Avis favorable

Dr. Cyril Ollivier

Dr Cyril OLLIVIER
Directeur de l'Ecole Doctorale
de Chimie Moléculaire

Campagne 2020 Contrats Doctoraux Instituts/Initiatives

Proposition de Projet de Recherche Doctoral (PRD)

Appel à projet ISim - Initiative Sces et ingénierie moléculaires 2020

Intitulé du Projet de Recherche Doctoral : Designing of supramolecular polymer assemblies barcode reader based on mass spectrometry tools

Directeur de Thèse porteur du projet (titulaire d'une HDR) :

NOM : **PRZYBYLSKI** Prénom : **Cédric**
Titre : Choisissez un élément : ou
Ingénieur de recherche CNRS - HDR
e-mail : cedric.przybylski@sorbonne-universite.fr
Adresse professionnelle : Campus Jussieu, 4, place Jussieu, tour 42-43 4ème étage,pièce
(site, adresse, bât., bureau)

Unité de Recherche :
Intitulé : Institut Parisien de Chimie Moléculaire (IPCM)
Code *(ex. UMR xxxx)* : UMR 8232

ED406-Chimie Moléculaire Paris Centre

Ecole Doctorale de rattachement de l'équipe & d'inscription du doctorant :

Doctorants actuellement encadrés par le directeur de thèse (préciser le nombre de doctorants, leur année de 1ere inscription et la quotité d'encadrement) : 0

Co-encadrant :

NOM : **BOUTEILLER** Prénom : **Laurent**
Titre : Directeur de Recherche ou HDR ☒
e-mail : laurent.bouteiller@sorbonne-universite.fr

Unité de Recherche :
Intitulé : Institut Parisien de Chimie Moléculaire (IPCM)
Code *(ex. UMR xxxx)* : UMR 8232

ED397-Physique Chimie des Matériaux

Ecole Doctorale de rattachement : Ou si ED non Alliance SU :

Doctorants actuellement encadrés par le co-directeur de thèse (préciser le nombre de doctorants, leur année de 1ere inscription et la quotité d'encadrement) : 5 à 50% d'encadrement (2 en 2017, 1 en 2018, 2 en 2019)

Cotutelle internationale : ☒ Non ☐ Oui, précisez Pays et Université :

Description du projet de recherche doctoral *(en français ou en anglais)*

3 pages maximum – interligne simple – Ce texte sera diffusé en ligne

Détailler le contexte, l'objectif scientifique, la justification de l'approche scientifique ainsi que l'adéquation à l'initiative/l'Institut.
Le cas échéant, préciser le rôle de chaque encadrant ainsi que les compétences scientifiques apportées. Indiquer les publications/productions des encadrants en lien avec le projet.
Préciser le profil d'étudiant(e) recherché.

Context.

Over the last three decades, supramolecular chemistry has constantly grown and is now considered as a central topic of the chemical sciences. Non-covalent interactions between (macro)molecules are now used as a usual tool to construct supramolecular architectures of increasing complexity and higher functionality which contribute, in nature, to achieve and regulate many functions and processes of life. Structurally-complex synthetic scaffolds have also been implemented as efficient and/or selective sensors or as catalysts. The polymer chemistry team (ECP) at IPCM, partner of this project, notably developed one-dimensional (1-D) supramolecular helical assemblies composed of 1,3,5-benzene tricarboxamide (**BTA**) monomers as a scaffold for asymmetric homogeneous catalysis such as hydrogenation of dimethyl itaconate or hydrosilylation of aromatic ketones. Unlike classical covalent systems, the composition of these catalysts can be easily tuned by mixing different monomers with the same BTA units that self-assemble leading to co-assemblies with unique properties compared to the respective homo-assemblies. For example, it has been demonstrated that BTA helical rods composed of an achiral metal complex and a complementary enantiopure monomer provided a good level of enantioselectivity in asymmetric catalysis. It led to catalysts with innovative properties. Further application of these systems will require a fine characterization of the co-assemblies to afford rationalization of the measured activity/selectivity according to structure/composition of the assemblies. However, whilst combination of several common analytical (FT-IR, UV, CD, SANS) and computational techniques (MM/MD) are used to gain information on **the geometry, hydrogen-bond pattern and composition of the assemblies**, no state-of-the-art technique has been introduced to precisely characterize the local structure e.g. the sequence of each monomers and the relative orientation of the distinct peripheral side chains.

Objectives.

