density and markedly affects their virulence. Due to its indirect mode of action, QQ is believed to exert limited pressure on essential bacterial functions and may thus avoid inducing resistance. Although many enzymes display QQ activity against various bacterial signaling molecules, their mechanisms of action are poorly understood, limiting their potential optimization as QQ agents. Here, we evaluate the capacity of three N-terminal serine hydrolases to degrade N-acyl-homoserine lactones (HSLs. Furthermore, by contrasting it with an enzyme displaying native QQ activity, we elucidated the structural-dynamic determinants and limitations associated with the relatively low QQ activity of ecPGA. Finally, guided by these considerations, we rationally designed ecPGA mutants and screened them for activity with signalling molecules from different bacterial species by repetitive molecular dynamics simulations. The most potent candidates were prioritized for experimental validation, which confirmed computational predictions of enhanced activity and modulated specificity. In-depth experimental and computational characterization allowed us to understand the structural basis for the observed modulation in our constructs – too dynamical or too restricted pocket of VAF and MSF variants compromised their activity with longer substrates [2]unconventional solutions. Methods based on targeting bacterial communication induced by signaling molecules, known as quorum sensing, are gaining increasing interest. Quorum quenching (QQ. Considering the predictive power of the presented approach, we aim to further progress with the following engineering campaigns toward applicable QQ antibacterial agents.

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III-26

Quantum Mechanical-Cluster Approach to Solve the Bioisosteric Replacement Problem in Drug Design

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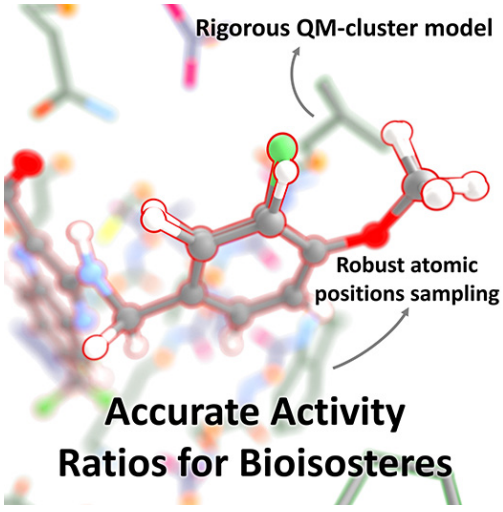
Bioisosteres are molecules which differ in substituents having very similar shapes. Bioisosteric replacements are ubiquitous in modern drug design, where they are used to alter metabolism, change bioavailability, or modify activity of the lead compound. Prediction of bioisosteres relative affinities with computational methods is a long-standing task; however, the very shape closeness makes bioisosteric substitutions almost intractable for computational methods which use standard empirical force fields.



Here [1], we design a QM-cluster approach based on GFN2-xTB [2] semi-empirical method and apply it to a set of H→F bioisosteric replacements. Our QM-cluster metodology based on few steps: extract ligand and the protein residues, which have at least one atom within 4 Å from the ligand, building convex hull and add residues penetrating it, move each atom (except for the fixed one) by 0.03(3) Å to create 101 different structures and find lowest energy during geometry optimization and finally calculate relative affinity. Finally, we estimate computational errors using bootstrap method.

The proposed methodology enables advanced prediction of biological activity change upon bioisosteric substitution of −H with −F, with the standard deviation of 0.60 kcal/mol, surpassing the ChemPLP scoring function (0.83 kcal/mol), and making QM-based ΔΔG estimation comparable to ~0.42 kcal/mol standard deviation of *in vitro* experimental measurement.

The speed of the method (~5 hours on a laptop) and lack of tunable parameters makes it affordable in current drug research.

T.V.L. and M.G.M. are grateful to the Russian Science Foundation for financial support (grant #22-73-10124).

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III-27

A novel Adaptive Biasing Force (ABF) variant that combines conceptual simplicity with improved convergence when applied to condensed-phase biomolecular problems

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Adaptive Biasing Force (ABF) is a popular free energy method that is available in several Molecular Dynamics simulation programs. In its most basic form, it enhances conformational sampling along a small number of predefined (transition) coordinates while determining the gradient of the free energy in the space of said coordinates. This gradient is finally integrated to obtain a Potential of Mean Force (PMF).[1][2] Attractive properties of this basic form of ABF include its conceptual simplicity and ease of set-up.

Unfortunately, the convergence rate of basic ABF is not always optimal, especially when applied to real-life biomolecular problems where the coordinate(s) span a relatively long distance. This spurred the development of a large number of more sophisticated but generally also more complex ABF variants, such as multiple-walker ABF (mwABF)[3] and extended-system ABF (eABF)[4]. Independently of these enhancements, it is commonly advised to improve convergence by defining highly problemspecific but complex coordinate(s) (possibly in an automated fashion through a path finding method) and/or stratifying the range of the coordinate(s) into windows[2]. However, all these refinements largely negate the upfront simplicity of the ABF method, requiring pre-existing knowledge of the system as well as some fundamental insight in free energy methods.

The premise of the present work is to examine and remedy the fundamental reasons for the convergence problems outlined in the previous paragraph. We discuss a general hysteresis mechanism that has not been given sufficient explicit attention in recent work on ABF and demonstrate how this mechanism causes basic ABF simulations on a few real-life biomolecular test cases to fail catastrophically. Furthermore, we present a new ABF variant that effectively addresses this issue without introducing additional parameters or complexity, thereby retaining the simplicity and ease-of-use of basic ABF. While our method can straightforwardly be combined with a number of the refinements listed in the previous paragraph, we anticipate that it will also be appealing “as-is” for use by inexperienced operators as well as for the purpose of automating certain types of free energy calculations.

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III-28

In-silico design of lipid-like compounds targeting oncogenic membrane protein KRAS4B through non-covalent bonds

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The cellular proliferation, survival, growth, and differentiation are highly influenced by the RAS genes, which encode four distinct isoforms: KRAS4B, KRAS4A, HRAS, and NRAS. One of the most common drivers in human cancer is the mutated peripheral membrane protein KRAS4B that promotes oncogenic signalling. To signal, oncogenic KRAS4B not only requires a sufficient nucleotide exchange, but also needs to recruit effectors by exposing its effector-binding sites while anchoring to plasma membrane where KRAS4B-mediated signaling events occur. The enzyme Phosphodiesterase-δ also plays an important role in sequestering KRAS4B from the cytoplasm and targeting it to cellular membranes. In this work, we present an in-silico design of a new lipid-like compound (LIG1, see in Figure 1) that has the remarkable feature of being able to target both an oncogenic mutant of KRAS4B-G12D and the phosphodiesterase-δ enzyme. LIG1 was found to lock KRAS4B-G12D in its GDP-bound state by adjusting the effector binding domain to be blocked by the interface of the plasma membrane, which hinders the nucleotide exchange. Meanwhile, it can tune GTP-bound KRAS4B-G12D to shift from the active state to its inactive state, resulting in a much less oncogenic behavior. The proposed drug is also observed to stably accommodate itself in the prenyl-binding pocket of phosphodiesterase-δ, which potentially compete with KRAS4B to bind with PDE-δ , hence, impairs KRAS4B enrichment at the membrane and suppress the proliferation of KRAS4B-dependent cancer cells. In conclusion, we report a lipid-like drug which can serve as a potential binder of mutated KRAS4B through molecular dynamics simulations, which has not been considered for drugs targeting RAS mutants. Our work provides a novel idea to target KRAS4B-G12D and can also foster drug discovery efforts for the targeting of oncogenes of the RAS family and beyond.

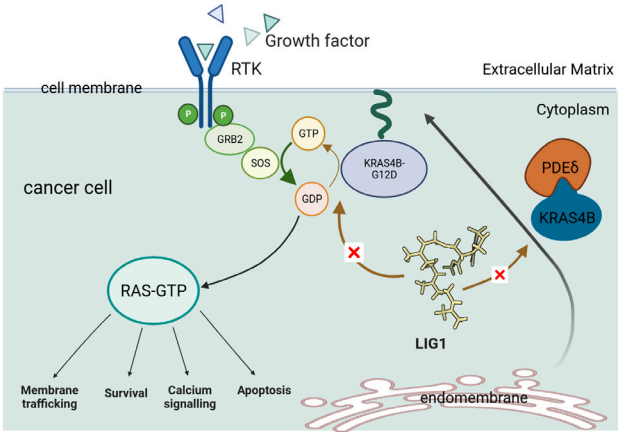

Figure 1: LIG1 is able to block the oncogenic KRAS4B abnormal signaling through two means: 1). competing with KRAS4B for binding to PDEδ, resulting an impaired enrichment of KRAS4B at the inner leaflet of PM; 2). decreasing its oncogenic behavior by inducing KRAS4B-G12D mutant to stay in its inactive state on PM.

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III-29

Investigating Hepatitis B Capsid Stability through Coarse-Grained Molecular Dynamics and Free Energy Calculations

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Virus-like particles (VLPs), noninfectious nanoparticles assembled from core viral proteins, are a promising platform for developing therapeutics, including drug carriers and gene therapy delivery systems.[1] Among VLPs, hepatitis B virus (HBV) core protein-based VLPs are particularly attractive for therapy applications because they can self-assemble in various expression systems, making them versatile and efficient nanocarriers.[2] The HBV capsid is composed of 120 dimers of core protein (Cp), which consist of 183 amino acids (Cp183) and contain two separate domains: the assembly domain at residues 1-140 and the C-terminal (C-ter) domain at residues 150-183 responsible for binding of nucleic acids.[3] The successful assembly of HBV VLPs is highly dependent on solution conditions, such as ionic strength and the presence of negatively charged nucleic acids. While there is significant knowledge on truncated Cp149 VLPs which lack nucleic acid binding regions, processing of VLPs with the full length of C-ter remains challenging due to processing and solubility difficulties. Therefore, researchers are also testing systems with intermediate lengths of C-ter.[3, 4]

In this study, we employ coarse-grained molecular dynamics with SIRAH force field and umbrella sampling simulations to assess the stability of capsid fragments (i.e. trimers of Cp dimers) with various C-terminal lengths in the presence and absence of a model DNA molecule and 37.5 mM NaCl. Our results show that the length of the C-terminal binding region significantly influences the binding energy between proteins, stabilising intermediate length dimers (C164, Cp167) and destabilising full-length dimers (Cp183). Moreover, we find that DNA-induced stabilisation is dependent on the length of the nucleic acid binding region, with shorter C-terminal domains exhibiting less dependence on nucleic acid content and thus being easier to process. Overall, our theoretical study provides valuable insights into the protein interactions that drive VLP assembly and has important implications for the design of robust and efficient gene therapy carriers. Specifically, our findings suggest that truncating the C-terminal domain of HBV core protein VLPs may facilitate their processing and enhance their potential as gene therapy carriers. This work highlights the importance of computational modelling and simulation in understanding the underlying mechanisms of VLP assembly and tailoring their design for specific applications.

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III-30

Prediction of Residual Dipolar Couplings for Enantiomer Assignment

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Residual Dipolar Couplings (RDCs) enable the determination of average distances and relative orientations of pairs of nuclei within molecules and can be measured using nuclear magnetic resonance (NMR) spectroscopy. When a chiral molecule is partially aligned through the interaction with a chiral alignment medium, for example Poly-γ-benzyl-L-glutamate (PBLG), the measured RDCs allow for an inference of the average alignment of that molecule and the estimation of the structure of the molecule. Predicting RDCs from a simulation and comparing them to experimental data thus allows for the determination of the relative and possibly absolute configuration of chiral molecules. [1,2] Therefore, such an approach is interesting for distinguishing enantiomers of drugs. However, the dynamics of the molecular alignment and its influence on RDCs, particularly the differences in alignment between enantiomers, have not been extensively explored from a theoretical standpoint.

Here, we demonstrate that classical all-atom molecular dynamics simulations can, in principle, predict RDCs even with very weak alignment and resolve differences between enantiomers. For that, we have used AMBER force field parameters and a simulation box with a restrained PBLG α-helix and the small chiral molecule in chloroform solution. We have found that much longer simulation times than those previously employed [3] are necessary to sufficiently reduce statistical uncertainty, depending on the strength of the alignment: In our case, it is generally very weak (~0.001-0.01) with no straightforward way to further lower the amount of sampling necessary.

