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Book of Abstracts

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”EuCompChem2025-Trinari Marco-Oral” QM/MM simulations of ground and excited state spectroscopic properties of molecular systems in aqueous solution

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The spectral properties of isolated molecules can differ significantly from those of the same molecules dissolved in aqueous solution [1]. Multiscale Quantum Mechanics (QM)/Classical models are highly effective in simulating solvated molecules by dividing the system into two components: the solute, treated at the QM level, and the solvent, modeled classically [2-4]. Among these approaches, QM/Molecular Mechanics (MM) methods have expanded considerably in recent decades and are now widely used to study the spectroscopic properties of solvated systems [1-3]. The success of this methodology lies in its ability to retain atomistic details of the solvent while accurately describing hydrogen bonding [1-3]. In this work, we investigate various ground state and excited state spectroscopic properties of molecular systems, like Tryptophan, in aqueous solution using fully polarizable QM/MM approaches [5], where the MM region is described using the Fluctuating Charges (FQ) and Fluctuating Charges and Dipoles (FQFμ) force fields [6-7]. The resulting QM/FQ and QM/FQFμ approaches are integrated with classical molecular dynamics simulations for an accurate sampling of both the ground and the excited state solute-solvent phase-space [1,8]. Computed results [9] are validated through a direct comparison with experimental data, demonstrating the robustness of our methodology.

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1805742 Tailoring surface functionalizion of nanoparticles for water purification

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Clean water is among the most important resources and there is a continuously rising need for energy-efficient, simple upcycling methods. We use molecular modelling to tailor nanoparticle functionalization for cost-efficient recovery of polluted water. So far, this has been demonstrated for extracting crude oil [1], micro-/nanoplastics [2], glyphosate [3] and polychlorinated biphyenyls [4]. The carrier material is given by iron oxide nanoparticles that offer simple extraction via magnetic interactions. To enable molecular recognition of specific pollutant species, self-assembled monolayers (SAMs) consisting of phosphonic acid derivatives are bound to the nanoparticle surface. We outline the assessment of unbiased molecular simulation models to describe the carriers, their functionalization by pure and mixed SAMs as functions of grafting density and the analyses of SAM-water interfaces. Based on such molecular understanding, dedicated molecular recognition motifs are envisaged to further boost pollutant extraction - whilst diminishing unwanted processes such as particle agglomeration.

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A Computational Study of Estrogen Affinity for GPER Using Molecular Dynamics and Enhanced Sampling

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G-protein coupled estrogen receptors (GPERs) play a critical role in cellular signalling; yet the precise nature of their interaction with estrogen (EST) remains a subject of debate [1–4]. While recent studies have questioned whether EST binds directly to GPER [4], our molecular dynamics (MD) simulations provide compelling evidence in favor of such an interaction. Using MD simulations, we identified a plausible EST-binding pocket within the GPER. Thermodynamic integration–based free energy calculations revealed a notable binding affinity at this site. Notabley, under elevated EST concentrations, EST molecule spontaneously localized to this pocket within microseconds, validating the predictions from our thermodynamic integration analysis. Structural characterization of the binding site uncovered key stabilizing interactions: three strong hydrogen bonds anchoring EST at both sides of the pocket, and a hydrophobic cavity accommodating its central nonpolar core. Together, these computational results strongly support a direct binding interaction between EST and GPER, providing novel insights into the receptor's function in EST-mediated signalling pathways.

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A Computational Study of the MOR1–PKR Interaction

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Opioids are one of the most commonly used group of drugs in pathological pain treatment due to their remarkable analgesic effect. The main target for opioids is the transmembrane receptor μ-opioid receptor 1 (MOR1), which belongs to the G protein-coupled receptor superfamily (GPCR). Several kinases, such as G protein-coupled receptor kinases, cyclic AMP-dependent protein kinase, protein kinase C, and mitogen-activated protein kinases, interact with opioid receptors, modulating their activity. We investigated the potential interaction between the MOR1 and the double-stranded RNA-activated protein kinase (PKR), which participates in different cellular processes, including immune responses, cell growth control, and responses to cellular stress. To obtain more details on this interaction, this work aims to apply a set of computational chemistry methods to formulate a hypothesis regarding the mechanism of interaction between MOR1 and PKR. Different approaches on protein-protein docking were employed to generate a diverse set of putative complexes, including affinity-based or artificial intelligence (AI) methods. Molecular dynamics (MD) simulations were performed for each suggested complex to collect data and allow further validation. Resulting trajectories revealed stable and unstable complexes, providing key information on residues importance for the interaction. Stability of complexes was determined by parameters such as distance, root mean square deviation (RMSD) and contact mapping. The importance of PKR self-phosphorylation was also observed in this study. Once characterized, the remaining complexes will undergo experimental validation and serve as base for identifying future drug candidates. However, the impact of this study is not limited to the experimental field: the ensemble of states generated in this study will support supervised machine learning models for complex validation, which might be extended to other kinases on the future. This work is funded by Sao Paulo Research Agency (FAPESP), grants 2023/07855-3 and 2024/09222-0.

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A DFT Study of CO2 Activation on Subnanometric Ni13 Particles Supported on MXenes.

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Nowadays CO2 emissions are one of the most critical aspects of the anthropic fingerprint, from fossil fuels utilization to general byproducts of industrial processes, since It is one of the main greenhouse

gases. However, CO2 is also a useful chemical in in many processes1,2: reverse water gas shift, hydrogenation of CO2 to methanol and dry reforming using CO2 and methane to produce H2, which in turns is tremendously useful as clean fuel or chemical reactant. CO2 is an almost inert gas, whose activation is strongly endothermic in every process. The research for materials capable of activating CO2 is thus very active. MXenes are a promising new family of materials that exhibit good properties for adsorbing molecules and metal ions or particles3. They are obtained from the chemical or physical etching of MAX phases, 3D material, to exfoliate the metal carbide or nitride sheet, with surface termination of different nature, depending on the solvent and the chemical used for its etching. Thus, MXenes offer a planar support valid for catalysis exposing two sides, maximizing the reacting surface. Due to their nature and composition, MXenes are versatile materials that have the potential to low costs and complexity of catalysts. Supported transition metal clusters and nanoparticles are the paradigm in heterogeneous catalysis. Nickel, in particular, is widely studied for its capability to activate small molecules, and in particular carbon dioxide. 4 Aim of this study is to characterize the interaction of carbon dioxide with a subnanometric icosahedral Ni13 particle supported on M-Xenes, unraveling the role of the interaction with the support. Preliminary results on the adsorption and dissociation of CO2 reveals a comparable activation, respect analogous models4, in which the CO2 shows an average of bending angle among all possible adsorption configuration (10 configurations) of 130° roughly, with a range of Eads of -0.57 eV. Moreover, the activation barrier is around 0.52 eV, which is comparable and even lower respect some references4.

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A Million-fold Increase in C-H Bond Acidity Gives Palladium a Key Advantage in C(sp3)-H Activation Compared to Nickel

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Title: A Million-fold Increase in C-H Bond Acidity Gives Palladium a Key Advantage in C(sp^3)-H Activation Compared to Nickel

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A Modular Software Approach to Intermolecular Interaction Analysis

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A Modular Software Approach to Intermolecular Interaction Analysis

Computational analysis of intermolecular interaction patterns, and prediction of optimal configurations, is a frequently encountered problem arising in a wide range of subjects, such as molecular docking, conformer analysis and crystal structure prediction. While different fields may employ their own preferred models operating under specific precision and accuracy requirements, the underlying approaches often involve similar algorithms and share transferable steps, creating a niche for modular software frameworks.

As an example for a computational approach, where applying established solutions on adjacent problems is facilitated, and experimenting with novel ideas embedded into confirmed solutions would be encouraged, we have developed a set of programs for multi-molecule geometry optimization, where we implemented existing algorithms as reference solutions and added three novel ideas as experimental components.

The first among the aforementioned contributions involves a variation on the simulated annealing algorithm, which has demonstrable success in crystal structure prediction problem [1]. Our method deviates on the basis of temperature assignments, and may prove advantageous in cases where the number of interacting entities is high.

In cases where the search space has lower dimensions, as it may be the case for fewer interacting molecules, we propose a method for bisecting the search space and preemptively eliminating areas based on predicted quality limits of search results.

Finally, we offer a coarse grained, low accuracy scoring function with fast evaluation that may be used for filtering and candidate reduction steps.

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A computational approach to the study of carbon nanodots for the determination of their structure and properties

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Since their discovery in 2004, carbon nanodots (CNDs) have emerged as a promising class of carbon-based nanoparticles due to their properties: intense photoluminescence, low toxicity, excellent biocompatibility and easy surface functionalization.[1] Their synthesis employs straightforward bottom-up and top-down methods, which dictate the functional groups present on their surface, their size and their photoluminescent response.[2] As a result, CNDs have found numerous applications, particularly in biological and biomedical fields.[3] Despite extensive experimental and computational studies, a comprehensive atomic-level understanding of their structural features and their correlation with optical properties remains incomplete.[4] To fill this gap, an explicit treatment of the electronic degree of freedom is required, along with a compatible computational method that balances efficiency and accuracy. Here, we present results on the application of a computational multiscale approach based on ab-initio DFT (Density Functional Theory) and semi-empirical (TB-DFT, tight-binding density functional theory) methods to the class of CNDs. The challenge lies in identifying more effective starting models than the ones currently used, which are mostly based on polycyclic aromatic hydrocarbons (PAHs).[5] We propose that progressively larger carbon clusters (CCs) can serve as effective structural models for CNDs, as shown in the figure reported below.

Our investigation focuses on CNDs with an amorphous carbogenic core, which is the less explored variant in the literature. We present results on the structural investigation of pure, doped, and functionalized carbon clusters. Specifically, we explore nitrogen doping and functionalization with -OH, -NH_2, -COOH, and -$CONH_2$ groups, in agreement with the most common precursors used in the synthesis of CNDs. In addition, their optical properties are investigated using TD-DFT (time-dependent density functional theory), both for the pure and functionalized structures.

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A fast and robust physics-informed machine learning force field for peptide simulations

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Machine learning force fields (MLFFs) have emerged in the past two decades aiming to combat the cost-accuracy trade-off of molecular simulations. Despite growing success, many MLFFs are still not able to reliably simulate flexible organic molecules at elevated temperatures. Addressing these challenges, DL_FFLUX [1] is a mature MLFF that maps atomic energies and multipole moments to geometries. By using the rigorous framework of quantum chemical topology [2] to define atoms and calculate their properties by partitioning the electron density, our method is physics-informed and future-proof. To ensure the robustness of our models, the training data is generated using well-tempered metadynamics [3] and sampled to contain the most diverse structures. Our Gaussian process regression (GPR) models are trained using the in-house software FEREBUS [4]. We demonstrate the performance of our models here on a short peptide of 42 atoms, Ac-Ala3-NHMe (TALA), exhibiting numerous local minima. Our GPR models of TALA demonstrate exceptional robustness in gas phase molecular dynamics simulations at temperatures as high as 1000 K, despite being trained only on 1000 geometries. The excellent extrapolation capability of the models is confirmed by their ability to relax unrealistic internal coordinates through the prediction of restoring forces. Achieving these results on a challenging molecule with high computational efficiency makes FFLUX a strong contender in the list of MLFFs.

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A molecular dynamics – based protocol to explore rearrangement and fragmentation mechanisms of ionized systems: application to a molecular model of protein – nucleic acid interactions

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The absorption of high-energy radiation and following photo-ionization leads to an enhanced reactivity towards processes such as rearrangements and fragmentations. While experimental techniques such as photo-electron photo-ion coincidence (PEPICO) spectroscopy can suggest the species formed at defined binding energies, ab initio molecular dynamics simulations can explore, from a theoretical point of view, the cation potential energy surface. An integrated experimental – computational approach has been employed to characterize the reactive behavior of ionized systems.

Benzyluracil (BU) has been chosen as model compound, since it can mimic the close interaction between uracil nucleobase and phenylalanine aminoacid in nucleic acid – protein complexes. UV light irradiation of BU leads to a photo-product with a covalent cross-link between the two moieties, but with reduced yield due to excited state deactivation.[1-3] Therefore, the reactivity of BU induced by ionization, rather than excitation, has been explored from both experimental and theoretical point of views. In particular, PEPICO spectroscopy allows to characterize the fragmentation channels induced by photo- ionized states at defined binding energies, revealing that BU isomers (5BU and 6BU) are resistant to fragmentation up to 12 eV, then dissociating, at higher energies, into a very complex pattern of fragments. On the other hand, ab initio molecular dynamics with excess kinetic energies have been performed to explore in depth 5BU and 6BU cation potential energy surfaces, allowing to identify the molecular identity of the detected fragments, as well as the pathways leading to them. The simulations and further energy refinements reveal that, at lower energies, ionized 5BU and 6BU can indeed rearrange, without fragmentation, giving cross- linked photoproducts, while higher energies are required instead to give fragmentation pathways, mainly involving the uracil moiety.[4] Such results allow a more detailed understanding of the interactions between proteins and nucleic acids induced by ionizing radiation, and suggest the optimal conditions to maximize the yield of the photo-product in cross-linking experiments, while avoiding the photo-damaging of the interacting nucleobase. [1] C.J. Fecko, K.M. Munson, A. Saunders, G. Sun, T.P. Begley, J.T. Lis, and W.W. Webb, Photochem. Photobiol., 2007, 83, 1394-1404 [2] G. Sun, C.J. Fecko, R.B. Nicewonger, W.W. Webb, and T.P. Begley, Org. Lett., 2006, 8, 681-683 [3] M. Valadan, E. Pomarico, B. Della Ventura, F. Gesuele, R. Velotta, A. Amoresano, G. Pinto, M. Chergui, R. Improta, and C. Altucci, Phys. Chem. Chem. Phys., 2019, 21, 26301-26310 [4] M. Valadan, F. Perrella, L. Carlini, G. Iuzzolino, J. Chiarinelli, F. Coppola, R. Richter, C. Schiano, A. Petrone, P. Bolognesi, L. Avaldi, C. Altucci, N. Rega, J. Chem. Phys., 2025, 163, 034305

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A novel replica exchange molecular dynamics variant for efficient conformational sampling and free energy calculations

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Molecular dynamics (MD) simulations are routinely used to study the atomistic behavior of molecular systems. Unfortunately, conventional MD simulations often struggle to adequately sample the full configurational space of the process of interest because the requisite timescales exceed practical computational limits. To overcome this, enhanced sampling techniques such as replica exchange molecular dynamics (REMD) are increasingly employed to accelerate free-energy barrier crossing and enrich configurational sampling. Over the past decade a host of REMD variants has emerged, among which multi-dimensional exchange schemes and hybrid approaches combining REMD with metadynamics or accelerated MD. The proliferation of these variants reflects both the diversity of molecular systems (from small peptides in explicit solvent to larger macromolecular systems) and the continual drive to balance sampling efficiency against computational cost [1,2,3,4].

REMD involves running multiple simulations of the system in different thermodynamic states (e.g., different temperatures or Hamiltonians) in parallel, periodically exchanging the conformations among them. This exchange reduces correlation times and improves sampling efficiency by allowing the system to overcome kinetic barriers through transitions into neighboring states with lower barriers. Effective REMD requires moderate overlap in configuration space between neighboring states to facilitate these exchanges. Typically, exchanges occur at predefined intervals by attempting to swap the “final” configurations, including all atomic positions and momenta, between the neighboring thermodynamic states [1,2]. This approach implies a trade-off between the number of replicas spanning a given range of thermodynamic states and the phase space overlap, potentially leading to situations where the “final” conformations from the neighboring states exhibit a smaller-than ideal

configurational overlap, thereby hindering efficient conformational sampling. Conversely, many closely spaced thermodynamic states are required to achieve optimal exchange rates in traditional REMD, partially negating its computational advantage.

In the present work, we introduce a new REMD variant that employs fewer thermodynamic states while maximizing exchange rates and therefore sampling efficiency. While we conceived this novel approach for the purpose of calculating adsorption free energies for disordered adsorbants, we demonstrate the method's validity by obtaining accurate solvation free energies for small molecules and accurate sampling of the conformational ensembles of short peptides.

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A sparse network community detection algorithm: applications to quantum chemistry and quantum computation

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Molecular Hamiltonian matrix reduction techniques based on hybrid quantum classical network community detection method.

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Accelerating Quantum Chemistry Simulations on Quantum Computers with Signal Processing

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davide.castaldo@phys.chem.ethz.ch Quantum phase estimation (QPE) is a flagship algorithm for quantum simulation on fault-tolerant quantum computers. However, recent resource estimates[1] suggest that surpassing classical simulation techniques requires millions of gates and hundreds of logical qubits. Consequently, significant effort is being devoted to developing QPE-like algorithms that could demonstrate practical quantum advantage on early fault-tolerant quantum computers—i.e., devices with error correction but a limited number of qubits[2] . A promising approach to reducing QPE's computational cost lies in recognizing that it estimates molecular energies by sampling the autocorrelation function in the time domain and performing a Fourier transform. This connection to signal recovery has recently inspired several methods for computing eigenvalues of quantum Hamiltonians using shallower QPE circuits[3–5]. Speeding up computation requires minimizing three key factors: (i) the total number of sampled points, (ii) the number of measurements per sampled point of the autocorrelation function, and (iii) the total length of the acquired signal. We adapt recent results from prolate Fourier theory[6] to design a quantum algorithm that simultaneously estimates ground and excited state energies while significantly shortening the total length of the sampled signal. At the same time, it demonstrates robustness to shot noise[7] . We perform a numerical analysis in both weak and strong correlation regimes, providing evidence that the algorithm achieves optimal (Heisenberg) scaling. Finally, we explore how the quality of the initial

input state affects the accuracy of the estimates, suggesting that these improvements could lead to a practical quantum advantage.

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Accurate Machine Learning Interatomic Potentials for Grignard Reagents

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Please see the attached file.

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Accurate Quantum Mechanics for slab calculations of semiconductor surfaces: The elusive case of the Si (111)-7x7 Surface

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Surfaces play a fundamental role in all materials processes, in most chemical processes and in the growth or formation of all solid-state materials, especially semiconductors and new 2-D materials. Over the years our ability to rigorously calculate their properties has improved, starting from simple model systems to more complicated systems. Computational advances aimed at handling larger and more complex systems and more accurately solving the wave equation for them is necessary to make progress in understand such systems. That is the case for the Si(111)-7x7 surface since it represents a complex large unit cell structure combining 49 primitive cells whose nature still remains elusive.

The Dimer-Adatom-Stacking fault model or DAS model for the 7×7 surface was proposed in 1985 and validated using Density Functional theory a dozen years later. Indeed, a Machine Learning Force Field demonstrated formation of the DAS structure by first melting the 2D slab to 1500K and then cooling it. [1] Recently the nature and our understanding of the Si (111)-7x7 surface has been questioned [2-4] due to the failures of all DFT calculations to describe a wide range of properties of this system [5]. The most obvious is the ground state of the widely accepted DAS structure that shows a metallic electronic structure whereas numerous experiments show a ˜0.1 eV (semiconducting) gap

at Ef. In addition, several structural measures including X-ray measurements show that the height of the adatoms predicted is at least 0.2 Å smaller than those measured, an error well beyond the accepted accuracy of DFT calculations.

Here we present all electron DFT calculations using CRYSTAL that more accurately describe the exchange-correlation, k-pt sampling, and the surface point group symmetry of the 7x7 than considered previously to evaluate the DAS structure. We discovered that preserving the quantum mechanical nature of a slab model of our surface is essential to correctly describing the quantum mechanical elements of the substrate as well as the adlayer to avoid introducing unnecessary 'spurious' boundary conditions. Our Hybrid DFT (B3LYP) calculations reveal that the starting DAS structure from a VASP PBE calculation relaxes to a new lower energy structure with distinctly different properties for the Si(111)-7x7 surface. This changes many of the structural features found using semi-local non-hybrid functionals (PBE, PBEsol and PBE-D3) calculated with VASP. Indeed, this resolves some of the paradoxes of this complex system. This work demonstrates the need for more accurate calculations and modeling of surfaces to reliably calculate their properties, their role in chemical processes, and to evaluate features in such novel 2-D materials.

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Advancing RNA Aptamer Therapeutics for Glioblastoma: Structural Characterization of the A40s Aptamer Targeting EphA2

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Advancing RNA Aptamer Therapeutics for Glioblastoma: Structural Characterization of the A40s Aptamer Targeting EphA2

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Glioblastoma (GBM) is a highly aggressive and lethal brain tumor, with GBM stem cells (GSCs) playing a central role in drug resistance and tumor relapse. The ephrin type-A receptor 2 (EphA2), which is overexpressed in both GBM and GSCs, has emerged as a promising target for innovative therapeutic strategies. [1] Previous studies identified the RNA aptamer A40s—a 30-nucleotide molecule selected via SELEX—as a selective EphA2 binder capable of impairing GSC proliferation, stemness, and migration.[2,3] To further refine A40s as a therapeutic candidate, we combined computational and experimental approaches. We predicted its secondary structure and explored its three-dimensional conformation using all-atom molecular dynamics (MD) simulations. Detailed analysis of the A40s–EphA2 interaction revealed key binding regions and structural determinants critical for specificity and stability. These results lay the groundwork for enhancing A40s' therapeutic potential and support its development as a next-generation EphA2-targeted treatment for glioblastoma.

Figure 1. EphA2/A40s complex.

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Advancing RNA-Ligand Binding predictions with Thermodynamic Integration and Alchemical Transfer Approaches

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RNA is emerging as a promising therapeutic target due to its central role in regulating diverse cellular functions. However, accurately predicting ligand binding affinities to RNA remains a major computational challenge, largely due to RNA's intrinsic flexibility and structural heterogeneity. In this work, we benchmark two alchemical free energy methods—Thermodynamic Integration (TI)1 and the Alchemical Transfer Method (ATM)2—to estimate binding free energies for a representative set of RNA–ligand. By systematically comparing these approaches, we assess their accuracy, robustness, and sensitivity to structural fluctuations. Our findings offer practical guidelines for modelling RNA–ligand interactions and contribute to the development of more reliable tools for RNA-targeted drug design. Ultimately, this work supports the rational design of novel, high-affinity ligands for RNA, advancing the discovery of next-generation RNA-based therapeutics.

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Advancing the Scope of Natural Orbital Functional Theory

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Natural Orbital Functional Theory [1,2] has emerged as a transformative framework for studying strongly correlated electronic systems, achieving an exceptional balance between accuracy and computational efficiency. Recent advancements have significantly broadened its applicability, driving breakthroughs in the analysis of large-scale systems, direct-dynamics simulations of chemical reactions, excited states, and quantum computing integration via the one-particle reduced density matrix (RDM).

This presentation will highlight an innovative optimization strategy that accelerates NOF calculations for large systems, enabling the study of unprecedentedly complex phenomena, such as the dissociation of a 1000-electron hydrogen cluster [3]. The discussion will also delve into insights from direct-dynamics simulations [4], supported by GNOF [5] calculations of the electronic structure, to analyze the making and breaking of chemical bonds in reactive processes. These simulations, combined with natural orbitals, elucidate the dynamical evolution of chemical bonds, as demonstrated in the F^- + CH3CH2Cl reaction [6].

Additionally, I will explore the use of NOFs in modeling excited states through the coupling of reconstructed two-particle RDM with the extended random-phase approximation, showcasing their

accuracy across various systems when compared to configuration interaction method [7]. The integration of NOFs into quantum computing, particularly within the Variational Quantum Eigensolver (VQE) framework, will also be addressed, emphasizing how leveraging the one-particle RDM allows for energy calculations with up to 90% reductions in quantum resource requirements [8].

These advancements collectively position natural orbital functional theory as a cornerstone methodology for tackling challenges in electronic structure calculations, offering transformative capabilities across classical and quantum computational domains.

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An improved guess for the variational calculation of charge-transfer excitations in large molecular systems

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An improved guess for the variational calculation of charge-transfer excitations in large molecular systems Nicola Bogoa, Zeyi Zhangb,c, Martin Head-Gordonb,c and Christopher J. Steina,d a) Department of Chemistry and Catalysis Research Center, TUM School of Natural Sciences, Technische Universität München, Lichtenbergstr. 4, 85748 Garching, Germany, christopher.stein@tum.de b) Pitzer Center for Theoretical Chemistry, Department of Chemistry, University of California, Berkeley, California 94720, USA. c) Chemical Sciences Division, Lawrence Berkeley National Laboratory, Berkeley CA 94720, USA. d) Atomistic Modeling Center, Munich Data Science Institute, Technical University of Munich, 85748 Garching, Germany.

Photo-induced charge transfer (PCT) plays a fundamental role in biological systems and organic electronics, and also arises in synthetic nanostructured materials. Whereas the targeted preparation of molecular materials with pronounced PCT improved significantly over the last twenty years, the typical system size limits the application of accurate excited-state electronic structure methods for the analysis of PCT properties. Furthermore, efficient methods like time-dependent density functional theory (TD-DFT) are characterized by systematic errors when general-purpose exchange-correlation functionals (XCFs) are applied to the calculation of charge-transfer (CT) excitations, a deficiency that led to the development of specialized XCFs [1] for the calculation of CT excitations. In our previous publication, [2] we demonstrated how variational DFT methods, in particular orbital-optimized DFT (OO-DFT) methods [3], constitute the most accurate low-scaling electronic structure approximation for the calculation of inter-molecular CT excitations using a general-purpose XCF. Conceptually, a rigorous theoretical foundation has recently been proven for ΔSCF [4] approaches in line with previous work by Görling [5]. In the present work, we implement a freeze-and-release electronic structure algorithm [6] in the Q-Chem software package [7] to improve the convergence of OO-DFT

calculations. The resulting electronic structure algorithm [8] is applied to the calculation of charge-transfer excitations in prototypical PCT systems with research applications in the field of organic semiconductors, namely a self-assembled Pd coordination cage [9] and two dye-semiconductor complexes [1]. We further discuss how the energies and properties change for different excited-state DFT methods and which reproduce the experimental results best.

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Assessing the dynamics of hemithioindigo-based photoswitches using multi-state molecular mechanics

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In the realm of nanotechnology and molecular engineering, photoswitches play a key role as structural elements converting light into mechanical work. In particular, switchable chromophores embedded in complex molecular environments – such as molecular machines and self-assembled monolayers on surfaces – offer unique opportunities for the precise control of material properties and molecular motion. A relatively new but emerging class of photoswitches is based on hemithioindigo (HTI) chromophores, which feature high thermal bistability, bright absorption bands in the visible region of the electromagnetic spectrum, and chemical durability. Upon photon absorption, HTIs readily undergo double bond isomerization, resulting in the formation of either Z- or E-isomers. By using HTI photoswitches as core structures, future photoresponsive (nano) devices are accessible via HTI functionalization to tailor the light-induced motion, aggregation, and self-assembly on substrate surfaces.

Excited state dynamics simulations are powerful tools to investigate the photoinduced processes in individual photoswitchable molecules. However, in most light-responsive devices, the motion of the photoswitch is strongly coupled to a complex environment – e.g. explicit solvent shells or ensembles of photoswitches – requiring an atomistic treatment of 1000s of molecules paired with ns-scale dynamics. While this presents a significant challenge for fully ab initio treatment, an approximate approach, as suggested by Duchstein et al. for azobenzene chromophores, involves multiple molecular mechanics models, each describing a separate electronic state under consideration. Here, we present an adaption of this methodology to the widely employed HTI chromophors. For this, we revisit the static theoretical description of the excited states of HTI using high-level multireference calculations and investigate the role of the triplet state in E-Z (photo-) isomerization. The multi-state molecular mechanics are demonstrated for the exemplary case of photoswitching on the lowest adiabatic triplet (T1) surface. For this molecular dynamics simulations were performed in different explicit solvation environments to gain atomic-scale insight into energetic and kinetic effects.

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Atomistic Insights into SEI Formation from Ionic Liquid Electrolytes on Sodium Metal: A DFT Study

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Sodium batteries have attracted increasing attention as cost-effective and sustainable alternatives to lithium-ion batteries. Sodium is naturally abundant, cheaper, and operates at a lower voltage than lithium [1]. Recently, metal anode batteries have gained prominence over metal-ion systems due to their higher theoretical capacities. However, sodium metal anode batteries using conventional organic electrolytes face serious challenges, including dendrite formation and unstable solid electrolyte interphase (SEI) layers [2]. Thus, the choice of electrolyte plays a critical role in improving battery stability and performance. Ionic liquids (ILs) offer promising solutions owing to their high thermal and electrochemical stability and excellent ionic conductivity [3]. To gain atomistic insights into SEI formation and stability, we investigated the interaction of the IL [PYR13][FSI] with the Na [001] surface based on density functional theory (DFT), using the Vienna Ab-initio Simulation Package (VASP). Van der Waals dispersion-corrected DFT calculations were performed using the GGA-PBE functional and PAW pseudopotentials for both cis and trans isomers of [PYR13][FSI], considering multiple adsorption configurations on Na [001] surface. The most stable configurations exhibited adsorption energies of -1.34 eV (cis-FSI) and -1.46 eV (trans-FSI), with no decomposition of IL observed during structural optimization. Subsequent analyses examined sodium migration from the surface to the IL, followed by dissociation of the FSI anion. The migrated Na atom tends to move back to the surface exhibiting a Bader charge transfer of approximately +1 |e|, indicating Na^+ character. The $[PYR13]^+$ cation remained intact in all cases. Nudged elastic band (NEB) calculations revealed a barrierless fluorine dissociation from FSI^-. Ab initio molecular dynamics (AIMD) simulations further confirmed FSI decomposition and the formation of key SEI components, including NaF, Na2O , and Na2S. Thus, this study provides critical insights into IL-based SEI formation on sodium metal, contributing to the development of safer, high-performance sodium-metal batteries.

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Atomistic Mechanisms of Phase Stability in Mn-Based Layered Oxide Cathodes for Sodium-Ion Batteries

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Manganese-based layered oxides (NaxMnO2) are promising cathode materials for next-generation sodium-ion batteries (NIBs) due to their high energy density and cost-effectiveness. [1] Among the key structural phases, P2 and O3 differ in oxygen stacking, with P2 exhibiting superior sodium-ion diffusion. [1] However, its electrochemical performance is hindered by solid-state phase transitions during Na+ insertion/extraction, leading to structural degradation and capacity fade. [2] A fundamental understanding of these transitions at the atomic level is crucial for improving long-term stability. In this work, we investigate the thermodynamic and kinetic factors governing phase evolution in P2-NaxMnO2. [3] Density functional theory (DFT) calculations reveal that phase stability and transformation pathways are dictated by cooperative Jahn–Teller effects (CJTE) from Mn3+ centres, Na+ ordering, and electrostatic/covalent interactions. To probe the kinetics of these transitions, we employ variable-cell nudged elastic band (VC-NEB) calculations, [4] identifying shear-driven gliding and tetrahedral transition states as dominant energy barriers in P2-to-P2' and P2-to-OP4/O2 transformations. Furthermore, we introduce structural distortion metrics as predictive descriptors of phase stability, offering a new approach to designing more resilient cathodes. [5] Our findings establish a comprehensive framework for optimizing Mn-based layered oxides by balancing thermodynamic stability and kinetic accessibility. This work provides critical design guidelines for enhancing

electrochemical durability in sodium-ion batteries, advancing their viability for large-scale energy storage.

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Automated Coarse-Graining to Accelerate Conformational Searches of Large Systems

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The conformational search of small molecules has become increasingly relevant in recent years after the significant speedups in computation chemistry, and the developments of new efficient algorithms for the task. In that regard, we recently published a new Global Optimization Algorithm (acronym GOAT)1, which has been shown to be among the best of its kind and can cover a wide range of systems, from organic drug-like molecules to metal complexes, to water clusters and even can deal with atomic clusters like nanoparticles.

In this work, we show a novel automatic algorithm for coarse graining of molecules, which allows for the use of such conformational search algorithms in much larger systems due to the reduced dimensionality. This algorithm automatically splits the system into chemically meaningful fragments using an efficient graph-based approach, and by projecting the gradient such that each fragment is treated as a rigid body with only translations and rotations, one can significantly reduce the dimension of the conformational search problem. Since these problems usually scale exponentially with the system size, the overall effect can be drastic, and systems with hundreds of atoms can be treated on a reasonable time scale, without losing too much accuracy since the full calculated gradient is still used.

We will show some results of the new approach, its advantages and shortcomings together with a general overview of the GOAT algorithm, which is already implemented in the ORCA software2, from version 6.0.

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Automated atropisomer predictions via a web app

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Atropisomerism is a form of stereoisomerism caused by restricted rotation about hindered single bonds.1,2 Atropisomerism plays a critical role in pharmaceutical drug development, where the stereochemical properties of a molecule can significantly impact its function. Approximately 30% of recently approved FDA drugs possess potential atropisomeric axes,3 highlighting the significance of accurately predicting and characterizing these features.

