Evaluation of the Ion Mobility Spectrometry – Mass Spectrometry (IM-MS) approach for high throughput and large scale metabolomic analyses

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Metabolomics is the study of low-molecular weight molecules (<1000Da) produced by cells and transformed during various regulatory pathways.[58] The whole metabolome of a biological sample can be analyzed without bias to detect and identify as many metabolites as possible. Metabolomics, therefore, permits to study or reveal perturbations in a biological system.

To conduct these studies many analytical techniques are currently used but Nuclear Magnetic Resonance (NMR) spectroscopy and Mass Spectrometry (MS) are the top two employed platforms nowadays. NMR spectroscopy is a quantitative, reproducible technique but NMR spectroscopy suffers from low sensitivity , estimated at 1 nmol metabolite for 1H NMR in Harry *et al.*, 2008.[59] On the other hand, MS is more sensitive than NMR and permits to detect more metabolites in a complex mixture. But in MS studies, a separation step is, usually, used such as Liquid Chromatography (LC) to increase the sensitivity and the metabolome coverage. The chromatographic separation drastically lengthens the analysis time and does not permit to distinguish many isomers. Direct Infusion MS (DIMS) approach was also successfully tested with some limitations such as matrix effects or unefficient isomer separation.[60]

Ion mobility spectrometry (IMS) is a technique to separate ionised compounds in the gas phase where an electric field is applied. Charged species shift differently according to their Collisional Cross Sections (CCS) a parameter linked to their size and charge.[61] Therefore, IM-MS studies are really promising for metabolomics as they permit to distinguish some unsolved isomers and to shorten the time of analysis compared to other hyphenated methods such as LC/MS.

Our research project aims to the development of a high throughput metabolomics approach based on a Trapped Ion Mobility (TIMS) coupled with a TOF analyser for large scale analysis. We, first, investigated the separation abilities of the TIMS-TOF instrument by considering two families of metabolites: 3 isomers couples of oestrogen derivates and 4 isomer couples of human milk oligosaccharides (HMO). Analytical parameters (additives, mobility resolution etc …) were considered to determine the best conditions to successfully separate all set of isomers. All compounds were, then, analyzed in complex matrices : human urine for the oestrogen derivates and breastmilk for the HMO. In parallel, a CCS database for more than 400 metabolites was constructed. It contains 1348 values for different type of adducts and will help to increase the level of confidence in the metabolite identification.

Acknowledgments: Nous remercions l'infrastructure MetaboHub (ANR-11-UNBS-010) pour le financement

[58] Chouinard, C.D., Nagy, G., Smith, R.D., and Baker, E.S. Ion Mobility-Mass Spectrometry in Metabolomic, Lipidomic, and Proteomic Analyses. *Comprehensive Analytical Chemistry*, **2018**.
[59] Harry, E.L., Weston, D.J., Bristow, A.W.T., Wilson, I.D., and Creaser, C.S. An approach to enhancing coverage of the urinary metabonome using liquid chromatography–ion mobility–mass spectrometry. *Journal of Chromatography B.* **2008**. *871*, 357–361.
[60] Rathahao-Paris, E., Alves, S., Boussaid, N., Picard-Hagen, N., Gayrard, V., Toutain, P.-L., Tabet, J.-C., Rutledge, D.N., and Paris, A. Evaluation and validation of an analytical approach for high-throughput metabolomic fingerprinting using direct introduction–high-resolution mass spectrometry: Applicability to classification of urine of scrapie-infected ewes. *European Journal of Mass Spectrometry*. **2018**. 146906671880645.
[61] Dodds JN, Baker ES. Ion mobility spectrometry: Fundamental concepts, instrumentation, applications, and the road ahead. *Journal of American Society of Mass Spectrometry*. **2019**. 30:2185–2195.

Synthesis of original fluorescent nucleosides

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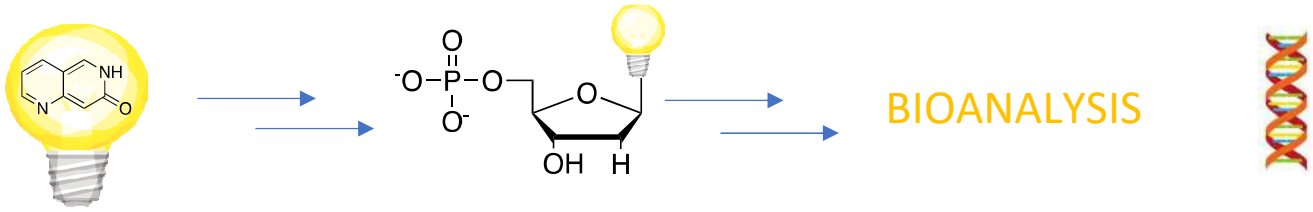
The development of new and original scaffolds is a perpetual quest in medicinal chemistry. Originality of the chemical structure is essential for patentability reasons in a very competitive economical context and for the expansion of chemical diversity. We are focused on the synthesis of novel heterocycles and on their development as new and original chemical series with potential medicinal interest.[1] [2]
We also know that fluorescence is, nowadays, one of the most powerful analytical tools in chemical biology. Fluorescent probes are widely used to target different kinds of small molecules or biomolecules in cells providing useful information about their locations, structural modifications, activations and also the visualization of biological processes. However, their applications for the analysis of nucleic acids are still limited. Intensive researches have been dedicated to find sensitive and selective probes able to interact with DNA without disturbing its groove. In this purpose, fluorescent nucleic acid base analogs (artificial nucleobases) have been engineered, but most of them are not applicable for now.[3] [4] Our challenge is to make fluorescent nucleobases sensitive enough with efficient optical properties without perturbing DNA. In order to reach this objective, we synthetized and developed naphtyridones as original fluorescent nucleobase analogs. We will present the synthesis and the functionalization of these new fluorescent heterocycles as well as their optical properties. Then we will present our first results concerning the preparation of the nucleobase-ribose pair systems.



Acknowledgments:

[1] W. R. Pitt, D. M. Parry, B. G. Perry, C. R. Groom, *J. Med. Chem.* **2009**, *52*, 2952-2963
[2] K. Passador, S. Thorimbert, C. Botuha, *Synthesis.* **2019**, *51*, 384–98
[3] W. Xu, K. M. Chan, E. T. Kool, *Nat. Chem.* **2017**, 9, 1043-1045
[4] Sinkeldam, R. W., Greco, N. J. & Tor, Y. *Chem. Rev*. **2010**, *110*, 2579–2619

Development of miniaturized analytical systems based on aptamers for the multi-detection of biomarkers

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Cancer is the second leading cause of non-accidental death in the world with around 10 million deaths in 2020. Early diagnosis and effective drug treatment would improve the prognosis and overall survival of the population. Current diagnostic methods, based on imaging or solid tissue biopsy have many limitations such as low sensitivity, which does not allow early diagnosis and sometimes turn out to be invasive[1].

Thus there is a need for early diagnosis of cancer based on liquid biopsy and the quantification of several biomarkers. The current methods for biomarkers analysis are based on immunoassays or even immunohistochemistry. However, these techniques often require multiple sample preparation steps, a long analysis time, are often non-reusable and allow only mono-target analysis. The main challenge relates to the risk of a misdiagnosis. In fact, a single biomarker is not specific to a single type of cancer.

There is thus a need for the conception of miniaturized analytical systems that would sort complex liquid biopsy samples and help identify specific targets for diagnosis. In this context my thesis project is oriented towards the "*Development of miniaturized analytical systems based on aptamers for the multi-detection of biomarkers*". These systems are called lab-on-a-chip (LOAC), a transportable device comprising a network of micro-channels and presenting various analytical steps ranging from sample preparation, separation of biomarkers, to their detection.

My work is directed according to two main challenges, namely, the creation of a three-dimensional zone of microsystem preconcentration and the release and the detection of biomarkers.

The first step is the *in situ* synthesis of Poly(ethylene glycol)diacrylate hydrogels by maskless lithography in order to encapsulate an aptamer which would allow molecular recognition of a biomarker. Once the biomarker is released, it can be detected during the final step. A fluorescence-coupled electrochemical approach can be developed for the detection step.

Références:

1. Sierra J, Marrugo-Ramírez J, Rodriguez-Trujillo R, Mir M, Samitier J. Sensor-Integrated Microfluidic Approaches for Liquid Biopsies Applications in Early Detection of Cancer. *Sensors*. 2020;20(5):1317

Asymmetric radical addition via chiral ion pairing

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If the control of anionic reactant is a well-known process for the formation of chiral stereocenter, the control of radical is still under investigation.[62] The development of this field as evolved following the evolution of radical precursor. Generation of radical can now be easily achieved using photocatalyst such as organic dye using some radical precursor such as alkyl trifluoroborate or silicate that have been developed by our laboratory.[63] Firstly, our focus was the development of silicate free of crown ether and new alkyl silicate such as cyclopropane-silicate. (figure 1) Their reactivity is currently/has been investigated.[64]

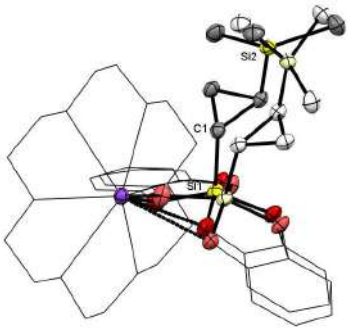
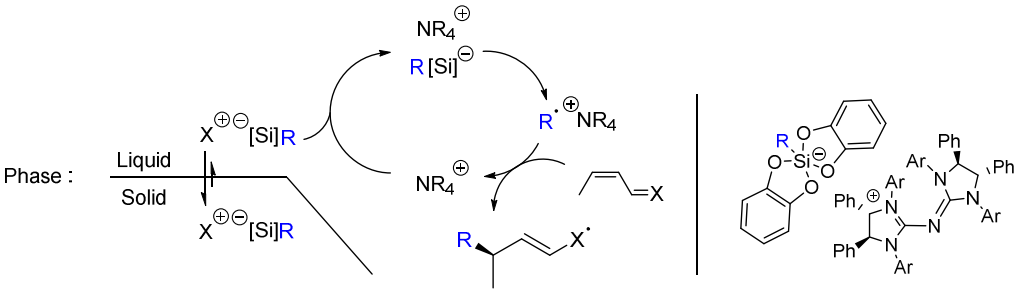


Figure 1: X-ray crystal structure of a cyclopropane silicate . Thermal ellipsoids are drawn at 25% probability level. Pyrocatechol ligands and crown ether are drawn as wireframe for clarity. Hydrogen atoms are omitted for clarity.