We estimate that specific interactions between the alignment medium and chiral molecules (such as hydrogen bonds) are important for the RDCs and their difference between enantiomers. For the molecules examined in this study featuring a hydrogen bond donor (the enantiomers of isopinocampheol, quinuclidinol and borneol), the alignment is primarily determined by the poses where a hydrogen bond to PBLG is formed. In addition, using the assumption of rigid molecules (inspired by [4]) and implicit solvation (based on [5]), we investigate the calculation of RDCs by Monte Carlo integration. We show that this approach has the potential for a much more computationally efficient prediction of RDCs given the same force field parameters as in the MD simulation.

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III-31

Förster Resonance Energy Transfer Applied to Drug Design

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The Förster resonance energy transfer (FRET) technique is an important tool in structural biology, due to its ability to monitor and measure distances in biological systems.[1] Albeit FRET is widely used to measure distances in fluorophore-tagged proteins, intrinsic FRET processes in protein-ligand complexes prevent straightforward application of Förster theory due to the lack of rotational freedom of the Trp and ligands involved and their relatively short separations. In this contribution, we aim at developing a novel technique to discover binding sites and characterize ligand binding modes in proteins by combining fluorescence spectroscopy with a novel multiscale computational methodology. Our methodology combines classical molecular dynamics (MD) simulations of predicted binding modes with polarizable quantum/molecular mechanical (QM/MM) calculations of FRET properties beyond Förster dipole and dielectric screening approximations.[1][2] We apply this approach to study the binding of several ligands to Human Serum Albumin (HSA), which presents several advantages to assess the novel methodology, like the presence of multiple binding sites, a single Trp residue, and binding FRET data reported for multiple ligands.[2][3] The ultimate objective of the project is to assess the ability of FRET simulations to characterize allosteric and cryptic binding sites and ligand binding modes for drug discovery targets.

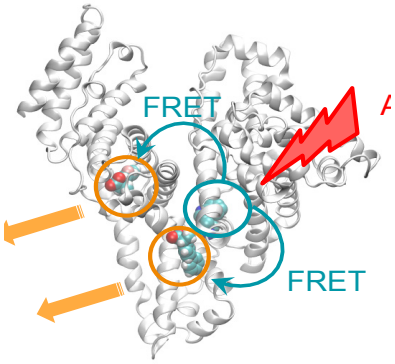

Figure 1: Schematic representation of Trp-to-ligand FRET process in HSA

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III-32

Multiscale investigation of the structural basis for photoacclimation in the cryptophyte alga PC577 and PE545 antenna complexes

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LPigment-protein antenna complexes perform a key task in photosynthesis, collecting sunlight and transporting the energy to the reaction centers.[1] Photoacclimation allows cryptophyte algae to adapt to varying sunlight intensity by changing the concentration of phycobiliprotein antenna proteins. However, recently a now mechanism has been observed that leads to shifts in the antennae absorption spectra. Evidence based on spectroscopy and X-ray christallography on H. pacifica PC577 and P. Sulcata PE545 antennae suggests that this mechanism involves the change of one of the tetrapyrroles bilin chromophores, rather than a change in protein sequence or structure.[2] In this study, we investigate the structural basis for this mechanism using multiscale computational methods.[3] We report classical molecular dynamics simulations for PC577 and PE545 and their single b subunits for the native complexes as well as several variants with mutated pigments. The trajectories were then used to start multiple DFT-based QM/MM Born-Oppenheimer molecular dynamic (BOMD) simulations, later processed to estimate the bilin transition energies and electronic couplings using polarizable QM/MM calculations. Excitonic absorption spectra were then computed using the Full Cumulant Expansion formalism.[4] Our results allow to discuss the identity of the pigments responsible for photoacclimation in cryptophytes.

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III-33

Towards understanding of mechanism and kinetics of Asn deamidation and Met oxidation in protein: a theoretical-computational approach

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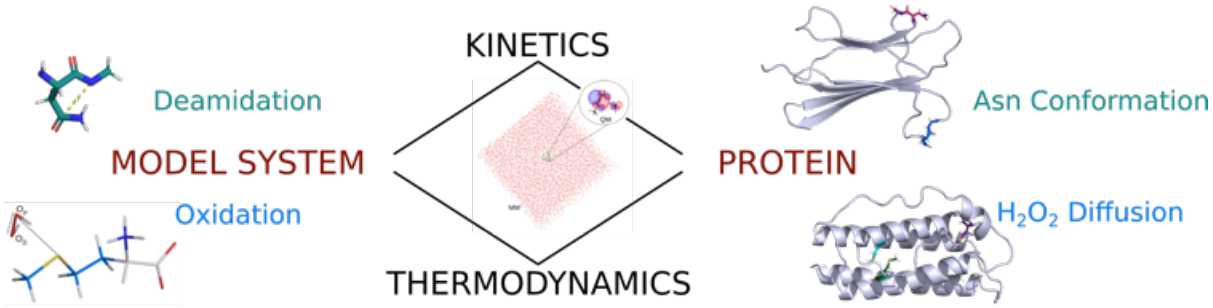
Chemical stability is a major challenge in the development of safe and effective biotherapeutics drugs[1]. Among Post Translational Modification (PTMs) of proteins, Methionine (Met) oxidation and Asparagine (Asn) deamidation are the most common non-enzymatic degradation pathways, both affecting biodrugs biological activity[2]. In light of such evidence, a deep understanding of reaction mechanisms and associated free energy barriers can contribute to avoid and prevent them.[3] To this end, we applied a hybrid theoretical-computational quantum mechanics/molecular mechanics (QM/MM) approach - the Perturbed Matrix Method (PMM)[4] - to the study of both reactions in full-solvated biological systems. The initial use of simple, but still realistic, models provided an accurate treatment of the kinetics and thermodynamics of Asn deamidation (unimolecular, four-steps reaction) and Met oxidation (bimolecular, one-step reaction), used as a line base for the subsequent modelling of reactions in proteins. Such an approach, validated by experimental data comparison[5], allowed us to evaluate the effect of the biological environment on the free energy profiles as well as on main environmental factors affecting the kinetics of these reactions.



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III-34

Charge Transfer Reactions through poly-Adenine and poly-7-deazaadenine double strands in aqueous solution: a theoretical-computational study

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The charge migrations through DNA represent a very interesting subject because they are relevant in different areas, ranging from biochemistry to technology [1]. Although so far, the high complexity of the system has partially hindered a complete characterization of the charge transfer processes in DNA and the need of a detailed explanation of the charge transfer along DNA, still representing a matter of debate [2], stimulated several theoretical-computational groups aiming to rationalize the available experimental data [3]. Unfortunately, in-silico approaches are still limited by the necessity to provide an accurate description of the electronic properties of the donor and acceptor over an extended sampling of the DNA molecule structures including the effect of a realistic dynamical perturbing environment, typically disregarded in the available models. To address the charge transfer kinetics in DNA by means of a general theoretical-computational approach specifically including the dynamical environment perturbation and DNA fluctuations, we made use of our model for the super exchange charge transfer (based on a previous work[4]) within a single step hole hopping between adjacent Adenine and 7-deazaadenine bases, as occurring in different double-stranded DNA molecules, and compared our results with the available experimental data [5].

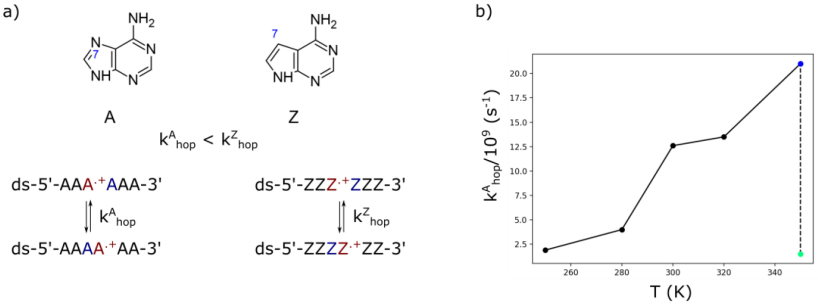

Figure. a) Upper: structures of Adenine (A) and 7-deazaadenine (Z), lower: charge transfer processes considered, underlying the higher charge transfer rate observed for Z strands; b) Temperature dependence of the kinetic rate constant of the charge transfer in poly-Adenine strand.

Our results, in good agreement with the experimental data, indicate the robustness of the previously developed model, the key role played by the thermal fluctuations and the double strands order parameters in promoting the charge transfer. Moreover, we clarify, on a thermodynamical basis, the effect of the enhancement of the Adenine → 7-deazaadenine mutation on the charge transfer kinetics.

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III-35

Unveiling the excited state dynamics of Indole in solution

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In this work, we investigate the relaxation mechanism and kinetics of the emitting electronic excited state of aqueous indole (see Figure A), the most studied model molecule for the spectroscopic properties of the amino acid tryptophan. This was achieved by using a general model for treating electronic state transitions [1] based on the Perturbed Matrix Method QM/MM approach [2]. Such an approach can provide accurate results at a much reduced computational cost when compared to other existing computational strategies [3]. Expanding on the results of a recent paper [4], where we laid out a static picture of the electronic structure of aqueous indole, here we reconstruct in detail the dynamics of the excited state and relate it to the time-dependent fluorescence signal.

According to our results, the relaxation process in solution can be properly described in terms of the transitions between two gas-phase singlet electronic states (^1L_a and ^1L_b), which subsequently irreversibly relax to the gas-phase singlet dark state ($^1\pi\sigma^*$; see Figure B). Comparing our results with the available experimental data shows that our theoretical-computational model is reliable, reproducing all the experimental observables rather accurately.

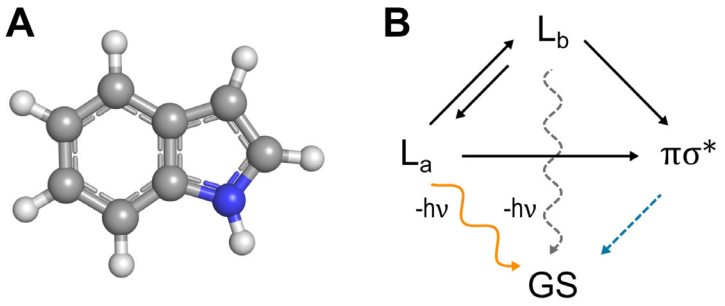

Figure: (A) Graphical representation of the indole molecule (Carbon in grey, Hydrogen in white, Nitrogen in blue). (B) Schematic description of the relaxation process according to our theoretical-computational model.

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IV-21

Unveiling the Origin of Amphiphilicity in Metal Superoxo Complexes: A Computational Exploration

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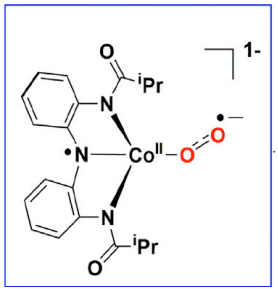
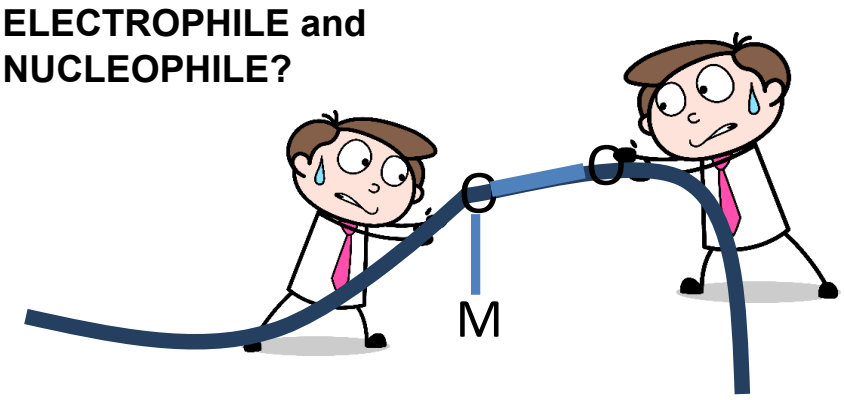
Metal super oxo species are key intermediates in catalytic cycles of biomimetic catalysts and natural catalysts i.e., enzymes. Even though oxygen is electrophilic, metal-bound oxygen species (oxo, peroxo, superoxo) behaves as both electrophile and nucleophile i.e., they have amphoteric property. DFT calculations were performed using the G09 suite of programs, employing the UB3LYP-D2/TZVP//UB3LYP-D2/LanL2DZ(Co),6-31G*(rest) level of theory, in order to understand the amphoteric properties of the biomimetic cobalt super oxo complex[1] (nucleophilicity and elctrophilicity in the context of aldehyde deformylation and oxidation of triphenylphosphine (TPP) reactions)[1]. In the inner sphere mechanism, the O–O bond cleavage is facilitated by the aldehyde C–C bond cleavage, which is enabled by the activation of the super oxo radical in a radical S_N2-like fashion which makes the inner sphere pathway more feasible compared to the outer sphere pathway[2]. The oxidation of TPP has a barrier of 40 kJ/mol, which involves the simultaneous O–O bond cleavage and the O–P (of TPP) bond formation. Again this step is caused by the activation of the super oxo radical in a radical SN2-like fashion. Therefore, the O-O bond homolytic breakage is identified as the origin of the amphoteric nature of the catalyst. These findings will help in understanding the reactivity of enzymes and biomimetic catalytic systems.





