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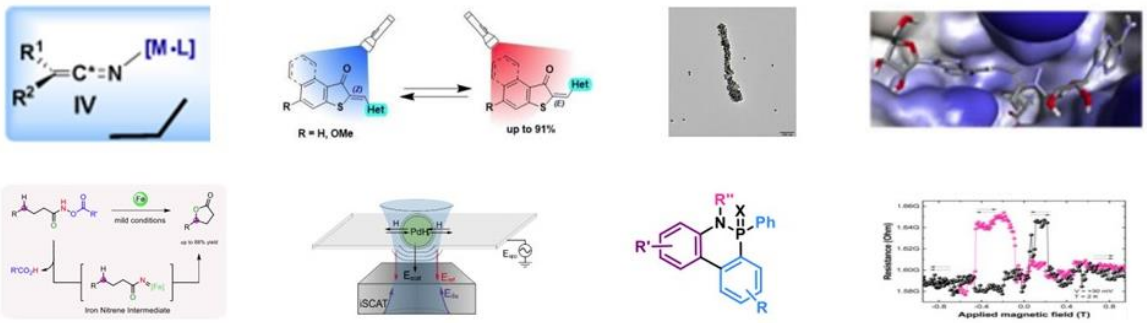

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Liste des communications orales

Type de communication : communication orale ☐ affiche ☐

"Modeling the effects of photo-induced drugs in a biological membrane model by molecular dynamics simulations"

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Résumé:

In this work we study, by molecular modeling and simulation, the effects of a photo-induced molecular switch based on a cyclocurcumin derivative on model lipid bilayers of different composition. Two systems consisting of 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC) as well as a mixture of three different lipids (DPPC, DOPC, cholesterol) were used to mimic cell membranes. The cyclocurcumin derivative can be used in light-activated chemotherapy to selectively induce cell death by perturbing cellular membranes due to its structural perturbation brought by the E/Z photoisomerization[1]. This approach is an appealing alternative to conventional photodynamic therapy (PDT) because it is operative also in absence of oxygen, and hence could be efficient for hypoxic tumors.

Classical molecular dynamics simulations were used to investigate the interaction of the chromophore with the lipid bilayers. We also used enhanced sampling simulations via the coupling of ABF and Metadynamics (meta-eABF) to determining free energy profiles for the penetration of the switch in the membranes.

Additionally, the effects of different concentrations of chromophore, as well as the photoswitching, i.e. E/Z photoisomerization, on the membranes structural parameters were investigated and compared. We show that the interaction with the DPPC-only membrane is highly dependent on the concentration, furthermore we also evidenced a transition in the arrangement of the photoswitches from ordered to disordered state[2]. In the more complex membrane, we showed that the cyclocurcumin derivative interacted differently, causing less profound damages and changes in the lipid bilayer[3]. However, for both membrane models we confirmed that the structural parameters of the bilayer are differently affected by the two isomers, and hence can be modulated through photoswitching, offering interesting perspectives for future applications.

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2) A. Delova, R. Losantos, J. Pecourneau, "Perturbation of Lipid Bilayers by Biomimetic Photoswitches Based on Cyclocurcumin", JCIM, 2022

3) A. Delova, R. Losantos, J. Pecourneau, M. Mourer, A. Pasc, A. Monari, "Modelling the effects of E/Z photoisomerization of a cyclocurcumin analogue on the properties of cellular lipid membranes", PCCP, 2023

Keywords: cyclocurcumin, molecular dynamics, photoisomerization, lipid membranes

Communication orale ☒ affiche ☐

Evaluation of NCN and NNN type nickel tridentate clamps for the preparation of N-metallated nitriles and application in the reaction of asymmetric α-cyanoalkylation

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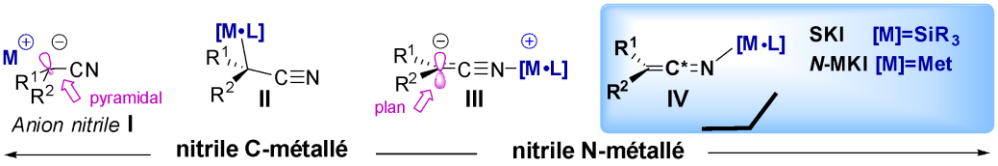
In the United States, in 2011, among the top 200 drugs sold, 21 have at least one quaternary center derived from a natural product and none of these stereocenters have been created by chemical synthesis.[1] It should be noted that the construction of two adjacent stereocenters is a major issue in organic synthesis. Therefore, the development of new strategies based on catalytic methods for the synthesis of enantiopure molecules with contiguous "all carbon" centers remains a very active area of research. In this context, α -cyanocarbanion complexes have emerged as valuable intermediates due to their excellent reactivity as nucleophiles and the possible transformation of the nitrile group into a wide variety of other functions. In this field, methodologies based on N-silylated (SKI) or N-metalated (N-MKI) ketene imines IV (scheme 1) have attracted particular attention as potent α-cyano carbanion equivalents, as they offer unique synthetic opportunities in asymmetric catalysis.



Regarding the enantioselective elaboration of vicinal stereocenters, significant works have been published on the application of N-silyl ketene imines (SKIs)[2,3] in aldol and Mannich reactions. However, these reactions possess a limited field of application due to the need for a strong base in stoichiometric amounts to generate the SKI species. On the contrary, N-metallated ketene imines can be easily formed in the presence of a mild base thanks to the coordination of the nitrile to the metallic center. However, such intermediate species remain scarcely reported. Nakamura [2] and very recently Shibasaki[4] have postulated their existence in asymmetric Mannich-type reactions catalyzed by, respectively, a NCN-Pd Pincer (Phebim-type) and a CCC-Ni pincer (bis-triazolylidene-type). Regarding the actual problematic associated with endangered noble metal such as Pd, we propose to widen the scope of more abundant and less expensive Ni derivatives by using tridentate NNN-Ni pincers in alpha-cyanoalkylation reactions involving imines or aldehydes.

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Keywords: N-silylated (SKI), N-metalated (N-MKI), stereocenters.

Type de communication : communication orale X affiche ☐

Shear flow induced aggregation of Aβ amyloid and diffusion in the interstitial brain space

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Résumé :

Fluid flows play a key role in many biological processes : from increase of reaction rates to protein partial unfolding, from transport phenomena to enhancement of proteins aggregation or reshaping and breakage of olygomeric aggregates. A precise characterization of the microscopic mechanisms underlying all these phenomena may play a crucial role in understanding physiological processes, like the formation of functional or phatological states of biological matter. This knowledge can also have several technological outcomes when applied to the design of biomimetic devices or pharmaceutical applications. An example of such process is the aggregation of Aβ peptides in the extracellular brain space [1], known to be one of the main causes of Alzheimer's disease, a highly impairing neurodegenerative pathology responsible for most of dementia cases. Despite having a central role in the progression of the pathology, a complete understanding of the microscopic processes of the formation of amyloid fibrils in vivo is still lacking. The formation of Aβ fibrils takes place in the brain interstitial space (ISS), a complex, dynamic environment containing neural cells, blood vessels and filled with the interstitial fluid [2]. Advancement in imaging techniques made it possible to have a three-dimensional representation of the brain's intricate structure with a high level of details [3]. In this work we used a multi-physics approach [4] to simulate amyloid aggregation under shear flow, showing that a key ingredient responsible for the speed up of the aggregation process is the balance between diffusive and advective components of the proteins' motion. We were also able to recover annular conformations of amyloid fibrils, as recently experimentally reported [5]. Finally, by simulating the fluid and the diffusion of particles subject to a velocity field in a realistically reconstructed portion of the ISS, we were able to rule out the hypotesis that the fluid flows drive the day-night clearance mechanism of biological waste such as amyloid aggregates.