We have developed an automated workflow that efficiently identifies bonds within molecules that could lead to atropisomerism and calculates their rotational barrier, atropisomer class, and half-life of interconversion via a thorough conformational searching and optimization procedure using density functional theory (DFT). Our workflow is benchmarked against an experimental dataset of 155

known rotational barriers and demonstrates a high degree of accuracy, achieving a correlation coefficient (r2) of 0.97 and a root mean square error (RMSE) of 1.6 kcal/mol. To facilitate user interaction and data exploration, we have developed a web application with streamlit (python) that allows non-experts to submit atropisomer screens, view results, and explore the effects of temperature on the half-life of interconversion, offering valuable insights into the dynamic behavior of atropisomers under different conditions. Additionally, this web application is part of a larger platform aimed at democratizing internal reactivity prediction workflows and computational databasing.

This work has a significant impact on pharmaceutical drug development, allowing for the rapid and detailed stereochemical classification of compounds at an early stage of development. By providing highly accurate insights into atropisomeric behaviours, our approach aids in the effective management of these compounds, boosting the efficacy of drug discovery and ensuring a safer therapeutic profile for novel pharmaceuticals.

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Bayesian Optimization for Conformational Energy Minimization

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Consideration of the conformation of chemical systems is a highly important initial step of a reaction modeling investigation in computational chemistry, since the error introduced due to a higher energy conformer can be on the order of, or greater than, the energy differences that explain reaction mechanisms and selectivities. Unfortunately, computationally cheap, low levels of theory that are required to perform a conformational search can provide unreliable approximations of the higher-level quantum mechanical conformational energies, and it is very difficult ahead of time to know if such a low-level method will accurately select the lowest energy conformers. In addition, the large computational cost of more accurate quantum chemistry calculations means that in general it is highly impractical to compute the energies of all conformers of a chemical system, and thus one cannot normally be confident that the lowest energy conformation has been accurately modeled. To address this, we develop a Bayesian optimization algorithm which, after an initial conformational search, uses its surrogate machine learning model to select conformers that are to be modeled with high-level quantum chemistry calculations, with the aim of locating the global minimum energy conformation. Our results find that the algorithm is very efficient; on average only approximately 13 conformers were sampled before the minimum was found and typically no more than 36 were required. This represents a very large saving in terms of computational cost, considering that even medium sized organic molecules may have tens or hundreds of conformers each. Importantly, our algorithm was also equally efficient for finding the lowest energy conformers of complex hydrogen bond-donating catalyst transition states, despite the large size and complexity of these systems. This idea promises broad application in mechanistic modeling with computational chemistry, potentially allowing for computational costs substantially lower than that associated with full conformational treatment, whilst allowing for greater confidence that errors due to conformation are reduced as far as is practical.

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Benchmarking the Performance of Density Functional Approaches in Describing Interactions Between Cation-exchanged Zeolites and Pharmaceuticals and Personal Care Products (PPCPs)

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Title: Benchmarking the Performance of Density Functional Approaches in Describing Interactions Between Cation-exchanged Zeolites and Pharmaceuticals and Personal Care Products (PPCPs) N.B.: See the attachment for the abstract.

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Big Data and Machine Learning for Reaction Design

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Reaction optimisation plays a fundamental role in the drug discovery process; for many this is at the reaction design stage[1]. This optimisation process is often expensive and time consuming, and generally follows one of two approaches, the first being the use of a chemist's intuition (this however relies on the chemist having knowledge of the reaction domain) with the alternative being a purely computational approach (this however has no understanding as to the underlying chemistry)[2]. We present a solution to this by capturing chemical intuition with a machine learning (ML) model trained on literature data to predict reaction outcomes, passing these predictions into the optimisation process to help guide it through its understanding of the chemical space. This capturing of chemical intuition in the reaction optimisation process can lead to experimental savings of up to 50% when trying to find the optimal reaction. With the approaches used not being limited to the reactions considered in this work, and the creation of a predictive model for reaction outcomes based on either in-house or publicly available data, this approach could be utilised to accelerate the optimisation process in general, reducing both the cost and time associated with it.

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CO2 Activation on Single-Atom Catalysts: Importance of the Supporting Matrix

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CO2 Activation on Single-Atom Catalysts: Importance of the Supporting Matrix

Single-Atom Catalysts (SACs) are emerging as a new frontier in heterogeneous catalysis.1,2 They are made of metal atoms atomically dispersed on a supporting matrix. Computational chemistry offers the ability to study catalytic processes with atomic-level precision, enabling the rationalization and even prediction of system properties. Among various chemical processes of interest, the reduction of CO2 (CO2RR) into valuable chemicals has attracted considerable attention.3 The analogy between SACs and coordination chemistry compounds has highlighted the importance of the supporting matrix.4 In this work, we rationalize CO2 activation on SACs using Density Functional Theory (DFT) calculations. Our analysis focuses on nine transition metals (Fe, Co, Ni, Ru, Rh, Pd, Os, Ir, Pt) and three distinct support materials: nitrogen-doped graphene (4N-Gr), a gold surface (Au(111)), and titanium nitride (TiN), an emerging material with unique properties.5,6 Our findings show that CO2 activation on SACs is generally challenging, often requiring dual active centers. SACs based on 4N-Gr and Au(111) show limited ability to bind CO2 molecules. In contrast, TiN emerges as a highly promising support, effectively promoting CO2 activation. This capability stems from the formation of bidentate adducts involving both the dopant and a surface titanium atom of the matrix. Furthermore, TiN-based SACs demonstrate the ability to favour *CO*OH adduct formation (*indicates an adsorbed species) over*COOH or *OCHO during the first electrochemical reduction step, showcasing enhanced reactivity. These results underscore TiN as a robust support material for SACs in CO_2RR, offering new perspectives for efficient CO2 conversion.

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CO2 hydrogenation on Ru-functionalized Zeolites: Development of Reactive Force Fields and Molecular Dynamics Simulations

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We present the development of a new ReaxFF reactive force field parametrization tailored for modelling CO_2 hydrogenation on ruthenium-functionalized zeolites. The force field is based on the CHOAlSi ReaxFF parameters and was reparametrized using extensive DFT data from a prior study, which characterized key elementary steps leading to CO, CH_4, CH_3OH, CH_2O and HCOOH gas products on a single Ru atom embedded in silicalite (Ru_1@S-1). Parameter optimization was carried out using the ParAMS module within the Amsterdam Modeling Suite, targeting accurate reproduction of DFT-calculated reaction energies, geometries and transition states [1]. The resulting force field was validated against the DFT dataset and employed in reactive molecular dynamics simulations to investigate product distributions under controlled temperature, pressure and CO_2/H_2 partial pressures. Additionally, the influence of increasing Ru loading on catalytic performance was explored. This work provides a transferable and computationally efficient tool for studying complex reaction networks in Ru-zeolite catalysts

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COMPUTATIONAL DESIGN OF A TETRAPERICYCLIC CYCLOADDTION WITH MULTIPLE BIFURCATIONS

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From the first ambimodal bispericyclic cycloaddition reaction reported by Caramella et al.[1] in 2002, the number of reactions observed to show a post-transition state bifurcation (PTSB) have steadily increased. [2,3] Many of these ambimodal transitions states (TSs) involve a single PTSB. That is, one TS leads to a reaction coordinate that bifurcates after crossing the TS region into two paths to different reaction products without an intervening minimum.[4] Others, show an ambimodal TS where the reaction coordinate splits into different paths leading to different cycloaddition products as a result of sequential bifurcations. [5]

In this work [6] we present the first example of a tetrapericyclic reaction featuring a single TS that leads to four distinct cycloaddition products: [4+6], [2+8], [8+2], and [6+4], without intervening minima. We used DFT calculations to design the tetrapericyclic TS by optimizing orbital interactions between reactants. Quasiclassical molecular dynamics simulations (M06-2X/6-31G) started at the TS were employed to investigate the nature of the potential energy surface (PES) governing this reaction.

Trajectory analysis confirmed the formation of the four products without intervening minima and allowed to stablish product ratios. We also found strong correlation between product ratios and geometric similarity to the TS, measured via root-means-square deviation (RMSD). Notably, the dynamically preferred product exhibits the smallest RMSD from the TS structure. Additionally, we identified three subsequent TSs interconverting the cycloadducts, further elucidating the role of PES topography in product selectivity.

Our findings provide new insights into the role of dynamic effects in complex reactions featuring PTSBs. These results offer a predictive framework for designing reactions with multiple product pathways, which could have significant implications for synthetic applications and controlling selectivity in reactions with PTSB. References [1] Caramella, P.; Quadrelli, P.; Toma, L. J. Am. Chem. Soc. 2002, 124, 1130–1131. [2] Hare, S. R.; Tantillo, D. J. Pure Appl. Chem. 2017, 89, 679–698. [3] Houk, K. N.; Liu, F.; Yang, Z.; Seeman, J. L. Angew. Chem., Int. Ed. 2021, 60, 12660–12681. [4] Singleton, D. A.; Hang, C.; Szymanski, M. J.; Meyer, M. P.; Leach, A. G.; Kuwate, K. T.; Chen, S. J.; Greer, A.; Foote, C. S.; Houk, K. N J. Am. Chem. Soc. 2003, 125, 1319–1328. [5] Xue,X.-S.;Jamieson,C.S, Garcia-Borràs,M.;Dong,X.;Yang, Z.; Houk, K. N. J. Am. Chem. Soc. 2017, 141, 1217–1221. [6] A. Martin-Somer, X.-S. Xue, C.S. Jamieson, Y. Zou, and K. N. Houk J. Am. Chem. Soc 2023, 145, 4221-4230.

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Capricious Companions: Polycations Show Sequence-Dependent DNA Affinity

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DNA is a fundamental molecule of life, and its folding is critical for gene regulation, medical applications, and disease prevention. While proteins like histones are known to drive highly ordered DNA packaging, both experimental and theoretical studies have shown that DNA duplexes can also associate selectively in the absence of proteins, mediated by small molecules such as polycations.1 In this work, we use atomistic unbiased and biased molecular dynamics (MD) simulations to investigate how double-stranded DNA interacts in the presence of polycations. First, unbiased simulations without polycations are used to characterize baseline features such as average interstrand distance. We then apply biased simulations with polycations to quantify the repulsive potential between DNA helices—results that we compare to experimental measurements.2 We explore how different polycations, including polyarginine and polylysine, affect DNA condensation in AT-rich and GC-rich sequences. Our findings show that condensation behavior is both sequence- and polycation-dependent, suggesting that DNA condensation is governed by more nuanced mechanisms than previously understood. These insights highlight the potential roles of non-protein biomolecules in DNA organization, with implications for chromatin structure and gene regulation.

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Chemical dynamical ensembles as compass to navigate the mutational landscape in enzyme engineering

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Enzymes are the key molecular machinery that enables chemical transformations on the timescale of life. Throughout evolution, enzymes have developed specific substrate scope, stereospecificity and catalytic proficiency. In recent years, routines to improve enzyme stability through amino acid substitutions have become commonplace. However, it is still more challenging to manipulate the catalytic scope of enzymes using computational methods without extensive trial and error.

In our research group, we have stablished a new metrics by analysis of enzyme conformational ensembles to explore the impact of remote mutations on enzyme function, including stability, connectivity to the active site, and overall enzyme dynamics1,2 (Figure 1). Additionally, we have developed SmarTSzyme,3 a python-based software tool that analyses quantum mechanics/molecular mechanics (QM/MM) trajectories of the reaction at the active site, to compare key interactions in both substrate and transition-state enzyme complexes. With SmarTSzyme, a shortlist of positions for protein engineering can be obtained, to speed up the identification of novel biocatalysts with improved efficiency for the studied chemical transformation.

Figure 1. (A) Metrics to evaluate the impact of remote mutations in enzyme function. (B) SmarTSzyme, a new tool to the selection of key amino acids to manipulate catalysis.

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Collective Bonding

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Cina Foroutan-Nejad Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland cina.foroutan-nejad@icho.edu.pl A century after G. N. Lewis introduced his foundational model of chemical bonding, its core principles remain central to our understanding of molecular structure.

Traditionally, neighboring atoms in a Lewis structure are assumed to share stabilizing interactions. However, this assumption begins to falter at the boundary between covalent and noncovalent bonding. Our work reveals that, in certain molecules with the general formula MAX_3—where M is a metal, A a nonmetal, and X an electron-rich or electron-withdrawing group—the interaction between adjacent M and A atoms can be destabilizing, Figure 1. Remarkably, the overall structure is preserved due to strong interactions between electron-deficient metals and the X groups.[1–6] This phenomenon gives rise to unconventional structures, such as the inverted $LiCF_3$, where lithium interacts preferentially with fluorine atoms over the central carbon in the gas phase. These collective interactions extend beyond organometallic compounds and offer insight into anomalous bond dissociation energies and stability trends across a wide range of molecules—from perhaloalkanes to the elusive cyclic C_6O_6. Our computational studies highlight the broad relevance of this concept in modern chemical bonding theory.

Figure 1. (a) The general Lewis structure of the molecules prone to collective bonding, and (b) the stabilizing/destabilizing nature of interactions in MAX3 clusters. While the 1,2 interactions in a Lewis structure are destabilizing or merely weakly stabilizing, the 1,3 interactions proved to be strongly stabilizing. Panels (c) and (d) provide schematic representations of the pyramidal and inverted MAX3. The inverted structures are distinguishable by their negative $\Delta\angle$M–A–X values defined as the difference between the $\angle$M–A–X angle and a rectangle (shown as a grey dashed line perpendicular to the M–A bond).

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Competition between divalent metal ions for HDAC8 enzyme active site: insights from theoretical studies

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HDAC8 is a histone deacetylase enzyme that plays a key role in the development of various diseases in humans, including cancers, neurodegenerative diseases, and alcohol use disorder1. Although HDAC8 is classified as a Zn-dependent metalloenzyme, the available information regarding the affinity of different divalent metal ions, such as Fe^{2+}, Ni^{2+}, Co^{2+}, and Mg^{2+}, toward the HDAC8 active site remains inconsistent and unclear, and the mechanism by which these ions compete for the HDAC8 enzyme's active site is still not well understood 2, 3. This raises the question of whether other divalent metal ions, such as Fe^{2+}, Ni^{2+}, Co^{2+}, and Mg^{2+}, can compete for the HDAC8 enzyme-active site 4. In this study, we aim to address the following questions: (1) Can other divalent metal cations (Fe^{2+}, Ni^{2+}, Co^{2+}, Mg^{2+}) found in the intracellular space compete with Zn^{2+} for the metal binding site in the HDAC8 enzyme? , (2) What is the order of increasing affinity of these metal ions (Fe^{2+}, Ni^{2+}, Co^{2+}, Mg^{2+}) towards HDAC8 in different dielectric media? Additionally, these questions become even more intriguing when the HDAC8 enzyme active site is bound with a histone deacetylase inhibitor (HDACi), forming an enzyme-inhibitor complex (HDACi-HDAC8), thus interfering with the HDAC8 enzyme function. To address these questions, we performed density functional theory calculations (DFT) combined with polarizable continuum model computations (PCM). The results obtained helped us understand how the metals interact with the HDAC8 enzyme's active site and compete with the

native metal, both when an inhibitor is bound and when it isn't, in both low-polar and polar solvents. The results will help designing more selective and isoform-specific HDACi with improved binding properties.

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Computation of vibrationally resolved spectra of organic radicals: from benchmarks to applied systems

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Abstratc for oral communication

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Computational Analysis of Mechano-Sensitive Chiral Luminescence in Organic Materials: a TDDFT Approach

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Difluoro-boron β-diketonate (DFB) amide derivatives, such as (S)-DFB-PhEt-amide and (S)-DFB-Hex-amide, have emerged as promising candidates for applications in optoelectronics and sensing due to their mechano-responsive chiroptical properties. Despite their potential, the molecular origins of these behaviours are still not fully understood. This work presents a detailed computational study designed to explore these systems, supported by comparison with experimental observations [1]. We employed Density Functional Theory (DFT) [2] and Time-Dependent DFT (TDDFT) [3] to investigate the crystal packing, excited-state electronic transitions, and chiroptical signatures of these materials. Results show that the accuracy of predicted geometries depends strongly on the chosen functional and basis set. TDDFT calculations reproduced UV/Vis and Circular Dichroism (CD) spectra in good agreement with experimental data [1]. Structural reorganization upon excitation directly influences

chiral emission [4], positioning these systems as relevant prototypes for CPL-active material design [5].

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Computational Design of Hybrid Polyoxometalate Structures for Advanced Chemical Catalysis

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In today's world, the quest for green alternatives has become paramount across industrial sectors such as chemicals, textile, pharmaceutical and agriculture because they are facing a persistent challenge with increasing energy consumption during operation of their chemical reactions. In this regard, polyoxometalates (POMs), metal oxide clusters composed of early transition metals in high oxidation states like V^{5+}, $Mo6^{+}$, and W6+, have gained attention as photocatalysts offering a clean, efficient, and environmentally friendly alternative to energy-intensive processes. However, most POMs exhibit absorption of solar energy in the UV/near visible-light region, which comprises only ˜5% solar light. The primary goal of this project is to investigate the photochemical mechanism of non-hybrid and hybrid POMs to underpin development of hybrid polyoxometalate structures for advanced chemical catalysis.

DFT and TDDFT have been used to explore the photocatalytic behaviour of the widely used tetrabutylammonium decatungstate (TBADT) catalyst. Geometries of the ground and valence excited states (S_0, S_1, T_1–T4) were optimised, along with the inter-system crossing (ISC) geometry between the lowest allowed singlet state and the doubly-degenerate triplet state, and spin-orbit coupling (SOC) constants. Three different basis set / ECP combinations (SRSC, CRENBL and Def2) and five different density functionals (BP86, ⊠B97x-D3, B3LYP, CAMB3LYP and LRC⊠PBE) were compared to identify the optimal basis set and functional combinations. The singlet and triplet states involved in the ISC process were identified. The optimized geometries of the oxidised [W_10 O_32]ˆ(4-)and reduced [W_10 O_32]ˆ(5-) forms were used to calculate the reduction potentials and it was compared to experimental CV data. Ongoing further calculations to model the electronic structure and related properties of the TBADT photocatalyst are expected to yield deeper insights into its reactivity and catalytic performance.

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Computational Screening and Design of Next-Generation Gold Nanoparticle-based Chemosensors.

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Ligand-coated gold nanoparticles (AuNPs) can serve as advanced nanosensors capable of selectively detecting organic molecules in solution. [1] When combined with NMR-based protocols, analyte signals can be probed directly without the need for secondary reporters or analytical standards. [1] A key aspect of such approach is the formation of self-assembled monolayers surrounding the AuNP core, resulting in transient binding pockets. Through tailoring and rational design of ligands, specificity and binding affinity can be finely tuned. [2] Yet, current methods to assess affinity and selectivity rely on costly and slow experimental assays. In our recent work, we reported a molecular-dynamics (MD) based approach for the design of AuNP-based chemosensors, compatible with NMR-based protocols, for the detection and quantification of 3-methoxytyramine, a prognostic marker of asymptomatic neuroblastoma. [3] Through this approach, the identified lead AuNP was experimentally validated and shown to outperform existing AuNP-based chemosensors, halving the limit-of-detection against previously reported AuNP-based chemosensors. Furthermore, this AuNP was experimentally shown to allow the detection of 3-methoxytyramine from complex mixtures – vital for the clinical application of chemosensors. Building upon that work, we now introduce a rapid and interpretable scoring function for AuNP-analyte binding. [4] Leveraging a dataset of high-quality experimentally determined binding affinities for AuNP-analytes, we trained a scoring function to predict binding affinities based solely on static cheminformatics descriptors (LogP, charge and chemical similarity) with exceptional accuracy (R^2 = 0.85, MAE = 0.45 kcal/mol) when validated against experimental data, enabling the efficient pre-screening of candidate ligands. [4] While we primarily focus on the application of chemosensors design and assessment, in principle, the scoring function can be applied to a variety of areas relying upon AuNP – small molecule binding such as catalysis and targeted drug-delivery to name a few.

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Computational Study of Catalytic Enantioselective Visible-Light-Mediated 6π-Photoelectrocyclization

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Computational Study of Catalytic Enantioselective Visible-Light-Mediated 6π-Photoelectrocyclization

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Photocatalyzed reactions are an excellent technique to generate chiral compounds. When combined with Lewis acid ligands, these processes can be driven by visible light, making them more economically viable and environmentally friendly. This work aims to investigate the mechanisms and origins of enantioselectivity in the catalytic, enantioselective, visible-light-mediated of aryloxy-hexenones [1-2] by developing a computational model capable of rationalizing the experimental findings.

The theoretical investigation is structured into five major areas: (i) photosensitizer excitation, (ii) energy transfer, (iii) formation of metal–chiral ligand–substrate complexes, (iv) absorption spectra of complexes, and (v) elucidation of reaction mechanisms. A general scheme is presented in Figure 1.

Figure 1: General mechanistic framework of the studied reaction. M = metal center, PS = photosensitizer. Blue lamp indicates visible-light irradiation.

The structures were optimized with Def-TZVPP/PWPB95//Def2-SVP/wB97X-D3BJ DFT methodology. TDDFT calculations identified significant bathochromic shifts in copper and tin complexes, facilitating visible-light absorption. Mechanistic studies uncovered that ring-closure is the stereochemistry-determining step. N-Oxide ligands displayed a high isomeric ratio for the complexation step. For the copper(II)-bisoxazoline complex, chiral induction significantly raised the energy barrier for disfavored enantiomers (ΔΔG‡ = 12.5 kcal/mol), highlighting the potential for high enantioselectivity. Multireference CASSCF/CASPT2 calculations confirmed an intramolecular charge-transfer character in the excitation, but with near zero force oscillator for all excitations.

Future work will explore dynamic excited-state processes using SHARC simulations and extend experimental validation to Ir-based photosensitizers and modified ligands. This integrated approach advances the rational development of enantioselective photochemical reactions under mild conditions.

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Computational approaches for understanding the origin of antioxidant properties in Hemocyanin enzymes

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Hemocyanins (Hc), proteins commonly known for its extracellular roles in oxygen (O2) sensing, transport, and storage in many invertebrates,[1] have an intriguing and poorly understood intracellular presence. Emerging evidence suggests a significant correlation between oxidative stress and increased intracellular Hcs levels, implicating an active role of Hcs in the antioxidant response.[2] In this study, we employ ab initio calculations (DFT and QM/MM) to unravel the binding features of reactive oxygen species (ROS) at the Hcs active site, using hemocyanin from the arthropod Limulus polyphemus as a model system, to elucidate its potential function in mitigating oxidative stress and contributing to cellular defense mechanisms. Our findings reveal novel states of the Hcs active site, unprecedented insights into its function as a ROS-scavenging enzyme, and a detailed elucidation of its mode-of-action, which highlights the pivotal role of Hcs in oxidative stress management and its potential contribution to the immune response. These insights broaden our understanding about the functional versatility of Hcs and serve as a foundation for the rational design and development of novel artificial enzymatic systems with ROS scavenging properties.

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Computational modeling of self-healing biobased asphalt materials

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At the dawn of artificial intelligence and self-driving laboratories for materials design, automated generation of unbiased atomistic models that capture the complexity of molecular fluids in a computationally efficient way is a persistent challenge. This lack of atomistic models is especially relevant for biobased oils and bitumen to be used in more resilient and sustainable roads. Pavements are majorly damaged by bitumen aging and fatigue cracking by traffic load. These issues can be mitigated by promoting asphalt self-healing mechanisms with encapsulated rejuvenators. These complex fluids are intrinsically challenging to model with molecular precision, given the large variety and complexity of organic molecules in its composition, which has hampered their bottom-up molecular design. To address this limitation, we have developed an author-agnostic computational framework to generate data-driven representative models of any complex mixture of organic molecules directly from Gas Chromatography-Mass Spectrometry (GCMS), thus reducing human biases in model creation and providing a platform for self-driven digital development of molecular organic fluids in self-healing infrastructure. Our method generates statistically representative molecular samples that simplify the complexity of the fluid in a limited group of molecules, while capturing the critical chemical features needed to describe the overall properties of the mixture. These models have been used to perform molecular dynamics simulations, and to predict reactivity and diffusion mechanisms in self-healing asphalt materials. The computational work is assisting the experimental development of rejuvenators that are encapsulated in biobased natural spores that completely heal a crack into an aged bitumen sample in 50 min.

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Conformational Dynamics and Order of Compactness of α-Synuclein Induced via C-terminal Truncation

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Abstract: C-terminal truncation of α-synuclein (α-Syn) has emerged as a critical modulator of its liquid-liquid phase separation and amyloid aggregation, processes that are closely linked to the pathology of neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD). While the functional implications of α-Syn truncation have been increasingly recognized, the molecular mechanisms by which C-terminal truncation alters α-Syn conformations remain poorly understood at the atomistic level. In this study, we systematically investigated the impact of progressive C-terminal truncation on α-Syn structure using molecular dynamics simulations across multiple force fields, including CHARMM36, CHARMM36-IDP, and AMBER99SB-ILDN. We simulated a series of truncation variants (residues 1–98 to 1–140) and compared their structural behavior to the full-length protein. In CHARMM36, truncated α-Syn variants that exhibited stable α-helical structures in the N-terminal and NAC regions gradually transitioned into short helices, β-sheets, and β-bridges during the simulation. The intrinsically disordered C-terminal region of the full-length protein interacted with the N-terminal helices, contributing to intrapeptide contacts. Truncation of this region disrupted these contacts, resulting in increased interpeptide interactions and enhanced helicity. Notably, the αS1–98 variant adopted a more compact conformation than αS1–140 in CHARMM36, a feature not consistently observed in other force fields. The performance of each force field is assessed from several structural parameters such as radius of gyration, root mean square deviation, percentage of secondary structure, and favorable conformations obtained for different force fields. Our findings suggest that C-terminal truncation significantly alters the conformational landscape of α-Syn, facilitating structural transitions associated with pathological aggregation. These results provide mechanistic insights into how truncation modulates α-Syn behavior and provide valuable insights for understanding its role in neurodegenerative disease progression.

Keywords: α-Synuclein, MD simulation, Free Energy Landscape (FEL), Contact Surface Area (CSA)
**strong text

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Controlling Polymorph Crystallisation Using Structured Ternary Fluids

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Structured ternary fluid (STF) mixtures consist of a small amphiphilic molecule, called a hydrotrope, that enhances the miscibility of two other immiscible components, typically oil and water. STFs, also called surfactant-free microemulsions or ultra-flexible microemulsions, have been shown to provide unprecedented control in the crystallisation of glycine polymorphs under ambient conditions.

Typically, crystallisation of glycine happens under kinetic control, resulting in the formation of the metastable α-glycine polymorph. However, restricted diffusion of glycine within the hydroxyl network of an octanol/water/ethanol (OWE) mixture allows crystallisation to proceed via a higher nucleation rate and slower crystal growth pathway. The STF mixture acts as a nanocrystal incubator, prolonging locally high glycine supersaturations and allowing nanocrystals to exist for extended times. This soft nanoconfinement means that crystallisation can occur under thermodynamic control, selectively producing slow-growing γ-glycine as the majority polymorph. Changing the STF composition and initial glycine supersaturation allows all three polymorphs to be targeted from the same OWE ternary mixture. The enhanced control of glycine crystallisation within this STF system has been investigated further using atomistic molecular dynamics simulations. Suitability of the glycine force field was assessed by calculating various solution and crystal-phase properties for the three ambient-pressure polymorphs. Namely, lattice energy, crystal density, hydration free energy, enthalpy of solution, solution density and polymorph free energy via the Einstein molecule method.

Non-bonded parameters of the best-performing force field were calibrated using a multi-objective Bayesian optimisation approach to achieve better performance in reproducing crystal-phase properties.

STF structure was evaluated for various compositions through calculation of radial distribution functions and spatial density profiles. Additionally, computing shear viscosity, cluster lifetimes and diffusion coefficients for individual components allowed us to assess the degree of glycine nanoconfinement.

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Cumulative latent instability (CLI) analysis of data-driven molecular dynamics simulations

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We aim to present a novel methodology for diagnosing latent instabilities within data-driven molecular dynamics (MD) simulations. Referred to as cumulative latent instability (CLI) analysis, this approach is grounded in the theoretical premise that all regression techniques, regardless of their capacity for extrapolation, are inherently prone to producing unreliable or artefactual predictions when applied outside their natural interpolation domain (NID) [1]. Drawing on quantum chemical topology [2] and leveraging the behavior of a Heaviside-like indicator function, we introduce the CLI index as a robust and well-behaved estimator for quantifying the accumulation of unreliable atomic energy predictions along an MD trajectory. CLI analyses indicate that the progressive buildup of latent instability is responsible for the eventual failure of data-driven MD simulations once a critical threshold is surpassed. Our experiments establish a strong correlation between the CLI index, the intrinsic quality of the model propagating the simulation, and the simulation temperature. We further observe that simulations in which the CLI index reaches saturation within 1 nanosecond may be considered effectively stable over indefinite timescales. Finally, a link is established between the CLI index and the principle of energy conservation. This work paves the way for more in-depth studies aimed at rationalizing and addressing the precarious robustness of current machine learning force fields (MLFFs). More specifically, the proposed methodology lays the foundations for a new class of physics-informed active learning protocols in which atomic CLI indices will guide the data augmentation process.

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DEVELOPMENT AND IMPEMENTATION OF QUANTUM-CLASSICAL STOCHASTIC METHODS FOR THE CALCULATION OF KINETIC RATES OF ELEMENTARY REACTIONS IN SIMPLE AND COMPLEX CONDENSED PHASE

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This work develops a model for interpreting macroscopic kinetic constants in elementary reactions, particularly when mass transport and chemical reactions occur on comparable timescales, as in en-

zymatic catalysis. We focus on bimolecular exchange reactions, specifically SN2 nucleophilic substitutions in haloalkanes, using bromide and chloromethane as a case study. Our approach employs a reaction-diffusion model inspired by Sevein and Moro [1], integrating mass transport with localized quantum-mechanical reactions. The governing equations consist of (i) a diffusive term, dependent on the diffusion coefficient and mean field interaction potential determined via steered molecular dynamics [2], and well-described by a modified Buckingham potential and (ii) a reactive term, modeled through a master equation parameterized with microscopic kinetic constants [3,4].

This model establishes a continuous description of macroscopic kinetic constants by linking the interplay of reaction and transport timescales. Despite simplifications such as neglecting rotational dynamics and separating barrier crossing from other relaxation processes the method accurately captures expected kinetic behaviors across a wide dynamic range. It estimates macroscopic kinetic constants in an ab initio fashion by correlating key molecular parameters: diffusion coefficients, interaction potentials, and microscopic rate constants. This framework enhances our understanding of reaction mechanisms in complex environments and provides a basis for future studies on reactive dynamics in liquids.

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DFT Simulation of Complex Reaction Networks: New Insights into the Speciation and Formation of Polyoxometalates

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In recent years our group has been working in the development of a new computational methodology, which we called POMSimulator,[1] to simulate the complex multi-species multi-equilibria taking place in the self-assembly processes leading to polyoxometalates. POMSimulator comprises automated workflows that rely exclusively on DFT-based results, and has been successfully applied to Mo, W, V, Nb and Ta isopolyoxometalates (IPAs). [2,3] The reaction networks can be applied to perform very long multi-time scale kinetic simulations on the formation of isopolyoxotungstanates, [4] what led to the discovery of a reaction mechanism that transforms the kinetic product {W12} in the thermodynamic product {W10}. We released recently the first open-source version of the code. [5] On the other hand, heteropolyoxoanions (HPAs) introduce far more complexity. We carried out a statistical analysis of the massive amounts of data produced by POMSimulator to reduce the reliance of the method on experimental formation constants. [6,7] More recently, we combined the predictions of our method with new Z-Ray total scattering data to investigate polyoxomolibdates speciation under hydrothermal conditions.[8]

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DFT study on the synthesis of urea through electrocatalytic co-reduction of CO2 and NO3- on Cu and Ag surfaces

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DFT study on the synthesis of urea through electrocatalytic co-reduction of CO2 and NO3- on Cu and Ag surfaces

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DFT study on the synthesis of urea through electrocatalytic co-reduction of CO2 and NO3- on Cu and Ag surfaces

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Data-free Inverse Molecular Design Using Reinforcement Learning and Quantum Chemistry

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The inverse design of molecules with target properties is a long-standing challenge in chemistry [1]. This fundamental paradigm shift in computational chemistry has the potential to accelerate the discovery of new functional compounds such as catalysts and drugs, moving beyond traditional rational design strategies [1]. Yet, de novo generation of molecules is challenged by the complexity of structure-property relationships and the lack of a unifying theory for inverse design. In the recent years, generative machine learning methods have emerged as powerful tools for this task, but current implementations are often limited by the need for large and high-quality datasets used for training [1,2]. In this contribution, a novel, data-free method for *de novo* molecular generation is presented. The academic-free software we developed, PROTEUS, is based on a deep reinforcement learning algorithm that generates candidate molecules, whose properties are computed on-the-fly with quantum chemistry software [3]. Thanks to the direct quantum mechanical feedback, the algorithm rapidly learns how to optimize the generation of promising candidates, effectively converging on (sub)optimal solutions. We demonstrate the capabilities of PROTEUS in the design of styrene derivatives with target isomerization energies. Despite the combinatorial complexity of the task –

spanning over 2 million solutions – PROTEUS quickly finds the optimal candidates without any pre-training, outperforming a reference baseline. Thanks to its general and data-free scheme, PROTEUS opens new avenues for transferable, systematic, and broadly accessible molecular design.