Our goal is to develop new innovative mass spectrometry (MS) strategies to gain further insight into the BTA based supramolecular architectures. Three clear milestones are planned according to their technical difficulty: (i) **Structure and stability of the homoassemblies** using screening of conditions for preparation/analysis of BTA homoassemblies under a gentle ionization mode i.e. electrospray. Preliminary results show the possibility of using MS to characterize hydrogen-bonded aggregates present in solution. The stability of the oligomers will be quantitatively assessed through the average energy required to dissociate them. Such values will be compared to known stability in solution obtained by FT-IR and CD spectroscopies and calorimetry techniques. (ii) **Local characterization of homoassemblies**: A BTA monomer with side chains of different sizes will be prepared and its assembly probed by a highly innovative ion mobility-MS (IM-MS) approach. The aim is to demonstrate the potential of this technique to discriminate isomers by their shape and size. (iii) **Local characterization of catalytic co-assemblies**. According to the conditions established in (i) and (ii), 1:1 mixtures between monomers functionalized with different groups will be investigated. The aim is to determine the composition (by m/z separation) and relative orientation (by IM-MS) of the functional groups in the co-assemblies.

Adequation of selected approach to objectives.

In recent years, **cooperative catalysis** has been proposed, which greatly improves reaction rates and even allows reactions that are not accessible by other methods. Remarkable advances were made with bifunctional organocatalysts in which two organic functions are **embedded in the same molecular framework via covalent bonds**. In the catalytic cycle, substrate(s) can be organized adequately favoring the formation of a well-defined, relatively constrained transition state, so that the chemo-, regio- and enantioselectivity of the reaction is well controlled in a way that is reminiscent of the working mode of enzymes. A well-known

example is the Takemoto catalyst which consists of a thiourea moiety (as an H-bond donor group for the activation of the electrophile) and a dimethylamino moiety (as a Brønsted base for the activation of the nucleophile) connected through two stereogenic centers. The relative orientation of the functional groups is crucial in order to get high activity and enantioselectivity, e.g. in Enantioselective Michael Addition (EMA) reactions. The ECP group is currently investigating a supramolecular variant of the Takemoto catalyst in which thiourea and 4-(dimethylamino)pyridine units are located at the periphery of two BTA co-monomers. The aim is to transfer the supramolecular chirality of the BTA scaffold to the organocatalytic functions in order to get high enantioselectivities in the EMA between 2-methoxy thiophenol and cyclohexenone. Catalytic mixtures are formed by mixing BTA monomers containing the thiourea (**BTA-thiourea**) and DMAP (**BTA-DMAP**) functions (**Fig. 1**) C_3-symmetrical monomers (containing three catalytic units) cannot be employed as a result of their low solubility. Accordingly, C_2-symmetrical monomers are preferred in which the lateral chiral alkyl chains are expected to yield soluble homochiral assemblies. Also, the co-assembly process is expected to yield a more or less statistical distribution of the catalytic units at the periphery of the supramolecular helices. However, thiourea and DMAP moieties that will be connected above each other in the co-assemblies, as a result of the hydrogen bond between their proximal amide functions, are expected to yield the most **cooperative assemblies**. The homo- and co-assemblies formed by BTA-Thiourea and BTA-DMAP monomers will be characterized by commonly analytical techniques assessed by the ECP team (see context) to get the geometry, hydrogen-bond pattern and composition of the helices. However, such techniques fail to provide any information on the local structure of the assemblies, and notably the sequence of the monomers and the orientation of the side chains. Innovative MS techniques will be implemented as a unique tool to determine the conditions to favour the formation of the catalytically selective alternated co-assembly. Based on our experience and considering the rare literature about MS analysis of supramolecular assemblies, a series of experiments will be performed, firstly on homoassemblies and then on co-assemblies, as regards the influence of sample preparation on the stability, diversity and size of detected species. Both BTA-Thiourea and BTA-DMAP monomers are expected to form long 1-D supramolecular assemblies in solution. Preliminary results confirmed the possibility of using MS (vide infra) to characterize fragments from such assemblies. Considering the co-assemblies, we will pay attention to the analysis of the MS fragments corresponding to $(BTA)_2$ and $(BTA)_4$. Non-alternated structures will be separated from the alternated ones according to their distinct m/z values. Taking into account the fact that identical measured m/z can correspond to various size oligomers (according to the charge states e.g. singly charged $(BTA)_2$ and doubly charged $(BTA)_4$, but also to several conformers (**Fig. 2A**), a second higher level separation will be achieved. This second order of sorting will be performed by employing an innovative MS technique able to discriminate forms according to charge states and allows determining whether fragments of similar molecular weight and/or