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IV-22

Designing Tryptophan Synthases for Stand-alone Functionality

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Many enzyme complexes are allosterically regulated by a protein partner making them inefficient as a stand-alone catalyst. However, the use of stand-alone protein units is desirable for industrial applications. Tryptophan synthase (TrpS) is a heterodimeric enzyme complex, forming an αββα arrangement. The α-subunit (TrpA) catalyses the IGP-retroaldol cleavage into G3P and indole. In Nature, it already exists a blueprint for a stand-alone TrpA protein named BX1 from Zea Mays (ZmBX1). ZmTrpA and ZmBX1 share the ubiquitously encountered (βα)8-barrel fold and show a high sequence identity of 63.3% However, ZmBX1 exhibits high stand-alone activity whereas ZmTrpA is a poor catalyst in the absence of TrpB. Similarly, TrpA from the Last Universal Common Ancestor (LBCA TrpA) depends on LBCA TrpB for enhanced activity (sequence identity with ZmBX1 is about 45.1%). Remarkably, ZmBX1, ZmTrpA and LBCA TrpA have two loop regions that are known to be important for the catalytic activity and the allosteric activation of TrpA: loop6 (residues 174-189 for ZmBX1) and loop2 (residues 56-76). These loop regions interact with β-subunit in the wild-type dimer[1,2]. We recently generated ZmTrpA variants with moderate stand-alone activity by replacing loop6 of ZmTrpA with the corresponding loop of ZmBX1 into[3]. Herein, we use Molecular Dynamics (MD) simulations and correlation-based tools in the apo and IGP-bound states to rationalize the differences between systems and design new variants. Thus, we aim to generate new LBCA TrpA variants with stand-alone functionality and also to elucidate the changes on the allosteric regulation between both subunits through TrpS evolution. This is done by computationally reconstructing the conformational landscapes associated with different key features (i.e. loop6 closure distance, catalytic distance…), and applying the correlation-based tool SPM[4] to design new stand-alone TrpA variants. The most promising TrpA enzymes have been experimentally validated, one of them exhibiting a more than 67-fold increase in k_{cat}/K_M, compared to the wild type enzyme.

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IV-23

An accurate and efficient hybrid Small Angle Scattering implementation including solvent effects

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The combination of Small-Angle X-ray and Neutron Scattering (SAXS/SANS or SAS) experiments with molecular dynamics (MD) simulations is an effective strategy for the characterisation of biomolecules in solution [1]. On the one hand, the limited resolution of SAS can benefit from the MD contribution, and on the other hand, the inaccuracy of MD can be reduced by integrating experimental data. Although very promising, the latter approach is hampered by its high computational cost. In particular, the multiple scattering intensity calculations performed on-the-fly alongside the MD simulation make this method prohibitively expensive, even on the latest High-Performance Computing systems. One way to overcome this limitation is to calculate the intensity of the system of interest on a coarse-grained model, thus aggregating the scattering behaviour of groups of atoms into larger particles [2]. Previously, we presented a hybrid resolution method that allows atomistic SAXS-restricted MD simulation by using a Martini coarse-grained approach to efficiently back-calculate scattering intensities [3]; in our last work, we enhance this technique by developing a novel hybrid-SAS method that is faster, more accurate, extended to the SANS intensity calculation and that is compatible with both proteins and nucleic acids. Furthermore, an implicit and user-definable solvation layer contribution is included in the calculation to allow the reconstruction of a more realistic scattering behaviour in solution. This layer depends on solvent-solute interactions and, being typically more electron/neutron dense than the bulk solvent, actively contributes to the scattering signal [4]. To ensure a fast and simple use of our method and to broaden its application, we have included it into PLUMED-ISDB [5], a module part of PLUMED [6], an open-source software designed to enhance and extend various MD engines or to be used as a stand-alone package to perform a wide range of advanced analyses of complex biomolecular systems.

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IV-24

Enhancing the Inhomogeneous Photodynamics of Canonical Bacteriophytochrome

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The functional and activity properties of proteins are closely linked to their three-dimensional structures. Conformational transitions play a crucial role in their biological action, particularly in signalling. Light triggers many vital processes. Light-activated molecular switches are usually based on photoisomerization. These switches consist of a protein and an attached light-absorbing small molecule called a chromophore. When light is absorbed, the chromophore undergoes a conformational transition that triggers a series of structural changes within the protein. [1][2]

The light-sensing conformational change is one of the primary mechanisms for converting light into molecular motion. In a complex derived from the bacteria *Deinococcus radiodurans* containing biliverdin IXα (BV) bound to bacteriophytochrome (BphP), a conformational change in the D-ring of the pyrrole chromophore leads to a switch between spectrally distinct red (Pr) and far-red (Pfr) forms. This process has been studied in atomic detail. [2]

A molecular dynamics (MD) method based on enhanced sampling (metadynamics) was used to overcome the energy barrier of the light-induced conformational transition. Our results, obtained by calculating the free energy barriers between the relevant metastable states, were in good agreement with experimental data. The enhanced sampling modeling of the BV-BphP complex contributed to the detection of fundamental conformational changes propagating through two experimentally defined signal transduction pathways. [2]

The results show that a thermal transition (dark inversion) between Pfr and Pr is possible via a previously unknown Pfr intermediate. This work improves our understanding of the mechanisms of BV photoisomerization. It also provides a detailed model of the intramolecular signal transduction pathways from the chromophore to other regions of the phytochrome protein, a system abundant in living matter. [2]

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IV-25

Insights into the mechanism of the C-terminal PIK3CA activating mutations

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PI3Kα is the most frequently mutated kinase in human cancers with mutations often occurring at the C-terminus. The C-terminus has a dual function in regulating the kinase, playing an auto-inhibitory role for kinase activity and also mediating protein binding to the cell membrane. When PI3Kα attaches to the cell membrane, it phosphorylates its substrate PIP2 and converts it to PIP3, initiating a signaling cascade for cell proliferation.[1] Oncogenic mutations in the C-terminus of PI3Kα lead to overactivation of the kinase,[2,3] however, the molecular mechanisms by which these C-terminal oncogenic mutations cause PI3Kα overactivation remain unclear. H1047R, G1049R, and M1043L mutants increase ATPase activity compared to the WT, and H1047R, G1049R, and a frameshift mutation (N1068KLKR) increase membrane binding compared to the WT.[2,3] Moreover, after comparing available crystal structures of the WT and H1047R mutant, different conformations of the C-terminus are observed with the H1047R mutant structure displaying an open C-terminal conformation associated with PI3Kα activation (Figure 1).[4]

To understand how C-terminal mutations of PI3Kα alter kinase activity, we perform unbiased and biased Molecular Dynamics simulations of the above-mentioned mutants and report the free energy needed for the C-terminal “closed to open” transition and associated conformational changes. H1047R and G1049R mutants have the lowest free energy for the transition compared to the WT, M1043L and N1068KLKR mutants. In the open state of M1043L mutant, a different direction of the C-terminus is observed, which corroborates with experimental work showing that M1043L has a lower membrane-binding ability compared to the other mutants.[3] To validate our findings, we compare the results from Molecular Dynamics simulations with the existing HDX-MS experimental data,[3,5] calculating the solvent accessibility of the residues and their hydrogen bonding, and find that the results align. The differences in the free energy needed for the closed to open transition and the observed conformational changes across the different mutants provide valuable insights into the molecular mechanisms underlying the C-terminal activation in oncogenic and WT PI3Kα.

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IV-26

Utilization of machine learning for prediction of docking scores

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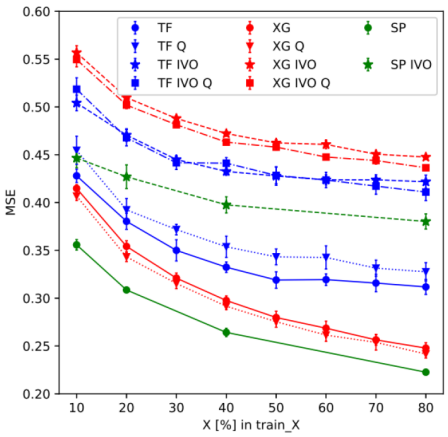
Inhibitory potential of ZINC15 [1], [2] in-vivo (59 884 compounds) and in-vitro-only (174 014) sets towards the SARS-CoV-2 main protease is calculated Autodock Vina 1.2.3 [3], [4]. The in-vivo set is used for ML training, validation, and testing (TensorFlow [5], XGBoost [6], SchNetPack [7]). The in-vitro-only set is used for the evaluation of prediction capability of ML models. Trained ML models are analysed with respect to their convergence during training period, prediction capability, and screening potential represented by ROC characteristics. Contributions to the prediction error are evaluated with respect to compounds' charge, number of atoms, and expected inhibitory potential (docking score). Methods for the prediction error estimation of new compounds, as well as various model parametrizations, are considered to improve the accuracy of ML models predictions.



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IV-27

Unraveling the Catalysis of GIIA sPLA2 through Classical and QM/MM Approaches

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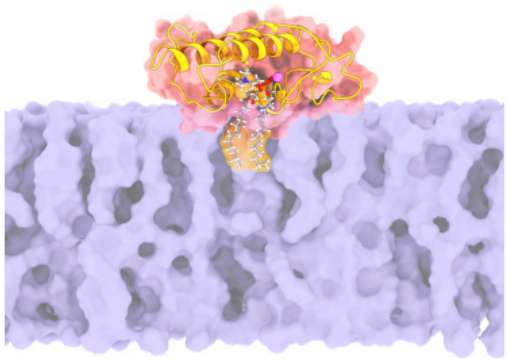
Phospholipase A2 (PLA2) enzymes are widely distributed across various organisms and play critical functions in human cell signaling pathways by hydrolyzing ester bonds in phospholipids. Elevated levels of GIIA sPLA2 have been detected in the synovial fluid of arthritis patients, revealing a regulatory role in inflammation [1], and sPLA2 isoforms have also been linked to metabolic disorders such as obesity and diabetes [2]. Consequently, identifying effective and specific sPLA2 inhibitors holds promise for developing improved pharmacological therapies. However, a comprehensive understanding of the sPLA2 catalytic mechanism, crucial for rational inhibitor design, remains limited. In this study, we investigate two mechanistic proposals for sPLA2 catalysis: the involvement of one or two water molecules in hydrolysis [3]. We focus on the human GIIA sPLA2 enzyme, employing classical molecular dynamics and hybrid QM/MM approaches (i.e. static modeling and umbrella sampling) at the PBE/MM level of theory, to characterize: i) the binding to a POPC/POPS phospholipid bilayer model, ii) and the proposed pathways in the hydrolysis of POPC, respectively. Our calculations suggest that the reaction pathways can be competitive, and the studied transition states closely resemble the structures of complexes with known inhibitors and substrate analogs. Altogether, these results provide valuable insights into PLA2 catalysis and offer potential guidance for the development of targeted inhibitors with significant therapeutic value.