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Decoding GPCR Activation: Minute-Scale Simulations Reveal a Novel Pseudo-Active State of the Adenosine A2A Receptor

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G protein-coupled receptors (GPCRs) represent membrane proteins of significant pharmacological importance, being the target of more than one-third of commercially available drugs. 1-5 These receptors are activated by orthosteric ligands, undergoing substantial conformational changes that facilitate the coupling with diverse effector proteins.6-7 To achieve precise control over the pharmacological response of drugs, it is crucial to illuminate the poorly understood aspects of gpcr activation. In this study, we elucidate the complete activation mechanism of the adenosine A2A receptor (A2AR), a class A GPCR, utilizing minute timescale molecular dynamics and free energy calculations. We thoroughly explore the conformational landscape of A2AR in its basal apo form and under various ligated conditions, revealing insights into ligand intrinsic activity and the receptor's lowest energy functional states. Notably, we identify a novel pseudo-active state (pAs) of the A2AR apo form stabilized by specific interactions involving "microswitch" residues, including the salt bridge between the class A conserved residues R5.66 and E6.30. In this "pAs" state, A2AR can couple to the Gs protein upon rearrangement of the intracellular end of TM6, providing unique structural insights into receptor functioning. This discovery paves the way for future signaling studies and offers a promising framework for drug design strategies aimed at developing A2AR-biased ligands. Our simulation protocol is generalizable and can be applied to study the activation mechanism of any GPCRs and to predict the intrinsic activity of ligands based on their effect on the receptor conformational dynamics, resulting in a valuable tool for investigations on GPCR activation and drug design.

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Decoding Photoluminescence Origins in Carbon Dots: A Molecular Fluorophore Perspective

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Understanding the origin of photoluminescence (PL) in carbon dots (CDs) remains a fundamental challenge due to the structural diversity and chemical complexity arising during their synthesis.

While early hypotheses attributed PL primarily to carbogenic cores, mounting evidence points to molecular fluorophores (MFs) and their dynamic interactions within the CD matrix as key contributors to the observed emission.[1, 2] In this contribution, we present a computational investigation into the nature of emissive states in CDs, focusing on the role of embedded or surface-bound fluorophores and their communication with surrounding domains.[3] Using density functional theory (DFT) and time-dependent DFT, we explore how noncovalent interactions, covalent bonding, and π–π stacking between MFs and functionalized polyaromatic fragments modulate excited-state properties.[4] These studies reveal the formation of charge-separated states and the conditions that promote energy or electron transfer between emissive domains. Furthermore, complementary molecular dynamics (MD) simulations of oligomer aggregation provide insight into the organization of less-ordered CD-like environments and the localization of their emissive sites. By integrating electronic structure calculations with structural models derived from MD, we elucidate how fluorophore arrangement and local electronic environments govern emission wavelength, and deactivation pathways. This multi-scale framework enhances our mechanistic understanding of PL in CDs and paves the way for rational design of materials with tailored emission characteristics.

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Deep learning force filed for lithium thiophosphates solid state electrolytes

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All-solid state (ASSB) batteries are one of the most promising alternatives of Li-ion liquid technology. ASSB have several advantages1, such as greater stability, better safety, and higher energy density2, but also an intrinsic, and still unsolved, problem caused by their solid nature, the low ion mobility. Amorphous Lithium thiophosphates, LPS (xLi2S-(1-x)P2S5) are among the most promising3 electrolytes. Optimizing their performance by tuning their composition in order to achieve high ion conductivities (at least 10-3 S/cm to be competitive with liquid electrolytes) is an extremely complicated task because we do not yet know the structure-properties relationship and the optimization process requires laborious trial-and-error laboratory procedures. Using molecular modelling we can help make this process much faster. Typically, computational approaches to electrochemistry involve ab-initio molecular dynamics (AIMD) methods, which despite their accuracy, are very slow and computationally intensive, compared to classical molecular dynamics (MD), that instead relies on parametric force fields (FF). Classical MD calculations on LPS are, at the moment, difficult to perform because they would need the development of a suitable FF whose analytical form is complicated because of the different states of chemical coordination that Li+ assumes in the amorphous solid. Nevertheless, it is important for the electrochemical community to have access to a quick and efficient way to model electrolytes such as LPS. To solve these issues, we have used deep learning molecular dynamics4, and generated a new deep learning force field (DLFF)7-8. The deep neural network5 has been trained using our ab-initio data, this way the DLFF has the high accuracy6 of the ab-initio level chosen for the training set and, being parametric, a high efficiency (classical MD level). Using this DLFF, we have performed fast ed accurate simulations on model systems beyond the actual limits of AIMD in size and time scales. This way we determined the electrochemical properties of different compositions of LPS in a quick and accurate way, rarely reached before. This approach will be crucial to determine electrochemical properties of LPS oxides (LPSO) and optimize their composition as well, making this technology competitive in a large-scale industrial environment.

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Design of fluoxetine derivatives for the treatment of Rett syndrome

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Rett syndrome is a genetic disorder affecting the development of both brain and nervous system, primarily impacting girls. It's a rare and orphan disease, meaning it has a prevalence of 1 in 10,000 to 15,000 girls, and furthermore, there's no enough development of therapeutic drugs to improve its symptoms [1]; it has recently been reported that the molecule fluoxetine has the capacity to reduce motor coordination deficits present in this syndrome [2]. Therefore, the present work will present a theoretical study on how chemical modification of this drug can improve its absorption, distribution, metabolism, excretion, toxicity, synthetic accessibility (ADMET-SA) properties, as well as its physicochemical properties, antioxidant capacity, and improved interaction with receptors involved in this syndrome, thereby enhancing fluoxetine's therapeutic effect.

Figure 1 (attached)

The present study was carried out using the CADAMA-Chem computational methodology [3], which is summarized in the following steps: 1) Fluoxetine derivatives (see Figure 1) were obtained through single or double functionalization with the functional groups -NH2, -OH, -OCH3, -SH, and -C=OH at the different sp2 carbons of the pristine molecule. 2) Subsequently, the ADMET-SA properties of over 600 derivatives were calculated, and 5 were chosen, which showed improved properties compared to pristine fluoxetine. Then, 3) for the 4 best derivatives, a conformational search was performed using semi-empirical potentials. Subsequently, using calculations with the DFT approximation, the acidity constant values and thus the acid-base equilibrium of each derivative were theoretically evaluated. For each ionic species of each derivative, 4) a primary antioxidant capacity study was conducted, and for those favored species, 5) a molecular docking interaction study of these derivatives with receptors relevant to this syndrome was performed. This study contributes to the design of drugs for orphan diseases, also provides a hope to improve the quality of life for those suffering from this illness.

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Design of new polymers for surface modification of fabrics: a multi-scale molecular modelling approach

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Soil-release polymers (SRPs) are important components of fabric care formulations. They play an important role in cleaning by modifying the surface of fabrics such as polyester. SRPs change the surface hydrophobicity, providing resistance to staining and preventing the redeposition of soils during the wash process. They have important environmental benefits, enabling effective cleaning of fabrics while using shorter, cooler wash cycles. This is significant from an environmental perspective as, typically, 10–15% of household energy is used by washing machines, and washing at 30 ℃ rather than 40 ℃ can reduce energy consumption by ˜40% per cycle.

The typical schematic structure of an SRP is shown here. They are traditionally built as tri-block copolymers with two (long) terminal hydrophilic chains designed to impart hydrophilicity to the surface, and a short central hydrophobic block designed to anchor strongly to a fabric surface. Most SRPs used today contain petroleum-sourced terephthalic acid, produced via the catalytic oxidation of petroleum-sourced p-xylene. However, there is a clear drive throughout industry to replace this with non-petroleum-based alternatives [1].

Two factors are known to be important: the binding strength of the central hydrophobic block to the polymer surface and the aggregation behavior of the polymer in solution. Hydrophobic oligomers tend to fold in solution to minimize contact with water, and so (typically) contact between this part of the polymer and the surface occurs in “folded form”. Moreover, there can also be a tendency for aggregate formation to occur in solution, and large aggregates are known not to stick to the fabric surface.

To understand the complex behavior of these polymers, we present a multiscale simulation approach. H-REMD is used to determine the folded structures of molecules in solution, and of the central core at polyester and spandex surfaces. μs MD is used to study initial aggregation behavior in solution and is used to parametrise and validate a dissipative particle dynamics (DPD) model of the polymer. The latter is used to simulate the full solution aggregation and surface adsorption behavior at a hydrophobic interface.

This multi-scale approach has facilitated the design of new biosourced “greener polymers”.

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Determination of Structures and Binding Energies of Europium Complexes Bound to Biologically Relevant Analytes

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Anion sensing is a crucial area of research due to its applications in medical diagnostics, environmental analysis and industry. Lanthanide complexes have been actively studied for anion sensing in biological media as they have a positively charged central cation that can provide strong electrostatic interactions with the anions. In addition, their unique photophysical properties such as high photoluminescence and quantum yield, and large stokes shift of about 200 nm, make them particularly useful to serve as biosensors.

Within this work, we investigate the geometries and binding energies of europium complexes bound to different biological anions using various computational methods. These results indicate that the

composite r2SCAN-3c method produces highly accurate results at a low computational cost. Proceeding to a conformer analysis, we highlight how the investigated complexes possess a large number of conformers differing widely in terms of the energetic and structural features. Finally, we study binding energies considering computational methods, solvation as well as the effect of counterions and protonation states highlighting that these effects play a prominent role. We believe that this work will set a solid background for future investigations of luminescent europium complexes and their anion binding properties.

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Development and Validation of the OL24 Force Field for DNA: Improved Modeling of Sugar Puckering and A/B Conformational Equilibria

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The A/B conformational equilibrium of DNA is essential for many biological processes, including protein-DNA recognition and the formation of DNA/RNA hybrid duplexes. However, existing AMBER force fields such as OL15, OL21, and bsc1 significantly underestimate the stability of A-DNA, which may lead to unrealistic conformational behaviour or even destabilization of protein–DNA complexes in simulations. Here, we present a refined DNA force field that significantly improves the description of sugar puckering by increasing the stability of the north puckering present in A-DNA. The new OL24 parameters were validated through extensive molecular dynamics simulations of canonical DNA duplexes, DNA/RNA hybrids, and protein–DNA complexes. OL24 maintains an accurate representation of canonical B-DNA and improves the description of the A/B conformational equilibrium in B-DNA duplexes in water. In addition, it enables improved modeling of DNA/RNA hybrids and protein-DNA complexes. Overall, OL24 represents a significant advancement in the force field description of nucleic acids, enabling more reliable modeling of DNA structure and dynamics.

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Development of molecular dynamics models of complex crystallisation mechanisms of pharmaceuticals

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Molecular modelling can give critical insight into the properties and behaviour of pharmaceutical crystals. Classical Molecular Dynamics enables modelling large systems accounting for solvent and thermodynamics effects. It also provides time resolved information otherwise inaccessible to stationary DFT calculations or Monte Carlo (simulations).

In the present work, we will discuss our development of molecular dynamics (MD) models for studying the interaction of excipients with crystalline nanoparticles of drug products. We will start by showing a test case of the nucleation of an active pharmaceutical ingredient (API), flufenamic acid

(FFA), in ethanol. Through the CHARMM/CGenFF forcefield and GROMACS engine, we have been able to model the interactions between FFA and ethanol. A supersaturated ratio (1:12) and undersaturated ratio (1:36) of uniformly distributed FFA in ethanol, as well as a pre-built crystal of FFA in ethanol, also at the supersaturated ratio (1:12), were all modelled at room temperature and atmospheric pressure. Each of these systems were analysed for up to 1μs. By using MD, we can analyse how the change in ratio of FFA:Ethanol affects the for non-classical nucleation behaviour, as well as finding which state is best for mesoscale cluster formation; a crystal of FFA in ethanol that first dissolves and then reforms, or uniformly dispersed molecules of FFA in ethanol.

We have also used Classical MD to model the crystallisation of a different API, indomethacin using the LASP method (liquid-antisolvent precipitation). Experimentally there were challenges in obtaining the stable polymorphic form of the API. A seeding approach was experimentally successful in driving the solid-state transformation, which we then computationally redesigned. The two different excipient combinations that were successful in driving the solid-state form transformation also had to be modelled. Our aims were to model the impact and influence of the seeding approach on the system, as well as the difference between the two excipient combinations.

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Effect of the CTF-1/Au(111) Interface in Enhancing Photocatalytic Water Splitting

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Covalent Triazine Frameworks (CTFs) are a class of 2D organic materials that have attracted increasing attention over the past decade due to their high density of surface-active sites, efficient charge separation, fast carrier mobility, low recombination rates, chemical stability, and tuneable band gaps [1,2]. In this study, water splitting was investigated on both free-standing and gold-supported CTFs. We examined how the interaction between the CTF and the surface influences the electronic properties, reaction free energies, and the overall reaction mechanism. Although the physical interaction between the substrate and the film is often neglected in similar studies, it can play a crucial role in designing more efficient photoanodes and photocathodes. In this work, we apply the computational hydrogen electrode (CHE) approach [3] to study both the oxygen evolution reaction (OER) and the hydrogen evolution reaction (HER), computing the free energy changes associated with each elementary step on multiple active sites. All calculations are performed within the framework of periodic density functional theory. Our calculations show that the interaction between CTF-1 and the Au(111) surface modifies the potentials of the photogenerated hole (U_h) and electron (U_e). Specifically, U_h increases from 2.61 eV for the CTF-1 monolayer to 3.01 eV for CTF-1 supported on the gold surface, while U_e decreases from 0.99 eV to 0.39 eV. These results suggest that the interaction with gold could enhance the ability of the system to oxidize water, thereby improving the efficiency of the OER step. Meanwhile, U_e still retains sufficient potential to drive the HER. In addition, calculations performed for the OER and HER at pH = 0 reveal that the interface also affects the free energy changes of the involved reactions. Notably, we find that the minimum potential required to drive the OER decreases from 2.15 eV for the CTF-1 free monolayer to 1.39 eV for CTF-1 supported on gold. For the HER, a similar trend is observed, with the free energy change shifting from 0.3 eV to −0.1 eV. This study highlights the potential role of the interface in modulating the water-splitting reaction. The resulting insights into the reaction mechanism contribute to the rational design of more efficient photoanodes and photocathodes for solar-driven water splitting.

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Elastic, mechanical and vibrational properties of antiperovskite nitrides ANCa3:A=As,Sb &Bi: A first-principles study

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Biomass-derived molecules represent a promising resource for the development of a sustainable chemical industry. However, their relatively large size and structural complexity pose significant challenges in elucidating their catalytic conversion mechanisms. In this context, computational chemistry offers powerful tools to complement experimental investigations. This work focuses on the industrially attractive thermocatalytic conversion of methyl-levulinate (ML) to ɣ-valerolactone (GVL), a versatile platform molecule, (Figure 1a) over tetragonal zirconia (t-ZrO2), an inexpensive yet industrially attractive catalyst. Despite its potential, strategies to enhance catalytic performance and mitigate deactivation remain limited due to insufficient mechanistic understanding.1,2 We employed a computational approach combining periodic density functional theory (DFT), enhanced sampling molecular dynamics, and machine-learned interatomic potentials3 to investigate the adsorption, activation, and conversion of ML on t-ZrO2 surfaces. Our simulations reveal the conversion of ML into strongly bound surface carboxylates involving t-ZrO2 surface oxygen atoms, as supported by the comparison of calculated vibrational spectra with in situ and operando DRIFTS experiments (Figure 1b). These stable intermediates hinder further transformation into angelica lactones (ALs), which have been proposed as key reaction intermediates, thus providing an explanation for the observed surface poisoning. Furthermore, our findings indicate that surface hydroxyl groups might play a crucial role in destabilizing these carboxylates, thereby promoting ML conversion in line with experimental data. These insights enable the identification of deactivation pathways and active species, and might guide the rational design of better performing catalysts.

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Electrochemically formed Single-Atom Centers of MXenes for the Selective Electrochemical Reduction of Nitrogen to Ammonia

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The electrochemical nitrogen reduction reaction (NRR) presents a sustainable route for ammonia production under ambient conditions. MXenes, with their unique physicochemical properties, have shown promise as electrocatalysts for NRR. However, the competitive hydrogen evolution reaction (HER) limits their selectivity. Here, we propose a strategy leveraging the in-situ electrochemical formation of single-atom catalyst (SAC)-like centers on MXenes under anodic polarization, combined with cathodic potential pulses to activate nitrogen reduction at these SAC sites. The DFT calculations reveal that such dynamically formed MXene-SAC sites suppress HER and enhance NRR activity by tuning adsorption energies and electronic properties. This work opens pathways to design potential electrocatalysts for sustainable ammonia synthesis.

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Electronic structure and charge transport properties in FASnI3-xBrx

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The challenge of finding an earth-abundant non-toxic perovskite material suitable for solar cell applications brought about FASnX3, where the formamidium (FA) molecule replaces the (usually) large A cation and Sn bypasses the use of Pb, while keeping the electronic band gap in the range suitable for the visible spectrum light absorption.[1]

We investigate systematically the electronic structure of the FASnI3-xBrx compound series by means of first-principles calculations. On the basis of hybrid density functional theory and including spin-orbit coupling effects, we demonstrate the indirect influence that the formamidium molecule has on the electronic band gap. The prevalent and thus unavoidable nature of the electron-phonon coupling[2] justifies our investigation of the temperature-dependent polaron mobility. Here, we base our approach in the form of variational Feynman path integral applied to the Fröhlich-type polarons[3], i.e. long-range polarons. In this case, we extract the phonon parameters from a Gamma-point density functional perturbation theory calculation. We analyze the influence of both electron and hole polarons formation on the temperature dependence on the band gap.

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Embedded machine-readable molecular representation for resource-efficient deep learning applications

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The practical implementation of deep learning (DL) methods for chemistry applications relies on encoding chemical structures into machine-readable formats that can be efficiently processed by computational tools. One Hot Encoding (OHE) and Morgan fingerprints (MF) are established representations of alphanumeric categorical data in expanded numerical matrices or vectors. We have developed embedded alternatives to OHE and MP that encode discrete alphanumeric tokens of an N-sized alphabet into a few real numbers that constitute a simpler matrix representation of chemical structures. The implementation of this embedded representations in training machine learning models achieves comparable results to traditional representations in model accuracy and robustness while significantly reducing the use of computational resources. Our benchmarks across molecular representations (SMILES, DeepSMILES, and SELFIES) and different molecular databases for Variational Autoencoders (VAEs), Recurrent Neural Networks (RNNs) and other DL models show a reduction in vRAM memory usage by up to 50% while increasing disk Memory Reduction Efficiency to 80% on average, in some cases. These encoding methods open new avenues for data representation in embedded formats that promote energy efficiency and scalable computing in resource-constrained devices, or in scenarios with limited computing resources. The application of these embeddings impacts other disciplines that rely on the use of OHE and MF.

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Embedding Models for Computational Spectroscopy: from Solvated Systems to Plasmonic Nanostructured Materials

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See attached file

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EuCompChem - Smart Solvent Selection: Combining In-Silico Insights with High-Throughput Experimentation - oral

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In the pharmaceutical industry, process design is the business process tasked with defining reagents, solvents and unit operations needed to develop a chemical route into a chemical process that meets cost of goods, throughput, quality and sustainability goals. Process design is a complex multi-objective, multi-parameter task, which requires careful planning and prioritisation to make the best of limited human and time resources. Planning the sequence of unit operations involved in a process and selecting appropriate solvents is possible, if the right physical property data is available. When experimental data is not available, predicted data can be generated in-silico with the help of quantum-mechanics based methods. Here, we present an overview of in-silico guided solvent design in the pharmaceutical industry. Specifically, we will cover how in-silico prediction may be coupled with high-throughput experimentations to guide solvent selection. We demonstrate innovative in-silico-guided methodologies for optimizing (1) aqueous extraction processes and (2) crystallization procedures. Finally, we present a fully automated data pipeline generating, harvesting

and storing physical properties predictions in an online database, to be later consulted by process chemists.

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EuCompChem 2025 - Argentieri

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Here you find my abstract for the conference attached. Title: *"Computational Analysis of Mechano-Sensitive Chiral Luminescence in Organic Materials: a TDDFT Approach"*

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EuCompChem 2025 - Inico Elisabetta - Oral

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Validating quantum chemical simulations of Oxygen Evolution on Single-atom catalysts

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Single Atom Catalysts (SACs) consist of isolated metal atoms stabilized on a support, maximizing the exposed active sites and showing behaviours that are reminiscent of coordination compounds[1,2] and are now widely investigated for catalytic approaches for the energy transition. Among them, Dual Atom Catalysts (DACs) are emerging as a promising frontier due to the possibility to use two catalytic centres. Starting from experimental results of the dual atom FeCo-N3O3@C[3], of which the structure is known, we investigate the reaction pathways for Oxygen Evolution and Oxygen Reduction Reactions (OER and ORR) with DFT calculations, providing evidence of the actual reaction mechanism which involves unconventional intermediates, that can form on single atoms. Previous studies reported that on single atom catalysts OER does not follow the classical four-electrons step mechanism,[4] as alternative pathways are possible due to the formation of unconventional intermediates *OH*OH, *OH*O and O2*.[5] In the case of DACs the picture is rather more complex due the very high number of possible adsorption configurations. Finally, the ab initio thermodynamic approach was combined with the generalized Butler-Volmer model, in order to include kinetic effects;[6] this permit to select which reaction pathway explains better the experimental data. Figure 1 reports a comparison between calculated and experimental polarization curves and the corresponding ORR pathway (panel b, c). This study provides an example of the potential combination of the structural information with atomistic details, quantum chemical calculations, and activity experiments to understand the complexity of the reactivity of Dual Atom Catalysts.

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EuCompChem2025 - Edoardo Buttarazzi - Oral

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Combining Theory and Experiments for Modeling the Conformational and Environmental Effects on the Spectroscopical Features of Red-Adsorbing Dyes

The development of efficient and economically viable dye-sensitized solar cells (DSSCs) hinges on a molecular-level understanding of the photophysical behavior of dye sensitizers.[1,2,3] Squaraine dyes, with their strong red-light absorption, are promising candidates; however, their performance is intricately modulated by conformational dynamics and environmental factors such as solvent polarity, pH, and temperature.[4,5,6]

In this study,[7] we present a comprehensive investigation into the electronic structure and vibrational properties of squaraine dyes, employing a synergistic approach that combines Density Functional Theory (DFT), Time-Dependent DFT (TD-DFT), and complementary spectroscopic experiments. The electronic and vibrational properties were characterized using range-separated hybrid functionals within TD-DFT, combined with the conductor-like polarizable continuum model (C-PCM) to simulate solvent effects, enabling accurate reproduction of spectral features across different environmental conditions. We demonstrate that: (i) the principal visible absorption feature is sensitive to conformational flexibility and protonation equilibria; (ii) solvent polarity exerts a significant influence on the position of the UV-vis absorption maximum; and (iii) vibrational spectroscopies (IR and Raman) serve as diagnostic tools for probing structural and protonation-state heterogeneity. While previous theoretical efforts have focused predominantly on vibronic couplings to interpret spectral line shapes, our findings highlight an additional layer of complexity arising from dynamic conformational and acid–base equilibria. This work illustrates the importance of integrating high-level theoretical modeling with experimental spectroscopy to capture the nuanced interplay between structure, environment, and optical response. The insights gained from three prototypical squaraines inform the rational design of next-generation dyes for DSSC applications.

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EuCompChem2025 Pierpaolo D'Antoni Oral

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Description of Charge-Transfer states for large systems by Range Separated functionals within polTDDFT

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Time-dependent density functional theory (TDDFT) has become the method of choice for simulating the optical properties of large molecular systems. Its favourable computational scaling and good accuracy, combined with ongoing efforts to improve algorithmic efficiency, are paving the way for the theoretical characterization of increasingly large and complex systems. Among the available schemes, PolTDDFT stands out for its balance between accuracy and computational cost [1]. Despite being formally exact, (TD)DFT relies on approximations for the exchange-correlation (xc) functional, whose exact form remains unknown. These approximations are responsible for known limitations of the method, most notably, its poor description of charge-transfer (CT) states. Head-Gordon, Weisman, and Dreuw were among the first to demonstrate that local xc functionals fail to capture nonlocal interactions like the electrostatic attraction between spatially separated charges in long-range CT excitations [2]. To overcome this issue, range-separated (RS) hybrid functionals were introduced, incorporating a distance-dependent fraction of exact Hartree–Fock exchange. In this work, we integrate the use of a RS functional (CAMY-B3LYP [3]) into the PolTDDFT/fitted-HDA computational framework [4] to address both the challenges of computational efficiency and accurate CT-state description. We assess the performance of our implementation by simulating the optical response of a well-known Donor–Acceptor–Acceptor triad [5] and comparing the results to both the benchmark Casida formulation of TDDFT and available experimental data.

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EuCompChem2025 – Andrea Grillo – Oral

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Zr-Doping of P2-NaxMn0.625Ni0.375O2-Layered Oxides for High-Energy Na-Ion Battery Cathodes: New Insights from First-Principles

Na-ion batteries (NIBs) are at the forefront of energy storage technology due to larger abundance of raw materials and enhanced cost-effectiveness compared to Li-ion counterparts [1]. Despite the great advances achieved in last decades, identification of efficient, stable and cheap component materials still hinders a convenient NIB commercialization. Following the route paved by different TM combinations in P2-cathode materials [2], we present a first-principles investigation at the PBE + U(-D3BJ) level of theory on Zr-containing NaxTMO2 (TM = Zr, Ni, and Mn), chosen for its potential to enhance structural stability and electronic properties [3,4]. We dissect the specific roles of different element sublattices during sodiation/desodiation processes. In addition, oxygen vacancies and TM anti-sites defects are addressed in the high-voltage range (%Na = 25% ⊠ 12.5%), and their related formation energies and both structural and electronic features are discussed. Experimental analysis (e.g. toward cyclic voltammetry and X-rays diffraction) provide key validation for computational results demonstrating the cathode stability and efficiency. All the theoretical insights and the validating experimental results can be useful for an optimal design for next-generations efficient and high-energy NIB cathodes with enhanced structural stability at high voltage and improved device sustainability.

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EuCompChem2025 – Christoph Riplinger – Oral

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Quantum chemical (QM) calculations for life science applications have traditionally been constrained to small model systems, or computationally inexpensive but lower-accuracy methods, due to computational limitations. Most biomolecular modeling approaches rely on empirical parametrization and thus, at least indirectly, on some sort of training, which introduces biases and restricts their applicability. In particular, crucial drug targets such as RNA and metalloproteins often fall outside the scope of conventional methods, requiring extensive parametrization efforts. Recent advances in quantum chemistry, alongside improvements in computing hardware, have enabled the application of high-accuracy QM methods – such as hybrid density functional theory (DFT) and coupled cluster (CCSD(T)) – to biomolecular systems.[1, 2, 3] These developments now allow for the accurate simulation of ligands in solution as well as in complex biological environments, including their chemical stability, potential degradation pathways, and photochemical reactivity. Moreover, the integration of QM calculations with machine learning models further enhances their predictive power, opening new avenues for drug discovery. In this talk, we illustrate how state-of-the-art QM approaches are applied across various stages of drug development, from predicting photochemical degradation to elucidating binding mechanisms in metal-containing proteins.

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EuCompChem2025 – David - Oral

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Capturing Chemical Reactivity and Entropy with Machine Learning Potentials

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Chemical reactions drive fundamental processes in both nature and industry. Understanding these reactions is crucial across diverse fields, from the chemistry of life's origins to the synthesis of pharmaceuticals and advanced materials. However, unraveling reaction mechanisms, thermodynamics, and kinetics—especially in complex environments involving solvents—poses significant challenge Experimental methods often lack the resolution to fully characterize transition states and energy landscapes, while quantum-level simulations are computationally prohibitive for large systems and long timescales. Recent advances in machine learning, particularly the development of machine learning interatomic potentials (MLIPs),1,2 offer a paradigm shift by providing quantum-accurate force fields at a fraction of the computational cost. These MLIPs enable molecular dynamics simulations that are several orders of magnitude faster than traditional ab initio methods, thus bridging the gap between quantum accuracy and accessible dynamical timescales. However, generating reliable reactive MLIPs remains nontrivial due to the complexity of chemical reactions and the need for extensive, diverse training datasets capturing all relevant reactive events.3 Here, we introduce ArcaNN (Automated training of Reactive Chemical Architectures with Neural Networks),4 a robust and flexible framework designed to automate and optimize the training of MLIPs for chemical reactions. ArcaNN integrates enhanced sampling techniques to efficiently explore reactive configurational space, coupled with a concurrent learning strategy that ensures adaptive refinement of the training set. The workflow orchestrates the key stages of training, exploration, and labelling, greatly reducing human intervention and making the generation of reactive MLIPs accessible to a broader scientific community. We apply this framework to organic reactions including the SN2 reaction, the Claisen rearrangement, and alkene hydroboration, explicitly modelling solvent molecules in a fully reactive manner. We will discuss the ability to generate long-timescale trajectories and trace accurate thermodynamic and especially entropic contribution along reaction coordinates,5 providing a more comprehensive picture of chemical processes. Overall, ArcaNN represents an advancement in the training of MLIPs for chemical reactivity, enabling detailed, efficient, and automated investigations of complex reactions in condensed-phase environments under realistic dynamical conditions.

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EuCompChem2025 – Dell'Orletta Gianluca – Oral

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Photobiocatalysis has recently emerged as a valuable strategy for conducting chemical reactions that are challenging with conventional organic chemistry tools. This approach involves the use of photenzymes, i.e. enzymes that absorb light to promote substrate conversion. The photexcitation of these catalysts enables access to electronic excited states with different properties compared to the ground state, thus providing new reaction modes. Additionally, the chiral active sites of these enzymes can control the stereoselective outcomes of these processes.

Although natural photoenzymes are rare, enzymes containing cofactors with latent photochemical properties can be activated by irradiation, thereby expanding the repertoire of available catalysts. Notably, Todd Hyster and coworkers discovered that the photoexcitation of flavin-dependent ene-reductases (EREDs) can facilitate non-natural transformations involving radical intermediates, such as the 5-exo-trig radical cyclization of alkene-tethered α-chloroacetamides to yield a chiral γ-lactam [1]. Specifically, they found that the triple mutant T36A-K317M-Y343F of Gluconobacter oxydans ene-reductase (GluER-G6) was very efficient in promoting this activity [2]. In a previous study [3] we explored the origin of the enantioselectivity of this reaction and we proposed an enatioinduction scenario in which the relative stability of prochiral transition states is dependent on a degree of freedom within the substrate, which is controlled by the enzyme through conformational selection.

Here, we present a computational study focused on the initial steps of the process promoted by GluER-G6, specifically the photoexcitation of the electron donor-acceptor (EDA) complex formed between the flavin cofactor and the substrate within the active site, and the mesolytic cleavage of the C-Cl bond. We employ a multiscale approach based on Molecular Dynamics (MD), Quantum Mechanics (QM), and the Perturbed Matrix Method (PMM) [4] to characterize the excited states, compute the spectrum of the EDA complex within the enzyme, and determine the kinetic constant for the mesolytic cleavage. We explain the low experimental quantum yield with a limited population (<10%) of EDA complex conformers (named EDAin) with a charge transfer state competent for the mesolytic cleavage. The accessibility of this state requires substrate bending positioning the chlorine atom near to the styrenic moiety [4]. We also find that the radical species obtained after the C-Cl bond breaking displays the correct prochirality for the stereoselective cyclization. This demonstrates that the conformational selection of EDA complex governs both mesolytic cleavage and enantioselectivity.

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EuCompChem2025 – Dipanshu Kumar – Oral

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The fate of the hesitating proton: Adsorption of Ethanol in H-ZSM-5

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EuCompChem2025 – Federico Rossi – Oral

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The description of conical intersections is a key requirement in non-adiabatic molecular dynamics. Standard Hartree-Fock and Density Functional Theory, with the corresponding TDHF and TDDFT methods for excited states, are unable to describe ground state conical intersections, as the ground state is decoupled from the excited states. As system size increases, multiconfigurational methods become unfeasible and the need for a cost-efficient method becomes crucial.