If several methodologies have already been employed for the non-covalent enantioselective catalysis such as hydrogen bonding, chiral anion or Bronsted acid, classical ion pairing (using chiral cation) has not been reported. Our strategy relies on the bisguanidinium cation developed by Prof. Tan and their ability to performed phase transfer reaction.[65] Taking advantage of the poor solubility of trifluoroborate and the developed silicate in apolar solvent, the phase transfer (solid-liquid) was achieved for the *in situ* generation of chiral radical precursor (scheme 1). Their aptitude to perform an asymmetric radical addition are currently under investigation.



Scheme 1: Proposed methodology

Acknowledgments:

[62] Proctor, R.S.J., Colgan, A.C. & Phipps, R.J., *Nat. Chem.* **2020**, *12*, 990-1004.
[63] Corcé, V.; Chamoreau, L.-M.; Derat, E.; Goddard, J.-P.; Ollivier, C.; Fensterbank, L., *Angew. Chem. Int. Ed.* **2014**, *54*, 11414-11418.
[64] Abdellaoui, M.; Millanvois, A.; Levernier, E.; Ollivier, C.; Fensterbank, L., *Synlett 2021*.
[65] L. Zong, X. Ban, C.W. Kee, C.-H. Tan, *Angew. Chem. Int. Ed.* **2014**, *53*, 11849-11853.

A versatile and sustainable one-pot synthesis of biobased poly(meth)acrylates

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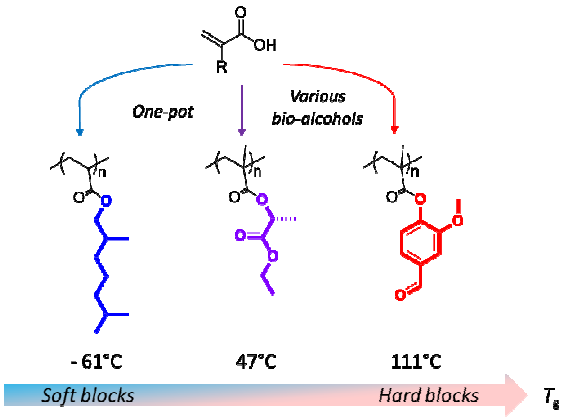
Sustainable polymers are materials ideally obtained from renewable resources *via* processes having a limited impact on the environment. Petroleum, which accounts for nearly 90% of the raw materials used in the industrial synthesis of polymers, is increasingly being replaced by various types of biomass.[66] For instance, acrylic and methacrylic acids can nowadays be derived from renewable resources.[67] Additionally, there is a wide variety of alcohols accessible *via* biorefineries that can be coupled to these acids to form biobased (meth)acrylates.[68] In this context, biobased poly(meth)acrylates make up for a promising class of materials, thanks to the variety of structures and properties they can exhibit.[69] Applications range from high-performance coatings to energy-storage materials, renewable plastics and biomaterials. The polymerization of (meth)acrylates derived from biomass is thus extensively studied,[70] but this field of research lacks a direct and easy methodology to access the desired monomers and subsequently (co)polymerize them into a various library of materials. With these considerations in mind, the first one-pot synthesis of poly(meth)acrylates from the corresponding (meth)acrylic acids was developed. This simple methodology gives access to numerous homopolymers, random and block copolymers, by taking advantage of robust and quantitative monomer preparation and polymerization steps. The first step ((meth)acrylate synthesis from (meth)acrylic acid and alcohol) is catalyzed by cheap and robust Lewis acids. Good functional tolerance was observed as esters and aldehydes remained unaffected. The by-products formed during this step were shown to have no impact on the polymerization step (same conversion, M_n and $Đ$ as in the stepwise synthesis of the same polymers). Thanks to the living nature of the RAFT polymerization process, block-copoly(meth)acrylates could be prepared by repeating the monomer preparation and polymerization steps without any intermediate purification. Size exclusion chromatography and matrix assisted laser desorption ionization-time of flight spectrometry permitted to confirm the obtention of copolymers. Finally, the (co)polymers were characterized by differential scanning calorimetry and thermogravimetric analysis: glass transition temperatures ranging from -61°C to 111°C could be observed, exemplifying the versatility of the one-pot process. This one-pot methodology gives access to new biobased poly(meth)acrylates in a sustainable way, as it avoids the purification steps associated with monomers and blocks preparation. The *E*-factor of the one-pot process was estimated to be more than three times lower than a stepwise approach.



Acknowledgments:
CNRS and ENSCP are thanked for financial support. H.F. gratefully acknowledges financial support from École polytechnique (AMX) for his PhD scholarship.

[66] M. A. Hillmyer, *Science* **2017**, *358*, 868-870.
[67] H. Fouilloux, C. M. Thomas, *Macromol. Rapid Commun.* **2021**, *42*, 2000530.
[68] M. A. Droesbeke, F. E. Du Prez, *ACS Sustainable Chem. Eng.* **2019**, *7*, 11633-11639.
[69] P. F. Holmes, M. Bohrer, J. Kohn, *Prog. Polym. Sci.* **2008**, *33*, 787-796.
[70] C. Veith, F. Diot-Néant, F. Miller, F. Allais, *Polym. Chem.* **2020**, *11*, 7452-7470.

A photostable red and NIR amphiphilic polymer photosensitizer with aggregation-induced emission for image-guide photodynamic therapy

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Cancer is one of the most serious diseases that severely threatens the health of human beings. [1] Photodynamic therapy (PDT) has attracted intensive attention in cancer treatment due to their promising potential advantages, such as minimally invasiveness, minor side effects, good specificity, negligible drug resistance and high efficiency.[2] The most important element of PDT is the photosensitizer which can produce reactive oxygen species (ROS) upon an appropriate excitation light to cause cancer cell death and tissue destruction [3]. The tradition fluorescent photosensitizer (porphyrin derivatives) suffers from the poor solubility and low ROS generation in aqueous media. Then, the fluorescent photosensitizer with aggregation-induced emission (AIE) received enormous attention due to its high emission and efficient ROS generation in the aggregate state. However, most AIE gens were self-assemble into nanoparticles by physical encapsulation, which could probably reduce the stability of the NPs and induce the premature disassembling of the AIE gens in complicated physiological environments.

In this project, the red and NIR emission molecule (2-((5-(4-(diphenylamino)phenyl)thiophen-2-yl)methylene)malononitrile) were induced into amphiphilic diblock copolymer, where the hydrophilic block is PEG and the hydrophobic block is the polymethylmethacrylate. A series of diblock copolymer with hydrophilic ratio of 14%~ 29% were synthesized. And these diblock copolymer could self-assemble into polymeric micelles with diameter of 30 nm and polymersomes with the diameter from 100 nm to 220 nm in water. The UV-Vis and fluorescent spectra show that these polymeric micelles and polymersomes were red and NIR emission. The ROS generation of the polymeric micelles were measured firstly using Rose Bengal as the reference (ROS yield: 75%) under a white light irradiation with a power density of 30 mW/cm2. The result shows that its ROS yield is 44%, which is higher than the clinical used PSs Photofrin (28%). It is demonstrated that their great potential as a powerful and safe photosensitizer for PDT.

Reference

1. Lin, H.; Chen, Y.; Shi, J. L. Nanoparticle-Triggered in Situ Catalytic Chemical Reactions for Tumour-Specific Therapy. Chem. Soc. Rev. 2018, 47, 1938–1958.
2. L. Chen, Y. Zhao, X. Sun, J. Jiang, F. Wu and K. Wang, Synthesis, singlet oxygen generation and DNA photocleavage of β, β′-conjugated polycationic porphyrins. J Porphyr Phthalocya, 2019, 23, 655-663.
3. Wang, H.; Yang, X. Z.; Shao, W.; Chen, S. C.; Xie, J. F.; Zhang, X. D.; Wang, J.; Xie, Y. Ultrathin Black Phosphorus Nanosheets for Efficient Singlet Oxygen Generation. J. Am. Chem. Soc. 2015, 137, 11376−11382.

Artificial Metalloenzymes from Bovine β-lactoglobulin with an N-functionalised N-Heterocyclic Carbene cofactor

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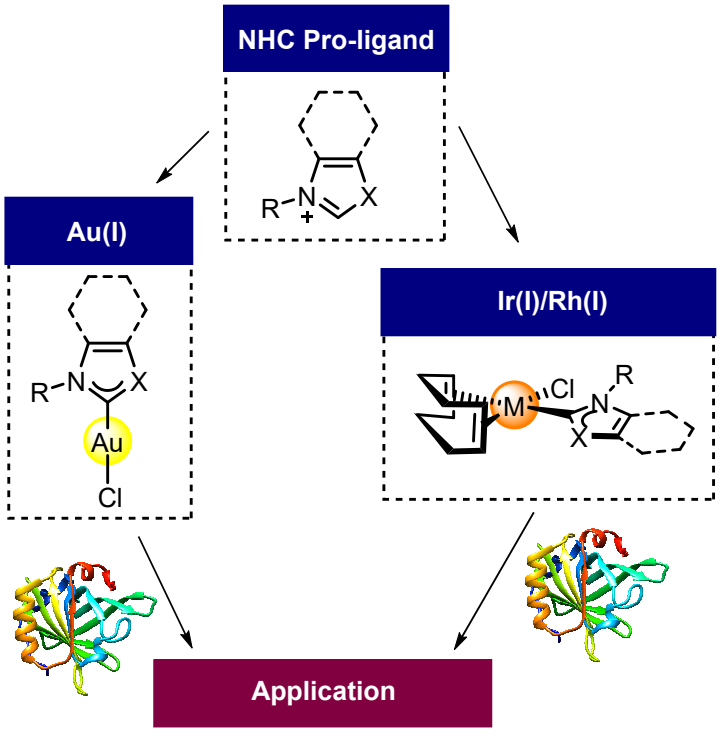
Bovine β-lactoglobulin is the most abundant protein in the whey fraction of milk. It displays a β-barrel structure including a narrow hydrophobic cavity allowing different ligands to bind with good affinity, particularly saturated and unsaturated fatty acids with a chain length ≥ 12 carbons.[71] A series of N-heterocyclic carbene (NHC) metal complexes featuring these fatty acid chains may allow the specific anchoring of the complex into bovine β-lactoglobulin (Scheme 1). The synthesis of these N-functionalised NHC metal complexes and its preliminary catalytic potential will be presented.