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Keywords: Molecular simulations, fluid simulations, proteins aggregation

Type de communication : communication orale ☒ affiche ☐

Easily Accessible Substituted Heterocyclic Hemithioindigos as Bistable Molecular Photoswitches

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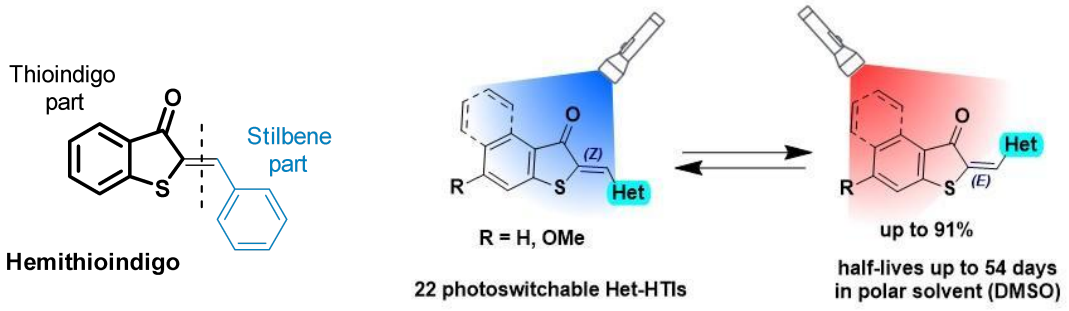
Résumé :

Small photoswitchable compounds have recently received a significant attraction because of their broad spectrum of applications from materials sciences to biology, including supramolecular chemistry and catalysis, to only name those. The capacity of these molecules to undergo reversible changes by simple irradiation with light makes them very attractive. To stand out from structures very explored such as azobenzenes,[1] Hemithioindigos (HTIs) retained our attention. Hemithioindigos, as indicated by the name, belongs to the class of indigoid photoswitches. In addition to being well-known for their properties as chromophores, they are an exceptional class of photoswitches[2] because of their combination of advantageous properties such as a strong absorption in the visible-light region, a fast photoisomerization or high bistability. Developing efficient HTIs as visible-light-responsive photoswitches for photo-controlled biological applications remains challenging and to respond to this, the redshifting by playing on the aromatic substrate of the stilbene part became a motivation for researchers working on photoswitchable scaffold[3].

This work presents the development of an efficient synthesis pathway of heterocycle-containing Hemithioindigos (Het-HTIs) with electron-rich and electron-poor heterocycles, the different structural modifications on the thioindigo moiety and the scrutinization of their photoswitching performances[4].



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Keywords: Chromophore, Hemithioindigo, Photoswitch, Photoizomerisation

Type de communication : communication orale ☒ affiche ☐

Probing solvent effect on vibrational spectra of organic chromophore using QM/MM approach and time-series analysis.

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Résumé :

As all spectroscopic properties, the vibrational response of a molecule is altered by the environment. The solvent molecular distribution around the solute strongly affects its vibrational motion and results in a modification of its spectroscopic signature. It becomes thus crucial to explicitly take into account the environment with a hybrid QM/MM approach while targeting the accurate modeling of such a property.

In this talk, we show that by performing a time-series analysis of the dipole moment and polarizability tensor along a QM/MM molecular dynamics trajectory, we successfully model the vibrational InfraRed and Raman spectra of an organic chromophore such as azadioxatriangulenium[1] ($ADOTA^+$) in water solution.[2] By comparing them with InfraRed and Raman spectra derived from the gas phase or at static level, we especially measure which vibrational modes are prone to solvent effects and anharmonicity. Furthermore, we explore the potential of machine learning to enhance and accelerate the QM/MM simulation of vibrational spectra.

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Keywords: vibrational spectroscopy; QM/MM; *ab initio* Molecular Dynamics; Time Series Analysis

Type de communication : communication orale ☒ affiche ☐

Imaging hydrogen storage at the nanoscale using *operando* optical microscopy

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Résumé : Hydrogen is a promising energy source toward clean energy transition, however the use of hydrogen gas as an energy carrier, requires optimizing its storage routes. Hydrogen can be stored, by electrochemical means, in the form of metal hydride in various solids at ambient temperature and pressure, without risk for explosions, and it becomes even more efficient if the material is nanostructured[1]. However, we have not yet identified materials that combine all the requirements for efficient electrochemical hydrogen storage applications in terms of high storage capacity, good hydrogen sorption thermodynamics and kinetics, and reversibility/cycling. It is therefore important to observe, understand and quantify kinetics and thermodynamics of hydrogen sorption process through *in situ* and dynamic observations at the nanoscale[2].
It can be achieved using local electrochemical probes such as nanoelectrodes or nanopipettes and the analyses of current fluctuation over time that revealed the highly complex nature of the processes (solution supersaturation, mass transport, reaction kinetic, etc.) at the nanomaterials[3].
A second approach to probe *operando* the electrochemical formation of nanobubbles relies on the coupling of electrochemistry to imaging techniques. Among them, optical microscopy offers several advantages such as simplicity, high throughput imaging and high sensitivity[3]. In this work, we demonstrate how label-free optical microscopy Interferometric scattering microscope (iSCAT) allows the dynamic observation and quantification of the kinetics of hydrogen insertion in Pd nanoparticles (Figure 1). This technique provides high temporal resolution imaging, revealing the degradation process of nanoparticles throughout the cycles of hydrogen storage and release. Insights gained from these observations are pivotal for engineering nanomaterials with enhanced electrochemical hydrogen storage capacities and optimized performance in storage/release cycles.

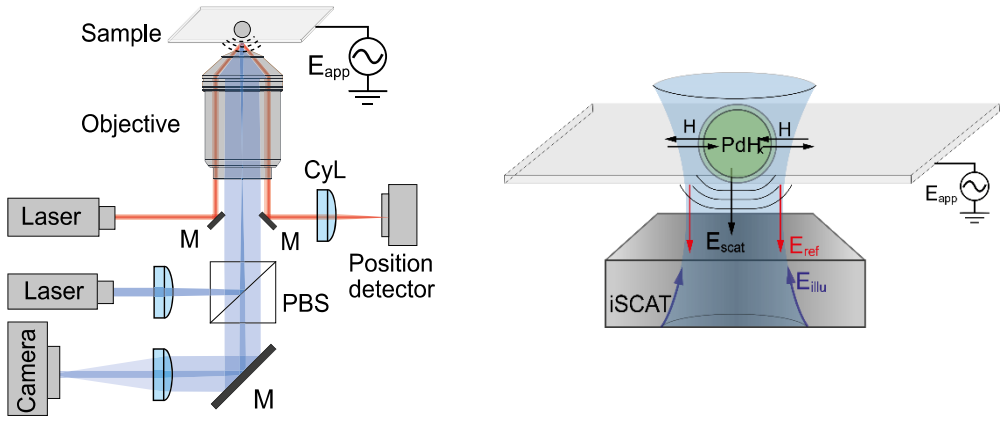

Figure1 Schematics of the iSCAT and the schematics of the and hydrogen insertion inside Pd nanoparticles.