Here we present a modified Hartree-Fock method, where the ground state is optimized in a lower-dimensional subspace, removing the projection along selected Hessian eigenvectors. In a final step, the energies of the ground and excited states are obtained by diagonalizing the Hamiltonian. Several applications will be presented and compared with TDHF and TDDFT in the Tamm-Dancoff approximation. A similar computational framework has recently been used to develop a coupled cluster method that correctly accounts for the geometric phase effect and avoids bifurcations of the solutions to the ground state equations.

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EuCompChem2025 – Francesco Mazza – Oral

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MCSCF/FQ Analytical Nuclear Gradients: A Novel Methodological Development for Multireference Multiscale Modeling

Multiscale approaches are valuable methods for accurately describing molecules embedded in complex environments, such as solutions. Among them, the Multiconfigurational Self-Consistent Field/Fluctuating Charges approach (MCSCF/FQ) [1] combines a multireference quantum mechanical method [2] with the FQ polarizable force field [3,4]. This combination captures the qualitative behavior of multireference systems and processes within their environment (e.g., aromatic molecules in solution, photochemical processes), where commonly used single-reference methods, such as TD-DFT, often fail. In addition, the atomistic and polarizable nature of FQ provides an accurate description of solute-solvent interactions, explicitly accounting for their mutual polarization. In this work, the MCSCF/FQ model has been extended to calculate analytical nuclear gradients, significantly enhancing the versatility of the method [5]. This development enables tasks such as geometry optimizations, vibronic spectra computations, and QM/MM molecular dynamics simulations. The MCSCF/FQ analytical nuclear gradients have been implemented in the OpenMolcas software [6] and validated against

numerical gradients. As an illustrative application, vibronic spectra of aromatic molecules in aqueous solutions have been computed (Figure 1). Results demonstrate an accurate reproduction of the experimentally observed spectral profiles and relative intensities, highlighting the capability of the MCSCF/FQ approach to capture both the multireference nature of the solute and the solute-solvent interactions.

Figure 1. (Left) Representative snapshot of benzene in aqueous solution. (Right) Vibronic spectra comparison: computed with the CASSCF(6,6)/FQ method (top) and experimental data from Ref. [7] (bottom).

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EuCompChem2025 – Gabriele Iuzzolino – Oral Contribution

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The Ultrafast Fluorescence of a DNA-Protein Photo-Crosslinking Model, interpreted by Non-Adiabatic Molecular Dynamics

Isolation of transient nucleoprotein complexes in their biological conformation is a challenging task: a promising technique is to induce in vivo crosslinking between the nucleic acid and the protein, by UV light. The photo-cyclization of 5-benzyluracil (5BU) to 1,2-indaneuracil has been proposed as a model reaction to study the mechanism of photo-crosslinking.[1] In competition with the reactive path, 5BU also exhibits an ultrafast radiative decay - probed by Fluorescence Up-Conversion (FlUC) – whose fastest component is debated to be due either to a decay from the upper excited states to S1, or to a vibrational relaxation of the first excited state.[2]

In this context, we present a theoretical study of the ultrafast photo-activated dynamics of 5BU in methanol, exploiting the framework of the DFT and TD-DFT[3]. At the same time, we propose a new protocol to simulate FlUC spectra, making easier the comparison between simulation and experiment.

We first characterized the ground-state thermal equilibrium and the photophysics, via an ab-initio molecular dynamics, exploiting the ADMP[4] extended Lagrangian formalism, the ONIOM[5] QM/MM partition scheme and non-periodic boundary conditions[6]: we discovered the presence of two conformers in equilibrium at room temperature and multiple excited states responsible for the absorption propaedeutic to the photocyclization, whose brightness depends by the conformation and microsolvation of 5BU.[7]

Thereafter, to give a molecular interpretation of the fluorescence signal, we conducted a non-adiabatic mixed quantum/classical molecular dynamics of 5BU in implicit (C-PCM) methanol, by adopting the Fewest-Switches Surface Hopping approach.[8] The initial conditions were generated by sampling a quantum Wigner distribution for each of the two conformers and for each involved transition.

The simulated time-resolved spectrum and the FlUC experiment have different time scales, since the first starts from the absorption regime and the latter, having an IRF of 300 fs,[2] starts from an already advanced point of the excited-state evolution of the system: our new protocol, based on the fit of the simulated spectral peaks, gave us a clear and direct comparison with the experimental data.

We were thus able to simulate the transient emission spectrum; we then performed a vibrational analysis through an innovative protocol, based on the wavelet transform of time resolved generalized modes extracted from the trajectories. We thus detailed the molecular mechanisms underlying the formation of the high-energy emission band, the red shift of the low-energy band and the ultrafast component of the decay of both bands.

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EuCompChem2025 – Giuseppe Amante – Oral

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Confinement Potential for QM and QM/MM Optimization with Implicit Solvent under Non-Periodic Boundary Conditions

A current limitation in the geometric optimization of solute/solvent clusters containing a large number of solvent molecules, also including an implicit model for the solvent bulk, both at the QM and QM/MM level, concerns the stability of solvent molecules placed within the cavity embedded in the dielectric medium. For example, molecules near the edge of the cavity tend to collapse toward the boundary rather than remain evenly distributed within the cavity itself, leading to unphysical minimum energy structures with overestimated solute-solvent interactions. This behavior arises from the dominance of explicit-explicit interactions over explicit-implicit ones, which leads to geometrically unstable or physically unrealistic structures. Indeed, dispersion-repulsion models currently available to account for non electrostatic explicit-implicit interactions are not adequate for large clusters, being developed to reproduce the solvation free energy of the solute in combination with the electrostatic contribution [1,2,3] rather then average van der Waals potentials for a large number of solvent molecules. Such models prove to be ineffective also in dynamic simulations, where the

adoption of non-periodic boundary conditions (non-PBC) is more suitable for a proper description of dispersion and repulsion forces [4,5,6,7].

In this work, we propose the integration of the non-PBC dispersion-repulsion term—also acting as a confinement potential—directly into the classical component of the quantum Hamiltonian. This approach enables a more realistic representation of the minimum energy structure, even for large solute-solvent clusters. We also present several case studies that demonstrate the effectiveness of the method, including structural optimization and the calculation of vibrational frequencies and vibronic spectra.

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EuCompChem2025 – Jennie Martin – Oral :Re-Using Computational Data: Fast Molecular Crystal Structure Prediction by Analogy to Prior Predicted Landscapes

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This talk discusses our work to develop a fast approach to organic molecular crystal structure prediction (CSP) by using previously predicted CSP landscapes of similar molecules to guide sampling within our structure searches. We discuss the method developed, initial results found, and the promise of the approach considering the 'big data' direction of the CSP field[1]. We will also touch upon potential applications of the approach to the discovery of porous materials.

With the growth of the materials discovery field, large amounts of structure prediction data are being generated – one recent study calculated the CSP landscapes of over 1000 small molecules[1]– and the impact of that data can be extended by exploring effective ways for its re-use when studying new molecules. One application, not reliant upon machine-learning, may be in using existing prediction data to aid further CSP, by use of analogy in the generation of trial crystal structures.

We discuss our approach to quickly generate CSP landscapes of target molecules, by generation and optimisation of analogues (Figure 1) of previously predicted crystal structures of similar molecules. The method demonstrates a proof of concept for how analogy-based CSP approaches used more commonly in the inorganic CSP community can also be used for molecular systems and could utilise previous computations – avoiding a reliance upon experimental structure data.

Tested on a variety of small organic systems, the method has shown promise in predicting the crucial low-energy regions of CSP landscapes with greatly reduced sampling compared to quasi-random approaches. Initial findings suggest a similarity of the CSP landscapes of similar molecules and demonstrate potential broad applicability of the approach.

The talk will introduce our work including generation of reasonable crystal structure analogues, the utility and efficiency of the approach in structure prediction, potential applications in materials discovery, and our thoughts on where the method can take advantage of the increasing availability of computational data.

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EuCompChem2025 – Laura Falivene – Oral

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Enhancing Catalyst Optimization with Robust Validation of MLR Models: A Systematic Workflow and Web Application L. Falivene1*, L. Cavallo2 1Università degli studi di Salerno, Via Papa Paolo Giovanni II, 84100 Fisiciano, SA, Italy 2King Abdullah University of Science and Technology, Thuwal, 23955-6900, Saudi Arabia*lafalivene@unisa.it

The development of efficient catalysts is a key driver of progress in chemical processes across various sectors, including pharmaceuticals and energy. However, catalyst optimization often relies on time-consuming and costly trial-and-error experimentation. Machine learning (ML), and in particular Multivariate Linear Regression (MLR), offers a promising strategy for predicting catalyst performance and accelerating discovery. [1-2] MLR models are well suited for small datasets and enable the identification of meaningful correlations between molecular descriptors and reaction outcomes. Nonetheless, ensuring the reliability of such models—especially when based on limited experimental data—remains a critical challenge. This contribution presents a robust validation workflow designed to assess MLR model reliability before application to catalyst design.[3] A dataset comprising 29 reaction classes and 514 reaction objectives serves as a testbed for evaluating models trained on reduced data. Both steric and electronic descriptors are included to capture structural effects on reactivity. Notably, a novel steric descriptor—percentage of distal buried volume (%VDBur)—is introduced, quantifying steric effects at varying distances from the catalytic center and enhancing model predictive accuracy. The proposed workflow systematically addresses common gaps in model validation and is broadly applicable to MLR-based approaches.[4] The models achieve strong predictive performance, with an average R^2 of 0.90 ± 0.07, and validation tests confirm their robustness. The %VDBur descriptor significantly improves prediction accuracy, underscoring the importance of distal steric effects. Moreover, the models successfully identify catalysts with superior performance compared to those in the training set. [1] S. M. Mennen, C. Alhambra, C. L. Allen, M. Barberis, S. Berritt, T. A. Brandt, A. D. Campbell, J. Castanon, A. H. Cherney, M. Christensen, et al., Organic Process Research & Development, 2019, 23, 1213–1242. [2] M. Seifrid, R. Pollice, A. Aguilar-Granda, Z. M. Chan, K. Hotta, C. T. Ser, J. Vestfrid, T. C. Wu, A. Aspuru-Guzik, Accounts of Chemical Research, 2022, 55, 2454–2466. [3] Z. Cao, L. Falivene, A. Poater, B. Maity, Z. Zhang, G. Takasao, S. Sayed, A. Petta, G. Talarico, R. Oliva, L. Cavallo, Cell Reports Physical Science, 2025, 6, 102348, 1–8. [4] Z. Cao, L. Falivene, A. Petta, L. Cavallo, COBRA 1.0: A web application for catalyst optimization by linear regression, https://www.aocdweb.com/OMtools/cobraMeitner

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EuCompChem2025 – Luca Cascone – Oral Contribution

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Photoinduced Proton Coupled Electron Transfer (PCET1,2) reactions constitute an important class of reactions of biological3 and technologic4 relevance. They are increasingly recognized in areas such as synthetic chemistry and photocatalysis as well as in energy transformation reactions in natural and artificial systems.5 From a mechanistic point of view, these reactions can be distinguished

by the degree of synchronicity and directionality by which both the proton and the electron are transferred following photoexcitation. Theoretical and computational methods can contribute to the molecular interpretation of the PCET mechanism and of spectroscopic data. We report a theoretical and computational study of photoinduced PCET reactions via organic catalyst excitation among the intracellular domain. We have studied the mechanism ruling the PCET reactions in a model system in aqueous solution, taking into account the numerous effects arising from the multi-layer biological system: the kinetics and the thermodynamics of PCET reactions in solution depend on a fine interplay of the electronic and the nuclear motion, as well as of solute-solvent interactions, which represent crucial features in standard electronic methods to properly describe the electronic density along the proton transfer coordinate and the resulting potential energy surface.6-8 To investigate the adiabaticity and the non-adiabaticity of the catalyst's excited electron states involved, Time-Dependent DFT (TD-DFT) calculations were performed alongside a clear investigation of the ground state properties. This allowed for the analysis of the proper reactive excited state species of the catalyst for the PCET reaction of interest. The next step consisted into simulating the PCET reaction with the molecular counterpart. The reaction pathway was analyzed by simulating various potential scenarios through a computational study of the excited states of the complex, in gas-phase first and then through a simulated solvation by water molecules. The TD-DFT was also adopted to simulate the steady-state and transient UV–Visible spectra of neutral and excited complex. By combining theoretical predictions with experimental data, we aimed to enhance the understanding of the reaction at an atomistic and molecular level, providing new insights beyond experimental observation. This study can contribute to a better understanding of the PCET reaction as well as to the interpretation of spectroscopic time resolved data9, that suggest an ultrafast kinetics of the PCET process.

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EuCompChem2025 – Maria_Voccia – Oral

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Heterocyclic Carbenes for Tunable Functionalization of Oxide Surface.

N-Heterocyclic carbenes (NHCs) [1] exhibit excellent ligand properties as surface modifiers, owing to their structural diversity, tunable electronic properties, and strong affinity for a broad range of elements. These features make them highly attractive for applications in materials science and catalysis. [2] To fully harness the potential of NHCs in nanotechnology, it is essential to develop a fundamental understanding of their interactions with various metal oxide surfaces. While their behavior on metallic surfaces such as Cu, Ag, Pt, and Au has been extensively studied and rationally designed, synthesized, and analyzed, [2-5] their adsorption characteristics on oxidic supports remain less explored. First results showed that NHCs on oxidized copper surfaces are preferentially bound to oxygen atoms, [5] at variance from what is commonly observed in organometallic coordination complexes. The desorption of cyclic urea species promoted the reduction of copper oxide surfaces. [5] In this study, we investigate the adsorption behavior and electronic interactions of diverse NHCs on a range of metal oxide surfaces, spanning from ionic (MgO) or covalent (SiO2) large-gap oxides to small gap TiO2 and Cu2O. By means of hybrid DFT calculations we show how NHCs can bind either to oxygen or metal surface species. The charge state of the adsorbed molecules (almost neutral when bound to surface cations, positively charged when bound to oxygen) and the interfacial dipole moment are drastically different in the two cases. The preferential adsorption mode depends on the oxide electronic structure, as well as on the molecule electronic and steric features. Our findings pave the way for the rational design of NHC-based assemblies for tuning nanopatterned structures on oxide materials. [6]

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EuCompChem2025 – Matthew Brown – Oral

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Machine learning potentials (MLPs) aim to bridge the gap between force fields and ab initio methods, allowing for accurate calculations with a reduced computational cost. This capability promises to benefit several research areas. For example, in crystal structure prediction, highly accurate methods are required to capture small energy differences between different crystal structures [1]. In the determination of protein structures MLPs offer an opportunity to improve upon calculations with traditional force fields which generally lack consistency [2].

FFLUX [3,4] force fields use Gaussian process regression (GPR) models trained on data from quantum chemical topology (QCT) calculations to predict intramolecular (or intra-system) energies and multipole moments up to the hexadecapole moment. These models allow for fully flexible molecules with geometry dependent electrostatic interactions. In previous studies focussing on liquid water [5], formamide polymorphs [6] and gas phase clusters [7,8], dispersion and repulsion have been represented by Lennard-Jones potentials.

Within our workflow, intermolecular interactions can be machine learned using the same QCT/GPR methodology, bringing FFLUX force fields closer to quantum mechanics. This talk highlights ongoing work to remove the need for external potentials such as the Lennard-Jones potential in our simulations. GPR models trained on clusters allow intermolecular repulsion to be modelled as well as intermolecular polarisation allowing for greater accuracy in calculations.

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EuCompChem2025 – Nico Di Fonte – Oral

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The integration of graph theory into the analysis of molecular dynamics (MD) simulations offers a powerful and versatile framework for addressing complex structural identification problems[1,2]. By representing atomic or molecular interactions as nodes connected by edges within a graph, it is

possible to use a vast array of well-established, highly-optimized algorithms originally developed for fields such as computer science, social networks, and transport systems, to analyze and interpret simulation data. We employ graph-based methods to investigate key structural features arising from MD simulations, including the formation and evolution of molecular aggregates and the identification of water channels within protein environments (Figure 1). These problems, often challenging to address with conventional spatial or density-based techniques, benefit significantly from the flexibility and scalability of graph approaches[3,4]. The cross-disciplinary nature of graph theory not only enhances computational performance but also allows access to new information in the study of molecular structures.

We are currently developing an open-source tool designed to make graph-theory analysis of molecular dynamics trajectories accessible and customizable for the broader scientific community. The tool will allow users to construct graphs from atomic or molecular data and to flexibly define node and edge criteria based on chemical identity of the nodes, distance thresholds, and hydrogen bonding. Leveraging the tunability of graph parameters, users can tailor the analysis to their specific system and research question, whether it involves detecting aggregating behavior, mapping solvent networks, or identifying functional pathways such as water channels in proteins. By building on widely used graph libraries, the tool aims to interface MD simulations with graph analytics in a way that is both robust and user-friendly.

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EuCompChem2025 – Nicole Ceribelli – Oral

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Li-ion solvation shell in PVDF-Based Quasi-Solid Electrolytes: A Molecular Perspective Nicole Ceribelli1, Giovanni Di Liberto1 and Livia Giordano1 1Department of Materials Science, University of Milano – Bicocca, via R. Cozzi 55, 20125 Milano, Italy n.ceribelli@campus.unimib.it

The development of high-performance Lithium-metal batteries has long been at the forefront of energy technologies, with the electrolyte being often the limiting factor directly affecting the performance and safety of the battery [1,2]. Among solid electrolytes, poly-vinylidene difluoride (PVFD)-based electrolytes have attracted increasing attention due to their promising mechanical properties and wide electrochemical stability. However, despite the high polymer permittivity ($\varepsilon' \approx 10–11$) which should allow efficient salt dissociation, there is growing evidence that the ionic transport in (PVFD)-based electrolytes requires the presence of a non-negligible amount of a liquid solvent [3]. Recent experimental studies have argued that residual DMF solvent, which is used during the electrolytes preparation to dissolve the polymer-salt system, solvates Li+ and contributes to the ionic diffuson [4]. Understanding the Li+ solvation and diffusion mechanism across this quasi-solid electrolyte (QSE) and the role of residual solvent on these properties is critical to advance the development of these battery systems. The delicate balance of interactions between the different electrolyte components can be difficult to capture by classical force field. We then investigated in depth the

role of DMF in the solvation and diffusion of Li+ via ab-initio computational methods [4,5,6]. First, the interaction of LiFSI salts with DMF molecules and PVDF chains has been computed by constructing Li+(FSI-)p(DMF)n(PVDF)m complexes. In addition, ab-initio molecular dynamics (AIMD) simulations have been performed to gain further insights on the diffusion of Li+(FSI-)p(DMF)n complexes in channels formed by PVDF chains. The atomic structures and binding energies (ΔE) of Li(FSI-)p(DMF)n(PVDF)m+ complexes, coupled with simulated Raman spectra, demonstrated that strong bonding occurs between Li+ ions and DMF molecules and that the amounts on the order of [DMF]/[Li+] ~ 2–3 are required to make QSEs able to practically work in a real environment [4]. Moreover, our AIMD simulations of extended LiFSI-DMF-PVDF system confirm the weak interaction between Li ion and PVDF and show the solvation structure of Li+, with DMF and FSI- ions solvating Li+ ions. Our results showed that the solvation shell is dynamic, and the diffusivity is higher in the presence of a DMF-dominated solvation shell, where the addition of the PVDF matrix can increase the diffusivity by providing structured diffusion channels, enabling better performance in agreement with the experimental results [4,6]. This molecular-level insight represent a step forward in understanding the diffusion mechanism of Li-ion in PVDF-based electrolytes and can be used for the rational design of next-generation electrolytes with improved performances. [1] K. Sashmitha, M. U. Rani, Polymer Bulletin 2023. [2] D. Zhou, D. Shanmukaraj, A. Tkacheva, M. Armand, G. Wang, Chem 2019. [3] Y. Wu, Y. Li, Y. Wang, Q. Liu, Q. Chen, M. Chen, Journal of Energy Chemistry 2022. [4] N. Vallana, E. Carena, N. Ceribelli et al. ACS Appl. Energy Mater. 2024. [5] E. Carena, L. Mezzomo, N. Vallana, N. Ceribelli et al. Small 2024. [6] N. Ceribelli, L. Giordano et al. submitted 2025.

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EuCompChem2025 – RIO – Oral

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Taming the Reactivity of Nickelate/Cation(s) Ion Pairs in Catalysis: DFT Insights

Metal-ate complexes are highly reactive species that can facilitate elementary steps in catalysis, such as oxidative addition or highly hindered C-C bond creation. Controlling their formation and tuning their reactivity is appealing, but this requires a detailed picture of the parameters governing their structure and their reactivity (ligand, solvent, additives, …). Our collaborators have recently developed a cyanoalkylation of ketone derivatives catalysed by a well-defined Ni(II) anionic catalyst (**Fig.a**).**[1]** The reaction involves the formation of nickelate-cation (Cat+) ion-pairs together with a ketenimine (N-coordination) / cyanoalkyl (C-coordination) equilibrium. This is a versatile and realistic model system to understand the structure - reactivity relationship in that class of catalytic active species.

The N- and C-coordination of cyanoalkyls is often described as a structural continuum.**[2]** Based on DFT modelling, we analysed the interactions between the substrate and alkali- or transition-metals complexes (Gaussian16/B3PW91-D3BJ/SMD(THF)/6-31++G\\/SDD(Ni,Cs) & associated basis sets). Alkali-metals favour N-metalation by displacing lone pairs on the nitrogen atom - similarly to an electric field (**Fig.b**). With transition-metals, the formation of more covalent M-C bonds (M = Ni, Cu catalysts) acts as a driving force, which can be modulated by tuning the ligand.

Based on these results, the cyanoalkylation mechanism is examined with emphasis on the nature of the cation (alkali-metal vs. ammonium). Compared to systems in the literature, the nickelate catalyst reduces the activation energy for C–C bond formation sixfold.**[3]** Preliminary results suggest that the Cs^+ cation arising from the base, does not affect the reaction kinetics or thermodynamics of the reaction (**Fig. c**). Current efforts focus on probing interactions between the nickelate and alkylammonium cations, featuring different steric and electrostatic properties for enantioselective applications in catalysis. These results will improve our understanding of chemical systems that are governed by environment effects (solvation, ion-pair formation, alkylammonium cation, …) and pose a modelling challenge.

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EuCompChem2025 – Raoul Carfora – Oral - Transient vibrational dynamics unveil the intricate mechanism of ultrafast photorelaxation in a molecular rotor

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Light-driven molecular rotary motors represent an elegant way to convert photon energy into controlled unidirectional motion and are thus directly linked to the development of nanoscale devices [1]. Among these, overcrowded alkene-based rotary motors have garnered significant interest as prototypical systems for investigating photoinduced structural dynamics [2]. Extensive experimental and computational studies were performed on these systems, in order to understand the interplay between nuclear and electronic degrees of freedom, which governs non-radiative relaxation pathways. Despite these studies, their ultrafast vibrational dynamics following photoexcitation is not fully resolved. In this work, we carried out a theoretical and computational study of the photoisomerization pathway of a second-generation molecular rotor (CPNY-F) [3]. Our approach, grounded in density functional theory (DFT) and its time-dependent version (TD-DFT) [4,5], combined with ab-initio molecular dynamics (AIMD) simulations [6-10] in both the ground and excited electronic states, along with the wavelet transform analysis [11,12], allowed us to map the evolution of key vibrational modes and identify those responsible for tuning electronic relaxation. Our simulations uncover the key role of transient vibrational dynamics in shaping the photorelaxation of CPNY-F in solution. Specific low-frequency modes, including torsions and pyramidalizations, modulate the emission properties and control access to non-radiative decay pathways. This work establishes a direct link between time-resolved vibrational activity and molecular function, offering a mechanistic basis for the design of efficient light-responsive systems.

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EuCompChem2025 – SaettaClara – Oral

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Single-Atom Catalysts on Goldene

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In single-atom catalysis, the interaction between isolated metal atoms and the supporting matrix plays a pivotal role in determining the stability and reactivity of the system. This has driven the search for novel supporting materials, particularly 2D materials, where graphene has been the predominant choice. Simultaneously, increasing attention is being given to Single-Atom Alloys (SAAs)[1], a subclass of Single-Atom Catalysts (SACs) where the supporting matrix is a metal itself. Recently, Kashiwaya et al.[2] reported the synthesis of goldene, a self-standing 2D monolayer of Au(111) described as the gold analogue of graphene. Motivated by this breakthrough, we explored a new class of SACs consisting of transition metal (TM) atoms stabilized on goldene. The atomistic nature of Au-ene requires simulations, where we rely on VASP with a PBE+U functional.[3,4] Through electronic structure calculations, we identified several systems that remain stable under both reducing and oxidizing conditions.[5] We then investigated their catalytic performance in the hydrogen evolution reaction (HER) and oxygen evolution reaction (OER), discovering that certain TM-goldene systems exhibit promising activity, with reactivity significantly different from the same TMs supported on bulk Au(111). Our analysis included a comprehensive evaluation of potential reaction intermediates, extending beyond the conventional species typically assumed in HER and OER.[6] This study provides strong theoretical evidence that SACs embedded in goldene could offer promising stability and catalytic reactivity.

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EuCompChem2025 – Samuele-Botticelli – Oral

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We introduce a new extension of the Mapping Approach to Surface Hopping (MASH) method, called Semifocused MASH (SMASH). To assess its accuracy, we compare SMASH with the Fewest Switches Surface Hopping (FSSH) method, both with and without decoherence corrections, on various molecular systems. Our results show that SMASH reproduces population dynamics with similar accuracy, while significantly reducing unphysical transitions involving large energy gaps. These findings establish SMASH as a viable approach for simulating nonadiabatic molecular dynamics.

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EuCompChem2025 – Sara Balocco – Oral

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Solid oxide fuel cells (SOFCs) and their reversible counterparts, solid oxide electrolyzer cells (SOECs), offer efficient routes for clean energy conversion water splitting and hydrogen storage [1]. However, efficient transport of oxygen ions and electrons in state-of-the-art solid-state electrolytes and electrodes typically requires high temperatures, which limit device durability and slow start-up times. Lowering the operating temperature necessitates advanced electrode materials, particularly mixed ionic-electronic conductors (MIECs) [2]. Among these, perovskite oxides have emerged as promising electrodes for both the oxygen evolution and reduction reactions (OER/ORR), though the efficiency of the two opposite reactions being usually largely different. Sr2Fe1.5Mo0.5O6-δ (SFMO) has attracted attention as a potentially bifunctional system due to its high electronic conductivity, redox-active B-site cations (Fe/Mo), and capacity to accommodate oxygen vacancies. Following previous works [3, 4], in this study, we investigate the impact of cationic substitution on oxygen vacancy formation and migration in SFMO via first-principles calculations, targeting improved oxygen ion transport. Two Fe:Mo ratios (1:1 and Fe-rich 3:1) are considered to assess the effect of B-site composition, while partial substitution of A-site cation (Sr) with smaller (Ca) and larger (Ba) cations at two Sr:Ca:Ba ratio (6:1:1 and 4:2:2) allowed us to probe the role of lattice strain. Structural, electronic and energetic properties are investigated using Density Functional Theory (DFT+U), revealing trends relevant to the optimization of SFMO as a bifunctional electrode material for low-temperature solid oxide technologies.

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EuCompChem2025 – Snezhana Bakalova – Oral Conformations of Model G-quadruplexes

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Conformations of Model G-quadruplexes Snezhana M. Bakalova, Jose Kaneti Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences Acad. G. Bonchev str., Block 9, 1113 Sofia, Bulgaria snezhana.bakallova@orgchm.bas.bg Our simplest model of a G-quadruplex consists of two guanine Hoogsteen-bonded quartets, stacked onto each other and neglects the connecting pentose—phosphate links of DNA or RNA. Amid the two quartets resides a K+, or Na+. The two alkali cations coordinate guanine oxygen atoms in a square antiprism. [1] Thermochemical DFT calculations show this structure is stabilized by more than 100 kcal.mol-1 with respect to isolated component molecules. The great complex stabilization, and its remarkable hydrophobicity, explain the exceptional self-association of guanine-rich strands of RNA or DNA into the noncanonical quadruplex secondary structure. Divalent and higher valence cations might in principle participate in the formation of G-quadruplexes as well. However, our calculations show that even the closest to alkali cations, Mg2+, does not produce the approximate square planar arrangement of G-quartets around the cation. The structure of the putative magnesium quadruplex is computed to have a saddle form instead of square planar.

Our hypothesis is that divalent and transition metal cations, building nonplanar guanine quartet complexes, are not capable of functions served by K+ and Na+ and possibly unwind secondary structures of DNA and RNA. [2] The roles of planar G-quadruplexes are possibly due to the additional stacking mode of interactions with potential ligands, facilitated by the planar guanine quartets, instead of just binding to hydrophilic grooves of canonical NA. This research has been funded by the Bulgarian National Research Fund via grant KP-06-N59/1 of 15.11.2021, and sponsored by grant D01-325/01.12.2023 and Consortium Petascale Supercomputer-Bulgaria and EuroHPC supercomputer.

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EuCompChem2025 – Speziani Michele - Oral

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Title: **Validating DFT predictions of CO_2 adsorption on TiO_2 via FTIR spectroscopy: a path toward efficient catalyst design**

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EuCompChem2025 – Suwala – Oral

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Cytochrome P450-mediated mechanisms play a significant role in drug metabolism, with estimates indicating that 75% of commercially available drugs are metabolized by only 6 of the 57 human CYP enzymes [1]. These heme-containing cytochromes P450 display a broad spectrum of ligand specificity [2], a property enabled in part by the flexible protein region adjacent to the binding site. Consequently, this flexibility challenges docking methodologies that rely on a rigid protein approximation, resulting in reduced reliability [2],[3]. This work [4] evaluates open-source docking engines in a high-throughput manner on a dataset of 128 ligands. We employ four notably different engines: RosettaFold-AllAtoms [5] (rfaa), GalaxyDock2 HEME [6] (gdock), AutoDock VINA [7,8] and GNINA [9]. Redocking and crossdocking simulations were employed to assess the docking protocols. In redocking, the ligand is docked into a protein that possesses the optimal binding conformation, whereas in crossdocking, the ligand is docked into a folded protein lacking the binding-specific conformational information, thereby necessitating adjustments. Consequently, crossdocking offers a more realistic representation of practical applications. To compare the engines, we introduced system-specific metrics focused on the heme iron atom and evaluated model performance using the mean absolute error. We report significant improvement for flexible rfaa full sequence prediction and during the presentation, we will outline our simulation workflow, elaborate on our system-specific metrics, benchmark results, and conclude with a discussion on the current challenges.

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EuCompChem2025 – Titeca – Oral

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Complex absorbing potentials for density functional theory

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Many molecules form a metastable anion that is higher in energy than the neutral ground state. These anions are also known as electronic resonances and are subject to spontaneous decay by ejecting the unbound electron, a process known as autodetachment. As conventional Hermitian quantum mechanics is only able to describe bound electrons, the description of metastable anions is beyond their reach.[1] One possible solution encompasses adding a complex absorbing potential (CAP) to the Hamiltonian, absorbing the diverging tail of the wave function and enabling a bound-state treatment.[2-4] The complex-valued nature of the CAP renders the resulting electronic energy, electron density and derived properties complex valued as well. The real part of the energy is understood in the conventional sense, whereas its imaginary part is directly related to the lifetime of the state.[1] The use of CAP for density functional theory has remained limited so far, comprising only local-density approximation functionals.[5] We present the implementation of CAPs for generalized-gradient approximation functionals, as well as applications to temporary anions of small molecules. Among these are chlorinated ethene derivatives which have been studied extensively before both experimentally and computationally,[6-11] providing us with an excellent case for testing the performance of our methods.

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Evaluating free energy landscape of ATP binding and consequent allostery in the helical bundle domain of pRN1 primase

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Primases are pivotal for DNA replication. Cellular archaeoeukaryotic primases consist of small catalytic and large accessory domains. The catalytic domain cannot synthesize the primer in the absence of accessory domain, which regulate the function of the primases.Analogously, the catalytic domain (Prim_Pol) of the archaeal plasmid primase (pRN1) is activated by a helical bundle domain (HBD) which promotes the synthesis of the dinucleotide. The DNA replication process is propagated by the binding of the DNA template in a sequence-specific manner in the presence of two ATP molecules bound to the HBD. Thus, the active state of the primase is contingent on binding of the two ATP to the HBD. Recent experimental investigations have revealed that the ATP binding allosterically controls the regulatory role of HBD resulting in a large structural change. Further, even though the

binding of two ATP molecules to the HBD is essential for the functioning of the primase, one the ATP is easily exchangeable. Herein, we have carried out atomistic Molecular Dynamics simulations to understand the role of ATP binding and the consequent structural and dynamical effects of the allostery of HBD as well as evaluating the free energies associated with the ATP binding to the HBD using enhanced sampling method.