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IV-28

Modeling energy-transfer processes in the light-harvesting complex CP29: first principles simulation of transient absorption spectroscopy

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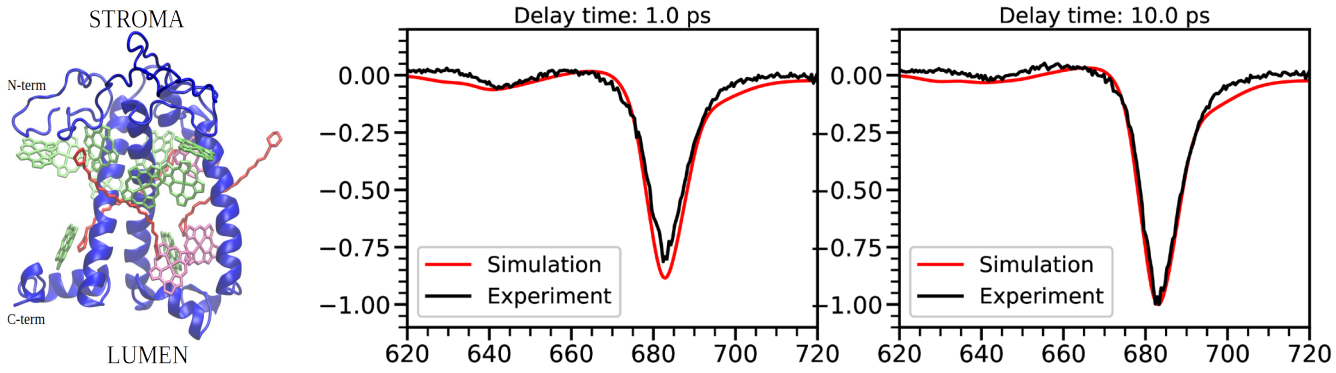
In photosynthetic organisms, light is absorbed by specialized molecular aggregates called light harvesting complexes (LHCs), protein scaffolds that host multiple pigments such as chlorophylls. The excitation energy is then funnelled by the pigment network towards reaction centres, where it is converted to chemical energy. These processes, called light harvesting, can be studied using transient absorption (TA) spectroscopy, as time-resolved spectral features are fingerprints of the LHC excited-state dynamics. However, the complexity of the signals arising from simultaneous processes prevents a complete interpretation of spectra. Atomistic simulations can help mapping all excited-state processes occurring during TA experiments. However, LHCs are challenging systems for computational chemists: LHCs are large systems where each chromophore experiences a specific and dynamic interaction with the protein. In addition, the simulation requires strategies to model excitation energy transfer (EET) and spectroscopy.

Combining molecular dynamics simulations with *ab-initio* multiscale methods has proven effective in modelling the excitation properties of such systems [1]. Here, we present a first-principles simulation of the TA spectra of the chlorophylls network in the CP29 minor LHC from plants. EET processes are modelled using Redfield-Förster (RF) theory [2] within the exciton framework. As reported in the **Figure**, the simulations can reproduce correctly the experimental [3] TA spectra in terms of bands position, lineshape and dynamics. This promising result suggests that RF theory can effectively model EET, which is induced by nuclear vibrations and by the protein environment under partial delocalization of the excited states.



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IV-29

Toward selective inhibitors of the metabolic repair enzyme PGP by virtual screening: unravelling the open and closed-cap PGP states as key for enzymatic inhibition

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Misleading phosphorylation and dephosphorylation can lead to several diseases. The sizeable superfamily of haloacid dehalogenase (HAD) phosphatases has gained increasing pharmacological interest over the last decade [1]. As a member, phosphoglycolate phosphatase (PGP), a metabolite damage control enzyme[2-4], has been proven as a pharmacologically actionable target [5]. However, its modulation in, for instance, autoimmune responses and cancer diseases remains largely untapped. Contrary to the well-known alkaline or tyrosine phosphatases, HAD phosphatases show a different catalytic dephosphorylation mechanism and are mostly insensitive against commonly used phosphatase inhibitors [1]. Thus, to further investigate PGP as a therapeutic target, new inhibitors need to be developed and understood in terms of their mechanism of action.

From the first resolved X-ray crystal structures of an inactive mutant of PGP in the presence and absence of a specific small-molecule inhibitor identified in a high-throughput screening campaign [5], we modelled the catalytically active PGP and investigated the mechanism of inhibition via docking and molecular dynamics (MD) simulations. The trajectories unveiled a preference for the closed-cap state of PGP in the presence of the inhibitor and clarified the dominant protein-ligand interactions [5]. Potential inhibitors should be able to lock PGP in the closed conformation while impeding substrate access. These findings provide a more plausible basis for virtual screening efforts directed towards improved PGP inhibitors.

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IV-30

Predicting RNA Structure by using Evolutionary Information captured by Unsupervised Language Models

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Non-coding RNAs (ncRNAs) possess functional significance that extends beyond transporting genetic information. They are involved in various regulatory mechanisms, including gene expression control, protein synthesis and molecular signaling. These functions are mediated through the structure adopted by ncRNAs. Understanding the trends and mechanisms behind RNA structure, holds great potential for uncovering more insights about these promising molecules with implications in disease mechanisms, diagnostics, and therapeutics. Inspired by the success of using evolutionary information in protein structure prediction, our research draws on the groundbreaking ESMFold[1] framework, that uses an unsupervised language model pre-trained on vast amounts of protein sequences from diverse organisms to efficiently capture conserved structural insights[2]. In a similar manner, we explore the suitability of DNABERT[3] and RNABERT[4], the only available pre-trained nucleic acid language models, for RNA structure prediction. Specifically, we employ traditional Machine Learning and Deep Learning models in order to refine the machine-learnt evolutionary knowledge of the language model and predict the secondary and tertiary RNA structures, represented as pairwise contacts. This approach has the potential to overcome the limited structural data availability problem by utilizing the features learnt from processing the abundant sequence data that the post-omics era yields, as a natural language. However, here, we show that neither the current nucleic acid language models are adequate to retrieve RNA structural information, nor any machine learning model can recognize structural patterns from those limited learnt features. Overall, this approach offers the potential to uncover novel ncRNA structure insights provided that suitable language models are developed.

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IV-31

Guanine-Thymine Wobble Misincorporation via Proton Transfer

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DNA polymerase is an enzyme that catalyzes the synthesis of DNA molecules by matching complementary deoxyribonucleoside triphosphates (dNTP) to the template DNA strand using the standard Watson–Crick base pair rules. However, when a noncomplementary dNTP diffuses into the active site during the polymerase dNTP sampling, the polymerase domain will transition from an open to an ajar conformation, thus forming a different nonstandard hydrogen-bonded base-pairing arrangement called wobble mispair[1]. While there are other sources of replication errors, the fidelity of replication primarily depends on the ability of polymerases to select and incorporate the correct complementary base [2].

Consequently, misincorporating a noncomplementary DNA base in the polymerase active site is a critical source of replication errors that can lead to genetic mutations [3]. In this work [4], we model the mechanism of wobble mispairing and the subsequent rate of misincorporation errors by coupling first-principles quantum chemistry calculations to an open quantum systems master equation [5]. This methodology allows us to accurately calculate the proton transfer between bases, allowing the misincorporation and formation of mutagenic tautomeric forms of DNA bases. Our calculated rates of genetic error formation are in excellent agreement with experimental observations in DNA. Furthermore, our quantum mechanics/molecular mechanics model predicts the existence of a short-lived “tunnelling-ready” configuration along the wobble reaction pathway in the polymerase active site, dramatically increasing the rate of proton transfer by a hundredfold, demonstrating that quantum tunnelling plays a critical role in determining the transcription error frequency of the polymerase.

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IV-32

Molecular Dynamics Simulations of Post-Translationally Modified Sp1

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Specificity proteins (Sp) are zinc finger (ZnF) transcription factors. There are nine members of the Sp family.[1] Sp1 is up-regulated for many cancers, including pancreatic, colon, gastric, breast and lung.[1]

Sp proteins are multidomain proteins, however, the DNA-binding region comprises of three individual Cys_2His_2 ZnF domains that are found towards the C-terminus of the Sp protein. Despite there being many members of the Sp family only three individual ZnF domains from the Sp1 protein have so far been characterised using nuclear magnetic resonance spectroscopy (PDB ID: 1VA1-3).[2] Within the DNA-binding domain, post-translational modifications (PTM) can occur. Sp1 is acetylated at Lys703, within the third ZnF (Sp1f3) of the DNA-binding domain which was shown by alanine scanning mutagenesis.[3-5] Acetylation at Lys703 has been shown to inhibit DNA binding.[3-5]

We performed all-atom molecular dynamics (MD) simulation for 500 ns in triplicate, to probe the behaviour of wild-type and acetylated Sp1f3. Due to the introduction of PTM, there is little conformational distribution to the ZnF fold. With the only exception being that the Lys703 is four times more solvent exposed when compared to the wild-type. Using clustering analysis, we then clustered the wild-type and acetylated and docked the clusters to the Sp DNA consensus sequence and performed further docked all-atom MD simulations.

Upon binding to the Sp DNA consensus sequence, there is a conversion from a α-helix to a 3_{10} helix between residues 705-708. The Sp DNA consensus sequence undergoes conformational change to accommodate the wild-type and acetylated wild-type. There are fewer long-term hydrogen bonds formed between the acetylated wild-type and the DNA consensus sequence compared to the wild-type. There are also on average fewer native contacts between the Sp DNA consensus sequence and acetylated wild-type.

To conclude, there are fewer native contacts and long-lasting hydrogen bonds between the acetylated wild-type and the Sp DNA consensus sequence, therefore it is unlikely that they remain in contact as long as the wild-type.

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IV-33

The importance of interfaces in bispecific antibody design

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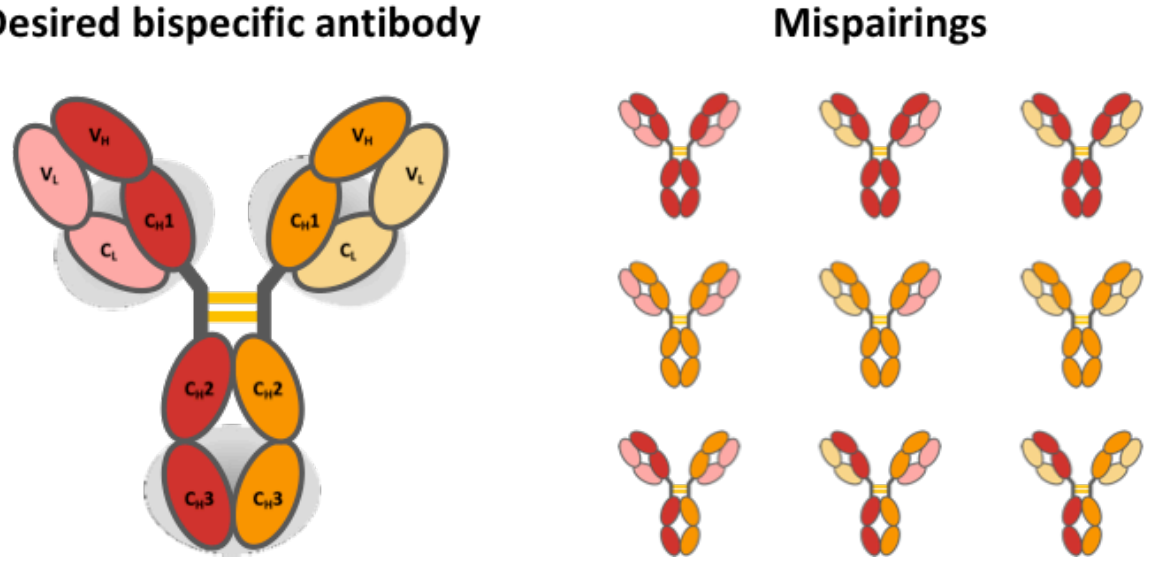
A new antibody format which has proven to be extremely useful as biotherapeutics are bispecific antibodies. These antibodies have a Y-shaped structure which consists of two different heavy and light chains. Due to the assembly of the four polypeptide chains, four interface types are formed, i.e., the V_H-V_L, the C_H1-C_L, the C_H2-C_H2, and the C_H3-C_H3 interface. As bispecific antibodies consist of two different antibody halves, they can bind two distinct targets. This results in various advantages over monospecific antibodies, like the recruitment of specific effector cells for cancer therapy, enhanced specificity due to simultaneous binding to epitope pairs, and the activation of two unique signaling pathways. However, the correct pairing of the chains is demanding as only one among the ten potential combinations produces the desired antibody. To overcome this challenge multiple design strategies have been developed, such as the knobs-into-holes approach and the charged interaction complementarity. Both methods can be used especially in C_H1-C_L and C_H3-C_H3 interfaces to enforce the correct heavy-light chain assembly as well as the heterodimerization of the heavy chains.