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Keywords: Electrochemical hydrogen storage; Operando optical microscopy; Pd nanomaeterials

Type de communication : communication orale ☒ affiche ☐

Synthesis of Bisubstrate Analogues to study RNA Methyltransferases

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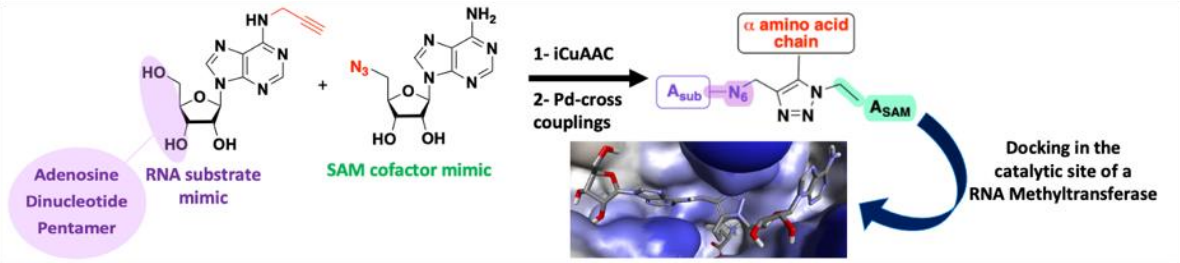
Abstract :

RNAs undergo numerous post-transcriptional modifications regulating their fate and function at the cellular level. Among these modifications, methylation at the N6 position of adenosine (m6A) in mRNA is crucial for RNA metabolism, stability, and various important biological events. m6A RNA methyltransferases (RNA MTases) are a family of enzymes that catalyze RNA methylation using the S-adenosyl-L-methionine cofactor at the N6 position of adenosine. While MTase RNAs are promising therapeutic targets, particularly for cancers, neurological and metabolic diseases, new molecules are needed to fully understand their roles in these diseases. In particular, the RNA recognition process and the molecular mechanism involved in methyl transfer need to be elucidated.

We report the synthesis of bisubstrates to study m6A RNA methyltransferases. These bisubstrates are molecules containing an analogue unit of S-adenosyl-L-methionine (SAM) covalently bonded by a triazole unit at the N6 position of a adenosine.[1] Recently, we report a new strategy for the synthesis of a new family of bisubstrate MTases analogues.[2] A procedure using two transition metal catalyzed reactions was used to introduce the α-amino acid motif mimicking the methionine chain of the SAM cofactor: a copper(I)-catalyzed iodo-cycloaddition reaction resulted in 5-iodo-1,2,3-triazole which was functionalized by pallado-catalyzed coupling to introduce the α-amino acid substituent.

Docking studies of these molecules in the active site of the ribosomal m6A MTase RlmJ and inhibition tests on human m6A MTase METTL5 have been performed, showing that the use of the triazole with an α-amino acid chain is an interesting motif to studies these methyltransferases. The synthetic method developed here improves the structural diversity of bisubstrate analogues to explore the active site of RNA methylation enzymes and develop potential novel inhibitors.



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Keywords: RNA methyltranferases; bisubstrates analogues; Nucleosides; RNA; iCuAAC; palladium cross-coupling.

Type de communication : communication orale x affiche ☐

Molecular dynamics simulations to investigate the emergence of allosteric effects

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Abstract :

Allostery is a mechanism where the enzyme catalytic efficiency depends of an effector binding in a region distal from the catalytic site. This enables the enzymatic regulation according to the environment. However, its fundamental is still not completely understood. It is well accepted that the allosteric effect emerges by the change of the conformational landscape caused by the ligand on allosteric binding site, leading to the change in the relative free energy of the active (relaxed states) and non-active (tense states) conformations.

Lactate/malate dehydrogenase (LDH/MalDH) superfamily is a good model to study the emergency of allosteric effect, because allosteric LDHs evolved from non-allosteric MalDH, and there are many intermediaries enzymes. Previous studies indicated that a catalytic residue Arg can sample relaxed and tense states. Recently, our collaborators produced three LDHs enzymes by specific mutations of a non-allosteric intermediary MalDH. Mutant 1 remains non-allosteric and mutants 2 and 3 presented homo-allosteric effects, and the crystal structure of mutant 3 has a tense conformation. Here, we applied molecular dynamics simulations with enhanced sampling to investigate the roles of the mutations in the conformational free energy landscape.

The simulations indicate that the MalDH and mutant 1 sample only the relaxed state and the free energy profile of MalDH shows that the relaxed state is much more stable than the tense state. Mutants 2 and 3 sample both states and tense state is even more stable than relaxed state in mutant 3. So, the simulations suggest that one of the mutations enables the allosteric regulation by the stabilization of the tense state (non-active conformation) of the catalytic residue Arg.

Keywords: Allosterism, Malate dehydrogenase, Free energy calculation.

Type de communication : communication orale ☒ affiche ☐

In-situ generation of Fe-porphyrin O_2 intermediate for greener oxygenation of indole derivative - Mechanism and reactivity.

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Résumé :

Oxidation reactions are widely used in industry such as pharmaceutic for the incorporation of a functional group onto an organic backbone. However, they generally require harsh conditions (temperature, pressure, strong and/or polluting oxidant), and are often stoichiometric and poorly selective. Taking into account the economic and environmental challenges, it is primordial to find greener and economically viable pathway to generate those products and synthetic intermediates.[1] Dioxygen is an abundant and easy accessible oxidant source. However, its triple state makes it unreactive and its activation barrier requires huge energy. Nature is able to easily activate O_2 in mild conditions. Metalloenzymes such as indoleamine 2,3-dioxygenase can perform highly efficient and selective oxidation of indole derivatives under physiological conditions through the reductive activation of O_2.[2] Getting inspiration from nature, we used iron-porphyrin in presence of dioxygen and electrochemistry to generate in-situ highly reactive O_2-intermediate and to finally induce di-oxygenation and mono-oxygenation of 3-methylindole.

Previously,[3] we have reported thanks to spectroelectrochemistry the O_2 activation mechanism by Fe-Porphyrin complexes revealing that different O_2-intermediate can be generated depending on the value of the applied potential and the reaction medium (presence or absence of proton).[4]

According to the pertinent potential and reaction conditions applied, the reactivity toward 3-methylindole can be tuned, promoting -superoxo, or –oxo intermediates.[5] The reactivity will be emphasized on the superoxo intermediate as it is the first one to be reach, thus requiring lower potential to be generated.

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Keywords: O_2 reductive activation; Fe(porphyrin); electrolysis, 3-methylindole, oxidation

Type de communication : communication orale ☒ affiche ☐

Grafting of Gold nanoparticles over TMV for in-Solution Sensing Applications.