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Exploring Electronic Structure in Thermally Activated Delayed Fluorescence Emitters Using Wavefunction-based Descriptors

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Thermally activated delayed fluorescence (TADF) systems, including multi-resonance (MR) and inverted singlet-triplet gap (INVEST) emitters, show great potential for applications such as organic light-emitting diodes due to their high emission efficiency. However, accurately predicting their electronic properties remains computationally challenging due to the delicate balance of electronic excited states involved, limiting efficient molecular discovery and design for industrial applications. This study investigates two important aspects of MR/INVEST emitters: their electronic structure and excited-state rate constants. First, we study the relationship between the electronic structure of MR/INVEST emitters and their energy gaps using wavefunction-based descriptors. These descriptors, originally proposed for ionic states, measure the distribution of charges in atomic centers based on the transition density matrix. Here, we directly analyze the transition density matrix connecting the singlet and triplet excited states involved in TADF. Our findings reveal a correlation between the wavefunction descriptor and the energy gap, with smaller (more negative) gaps corresponding to higher descriptor values. The descriptors also distinguish excited states involved in TADF within the triplet manifold, making it a potential cheap measure for identifying molecules with a small singlet-triplet energy gap. Then, we identified the potential deactivation pathways using vibronic calculations. We calculated excited-state decay rate constants, including fluorescence, direct and reverse intersystem crossing (RISC), where we assess the importance of Herzberg-Teller effects and broadening functions, among other parameters. Optimized structures and Hessians are obtained at (TDA)-DFT/CAM-B3LYP, and excitation energies are calculated using SCS-CC2 and ADC(2) to ensure accurate energy values for rate calculations and energy gaps. Overall, the calculated RISC rate constants align well with experimental values, typically within one order of magnitude, with the Herzberg-Teller correction playing a dominant role.

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Functionalization of NU-1000 MOFs with Phosphonate Ligands: An Ab-Initio DFT and NMR Study

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Metal-organic frameworks (**MOFs**) have emerged as a revolutionary class of materials characterized by remarkable versatility and extensive applications across various scientific disciplines. MOFs, composed of metal nodes interconnected by organic linkers, exhibit exceptional tunability, high surface areas, and intriguing porosity. These distinctive attributes confer upon MOFs extraordinary properties, making them highly sought after for diverse applications encompassing gas storage and separation, catalysis, sensing, and drug delivery systems.

Within the diverse range of MOFs, the **NU-1000** structure has attracted significant attention due to its remarkable properties and potential applications across various disciplines. NU-1000 is an exceptionally robust and highly stable MOF characterized by a meticulously defined structure composed of 558 atoms (264 carbon, 180 hydrogen, 96 oxygen, and 18 zirconium) within its unit cell. The deliberate design and synthesis of NU-1000 serve as a platform for investigating the fundamental principles governing MOF behaviour and provide a roadmap for advancing sophisticated functional materials.

In this study, ab-initio density functional theory (**DFT**) calculations were used to investigate the functionalization of the Zr6 cluster-nodes, particularly focusing on their catalytic and reactive properties with phosphonate molecules. The adsorption energies and structural parameters of the NU-1000 structure were examined in the presence of five distinct phosphonate molecules, Fig 1. Nuclear magnetic resonance (**NMR**) spectra simulations are conducted to elucidate the diverse chemical shift ranges that the various atomic reconstructions can exhibit, contingent upon their atomic adsorption (coordination) within each type of 31P NMR. This comprehensive analysis aims to provide an exhaustive overview of each type of Phosphonate molecule. A comparison between the simulated and experimentally measured spectra establishes the reliability of the DFT calculations. This work, conducted as part of the PHOSPORE project, advances the understanding of MOFs and facilitates the tailored design of MOFs for a wide range of applications in catalysis and functional materials.

Figure 1. NU-1000 components and functionalizing molecules: (a) Zr6 node, (b) organic linker. Phosphonate molecules studied: (c) Phenylphosphonic acid, (d) Phenyl di-phosphonic acid, (e) Phenylphosphinic acid, (f) Phenyl di-phosphinic acid, (g) Propylphosphonic acid.

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G-Quadruplexes Spontaneously Bind Small Molecules

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Guanosine-rich tracts of nucleic acids self-assemble into stacks of stable square planar guanine quartets, having specific regulatory roles on their own function. The meaning is, possible stable aggregates of biomolecules control storage and transfer of information potentially involved in complete cell life cycles. [1] Smaller molecules are the human means to interfere with these cycles with medicinal or other purposes. [2] We assumed the stacking mode of association of ligands and G-quadruplexes as the one to provide certain selectivity requisites to expected effect on chosen biological systems. [3, 4, 5] Stabilization of stacked ligand – G-quadruplex aggregates depending on their affinity has the potential of defining quantitative relationships with potentially useful therapeutic propeties.[6] This research has been funded by the Bulgarian National Research Fund via grant KP-06-N59/1 of 15.11.2021; and sponsored by grant D01-325/01.12.2023 and Consortium Petascale Supercomputer-Bulgaria and EuroHPC supercomputer.

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Global and Local Electrophilicity as Measure of Endocrine Disruptor Genotoxicity

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See attachment

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Guiding the Discovery of Single-Atom Catalysts with Quantum Chemical Simulations

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Single Atom Catalysts (SACs) are an emerging frontier in the field.1 Computational chemistry offers a valid framework to access the atomistic details of catalytic processes, to rationalize or even predict novel systems. The state-of-the-art approach to model and to rationalize these objects takes insight from heterogeneous catalysis.2 In this presentation I will discuss the key ingredients to guide the discovery of SACs. SACs can be considered "solid-state" analogues of coordination chemistry compounds,3 which undergo a very different reactivity from solid surfaces. We show that the same can occur on SACs and this has relevant implications to the predictions.4,5 In addition, we propose an approach to predict the stability of SACs under experimental working conditions.6 We show evidence suggesting that self-interaction corrected schemes should be adopted due to the atomic-like character of SACs.7 Density functional theory numerical simulations demonstrate that these ingredients must be considered to provide reliable predictions about the activity of SACs.8 These studies provide an example of the important analogies between the chemistry of SACs and that of coordination compounds. The results underline the key ingredients to be accounted when attempting to provide predictions with computational frameworks, and aspect of dramatic importance to guide the discovery of new SACs.

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High-accuracy QM in life sciences: From drug properties to binding

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Most computational methods for biomolecular modeling rely on empirical parametrization, limiting their predictive power and applicability. This challenge is particularly pronounced for complex biomolecular targets such as RNA, metalloproteins, and targets for covalent binding, which often fall outside the applicability domain of standard force fields and require extensive parametrization efforts. In this talk, we introduce a new computational approach that enables the accurate calculation of interaction energies between fragments of ligands and fragments of the target's active site. This method builds upon the DLPNO-CCSD(T) framework, leveraging recent algorithmic advancements that enhance both accuracy and efficiency.[1, 2] By systematically decomposing the interaction energy, we provide detailed insights into the nature of ligand-target binding, identifying key interactions that drive molecular recognition. We demonstrate the power of this approach through applications to biomolecular systems, including protein-ligand and RNA-ligand interactions. By dissecting the energetic contributions of specific fragments and functional groups, we offer a deeper understanding of binding mechanisms, which can be directly applied to rational drug design and biomolecular engineering. Additionally, we discuss best practices for the method's application in real-world biochemical studies. This new fragment-based interaction energy analysis provides a valuable tool for deciphering complex biomolecular interactions, offering both high accuracy and practical applicability in drug discovery and structural biology.

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How dispersion interactions at the excited state can tune photochromism of embedded chromophores?

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The importance of dispersion forces for structural stability, molecular recognition, reactivity, and catalytic properties in molecular systems, from materials to biology, is well recognized. For instance, the relaxation dynamics of the initial excited state involved in the photoisomerization process of chromophores are highly influenced by their surrounding environment. [1] Since computational schemes exclusively accounting for the effect of the protein atomic charges can lead to a qualitatively wrong picture, [2] modeling a responsive protein environment is fundamental to successfully capture its tuning effects on the chromophore. However, our current knowledge of how dispersion affects excited chromophores interacting with the surrounding environment remains limited. [3] Current multiscale quantum/classical models that employ an atomistic description of the environment are generally based on electrostatic or polarizable embedding protocols and dispersion is described using Lennard-Jones or other empirical models. In this talk, we introduce a customized state-specific model designed specifically to investigate excited systems using a quantum/classical hybrid multiscale protocol [4]: the atomistic polarizable environment that includes dispersive interactions responds to the excited state electron density of the chromophore, and we call this model QM/MMpol-cLR3 [7]. Here we show that QM/MMpol-cLR3 is able to accurately capture solvatochromic shifts in two paradigmatic systems where dispersive interactions with the environment prevail, azulene and bacteriochlorophyll a (BChl a) in low polarity solution. Our analysis, surprising, indicates a different origin for dispersion shifts in these two cases. Finally, we apply the model to the BChl a pigments of LH2 of purple bacteria, showing that heterogeneities in the atomistic environment led to significantly different dispersion shifts in the BChl pigment.

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Identification of new druggable binding sites of Sars-Cov-2 nsp10, nsp14, and nsp16 proteins by using computational alanine scanning mutagenesis

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SARS-CoV-2 is the etiological agent for the novel coronavirus disease 2019 (COVID- 19) global pandemic. Coronavirus replicates in host cell cytoplasm via a large membrane-associated RNA replication/transcription machinery comprising at least sixteen virus-encoded non-structural proteins (nsp1 to nsp16) [1]. Among non-structural proteins nsp10, nsp14 and nsp16 are the key components of RNA methylation process [2-4]. Accordingly, the design of peptide and peptidomimetics capable of inhibiting the interaction of nsp10 with its partner proteins nsp14 and/or nsp16 represents a promising approach for the development of new anti-viral drugs. In the frame of a multidisciplinary project (PRIN2022 Prot. 2022MBK24T), in order to identify the druggable binding sites of Sars-Cov-2 nsp10, nsp14, and nsp16 proteins, we performed hotspot prediction by means of computational alanine scanning (CAS) mutagenesis experiments on all available experimentally determined Sars-CoV-2 nsp10, nsp14, and nsp16 structures. The structures were clustered according to the protein conformational/functional state and the effect of each mutation on the binding affinity (mutation energy, ΔΔGmut) was calculated together with the root means square fluctuation (RMSF) value of each predicted hot spot residue. The predicted hot regions may include binding sites for alternative or simultaneous ligands, according to the protein functional state, providing important information to drive the design strategy.

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Impact of Applied Electric Bias on Oxygen Reactivity and Oxide Diffusion at Lanthanum Strontium Manganite Electrode Surfaces

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Lanthanum Strontium Manganite (LSM) is a widely used cathode material in solid oxide fuel cells (SOFCs) due to its stability and catalytic activity in oxygen redox reaction (ORR) [1, 2]. Although its surface properties have been extensively studied [3], the effects of electric polarization on chemical reactivity and oxide diffusion remain largely unexplored. In this study, we employ state-of-the-art density functional theory (DFT) calculations with an applied electric field [4] to investigate the structural, electronic, and catalytic properties of the pristine and defective LSM (001) surface, focusing on oxygen migration and vacancy dynamics. We first characterize the surface geometry and electronic structure, assessing how surface reconstitution and oxygen vacancy formation energies influence catalytic activity. To simulate realistic SOFC conditions, we apply an external electric field during both vacancy formation energy calculations and climbing-image nudged elastic band (CI-NEB) simulations to model oxide ion migration. Additionally, we examine the ORR on both pristine and defective LSM surfaces under applied potentials, elucidating the role of vacancies in modulating catalytic activity. Our findings reveal how polarization and surface-specific effects influence oxygen transport and ORR kinetics, providing a more comprehensive picture of LSM's catalytic behavior. By integrating advanced computational techniques with an electrochemical perspective, this work offers valuable insights on the possible modulation of LSM electrocatalytic properties via electric bias, and contributes to the rational design of more efficient cathode materials for application in SOFCs.

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In silico Engineering of Piezoelectric Biomolecular Assemblies

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The ability of certain materials to generate electric charge in response to mechanical stress is derived from their non-centrosymmetric crystal structures, which produces a wide array of applications in sensing, actuation, and energy harvesting1. Organic molecular crystals, characterized by their structural tunability, sustainability, and biocompatibility, present a promising platform for the next generation of piezoelectric materials2. Utilizing crystal engineering and Density Functional Theory (DFT), we have developed CrystalDFT - a structured database of crystals accompanied by predicted electromechanical properties3. This dataset reveals a diverse range of piezoelectric responses, featuring a considerable number of materials exhibiting natural (unpoled) longitudinal piezoelectricity, which is essential for conventional piezoelectric applications. A focused study was also carried out on hydrated organic crystals, performing a high-throughput DFT screening and identifying thirty hydrates with longitudinal piezoelectric coefficients exceeding 10 pC/N, including one material achieving an impressive 386 pC/N. These results underscore the significance of hydrogen bonding in enhancing dipole alignment and facilitating polar crystal phases. These results led us to further investigate structure - property relationships, whereby we designed and synthesized a series of halogenated pyridin-3-ol derivatives (2-X-pyridin-3-ol; where X = Cl, Br, I). These crystals, stabilized by both hydrogen and halogen bonding4, demonstrate high DFT-predicted shear piezoelectric responses of up to 99.19 pC/N. Experimentally-validated shear response of 54–74 pC/N in

were accompanied by longitudinal responses ranging from 5 to 10 pC/N. Overall, these studies showcase the effectiveness of computational screening and molecular design in steering the discovery of high-performance organic piezoelectrics, bridging the gap between theoretical insights and practical applications in the development of sustainable electromechanical materials.

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Indoloindolizines: The Complete Story of a Polycyclic Aromatic Scaffold from Theoretical Design to Organic Field-Effect Transistor Applications

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The development of stable and tunable polycyclic aromatic compounds (PACs) is crucial for the advancement of organic optoelectronics. Conventional PACs, such as acenes, often suffer from poor stability due to photooxidation and oligomerization, which are linked to their frontier molecular orbital energy levels. To address these limitations, we designed and synthesized a new class of π-expanded indoloindolizines by merging indole and indolizine moieties into a single polycyclic framework. We developed a scalable synthetic protocol to produce a wide range of π-expanded derivatives. The structural, electronic, and optical properties of these compounds were extensively characterized. We achieved precise modulation of the electronic structure by controlling the aromaticity of specific rings. Benzannulation at targeted positions allowed fine-tuning of the HOMO–LUMO gap, leading to distinct shifts in the optoelectronic properties. Single-crystal X-ray diffraction confirmed their molecular structures, while theoretical calculations provided insights into the observed experimental trends. These indoloindolizines exhibit vivid colors and fluorescence across the visible spectrum and enhanced stability against photooxidation. Reactivity studies demonstrated high regioselectivity in electrophilic substitutions, highlighting the indole-like behavior of these compounds and opening avenues for further functionalization. To showcase the practical utility of our design rules, we fabricated organic field-effect transistors (OFETs) using the newly developed indoloindolizines, which revealed remarkable performance with ambipolar charge transport properties. Overall, our work establishes indoloindolizines as a promising platform for the development of stable, tunable organic materials for optoelectronic applications. Through rational molecular design, we have provided a new pathway for molecular innovation in organic electronics.

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Instantaneous pKa assessment from molecular dynamics simulations

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We demonstrate the application of our innovative 'instantaneous pK' approach to the molecular dynamics simulation of crystallite models exposed to an acidic solvent environment. For this, the bulk solution properties pH and pK are scrutinized into local aspects and effectively characterized for individual molecules of crystal faces, edges and steps, respectively. To illustrate this concept, we introduce two prototype cases: the acid-induced dissociation of i) calcite and ii) carbamazepine

(CBZ, form III) drugs. We find acid-induced calcite dissociation follows a rather intuitive mechanism, namely the protonation of crystal edges/steps leading to ion-by-ion dissociation of HCO3– and Ca2+ species into water. In contrast, our simulations of CBZ solvation at pH = 3 and pH = 2, respectively, reveal a more complex dissolution behavior. The molecular crystals were found to accommodate a substantial degree of CBZ protonation without drug release to the solvent. Instead, the crystallite edges and corners are re-arranged in favor of a surprisingly stable core–shell structure, featuring a CBZ core and a mixed CBZ/CBZH shell of +0.005 and +0.03 C m–2 surface charge at pH = 3 and pH = 2, respectively. The resulting crystallite models are persistent and even more drastic acidity is needed to enable actual dissociation of CBZH into water.

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Integrated Database of Force-Field Parameters, Experimental Measurements and Molecular Dynamics Simulations as a Tool for Force Field Development

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Molecular Dynamics (MD) simulation is a crucial computational tool for investigating nucleic acids (RNA, DNA), proteins, and other (bio)molecular systems, generating large volumes of data daily. However, the interoperability and reusability of these datasets remain significant challenges.[1] We present IDA (Integrated DAtabase of force fields and datasets from experiments and MD simulations), an innovative platform designed to support a broad range of MD simulation types.[2] IDA accommodates outputs from standard simulations, importance sampling techniques, simulated annealing, and enhanced sampling methods such as replica-exchange approaches. Upon upload, datasets are converted into an internal, standardized format optimized for reuse, enabling users to perform diverse analyses and access results instantly. In addition to simulation data, IDA stores experimental datasets – primarily NMR data – and retrieves relevant information from public databases. A key feature of IDA is its integration of widely used force fields (FFs) in the Universal Molecular Force Field Format (UMFFF). This format includes dedicated files for each molecular type (e.g., RNA, DNA, proteins, solvents, counterions). FF libraries from major MD engines (e.g., AMBER, GROMACS) are automatically converted into UMFFF upon upload and can be exported back into their original formats, ensuring compatibility across platforms. This allows users to initiate new simulations in their preferred MD engine, compare uploaded FF libraries with existing ones, and identify FFs associated with submitted topologies. Unlike existing MD databases,[3] IDA is specifically designed to support force field development by interlinking simulation datasets, experimental data, and FF libraries. It offers a framework for evaluating the performance and accuracy of both established classical non-polarizable FFs and newly developed ones. This integrated environment enables data mining from large, heterogeneous datasets and enhances the predictive power and reliability of MD simulations. Ultimately, IDA aims to facilitate the parameterization of new force fields by providing advanced analytical tools that leverage reweighting techniques and machine learning – both of which rely on accurate, consistent, and well-structured data.

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Interfacial Passivation Between $CsPbI_3$ and Hole Transport Layers: Experimental and Theoretical Insights

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Lead halide perovskites (LHPs) are promising materials for solar cells, offering outstanding optoelectronic properties, low-cost fabrication, and power conversion efficiencies. Among them, caesium lead triiodide ($CsPbI_3$) stands out for its superior thermal stability. However, it remains prone to phase instability, moisture sensitivity, surface defects, and interfacial recombination, which limit performance. Addressing these limitations requires effective interface engineering strategies to optimize charge transport, suppress non-radiative recombination, and enhance material stability. We investigated $CsPbI_3$ interfaces with hole transport layers (HTLs) and passivants using both computational and experimental approaches. Through Density Functional Theory (DFT) calculations we provided insights into interfacial adhesion and electronic structure modifications, which are critical for optimizing device design. Experimentally, we explored interface passivation using P3HT, OABr, and OAI to enhance interfacial quality and improve optoelectronic properties. We analyzed the interaction of $CsPbI_3$ with HTLs such as 2-PACz, PTAA, and Spiro-OMeTAD, as well as the passivant P3HT. Preliminary DFT results indicate that $CsPbI_3$ exhibits stronger interaction with Spiro-OMeTAD that is chosen as HTL in fabricated devices . Experimentally, we find that passivants such as OABr and OAI enhance photoluminescence, suggesting a reduction in non-radiative recombination, consistent with previous studies on similar perovskite compositions. This combined computational and experimental approach provides insights into interface engineering strategies for $CsPbI_3$ perovskite solar cells.

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Interpretable Models for Targeted CO_2 Membrane Design

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The design of polymer membranes with high CO_2 selectivity is essential for advancing gas separation technologies and carbon capture [1]. In this work, we develop highly interpretable machine learning models to predict the permeability of polymer membranes—particularly towards CO_2 and N_2—based on the chemical structure of their repeat units. A key challenge in this field is the scarcity and incompleteness of available permeability data[2][3]. To address this, we implemented data imputation strategies that significantly reduced error, especially when including crucial experimental

parameters such as measurement temperature and pressure. The models were trained on permeability data for six gases (He, H_2, O_2, N_2, CH_4, CO_2), and achieved good predictive performance for CO_2 and N_2 permeability.

As molecular descriptors, we employed MACCS keys, which yielded promising results despite their simplicity. The machine learning models are based on decision tree architectures, with the XGBoost regressor standing out due to its high accuracy and computational efficiency. We are currently evaluating the integration of more complex molecular fingerprints and plan to apply feature selection to retain only the most informative descriptors. In parallel, we are expanding our dataset by incorporating additional polymer entries to enhance the applicability domain of the models. Overall, this work supports a data-driven and interpretable approach to targeted membrane design for efficient CO_2 capture.

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Investigating Anti-Kasha dynamics with quantum-mechanically derived force-fields and non-adiabatic molecular dynamics.

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It was recently reported that Pt quinoxdt dithiolene complexes show a photochemical response, which markedly depends on the excitation wavelength revealing an anti-Kasha (AK) behavior. AK response originates from a competition between the functional process in upper photo-excited states and internal conversion towards the lowest excited state of a given multiplicity. Experimental evidence shows that internal conversion, which is typically a few femtoseconds, is in these systems astonishingly slowed down to 1-2 ps.[1-2] In addition, the excitation to higher excited states allows the molecular system to access long-lived conformational configurations not accessible from the lowest excited state. Such systems have raised considerable interest because of the possibility to conceive multi-response molecular devices or to explore novel photochemical routes. This rich body of experimental evidence motivated us to start a computational study based on time-dependent density functional theory aimed at clarifying several unanswered questions: the cause of such low efficient internal conversion, illustrating the complete photocycle including possible intermediated states, revealing is the structure of the long-lived configuration. In this contribution, we will explore the excited state dynamics using two complementary approaches: Surface Hopping including Arbitrary Couplings (SHARC)[3-4] and quantum-derived force field Joyce[5-7]. The former allows for tracking down non-adiabatic molecular dynamics of the earliest moments after excitation (for instance Figure 1 shows the total singlet and triplet state population from different excited states). The latter will allow us to explore longer time scales and adopt a statistical approach.

Figure 1: Non adiabatic molecular dynamics from states S4 and S10, grouped by total Singlet and Triplet populations, calculated by SHARC. According to experimental and computational evidence, the excitation of S4 and S10 induce Kasha and anti-Kasha responses from the system, respectively. The latter is evident from the remarkable extension of the single states population.

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Iron Phthalocyanine Electrocatalysis in Aqueous Media: Is Water Simply a Solvent?

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Iron Phthalocyanine Electrocatalysis in Aqueous Media: Is Water Simply a Solvent? Alessandro Bonardia, Shuai Xub, Giovanni Di Libertoa, Gianfranco Pacchionia aUniversità degli Studi di Milano-Bicocca, Dipartimento di Scienza dei Materiali, Via Roberto Cozzi 55, 20125 Milan, Italy bSchool of Water and Environment, Chang'an University, 710064, Xi'an, P.R. China alessandro.bonardi@unimib.it The accurate modeling of redox processes in single-atom catalysts (SACs) remains a major challenge in computational electrocatalysis, particularly when dealing with transition metals like iron[1]. Iron phthalocyanine (FePc) is widely employed as a molecular analogue for Fe-based SACs supported on carbon- based materials, such as nitrogen-doped graphene[2]. While experimental studies clearly indicate a Fe(II)/Fe(III) redox transition occurring under oxidative conditions, standard density functional theory (DFT) calculations often fail to reproduce this behavior, incorrectly localizing the oxidation on the ligand rather than the metal center[3,4]. In this work, we investigate the origin of this discrepancy through a systematic series of DFT calculations, employing hybrid functionals and explicit solvation models. Our results show that the root cause of the divergence between theoretical and experimental results does not lie in the functional choice but in the representation of the iron coordination environment. By introducing one or two water molecules as axial ligands, we observe a significant shift in the relative energies of the Fe-centered and ligand-centered orbitals, leading to the correct prediction of an Fe oxidation. This modification not only recovers the correct qualitative interpretation of the oxidation process, but also leads to calculated redox potentials that match experimental values within 0.1–0.2 V. These findings underline the essential role of water, not merely as a bulk solvent, but as a direct ligand capable of modulating the electronic structure and, thus, reactivity of the active site. Beyond FePc, the implications extend to a broad class of Fe-based SACs, suggesting that any reliable computational study must explicitly account for solvent coordination effects. This work offers a practical guideline for improving the predictive power of quantum chemical models in electrocatalysis, highlighting that: 1) redox properties of transition metal complexes and graphene-based SACs are strongly influenced by the coordination environment, including solvent molecules; and 2) modelling of those systems requires the inclusion of water to correctly describe their redox behavior. [1] B. Chang, S. Wu, Y. Wang, T. Sun, Z. Cheng, Nanoscale Horiz., 2022, 7 (11), 1340-1387. [2] S. Ye, F. Liu, F. She, J. Chen, D. Zhang, A. Kumatani, H. Shiku, L. Wei, H. Li, Angewandte Chemie, 2025, 137 (23). [3] M. S. Liao, J. D. Watts, M. J. Huang, Journal of Physical Chemistry A, 2005, 109 (35), 7988-8000. [4] C. J. Ziegler, V. N. Nemykin, Dalton Transactions, 2023, 52 (43), 15647-15655.

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Lighting Up Non-Canonical DNA: Theoretical Insights into Photodriven Mechanisms

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Since the 80s, when Ned Seeman [1] first envisioned the idea of building artificial structures using DNA, the field of DNA nanotechnology [2] has grown exponentially, especially due to the potential of combining light and DNA in applications beneficial to humans, such as phototherapy and optoelectronics. However, two main factors have limited its expansion: on one hand, canonical nucleobases do not exhibit optimal optical properties (such as fluorescence or energy transfer), and on the other, the theoretical description of such complex mechanisms in such large structures has been challenging.[3] With this aim in mind, we have characterized the main excited-state processes triggered by light absorption in non-canonical DNA structures. Specifically, we have modelled guanine quadruplexes (G4), both in solution and when interacting with photoswitches, as well as I-motifs and metallo-DNAs, using molecular dynamics and quantum chemical calculations.(4, 5) Interestingly, some of these structures exhibit behaviour distinct from that of canonical DNA strands, such as enhanced fluorescence or the charge-transfer mediated population of characteristic triplet excited states, boosting their potential biomedical or technological applications.

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Locally Concentrated Electrolytes for Al-S Batteries, a Molecular Simulation Investigation

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Locally Concentrated Electrolytes for Al-S Batteries, a Molecular Simulation Investigation

Aluminum-sulfur (Al-S) batteries are emerging as a promising alternative to lithium-ion (Li-ion) batteries due to their lower cost, safety, and environmental advantages[1-2]. Aluminum, being abundant and less reactive than lithium, enhances battery stability and affordability, making Al-S batteries suitable for energy storage[3]. However, challenges like electrolyte viscosity and aluminum reactivity must be addressed. Room- temperature ionic liquids and deep eutectic solvents (DES) based on AlCl3 show potential for improving electrolyte performance. Adjusting the AlCl3 ratio in these electrolytes influences ionic composition[4], crucial for efficient aluminum plating and stripping. The addition of low-viscosity cosolvents like 1,2- difluorobenzene (dFBn) helps mitigate viscosity issues, enhancing battery efficiency.

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ML-enhanced integral equation theory for solvent-mediated effective potentials

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Solvation effects on thermodynamic properties of chemical systems can be captured by integrating-out the solvent degrees of freedom for a given geometric solute configuration to yield an effective solvent-mediated free energy surface ("potential of mean force", PMF). Based on this philosophy, a plethora of "implicit solvation models" has emerged over the years, from continuum electrostatics approaches for classical and quantum-electronic molecular solutes, which essentially address the solvent integration task iteratively for each spatial solute configuration, up to very efficient non-iterative approaches such as the Generalized Born (GB) model for the electrostatic component of the PMF. However, increasing computational efficiency typically goes hand in hand with reduced accuracy.

An implicit iterative solvation approach that can be parametrized to produce highly accurate free energies is provided by integral equation theory, namely the "3D reference interaction site model" (3D RISM) and its extension to quantum-electronic solutes, "embedded cluster RISM" (EC-RISM), which we developed over the past years for aqueous and non-aqueous solvents.1-6 By accounting for solvent granularity and directional solute-solvent interactions, EC-RISM can be tuned to surpass implicit solvation approaches in terms of quantitative agreement with experiment, as is demonstrated for chemical reaction thermodynamics in solution and spectroscopic observables.

Further progress is possible by using message passing neural networks (MPNN) with special atom-local RISM-derived descriptors, as is demonstrated on predictive calculations of hydration and tautomerization free energies in aqueous solution. This provides a route towards using pure EC-RISM and, as a perspective, MPNN-EC-RISM data as reference for training fast and accurate, non-iterative machine learning free energy potentials (MLFEP), for which first results are presented. A crucial factor in this context is the limited experimental reference data availability and their possibly large uncertainty, particularly for instance for aqueous tautomerization reaction thermodynamics. A purely theory-driven approach for identifying unreliable experimental data points based on a consistency analysis of diverse methods is discussed.

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Machine Learning potentials for Amorphous Solid Electrolytes in Sodium All-Solid-State Batteries: investigating the Mixed Glass Former Effect

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The topic of solid electrolytes for energy storage systems is both fascinating and crucial from an environmental and sustainability perspective. Liquid electrolytes, commonly made from lithium compounds, face low stability and high cost. Furthermore, lithium extraction is not sustainable for the environment or local communities. Thus, researchers are eager to develop safer and more ecological alternatives. All-solid-state sodium batteries (ASSSBs) are promising candidates for grid-scale energy storage, but there is still much to understand about the electrochemical stability of solid electrolytes with sodium. Amorphous sodium phosphorus sulfides (NPS) show a high critical current density, but they suffer electrochemical instability with electrode materials. To overcome this limitation, while maintaining the conduction properties, the mixed glass former (MGF) effect can be used partially substituting phosphorous with silicon (NPSiS). Previous experimental studies on these compositions, such as those by Shastri et al. [1], have shown that modifying the ratio of these network formers can significantly influence conductivity, but the relationship between their composition, structure, and properties at the atomic level remains unclear. Molecular Dynamics is the most effective computational method to investigate the properties of NPS and NPSiS solid electrolytes: however, studies on these systems are hindered by the lack of classical interatomic potentials, while the high computational cost of ab initio methods limits their feasibility for extensive structural analysis. Machine Learning techniques, instead, offer a promising solution to develop new reliable potentials for various materials. In this work, we developed Machine Learning interatomic potentials (MLIPs) trained on NPSiS compositions. The developed MLIP was used to study how the composition of sodium-based amorphous electrolytes affects their atomic structure and ionic conductivity focusing on the mixed glass former effect given by silicon. The studied compositions are y Na_2S + (1−y) [x SiS_2 + (1−x) PS] with x = 0.5 or 0.67 and y varying from 0.1 to 0.9, for which experimental data are available [1]. This allowed us to identify also which structural features promote or hinder sodium ions diffusion within solid-state electrolytes, helping the understanding of the composition-structure-conductivity relationship, which is fundamental to efficiently develop new amorphous electrolytes with tailored properties. [1] A. Shastri, D. Watson, Q. Ding, Y. Furukawa, S.W. Martin, Solid State Ionics, 2019, 340, 115013. [2] M. Bertani and A. Pedone, J. Phys. Chem. C, under revision.

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Mechanistic Insights into the Fe(II)-Catalyzed ROP of Challenging Aliphatic Lactones: A DFT Study

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Mechanistic Insights into the Fe(II)-Catalyzed ROP of Challenging Aliphatic Lactones: A DFT Study

The growing concern over plastic pollution and microplastic contamination has intensified efforts to identify sustainable alternatives to fossil-derived polymers. In this context, aliphatic polyesters from cyclic esters (lactones) have emerged as promising candidates, particularly when designed for biodegradability or chemical recycling to monomer (CRM) [1]. While efficient polymerization strategies exist for strained monomers like lactide and ε-caprolactone, δ-substituted δ-lactones remain poorly explored due to their low ring strain and substitution at the δ-position, which limit reactivity. Nevertheless, these monomers are naturally occurring, commercially available, and widely used in the flavor and fragrance industries, making them attractive for sustainable materials research. Recently, new highly active three-coordinate pyridylamido Fe(II) complexes (Fig1a) have been reported for the ring-opening polymerization (ROP) of lactide and ε-caprolactone[2,3]. In this study, we extend their application to the ROP of more challenging monomers, such as δ-hexalactone, δ-nonalactone, δ-undecalactone, and ε-decalactone (in Fig1b the investigated monomers). A compre-

hensive Density Functional Theory (DFT) investigation was performed to explore the polymerization mechanisms promoted by the iron catalyst. The study evaluates various mechanistic pathways (Fig1c), including the role of the alcohol as an initiator and the potential formation of dimeric catalytic species. Differences in monomer reactivity are rationalized based on the side-chain length and steric effects. These insights contribute to understanding structure–reactivity relationships in iron-based ROP catalysis and support the design of next-generation recyclable polyesters.