Scheme 1

[71] Maux et al., T. *Dairy Sci. & Technol.*, **2014**, *94*, 409 - 426

CO-IMMOBILIZATION OF AN Rh CATALYST AND A KEGGIN POLYOXOMETALATE IN THE UiO-67 METAL-ORGANIC FRAMEWORK: PHOTOCATALYTIC PROPERTIES FOR CO_2 REDUCTION

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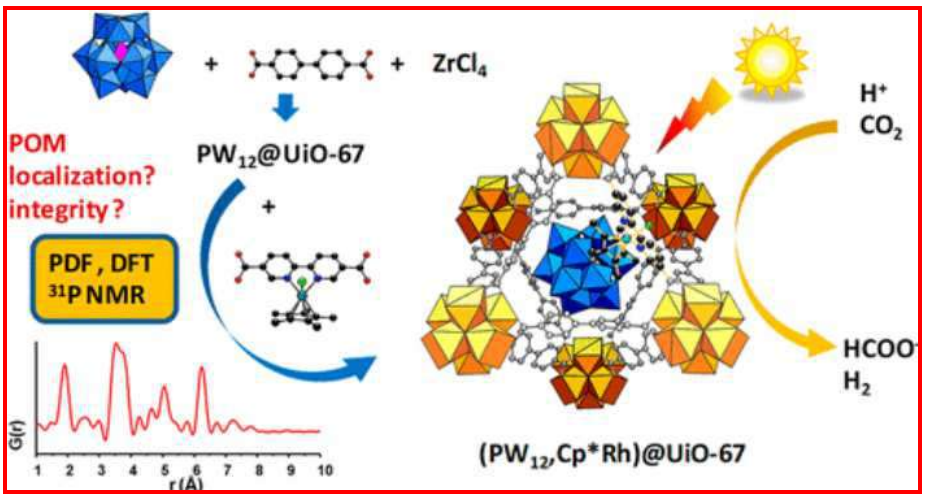
Summary: In the current energetic crisis, one major challenge concerns the development efficient and recyclable heterogeneous photocatalysts able to perform solar energy conversion.
The catalytic complex Cp*Rh(bpydc)Cl_2 and Keggin-type polyoxometalate $[PW_{12}O_{40}]^{3-}$ were coimmobilized in the Zr based metal-organic framework UiO-67. The photocatalytic activity of the composite were evaluated, both formate and H_2 production were doubled when compared to the POM–free Cp*Rh@UiO-67 catalyst. DFT calculation allows identifying two possible location for the POM: one at the center of a UiO-67 pore with the Cp*Rh complex pointing toward an empty pore and one off-centered with the Cp*Rh moiety pointing toward the PW_{12} unit. In depth characterization via ^{31}P and ^{13}C MAS NRM, N_2 adsorption isotherm, X-Ray diffraction and Pair Distribution Function allows to assess the composite stability before and after catalytic experiments.



Acknowledgments: Alex Lemarchand, Mathis Duguet, Pierre Mialane, Maria Gomez-Mingot, Catherine Roch-Marchal, Thomas Pino, Minh-Huong Ha-Thi, Mohamed Haouas, Marc Fontecave, Anne Dolbecq, Capucine Sassoye, and Caroline Mellot-Draznieks

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[1] Y. Benseghir, A. Lemarchand, M. Duguet, P. Mialane, M. Gomez-Mingot, C. Roch-Marchal, T. Pino, M.-H. Ha-Thi, M. Haouas, M. Fontecave, A. Dolbecq, C. Sassoye and C. Mellot-Draznieks, *J. Am. Chem. Soc.*, **2020**, 142, 9428-9438

Synthesis and characterization of nanomaterials for controlled drug release in response to external stimuli

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As some diseases are difficult to treat due to their complexity and physiological constraints, and that undesirable side effects occur in current therapies, the development of new strategies is necessary to enable detection, therapy and monitoring.[72] In this work, different nanoparticles (NPs) with magnetic and optical properties are prepared, to be capable of carrying and releasing drugs in response to external stimuli such as light exposure.[73] The aim is to obtain theragnostic tools with reduced side effects for both early detection and monitoring of the disease.

On one hand, a work has been carried out on the synthesis of Janus-type inorganic nanoparticles with magnetic and luminescent properties (up conversion), generating an epitaxial growth of the magnetic fraction (magnetite) on luminescent nanoparticles ($NaYF_4$:TmYb) with the concentration of the iron precursor as a variable, finding the necessary proportions to have both luminescent and magnetic properties. The NPs were characterized by SEM, fluorescence spectroscopy (F.S.) and magnetization, having nanometric sizes and demonstrating their magnetic and luminescent properties, finding their capacity to emit visible and UV light when irradiated by near infrared light (NIR).[74]

On the other hand, the synthesis of the photosensitive random amphiphilic copolymer Poli(NIPAM-co-SPMA), was optimized. This copolymer contains the hydrophobic spiropyran that, when irradiated by UV light, changes its structure to a zwitterionic state with hydrophilic property, in a reversible photoisomerization process.[75] The polymer was first characterized by NMR. A deep study and characterization of its self-assembly nanostructuration (in water or PBS in different ionic strengths) was then performed. For this purpose, the micelle-like aggregates have been characterized by DLS and capillary electrophoresis (C.E.), evidencing that the material is sensitive to UV light incidence and pH change. In addition, the micelle-like aggregate formation was further studied by DLS and C.E to control its size and charge, and the nanostructure was demonstrated stable.

Work is currently underway on the formation of the nanovehicle (JNP in the aggregate-type micelle) whose size, stability and magneto-luminescent properties will be characterized by the various methods described previously. Then, the trapping of the model drug Doxorubicin within these decorated NPs will be studied, as well as its subsequent release through the incidence of NIR light, the trapping and release being evidenced through both electrophoretic and electrochemical methods.

Acknowledgments: Gregory Lefevre | CONACYT – Mexique | Campus France

[72] C. Blanco-Andujar, et. Al., *Annual Reports section "A" (Inorganic Chemestry)*, **2010**, *106*, 553-568.
[73] Jiang, F., Chen, S., Cao, Z., & Wang, G, *Polymer*, **2016**, *83*, 85-91.
[74] Raza, A., Hayat, U., Rasheed, T., Bilal, M., & Iqbal, H. M., *Journal of Materials Research and Technology*, **2019**, *8(1)*, 1497-1509.
[75] Kortekaas, L., & Browne, W. R., *Chemical Society Reviews*, **2019**, *48(12)*, 3406-3424.

Heterogenization of molecular catalysts for the Electrochemical Reduction of CO_2: the case of Nickel Cyclam

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Catalysis for CO_2 electroreduction into energy-dense products, such as CO, formic acid, hydrocarbons and alcohols, represents one of the most promising strategies for CO_2 utilization. Homogeneous catalysts can be immobilized on heterogeneous conductive supports to generate cathode materials for electrolyzers: such heterogenized molecular systems thus combine the advantages of a solid material (e.g., easy recovery of products and catalysts, efficient electron transfer from the electrode support to the catalyst, high Turnover Numbers) with those of molecular complexes (e.g., synthetic control of the electronic properties and the coordination environment of the active sites). This class of hybrid catalysts for CO_2 reduction has been recently described in review articles.[1,2] In this context, $[Ni(cyclam)]^{2+}$ is known to be a good, stable and selective molecular catalyst for CO_2 electroreduction, however, to our knowledge, there is only one precedent for electrode surface modification with $[Ni(cyclam)]^{2+}$ for electrocatalytic CO_2 reduction[3] and this hybrid material proved quite inefficient and poorly selective. Additionally, there is no precedent for the non-covalent immobilization of $[Ni(cyclam)]^{2+}$ on carbon-based nanostructured electrodes. In the present research, a novel cyclam derivative carrying a pyrene moiety was readily synthesized for the sake of immobilizing a $[Ni(cyclam)]^{2+}$ complex at the surface of a carbon-based electrode. The pyrene-modified complex was immobilized on a carbon nanotube-coated gas diffusion electrode using a non-covalent approach and the novel electrode was characterized electrochemically for CO_2 electroreduction. The complex proved to be much more active in the immobilized form than under homogeneous conditions, with Faradaic Yields for CO production above 90% and current densities up to 10 $mA.cm^{-2}$ in acetonitrile/water mixture. The hybrid electrode proved highly stable, leading to impressive turnover numbers (61460 after 4 h electrolysis). This is remarkable since the electrode support is carbon-based and not mercury, so far the best electrode material for CO_2 electroreduction catalysed by $[Ni(cyclam)]^{2+}$ [4]. The present study confirms the benefits of incorporation of molecular catalysts onto electrode surfaces using the pyrene-CNT approach for CO_2 electroreduction. Additionally, it shows that the $[Ni(cyclam)]^{2+}$ complex provides an excellent platform on which further improvements of hybrid electrodes can be brought.

Acknowledgments:
This project has received funding from the European's Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 765376

[1] Sun, C.; Gobetto, R.; Nervi, C., *New J. Chem*. **2016**, 40, 5656–5661.
[2] Sun, L.; Reddu, V.; Fisher, A. C.;Wang, X., *Energy Environ. Sci*. **2020**, 13, 374–403.
[3] Zhanaidarova, A.; Moore, C. E.; Gembicky, M.; Kubiak C. P., *Chem. Commun*. **2018**, 54, 4116–4119.
[4] Wu, Y.; Rudshteyn, B.; Zhanaidarova, A.; Froehlich, J. D.; Ding, W.; Kubiak, C. P.; Batista, V. S., *ACS Catal*. **2017**, 7, 5282–5288.

Study of the cytotoxicity and intracellular fate of half-sandwich iridium complexes as potential anticancer drugs

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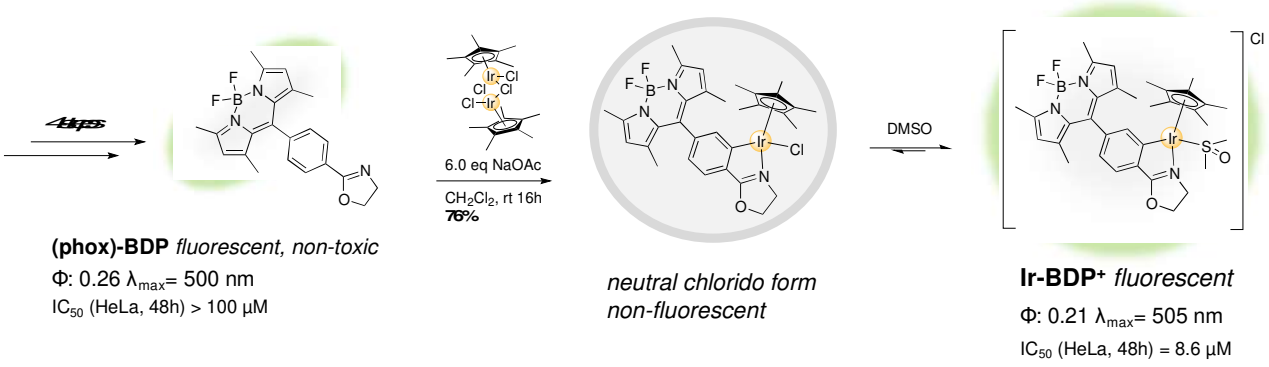
The development of novel metallo-drugs with cytotoxic properties as potential anticancer drugs is of increasing interest.[1] Half-sandwich complexes of iridium (III) including various coligands are currently investigated to this purpose but their molecular mechanism of action is still poorly understood.[2] In this line, we recently introduced a series of 10 complexes including phenyloxazoline derivatives as C^N chelating ligands and showed that their cytotoxicity on HeLa cells was partly linked to their ability to raise the level of intracellular H_2O_2.[3]

A convenient strategy to get insight into the mechanism of action of metal-based drugs is to append a fluorescent reporter group which enables intracellular tracking and thus analysis of their subcellular distribution.[4] To this end, we introduced an iridium complex comprising a modified phenyloxazoline ligand to which was appended a BODIPY entity. BODIPY derivatives are bright, highly photostable fluorophores whose emission properties are generally insensitive to pH changes or polarity.[5] Results of this strategy will be presented in two human cell types: the well-known HeLa cervix cancer cell line and immortalized normal diploid cells (hTERT-RPE).