Haziq Naseer Khan †, Cora Moreira Da Silva †, Nathaly Ortiz-Pena ‡, Stéphanie Lau-Truong† , Tomas Moravec¶, Damien Alloyeau ‡ and Nguyet Thanh Ha Duong † *

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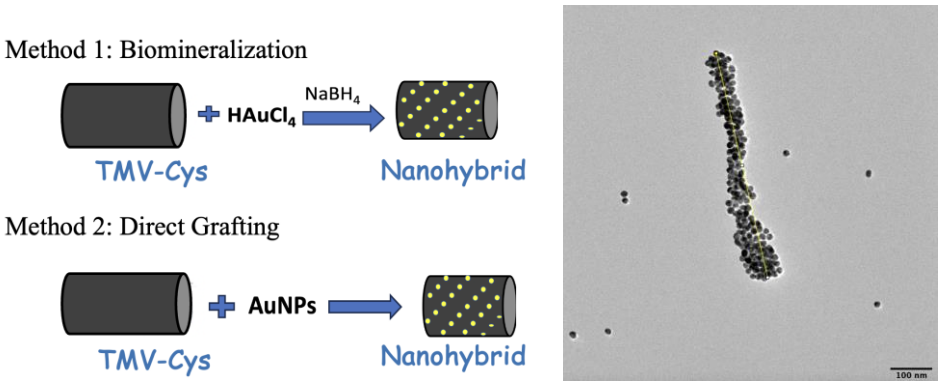
Résumé :

The utilization of biomolecular templates has enabled the preparation of hybrid materials with complex structures. The nanotechnology field finds plant viruses fascinating due to their symmetrical properties, polyvalent nature, consistent size distribution, and capacity for self-assembly**.** A promising approach in recent years has been to utilize plant virus capsids as templates for organizing 3D nano-objects, leading to the creation of novel functional nanomaterials. In recent times the use of these bio-templates (hybrid nanostructures) has increased significantly due to their possible applications in biomedical imagining, drug delivery systems, biochemical sensing and catalysis etc. Tobacco mosaic virus (TMV) is able to withstand exposure to both thermal and chemical treatments due to its robustness. It is completely harmless for humans, and it can be modified with different functional materials [1-3].

In this study, we investigate the use of mutated TMV with Cysteine on the outer surface (TMV-Cys) as a template for the synthesis of nanohybrid of AuNPs with controlled size and morphology. Biomineralization and direct grafting were the two methods to implant AuNPs over TMV-Cys (Scheme 1). We studied the growth mechanism of NPs over TMV-Cys by in-situ TEM experiments accompanied with the fluorescence quenching experiment. Additionally, the surface functionalization of the nano-hybrid (TMV-C + AuNPs) was examined with Raman reporter molecules (BPE). We showed here that the resulting AuNP-TMV-C nano-hybrid has the potential to serve as an efficient and versatile tool for in-solution SERS applications, including the detection of biomolecules.



(a) (b)

Fig 1: (a) Schematic representation of the two chemical strategies used to bind AuNP to TMV (b) TEM image of the AuNPS grafted onto TMV-C

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Keywords: Plant virus, Plasmonic, SERS, biomineralization

Type de communication : communication orale x

Novel Approaches to Corrosion Analysis through Data-Driven Computer Vision and Reflective Microscopy

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Résumé :

Stainless steel and other metals have been vital to human progress, forming a protective film on their surfaces that lowers corrosion rates. However, localized corrosion remains a risk, particularly when aggressive species like chloride ions attack the surface film. Recent advances in optical microscopy have enabled in-situ investigation of localized corrosion, generating vast amounts of data that require new data analysis and computer vision techniques. This study discusses such techniques and their application in analyzing the generated data.

We conducted a study on the electrochemical corrosion of stainless steel 316L in a NaCl solution using an opto-electrochemical method. To promote pitting formation, the samples were polarized. Optical images of high resolution were captured reaching a frame rate of 15 Hz. Our results shed light on the kinetics of pitting corrosion, variations in the surface film based on potential, the local phase composition, interactions between neighboring pits, and the spatial patterns of pitting formation. For data interpretation, we used machine vision algorithms and applied statistical methods to assess the spatial and temporal randomness of pitting formation and growth dynamics. This study emphasizes the potential of modern data analysis techniques in providing deeper insights into corrosion mechanisms.

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Keywords: pitting corrosion, optical microscopy, computer vision, machine learning

Type de communication : communication orale ☒ affiche ☐

Title: ***Macrocyclic 'Chemical Nose Sensor Array' for identification and prediction of preeclampsia outcomes in patient serum samples***

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Abstract : The biomolecular composition of body fluids are a direct reflection of severity and progression of diseased states[1]. We aim to investigate a non-specific serum-based, 'chemical nose' diagnostic approach that mimics the differential sensing of the human olfactory system[2-6], thereby generating a unique fingerprint that can be tied back to the respective serum composition.

We have developed such a sensor array with cross-reactive synthetic receptors based on the host- guest interaction of triphenylamine derivatives(TPA) with the macrocycle Cucurbit[7]uril(CB[7]). The host-guest inclusion complex of TPA-CB[7] imposes a structural confinement on the TPA's and enhances their fluorescence intensity, while CB[7] provides diverse binding modes for generation of distinct fluorescent fingerprints upon interaction with biomolecules. This sensing strategy has been extended to a droplet-based microfluidic device to evaluate the array with reduction in sample volumes in the nanolitre range. Pre-existing cohorts of preeclamptic serum samples have been assessed and the generated fluorescence signatures along with available clinical and biological data has been processed by suitable statistical approaches such as supervised clustering by Linear Discriminant Analysis to obtain classifiers for PE occurrence and outcomes.

We have thus far been able to optimize the photophysical properties of the sensor array and generate fluorescence fingerprints to discriminate a diverse range of 14 protein analytes. The array has been tested for its ability to capture diversity in biofluids like serum and provide successful discrimination of the protein analytes in this complex media. The capacity of the chemical nose to discriminate between preeclamptic and non-preeclamptic patient samples has been evaluated with 17 serum samples to establish a proof of concept with 100% accuracy. The system has further been optimized on a dedicated droplet-based microfluidic platform, where the detected fluorescence output signal has been correlated with the initial droplet composition to provide discrimination of selected proteins analytes with 100% accuracy.

Herein, we have developed a 'chemical nose' sensor for fingerprinting and pattern recognition of biomolecules. The ability of this system to detect changes in spectral signatures of serum will provide a new diagnostic methodology for complex diseases like preeclampsia[7-8] and will enable us to propose a strategy for big data analysis based on chemical sensing and machine learning.

Type de communication : communication orale ☒ affiche ☐

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Keywords: *Chemical nose* sensing, fluorescent sensor array, host-guest interactions, cucurbit[7]uril, preeclampsia, pattern recognition.

Type de communication : communication orale ☒ affiche ☐

Protein-Protein interactions in the Purinosome Metabolon

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Résumé :

Purine synthesis consists of two pathways, the salvage pathway, which operates under normal physiological conditions, and *de novo* synthesis. The latter comes into play when purine levels are depleted, triggering a more energetically intensive pathway in which the purinosome is assembled[1].

The purinosome is a case of a metabolon, where metabolic enzymes are spatially and temporally organized into multi-enzyme complexes. This has plenty of advantages, but a remarkable one is that the substrates can be transferred directly from one active site to another, a phenomenon known as "channeling."[2].

In *de novo* synthesis, ten chemical steps are involved in converting phosphoribosyl pyrophosphate (PRPP) into inosine monophosphate (IMP), with the participation of six enzymes. These enzymes form a complex and reversibly compartmentalize within cells during specific stages of the cell cycle[1].

By employing molecular dynamics simulations at a coarse-grained level, we explored two different scenarios for the purinosome. In fact, in the absence of an experimental quinary organisation of the six enzymes, we were forced to generate the spatial organization of the complex. We constructed two scenario. In each scenario, we conducted geometrical and spatial analyses to assess their respective advantages and disadvantages. While many studies have attempted to determine the size of one single purinosome, consensus suggests it is unlikely to exceed 300 nm in diameter[3]. Our studies, however, reveal significant deviations from these results.

Furthermore, we conducted studies to investigate the behavior of the first ligand in the reaction, phosphoribosylamine (PRA), within PRPP. Consequently, an analysis of how it behaves upon encountering its binding site in the second protein of the pathway provides clear evidence of the importance of the channeling mechanism.