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Metal affinity/selectivity of benzamide-based inhibitors of histone deacetylase: a DFT study

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Histone deacetylase inhibitors (HDACi) have demonstrated emerging therapeutic potential in cancer treatment by inhibiting the activity of histone deacetylase enzymes (HDACs)1. Currently, only a limited number of HDACi have been approved by drug regulators for use as anticancer drugs. SAHA, a hydroxamic acid, was the first drug approved in 2007 by the FDA as an anticancer agent2. Chidamide 3, a benzamide, was approved by drug regulators in China in 2014 and in Japan in 2021 for the treatment of peripheral T-cell lymphoma. Several other benzamides, including mocetinostat, entinostat, and zabadinostat 4,5, are currently undergoing clinical trials. Benzamides, as zinc-dependent inhibitors of histone deacetylases (HDACi), bind to the active site of the HDAC enzyme. Even though these molecules are chemically different, they all work in a similar way: their functional group binds to the metal ion in the active site of the histone deacetylase enzyme. Several important questions regarding the physicochemical properties and metal affinities/selectivities of the benzamide-based HDACi (Chidamide, Mocetinostat, Entinostat, and Zabadinostat) considered in this study remain unanswered. First, what is the preferred geometry of the studied benzamide-based HDACi? Second, how do the structural factors influence the affinity/selectivity of these molecules when binding to essential metal cations? Last, but not least, what is the preferred mode of binding to the metal ions? The study utilized density functional theory calculations and polarizable continuum model computations to study the physicochemical properties of the selected benzamide-based HDACi. The geometry of selected benzamide-based HDACi, along with their binding patterns and metal affinity/selectivity, was studied. Furthermore, the results obtained revealed the key factors that govern their metal-ligating capabilities and the thermodynamics of the binding of benzamide-based HDACi to different biogenic metal ions (Zn2+, Fe2+, and Mg2+) providing insights for improving their metal-ligating properties.

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Methanol Desorption from ZnO Surfaces: Key Factors and Catalytic Insights

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The catalytic hydrogenation of CO_2 to methanol is a pivotal reaction in emerging carbon-capture-and-utilisation schemes,[1] yet its overall rate can be limited by how efficiently methanol can disengage from the oxide support. Although ZnO is the industrially preferred promoter for Cu-based catalysts, the atomistic factors that control methanol binding, surface diffusion, and final desorption on different ZnO facets—and in the presence of water or oxygen vacancies—remain poorly quantified in-operando conditions. A predictive picture is hampered by the wide disparity of relevant timescales, ranging from sub-picosecond bond vibrations to second-long rare events.

Here we combine ab-initio molecular dynamics with active-learning neural-network potentials and enhanced-sampling simulations to quantify dissociation, diffusion, and desorption of CH_3OH on the four most stable ZnO facets—(100), (110), (111), and $(00\bar{1})$.[2]

The $(00\bar{1})$ surface proves the least retentive: methanol adsorbs weakly and departs rapidly. Both (110) and (100) facets stabilise adsorbed methanol through a cooperative Zn–O–H hydrogen-bond network, leading to slower release and hindered surface diffusion. The (111) facet behaves differently again, undergoing spontaneous reconstruction that favours methanol dissociation into methoxy and hydrogen, effectively locking the fragment to the surface and suppressing molecular desorption. From these models we then inquired the dissociation/recombination of the methanol to/from methoxy, the diffusion on each surface of the molecules, (see Figure 1) and the effect provided by the presence of water molecules on each surface-type.

These facet-resolved free-energy landscapes and rate constants provide a microscopic rationale for the activity on ZnO-based catalysts and offer quantitative targets for tailoring ZnO morphology, defect density, and reaction environment to optimize methanol synthesis.

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Mixed Halide Effects on Structure and Electronic Properties in Perovskite-Inspired Materials

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Lead halide perovskites have garnered significant attention for optoelectronic applications due to their outstanding properties, such as high absorption coefficients, tuneable bandgaps, long charge carrier lifetimes, and excellent defect tolerance. However, their widespread use is hindered by the toxicity of lead, prompting the search for environmentally benign alternatives. Bismuth-based perovskite-inspired materials have emerged as promising lead-free candidates, offering comparable electronic characteristics and enhanced stability [1].

In this study, we employ density functional theory (DFT) to systematically investigate the structural, electronic, and carrier transport properties of the mixed-halide system Cs3Bi2(I1-xBrx)9 exploring several compositions with x ranging from 0 to 1. We predict a composition-driven phase transition from the iodine-rich P63/mmc phase to the bromine-rich P-3m1 phase occurring near 42% Br content. The P63/mmc structure is found to be stable below ˜39% Br, while the P-3m1 phase becomes energetically favourable above ˜44% Br, in agreement with experimental trends [2].

The bandgap generally increases with higher Br concentrations, consistent with experimental observations. Effective mass calculations reveal that electrons consistently have lower effective masses than holes across all compositions, indicating higher electron mobility. Additionally, hole localization becomes more pronounced with increased Br content, likely due to self-trapping effects associated with Br atoms, which could impact overall charge transport [3].

These findings highlight the pivotal role of halide composition in tuning the phase stability, electronic structure, and charge transport properties of Bi-based perovskite-inspired materials. The insights provided here are instrumental for the rational design and optimization of lead-free materials for next-generation photovoltaic and photocatalytic applications.

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Modeling vertical excitation energies in solution using the Density matrix renormalization group/Fluctuating charges approach

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Modeling vertical excitation energies in solution using the Density matrix renormalization group/Fluctuating charges approach

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The investigation of electronic transitions in solution is a useful tool to gather information on systems involved in important biological or chemical processes. However, solvated systems are composed of a very large number of atoms. Therefore, from a computational point of view, a reasonable way to address this is to resort to multiscale modeling [1,2]. Among these methods, hybrid Quantum Mechanics (QM)/Molecular Mechanics (MM) methods have proven to be particularly successful [3,4] because they are capable of describing specific solute-solvent interactions, such as hydrogen bonding patterns, that can play a role in shaping spectroscopic signals [5]. Furthermore, many interesting solvated systems comprise solute with complex electronic structures, e.g. conjugated systems, chromophores in photosensitive proteins or transition metal enzymes. These complex electronic structures need to be described by an accurate multiconfigurational QM approach. To this purpose, we present a QM/MM strategy based on the coupling of the Density matrix renormalization group (DMRG) method [6,7] to the Fluctuating Charges (FQ) force field (DMRG/FQ) [9]. This is based on the framework of our recent CASSCF/FQ [8] method and permits treating large solute molecules using active spaces of more than 20 electrons in 20 orbitals. The resulting DMRG/FQ method is then applied to the calculation of vertical excitation energies and solvatochromic shifts of a set of molecules in solution. A detailed comparison to reference and experimental data is made. This work paves the way for future applications on biological systems.

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Modelling Soil-release Polymers on Fabric Surfaces: A Multiscale Study using DPD and Enhanced Sampling MD Simulations

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Soil release polymers (SRPs) are amphiphilic polymers found in modern detergent formulations, whose primary operations are to modify synthetic fabric surfaces to allow water transport and to prevent the redeposition of oil-based soil particles during the wash cycle.1 In this work, SRPs are modelled at fabric surface-water interfaces using dissipative particle dynamics (DPD) and Hamiltonian replica exchange molecular dynamics (H-REMD), the latter of which lowers energy barriers to allow us to explore conformations that are outside of the timescale of conventional MD.2

DPD is a mesoscale, coarse-grained modelling technique, that falls on length and time scales somewhere between atomistic simulations and macroscale simulations.3 This makes it ideal for observing mesoscale phenomena at longer timescales, while still retaining some chemical detail. We describe the process of parametrising and validating these simulations and explore how changes in polymer

structure affect surface binding and solution aggregation. Combined with enhanced sampling methods (H-REMD and umbrella sampling), we can accurately extract free energy curves to gain a quantitative understanding of the surface-polymer interactions.4 By collaborating with synthetic chemists and industry partners, this work will help in screening for more effective greener candidates.

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Modelling of a Biocatalytic Unit for Efficient CO2 Conversion to Formate Based on Enzyme Crystal

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Global warming and climate change are directly related to increased atmospheric CO2 levels, which are currently higher than ever and continue to growth. Current strategies for CO2 reduction are mainly emission mitigation strategies, so that the rate of increase of global CO2 emissions from fossil resource utilization has slowed recently. However, utilizing CO2 as a carbon source for production of high-in-demand chemicals could represent a win-win strategy by both replenishing fossil-fuel processes and simultaneously assisting in mitigating CO2 accumulation and climate change. In the field of enzymatic reactions, formate dehydrogenase (FDH), that catalyses the interconversion between CO2 and formic acid through an oxidoreductive process, could represent a suitable biomimetic catalyst for effective and sustainable CO2 fixation and direct conversion into formate. The overall goal is to develop a new bio-enabled material capable of effective conversion of CO2 to alternative fuels and chemicals, where the complex chemical processes carried out in bacteria or living cells are reproduced by a biomimetic artificial system composed of individual enzymes in their active form, closely packed to reach the highest possible density and embedded into bacterial-like coats able to preserve the enzymes in working conditions. The crystallographic structures derived from different organisms with similar sequence, but essentially different characteristics, were examined; the most significant difference concerns the presence (metal-dependent) or absence (metal-independent) of metal in the cavity. Among the metal-containing FDHs, five were found to be unaffected by the presence of oxygen. Among them, that with pdb entry 8J83 is the only one characterized structurally by crystallography and has an alpha domain containing the active site and a beta domain, which serves for NAD docking and is called a diaphorase unit.[1] The metal ion, W, in the active site is coordinated by six ligands in a trigonal prismatic geometry. The rectangular base of the prism is formed by the two dithiolene groups of the bis-MGD (metal-binding pterin guanine dinucleotide cofactor). The other two sites are ligated by the cysteine sulfur and oxygen (Figure 1). A series of alpha domain variants was analysed to select that exhibiting the best compatibility with the beta domain of the 8j83 protein and then, exploiting the system for in silico study of the catalytic process for CO2 conversion into formate.

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Molecular Chameleon: How a Ligand Adapts to Double-Stranded and G4 DNA with Distinct Fluorescence Signatures

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DNA can adopt a variety of secondary structures beyond the canonical double-stranded form (ds-DNA). Among these, the guanine quadruplex (G4) has been widely studied for its role in gene expression and cancer, as G4s are found in many oncogenic promoters and at telomeres [1]. This has driven efforts to detect and track G4s in cells using near-infrared fluorescent probes [2]. A key example is the tripodal quinone-cyanine dye [QCy(MeBT)$_3$], featuring three N-methylbenzothiazolium cations linked by dimethine chains, which was the first reported switch-on fluorescent probe able to distinguish between dsDNA and G4 through different fluorescence colors [3]. However, the mechanisms behind this unique behavior remain largely unclear.

In this study, multiscale modeling is employed to rationalize the photophysical properties of QCy(MeBT)$_3$. Different conformers, generated by rotation around flexible bonds, were first identified, and a PCM corrected linear response study revealed a wide range of emission wavelengths depending on their conformation. Rigid molecular docking was then performed to obtain unbiased starting structures for molecular dynamics (MD) simulations, with the force field parametrized through ab-initio calculations. Binding affinities were estimated using MMPBSA, and the photophysics of the best-binding conformers was investigated at the QM/MM TDDFT level by extracting a statistically significant number of MD snapshots. Notably, the best dsDNA-interacting conformers showed lower emission wavelengths than G4-interacting ones, in excellent agreement with experiments. Moreover, the minor groove binding mode observed with dsDNA matched previous studies on an analogous ligand [4]. Finally, MD trajectory analysis is used to investigate the origins of the conformers' differential stability between dsDNA and G4, potentially helping the design of new ligands.

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Molecular Dynamics Investigation of the Self-Assembly of Two-Antennary Oligoglycine in Aqueous Solution

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Two-antennary oligoglycines represent a novel class of biocompatible amphiphilic compounds, rationally designed through preliminary molecular modelling [1]. These molecules consist of a central hydrophobic alkyl core bound to two hydrophilic oligoglycine chains, forming a symmetric bola-amphiphilic structure. In aqueous media, they spontaneously assemble into stable supramolecular structures called tectomers [2]. The size and shape of these assemblies can be tuned by adjusting conditions such as pH, temperature, ionic strength, and oligoglycines concentration [2,3]. Due to their unique structure and tunable properties, two-antennary oligoglycines bear great potential for applications in various fields such as nanotechnology, pharmaceutics, and medicine. Despite the growing experimental interest, their molecular-level self-assembly behaviour remains poorly understood from a theoretical point of view. In this work, we present an atomistic molecular dynamics study of the conduct of diantennary oligoglycine in bulk aqueous media solution. The self-assembly process of the amphiphilic molecule is thoroughly investigated, with detailed characterisation of the resulting supramolecular entities in terms of size and morphology. Key features such as self-assembly kinetics and secondary structure formation are analysed. The simulations reveal that within 500 ns the oligoglycine molecules form spherical aggregates. The tectomers are stabilised predominantly by intermolecular hydrogen bonds between the oligoglycine segments, accompanied by a reduction in intramolecular hydrogen bonding. Additionally, the zeta potential of the formed tectomers is calculated and is found to be in good agreement with available experimental data. These findings

contribute to deeper understanding of the bulk self-assembly of two-antennary oligoglycines and offer new perspectives for their potential applications.

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Molecular Dynamics Study of Uranium Extraction from TBP/Dodecane Solutions Using Amidoxime-Grafted Silica

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The production of energy from nuclear sources generates a variety of radioactive wastes, and in particular Radioactive Liquid Organic Waste (RLOW). RLOW contains a wide range of organic molecules and radioactive species along with halogens, heavy metals, nitrates, carbonates, sulfates and other components. To be compatible with existing waste management systems, RLOW must undergo pre-treatment. Current treatment methods of RLOW consists in incineration-vitrification and hydrothermal oxidation, and complementary methods are being researched in order to selectively remove the radioactive species from the liquids.

Recent studies have demonstrated that functionalized silica materials exhibit strong potential for uranium extraction from acidic sulfate solutions via liquid-solid extraction [1,2]. Molecular dynamics simulations have contributed to giving insights on phenomena surrounding the speciation of uranium by ligands grafted onto mesoporous silica at the aqueous phase/solid interface [3].

Extending our study to organic-phase systems, we simulate a TBP/dodecane solution of uranyl nitrate in contact with amidoxime-grafted silica. The objective is to examine the speciation behavior of uranyl cations at the organic-phase/solid interface and to assess the influence of water and acid in the solvent phase. A key challenge lies in developing a simplified yet realistic surface model while incorporating polarization effects in classical molecular dynamics simulations. With our results we intend to offer insight into uranium coordination and extraction mechanisms in organic medium relevant to RLOW treatment.

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Molecular Simulation of Graphene Oxide-Ionic Liquid Electrolyte Interface in Sodium-Ion Batteries Using DFTB-MD

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Molecular Simulation of Graphene Oxide-Ionic Liquid Electrolyte Interface in Sodium-Ion Batteries Using DFTB-MD Mirella Fonda Maahurya,b, Aditya Wibawa Saktib,c, Hiromi Nakaib aChemistry

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Since the widely accessible and abundant sodium-ion batteries are available, they can be used as a substitute for lithium batteries. For sodium-ion batteries (SIB), the carbon-based anode is a good option because it is abundant and non-toxic. On the other hand, Ionic liquid electrolyte holds promise for electrolytes because of their reversible capacity, high temperature operating capabilities, and recyclable nature. In this work, we report on the molecular dynamics of the interface between graphene oxide (GO) as an anode and NaFSA/[C3C1Pyr]FSA as ionic liquid electrolytes in sodium-ion batteries using the density-functional tight-binding (DFTB) method with an in-house parameter set [1]. The DFT-D3 Grimme's dispersion correction with the Becke-Johnson damping [2] was employed to account for all intermolecular interactions. The adopted system contains GO and electrolyte; The electrolyte concentration was varied and paired with epoxide graphene (GO1) and hydroxy graphene (GO2), respectively. The reason for varying the concentration is to investigate how the electrolyte concentration change will affect the firmness of the anode-electrolyte interface and the sodium-ion diffusion. The concentration was varied in mole fraction units, the variations were 0.1, 0.2, 0.4, 0.6, and 0.8. Based on the obtained trajectories and time-course changes of the chemical species, the firmness of the solid-electrolyte interface is influenced by the electrolyte concentration. Solid-electrolyte interface (SEI) is formed by the electrolyte's decomposition on the anode, which affects the overall performance of the battery [3]. The common electrolyte decomposition products areF2NO5S2-, F2NO4S2-, and C8H18N+. The optimum concentration, which contains the least electrolyte decomposition products, is 0.4. The decomposition product interacts with sodium ions and impacts the sodium-ion diffusion. The intermolecular interaction between sodium ions and the electrolyte decomposition product is quantitatively described with radial distribution function (RDF) and connection matrix (Cmat) analysis. The sodium ion diffusion is quantitatively estimated by diffusion coefficient analysis. Based on the qualitative and quantitative analysis, we suggest that sodium ion follows a vehicular mechanism of diffusion for the GO1-adopted system. On the other hand, for the GO2-adopted system, the diffusion process is ion hopping.

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Molecular Simulations of Methanol Valorisation to Sustainable Aviation Fuels over Zeolites

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The methanol-to-olefins (MTO) process utilizes acidic zeolites to convert methanol into olefins and plays a pivotal role in the production of Sustainable Aviation Fuels (SAFs)1. This process involves a complex network of reactions, with multiple competing pathways and mechanisms2. The initial and critical step is the dehydration of methanol to form dimethyl ether (DME)3. Experimental and computational studies have revealed two main reaction pathways for this step, whose predominance depends strongly on the operating temperature4. Given the central role of this step in shaping the subsequent formation of the so-called hydrocarbon pool, it is essential to achieve a clear and detailed molecular-level description. However, current modeling approaches fall short of capturing

the realistic complexity of the process under operando conditions, limiting their ability to provide accurate thermodynamic and mechanistic insights5. In addition, a systematic exploration of the broad physico-chemical space—defined by variations in temperature and zeolite topology—is still lacking, yet crucial for initiating an effective in silico screening aimed at process optimization. In this work, we address these challenges by employing metadynamics simulations coupled with machine learning potentials (MLPs), exploring a range of temperatures (600–800 K) and zeolite frameworks (chabazite, ZSM-5, and mordenite). This approach enables the investigation of reaction mechanisms with atomistic resolution, estimation of energy barriers, and construction of free energy profiles. Using metadynamics simulations powered by MLPs trained on accurate ab initio data, we elucidated both the associative and dissociative pathways involved in methanol dehydration. The resulting free energy profiles allowed us to determine the thermodynamic and kinetic parameters associated with each mechanism. By comparing these parameters, we identified the dominant reaction pathway for the methanol-to-DME conversion under different conditions. This study establishes a robust framework for mechanistic analysis of catalytic reactions in complex environments and provides fundamental insights into the MTO process. Our findings aim to support the development of more efficient catalytic systems and contribute to the broader goal of advancing sustainable and economically viable energy solutions. (1) Van der Mynsbrugge, J.; Moors, S. L. C.; De Wispelaere, K.; Van Speybroeck, V. ChemCatChem 2014, 6 (7), 1906 1918. https://doi.org/10.1002/cctc.201402146. (2) Wang, S.; Chen, Y.; Qin, Z.; Zhao, T.-S.; Fan, S.; Dong, M.; Li, J.; Fan, W.; Wang, J. J. Catal. 2019, 369, 382–395. https://doi.org/10.1016/j.jcat.2018.11.018. (3) Blaszkowski, S. R.; Van Santen, R. A. J. Phys. Chem. B 1997, 101 (13), 2292–2305. https://doi.org/10.1021/jp962006+. (4) Ghorbanpour, A.; Rimer, J. D.; Grabow, L. C. ACS Catal. 2016, 6 (4), 2287–2298. https://doi.org/10.1021/acscatal.5b02367. (5) Barducci, A.; Bussi, G.; Parrinello, M. Rev. Lett. 2008, 100 (2), 020603. https://doi.org/10.1103/PhysRevLett.100.020603.

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Multi-level coupled-cluster description of crystal lattice energies

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

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Multiple Photoinduced Charge Separation in Covalent Molecular Triads: Insights from DFT

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Multiple Photoinduced Charge Separation in Covalent Molecular Triads: Insights from DFT

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Efficient solar energy conversion is a major challenge in relation with climate change, which requires to stop using fossil fuels as primary energy sources. One solution to this problem is the development of solar fuels, among which, dihydrogen can be obtained through water photolysis[1].

Scheme 1: molecular D-PS-A triad and its Charge Separated States (CSS1 and CSS2) populated through sequential PETs

A key concept in this reaction, which requires the formal exchange of four electrons, is photoinduced electron transfer (PET). While this process is well understood for a single charge separation in donor-photosensitizer-acceptor (D-PS-A) triads[2], systems allowing the separation of two charges are uncommon[3], and no covalent non biological D-PS-A triad able to undergo double PET has been yet reported in the literature. The current challenge and the purpose of our work is to better understand multi-electron processes in these systems. The initial design of covalent molecular triads D-PS-A takes advantage of potential inversion[4], a phenomenon that is observed only with certain types of two-electron donors and acceptors, for which the second redox process is less demanding than the first one, mostly due to structural variations. The photosensitizers used are earth-abundant high-potential molybdenum complexes[5]. The desired double photoinduced charge separation process is shown on Scheme 1.

Our theoretical analysis of these systems is based on thermodynamic data, such as standard potentials or Gibbs energies obtained through DFT-based methods, as well as on the determination of reaction pathways for charge separation and recombination, both thermal and photochemical, using Nudged Elastic Band (NEB), time-dependent DFT (TD-DFT), and spin-flip TD-DFT calculations. This poster discusses about initial triad designs and future guidelines established during my first and second years of PhD.

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Multiscale Computational Design of Luminescent Nanoparticle Supercrystals

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The project will introduce a rational design of ligands to finely tune nanoparticle shell thickness and density, complemented by functionalization strategies for supercrystals aimed at reinforcing interparticle interactions and reducing inter-nanoparticle spacing. Ab initio simulations based on density functional theory (DFT) are employed to predict electronic, structural, and magnetic properties of novel materials. First-principles simulations also support the design of heterostructures with tailored quantum behaviors, guiding experimental synthesis and characterization.. Overall, this theoretical framework supports the rational design of next-generation superconducting nanomaterials. We integrates advanced computational techniques with a multiscale modeling to investigate superconductivity at the nanoscale, by playing with nanoparticles size and surface chemistry toward a library of highly stable and strongly coupled structures. To this end, we aims to overcome the vulnerabilities of these materials through the assembly of nanoparticles into supercrystals, development of 3D supercrystals, optimization of ligand design. The formation of supercrystals will improve experimental testing in optoelectronic devices.

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Multiscale Computational Study of Metal (Per)Oxides in Thermoplastic Vulcanizate

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Unai Calvo, Fernando Ruipérez, Aizeti Burgoa, Jon Mattin Matxain POLYMAT, Centro Joxe Mari Korte, Avda. Tolosa, 72, 20018, Donostia-San Sebastian, Spain unai.calvo@polymat.eu In this work, we investigate the interactions at the interfaces of metal (per)oxides with thermoplastic vulcanizates (TPVs), specifically focusing on the XHNBR/PA6 system. XHNBR (carboxylated hydrogenated nitrile butadiene rubbre) combined with PA6 (polyamide 6) forms a high-performance TPV with enhanced mechanical and chemical resistance, widely used in automotive and industrial applications. The incorporation of metal (per)oxide nanoparticles plays a key role in crosslinking and improving thermal stability [1-2], yet zinc oxide (ZnO), the most common additive, raises environmental and health concerns. Our study aims to identify a safer alternative by analysing the interactions between metal oxides and both XHNBR and PA6 using quantum chemical calculations, considering cluster and surface model for the metal oxides and different representations of the polymeric materials, including isolated functional groups, monomers, and dimers. The results show that both cluster and surface models exhibit similar interaction patterns with XHNBR and PA6, with predominantly electrostatic interactions, although ZnO presents a slightly more covalent character. To explore the PA6/XHNBR interface, we employ a clustering approach to efficiently sample representative configurations, ensuring a thorough analysis of interfacial interactions. Furthermore, we extend our study to molecular dynamics (MD) simulations of the composite material to predict its mechanical properties [3]. For the development of the methodology for the analyse, we studied the polypropilene (PP) polymeric matrix's mechanical properties. This multiscale approach provides a comprehensive understanding of the role of metal (per)oxides in TPVs, aiding in the design of safer and more efficient formulations. [1] Beitia, A. B. Design and development of high-performance thermoplastic vulcanizates with vibration damping properties, 2020, p 1. [2] Aizeti Burgoa, Ricardo Hernandez, and Jose Luis Vilas. New ways to improv the daping properties in high-performance thermolastic vulcanizates. Polymer International, 69(5):467-475, February 2020. [3] Pervaje, A. K., Psquinelli, M. A., Khan, S. A., & Santiso, E. E. (2022) Multiscale Constitutive Modeling of the Mechanical Properties of Polyropylene Fibers from Molecular Simulation Data. Macromolecules, 55(3), 728-744. https://doi.org/10.1021/acs.macromol.1c00630

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New TDDFT Algorithms, Protocols and Analysis Tools for the Study of Optical Properties and Plasmons of Large Metal Clusters

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A recent algorithm to solve the TDDFT equations in the space of the density fitting auxiliary basis set has been developed and implemented in ADF/AMS [1]. The TDDFT equations are recast to a non-homogeneous linear system, whose size is much smaller than in Casida formulation, allowing to calculate a wide portion of the absorption spectrum for large systems. The method extracts the spectrum from the imaginary part of the polarizability at any given photon energy, avoiding the bottleneck of Davidson diagonalization. The new algorithm also benefits from a recent very efficient extension to hybrid functionals [2,3] and is supported by many analysis tools. Recent applications to ligand protected [4], chiral metal clusters [5,6] and plasmonic systems [7] will show the potentiality of the method.

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No Heme-Chlorite Adduct in the Catalytic Cycle of Chlorite Dismutase: Insights From QM/MM and Dynamics Calculations

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Chlorite dismutase (Cld) is one of the rare enzymes capable of forming oxygen-oxygen bonds. Cld has been identified in a very small number of anaerobic bacteria that can use perchlorate as the final electron acceptor in their electron transport/respiration chain. It has been proposed that the catalytic cycle of Cld involves the binding of chlorite to the enzyme's active site, followed by the cleavage of one of the Cl-O bonds, leading to the formation of a high-valent iron-oxo center and a ClO radical/ion, and then a reorientation to the oxygen atom bound to iron, followed by the release of chloride and molecular oxygen. However, direct experimental confirmation of the existence of a chlorite-heme adduct in Cld is still unavailable, nor is it clear what the coordination mode of chlorite is. Moreover, reaction intermediates have not been directly observed in experiments. Previous DFT calculation from us and others have concluded that hemes cannot form stable adducts with chlorite – unlike, e.g., metallacorrins such as cobalamin [1]. This paper reports the results obtained from QM/MM optimization and QM/MM molecular dynamics calculations on the catalytic cycle, revealing compelling computational evidence that a chlorite-heme adduct in Cld is unlikely to be observable experimentally.

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under project POC/398/1/1/124155 - co-financed by the European Regional Development Fund (ERDF) through the Competitiveness Operational Program for Romania 2014-2020 and by the CLOUDUT Project, co-funded by the European Fund of Regional Development through the Competitiveness Operational Programme 2014-2020, contract no. 235/2020.

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Noncovalent interactions in DFT without empirical potentials

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Weak non-covalent interactions remain a challenging area for most Density Functional Approximations, and the inclusion of empirical potentials has proven to be an effective way to address their limitations. Recently, we have proposed an alternative approach based on the coupling of a non-empirical double hybrid functional, PBE-QIDH, with a specifically developed basis set named DH-SVPD. This basis set was constructed using a dedicated procedure that does not involve any fitting to external reference data [1]. The results obtained across a wide range of benchmark datasets [2-4] demonstrate that our protocol, PBE-QIDH/DH-SVPD, provides interaction energies that are at least as accurate as those obtained with comparable functionals combined with large triple- or quadruple-ζ basis sets and dispersion corrections. The rationale behind this performance can be attributed to improvements in the description of electronic molecular properties induced by our protocol.

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On the allostery of european ALDH2 enzyme: an in-depth computational investigation

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Allostery is a biological phenomenon that plays a pivotal role in regulating the metabolic pathways, such as feedback inhibition and feedforward activation, in which the three-dimensional structure of proteins could create surface pockets recognized by modulators. The binding of modulators elegantly affects the orthosteric pocket via a dense connection of amino acids between the allosteric and active sites. Thus, the knowledge of such allosteric pathways is fundamental to enhance the design of promising pharmaceutical molecules for personalized medicine. Mitochondrial Aldehyde

Dehydrogenase 2 (ALDH2) is a key enzyme in the cellular detoxification of aldehydes after alcohol assumption, and its malfunctioning is associated to mitochondrial anomalies, alteration of the energy production metabolism and cardiomyopathies. The focus on the allosteric inhibition is driven by the well-substantiated advantages of the allosteric modulators with respect to the competitive ones, such as the high specificity and minor adverse effects, vital for the design of a drug [1]. In this study, European ALDH2 modulation is deeply investigated, starting from experimental evidence of two inhibitors of its enzymatic activity, quercetin and one of its metabolites [2]. Molecular dynamics simulations and molecular docking provide the means to deepen highlight the structural effects after the inhibitor binding and to propose a novel allosteric pocket, thorough the application of MD analysis tools. Furthermore, it was applied a Python package, MDiGest, which is a potent object-oriented toolkit to target protein hubs, amino acid communities and allosteric networks of biological systems through pairwise correlations extrapolated from the MD simulations [3].

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Optimizing polyethylene glycol coating for stealth and biocompatible nanodiamonds

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Nanodiamonds (NDs) have emerged as potential candidates for versatile platforms in nanomedicine, offering unique properties that enhance their utility in drug delivery, imaging, and therapeutic applications. To improve their biocompatibility and nanomedical applicability, NDs are coated with organic polymer chains, such as polyethylene glycol (PEG), which are well known to prolong their blood circulating lifetime by reducing the surface adsorption of serum proteins. Theoretical simulations are useful tools to define, at the atomic level, the optimal parameters that guide the presentation of the coating chains in the biological environment and the interaction of the coated NDs with proteins. In this work [1], we perform atomistic molecular dynamics (MD) simulations of several PEGylated spherical ND models, immersed in a realistic physiological medium. In particular, we evaluate the effect of the polymer chains terminal group, length, grafting density and of the ND core dimension on both the structural properties of the PEG coating and on the interaction of the nanoconjugates with the aqueous phase. Among all the parameters evaluated, we find that the PEG grafting density and the PEG chain length are key factors in determining the dynamic behavior of PEGylated nanosystems in solution, whereas the PEG terminal group and the ND dimension only play a marginal role. These factors can be strategically adjusted to identify the optimal conditions for enhanced clinical performance. Finally, we demonstrate the function of the PEG coating in preventing the aggregation of two ND particles. We believe that this computational study will provide valuable insights to the experimental community, supporting the rational design of polymer-coated inorganic NPs for more efficient nanomedical applications.

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Optimizing the mRNA Binding Affinity of Antisense Oligonucleotides with Simple Nucleobase Modifications

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Optimizing the mRNA Binding Affinity of Antisense Oligonucleotides with Simple Nucleobase Modifications

Antisense therapy has emerged as a powerful strategy for treating genetic disorders—particularly rare "orphan" diseases—as well as viral infections and, more recently, certain cancers.[1] Antisense oligonucleotide (ASO) therapeutics rely on high-affinity, sequence-specific hybridization to target mRNAs and modulate gene expression via RNase H recruitment, splice-site alteration, or steric blockade of ribosome assembly[2], thereby suppressing or altering production of disease-related proteins and mitigating pathological processes. Chemical modifications—such as 2'–O–methylation, locked nucleic acids, and phosphorothioate backbones[3]—are routinely employed to enhance stability and binding strength; however, their effects on hybridization thermodynamics and kinetics remain highly context-dependent and difficult to predict experimentally.