(phox)-BDP *fluorescent, non-toxic*
Φ: 0.26 λ_{max}= 500 nm
IC_{50} (HeLa, 48h) > 100 µM

neutral chlorido form
non-fluorescent

Ir-BDP$^+$ *fluorescent*
Φ: 0.21 λ_{max}= 505 nm
IC_{50} (HeLa, 48h) = 8.6 µM

*Scheme: Synthesis and characterization of **Ir-BDP**, a cytotoxic fluorescent half-sandwich iridium (III) complex*

Acknowledgments:

IPV Programme of Sorbonne Université, SiRiC Curamus, ITMO Cancer Programme of INCA/Aviesan

References:

[1] Z. Liu, A. Habtemariam, A. M. Pizarro, G. J. Clarkson and P. J. Sadler, *Organometallics*, **2011**, 30, 4702–4710.

[2] J. M. Hearn, G. M. Hughes, I. Romero-Canelón, A. F. Munro, B. Rubio-Ruiz, Z. Liu, N. O. Carragher and P. J. Sadler, *Metallomics*, 2018, 10, 93–107.

[3] R. Ramos, J. M. Zimbron, S. Thorimbert, L.-M. Chamoreau, A. Munier, C. Botuha, A. Karaiskou, M. Salmain and J. Sobczak-Thépot, *Dalton Transactions*, **2020**, 49, 17635–17641.

[4] E. Bodio, P. Le Gendre, F. Denat and C. Goze, *Advances in Inorganic Chemistry*, Elsevier, **2016**, vol. 68, pp. 253–299.

[5] A. Loudet and K. Burgess, *Chemical Reviews*, **2007**, 107, 4891–4932.

Deciphering the biosynthesis of the hybrid PKS-NRPS derived metabolites pyrrocidines produced by the maize endophytic fungi Sarocladium zeae.

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The fungi *Sarocladium zeae* is a maize endophyte and recognized as having a protective effect on its host plant against microbial pathogens. This bioactivity is likely due to the production of two secondary metabolites, the pyrrocidines A and B. Indeed, these compounds exhibit antifungal and antibiotic activities [1], as well as cytotoxicity [2]. Preliminary works based on isotopic incorporation suggested that a **hybrid polyketide synthase - non ribosomal peptide synthetase** (PKS-NRPS) is involved in the biosynthetic pathway of these complex polycyclic structures [4][5].

PKS-NRPS gene cluster 47:

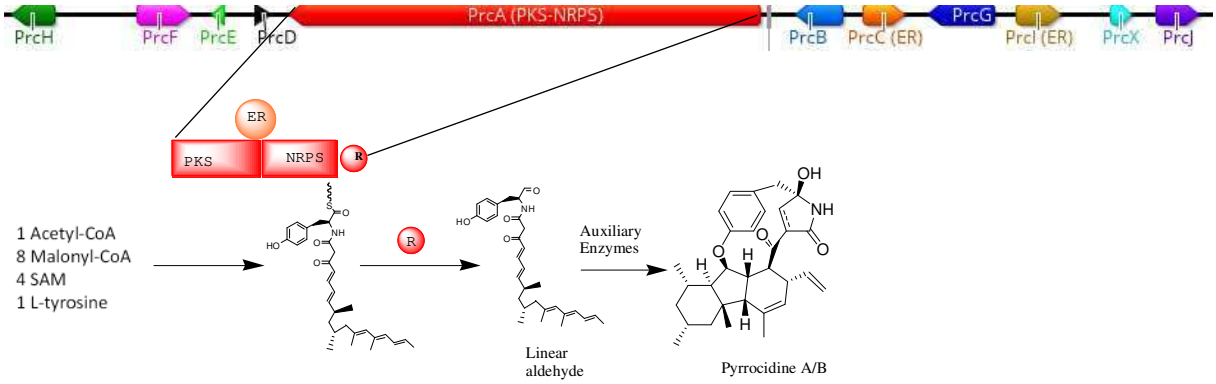

Figure: biosynthetic gene cluster at the origin of pyrrocidines and biosynthetic pathway involving a PKS-NRPS

The study of the biosynthetic pathway and its mode of regulation constitutes a prerequisite to the understanding of the ecological role of pyrrocidines in the tri-partite interaction involving the endophyte, the host plant and the pathogen. It is also a key step for the discovery of 1) enzymes with new activities involved in the building of these molecules and 2) bioactive molecules by microbial engineering (via combinatorial biosynthesis or mutasynthesis) as well as by genome mining. The genome of *Sarocladium zeae* was sequenced in our group and bioinformatic analysis allowed us to identify a putative gene cluster for the biosynthesis of pyrrocidines. In order to gain insights into the biosynthetic pathway, several critical genes of the cluster were inactivated in the fungi. This gives rise to the accumulation of new metabolites which were isolated and characterized by NMR and mass spectrometry. The formation of these compounds allowed us to propose a biosynthetic pathway for the pyrrocidine family molecules. The latest results will be presented.

[1] D.T. Wicklow, S.M. Poling, *Phytopathology* 99 (2009) 109‑115.
[2] S. Uesugi, N. Fujisawa, J. Yoshida, M. Watanabe, S. Dan, T. Yamori, Y. Shiono, K.-I. Kimura, *J. Antibiot.* (Tokyo) (2015).
[4] H. Oikawa, *J. Org. Chem.* 68 (2003) 3552‑3557.
[5] A. Ear, S. Amand, F. Blanchard, A. Blond, L. Dubost, D. Buisson, B. Nay, *Org. Biomol. Chem.* 13 (2015) 3662‑3666.

Imines reduction using well-defined low-valent cobalt complexes

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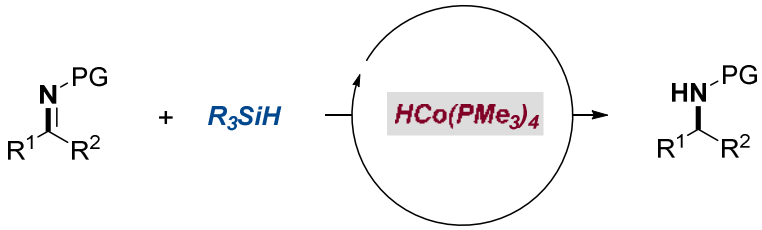
Low-valent cobalt complexes have been widely used due to their interesting reactivities. Our group has been working on well-defined complexes bearing simple trimethylphosphine as ligands and have shown that these types of complexes are very efficient on various reactions such as C-H bonds activation;[76] alkynes hydrosilylation[77] or hydroboration.[78] In this communication we will report the hydrosilylation of a large range of aryl and aliphatic ketimines using $HCo(PMe_3)_4$ as catalyst. In the literature, examples of imines hydrosilylation can be found, but mainly using rare transition metal complexes such as Ru, Rh, Ir or Pd which remain expensive.[79] Indeed, only few examples of abundant transition metal complexes such as Fe and Ni have been reported for the moment[4]. It is noteworthy to mention that, in most of the cases, only aldimines are reduced; that ketimines require harsher conditions and that scarce examples of aliphatic ketimines hydrosilylation have been reported. Very few examples of imine reductions catalyzed by cobalt complexes have been reported which require harsh conditions under H_2 pressure. To the best of our knowledge, this is the first example of imine hydrosilylation catalyzed by cobalt complexes. The reaction tolerates a broad range of substrates, silanes and protecting group on the imine. Mechanistic investigations have been conducted in order to propose a catalytic cycle. X-Ray structure of a dihydride Co(III) intermediate, resulting of the oxidative addition of the hydrosilane on the Co(I), has been obtained. In addition, labelling, competition, kinetics experiments, DFT calculations and NMR monitoring have also been carried out in order to go further in the mechanistic insights.



- ***large scope of substrate (49 examples)***
- ***several hydrosilanes can be used***
- ***various protecting groups on the imines (9 examples)***
- ***isolation of [H2CoSi] intermediates and X-Ray structure***
- ***mechanistic studies : kinetics; deuterium and competition experiments***

Acknowledgments: This work was supported by CNRS, MRES and Sorbonne Université. We would like to thanks Dr. Etienne Derat for the DFT calculations and Geoffrey Gontard for the X-Ray structure resolution.

[76] Fallon, B. J.; Derat, E.; Amatore, M.; Aubert, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A.; Petit, M. *J. Am. Chem. Soc.* **2015**, *137*, 2448-2451.
[77] Rivera-Hernández, A.; Fallon, B. J.; Ventre, S.; Simon, C.; Tremblay, M.; Gontard, G.; Derat, E.; Amatore, M.; Aubert, C.; Petit, M. *Org. Lett.* **2016**, *18*, 4242-4245.
[78] Ferrand, L.; Lyu, Y.; Rivera-Hernández, A.; Fallon, B. J.; Amatore, M.; Aubert, C.; Petit, M. *Synthesis* **2017**, *49*, 3895-3904.
[79] Li, B.; Sortais, J.; Darcel, C. *RSC Adv.* **2016**, *6*, 57603-57625.