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Keywords: purinosome; molecular dynamics; metabolon

Type de communication : communication orale ■ affiche □

Unravel the relationship between structure, flexibility and reactivity of RNA using biased molecular dynamics simulations

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Ribonucleic acid (RNA) molecules are involved in most steps of the genetic expression including catalysis of central cellular functions. RNA functions crucially rely on both the specific tridimensional (3D) folding of the molecule, which in turn depends on the sequence and on how nucleobases pair through hydrogen bonds (secondary structure)[1], and its conformation. This relationship is even more crucial for protein-RNA complexes. Hence, the determination of RNA tridimensional structures is fundamental for understanding their function. However, obtaining high-resolution 3D structures via X-ray crystallography, cryo-EM and NMR is still a challenge.[2] To overcome the lack of 3D structures, in the last decades, several low-resolution techniques have been developed, like chemical probing, whose data have been integrated into the prediction of secondary (2D) and 3D RNA structures with different levels of detail.[3-5] In particular, the SHAPE (Selective 2'-Hydroxyl Acylation analyzed by Primer Extension) technology provides quantitative reactivity information for each nucleotide and has become the most popular among these techniques since it does not depend on the nature of the nucleotide unlike other chemical probing techniques and is amenable to high-throughput protocols. The probes are small-molecule electrophiles that acylate the 2'-hydroxyl group to form a 2'-O-adduct.[6] Although this approach is very popular and it is known that the SHAPE reaction is dependent on the local structural properties of each nucleotide, it has not yet been understood why different reactivities can be obtained for the same nucleotide depending on the probe used and several questions associated with the relationship between structure, conformation, flexibility, and reactivity are still open. To overcome this, with the aim of using SHAPE data to predict bound and unbound RNA structures, we performed biased all-atom molecular dynamics simulations, on a stable tetraloop of *Bacillus subtilis* yiJ S-box (SAM-I) riboswitch using three different SHAPE probes. On this system, SHAPE data are accessible in the literature or have been obtained in our wet lab. We analyzed the correlations between different geometrical parameters and the chemical reactivity. Our investigations confirm that SHAPE reactivity is guided by the local flexibility of the different chemical moieties and the ribose, but also by the attack orientation of the SHAPE probe. These results confirm the importance of the attack angle and the need to extend this study to the entire structure of this aptamer.

Keywords: Biased molecular dynamics, SHAPE reactivity, RNA structure

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Type de communication : communication orale ☒ affiche ☐

New brightness to an old story: Designing smart material metal complexes by molecular modelling.

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Résumé :

The development of photoactive smart materials, phototherapeutic devices, and catalysts has led to an increasing consumption of a large number of rare and expensive metals. Thus, a consistent pressure is put on the most employed ones, which are bound to become even rarer and more expensive in the forthcoming decades. Even if the properties of rare metal complexes are well known, there is still a stringent need to explore their peculiar reactivity to fully understand them, and propose more efficient solutions.

We have explored the behavior of a ruthenium complex, $[RuCl(NO)py_4]^{2+}$, which photoisomerizes following a two photon absorption (TPA) mechanism (a).[1] Surprisingly, the photoisomerization quantum yield of this system changes as a function of the nature of the counter-ions. Indeed, a quantum yield of 76% is observed with PF_6 counter-ions while 11% in presence of Cl^-. [2] Furthermore, this system is known to be able to photorelease radical NO that can be useful for different applications, more specifically for oxygen independent photodynamic therapy. Using DFT and CAS-PT2 calculations, an explication of this variation is proposed, while the NO release is explicated.

On the other hand, two series of palladium(II) complexes[3] supported by a phosphine-iminophosphorane ligand built upon an ortho-phenylene core were investigated to study the non-innocent influence of the N substituent. Each series are composed of four different substituents: an isopropyl (iPr), a phenyl (Ph), a trimethylsilyl (TMS) group or an H atom (**H**) (b). Molecular modelling has rationalized the regioselectivity of the chloride monosubstitution by isocyanide and related the different properties to the differences in the electronic structure induced by the non-innocent ligand. In particular differences between the TMS- and H-containing complexes *vs* the iPr and Ph ones were observed. This suggests that the nature of the N substituent is far from innocent and can help tune the reactivity of iminophosphorane complexes useful in metal catalysis.

Understanding the properties of these rare metal complex is fundamental in paving the way to the rational design of smart materials or therapeutic devices. Molecular modeling, offering a cutting-edge resolution at atomistic or electronic level is, thus, bringing a new light to an old story, whose potentiality will fully shine in the near future.

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Keywords: Theoretical chemistry; Metallic complex; Photochemistry

Type de communication : **communication orale**

FGFR3 kinase mutation and its impact on Infigratinib inhibition

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Résumé :

Fibroblast Growth Factor Receptor 3 (FGFR3), belonging to the tyrosine kinase receptors family, plays a pivotal role in regulating cell growth and differentiation[1]. Various mutations of this receptor have demonstrated its implication in several bone pathologies such as achondroplasia – the most frequent form of dwarfism. Therefore, some years ago, the hypothesis that the inhibition of the kinase domain of FGFR3 could counteract dwarfism was posed[2]. To this extent, the use of Infigratinib, that target the ATP binding site of FGFR3, is recently entered the third phase of clinical development[3].

Recently, biologist collaborators identified a specific mutation in the kinase domain of FGFR3 (N540K) that worsened the development of dwarfism. Given the fact that the N540K mutation is neither located in the catalytic site nor the activation loop, a computational study was realized to lead deeper understanding of its specific role. In this sense, molecular docking, molecular dynamics (MD), Gaussian-accelerated MD, and free energy determinations through umbrella sampling were engaged.

Visualization and structural analysis highlight an original role of a loop in FGFR3 that stabilizes the interaction of Infigratinib. Interestingly, when the asparagine is replaced by lysine for the mutant a specific electrostatic network with the charged residues appears and favors the approach of the protein loop toward Infigratinib. Structural properties of the N540K mutated version of FGFR3 exhibit a distinct configuration favoring interaction with specific ligands, thus opening new developments of inhibitors with better selectivity for this receptor.

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Keywords: molecular dynamics, kinase, Infigratinib

Type de communication : communication orale ☒ affiche ☒

Unlocking Novel P-Containing Scaffolds by Exploration of a Catalyzed Intra-Molecular EDA Intermediate

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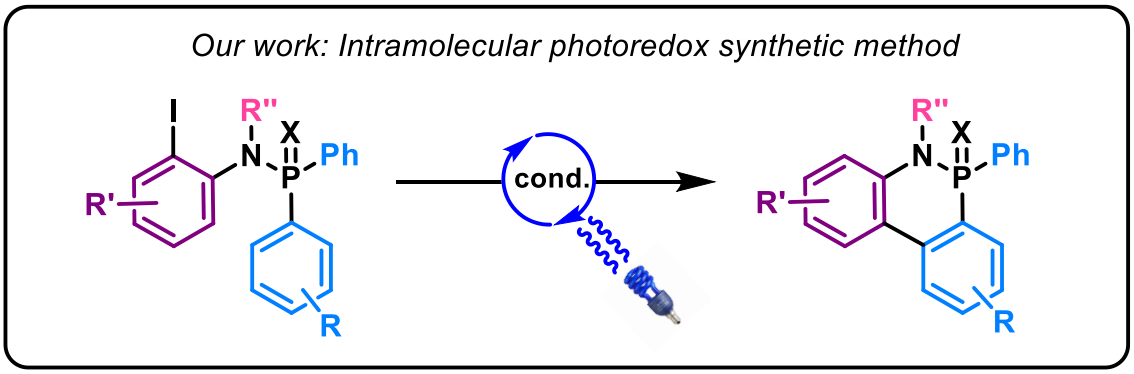
Résumé:

Cyclic diaryl phosphinamides have been recently explored in organic synthesis. Indeed, this type of compounds showed interesting photophysical properties as organic electroluminescent materials[1] that can be used in Organic Light-Emitted Diodes (OLEDs)[2]. Additionally, cyclic diaryl phosphinamides, that contains a stereogenic phosphorous atom[3], can also be used as ligand in catalysis[4]. Thus, the development of new strategies to build efficiently these compounds is desirable.