An integrated quantum-mechanical and molecular-dynamics approach has been undertaken to dissect, at atomic resolution, the influence of minimal nucleobase substituents on ASO–mRNA binding affinity. Density functional theory calculations quantify the impact of introduced substituents at key positions of pyrimidine and purine rings on hydrogen–bonding energies and base-stacking interactions. Complementary long, explicit-solvent MD simulations combined with free-energy profiling reveal how each substituent alters duplex conformational flexibility and solvent-mediated contacts.

Preliminary insights suggest that even small, site-specific nucleobase modifications can meaningfully modulate binding affinity: some substituents enhance base-pairing and stacking interactions while promoting local duplex rigidity, whereas others introduce additional bonding potential but encounter solvent competition, leading to more moderate net effects. These emerging structure–activity trends provide a qualitative roadmap for prioritizing minimal nucleobase alterations in ASO design, pending quantitative validation.

Future work will expand this QM/MD framework to introduce minimal substituents across additional ASO regions—including the sugar and backbone—and to evaluate their impact on RNase H recruitment and other mechanisms of action. Insights thus gained will be applied to design mixed-chemistry oligonucleotides targeting clinically relevant transcripts, broadening the strategy toward next-generation antisense therapeutics with optimized activity and specificity.

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Physics-Informed Generative GPT Models (PINO-GPT) for Drug Discovery

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Innovation: Utilizes Fourier Neural Operators (FNOs) to model continuous 3D physical landscapes (hydrophilic/hydrophobic surfaces). Embeds physical properties directly into the molecular generation process, enhancing physical realism and relevance.

Methodology: Evolution from LSTM-based generators [2] to GPT-based transformers to current dual-FNO-enhanced PINO-GPT architectures. FNO layers process spatial physical fields, enabling

generation of molecules optimized for orthosteric binding pockets. Fine-tuning enables adaptation to experimental constraints in GPCRs (e.g., agonist activity).

Results: Outperforms traditional sequence-based and diffusion-based models [3] in structure-informed drug generation tasks. Experimental validation (binding and functional assays) confirms predictive performance and real-world applicability.

Impact: Bridges computational design and wet-lab validation. Enables more interpretable, physically grounded, and experimentally aligned GenAI workflows in drug discovery.

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Physics-informed ML hydration free energy models with EC-RISM augmentation: Physicality matters

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The accurate prediction of hydration free energies (HFEs) is an important task in different areas, as the thermodynamic cost of solvation is one of the key factors in processes from protein-ligand binding to chemical reactions. Hence, much effort has been spent in predicting the HFE from electronic structure calculations and molecular dynamics simulations as well as, in recent years, machine learning (ML) methods,1 for which large and reliable datasets are needed.

Training data dependence can be reduced using physics-informed ML, where measured or calculated properties representing the underlying physics of the molecules and their interactions are used as additional input features.2 Here we present a physics-informed ML method that combines the Embedded Cluster Reference Interaction Site Model (EC-RISM)3 with a Message Passing Neural Network (MPNN).4 The solute is represented by a graph, where atoms are described by partial charges and Lennard-Jones parameters together with "local" atomic free energies (LFEs)5,6 adding up to the total HFE. Augmenting with EC-RISM HFEs, we demonstrate state-of-the-art accuracy on independent HFE datasets, including SAMPL challenge data.7,8 This model as well as a range of related approaches with varying numbers of physical features is then employed to predict the HFEs of tautomers. These HFEs are combined with high level gas phase data to calculate the aqueous tautomerization free energies for a curated Tautobase9 subset. We compare the performance of our physically augmented HFE prediction approach to literature HFE models, both for independent HFE datasets and for the Tautobase subset. We demonstrate that a good HFE prediction performance does not automatically translate into performing well on the solvation contribution to the aqueous tautomerization free energy, illustrating the importance of physicality for predicting reaction thermodynamics in solution by accounting for relevant physical features.

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Predicting molecular excitations induced by a high-velocity massive charged particle

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The objective of the conducted research was to develop a quantum chemical method that enables modeling of interactions between high-velocity, massive, charged particles and an arbitrarily chosen molecule. The proposed method finds broad application across various fields of science. In the context of radiotherapy, a tool capable of accurately describing excitations induced by protons is highly desired to calculate the rate of energy transfer from the high-velocity particle to tissues [1]. Simultaneously, the ability to predict transition probabilities between molecular electronic states, induced by massive, charged particles, can significantly contribute to the development of high-energy physics, particularly in the search for particles that could potentially constitute dark matter [2]. This study focused on the second of the mentioned applications. Two alternative approaches to modeling the interaction between a particle and a molecule were presented, both based on the time-dependent perturbation theory formalism. The massive, charged particle was treated as a classical point particle generating a standard electric potential. The main focus was placed on molecular excitations, neglecting processes such as ionization or electron capture. Excitation probabilities were calculated for water molecules, LAB (linear alkylbenzene) molecules, and argon atoms, induced by a hypothetical dark matter particle (gravitino). In calculations, two possible velocities were investigated, corresponding to a gravitino bound to the Solar System or the Milky Way Galaxy. Excitation cross sections and characteristic times between excitations were presented for both of them. The results enable the prediction of the gravitino's signature in the analyzed detectors. Moreover, it was demonstrated that detectors containing LAB are the most suitable for conducting this type of experiment [3].

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Prediction of enhanced superconductivity in cyclo-H12Bi/Pb involving a resonant hydrogen structure

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Hydrogen-based compounds demonstrate high-temperature superconductivity under pressure, offering promising avenues for exploring metal hydrides with elevated critical temperatures (c), while hydrides comprising H2 molecular units were previously deemed unfavorable.1 Searching for new forms of hydrogen within metal hydrides promised a route for developing novel high-temperature superconductors. In this study, we utilized the evolutionary algorithm alongside first-principles calculations to investigate the high-pressure crystal structure of the BinHn (=7–18) system. Notably, we discovered stable cyclo-H12Bi/Pb compounds in which the H12 resembles cyclohexanelike cyclo-H12 rings. These compounds are stable above 180 GPa and exhibit a higher c than BiH8 composed of H2 units. In cyclo-H12, the hydrogen has a slightly elongated intramolecular H-H length compared to BiH8, while the intermolecular H-H distance is much shorter than in H cages, forming a resonant structure. The resonance led to in-/out-of-plane vibration modes for the six H2 units in cyclo-H12, forming broad mid-frequency vibrational bands and boosting the electron-phonon coupling. These findings highlight the cycloform of hydrogen-based hydrides as promising candidates for high c superconductors, propelling further exploration of superconductivity in binary superhydrides with different forms of hydrogen.2

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Predictive Quantitative Non-Covalent Interaction Index

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Non-covalent interactions (NCIs) are fundamental to the structure, stability, and function of molecular systems across chemistry and biology [1]. The Non-Covalent Interaction (NCI) method offers a visual and intuitive means to identify regions of weak interactions by analysing low-density and low-gradient features in electron density data. Since its introduction, NCI has become a widely adopted qualitative tool owing to its ease of use, speed, and ability to provide clear visualizations of interaction zones [2]. However, establishing a direct quantitative link between NCI indices and interaction energies was a challenge [3].

In this work, we developed a quantitative framework linking the NCI index—obtained from integrating relevant volumes in electron density—to interaction energies with high accuracy. Using symbolic regression algorithms [4], we systematically analysed how the NCI index correlates with reference CCSD(T) energies across various small molecular complexes [5], including hydrogen-bonded and dispersion-dominated systems. Our results revealed a meaningful, interpretable equation that connects the NCI index with interaction energies, demonstrating reliable predictive capabilities. It furthermore enables the division of the energy into polar and non-polar components, see Figure 1.

The development of this quantitative model offers a computationally efficient alternative to conventional ab initio methods, enabling rapid estimation of interaction energies and paving the way for streamlined analysis of complex systems, such as biomolecular assemblies and materials, by providing fast and meaningful estimates of interaction energies directly from electron density data.

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Quantifying molecular chiral properties in solution using Ensemble Steric and Electrostatic Chirality (ESEC) descriptors

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Enantiomers of chiral molecules behave differently in chiral environments. This is typically due to interactions with a chiral host system, such as a chiral reagent or catalyst in a synthetic context, a target protein in the context of drug discovery or a chiral stationary phase in chiral chromatography. The most obvious route for studying these interactions in solution phase is through MD simulations that include both the aforementioned host system and the (chiral) guest molecule of interest. However, doing so is laborious and computationally intensive, and in many cases poorly eligible for automation. For such purposes, it would be more convenient if generic chiral properties

of the molecule of interest could be calculated and correlated with differences in behavior between its enantiomers.

While considerable effort has been invested into developing chiral molecular descriptors,[1][2] existing chiral descriptors are hard to interpret and often yield acceptable results only when applied to highly congeneric molecules. Therefore, we developed universal chiral descriptors based on a molecule's asymmetric microscopic properties using the 2 distinct approaches in figure 1: (A) scalar triple products of molecular vector properties, and (B) descriptors that attempt to quantify the amount of twist in the overall molecular shape. Because both approaches give rise to conformation dependence, descriptor values were averaged over a conformational ensemble obtained by Molecular Dynamics. In addition, a method is introduced that attempts to quantify the asymmetry of the distribution of the descriptor values over the conformational ensemble. As a proof-of-concept, the resulting "Ensemble Steric and Electrostatic Chirality (ESEC) descriptors" were applied to construct Quantitative Structure-Enantioselectivity Relationships (QSER) for chiral High-Performance Liquid Chromatography (HPLC) on a set of known chiral pharmaceuticals.

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Quantum Computing for Industrial Materials: A Johnson Matthey Perspective

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Johnson Matthey (JM) envisions a cleaner, healthier world for present and future generations. As global leader in sustainable technologies, the company leverages science to accelerate the net-zero transition for its clients. Through scientific innovation, the company improves the lives of millions worldwide. JM is focused on facilitating four critical transitions: reducing transport emissions, transforming energy emissions, decarbonizing chemical production, and establishing a circular economy.

Quantum computing, while still in its early stages, holds immense potential to revolutionize various industries by tackling problems currently intractable for even the most powerful supercomputers. Some potential roles of quantum computing include simulation (Scientific Research and Engineering) and machine learning.

As a company, we are strategically harnessing the power of quantum computing to address real-world industrial challenges in materials science and beyond. Seeing the transformative possibilities of this emerging technology, JM is actively pushing for its industrial use. This is complemented by active collaboration within the quantum computing community through initiatives like feasibility studies (e.g., Innovate UK), participation in quantum computing events, and our consistent involvement in the National Quantum Computing Centre (NQCC) Quantum Hackathon.

JM's exploration focuses on high-impact industrial applications, including catalyst simulation for designing more efficient materials, quantum resource estimation for future planning, quantum machine learning for enhanced data analysis, and advanced Density Functional Theory for more accurate materials modelling. Our commitment to the field is further evidenced by participating in scientific publications.[1],[2]

JM is proactively shaping quantum algorithm development[3] to directly benefit our industrial future. As part of that, we've explored different real-world challenges with quantum computing using feasibility studies in collaboration with partners from Academia and Quantum Industry. A selection

of materials will be presented and discussed emphasising on what was the value from JM's industrial perspective. With a keen eye on near-term applications in quantum chemistry and materials science, JM is leveraging our deep expertise to effectively utilise quantum computing for tangible business value.

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Quantum-Mechanics Based Multiscale Modeling and Rational Design of Insulin Analogs with Improved Binding Affinities

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Accurate modeling of electronic effects in protein–protein interactions (PPIs) remains a significant challenge in computational biophysics. Classical force fields fail to describe polarization and charge transfer, while full quantum mechanical (QM) methods are often computationally prohibitive. To address this, we developed a multiscale protocol that integrates molecular dynamics, system fragmentation, semiempirical quantum mechanics (PM6-D3H4S/COSMO2), and virtual glycine scanning (VGS) to dissect residue-level contributions to protein interface energetics [1]. Using the insulin–insulin receptor complex as a model, we applied this approach to evaluate the impact of point mutations at seven key positions within the receptor-binding region. The calculated changes in binding free energy (ΔΔG) show strong correlation with experimental binding data and clearly outperform classical Molecular Mechanics/Generalized Born (MM/GB) approaches. Notably, our scoring protocol is conceptually linked to the recently published SQM2.20 scoring function for protein–ligand systems, which yields DFT-quality predictions with practical speed [2]. Building on these insights, we designed a series of novel insulin analogs predicted to exhibit enhanced receptor binding. Several promising candidates—such as A19Phe, B16Arg, and B26Lys— are being synthesized and are currently undergoing experimental evaluation. These analogs were selected based on favorable QM-predicted interaction profiles, taking into account both individual residue contributions and the overall binding energetics. Preliminary experimental results confirm improved receptor binding for several variants, supporting the predictive power of our quantum-informed design strategy.

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Reaction Force Constant As a Descriptor of the Principle of Non-Perfect Synchronization

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Reaction Force Constant As a Descriptor of the Principle of Non-Perfect Synchronization

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In this study, a small set of 1,3-dipolar cycloaddition reactions (see Scheme 1) that proceed at the same exothermicity is presented [1]. Our main objective was to extend the application of the reaction force constant concept [2] to gain an understanding of the reactivity principles. Inspired by a recent article where we show that the Bell-Evans-Polanyi principle is fulfilled under the condition of an equal degree of (a)synchronicity [3], here, we demonstrate that the reaction force constant (see Figure 1) is also a suitable descriptor to quantify the principle of non-perfect synchronization proposed by Bernasconi as a way to understand deviations from the Bell-Evans-Polanyi principle.

Scheme 1

Figure 1

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ReaxFF development for rWGS reaction on Ni/Cu alloys: Effects of Cu content and distribution

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The reverse Water-Gas Shift (rWGS) reaction enables the conversion of CO2 into CO, a key intermediate for e-fuel synthesis. Ni-based catalysts are active for rWGS but suffer from limited selectivity due to the competing methanation reaction. In contrast, Cu-based catalysts exhibit high selectivity but lower activity. Alloying these metals has been explored as a strategy to improve the catalyst performance. To gain deeper insight into the behaviour of these types of catalysts, we developed ReaxFF reactive force field parameters. The new Ni/Cu/C/O/H_2025 force field was built on our previously developed force field for rWGS on Ni, alongside parameters from a previously published force field for Cu catalysts. To re-optimize the parameters, we used DFT calculations as reference data alongside optimization algorithms such as the GA-ANN hybrid method (Genetic Algorithm - Artificial Neural Network). Our simulations examined how surface composition and atomic distribution influence catalyst performance. On a (100) surface, a Cu:Ni ratio of 1:3 resulted in catalytic behaviour comparable to pure Ni(100), while increasing Cu content to 1:1 reduced activity by ˜30% but significantly enhanced selectivity, decreasing side product formation by nearly 50%. Dynamic simulations at various temperatures enabled the construction of Arrhenius plots, yielding apparent activation energies in close agreement with DFT values. Additionally, we analysed hydrogen distribution across different surface structures, finding that NiCu alloys exhibit higher subsurface H concentrations than pure Ni, potentially impacting H_2 adsorption and desorption. Finally, we analysed different reaction pathways for CO2 activation and CO desorption that are related with the origin of the selectivity towards CO formation.

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Semiclassical Methods for Quantum Nuclear Dynamics in Condensed Phase

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Semiclassical methods are based on classical molecular dynamics and they recover quantum mechanical effects by summing the contribution over all the classical paths of the Feynman Path Integral propagator. In Miller's semiclassical initial value representation (SCIVR)[1] formulation of the Herman-Kluk propagator, the sum over frozen guassian wavepackets reproduces quantum effects, including zero point energies, tunneling and quantum anharmonicity. The Milan Semiclassical Group has implemented SCIVR for nuclear spectra calculations up to as many degrees of freedom as in a typical condensed phase simulation. In this presentation I will show how our ab initio divide-and-conquer "on-the-fly" QM/MM semiclassical molecular dynamics approach[2-4] is able to reproduce the experimental IR spectra of thymidine in water and that one of formic acid adsorbed on Anatase (101) surface, as a prototype adsorption reaction of gas Brønsted acid on oxides. In the first case, we show the importance of solute-solvent reciprocal polarization effects that the molecule and the water solvent exert on each other, and nuclear zero-point energy effects. In the second case reported in the picture below, we find that the acid proton forms an extraordinarily short and strong hydrogen bond with the surface oxygen, that can be compared to that one of ice at high pressures. We believe that this is at the root of a substantial redshift with respect to the typical free OH stretching frequency, which eludes its straightforward detection. In conclusions, I will show how our semiclassical methods are an accurate and practical tool to study quantum vibrational spectroscopy in solution and condensed phase, incorporating high-level and computationally affordable descriptions of both electronic and nuclear problems. Possibly, I will also show possible future developments[7] about vibrational dynamics. [1] W. H. Miller, J. Phys. Chem. A, 2001, 105, 2942-2955 [2] M. Ceotto, G. Di Liberto, R. Conte, Phys. Rev. Lett., 2017, 119, 010401 [3] R. Conte, G. Mandelli, G. Botti, D. Moscato, C. Lanzi, M. Cazzaniga, C. Aieta, M. Ceotto, Chem. Sci., 2025, 16, 20-28 [4] R. Conte, C. Aieta, M. Cazzaniga, M. Ceotto, J. Chem. Phys. Lett., 2024, 15, 7566-7576 [5] D. Moscato, G. Mandelli, M. Bondanza, F. Lipparini, R. Conte, B. Mennucci, M. Ceotto, J. Am. Chem. Soc., 2024, 146, 8179-8188 [6] E. Fallacara, F. Finocchi, M. Cazzaniga, S. Chenot, S. Stankic, M. Ceotto, Angew. Chem. Int. Ed., 2024, 63, e202409523 [7] M. Ceotto, J. Chem. Phys., 2025, 162, 064108

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Sequential MD-QM approach to compute chemical properties of Brønsted amorphous aluminosilicate catalysts

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Sequential MD-QM approach to compute chemical properties of Brønsted amorphous aluminosilicate catalysts Charles Rubirigi, Benoît Champagne NISM (Namur Institute of Structured Matter), University of Namur (UNamur), B-5000 Namur, Belgium charles.rubirigi@unamur.be

Amorphous silica-based materials are often used as support for catalysis experiments. The insertion of heteroelements (i.e., neither a silicon nor an oxygen atom) leads to the formation of Brønsted or Lewis acid sites.1 Despite their widespread use, these materials are still complex to characterize. Moreover, their amorphous nature further complicates the task.2 In this context, computing chemical

properties with quantum chemical methods can bring insights into such materials. However, the large size of these systems implies the use of models to limit the computational effort.3

The present work shows a complete route to compute chemical properties on amorphous Brønsted aluminosilicate catalysts using a cluster approach. The amorphous network is generated using classical molecular dynamics via a thermal treatment called melt-and-quench. Particular attention is devoted to the catalyst shape and silanol coverage. The quality of the final amorphous network is assessed through geometrical analysis implying primitive ring size analysis. Density Functional Theory calculations are then performed on hemispheres extracted from the amorphous silica framework, where the central silicon atom is replaced by an aluminum atom. The impact of cluster size on the prediction of chemical properties is illustrated by deprotonation energies and chemical shift calculations. The influence of the XC functional on those quantities is also discussed.

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Structural Drivers of Na diffusion in oxy-thiophosphate amorphous electrolytes. A Machine Learning Molecular dynamics study in the framework of the EcosistER project.

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The global growing demand for energy storage is pushing the research for new battery materials with improved performance, safeness, and environmentally friendly synthesis, usage, and disposal. All-Solid-State Sodium Batteries (ASSSB) are attracting increasing attention from both academia and industry as strong candidates for grid-scale energy storage. However, their development requires highly conductive and electrochemically stable Solid-State Electrolytes (SSEs). Among the possible candidates, Glassy Solid Electrolytes (GSEs) are particularly promising as they can potentially meet all the requirements for a good SSE. They can achieve ionic conductivities comparable to those of liquid electrolytes while preventing dendrite growth and fire hazard[1]. Using sodium as a charge carrier allows avoiding the ethical concerns associated with lithium mining and mitigates possible supply chain issues, thanks to the higher Na abundance. The development of ASSSBs needs a huge effort in the study of a suitable SSE. Most of the GSE studied so far are based on sulfide glasses which offer high conductivity but suffer from high reactivity with atmospheric compounds. Recently, mixed oxy-sulfide (MOS) glasses have been explored as a way to combine the chemical stability of oxide glasses with the conductivity of sulfide ones. From a computational perspective, the lack of classical interatomic potentials for these systems limits their structural investigations, as ab-initio methods are constrained by their computational cost. In this work, we developed a Machine Learning Interatomic Potential (MLIP) to study the structure of MOS glasses and correlated it with the Na diffusion[2]. The accuracy and computational efficiency of the MLIP allow us to perform simulations beyond the capabilities of ab-initio methods, identifying structural units that promote or hinder Na diffusion and relating them to the glass composition, thus paving the way for the design of new GSE with tailored properties. This project is funded under the PNRR Miss. 4, Comp. 2, Inv. 1.5, NextGenerationEU-Avviso 3277/2021 – ECS_00000033-ECOSISTER-spk06.

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Structural, electronic and electrochemical properties of NASICON-based positive electrodes for Na-ion Batteries

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Sodium-ion batteries (NIBs) are a sustainable alternative to lithium-ion batteries (LIBs) due to the abundance and low cost of sodium [1]. Although NIBs and LIBs operate based on similar principles, the differences in ionic radius and standard electrode potential between the two ions require the development of new cathode materials. NASICON-type materials (Natrium Super Ionic CONductors), such as $Na_3VFe(PO_4)_3$, are promising candidates due to their their high ionic conductivity, excellent thermal stability, and remarkable structural flexibility, which allows for a wide range of chemical combinations [2]. $Na_3VFe(PO_4)_3$ crystallizes in the C2/c space group and has a three-dimensional structure composed of $(PO_4)^{3-}$ tetrahedra with a structural role, and TMO_6 octahedra (TM = V, Fe) containing redox-active elements. This arrangement gives rise to two types of interstitial sites for sodium ions [3]. This project aims to analyze the structure–property relationships of $Na_3VFe(PO_4)_3$ using first-principles methods based on Density Functional Theory (DFT). The initial level of theory involves the use of the semi-local PBE exchange-correlation functional, combined with the Tkatchenko-Scheffler scheme to account for Van der Waals dispersion forces, and further refinement of the electronic structure using the hybrid functional HSE06 [4]. The bulk study included geometric optimization of supercells at different levels of sodium content to simulate the charge/discharge process, with the goal of identifying possible structural distortions. Subsequently, the surface interaction between $Na_3VFe(PO_4)_3$ and magnesium oxide (MgO) was investigated. Mg^{2+} ions tend to substitute iron ions within the material, acting as "lattice disordering agents"; if inserted, they could enhance Na^+ ion diffusion and reduce mechanical stress during cycling, thereby extending the material's cycle life [5] . In conclusion, the results of this thesis will provide new insights into the fundamental properties of $Na_3VFe(PO_4)_3$ and the potentially beneficial effects of Mg doping.

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Structure and Properties of Carbon Dots

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Carbon dots (CDs) are extensively studied nanomaterials with broad application potential due to their bright, tunable photoluminescence (PL), high (photo)stability, low toxicity, and excellent biocompatibility, as well as their emerging promise in photocatalysis. However, understanding the origins of their PL and photocatalytic (PC) behavior remains incomplete [1,2], largely due to the structural complexity and variability of CDs. To address this, we employ a comprehensive suite of computational chemistry methods to explore their structure–property relationships. Using ab initio calculations, we investigated the reaction mechanisms underlying CD formation from simple precursors such as citric acid and ethylenediamine, successfully identifying early-stage pathways that align with experimental results [3]. Reactive molecular dynamics simulations provided further

insights into intermediate structures formed during later synthesis stages. Classical all-atom molecular dynamics simulations revealed the structural organization of CDs [4], including the localization of molecular fluorophores [5] formed during synthesis. Additionally, quantum mechanical and hybrid QM/MM calculations demonstrate how the optical properties of prototypical fluorophores are modified through dimerization, and noncovalent and covalent confinement within the CD structure [6]. The developed models can be further used to understand behavior of CDs, e.g., in sensing applications [7,8]. This work underscores the power of combining state-of-the-art theoretical approaches with modern experimental techniques to unravel the complex structural and optical properties of CDs and similar nanomaterials.

The work was supported from ERDF/ESF project TECHSCALE (No. CZ.02.01.01/00/22_008/0004587).

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Structure-Guided Identification of CRAT-Modulators: Toward Therapeutic Correction of CRAT Deficiency and Host-Directed Antimicrobial Strategies

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Carnitine O-acetyltransferase (CRAT) is a mitochondrial enzyme central to acetyl-CoA/carnitine homeostasis and metabolic flexibility. Mutations in the CRAT gene, such as the p.Tyr110Cys variant associated with early-onset Leigh syndrome, impair mitochondrial function and energy metabolism [1]. Here we present a structure-based virtual screening and docking workflow that enabled the identification of candidate small-molecule modulators targeting CRAT's carnitine-binding site [2]. Using homology modeling, molecular dynamics, and docking simulations (AutoDock4.2), we screened a curated chemical library against both wild-type and p.Tyr110Cys CRAT variants [2]. Prioritized ligands were validated through in vitro enzymatic assays on recombinant proteins and patient-derived fibroblast lysates [2]. Compounds such as artemisinin showed variant-selective activation, highlighting therapeutic potential. Beyond their relevance for treating inborn mitochondrial disorders, several ligands identified through this workflow [2] may hold promise for modulating host immune and metabolic responses during infection. Remarkably, CRAT shares a conserved catalytic core, acyl-carnitine binding architecture, and overall structural similarity with structurally related carnitine acyltransferases, including CROT, CPT1/2, and CRAT, underscoring the potential to extrapolate ligand scaffolds or selectivity principles across this enzyme family [3]. Given CRAT's role in regulating acetyl-CoA flux, mitochondrial homeostasis, and energy distribution, its pharmacological activation could support immune cell function and tissue resilience under stress conditions such as bacterial, fungal, or viral infection. In this context, CRAT-targeting compounds may serve as host-directed therapeutic agents, capable of reinforcing metabolic defenses without directly targeting the pathogen, an attractive strategy in the era of rising antimicrobial resistance. This work highlights the broader translational potential of CRAT modulators across both metabolic and infectious disease domains.

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Tailored Design of Antimicrobial Peptides through Artificial Intelligence

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The escalating threat of antibiotic resistance underscores the urgent need for innovative therapeutics, with antimicrobial peptides (AMPs) emerging as viable alternatives due to their diverse mechanisms of action (Fjell et al., 2011). This study introduces a systematic strategy to design two classes of AMPs with distinct bactericidal mechanisms: proline-rich peptides, which disrupt intracellular protein synthesis, and arginine-rich peptides, which destabilize bacterial membranes. Machine learning (ML) models trained on sequence-function data revealed critical physicochemical determinants for each class. For proline-rich AMPs, charge distribution and hydrophobicity patterns were identified as pivotal features, aligning with their role in intracellular targeting (Krizsan et al., 2015). In contrast, arginine-rich AMPs were governed by high charge density and membrane interaction motifs, consistent with their membrane-disruptive activity (Melo et al., 2009). Leveraging these insights, we utilized the generative AI model ESM-2 (Lin et al., 2023), fine-tuned on ML-classified sequences, to design 50 novel AMPs. Generated sequences were optimized for class-specific properties: proline-rich peptides prioritized structural motifs linked to protein synthesis inhibition, while arginine-rich variants emphasized cationic and amphipathic traits for membrane targeting. This integrative approach—combining ML-driven feature analysis with AI-powered sequence generation—advances the rational design of mechanism-specific AMPs. By elucidating sequence-function relationships and enabling tailored peptide engineering, our framework provides a scalable blueprint for developing next-generation antimicrobials (Porto et al., 2018).

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Tailoring catalytic activity of MoS2 catalyst through functionalization with Brønsted-acid ligands: A Computational and experimental study for enhanced Hydrogen Evolution Reaction in Alkaline Media

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The HER conducted in alkaline electrolytes could pave the way to produce hydrogen as a green fuel, as it enables the use of cost-effective and abundant transition metal-based catalysts.1 However, the slow water dissociation kinetics in alkaline environments still hinders its development.2,3 Recent advances have highlighted the potential of transition metal dichalcogenides, such as MoS2, as low-cost, effective alternatives for HER catalysis.4 However, molybdenum disulfide still faces challenges, including hydrophobicity and limited performance in alkaline conditions. Surprisingly, chemically

exfoliated MoS2 flakes functionalized with Brønsted-acid end-capped aryl groups, such as carboxylic and sulfonic, have shown activity in HER under pH conditions dependent on the acid strength of the pendant group. With the goal of designing and developing more efficient catalysts for HER in alkaline environments, this unexpected behavior was rationalized through a detailed theoretical study. The electronic and steric properties of these modified surfaces, together with mechanistic insights into the water dissociation process and molecular dynamics simulations, helped define the kinetic framework and clarify the relationship between catalytic performance in alkaline environment and the chemical and electronic nature of the surface modification. This study explores how sulfur vacancies (Vs) and surface functionalization with Brønsted-acid end- capped aryl fragment ligands impact the hydrogen evolution reaction (HER) activity of 1T-MoS2-based catalysts. Specifically, we focus on the Volmer step in the HER process, which involves water adsorption on the catalyst surface and its subsequent dissociation to form H*and OH* species, a key rate- determining step in alkaline media. We computed the adsorption energies of H2O on both stoichiometric and sulfur-defective 1T-MoS2 catalysts, including functionalized models. Our results show that water adsorption is thermodynamically unfavorable on stoichiometric 1T-MoS2 due to repulsive interactions with sulfur atoms. In contrast, sulfur-defective catalysts exhibit significantly stronger water adsorption, especially when functionalized with ligands that further stabilize the system by enhancing the exposure of molybdenum (Mo) sites. Through nudged elastic band (NEB) calculations, we found that the presence and nature of the organic ligands significantly influence the overall reaction kinetics. The aromatic ligands, interacting with hydrogen atoms from the water molecules, guide the water toward the channel formed by neighboring ligands, facilitating its approach to the surface. Notably, the vacancy site interacts more readily with water only in the case of the Ar-SO3– ligand, which facilitates the subsequent dissociation step, in agreement with experimental data. Additionally, ab initio molecular dynamics (AIMD) simulations confirmed that the wettability of the catalysts improves in the presence of sulfur vacancies. In conclusion, this study demonstrates that sulfur vacancies and surface functionalization with organic ligands significantly influence both water adsorption and dissociation, offering valuable insights for optimizing HER catalysts under alkaline conditions. Our findings suggest that tuning vacancy sites and ligand chemistry can enhance the catalytic efficiency of 1T-MoS2-based materials, enabling efficient hydrogen production across a broad pH range and advancing the design of HER catalysts.

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Targeting Mitochondrial ADP/ATP Carriers: Virtual screening of chemical libraries highlights new small molecules with potential therapeutic applications

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Mitochondrial carriers (MCs) are proteins that transport a wide range of metabolites, nucleotides, and coenzymes across the inner mitochondrial membrane [1]. Among them, the mitochondrial ADP/ATP carriers (AACs) are specifically responsible for the import of cytosolic ADP, and the export of matrix ATP, by switching between cytoplasmic-open (c-conformation) and matrix-open states (m-conformation) [2]. This process is essential for energy production, maintaining cell viability and regulating the mitochondrial permeability transition pore [1],[2]. Remarkably, the dysregulation of AAC expression/function was observed in aggressive tumors, whereas mutations affecting AACs were associated to the onset of rare diseases. Thanks to the existence of a few crystallized carrier structures, it was possible to create 3D comparative models of the four human AAC members to perform virtual screening of chemical libraries to identify new small molecules with high

affinity for the investigated mitochondrial carriers. Notably, AACs were crystallized in complex with two well-known inhibitors, namely the pro-apoptotic Carboxyatractyloside (CXT), stabilizing AACs in c-conformation, or the anti-apoptotic Bongkrekic acid (BKA), stabilizing AACs in the m-conformation. Starting from the re-docking of the two face-selective AAC-inhibitors, it is possible to search for high-affinity ligands structurally related to the characterized inhibitors searching for pro-apoptotic or anti-apoptotic small molecules able to regulate mitochondrial permeability transition pore (mPTP) opening and AAC function. The constructed 3D models of human AACs in c- and m-conformation were used to perform a virtual screening of 17248 selected compounds extracted from the KEGG Compound library (10839 compounds), the SelleckChem library (716 mitochondrial targeted compounds), the KEGG-drug library (3703 compounds) and the Diversity library (1990 compounds). Among the top-scoring compounds, resulting from the analysis of all the investigated chemical library, a few molecules displayed strong predicted binding affinities. i.e., Flavoxanthin and Momordin, known for their anti-inflammatory and pro-apoptotic activities, show a binding energy between -11.47 and -13.94 kcal/mol. This may suggest a possible role of negatively charged carboxylates (observed in Flavoxanthin, like those observed in CXT) or insaturations (observed in Momordin, similar to those observed in BKA) in stabilizing interactions within the AAC binding cavity. Other promising small molecules included sennoside, amaranth, gomphrenin-I, prebetanin, esmeraldin B, GDPhexose, and atractyloside, a well-known mitochondrial ADP/ATP carrier inhibitor. In vitro validation of the predicted high affinity small molecules is ongoing by using proteoliposomes and isothermal titration calorimetry.