To gain deeper insights into these two different constant domain interfaces conventional molecular dynamics simulations have been employed. These simulations investigated the dynamics of one homodimer and two heterodimers – one charged interaction and one knobs-into-holes variant. Notably, the results revealed that, although these interfaces share a similar structure, the orientation of the domains relative to each other differs between C_H1-C_L and C_H3-C_H3. Further investigations have exposed that the C_H1-C_L interface is mainly stabilized by hydrophobic interactions, while the C_H3-C_H3 interface additionally includes electrostatic interactions surrounding the hydrophobic core. Moreover, we have observed that the design strategies for bispecific antibodies can alter the characteristic interaction profiles of the C_H1-C_L and C_H3-C_H3 interfaces.

Hence, this study has broad implications in the field of designing bispecific antibodies, as it elucidates the distinctions between the constant domain interfaces (C_H1-C_L and C_H3-C_H3) and the impact of design strategies on the resulting interaction patterns. These findings contribute significantly to the rational and efficient design of bispecific antibodies for enhanced therapeutic applications.

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IV-34

Stability Assessment of Isoniazid (INH) and Phenol Hydrazide Supramolecular Synthons in Tuberculosis Drugs: A Comparative Study via Benzaldehyde-Derived Phenolic Hydrazone Formation

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Hydrazones and N-acylhydrazones, categorized as Schiff bases, exhibit crucial anti-inflammatory attributes which hold particular significance in the context of tuberculosis (TB) pathogenesis. In this study, geometric optimisation, QST-3 transition state and frequency calculations were performed based on density functional theory (DFT) B3LYP 6-31G on Gaussian09 to assess the theromodynamic stability and favourability of phenol hydrazide synthons by reacting with benzaldehyde. Our results of the optimised phenylhydrazone derivatives from 4 synthons showed an average Gibbs free energy of -1125.130 Hartrees with 0.288 correction in comparison to -817.723 Hartrees with 0.195 correction in INh-benzhydrazone, suggesting that the presence of hydrazone functional group linkages in these compounds contributes to their more stable pharmacological potential hence as promising candidates for novel TB treatments.

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IV-45

Investigating the allosteric inhibition mechanism of I2 ligands in MAO-B using MD simulations with organic solvent/water mixtures

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The imidazoline receptors (IRs) are a group of pharmacologically characterized receptors involved in several physiological functions and are classified as I1-IRs, I2-IRs, or I3-IRs based on their affinity for different radioligands. I2-IRs are relevant in human brain disorders like depression, Alzheimer's[1], Parkinson's[2], and glial tumors. Highly affine and selective I_2-IR ligands have shown great potential as neuroprotective agents,[3] however, to date efforts aimed at identifying the molecular structure of I_2-IRs have been unsuccessful. Evidence suggests neuroprotective effects of I2-IR ligands may be linked to interactions with different proteins[4,5], particularly monoaminoxidase-B (MAO-B)[6], involved in dopamine deamination.

In this work, we employed molecular dynamics simulations using solvation boxes of water/organic solvent mixtures[7] to characterize putative I2-IR sites within the structure of several potential I2-IRs. Probes like ethanol, iso-propanol, pyridine, and water were utilized to reveal high-affinity interaction spots for I2-IR ligands. Density analysis of retained solvent molecules provided valuable insights into binding sites for I2-IR ligands. Among these proteins, our objective is initially to investigate the entrance and exit pathways of MAO-B substrate Dopamine and its aldehyde metabolite Dopal. By comparing these pathways with the interactions of 2-BFI I2 ligand, we aim to uncover the mechanism through which I2 ligands regulate MAO-B. We will investigate the regulation of MAOB by 2-BFI I2 ligand, which is likely achieved by disrupting the normal enzyme turnover and potentially competing for binding sites along the product pathways.

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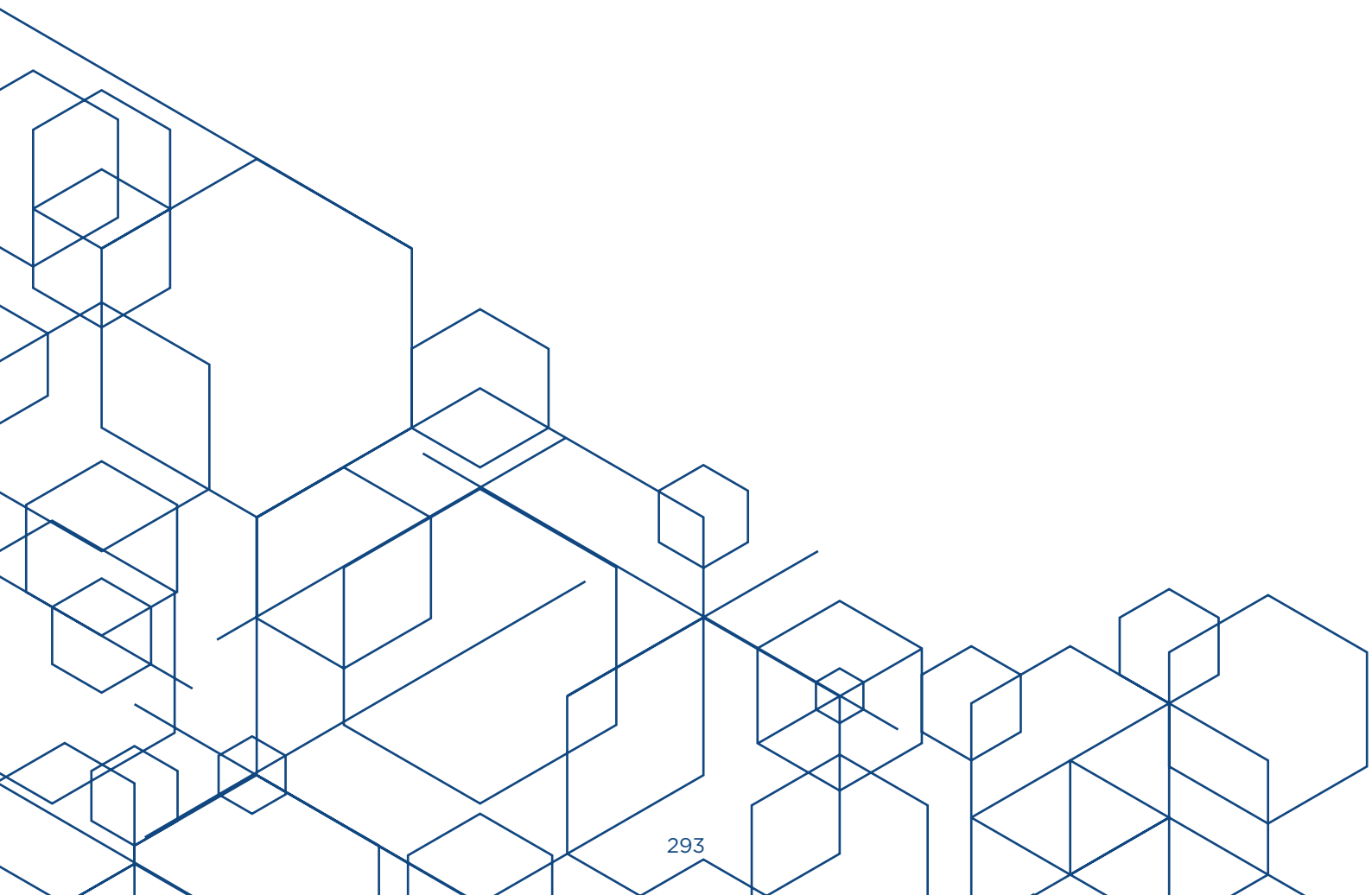
ARTIFICIAL INTELLIGENCE IN CHEMICAL RESEARCH



I-35

Quest for Potential Singlet Fission Chromophores in a Dense Jungle of Unsorted Flora: Taming of a Shrewd Dataset

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The excitation of a singlet fission chromophore with one photon can generate two triplet excitons, which is potentially able to double the efficiency of the solar cells based on it. Therefore, the singlet fission materials are regarded as a new generation organic photovoltaics but it is not easy to identify them. Recently, a lucky hint was acknowledged: molecules with low-to-intermediate diradical character should satisfy the thermodynamic requirements for effective singlet fission [1].

Since the diradical character is a theoretically derived quantity, a low-cost strategy to find new singlet fission candidates by computational high-throughput screening is viable. Our dataset comprises several hundreds of thousands of compounds containing up to 40 non-hydrogen atoms, randomly extracted from the PubChem database [2]. The corresponding descriptors are generated by semi-empirical methods and chemometric programs, while the diradical character is estimated at the *ab initio* level of theory. Thus, we obtain a structurally diverse but fairly imbalanced dataset, which is known to be a challenge for the conventional machine learning approaches. We suggest different binary classification models accounting for the disbalance between the classes which can dig out the precious molecules with low-to-intermediate diradical character indicative of potential singlet fission propensity.

The authors acknowledge the support of project ML4SF, grant КП-06-Н39/2/09.12.2019.

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I-36

Multi-objective and structure-aware (MOSA) generative drug design: model development

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Nowadays, drug design is increasingly infused with computational methods, ranging from an explanatory role to a steering one. In particular, artificial intelligence (AI) is a technology that is currently being explored extensively in this context. Indeed, various academic outputs can be found on the introduction of AI techniques within drug design case studies, for instance the programs STRIFE [1] and DiffSBDD [2]. However, their general applicability within drug design campaigns remains limited.

This contribution envisions the development of a generally applicable generative AI drug design model that takes into account all the required objectives and the 3D structural interaction between the ligand and target protein. Various constructions sites are ongoing to establish the envisioned MOSA model, listed in an approximately chronological order (see Figure): 1) an evaluation of the state-of-the-art, 2a) the description of the interaction between the ligand and target [3], 2b) discussion groups to grasp the elements necessary for lowering the threshold towards actual application (by medicinal chemists), 3a) the design/implementation of a sophisticated and best-suited AI architecture, and 3b) the inclusion of chemical and pharmacological (experimental) information in the form of generation-steering scoring functions. The ongoings of this model's development will be expounded.

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I-37

Machine learning reaction barriers in low data regimes: A horizontal and diagonal transfer learning approach

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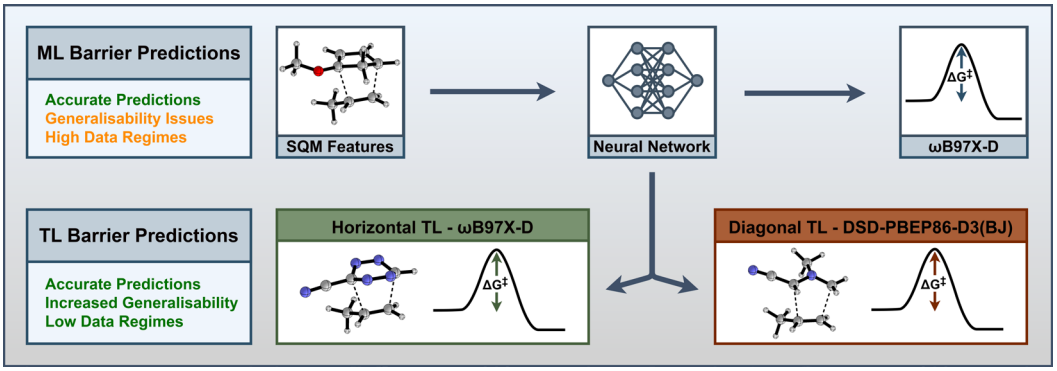
Density functional theory (DFT) is a dominant tool in the context of organic chemistry; frequently, DFT is used in reaction design and the prediction of mechanisms and barriers. While DFT provides sufficient accuracy for many of these tasks, it is accompanied by a significant computational cost. Recent approaches have focussed on coupling semi-empirical quantum mechanical methods (SQM) with machine learning (ML) to predict reaction barriers, thus circumventing the high computational cost to achieve high accuracy predictions.[1] These accuracies are however coupled with a tendency for these models to struggle when predicting outside of the chemical space occupied by the training data; generalisation to new reactions remains a challenge and large datasets are required to obtain these accuracies. To address this issue of high data requirements and low generalisability, we implement two novel transfer learning (TL) approaches, horizontal TL (hTL) and diagonal TL (dTL), which leverage the previous model's knowledge to predict at a higher level of theory (LoT) and a higher LoT on a new chemical space, respectively.