Synthesis of surface modifying copolymers

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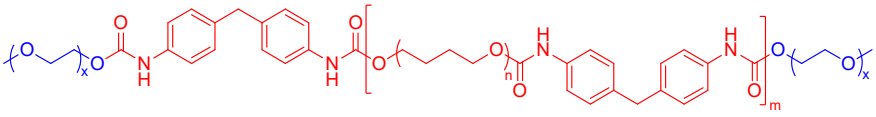
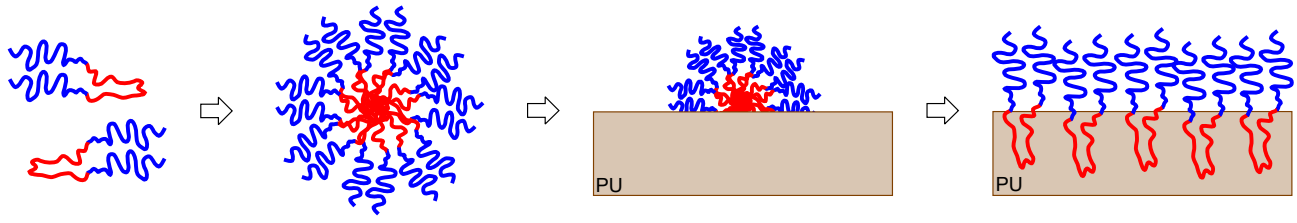
Polyurethanes (PU) are widely employed as materials for implantable biomedical devices due to their outstanding mechanical properties and reasonably good biocompatibility. Nonetheless, the interaction of PU materials with the host not rarely lead to adverse reactions that range from inflammation to fibrosis, bacterial infections, or thrombosis.[80] Many studies have been conducted do graft antiadhesive brushes onto the surface[81] or blend surface modifying additives into the base polymer.[82] Frequent drawbacks of these strategies include, respectively, the use of active and potentially toxic substances and the potential loss of mechanical properties.

We seek to circumvent these problems by modifying the surface with a non-covalent strategy with long-lasting effects. To do so, we seek to synthesize amphiphilic block copolymers that self-assemble in water to form polymeric micelles. These polymeric micelles will be adsorbed to the surface and the polymer chain of the hydrophobic part will then penetrate the top layer of the material anchoring them irreversibly.
Multiple candidates for both blocks were evaluated based on their intrinsic properties and interactions with a model medical grade polyurethane (Pellethane® 2363-80AE). Polyurethane-Poly(ethylene glycol) (PU-*b*-PEG) triblock copolymers with various sizes have been prepared, self-assembled in water and their antifouling properties studied, as well as their capacity to modify the surface properties of the model PU substrate.



PEG-PU-PEG



Polymeric micelle formation | Polymeric micelle Adsorption | PU block insertion

Acknowledgments: This project is funded by PSL University and Chimie ParisTech through a doctoral contract

[80] H. Park, K Park, *Pharmaceutical Research* **1996**, *13*, 1770–1776.
[81] A. Chauhan, A. Bernardin, W. Mussard, I. Kriegel, M. Estève, JM. Ghigo, C. Beloin, V. Semetey, *The Journal of Infectious Diseases* **2014**, *210*, 1347-1356.
[82] M.L. Lopez-Donaire, J.P. Santerre, Journal of Applied Polymer Science **2014**, *131*, 40328-40342.

New eco-friendly pathways for the synthesis of insect pheromones by iron-catalyzed cross-coupling: development, industrial applications, and mechanistic aspects

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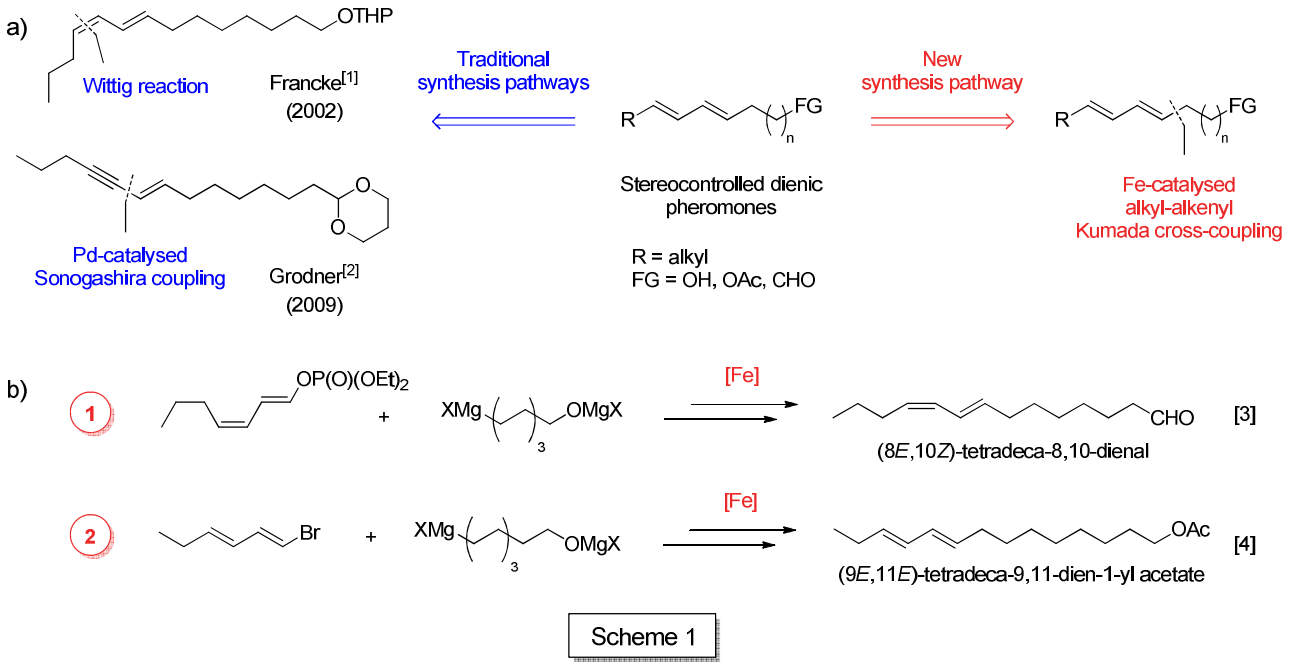
Unlike the use of pesticides, which currently causes significant ecological issues, biocontrol based on use of pheromones is an eco-friendly solution for the protection of a wide range of crops, vineyards, and plants against pests. In addition, pheromones are fully biodegradable and specific to the sole target species, and they do not display toxicity to human health. However, at this time, few pathways for the synthesis of insect pheromones reported in the literature are applicable on an industrial scale. Indeed, the key step of the synthesis, the introduction of the C=C unsaturations, traditionally involves expensive and waste generating methodologies such as Wittig reaction[1] or Pd-catalysed cross-coupling[2] (Scheme 1a).

To address this issue, we developed new synthetic routes relying on iron-catalysed cross-coupling as a key step, capitalizing on the low eco-toxicity and the cheap cost of this metal. In the first example given in scheme 1b, a short six-step convergent high-scale synthesis of the horse-chesnut leaf miner sex pheromone is achieved with an overall yield of 40%.[3] Importantly, neither ligands nor additives are used to perform the key stereoselective iron-catalysed Kumada cross-coupling. In the second example, we tried to replace the dienyl phosphate by a stereocontrolled bromodiene for atom economy, cost, and practical issues to achieve another sex pheromone synthesis. Again, no ligand or additive is used thanks to the -OMgX moiety which seems to improve the stereoselectivity and the efficiency of iron-catalysed cross-coupling.[4] Mechanistic investigations are under progress to explain this point.



Scheme 1

Acknowledgments:

1) A. Francke, et all., *Naturforsch*. **2002**, 57, 739–752 ; 2) J. Grodner, *Tetrahedron*. **2009**, 65, 1648-1654 ; 3) P. Chourreu, O. Guerret, L. Guillonneau, E. Gayon, G. Lefèvre, *Org. Process Res. Dev*. **2020**, *24, 7*, 1335-1340 ; 4) P. Chourreu, O. Guerret, E. Gayon, G. Lefèvre. *Redaction in progress.*

AIE-polymersomes with a Bright Far-Red/Near-Infrared Emission for Photodynamic Therapy

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Photodynamic therapy (PDT) is an emerging therapeutic modality for tumors treatment in clinic with minimal invasiveness, in-situ workability and high spatiotemporal precision. However, some issues are supposed to be addressed in PDT, such as the water-solubility of photosensitizers, biocompatibility, circular blood time, biodistribution and so on. Currently, construction of an organic nano-agent is an efficient method to overcome those problems, and to date, liposomes and polymersomes equipped with photosensitizers have been reported for PDT. However, in the most cases, photosensitizers are encapsulated by physical adsorption, where hydrophobic interactions act as driven force. Even though, liposomes constructed from PSs-functionalized lipid have been reported, the assemblies were fabricated by blending several components, which not only resulted in a low load efficiency of PSs but also caused biodistribution problem of PSs. Herein, an AIE-polymersome with reactive oxygen species generation based on PEG-b-P(CN-NAG)$_7$ has been constructed for the first time. The polymersomes have a diameter of around 90 nm, which locates in the range of "ideal size" (70 nm – 200 nm) for a drug-delivery carrier. The AIE-polymersomes exhibit good biocompatibility by MTT assay and have a moderate fluorescent quantum yield (Φ = 0.17). Meanwhile, the load efficiency of MeTTPy for the polymersomes reaches up to 0.46 and the efficiency of reactive oxygen species (ROS) generation is measured to be 0.34. Benefiting from AIE property and ROS generation, the AIE-polymersomes will be applied in image-guided photodynamic therapy (PDT) in vitro cancer cell ablation.

Acknowledgments:

We acknowledge the French National Research Agency (project ANR-16-CE29-0028). Zhihua ZHANG thanks the China Scholarship Council for funding his PhD scholarship. We thank Sylvain TREPOUT in institute curie for cryo-EM technique.