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The Effect of Chalcogen–Chalcogen Bond Formation in the New Delhi Metallo-β-Lactamase 1 Enzyme to Counteract Antibiotic Resistance

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Antibiotics resistance is rapidly becoming an important needing of nowadays society, due to the inefficiency of many widely adopted drugs, such as penicillins and carbapenems. This takes place because a number of bacteria involved in the onset of severe human's diseases, like Escherichia coli, Klebsiella pneumoniae, Acinetobacter, Pseudomonas aeruginosa, and Enterobacter cloacae, have developed defensive enzymatic response to the antibiotic's activity. Among these enzymes, there is the New Delhi metallo-β-lactamase 1 (NDM-1) that can efficiently hydrolyze β-lactam containing compounds. NDM-1's knockout is therefore of interest for new therapies that inhibit the enzyme selectively, to avoid the chemical alteration of antibiotic. Promising results of NDM-1 inhibition have been recently obtained in presence of ebselen (EbSe), a molecule with wide range of already-known beneficial for human health. The enzyme has resulted indeed inhibited and, more intriguingly, its Zn2 cation of the active site pocket is removed. The mechanism remains poorly understood and it is therefore of high interest to acquire detailed understanding of it. Aiming to contribute to such needing topic, the current presentation concerns an in-depth computational investigation on the interaction between NDM-1 and EbSe, based on density functional theory calculations and μs-molecular dynamics simulations. [1] The reaction mechanism is elucidated employing large quantum chemical cluster active site model and considering different mechanistic proposals. It is unveiled that Cys208 of Zn2's coordination sphere attacks the Se atom of the ligand, favoured by proton donation of active site Lys211. The effect of chalcogen atom is further investigated considering the ebsulfur, where Se is replaced by S atom. Extensive molecular dynamics simulations allowed to detect the consequences of the covalent-bond formation to the inhibition from both structural and energetic point of view. The role of active site L3 and L10 loop and the energetic feasibility of Zn2 expulsion have been highlighted, thus providing a complete scenario on the activity of the enzyme. [1] [1] G. Ciardullo, M. Prejanò, A. Parise, N. Russo, T. Marino, J. Chem. Theory Comput. 2025, 21, 1422–1431

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The Hard Truth: How Composition and Structure Shape the Mechanics of Aluminosilicate Glasses

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Hardness [1] is a key property that determines how solid materials respond mechanically to applied stress. Understanding the mechanisms underlying hardness at the atomic scale is crucial for designing materials with enhanced mechanical performance. In this work, we employ molecular dynamics (MD) simulations to perform nano-scale indentation tests, offering new insights into the fundamental processes that influence hardness in oxide glasses. Our study specifically investigates how the atomic structure of aluminosilicate glasses is modified during their interaction with a diamond cone-shaped indenter. We focus on the albite–anorthite compositional series, which spans from sodium-rich albite ($NaAlSi_3O_8$) to calcium-rich anorthite ($CaAl_2Si_2O_8$). This compositional variation enables us to explore how the replacement of monovalent sodium ions with divalent calcium ions affects the charge compensation of AlO_4^- tetrahedra and the resulting reorganization of the glass network. In addition to nanoindentation, we present a detailed analysis of the surface characteristics of the glasses, including surface roughness and topographical evolution before and after deformation. The simulations reveal how surface morphology is influenced by composition and mechanical loading. To further complement the mechanical characterization, we also perform two additional sets of simulations: hydrostatic compression and uniaxial elongation [2]. These tests allow us to evaluate the elastic and plastic response of the glass networks under different stress states, providing a more complete picture of the mechanical behavior. By combining these simulations, we assess changes in structural parameters such as bond angles, coordination numbers, and network connectivity across different loading conditions. The effects of densification, both at the surface and in the bulk, are systematically examined across the compositional series. Variations in elastic moduli, residual stresses, and permanent deformation are linked to the underlying atomic rearrangements induced by mechanical stress. This investigation offers a comprehensive understanding of the nanoscale mechanical behavior of aluminosilicate glasses. By exploring the interplay between chemical composition, atomic structure, and mechanical performance, our study provides valuable insights for the rational design and optimization of glassy materials for advanced technological applications, including protective coatings, optical devices, and micro-electromechanical systems.

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The NPC1L1 sterol transporter: dynamics and interaction with natural compounds with inhibitory activity

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The NPC1L1 sterol transporter: dynamics and interaction with natural compounds with inhibitory activity

Niemann-Pick C1-Like 1 (NPC1L1) is a transmembrane protein (*Figure 1*) essential for cholesterol uptake in cells, which starts with the binding to the extracellular N-terminal domain (NTD). The cholesterol molecule then passes through a tunnel connecting the luminal domains to the transmembrane sterol sensing domain (SSD), from which it is finally released into the membrane. Both the NTD and the SSD domains play crucial roles. Experimental tests have shown that the NTD deletion results in a significantly reduced cholesterol uptake [1]. On the other hand, the SSD associates with flotillins, proteins located in the cytosol that have been reported to be essential for efficient cholesterol uptake [2] and are likely involved in the endocytosis. Ezetimibe [3], an inhibitor of NPC1L1 activity, is believed to act in two ways, i.e. by blocking the tunnel for cholesterol transport and by inducing long-range conformational changes in the SSD, thus influencing its binding to the flotillins. Other NPC1L1 inhibitors include natural compounds such as polyphenols and sterols, which have been shown to decrease cholesterol uptake [4]. Overall, a clear and comprehensive picture of NPC1L1 mechanisms and inhibition is still not available. In this work, we first focused on 13 sterols extracted and characterized from Sorghum bicolor by colleagues of our university. Considering the similarity of plant sterols to the cholesterol, we hypothesized that they bind the NTD in a similar way. Molecular docking followed by MM/GBSA calculations showed that several plant sterols have a greater affinity for the NTD compared to cholesterol. *In vitro* assays will be performed to confirm our findings. Moreover, we are studying the dynamics of NPC1L1 by performing molecular dynamics (MD) simulations in a membrane model [5] for the apo, cholesterol-bound, and ezetimibe-bound structures. Principal component analysis on the MD trajectories showed that the motion of the NTD is linked to the motion of residues of the SSD, thus suggesting the existence of a concerted mechanism in which the two domains work together. These preliminary results provide new insights into NPC1L1 function and its interaction with sterols, and may contribute to a better understanding of cholesterol uptake inhibition.

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The Structure of the Ferroelectric Nematic Phase: Insights from Molecular Dynamics Simulations

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The reported experimental discovery of a ferroelectric nematic (NF) phase is an exciting new development in liquid crystal research. [1-3] The new phase has several potential applications in displays and novel technology due to its unprecedented polarization. However, the origins of the phase are poorly understood, leading to derivatives of the first two mesogens to be discovered, making up most of the known NF mesogens.[1] At a molecular level, the phase is unusual, as often molecules with large dipole moments preferentially align with anti-parallel dipole ordering, as seen (for example) in cyanobiphenyl-based nematics, such as 5CB. However, in the NF phase, large molecular dipoles preferentially align in a parallel direction. [4]

Here, we report state-of-the-art atomistic molecular dynamics simulations of an NF mesogen: "DIO-F" (Fig. 1). We initially use quantum chemical calculations to optimise a new force field for DIO-F, and from molecular dynamics simulations of up to 648 molecules, we obtain excellent predictions of phase properties and transition temperatures. The NF phase is obtained by cooling an isotropic phase and allowing the NF phase to grow slowly over hundreds of nanoseconds of simulation. Cylindrical distribution functions are calculated to investigate the role of specific preferred intermolecular pairings. The calculations allow different explanations for the stability of the NF phase to be probed. NF stability is found to be promoted by a combination of local quadrupolar interactions and microphase separation of hydrophobic parts of the molecule. These interactions are sufficient to overcome the tendency for anti-parallel dipole alignment that is seen in many low molecular weight nematic and smectic systems.

Figure 1: Visualization of a ferroelectric nematic phase of "DIO-F ".

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Theoretical Design of Optoelectronic Properties in TM-Doped Au Nanoalloys

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In this work, we employ time-dependent density functional theory (TDDFT) to investigate the optical properties of Au-based hybrid bimetallic nanoalloys, modeling their growth via classical molecular dynamics using the LoDiS package and metal–metal interactions based on the second-moment approximation of the tight-binding scheme (TBSMA). Transition metals (TMs) selected from Au, Ag, Pd, Pt, and Rh are considered, with the analysis constrained to icosahedral seeds—a favorable geometry for such TMs at seed sizes ranging from 0.7 to 3.2 nm. By implementing the complex polarizability TDDFT (PolTDDFT) algorithm, an efficient method able to solve the TDDFT equations for large systems and for a wide energy interval, we explore such systems spectral features as a function of size, shape and chemical composition. Within the same chemical composition the size of the systems determines rather a system has a metallic or molecular- like behavior while their spatial arrangement of atoms governs the emergence of intrinsic chirality, assessed through circular dichroism (CD). Through linear absorption spectra of the analyzed systems we identify the key electronic transitions between ground and excited states, providing preliminary insights into potential collective excitations of conductive electrons, such as plasmons. This last feature is further examined by using the individual component map of oscillator strength (ICM-OS), a diagnostic tool that pinpoints plasmonic excitations based on occupied–virtual state contributions at specific energies. Combined with a fragment-based analysis, this approach allows to discern the role of individual metallic components, revealing whether a particular element promotes those collective electronic behavior in Au or rather their influence suppresses the plasmonic response.

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Theoretical Insights into CO_2 Activation on α-Bi_2O_3 under Operating Conditions

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Theoretical Insights into CO_2 Activation on α-Bi_2O_3 under Operating Conditions

The increasing use of fossil fuels over recent decades has triggered a global energy crisis, marked by the rapid depletion of these resources and the substantial release of carbon dioxide (CO_2) into the atmosphere [1]. CO_2 levels are projected to reach 570 ppm by 2100, a rise that contributes to critical environmental challenges such as global warming, polar ice melt, and ocean acidification [2]. To mitigate these effects and move toward a carbon-neutral cycle, strategies that utilize CO_2 as a feedstock for producing value-added chemicals have become increasingly important. Among these,

the electrochemical CO_2 reduction reaction (CO_2RR) has emerged as a promising approach for CO_2 conversion under mild conditions. However, several challenges need to be addressed: CO_2 activation is energy-demanding due to its high thermodynamic stability, CO2 conversion efficiency is generally limited by the competing Hydrogen Evolution Reaction (HER), and the selectivity towards specific products is low [3]. In recent years, bismuth-based electrocatalysts have gained much attention owing to their low toxicity, cost-effectiveness, abundance, and high selectivity for CO_2 conversion to formate or formic acid via electrochemical CO_2RR [4–6]. Nonetheless, achieving substantial progress requires a deeper microscopic understanding of the underlying processes. Due to their explicative and predictive power, ab initio calculations play a key role in the energy scenario as they characterize from an atomistic perspective the complex materials and give insights into the catalytic mechanisms. Previous computational studies on CO_2RR on Bi_2O_3 have focused on pristine and defective surfaces [6], or the influence of decorating metallic nanocluster (NC) [7]. In this work, we extend these efforts by investigating the thermodynamically stable α-phase of Bi_2O_3 as a potential electrocatalyst for CO_2RR, taking into account the impact of oxygen vacancies and the role of an externally applied bias (i.e., operating electrochemical conditions) [8].

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Theoretical Investigation of Solvent-Driven Dynamic Stereochemistry

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VCD (vibrational circular dichroism) spectroscopy is established as a common and reliable method for investigating the absolute configuration of small molecules.1 However, in order to obtain a detailed understanding of the preferred conformation, suitable computer-assisted methods are necessary to enable a reliable conformational search and predict the experimental spectrum.1 Yet, the experimental and theoretical methods reach their limits or become more difficult once solvent effects become relevant and thus have to be taken into account as solvation can modulate conformational ensembles. More polar solvents, such as DMSO, can result in strong interaction with the investigated molecule, necessitating consideration of explicit microsolvation.1 To overcome this problem, a new approach using the EC-RISM solvation theory (Embedded Cluster Reference Interaction Site Model)2 was investigated. EC-RISM combines quantum mechanical calculations with the statistical mechanics-based 3D RISM solvation model in an iterative and self-consistent process and can be used for the direct determination of relative conformer free energies and their populations in solution. This approach provides added value over implicit solvation theories such as PCM (Polarizable Continuum Model) due to consideration of solvent site density correlation and distribution functions around a molecule of interest.3,4,5 Furthermore, a spatially resolved solvation free energy density is accessible that allows for assigning the contribution of certain solvent regions to the overall solvation effect.6 According to the most densely populated positions the relevant interactions between the solvent and solute can be predicted and applied for the placement of explicit solvent

molecules. To evaluate this approach, two different compounds (Fig. 1) were analyzed in DMSO and chloroform solution, emphasizing solvent-driven conformational changes as well as the competition between intra- and intermolecular interactions.7,8

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Theoretical chemistry investigation of H12-M2-(DOBDP)3, a new mixed electron and proton conductivity MOF

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Metal-organic frameworks (MOFs) with mixed proton and electron conductivity (MPEC) are promising materials for electrochemical energy systems. So far, a very small number of 2D MOFs have been shown to exhibit both types of conductivity. Two new 3D MOF candidates have recently been investigated in an experiment-theory collaboration [1], having the general formula H_{12}-M_2-$(DOBDP)_3$ with M being Fe^{3+} or Al^{3+}, and H_6-DOBDP is the 2,5-dihydroxy-1,4-benzenediphosphonic acid. Both MOFs follow up to 4 hydration-driven phase transitions, consisting of scaffold breathing and bending, rendering X-ray diffraction (XRD) resolution and other measurements challenging or impossible. Quantum chemistry methods at the Density Function Theory level of approximation with Periodic Boundary Conditions have therefore been carried out, following a recently published methodology [2] (calculation parameters, basis sets, and exchange-correlation functionals), in order to rationalize the behavior and the structural features of the scaffolds for the different hydration level phases. Geometry optimization, band structure, XRD, and density of state calculations allowed 1) to determine the iron centers spin multiplicity, 2) to show the integrity of the scaffolds even under strong distortions, 3) to propose mechanisms driving the transition phases, 4) to rationalize the ion-exchange experimental results, and 5) to better understand the electronic conductivity mechanism.

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Theoretical study of antenna-chromophore mechanism in luminescent lanthanide complexes

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Rare-earth complexes are attracting attention as clean energy conversion materials utilizing chromophores for efficient photo-excited energy conversion that emit light having well defined narrow bands in different spectral ranges with long lifetimes and high quantum yields. The dithiocarbamate ligands (*dtc*, S2CR) are a special class of chromophores that have been poorly studied in relation to their sensitization ability of the lanthanide luminescence. The presence of dtc ligand in Ln(III)-phen complexes leads to alteration of the Ln luminescence. Moreover, the europium complex possesses unusual orange color, which changes to yellow under temperature decrease. Ln(S2CR)3(phen) complexes are suitable materials for novel electronic devices and precursors for preparation of lanthanide sulphide nanoparticles for photocatalytic applications. Various ambiguous mechanisms and interpretations of the observed optical features have been proposed in the previous reports. For detailed explanation of the photophysical properties of Ln(S2CR)3(phen) complexes (Ln = Eu, Sm; R = N(C2H5)2, N(C4H8)) we examined them by theoretical modelling in solution and solid phase at various temperatures.1 DFT/TDDFT/ωB97xD and multireference SA-CASSCF/NEVPT2 calculations with perturbative spin–orbit coupling corrections and semiempirical methods are applied to construct the Jablonski energy diagrams. The excited-state energy transfer mechanism is discussed regarding the competing excited state processes and possible sensitized mechanism of the metal-centered emissions. The theoretical estimations are supported by experimental data (single crystal X-ray diffraction analysis, powder XRD, TG-DTA, EPR, IR, UV-Vis, photoluminescence spectra). The combined theoretical and experimental research gives a new insight concerning: 1) ground state electron density distribution in the studied complexes, which produces a partial reduction of Eu(III); 2) interligand n(dtc)-⊠*(phen) charge transfer character of the first excited state (dark state), which favors the S1-T1 intersystem crossing or S1(phen)-Ln energy transfer over the S1-S0 (fluorescence); 3) appropriate T1-Ln(acceptor) energy resonance for effective excited state energy transfer. The established energy transfer mechanism and the key factors controlling the effective luminescence may help to carry out the targeted synthesis of new lanthanide materials with selected chromophore ligands with desired optical or magnetic (Eu2+) properties.

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Theoretical tautomer prediction as a testbed for theory-based experimental uncertainty analysis

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Theoretical tautomer prediction as a testbed for theory-based experimental uncertainty analysis

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Thermodynamic Stability of MgSc2Se4 Surfaces

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Magnesium-based batteries represent a promising post-lithium battery technology due to magnesium's low cost and high natural abundance. Among the few materials exhibiting good Mg ion conductivity, the spinel phase $MgSc_2Se_4$ stands out as a particularly promising solid electrolyte candidate.[1] While the bulk properties of $MgSc_2Se_4$ are already well understood, advancing toward practical applications requires comprehensive understanding of interface behaviour in complete battery systems. This work focuses on elucidating surface stability and restructuring phenomena of $MgSc_2Se_4$. We employed periodic density-functional theory to investigate experimentally relevant surface facets, providing insights into atomic-scale behaviour at its surface. Based on ab-initio thermodynamics, we constructed a phase diagram mapping $MgSc_2Se_4$ surface stability as a function of the chemical potentials of its atomic species.[2],[3] Our results reveal the relative stability of different surface terminations and planes. These findings provide fundamental insights into $MgSc_2Se_4$ surface properties essential for understanding and optimising solid-state magnesium battery performance.

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Towards Highly Specific Theranostics via Engineered Nanoparticles Mimicking Extracellular Vesicles: Focus on Envelope Dynamics

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European project MIMIC-KeY (www.mimickey.eu) aims at creating synthetic extracellular vesicles (EVs) and demonstrating their use with the specific delivery of therapeutic cargo for treating lysosomal bone metabolic disease. Here we present a brief report on computational analyses that assisted the design of artificial nanoparticles consisting of a breakable organosilica core (allowing high payload encapsulation efficiency and controlled release) surrounded by a single-stack lipid bilayer envelope, notably allowing to host proteins.

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Towards a Generalizable Machine Learning Potential for Water Adsorption within MOFs

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Direct air capture (DAC) is a promising strategy to mitigate atmospheric CO_2 concentrations, requiring adsorbents with high CO_2 affinity and low water affinity. Metal–organic frameworks (MOFs) are attractive candidates for DAC due to their structural tunability and high porosity.

While high-throughput computational screening studies have been conducted to find the optimal MOFs1, accurately predicting water adsorption enthalpy remains challenging, as classical force fields often fail to capture hydrogen bonding and typically assume a rigid framework. These limitations can be addressed using machine learning potentials (MLPs) trained on flexible MOF structures with one adsorbed H_2O. For example, in CAU-10 with one H_2O molecule per unit cell, the water adsorption enthalpy predicted by the universal force field (UFF) is 26 kJ/mol, which is significantly lower than the experimental value of 52 kJ/mol. In contrast, the MLP predicts 44.5 kJ/mol, which is in much better agreement with experiment.

We develop a data-efficient approach to train a generalizable MLP for Al-MOFs, achieving energy errors below 1 meV/atom and force errors below 30 meV/Å, with fewer than 400 configurations required per MOF. Validation against experimental data for five Al-MOFs confirms the accuracy of our method, enabling DFT-level predictions of water adsorption enthalpy for DAC screening.

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Trends in Competing Oxygen and Chlorine Evolution Reactions over Electrochemically Formed Single-Atom Centers of MXenes

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Single-atom catalysts (SACs) have been developed as a promising alternative for the design of highly active and selective catalysts, with experimental evidence confirming their successful synthesis. In a SAC catalyst, typically a transition metal – most commonly a precious metal – is embedded onto a support, and the resulting active site catalyzes chemical transformations relevant to energy conversion with high activity, selectivity, and maximum atomic efficiency. A typical selectivity problem encountered in the chemical industry refers to the competing oxygen (OER) and chlorine (CER) evolution reactions. While mixed-metal oxides, such as RuO2, IrO2, and TiO2, have been dominating the field of CER catalysis over the last 50 years, the selectivity of the competing reaction channels still imposes a challenge. [1-3]

Recent advances in SAC-based materials have revitalized this area of research by opening new avenues for the design of selective CER catalysts. While the recently synthesized SAC-based CER catalysts still rely on expensive platinum-group metals, low-cost alternatives based on earth-abundant elements have yet to be developed [4].

In this contribution, we demonstrate that SAC sites can also be formed electrochemically through water-mediated surface oxidation on the basal planes of MXenes, a class of two-dimensional materials composed of transition-metal carbides and nitrides [5]. Electrochemically formed SACs on MXenes could represent a promising alternative to CER catalysts as they eliminate the need for precious metals. By employing density functional theory (DFT) calculations combined with a descriptor-based analysis, we elucidate the relationship between in situ-formed SAC structures on MXenes and their catalytic performance in the competing oxygen (OER) and chlorine (CER) evolution reactions

[6-7]. In total, 48 different SAC motifs are systematically screened to identify activity and selectivity trends in CER and OER. Our results highlight that group V-based MXenes (V2X, Nb2X, and Ta2X) as promising candidates for selective CER, thus providing first evidence that electrochemically formed SACs based on MXenes can be exploited as efficient catalytic materials for energy conversion and storage processes [8].

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Tubulin polymerization inhibition, molecular structure and ligand-enzyme interactions of [1,3]thiazolo[3,2-a]benzimidazol-3(2H)-one derivatives

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It is known that the synthesis of tubulin and microtubules is part of the processes of cell division which makes it a potential target in the development of new chemotherapeutic agents for cancer as well as parasitic infections treatment [1]. Several binding sites are known on the surface of tubulin, but the best studied for the purpose of designing polymerization inhibitors are the colchicine and taxine sites [2]. The potential of the benzimidazole structure in anticancer therapy is well known. There are a number of representatives of this class of compounds that are actively used as anti-cancer agents, such as bendamustine, nocodazole and denibulin [3]. On the other hand, benzimidazole carbamates such as albendazole, mebendazole, carbendazim and other derivatives, show a high therapeutic index, broad spectrum activity against nematodes, cestodes and trematodes. However, anthelmintic resistance limits their action frequently and motivates the discovery of new compounds with anthelmintic activity. Benzimidazole compounds bind to the colchicine binding site of β-tubulin in the parasitic cells, thus effecting its polymerization, disrupting the microtubule functions and leading to the of parasites death. Herein we present an in vitro evaluation on ability of 2-substituted-[1,3]thiazolo[3,2-a]benzimidazol-3(2H)-ones to interfere with tubulin polymerization, DFT characterization of the molecular structure of the compounds and molecular docking study on tubulin-ligands interactions. It was found that Z conformation of the exocyclic double bond is the more stable, and for compounds with a heterocyclic fragment, where rotation about the C-C bond to the aryl fragment leads to distinguishable conformers, s-cis is more favorable. The interaction of the 2-substituted-[1,3]thiazolo[3,2-a]benzimidazol-3(2H)-ones with tubulin was explored by molecular docking at the colchicine binding site and provided useful insights on the structure-activity relationship.

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V-Nitrogenase reduction of carbon monoxide: A multiscale computational investigation

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Nitrogenases are enzymes that reduce atmospheric nitrogen (N2) into bioavailable ammonia (NH3), thereby facilitaIng the nitrogen cycle and enabling life on Earth [1,2]. Nitrogenases can be divided into three main classes based on the idenIty of the heteroatom in the acIve site: molybdenum nitrogenase (Mo-nitrogenase), vanadium nitrogenase (V-nitrogenase), and iron- only nitrogenase (Fe-nitrogenase) [3,4]. Mo-nitrogenase, the most acIve and extensively studied among the three classes, has provided valuable insights into nitrogen fixaIon[5]. However, recent aWenIon has shiXed towards V-nitrogenase due to its remarkable ability to bind carbon monoxide (CO) in its resIng state and reduce CO predominantly to ethylene under turnover condiIons [6,7]. The availability of (recent) high-resoluIon (˜1Å) X-ray structures of V-nitrogenase provides an excellent starIng point for computaIonal invesIgaIons [8,9]. Here, we employ a hybrid quantum mechanical (QM)/molecular mechanical (MM) approach combined with the Broken Symmetry [10] method to invesIgate the electronic and magneIc properIes that facilitate CO binding to the resIng state of V- nitrogenase. Understanding enzymaIc CO capture and reducIon informs the design of new enzymes with great biotechnological potenIal. [1] Wilson, P. W.; Burris, R. H. The mechanism of biological nitrogen fixation. Bacteriological Reviews 1947, 11 (1), 41–73. [2] Burgess, B. K.; Lowe, D. J. Mechanism of Molybdenum Nitrogenase. Chem. Rev. 1996, 96 (7), 2983–3012. [3] HoVman, B. M.; Lukoyanov, D.; Yang, Z.-Y.; Dean, D. R.; Seefeldt, L. C. Mechanism of Nitrogen Fixation by Nitrogenase: The Next Stage. Chem. Rev. 2014, 114 (8), 4041–4062. [4] Jasniewski, A. J.; Lee, C. C.; Ribbe, M. W.; Hu, Y. Reactivity, Mechanism, and Assembly of the Alternative Nitrogenases. Chem. Rev. 2020, 120 (12), 5107–5157. [5] Burgess, B. K. The Iron-Molybdenum Cofactor of Nitrogenase. Chem. Rev. 1990, 90 (8), 1377–1406. [6] Lee, C. C.; Hu, Y.; Ribbe, M. W. Vanadium Nitrogenase Reduces CO. Science 2010, 329 (5992), 642–642. [7] Hu, Y.; Lee, C. C.; Ribbe, M. W. Extending the Carbon Chain: Hydrocarbon Formation Catalyzed by Vanadium/Molybdenum Nitrogenases. Science 2011, 333 (6043), 753–755. [8] Rohde, M.; Laun, K.; Zebger, I.; Stripp, S. T.; Einsle, O. Two Ligand-Binding Sites in CO-Reducing V Nitrogenase Reveal a General Mechanistic Principle. Science Advances 2021, 7 (22). [9] Rohde, M.; Grunau, K.; Einsle, O. CO Binding to the FeV Cofactor of CO-Reducing Vanadium Nitrogenase at Atomic Resolution. Angew. Chem. Int. Ed. 2020, 59 (52), 23626–23630. [10] Lovell, T.; Li, J.; Liu, T.; Case, D. A.; Noodleman, L. FeMo Cofactor of Nitrogenase: A Density Functional Study of States MN, MOX, MR, and MI. J. Am. Chem. Soc. 2001, 123 (49), 12392–12410.

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VIRTUAL CHEMIST or computer-aided design in asymmetric catalysis

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The field of asymmetric catalysis has revolutionized organic synthesis over the past fifty years, not only by making new reactions possible or faster, but also by promoting the synthesis of a single stereoisomer as the main product.[1] However, the development of new chiral catalysts remains a real challenge that often results in a long and laborious process, requiring the synthesis and evaluation of several ligands and catalysts in an iterative manner. To address these challenges, the Moitessier group developed VIRTUAL CHEMIST (VC), a computational platform integrating physics-based methods to predict stereoselectivity.[2] While VC has successfully reproduced over 350 stereoselectivities across multiple reaction classes, its accuracy remains insufficient for ranking catalysts.

This talk presents a new approach to enhance VC by integrating machine learning and transition state optimization to improve both accuracy and efficiency. A refined transition state search algorithm will be discussed to selectively optimize promising catalysts. This machine learning model trained on VC-generated data will predict catalytic performance, even for reactions with limited experimental data. Finally, generative models will be employed to design novel catalysts, with experimental validation of computationally predicted candidates. This will be demonstrated on an asymmetric organocatalyzed Diels-Alder reaction where the reaction mechanism was studied more thoroughly. In particular, our group was able to show that the pKa of various catalysts could be linked to the catalytic activity and hence build a pKa predictor based on Graph Neural Network to include this information within our platform.[3] By merging computational and experimental chemistry, this research aims to accelerate catalyst discovery, making computational tools more accessible for organic chemists and advancing the integration of Machine Learning in reaction design.

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Vacancy Engineering of Nitrogen-Doped Graphene for Stabilizing Iron Single-Atom Catalysts: Unveiling the Balance Between CO_2 Reduction Activity and Stability

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The development of efficient and sustainable catalysts is a cornerstone in the global effort to address pressing environmental challenges, particularly the conversion of carbon dioxide (CO_2) into value-added products. Among the emerging strategies, single-atom catalysts (SACs) have garnered significant attention due to their exceptional atom utilization, tunable electronic properties, and potential for high catalytic selectivity [1, 2, 3]. Precise defect engineering in nitrogen-doped graphene (NG) presents a powerful strategy for the design of advanced SACs [4]. Here, we employ spin-polarized density functional theory (DFT) calculations to systematically investigate the stability of graphene vacancies and their role in anchoring iron atoms for carbon dioxide reduction reaction (CO_2RR). Our work identifies key trends linking vacancy type, nitrogen doping patterns, and iron binding energies, revealing that vacancy stabilization is highly dependent on defect size and nitrogen configuration. Beyond thermodynamic considerations, we demonstrate that catalytic activity and stability are not necessarily correlated. Through detailed energy profile analysis of CO_2RR intermediates, we find that the most thermodynamically stable Fe–N arrangements do not always correspond to the lowest activation barriers. Instead, kinetically favorable, less stable Fe–N configurations provide superior catalytic performance. Furthermore, the oxidation state of iron, the local charge environment, and the solvent effect critically modulate both the stability and reactivity of Fe@NG sites. These findings highlight a crucial trade-off between stability and activity in SACs design and opens avenues for the rational development of highly efficient SACs for sustainable energy applications.

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Water assisted Interfacial Polymerization of TEPA and HMDI at the Water/Hexadecane Interface

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Interfacial polymerization (IP) between tetraethylenepentamine (TEPA) and 4,4'-methylenebis(cyclohexyl isocyanate) (HMDI) at the water/hexadecane interface proceeds too rapidly to effectively control reaction kinetics or tailor polymer morphology. To elucidate the underlying mechanism, we performed quantum mechanical (QM) calculations, molecular dynamics (MD) simulations, and experimental verification. QM results reveal that a single water molecule significantly lowers the proton transfer energy barriers to 3.6, 4.0, 4.4 kcal/mol, compared to 15.5, 17.8, 23.9 kcal/mol of direct proton transfer (in vacuum, implicit hexadecane, and implicit water). Acting as a proton transfer bridge, the water molecule forms hydrogen bonds with both TEPA and HMDI, thereby facilitating the reaction at the interface. MD simulations show preferential adsorption of HMDI at the interface and high solubility of TEPA in water. Experimental data further confirm that polymerization occurs mainly in the hexadecane phase near the interface. This study provides the first direct evidence for water-mediated catalysis in interfacial polymerization and offers a foundation for designing better-controlled IP systems with tunable morphology and kinetics.

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aims PAX: Automated, Parallel Active Learning for Machine Learning Force Fields

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aims PAX: Automated, Parallel Active Learning for Machine Learning Force Fields

We present ab initio molecular simulation Parallel Active eXploration (aims PAX), an automated framework for constructing diverse and high-quality datasets for training machine learning force fields (MLFFs) [1] through active learning (AL). This software combines the electronic structure code FHI-aims [2] with the MACE MLFF [3, 4], offering a user-friendly approach for efficient dataset creation. Through a parallelized, automated AL algorithm that leverages continual learning and simultaneous sampling across multiple trajectories, our approach minimizes user intervention and optimizes computational resource use.

We showcase the framework by applying it to a peptide with 100 atoms, generating a balanced dataset with under a thousand DFT reference calculations. The resulting MLFF enables stable, nanosecond-

scale molecular dynamics simulations, reducing the computational time needed for dataset creation by up to three orders of magnitude.

Additionally, we investigate an organic molecule adsorbed to an inorganic surface where the dynamics are dominated by weak interactions between the surface and molecule. These often pose a challenge for standard MLFF training procedures. To address this, we use an intermolecular force uncertainty measure and dynamics loss function inside aims PAX to improve a model's description of intermolecular interactions. This highlights the software's flexible nature, facilitating quick implementation of new tools for specific systems and problems.

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