Using both hTL and dTL approaches upon models built on Diels-Alder reactions, we achieve mean absolute error (MAE) reaction barrier predictions below the chemical accuracy threshold of 1 kcal mol^{-1}. This impressive performance is especially evident in the extreme low data regimes; with only 33 and 39 new datapoints needed to achieve these values. The limited number of new reactions required to attain accurate reaction barrier predictions at a fraction of the computational cost highlight hTL and dTL as powerful tools to provide early-stage insight into reactions without the requirement of high-throughput experimentation/computational screening. We believe that these TL approaches can be applied to a variety of different reaction classes to predict reaction barriers as well as further usage across a plethora of different disciplines, including pharmaceutical and synthetic chemistry, ML, and reaction modelling.

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I-38

Machine learning approaches to predict Michael addition reaction barriers

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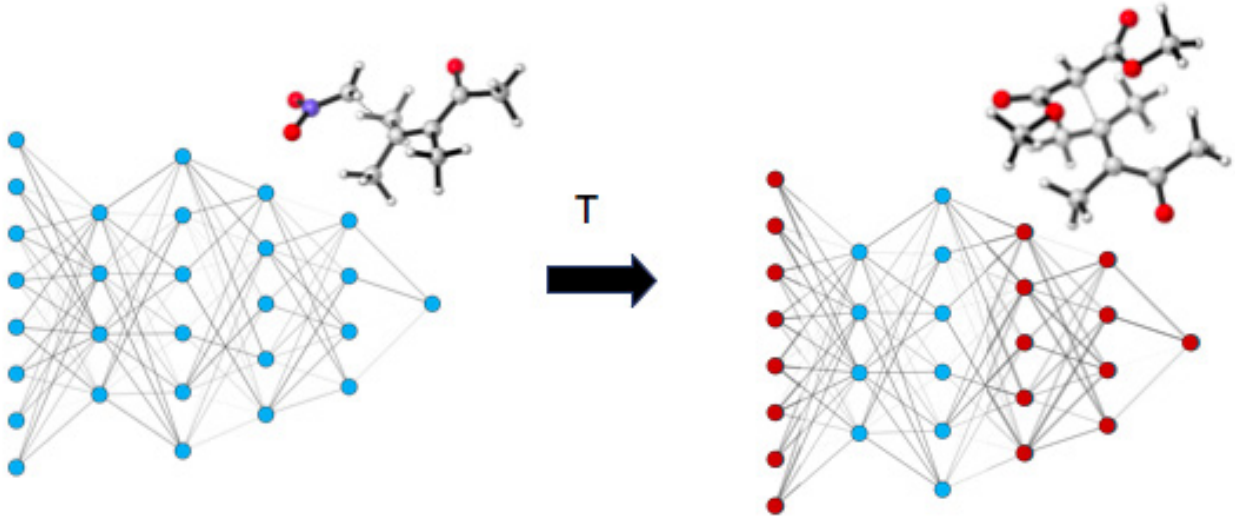
Density Functional Theory (DFT) is a pivotal tool in modern organic chemical modelling, allowing exploration and design of synthetic pathways, as well as mechanistic insight into reactions.[1–3] However, when dealing with large systems or a huge number of reactions, the cost scaling for accurate DFT calculations is unfeasible. As an alternative, it has been shown that a machine learning model, trained on semiempirical quantum mechanical (SQM) data, can produce predictions in seconds that approach the accuracy of DFT calculations, at a fraction of the time and cost.[4] The next frontier is pushing these models to cover a larger chemical domain or require less data to perform effectively. Using machine learning techniques, these boundaries can be challenged. We demonstrate a drastic improvement of a model's ability to make predictions, when trained on fewer data points. This process is initialised by first training a model to predict the activation free energy of a set of Michael additions with a given nucleophile. Through transfer learning (TL) we adapt this model, retraining parts of the network to predict the barriers of Michael additions with an alternative nucleophile. This process requires 60% less training data to obtain the same level of accuracy as a model trained from scratch. This is most applicable to synthetic chemists, who could quickly tailor a pre-trained model to a new reaction, leveraging knowledge from the model's source database to inform predictions on a new target, minimising the requirement for costly DFT calculations in the process.



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I-39

An On-the-fly Deep Neural Network for the prediction of time-resolved spectroscopy

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The development of ultrafast techniques and advanced levels of theory in X-Ray spectroscopy offer capabilities which can deliver new insights into complex structural systems and reaction dynamics. The implementation and execution of these techniques, however, is often attended by prohibitive costs and daunting timescales, with computation times scaling up to N^7 for N electrons at high levels of theory such as coupled-cluster and other post HF methods, and massive energetic commitments required to exercise the valuable beam-time required for ultrafast spectroscopy. Recent developments in artificial intelligence algorithms present new opportunities for the cost- and time-effective augmentation and supplementation of such studies.

In this spirit, we develop and expand on our deep neural-network architecture, XANESNET, which can simulate near-edge X-Ray spectra when presented with geometric molecular structures. The execution of thousands of predicted spectra from the trained architecture can be completed in seconds. The architecture has previously demonstrated success when applied to several transition metal K- and L-edges[1,2]; in this work, we show that XANESNET has been successfully expanded to the time-resolved domain as it tracks the dynamic ground- and excited-state spectral features of the sulphur K-edge from trajectories of the humble ring system 1,2-dithiane over time.[3] XANESNET predicts the time-resolved spectra to accuracies of sub-10% for the ensemble of trajectories, accurately replicating the evolution of fine spectral features.

We additionally demonstrate the supply of a metric for judging when the model has attained optimal gains from the quantity of training data supplied via an ensembling technique. Preliminary investigations into the application of a superior atomic descriptor, SOAP, and the development of a generalist model to predict the sulphur K-edge calculated from 130,000 molecules from the gbd13 dataset are also presented.

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I-40

Computational and Machine Learning Exploration of the Properties of High-Energy Molecular Crystals

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The discovery of new high-energy materials (HEM) is a long-standing challenge. The evaluation of new candidate materials requires labor-intensive, dangerous, and expensive trial-and-error experiments. The prediction of new candidates' performance and safety assessment prior to experimental procedures is important to accelerate the discovery of new HEM by careful screening of many possible candidates.

However, relevant HEM properties like detonation velocity and stability are challenging to predict since these depend on several factors such as crystallization conditions, molecular size and shape, conformational flexibility, noncovalent (hydrogen bonds), stacking interactions, electrostatic and dispersion interactions. Additional properties can also be difficult to predict for a wide spectrum of molecules.

In the current work, we used a data set of 300 HEM molecules and datasets of 10K HEM-like molecules to perform extensive density functional theory (DFT) calculations on the molecular structure (such as molecular volume, polarizability, and vibrational frequencies) and crystal properties. We used the results as new descriptors for machine learning algorithms, in order to predict the stability and performance the HEMs.

I-41

Smooth Sailing in Rough Waters of Excited States: A Data-Based Approach

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The performance of machine learning algorithms for electronically excited states is far behind ground-state applications.[1] The problem lies in the high complexity of reference electronic-structure calculations, subtle dependencies among densities of states and insufficient smoothness of the modelled properties in the vicinity of state crossings and conical intersections. We proposed several machine-learning approaches to overcome these limitations allowing us to efficiently model excited-state properties both in the configuration and in the chemical space.[2,3]

Electronic-structure codes provide us with energy-ordered adiabatic states. However, adiabatic states are usually not smooth in the whole configuration space as they form conical intersections. Therefore, it is advantageous to switch to a smooth diabatic basis via a geometry-dependent unitary transformation. Unfortunately, diabatization is also an outstanding problem. We tackle both problems at once.[3] We use machine learning to correct for deficiencies of a simple property-based diabatization which provides us in return with smooth properties that can be easily learned. We need only a small amount of training data and we observe the increase in prediction accuracy by up to two orders of magnitude.

There are additional obstacles when learning across different chemical species in the chemical compound space. Modern molecular representations and machine learning models are usually designed using contributions from atomic environments and assume some kind of additivity. Such an approach is advantageous for extensive or local properties such as molecular energy or atomic forces, but it is suboptimal for global intensive properties such as transition and excited-state properties. We propose new representations and kernels more suitable for these properties.

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I-42

Evolution of reactive species through neural network perception and response: wazowsky simulation

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The motion of species towards the fulfillment of tasks is reproduced through the use of a neural network procedure that emulates their perception of the environment and their response. Such species, termed Wazowsky(w)-species, may participate in interactive processes that take place in biochemical reactions, as macromolecules approach and interact with one another, or as chemical species react and diffuse. The approach can also be applied in the evolution of collections of macroscopic objects, as well as in animal population dynamics. The procedure is applied to a prey-predator reaction mechanism with drift in space. We observe realistic rates for the concentration of the chemical species. The generalization of the use of self-aided species to complex reactive systems can simplify their complex kinetic behavior through the replacement of their many-body dynamics with the execution of tasks of w-species.

I-43

Exploration of redox potential in chemical space

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Redox potential plays a crucial role in many applications, and accurately estimating it can be time-consuming and resource-intensive. In this study, we present a novel method for fast estimation of redox potential using message passing neural networks (MPNN). By training on a given dataset, we achieved the lowest mean absolute error (MAE) among existing approaches, reported in the literature, making our method state-of-the-art. Furthermore, we combined our MPNN approach with an evolutionary algorithm to explore the vast chemical space for potential good candidates. Our method has the potential to greatly accelerate the discovery of new catalysts and materials for redox reactions, ultimately contributing to the development of more efficient and sustainable chemical processes.

I-44

Unveiling the Mechanism: Exploring a Solution-Mediated Pathway for Solid Electrolyte Interphase Growth in Lithium-Ion Batteries

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Lithium-ion batteries (LIBs) are widely utilized as battery technology, powering numerous portable devices and electric vehicles. [1] In the initial cycle, a protective layer known as the solid electrolyte interphase (SEI) forms on the surface of the anode, playing a critical role in the long-term performance and cyclability of LIBs. However, understanding the comprehensive growth and composition of the SEI at various scales remains a challenge in both experimental and computational approaches. This is due, in part, to the multiscale nature of the process, where molecular-scale chemistry dictates the composition of the SEI over hundreds of nanometers.

In this study,[2] we present a multiscale approach that aims to thoroughly characterize the growth and composition of the SEI by employing a chemistry-specific reaction network. Through the generation of more than 50,000 simulations representing diverse reaction conditions, our findings challenge established models by revealing that the organic SEI forms and expands via a solution-mediated pathway. This occurs through the aggregation of SEI precursors at a significant distance from the surface, facilitated by a nucleation process. Subsequently, the rapid growth of these nuclei leads to the development of a porous layer that eventually covers the electrode surface.

This discovery addresses the paradoxical situation wherein the SEI can only form near the surface where electrons are available, yet ceases to grow once this narrow region near the electrode is filled. Additionally, we have identified key reaction parameters that determine the thickness of the SEI, offering an opportunity to design electrolytes and additives to tailor the SEI properties. This rational design approach holds promise for optimizing battery performance and extending battery life.

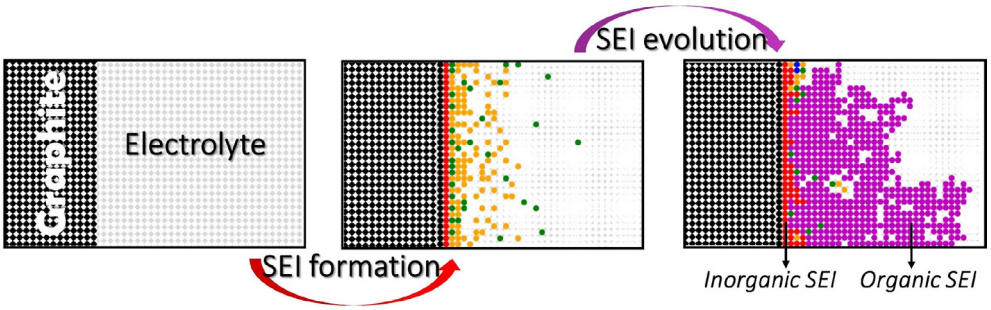

Figure 1. Schematic illustration of SEI formation and growth at the anode-electrolyte interface in LIBs.