In this aim, we focused our research projects on the development of a new and innovative photoredox synthetic method to build a carbon-carbon bond, *via* the formation of an intramolecular EDA complex and the generation of a carbon radical.

In this work, we have developed diphenylphosphinic amide precursors in order to access to a broad scope of cyclic uncommon diaryl phophinamides derivatives.



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Keywords: visible light photocatalysis, EDA complex, phosphinamide, carbon-carbon bond

Type de communication : communication orale

Molecular mechanism of B. subtilis rRNA maturation by M5: a simulation challenge

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Abstract

The final maturation of rRNAs is a step of ribosome biogenesis performed in bacteria by RNases at the level of the assembled pre-ribosome. In Bacillus subtilis, the final maturation of the 5S rRNA is mediated by RNase M5 which cleaves the double-stranded rRNA precursor on both sides. This reaction requires a cofactor of the ribosomal protein ribosomal protein (UL18), which allows the rRNA to adopt the appropriate conformation for recognition and cleavage. Previous work has suggested that cleavage occurs in two steps: removal of the 3' extension before cleavage of the 5' strand [1]. In a recent work [2] carried out by the team of C. Tisné at IBPC (UMR8261), the details of the interaction between M5 and the 5S ribosomal subunit were obtained by combining cryo-EM of the complex and X-ray structures of the two domains of M5 in solution.

Two Mg^{2+} ions were recently observed in a crystal structure of the protein [3]. However, the exact role of these magnesium ions is still unknown, as well as their precise location in the complex, which might be different from that observed in the protein alone. It is still unclear whether they are both involved in the cleavage reaction per se, or whether they have a purely structural function for the protein and/or the rRNA.

In this work, our goal is, using molecular simulations, to complement the available experimental data and provide additional insights into the M5-rRNA complex structure and dynamics, the mechanism of the cleavage step, and to investigate the reorganization that should occur following the 3’ end cleavage.

Starting from the superposition of the cryo-EM and X-ray structures obtained by the experimental team in order to obtain the position of the ions within the complex, we soon realized that traditional force field descriptions of the systems led to strong instabilities in the active site structure. The distance between the two magnesium ions is initially very short, i.e. 4.23 Å, but increases rapidly. We thus tested different force fields in order to model as well as possible the interactions between magnesium and the oxygens of its coordination sphere, benchmarking them on a small model system. With that, we then use long simulations of the complex before and after cleavage to investigate its structure and dynamics, as well as its reorganization following cleavage.

Keywords: RNA-Protein interactions, force field, conformational change

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Type de communication : communication orale ☒ affiche ☐

Towards Green Chemistry Processes: Iron-Catalyzed C(sp^3)-H Lactonization Using Hydroxylamine Derivatives

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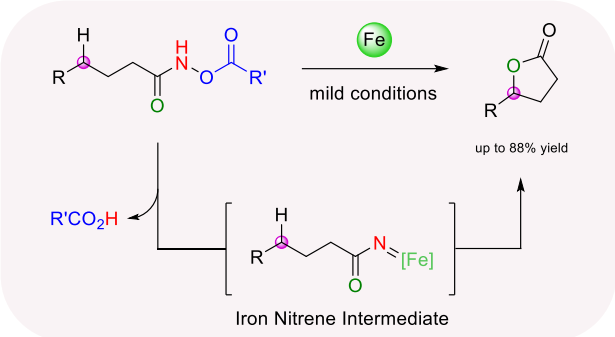
Résumé :

Lactones are highly valuable intermediates in the synthesis of many natural products, as well as prominent scaffolds in bioactive compounds.[1] Direct functionalization of C-H bonds represents the most straightforward route to these compounds in the context of sustainable chemistry. There has thus been an ongoing effort into the development of efficient and robust methodologies for C-O bond formation.[2] However, most of these developed processes are poorly atom economical, require external oxidants, and are based on the use of rare and expensive transition metals such as palladium.[3]

Nitrenes are well-known for their ability to perform aziridination, alkene difunctionalization and C-H amination.[4] Our group aims to achieve sustainable nitrene transfer processes using iron as the catalyst and hydroxylamines as the nitrogen source.[5] Iron is cheap, abundant, and non-toxic while hydroxylamines are bench-stable, easily accessible, and can form a metallonitrene intermediate in the presence of a transition-metal without the addition of external oxidants.[6] During our investigation on C-H amination, we hypothesized that we could deviate the reactivity of nitrenes to favour a C-H oxygenation process.

In this communication, we will present in detail our recently developed iron-catalyzed lactonization using hydroxylamine derivatives. This sustainable process allows for an efficient access to new C(sp^3)-O bonds, yielding various lactone derivatives in good-to-excellent yields using very mild conditions.



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Keywords: green chemistry; nitrene chemistry; iron catalysis.

Spin filtering effects at graphene/molecules interfaces

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We present a bias-controlled spin-filtering mechanism in spin-valves including a hybrid organic chain/graphene interface [1]. Wet growth conditions of oligomeric molecular chains would usually lead, during standard CMOS-compatiable fabrication processes, to the quenching of spintronics properties of metallic spin source due to oxidation. We demonstrate by X-ray photoelectron spectroscopy that the use of a protective graphene layer fully preserves the metallic character of the ferromagnetic surface and thus its capabillity to deliver spin polarized currents. We focus here on a small aromatic chian of controllable lengths, formed by nitrobenzene monomers and derived from the commercial 4-nitrobenzene diazonium tetrafluoroborate, covalently attached to the graphene passivated spin sources thanks to electroreduction. A unique bias dependent switch of the spin signal is then observed in complete spin valve devices, from minority to majority spin 84 ABSTRACTS carriers filtering. First-principles calculations are used to highlight the key role played by the spin-dependent hybridization of electronic states present at the different interface [2].