Study of the influence of matrix and extraction method on the source inference process of ignitable liquids by an untargeted chemometric approach

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Summary : Identifying the perpetrator of arson is a real challenge for forensic analysts since the physical traces associating a criminal with this type of crime scene are often destroyed. If an ignitable liquid was used to start the fire, and its residual presence can be detected, a source inference approach with other ignitable liquids is likely to provide investigative or evidentiary support. Source inference is a process of association, a method that consists of evaluating the possible common source between two unknown ignitable liquids, in particular between a liquid found at the arson site and a liquid found in an external source (jerry can, clothes found in the vicinity...). This determination is based on the comparison of similarities and/or differences in the chemical composition of the ignitable liquids being investigated. This comparison is easier when the ignitable liquid is in its liquid form, pure or even partially altered. However, due to the destructive nature of fires, the samples received in the laboratory for analysis consist mainly of solid materials in which liquid residues have sorbed, and most often these samples have been deteriorated by the fire. Although it is now possible to link two altered or unaltered ignitable liquids sharing a common source by source inference**1**, it is nevertheless difficult to extend this question to the burnt residues frequently received for analysis, which allow to trace the origin of a fire. The matrix effect, which includes the effect of any substrate present in the debris, is also extremely important in this type of specimen, since compounds from the substrates can compromise the extraction of ignitable liquids, emitting numerous interfering compounds from the raw material, its combustion as well as its pyrolysis, affecting the interpretation of the presence or absence of ignitable liquids in the analyzed debris. As a result, an alteration of the profiles is systematically observed, which increases the level of complexity of a source inference approach. In previous works, the analysis of liquid gasoline samples allowed to link two liquid samples independently of their mode and degree of alteration thanks to the development of a similarity calculation algorithm**1**. In this work, we propose to study the matrix contribution to the problem of source inference in forensic science by using the multivariate chemometric methods already developed. First, the selection of gasoline samples (representative of very different chemical compositions) was carried out by a first screening by principal component analysis (PCA). The choice of the matrix was focused on clothing (100% cotton or 100% polyester T-shirts), little studied until now, but often found at fire sites. Fire samples were simulated in the laboratory with these species and fabrics. They were then analyzed by thermodesorption followed by gas chromatography coupled to single quadrupole mass spectrometry (TD-GC-MS, in full scan mode). A data processing and analysis step is then performed: after a data pre-processing phase (detection, integration and alignment of chromatographic peaks), the variables of interest (areas, retention time and m/z) are then extracted in the form of data matrix which are processed by an algorithm under Matlab (R2019b). This algorithm builds a model based on the ROC (Receiver operating characteristics) curve using a large dataset of gasoline samples from known sources, taking into account the intra- and inter-variability of these samples. This model is then applied to unknown gasoline samples to predict a possible link. After identifying the signals from the matrix, we have shown that it is possible to link two liquids of gasoline extracted from the fabric, working on a very small number of samples. These results will allow us to extend the study path for more complex matrix with larger data sets.

Acknowledgments:

1. Figueiredo M, Jouan-Rimbaud Bouveresse D, Cordella CBY, Archer X, Bégué JM, Rutledge DN. 2019;301, 190–201.

Cobalt-catalyzed desulfonylative 1,4 radical aryl migration: Synthesis of α-aryl amides

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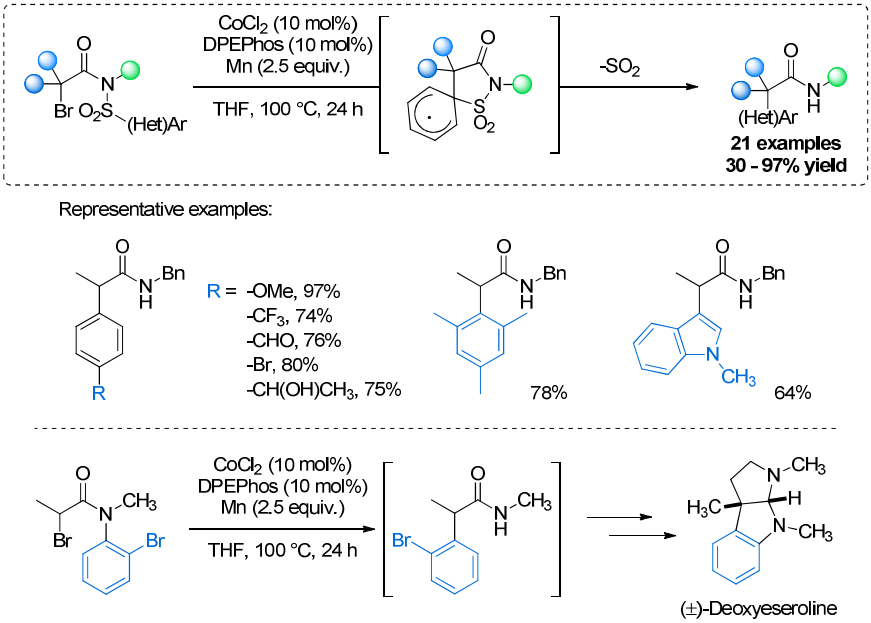
Access to important pharmacophores by sustainable methods is one of the most important challenges of modern organic chemistry. Over the last ten years, our group has been interested in the development of earth-abundant metal catalyzed reactions (*eg*. Fe, Ni, Co, Cu) to avoid the use of heavy metals (*eg*. Pd, Rh, Ru).[83] Recently, a special focus was dedicated to the synthesis of α-aryl amides,[84] a moiety present in a wide range of drugs such as amoxicillin or penicillin G. An original access to α-aryl amides from α-halo *N*-arylsulfonyl amides through a cobalt-catalyzed desulfonylative radical aryl migration was discovered.[85,86] This method allowed the access to a variety of α-aryl amides in high yields and showed a very good tolerance toward functional groups such as aldehydes or free alcohols. This reaction was also suitable for the synthesis of sterically hindered α-aryl amides, which can be challenging to obtain using other methods.[87] Mechanistic studies were conducted and a radical mechanism was hypothesized for this transformation.

This method represents a new, efficient and reliable tool for the synthesis of α-aryl amides. Its synthetic utility was illustrated by the synthesis of (±)-deoxyeseroline, an acetylcholinesterase inhibitor.



Acknowledgments:

[83] A. Guérinot; J. Cossy, *Acc. Chem. Res.* **2020**, *53*, 1351 – 1363

[84] E. Barde; A. Guérinot; J. Cossy, *Org. Lett.* **2017**, *19*, 6068 – 6071

[85] Reviews: a) A. Studer; M. Bossart, *Tetrahedron* **2001**, *57*, 9649 – 9667 ; b) Z.-M. Chen; X.-M. Zhang; Y.-Q. Tu, *Chem. Soc. Rev.* **2015**, *44*, 5220 – 5245 ; c) W. Li; W. Xu; J. Xie; S. Yu; C. Zhu, *Chem. Soc. Rev.* **2018**, *47*, 654 - 667

[86] N. Gillaizeau-Simonian; E. Barde; A. Guérinot; J. Cossy, *Chem. Eur. J.* **2021**, *27*, 4004 – 4008

[87] F. Bellina ; R. Rossi, *Chem. Rev*. **2010**, *110*, 1082 – 1146

Design, synthesis and photophysical and biological evaluations of new fluorescent analogs of Trypan blue targeting the Vesicular GLUtamate Transporters (VGLUTs)

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Glutamate is the main excitatory neurotransmitter of mammalian central nervous system (CNS) and is involved in all brain functions.[88] Dysregulation of glutamatergic transmission in certain cerebral structures has been shown to be correlated to or even implicated in pathophysiological conditions such as Alzheimer's, Parkinson's and Huntington's diseases, amyotrophic lateral sclerosis, epilepsy and glutamatergic excitoxicity following cardiovascular events like myocardial infarctions and strokes2-5.[89] Glutamatergic neurotransmission depends on several proteins, namely membrane receptors, like AMPA and NMDA ionotropic receptors, membrane transport proteins (EAATs) and Vesicular GLUtamate Transporters, or VGLUTs, which comprise three isoforms, namely VGLUT1-3, whose distribution and functions within the brain are different but complementary.[90] These latter are the only functional and anatomical specific biomarkers of glutamatergic transmission and it has been shown that inhibition of their activity by small organic ligands could modulate brain functions. The most promising ones, because of their affinity for and selectivity towards the VGLUTs, are derived from Trypan blue. A lead compound, called LSP5-2157, has been developed in our laboratory and proved to modulate neuronal phenomena resulting in, for instance, inhibition of long-term potentiation in hippocampal cells or even loss of hearing in a mice model. Unfortunately, pharmacokinetic issues arise when using LSP5-2157 in integrated biological models, as shown by the drop of its biological activity (IC50 from 39 nM to 1 mM).[91] This is due to the amphilicity of the molecule resulting in low penetration of the blood-brain barrier and problems of bioavailability. To circumvent this, we aim at developing new analogs of Trypan blue with optimal logP and vectorization properties, while still improving affinity for VGLUTs and trying to get molecules selective for each subtype of VGLUTs. Moreover, fluorescent properties, which are expected to be improved, are added to our analogs for making them useful as pharmacological tools, mainly in fundamental studies of glutamatergic transmission, as they can be visualized by super-resolution fluorescence microscopy techniques, such as STED and STORM techniques. All together, these optimizations could enable good pharmacological tools and/or drug candidates to be used in helping deciphering mechanisms of VGLUTs in particular and glutamatergic transmission in general or in the diagnosis of neurological disorders and even treatment of such diseases.

Acknowledgments : Nicolas Pietrancosta (PhD supervisor), staffs of LBM and the team "Neuropharmacologie des VGLUTs - Systèmes glutamatergiques normaux et pathologiques".

[88] Magi, Simona, et al. *International Journal of Molecular Sciences*, 20, **2019**, 5674.

[89] a) Poirel, Odile, et al. "Moderate Decline in Select Synaptic Markers in the Prefrontal Cortex (BA9) of Patients with Alzheimer's Disease at Various Cognitive Stages." *Scientific Reports*, 8, **2018**, 938. b) Kashani, Alireza, Catalina Betancur, et al. "Altered Expression of Vesicular Glutamate Transporters VGLUT1 and VGLUT2 in Parkinson Disease." *Neurobiology of Aging*, 4, **2007**, 568–78. c) Fan, M., and L. Raymond. "N-Methyl-d-Aspartate (NMDA) Receptor Function and Excitotoxicity in Huntington's Disease." *Progress in Neurobiology*, 81, **2007**, 272–93. d) Belov Kirdajova, Denisa, et al. "Ischemia-Triggered Glutamate Excitotoxicity From the Perspective of Glial Cells." *Frontiers in Cellular Neuroscience*, 14, **2020**, 51. e) Sanacora, Gerard, et al. "Targeting the Glutamatergic System to Develop Novel, Improved Therapeutics for Mood Disorders." *Nature Reviews Drug Discovery*, 7, **2008**, 426–37.

[90] El Mestikawy, Salah, et al. "From Glutamate Co-Release to Vesicular Synergy: Vesicular Glutamate Transporters." Nature Reviews Neuroscience, 4, 2011, 204–16.

[91] Poirel, Odile, et al. "LSP5-2157 a New Inhibitor of Vesicular Glutamate Transporters." Neuropharmacology, 164, 2020, 107902.