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I-45

Transferability of actively-learned training data sets for machine learning potentials

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The promise of machine learning potentials (MLP) – an ab initio level potential energy surface, where the cost of running simulations is similar to empirical force fields - is quite enticing for many researchers using molecular simulations as a central tool in their research. The foundation of a reliable MLP is its training data set. It should cover all relevant areas of a system's configuration space, while consisting of as few structures as possible to avoid unnecessary and potentially expensive ab initio reference calculations. Therefore, data driven active-learning methods such as Query by committee (QbC) have gotten an increasing amount of attention in MLP research. In QbC, a training set is constructed iteratively by evaluating the standard deviation of predictions of multiple, slightly different MLPs to select only the most relevant structures for a data set out of a large set of candidates. However, this process is always executed with and for one specific MLP architecture and one specific electronic structure method. The obtained training data set is therefore inevitably linked to these choices. The question we address in this poster is that of transferability of actively learned training data sets to different reference methods and MLP architectures. We will use a - high quality - actively learned training data set for water systems [1] and explore how accurate and reliable its predictions remain when changing either the reference method or the MLP architechture.

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II-36

Transfer learning for heterocycle retrosynthesis prediction

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Small heterocycles play a central role in synthetic and medicinal chemistry, with most pharmaceuticals and agrochemicals containing at least one of such rings.[1] These motifs effectively modulate the shape, pharmacokinetics, and binding properties of drugs. However, the limited availability of synthetic protocols for ring-forming reactions hinders the incorporation of new heterocycle scaffolds into drug-like molecules. Furthermore, computer-aided synthesis planning tools, despite their promise, still exhibit poor performance in ring-breaking reactions.

In this contribution, we describe our efforts to enhance the predictive power of retrosynthesis prediction tools towards heterocycle compounds by combining transfer-learning strategies[2] and the transformer model.[3] To achieve this, we use a general dataset of chemical reactions together with a carefully curated dataset of ring formations only. We comparatively analyse different domain adaptation approaches and identify those that work best for this task. We evaluate the accuracy of our model and the viability of the proposed ring-breaking disconnections as well as general chemistry disconnections against a base model. Additionally, we showcase the applicability of our tool on drug-like molecules. Lastly, we introduce a method for further fine-tuning the model on newly published reactions.

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II-37

Exploring complex interfaces with DFT-MD: from enhanced sampling to machine learning

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Knowledge of dynamics at interfaces is a powerful means to provide perspectives on reaction mechanisms. With high-performance density functional theory-based molecular dynamics (DFT-MD), an extensive investigation on different catalytic systems with explicit inclusion of environment (e.g. solvent) at ambient conditions is possible. In our work, we have, for instance, identified the phenomenon of transferring oxygen atoms from sub-layer to surface as the possible degradation for $LaTiO_2N$, through DFT-MD simulation with water as explicit solvent. Moreover, we have detected the preferential in-plane hydration structure of the first water layer at (001)-WO_3 and (100)-WSe_2 facets[1], and the role of solvent for the (110)-RuO_2 surface wettability and mechanical properties was analyzed[2]. Despite the great power of DFT-MD in capturing the dynamics of atoms, combining it with enhanced sampling is highly desirable for sophisticated elucidation of reaction mechanisms and calculation of free energy surfaces. In our well-tempered metadynamics simulation of (110)-RuO_2 aqueous interface, not only was the free energy barrier of OER assessed, but also we revealed a water-assisted OER mechanism by a crucial proton transfer step[3]. Crucial parameters in such simulations are the so-called collective variables (CVs), which are usually selected based on chemical intuition and thus biased and not universally transferrable to all systems. We have therefore developed a deep autoencoder neural network (DAENN) for discovering general purpose CVs[4]. The developed autoencoder is capable of searching for hidden CVs in expanded configuration space automatically. To help other people to use the DAENN algorithm, we have developed the open-source DeepCV package[5].

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II-38

New representations for chemical machine-learning

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Chemical (molecular, quantum) machine learning relies on representing molecules in unique and informative ways. In this poster, we introduce two new representations – a quantum-inspired molecular and atomic representation called Matrix of orthogonalized Atomic Orbital Coefficients [1] (MAOC) and a fragmentation-based technique called Matrix of Fragment Similarity Representation (MFSR). MAOC is based on a cost-effective localization scheme that represents localized orbitals *via* a predefined set of atomic orbitals. The latter can be constructed from small atom-centered basis sets in conjunction with a guess electronic configuration of the molecule. Importantly, MAOC is suitable for representing monatomic, molecular, and periodic systems, and can distinguish compounds with identical compositions and geometries but distinct charges and spin multiplicities. MFSR is instead uniquely suited for mapping and exploring the chemical space of compounds composed of specific building blocks. Most industrially and biologically relevant macromolecules are formed as a combination of finite building blocks (e.g., all proteins are a combination of just 20 aminoacids), and MFSR can predict their properties in less than a fraction of a second and with the quantum-chemical accuracy. Moreover, MFSR allows even the most entangled deep learning models to be decodable in a form that chemists can easily understand.

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II-39

EquiReact: Equivariant Neural Network for Reaction Properties

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While machine-learning predictions of molecular properties have become routine, a roadmap to tackle properties of reactions – the core of chemistry – is still emerging. When designing a model, one of the key choices to be made is the nature of the input required: molecular graphs (or equivalent) of the participating molecules or their 3D structures.

Structure-based representations have been proven to be highly predictive when combined with kernel ridge regression methods [1,2]. On the other hand, state-of-the-art deep learning models use molecular graphs generated from SMILES. Adding structural information has not yet led to improvements [3]. Moreover, these models heavily rely on pre-existing atom mapping between reactants and products, implying knowledge of the reaction mechanism, obtaining which is another non-trivial task.

In this work, we introduce EquiReact, an equivariant neural network capable of predicting properties of chemical reactions from the xyz coordinates of reactants and products. EquiReact is optimized and tested on a dataset of diverse organic reactions of small molecules [4] and on a specialized dataset of [3+2] cycloaddition reactions [5]. It yields competitive results for both cases, outperforming the baseline model without atom mapping, proving the usefulness of 3D structural information.

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II-40

ML predictions for chemical reactions: Designing dedicated physics-based representations

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Predicting properties of chemical reactions remains a challenging task for machine learning models. In particular, targeting reaction barriers without knowledge of the true transition-state structure has led to the development of various models: from carefully engineered representations combined with kernel ridge regression to graph-based neural networks. In this context, it has been shown that combining the physics-based representations of reactants and products participating in the reaction could emphasis the underlying structural changes thus affording reliable and promising descriptors.[1]

Recently we introduced a new class of molecular representations based on an initial guess-level electronic structure: the Spectrum of Approximated Hamiltonian Matrices (SPA^{H}M).[2] It proposes three variants: SPA^{H}M(e), a global representation formed by the molecular orbital energies, and SPA^{H}M(a) and SPA^{H}M(b), two local representations built upon the local electron densities to describe atomic and bond-based environments, respectively. The bond focus of SPA^{H}M(b) inspired us to extend the family with reaction-dedicated counterparts.[3]

In this work we demonstrate the modularity of the SPA^{H}M pipeline in designing dedicated representations for chemical reactions. Moreover, we evaluate their interpretability and performance when predicting reaction barriers for several databases including both diverse and more specific chemistry. Finally, we compare the best performing physics-based representations to graph-based neural network models, illustrating the competitive power of structure-based fingerprints against less informed/instructed models.[4]

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4 P. van Gerwen, M. Franke, Y. Calvino Alonso, and C. Corminboeuf (2023) *In preparation*

II-41

Interpreting machine-learned kinetic predictions

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Kinetic predictions are vital for rationalising selectivity and discovering lower energy pathways to new and exciting molecules. Previously, Density Functional Theory (DFT) has been employed for this task, but due to DFT's poor description of solvent and entropy, Machine Learning (ML) has become a more favourable alternative. Current rate-predicting ML models provide the required accuracy of ~1 log*k* unit, but uncertainty remains about whether the structure-activity relationships learned by these models align with established chemical principles. In this work, we interpret kinetic predictions made by two ML models: an in-house Bidirectional Encoder Representations (BERT) model, and the state-of-the-art Random Forest (RF) model from the literature.[1] Bimolecular Nucleophilic Substitution is employed as a model system owing to its widely accepted reactivity rules. Both the BERT and RF learn key steric and electronic effects associated with SN2 reactivity, as well as the mathematical relationship between log*k* and temperature. We also highlight some expected model limitations such as target value extrapolation. By providing transparency to machine-learned kinetic predictions, we aim to increase chemists' confidence in utilising these tools to guide synthetic design.

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II-42

Using Machine Learning to Access Challenging Hydrogenations: A Combined Theoretical and Experimental Approach

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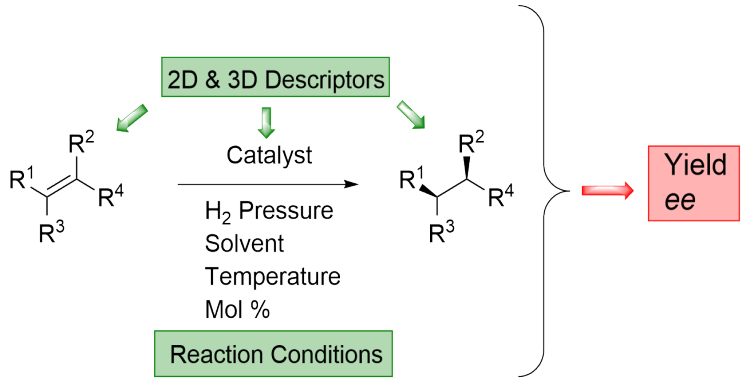
Asymmetric hydrogenation reactions of tetra-substituted olefins provide direct access to compounds containing 1,2-contiguous stereocentres, which are of great relevance to the production of pharmaceuticals. However, compared to di- and tri- substituted substrates, the enantiomeric excess (*ee*) of these reactions is generally poor, and thus, fewer examples have been reported in the literature.[1]

In this work, machine learning techniques were initially trained to predict the ee of asymmetric hydrogenation reactions of tetra-substituted olefins using examples that have been reported in literature. Several regression and classification machine learning methods were implemented, with the best models producing a mean absolute error of 9.95% *ee* and an accuracy of 89%, respectively.



Due to the reporting bias that exists in literature publications,[2] however, more experimental data of reactions leading to lower *ee* values is required to improve the predicted performance of machine learning models. Thus, further work has focussed on creating a more diverse experimental dataset to counteract this imbalance and add to the current landscape of transition-metal/ligand/substrate combinations of this reaction. Furthermore, the initial machine learning models can be used to guide the development of this experimental dataset by predicting the *ee* of novel asymmetric hydrogenation reactions, allowing the predictive ability of the model to be further probed through the comparison of the predicted and experimental *ee* values. By adopting this method, the resulting machine learning models can be improved, providing a useful tool for the prediction of *ee* and reaction optimisation of asymmetric hydrogenation reactions of tetra-substituted olefins, while additionally giving valuable insight into the transition-metal chiral catalysts that result in successful reaction.

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II-43

Analysis and Prediction of the Direct C-H Arylation Reaction

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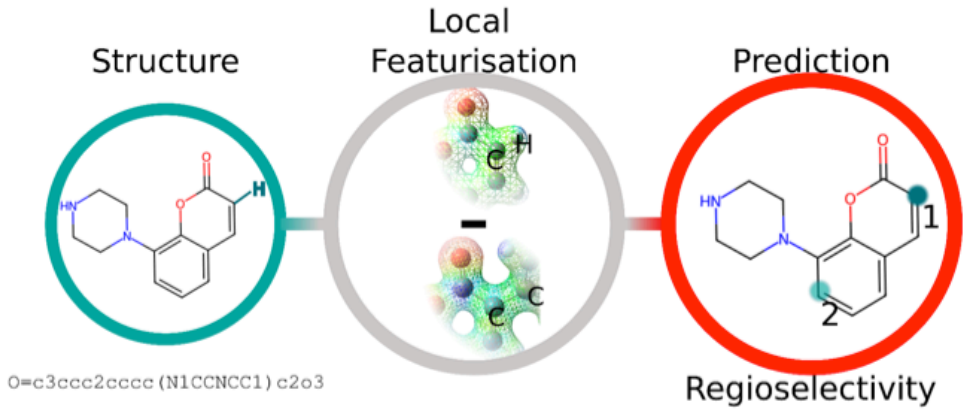
C-H bond functionalisation is and has been a hot topic in chemistry for the development of efficient synthetic routes, particularly for complex molecules. Due to the myriad of C-H bonds in organic molecules, it is challenging to know which bond is most likely to be functionalised in a given synthesis to achieve regioselective product formations. To address this challenge, we aim to capture the intrinsic reactivity of the C-H bonds within a substrate and the correlation with the regioselectivity of the direct arylation reaction [1]. This reaction was chosen owing to its importance in synthesising druglike molecules.