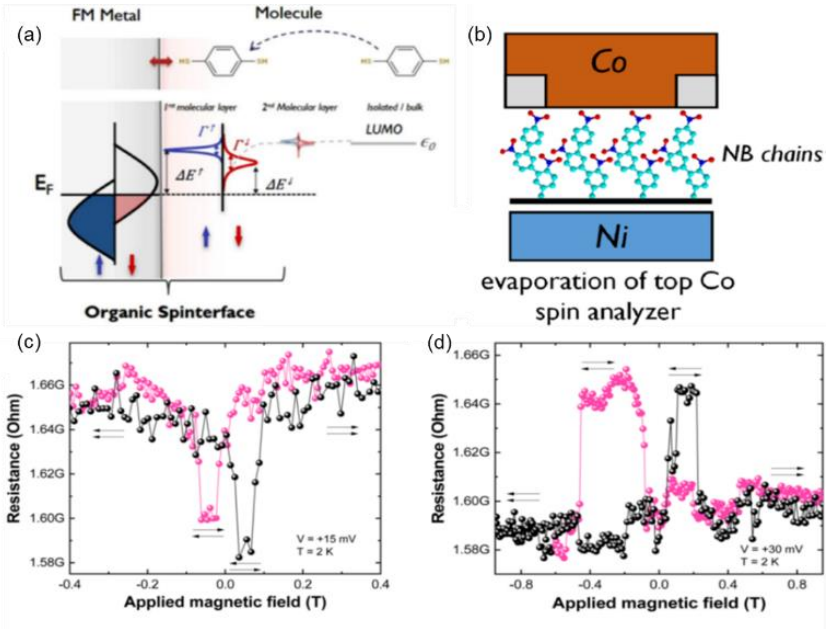

Figure: a). Schematic explaining the hybridization between a ferromagnetic surface and a molecular orbital. Extracted from Delprat *et al*., *J. Phys. D: App. Phy.* **51** 473001 (2018) b). Schematics of the molecular magnetic junction. c) and d). Magnetoresistive signals measured in Ni/graphene/molecule/Co magnetic junctions.

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Liste des posters

Type de communication : communication orale ☒ affiche ☐

DNMT1 and cancer: design of selective inhibitors as molecular chemical tools in epigenetic pharmacology

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Résumé :

Epigenetic modifications have been widely implicated in many diseases, such as DNA methylation, related to the development and progression of many diseases, including certain cancers[1, 2]. DNA methylation is mainly catalyzed by DNA methyltransferases (DMNTs), including DNMT1 and DMNT3. These enzymes play different roles during carcinogenesis, but DNMT1 and DNMT3 function in DNA methylation are not yet fully understood. Currently DNMT inhibitors target DNMT1 and DNMT3 without selectivity, in this case, the discovery of selective non-nucleoside compounds of DNMT1 could be a breakthrough in understanding the molecular mechanisms of carcinogenesis as well as in clinical therapeutics.

Our first docking study has identified two promising chemical structures capable of binding with the intermediate binding domain of DNMT1 with high bond energies. We have found some efficient synthetic pathways to obtain these two series of promising compounds in three to five steps. Until now, we obtained 16 final compounds, and we conducted the biological test on DNMT1 and DNMT3 activity. Finally, we have identified a potential compound that can selectively inhibit DNMT1, interestingly, except this compound, two of our final compounds have specific inhibitory effect on DNMT3, this can be a innovative result as no DNMT3-specific inhibors have emerged before.

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Keywords: DNA methylation; DNMT1; DNMT3.

Type de communication : communication orale ☐ affiche ☒

Investigating phase formation of $BiFeO_3$, $Bi_{x-1}Ca_xFeO_3$ and $BiFe_{1-x}Mn_xO_3$ by Polyol process

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Résumé :

Due to its valuable high stability, narrow bandgap, and large ferroelectric polarization that can be exploited at room temperature, the multiferroic bismuth ferrite (BFO) material is being studied for photovoltaic applications. Ideally, semi-conductors used for photovoltaic and photocatalytic conversions should : a) present a band gap small enough to absorb the entire solar spectrum and b) prevent the recombination of electrons and holes. BFO-doped nanoclusters can currently fulfill these two roles because the presence of transition metals creates new electronic levels in the bandgap near the Fermi level, allowing the capture of solar photons of lower energy that can be reduced by doping. Although several synthesis techniques have been used for preparing BFO NPs, the kinetics of reaction leads to a mixture of $BiFeO_3$ as a major phase along with other impurity phases. The polyol process is a practical method that allows tailoring size, shape, and compositions. In this study, the polyol protocol ideal conditions were explored. Optimal conditions were used for doping BFO perovskite structure with calcium and manganese in different stoichiometries (x=0.05, 0.1, 0.2). The effects on structural, optical, and magnetic properties were investigated by XRD, SEM, EDS, diffuse UV-Visible, and VSM techniques. The average particle size of 40 nm decrease when doping with manganese and calcium as well as a reduction of bandgap (2.02 to 1.70 eV). BFO-doped nanoclusters exhibited enhanced magnetic properties.

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Keywords: Ferroelectric-photovoltaics, bismuth ferrite, polyol process,

Phenanthridine-Based Photoactivable Protecting Groups for One- and Two-Photon Excitation

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Abstract:

The development of photoactivable protecting groups (PPG) has been a cornerstone in the field of chemical biology, enabling precise spatiotemporal control over biological processes and the release of bioactive molecules. In this study, we introduce a novel family of protecting groups based on a phenanthridine core which exhibit one- and two-photon photoactivation properties.

A small library of compounds was synthesised with a modest one-photon disappearance quantum yield but with absorption wavelengths above 400 nm which place their absorption range closer to the "biological window" than the most commonly used PPGs (i.e, α-CNV, NVOC, MNI, MDNI). Our results lay the foundation for a new generation of photosensitive cages with exciting potential for optimisation. Furthermore, DFT calculations allowed us to better understand Intramolecular Charge-Transfer (ICT) behaviour and other relevant photochemical properties of this new class of molecule allowing finer tuning for further development.

Overall, this study represents a significant step forward in the development of photoactivable protecting groups, opening up new possibilities for the controlled release of bioactive compounds under one- and two-photon activation. Our initial library will serve as a starting point for future optimisations and the design of even more efficient derivatives, promising exciting prospects and applications.

Type de communication : communication orale ☐ affiche ☒

Investigation of factors driving β phase of PVDF-$CoFe_2O_4$ hybrid films

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Résumé :

Artificial multiferroics made of polymers and nanoparticles (NPs) combine the properties of NPs and polymers well, so that this kind of hybrids not only have piezoelectric and ferroelectric properties of NPs, but also have flexibility, and easy deployability of polymers.

Many recent works have focused on Polyvinylidene fluoride (PVDF). Among five crystalline phases of PVDF, β-PVDF is highly polar, resulting in higher piezoelectric and ferroelectric constants. It has been assumed that polar species are promoting the crystallization of this polymorph. Introducing nanofillers (e.g. nanoparticles) into polymer also can induce the crystallization of β polymorph, and a suitable surface functionalization of the fillers can enhance the crystallization of the β phase.

Presently, dimethylformamide (DMF) is the solvent most used for processing PVDF. It is highly polar but also highly toxic as one can see on the hazard statements. Hence, it is not very suitable for large-scale synthesis and further recycling of these magnetic hybrids. So, it's necessary to explore non-toxic solvents for PVDF processing.

In our research, we studied on the processing of magnetoelectric hybrid self-standing films in new eco-friendly solvent blends, dimethylsulfoxide (DMSO), diacetone alcohol (DAA) and their blends, which were chosen considering their solubility parameters regarding those of the polymer (according to the Hansen's model) as well as their polarity, to ensure the crystallization of β phase.

Besides, we're studying on whether and how different shapes of nano $CoFe_2O_4$ will drive the crystallization of β-PVDF now.

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3. F. Mammeri, Nanostructured flexible PVDF and fluoropolymer-based hybrid films. Frontiers of Nanoscience 14 (2019) 67-101.

Keywords: PVDF; process; β phase; non-toxic; $CoFe_2O_4$.

Molecular modeling of plasmodesmata organization by MCTP proteins

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Abstract

In plants, intercellular communication is primarily achieved through plasmodesmata. These membrane pores cross the cell wall and create symplastic continuity between cells [1]. Plasmodesmata are crucial in coordinating developmental processes and defense mechanisms against pathogens.[2] They are also hijacked by viruses that can structurally modify them to propagate their viral genome from cell to cell.