Insights on Nitro Arenes Suzuki-Miyaura Coupling

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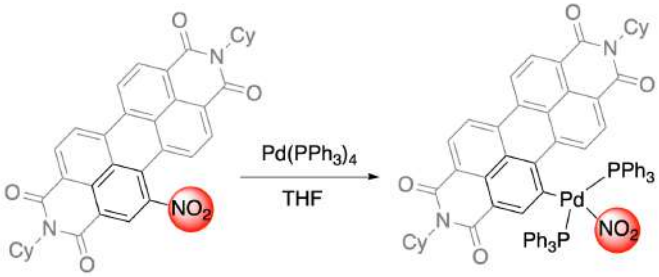

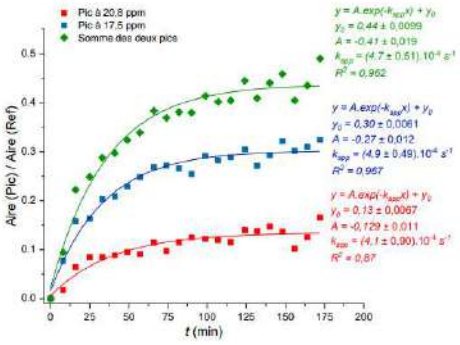

The Suzuki Miyaura coupling of nitro-arenes has recently been developed.[92] On one hand, it has been performed under hard conditions (Palladium-BrettPhos/$K_3PO_4.nH_2O$/18-crown-6 in 1,4-dioxane at 130°C) for a wide range of nitro-benzene derivatives. On the other hand, this reaction was completed with the very specific nitro perylenediimide (PDI-NO_2) substrate[93] under very smooth conditions: we show that the reaction works at room temperature in THF with $Pd(PPh_3)_4$ as a catalyst. Although some mechanistic studies have been performed on the palladium-BrettPhos catalytic system showing the presence of a nitro derivative η^2-complex; nothing was reported to explain the singularity of the PDI-NO_2.

We combined electrochemistry, NMR and UV-vis spectroscopies and DFT calculations, to study the mechanism of this reaction and tried to widen its substrate scope. Previous DFT studies highly suggest that the oxidative addition is the rate limiting step.[94] Therefore, the PDI-NO_2 oxidative addition complex was synthetized and characterized by NMR, electrochemistry, and UV-visible. Reaction kinetics were monitored by ^{31}P and ^{1}H NMR showing a first order for both reactants ruling out any resting state before the oxidative addition, especially the η^2-complex.

Then, we tried to rationalize why the reaction occurs in smooth conditions for this substrate but fails for smaller benzene and naphthalene derivatives. We firstly hypothesized that expanded π-systems facilitate the process. That was proved to be insufficient as the reaction also failed with 1-nitro pyrene and 9-nitro anthracene. Because of the gap between the reduction of the PDI-NO_2 (E = -0.34 V vs Ag|AgCl) and the 1-nitropyrene (E = -0.93 V vs Ag|AgCl) we investigated the correlation between reduction potential of the substrate and both the yield of the Suzuki Miyaura coupling and the activation energy calculated by DFT. All the compounds tested have a reduction potential lower by at least 0.3 V than PDI-NO_2 and do not undergo oxidative addition. Additional RPE studies are currently in progress in order to determine if a SET is involved for the PDI-NO_2 substrate in order to explain the different substrate reactivity.

Acknowledgments:
Jules Schleinitz thanks the Ecole Normale Supérieure for 3 years contract as “Agrégé Préparateur”.

[92] M. Ramu Yadav, M. Nagaoka, M. Kashihara, R. Zhong, T. Miyazaki, S. Sakaki, and Y. Nakao, *Journal of the American Society* **2017**, *139* (28), 9423-9426.
[93] Ron-Lin Zhong, M. Nagaoka, Y. Nakao, and S. Sakaki, *Organometallics* **2018**, *37* (20), 3480-3487.
[94] Rayane El-Berjawi, P. Hudhomme, *Dyes and Pigments,* **2018**, *159*, 551-556.

Design and synthesis of bioactive material by two photon polymerization

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Summary

The cell microenvironment plays a major role in biology and emerges as a key determinant of cell behavior and cell functions in many biological processes.[95] The extracellular matrix (ECM) within the cell microenvironment constitutes a structural foundation for cells but also as a source of three-dimensional (3D) biochemical and biophysical cues that trigger and regulate cell behaviors. Increasing evidence suggests that the 3D character of the microenvironment is involved for development of many critical cell responses observed in vivo, requiring the development of functional and biomimetic materials for engineering the 3D cell microenvironment. Progress in the design of such materials may improve control of cell behaviors in 3D and advance the fields of tissue regeneration, in vitro tissue models, as well as the development of the next generation medical device for medicine. Main key challenges in the field consist in dissecting the roles of chemistries, microtopographies, and mechanics in the cell microenvironment. However, the field is emerging and through functional and biomimetic material designs, tremendous progress in engineering the cell microenvironment as well as the development of applications in tissue engineering and medical device are expected. New materials and fabrication technologies are emerging rapidly (e.g. two-photon polymerization (TPP)).

Recently both hosting laboratories produced hexagonal lattices to probe systematically the microtopography-induced formation of epithelial cell protrusions. Lattices of hexagons of various sizes (from 1.5 to 19 µm) and 5-10 µm height were generated by two-photon polymerization in NOA61 (Norland Optical Adhesive) or poly(ethylene glycol) diacrylates derivatives (PEGDA).[96] They found that cells were exhibiting one unique and unexpected behavior by generating numerous, extensive and deep basal protrusions for hexagons inferior to cell size (3-10 µm), while maintaining a continuous epithelial layer above structures. This highlights the effect of microtopographies on cell behavior.

Off-stoichiometry thiol–ene (OSTE) was firstly developed by Tommy Haraldsson and Fredrik Carlborg at the group of micro and nanosystems to mind the research-to-application gap for lab-on-chip.[97] Different from traditional thiol-ene chemistry, OSTE has a powerful control of the excess function group on the surface of cured materials, that is to see a directly precise and permanent surface modification. Taking the effect of easily controlled surface chemistry into account, we chose OSTE resin as a potential material for cells. By tuning the ratio of the thiol group and alkene group in the components, we studied the toxicity of OSTE resin with and without surface modification for MDCK cells, providing support for the combination of surface modification and microtopographies of 3D cell scaffold by two photon polymerization in the coming step.

Acknowledgments: Thanks to the support from Guangzhou Oversea Study Program.

[95] G. Huang, F. Li, X. Zhao, Y. Ma, Y. Li, M. Lin, G. Jin, T. J. Lu, G. M. Genin, F. Xu, *Chem. Rev.* **2017***, 117,* 12764 – 12850.
[96] S. Coscoy, J. Octon, Q. Tseng, F. Amblard, S. Baiz, L. Perquis, B. Rhoné, V. Semetey, *Biointerphases* **2018***, 13(4)*:041003.
[97] Carlborg, Carl Fredrik, Tommy Haraldsson, Kim Öberg, Michael Malkoch, and Wouter van der Wijngaart, *Lab on a Chip* **2011**,*11(18)*, 3136-3147

Coordination-induced supramolecular hierarchical assemblies of cyclodextrins

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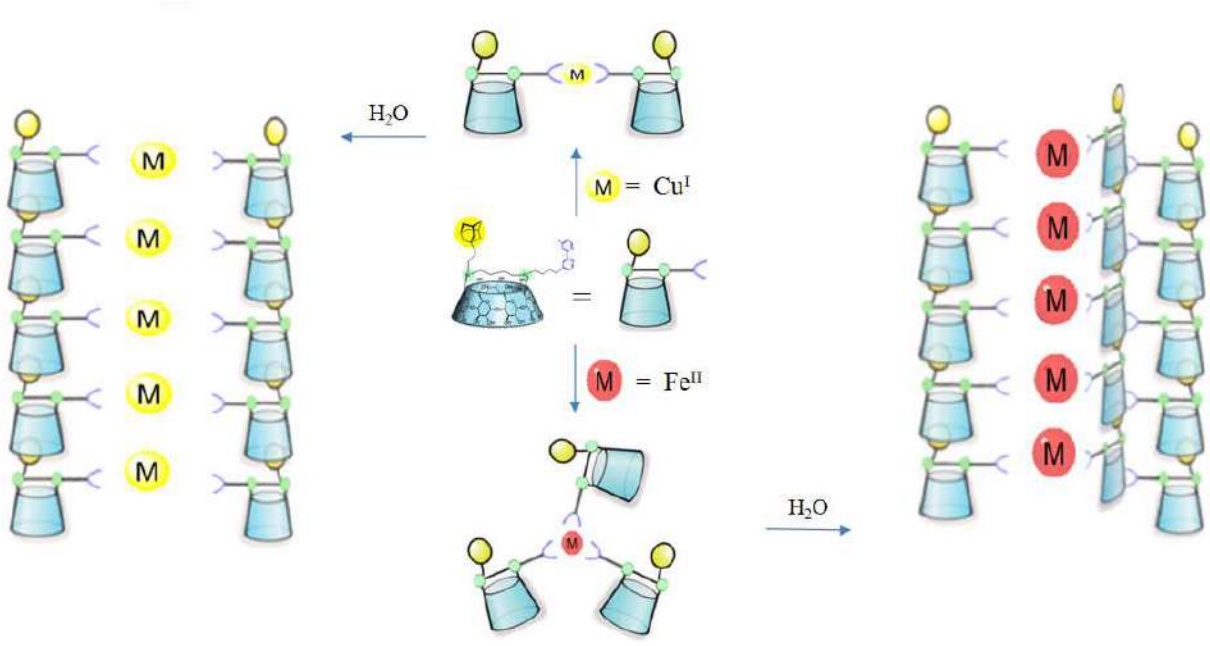
Cooperative self-assembly[98,99]is a powerful tool to construct elaborate architectures in a bottom-up approach. For example, nature heavily relies on cooperativity to build the highly complex components of organisms from smaller units.[100] Despite a lot of effort being invested in this field, there is no reliable system forming well-defined monodispersed and tunable fibrilar objects where the diameter of the cross-section is monodispersed and that can be tuned with an atomic precision in the range one to ten nanometer. We wish to develop here such a system based on precisely functionalized cyclodextrins.

We will study here hierarchical supramolecular assemblies using cyclodextrins and metal complexes. To this end, we have associated a self-assembling cyclodextrin with a ligand that can coordinate a metal. The cyclodextrin associated to a hydrophobic molecule forms 1D fibers, that will associate in a controlled manner by coordination with metals having different geometries and therefore the assembly will adopt different fibrilar forms.



Structures of precisely functionalized cyclodextrins and the assembly will adopt different fibrillar forms

Acknowledgments:

[98] C. A. Hunter,H.L.Anderson, *Angew.Chem. Int. Ed* **2009**, *48*, 7488.
[99] C. Rest, R. Kandanelli, *Chem. Soc.Rev.* **2015**, *44*, 2543.
[100] B. J. G. E. Pieters,M.B.van Eldijk, *Chem. Soc.Rev.* **2016**, *45*, 24.