Our approach relies on developing local featurisations of the C-H bonds within an organic substrate molecule by combining electronic, steric and topological information as well as utilising existing QML representations to capture the “uniqueness” of a given C-H bond. This permits the discrimination of C-H bonds in different chemical environments. We use these featurisations to train machine-learning models on curated computational and experimental databases for the prediction of regioselectivity. The performances of these models are compared against each other as well as previously reported regioselectivity prediction models. Our results improve with the inclusion of reaction-relevant information in the featurisations (e.g., a difference between the local featurisation of the formed product and the original substrate) and models that are inherently based on similarity, such as the k-nearest neighbour regressor. Owing to the local nature of the representations, our approach is transferable over a wide range of substrate classes.

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II-44

Semi-supervised contrastive learning for mode of action prediction

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The Cell painting assay is a high-content screening method, which provides valuable information about the bioactivity of compounds by analysing the phenotypic and morphological changes of the cells after compound treatment. The datasets of microscopy images created by this assay are often large and high dimensional, which requires computational methods to identify compounds with similar pharmacology. Predicting the mode of action (MoA) of compounds is in many cases challenging, since compounds may have complex pharmacodynamic and pharmacokinetic properties [1]. Furthermore, pharmacological annotations are often difficult to obtain and usually only a small subset of a compound library has proper annotations available. In this study, we annotated our compounds by using the PubChem API to extract available medical subject headings (MeSH) pharmacological classifications [2]. Established methods so far mainly rely on software such as CellProfiler [3] to calculate morphological features and in this work, we used machine learning since it has shown to be very effective for leveraging image-based information [1]. Supervised [4,5], self-supervised [6] and unsupervised [7] machine learning based methods were already previously used to learn features from microscopy images for MoA assignment, where most works only trained and evaluated their models on annotated subsets. In this work semi-supervised contrastive learning [8] was used to learn accurate representations of microscopy images from the BBBC022 and BBBC036 datasets [9], which allows us both to incorporate the ground truth labels during training and make use of the larger amount of unannotated data. The learned embeddings of the microscopy images were subsequently used as input for downstream machine learning (Figure 1). We used a multi target random forest, to predict the MeSH classes of the compounds. Our work improved downstream performance compared to CellProfiler and a self-supervised contrastive learning-based approach [6]. Finally, we further validated our approach, by using our models to predict the MeSH classes of unannotated compounds in the datasets and performed a literature search to evaluate how many predictions could be confirmed from the literature.

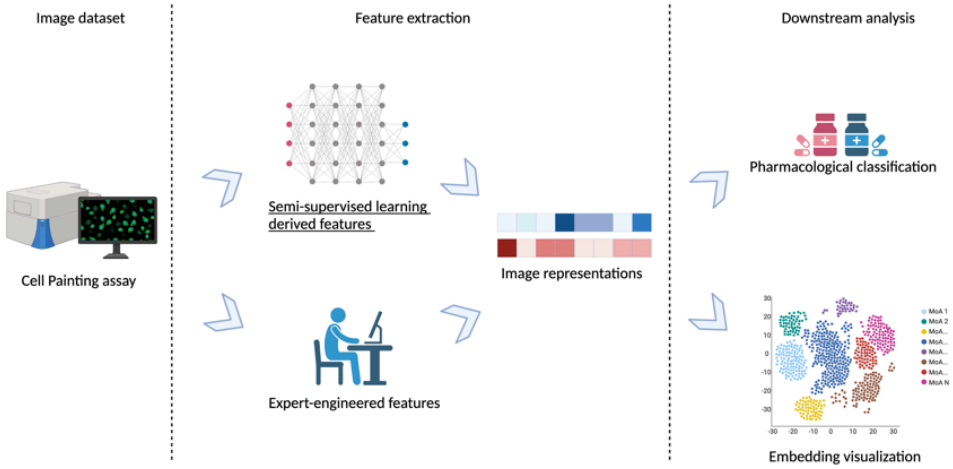

Figure 1: Workflow for calculating computer vision-based morphological profiles from Cell Painting microscopy images, which can be used to visualize the relationship between the different treatments and to predict the pharmacological classes of the compounds.

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II-45

ART-SM: An AI-based Framework for Transforming Coarse-Grained Molecules to Atomistic Resolution

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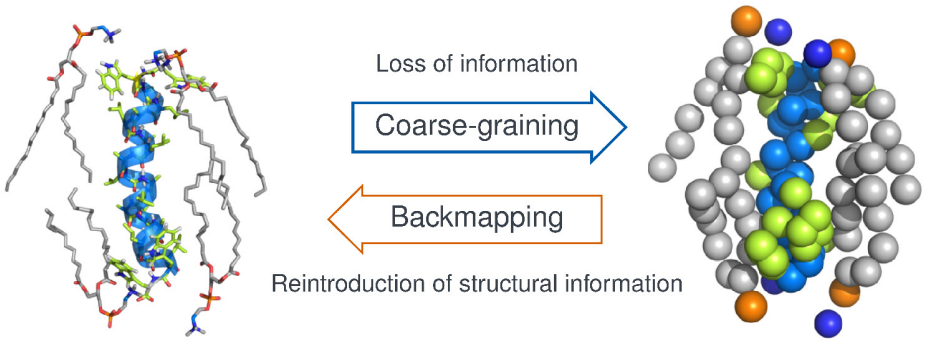
Molecular dynamics (MD) simulations offer an unparalleled spatial and temporal resolution, surpassing the capabilities of current experimental methods, and play a crucial role in revealing essential biochemical mechanisms important for understanding the development, progression, and treatment of serious diseases such as cancer. Despite their great success, system sizes and simulation times are still confined to the nanometer and microsecond scales for atomistic simulations. To overcome these limitations, sequential multiscale molecular dynamics simulations switch between atomistic and coarse-grained resolution of the molecular representation, allowing to study processes over longer timescales and simultaneously recover atomistic details. Thereby, the reverse transformation from low to high resolution, also called backmapping, is particularly challenging as structural information has to be reintroduced.



Current state-of-the-art methods often neglect the Boltzmann distribution, fail to recover correct stereochemistry, require extensive user input or have to be re-trained for new systems. With these drawbacks in mind, we developed AI-based Reverse Transformation of Small Molecules (ART-SM), a fragment-based framework that directly learns the Boltzmann distribution from atomistic simulations. Our method extends traditional approaches by identifying all main conformations from atomistic data and selecting the most appropriate based on the CG structure, instead of using only one rigid conformation. Furthermore our method optimizes bonds, angles, and dihedral angles to effectively connect the fragments. In the future, our framework will be extended to lipids, proteins and selected materials, increasing its versatility and applicability to a diverse range of biological systems.

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Machined Learned Potential for Organolithium Compounds in Solution

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Organolithium compounds are some of the most important reagent used in organic synthesis today, and the addition of lithium halides has been shown to be beneficial for multiple organometallic reactions.[1] A particular case is the enhanced reactivity of Grignard reagents in the presence of LiCl (Turbo-Grignard RMgX-LiCl).[2] Despite their extensive use in experiments, the enhancing role of the lithium compounds is not completely understood. It is found that their reactivity is closely related to their aggregation state, and to characterize the mechanism one would need to sample a large array of possible species in solution.[3] Ab initio molecular dynamics simulations (AIMD) provide a sensible route to investigate these properties, but computational cost limits the scope of these studies in terms of sampling time and system size. Recently it has been shown that machine learned potentials (MLP) is a viable alternative, which provides accurate results at a much lower cost.[4] Thus, we have developed a MLP through active learning to identify possible solvated structures for lithium alkyls, lithium halides and the mixture of them in tetrahydrofuran (THF). It reproduces free energy surfaces of comparable accuracy to AIMD and obtains structures that has been observed experimentally and theoretically. In the future we would like to use the MLP to investigate the mechanism of halide incorporation into lithium alkyl aggregates, as well as the effect of changing the -R and -X group in the Turbo-Grignard reagent.

This work was supported by the Research Council of Norway, through the Centre of Excellence Hylleraas Centre for Quantum Molecular Sciences (grant no 262695) and the Pioneer Research Grant MetalSynergy (grant no 314009), and by the Norwegian Supercomputing Program (NOTUR) (Grant no NN4654K).

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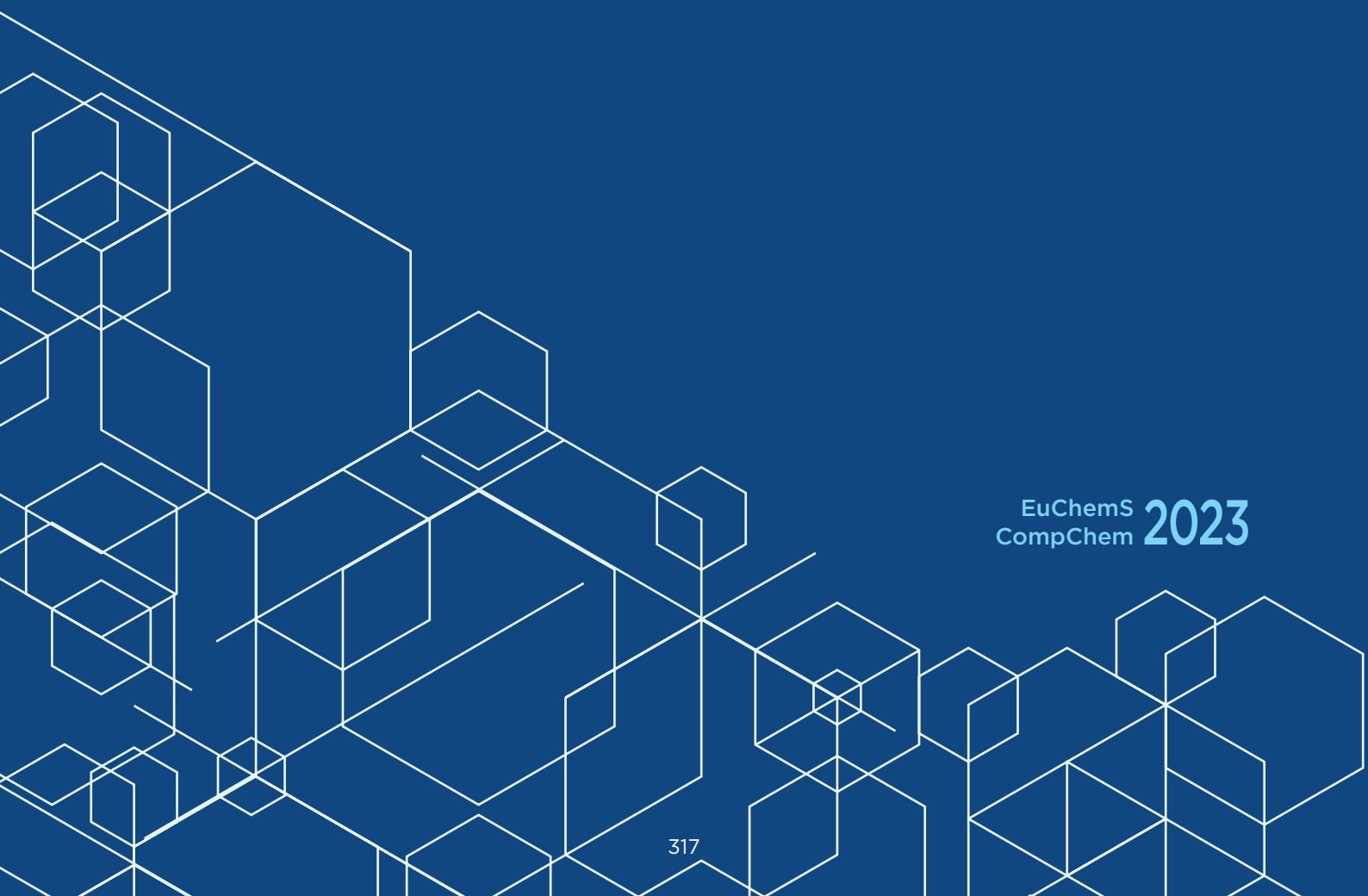
LIST OF PRESENTERS



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