Plasmodesmata have a unique membrane organization: they are crossed by a "tube" of endoplasmic reticulum (ER), which is in intimate contact with the plasma membrane (PM), delimiting the pores. The two membranes are only a few nm apart (~10 nm) and connected by "tethers". The multiple C2 domains and transmembrane region protein (MCTP) family, critical regulators of cell-to-cell signalling in plants, act as ER-PM tethers, specifically at plasmodesmata [2,3]. However, the molecular mechanism and function of membrane tethering within plasmodesmata remain unknown. Furthermore, MCTP proteins are still poorly known at the level of the 3D structure.

Thus, we first generated structural models of A. thaliana MCTP by different prediction methods using deep learning like AlphaFold and RosettaFold [4], [5]. Then, we compare them by computing contact maps. Further, the movement of transmembrane regions in the lipid bilayer was characterized by coarse-grained simulation using the MARTINI3 force field and principal components analysis. We were finally able to extract representative conformations from our simulations.

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Collectivity in self-assembled protein filaments involved in homologous recombination

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HR is a critical genomic repair mechanism that begins with the self-assembly of recombinase proteins like RecA onto single-stranded DNA. This assembly binds together to create a helical nucleoprotein filament [1]. The filament includes DNA from other parts of the genome in search of a homologous sequence to utilize as a repair template. Mechanical stress develops within the filament as the incorporated DNA extends by around 50%.

Our research employed molecular dynamic simulations to investigate how nucleoprotein filaments react to internal stress. We studied filaments ranging in length from 9 to 54 incorporated base pairs, as well as local (protein-protein and protein-DNA interactions) and global (curvature, winding) deformations and their correlations [2].

Our findings show that the distribution of stress inside the filament varies with DNA length. Surprisingly, the areas of the genome where DNA enters or exits in the B-form serve an unanticipated role in stress transmission. These findings offer light on the instability of small nucleoprotein filaments, which are essential in the kinetic proofreading process of HR [3].

In conclusion, while mechanosensitivity in protein filaments is often associated with external forces, HR's nucleoprotein filament shows the dynamic response of stress accumulation within an oligomeric filament.

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Type de communication : communication orale ☐ affiche ☒

STUDYING THE HEALTH EFFECTS OF URBAN AIR QUALITY AT THE LABORATORY: THE RESULTS OF THE ATMOSPHERIC SIMULATIONS USING THE POLLURISK PLATFORM

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Résumé :

This study aims to present the PolluRisk platform, dedicated (1) to experimentally simulate urban atmospheric situations in the framework of case studies and (2) to expose murine models to these simulated atmospheres to study the health impacts on the respiratory, cardiovascular, gastric and nervous systems.

Atmospheric pollution is a major health risk leading to 4 million premature deaths annually worldwide (World Health Organization). However, the assessment of the health effects resulting from the exposure to atmospheric pollution has shortcomings. Experimental and epidemiological studies evaluate the impacts of some pollutants so-called “indicators” with higher concentrations than their levels in real atmospheres. However, it is key to take into account the synergistic effects of atmospheric pollutants. Therefore, we have developed an innovative experimental platform (PolluRisk) to improve our knowledge of the toxicity of urban atmospheric pollution (Coll *et al*., 2018).

The PolluRisk platform includes: (1) the simulation chamber CESAM ensuring the controlled generation of simulated atmospheres representative of urban case studies, (2) the isolators coupled to the chamber allowing the exposure of preclinical models to the simulated mixture, (3) the various analytical techniques aiming to analyze the gas and particle phases. The chamber consists of a stainless-steel reactor and its volume (4.2 m3) allows the use of very low concentrations of precursors to reproduce their trace levels in real atmospheres. The chamber is equipped with an artificial irradiation system that replicates the solar radiation in the troposphere (Wang *et al*., 2011). A mixture of volatile organic compounds (VOCs), based on the chosen case study, in addition to NO are transferred throughout the experiment to the chamber through a continuous flow. The photooxidation of these VOCs generate secondary pollutants, including gaseous compounds and secondary organic aerosols (SOAs). Additionally, we inject in the chamber inorganic particles of ammonium sulfate which act as contact surfaces for the condensation of oxidized products during the formation of SOAs. Other particles (soots, mineral dust …) can also be generated and transferred into the exposure device depending on the target atmosphere. Our results highlight the presence of species from different chemical families identified in the particulate phase through offline analytical techniques applied to sampled filters and in the gaseous phase using online techniques. The presence of carboxylic acids validates that the simulations carried out with the PolluRisk platform reproduce oxidation and functionalization processes of the organic matter, as it is the case in realistic urban atmospheres. Finally, we succeeded in simulating atmospheric situations during the 2020-2023 campaigns, for 48 hours to 7 days.

Type de communication : communication orale ☐ affiche ☒

In conclusion, as part of the conducted work, we managed to develop an experimental platform to expose living organisms to atmospheric mixtures with multiple gaseous and particulate compounds from different chemical families, including hydrocarbons, carbonyls and carboxylic acids. This consists of an innovative way to reproduce the urban atmospheres of cities such as Beijing or Paris in all their complexity.

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Keywords: Air Quality, Simulation Chambers, Atmospheric Pollution, Health Impacts

Type de communication : communication orale ☐ affiche ☒

Structure-function study of the mysterious pseudopaline exporter CntI of *Pseudomonas aeruginosa*

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Objectives: Metal homeostasis is essential for bacterial metabolism. Metal capture is secured by secondary metabolites called metallophores. In the Gram-negative pathogen *Pseudomonas aeruginosa* (P.a.), pseudopaline (Pp) has been discovered as an essential metallophore [1], in particular during airway mucus infection [2]. Trafficking of Pp could be a promising antibacterial target, and we decided to focus our work on understanding the molecular basis of Pp transport by the inner membrane exporter CntI of the drug/metabolite superfamily (DMT), predicted as 10 transmembrane α-helical membrane protein of 31 kDa. In order to solve the crystal structure of CntI, we first need to optimize its production, purification and stabilization with detergent, at high concentration. We will present results of CntI purification, concentration, biochemical and biophysical characterization for crystallization purpose.

Methods and Results: first attempts of CntI-Histag purification by Ni^{2+} affinity gave a very low yield (< 0,1 mg / L culture). We manage to improve the yield up to 1,2 mg / L culture after extending the affinity tag and optimization of the stabilizing buffer by thermofluor assay. Thanks to SEC-MALS analysis (Size Exclusion Chromatography - Multi Angle Light Scattering), we identify the best concentration protocol to avoid excess of free detergent micelles for crystallization [3]. Besides, SEC elution profile shows a dimeric form of CntI which seems sensitive to pH and reducing agent (e.g. TCEP). Finally, promising crystals of CntI were obtained by hanging-drop and LCP (Lipid Cubic Phase) approaches. In the meantime, analysis of the 3D model structures of CntI docked with Pp(R) and Pp(S) substrates highlighted specific residues of the binding pocket, such as R73.

Conclusions: We managed to optimize the purification, concentration and stability of CntI for crystallization. We now need to optimize crystal quality to obtain high resolution structure. 3D model of CntI and docking analysis with Pp showed residues to explore *in cellulo* to understand Pp transport mechansim.

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Keywords: Membrane transporter, metallophore, *Pseudomonas aeruginosa*, structural biology.