Synthesis, Characterization and Antiparasitic Activity of Organometallic Derivatives of the Anthelmintic Drug Albendazole

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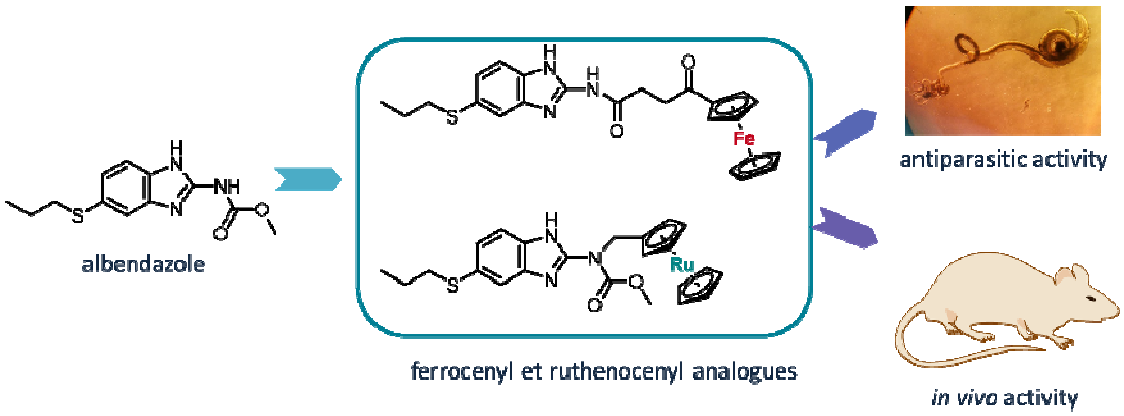
Helminthiases, a group of neglected tropical diseases, affect more than one billion people mainly in tropical and subtropical regions. Moreover, major intestinal protozoa have a significant impact on global public health. Albendazole (ABZ) is a broad-spectrum anthelmintic recommended by the World Health Organisation (WHO). However, drug resistance is emerging due to its widespread use. In order to tackle this problem, taking into account the spectacular results obtained with the organometallic derivatization of the antimalarial drug chloroquine, we have prepared, in this study, a series of new ferrocenyl and ruthenocenyl derivatives of the organic drug ABZ and assessed their activity against different helminths and protozoans, namely *Trichuris muris*, *Heligmosomoides polygygrus*, *Schistosoma mansoni*, *Giardia lamblia*, *Haemonchus contortus* and *Toxoplasma gondii*. The ferrocene-containing ABZ exhibited over 70% activity against *T. muris* adults in vitro at 200 µM and no toxicity to mammalian cells (IC50> 100 µM). *H. polygyrus* adults were not affected by any of the derivatives tested. Against *T. gondii*, the ferrocene-containing ABZ analogues showed better *in vitro* activity than ABZ and low toxicity to the host cells. The activity of the analogous ruthenocenyl compound against *S. mansoni* and *T. gondii in vitro* might be attributed to its toxicity towards the host cells rather than a specific antiparasitic activity. These results demonstrate that the derivatives show a species specific *in vitro* activity and the choice of the organometallic moieties attached to the organic drug is playing a very important role. Two of our organometallic compounds, were tested in *T. muris* infected mice. At a 400 mg/kg dose, the compounds showed moderate worm burden reductions but low worm expulsion rates. Overall, this work, which is one of the first studies reporting the potential of organometallic compounds on a very broad range of parasitic helminths and protozoan, is a clear confirmation of the potential of organometallic complexes against parasites of medical and veterinary importance.



Acknowledgments:
Thanks to Olivier Blacque for the analyzing of X-ray crystallography. Thanks to Jennifer Keiser for giving the support of Animal testing. Thanks to Sabrina Lebrequier and David-Alexandre Buisson for excellent analytical support (Université Paris-Saclay, Service de Chimie Bio-organique et Marquage, CEA, 91191, Gif-sur-Yvette, France).

Synthesis, characterization, and electrophoretic separation of graphene-based quantum dots

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Graphene-based quantum dots have gained much attention in medical research due to their biologically-suitable characteristics such as low toxicity [1], biocompatibility [2] and chemical and photo-stability [3] and their ability to be used as multifunctional nanoplatforms. In addition, they posess tunable optical, electrical, chemical and structural properties [4]. With developments in biomedicine and the need for therapeutic drugs that are not harmful to the biological systems, there is a great need to have a well-rounded understanding of these nanostructures in terms of their functionality and behaviour in different environments. The work reported herein looks at 3 different types of quantum dots, namely, graphene quantum dots (GQDs), nitrogen doped graphene quantum dots (NGQDs) and graphitic carbon nitride quantum dots (gCNQDs), synthesized by optimized methods and characteriszed using various techniques. Capillary electrophoresis is also employed in order to determine the overall surface charge, size and dispersity in each sample batch.

Acknowledgments:
This work was supported by the Department of Science and Technology (DST) and National Research Foundation (NRF), South Africa, through DST/NRF South African Research Chairs Initiative for Professor of Medicinal Chemistry and Nanotechnology (UID 62620), Rhodes University/DST Centre for Nanotechnology Innovation, Rhodes University, South Africa, as well as Chimie Paristech, PSL and Campus France, Paris, France.

References :

1.Shen, Y. Zhu, X. Yang and C. Li, Graphene quantum dots: emergent nanolights for bioimaging, sensors, catalysis and photovoltaic devices , *Chem. Commun.* **(2012)** 48, 3686-3699.

2. E-P. Jang, W-S. Song, K-H. Lee, H. Yang, Preparation of a photo-degradation- resistant quantum dot–polymer composite plate for use in the fabrication of a high-stability white-light-emitting diode, Nanotech. 4 **(2013)** 957-4484.

3.D. Qu, M. Zheng, P. Du, Y. Zhou, L. Zhang, D. Li, H. Tan, Z. Zhao, Z.Xie, Z. Sun, Highly luminescent S, N co-doped graphene quantum dots with broad visible absorption bands for visible light photocatalysts, Nanoscale, 5 **(2013)** 12272-12277.

4.P. Elvati, E. Baumeister, A. Violi. Graphene quantum dots: effect of size, composition, and curvature on their assembly, RSC Adv. 7 (2017) 17704-17710.

Polyoxometalate-Supported Bioinspired Catalysts for Small Molecules Activation

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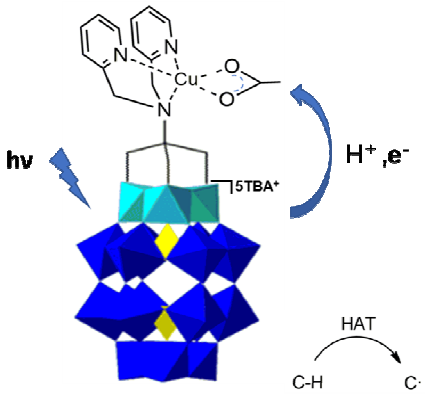
The efficiency of metalloenzymes does not only depend on the first coordination sphere of the metal sites but also on the secondary interactions, and in particular on electrons and protons relays.[1] Polyoxometalates (POMs) are a series of molecular metal oxide clusters which could work as the reservoir of protons and electrons.[2][3]

Our aim is to graft bioinspired complexes onto the POM skeleton to mimic the metalloenzymes. Multidentate organic ligands at the POM surface will provide the first coordination sphere, while the POM could provide the required secondary interactions to induce or improve reactivity.

I will present the platforms obtained via covalent grafting of the ligands (N, N-bis(2-pyridylmethyl)-N-propargylamine) and their characterization, some complexes thereof and their reactivity.



Acknowledgments:

[1] C. S. Mota *et al.*, *J. Biol. Inorg. Chem.*, **2011** *16,* 1255–1268.
[2] A. Proust, B. Matt, R. Villanneau, G. Guillemot, P. Gouzerh, and G. Izzet, *Chem. Soc. Rev.*, **2012,** *41*, 7605–7622.
[3] J. Zhang, A. M. Bond, P. J. S. Richardt, and A. G. Wedd, *Inorg. Chem.*, **2004,** *43,* 8263–8271.

Development of microfluidic devices with integrated electrochemical detectors using 3D printing technology

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Electrochemical (EC) detection is perfectly suited for the microchip format since the microelectrodes may be fabricated using many of the same procedures that are used to construct microchips. As excellent works using emerging materials for electrodes fabrication have been reported by several groups [1011–3], there is increasing interesting in the use of integrated electrodes in microchip capillary electrophoresis (MCE) systems. However, EC detection is poorly developed in MCE as relevant interferences may occur. The authors have been reported issues which complicates microfluidics, capillary electrophoresis, and EC development. Still, manufacturing MCE-EC systems faces many challenges such as the compatibility of the electrode composition with the substrate of the device, the alignment necessity of the electrodes for detection and which detection mode is suitable for the system[4].[102] In this context, we decided to use 3D printing technology as the approach to overcoming all this fabrication issues which can reflect in the analytical performance of the obtained devices.

3D printing technology is a versatile way to assemble complex pieces in simple and automated steps. This technique offers good precision to define microchannels and microstructures with benefits for instance high resolution, variety of materials and customization in the development of devices when compared with 2D devices. Therefore, we have optimized a stereolithography (SLA) 3D printer to attend the requirements to manufacture microfluidics. At the same time, we have created microdevices with electrode channels to overcoming the alignment necessity of this electrodes for EC detection in MCE systems. Furthermore, these channels have been filled by custom formulation material to perform as electrodes. In conclusion, we have established a simple protocol for the creation of a microfluidic device with integrated electrodes using SLA-based 3D printer to build a low-cost system of analysis.

Acknowledgments :
CAPES-COFECUB, CNPq, FAPESP (2018/06478-3), INCTBio, Institut Pierre-Gilles de Gennes (Équipement d'Excellence, "Investissements d'avenir", program ANR-10- EQPX-34).

[101] a) C. Chagas, T. Cardoso, W. Coltro, *Methods in Molecular Biology* **2019,** 1906, 133-142. b) D. Meneses, D. Gunasekara, P. Pichetsurnthorn, J. da Silva, F. de Abreu, S. Lunte, *Electrophoresis* **2015**, 36, 441- 448. c) J. Gouyon, F. D'Orlyé, S. Griveau, F. Bedioui, A.Varenne, *Electrochim Acta.* **2020**, 329, 1-10.
[102] Y. Yik, S. Li, *Trends Anal Chem*. **1992**, 9, 325-332.