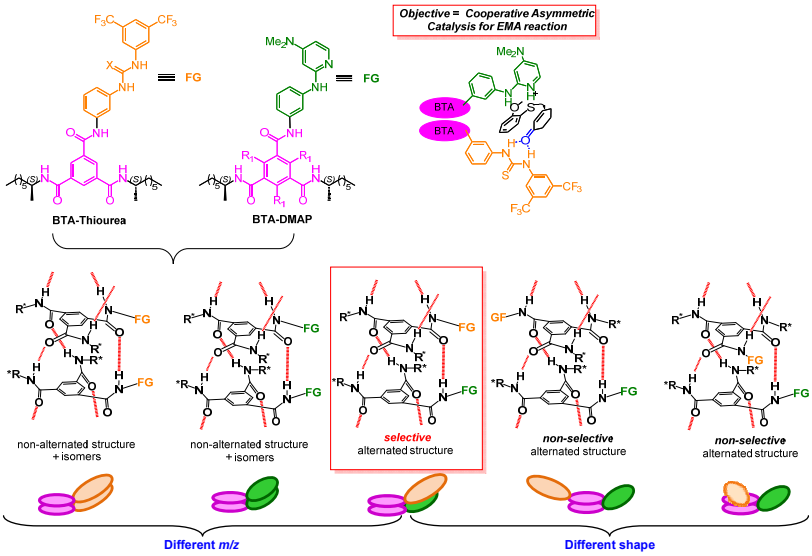

Fig. 1. Structure of the BTA monomers including BTA core (pink) with various bulky functional groups (FG) of BTA-Thiourea (orange) and BTA-DMAP (green) and some resulting $(BTA)_2$.

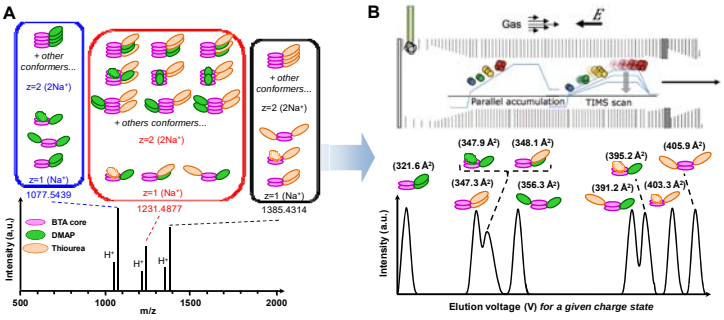

Fig. 2. Simulated MS data which could be obtained from BTA-thiourea and BTA-DMAP co-assemblies. (A) High resolution MS spectrum depicting the detection of oligo(BTA)$_n$ with n≥2, but failing to discriminate isobaric structures and (B) Theoretical arrival time distribution of the 9 conformers of (BTA)$_2$ co-assemblies. The number in brackets refers to collision cross section (CCS) calculated in N_2 as drift gas and with the exact hard sphere scattering (EHSS) method after a MM2 energy minimization.

m/z can correspond to different folding of assemblies. Such dimensional feature could be pinpointed using ion mobility mass spectrometry (IM-MS) experiments where **architectures with the same m/z can be differentiated according to their shape in the gas phase**. An example is given for the (BTA)$_2$ with calculated theoretical collision cross section (CCS) (**Fig. 2B**).

Position of the project in regard to the Initiative Sciences et Ingénierie Moléculaire.

This project gathers two complementary teams expert in the fields of mass spectrometry (CSOB team) and supramolecular polymers synthesis (ECP team) to address a unique scientific challenge. Hence, the success of this project will strengthen the visibility of Sorbonne Université in the field of supramolecular assemblies and will position us as a forefront actor by affording innovative tools for the establishment of synthesis process/catalytic effect relationship. It is therefore very structuring and beneficial for the visibility of chemical research of Alliance Sorbonne Université. If the short term objective of this project is reached, a solvent/ionization couple rationalization and a stability ranking of assemblies as regards size and substituent will be established. It will also allow for the first time to highlight the presence of several possible conformers, constituting a fingerprint which could be used to drive monomer synthesis according to catalytic performances. Therefore, this project fits perfectly in the central Initiative Sciences et Ingénierie Moléculaire objective.

Highlight partners complementarity.

Two teams are involved in this project. Partner 1 is a recognized national pillar in the development of innovative MS based methodologies, gathering analytical, fundamental and instrumental aspects. Cédric Przybylski will be the PhD supervisor. He has longstanding experience in the field of analytical development for analysis of supramolecular objects and in the understanding of fundamental aspects, respectively, leading to particular relevant publications in the field. On the other hand, Partner 2, Polymer chemistry team (ECP) is an internationally recognized group for its expertise in the field of hydrogen-bonded supramolecular polymers. Laurent Bouteiller has shown a strong interest and successful results in the synthesis of supramolecular BTA platforms, with chiral and tunable features devoted to selective catalysis. Their outstanding research has been emphasized by several recent papers published in high impact journals. Laurent bouteiller will be the co-supervisor of the PhD student. Synergy expected from such transversal and complementary skills clearly appears as a primer to initiate future rich interactions within the Initiative Sciences et Ingénierie Moléculaire framework and beyond. The candidate will be preferentially an analytical chemist with a strong background or first experience in supramolecular chemistry.

Representative publications.

1) Li Y., Hammoud A. Bouteiller L., Raynal M. J. *Am. Chem. Soc.*, **2020**, 142, 12, 5676. 2) Zimbron, J. M.; Caumes, X.; Li, Y., Thomas, C.M., Raynal M., Bouteiller L., *Angew. Chem. Int. Ed.*, **2017**, 56, 14016. 3) Desmarchelier, A., Caumes, X., Raynal, M., Vidal-Ferran A., van Leeuwen P.W.N.M., Bouteiller L., *J. Am. Chem. Soc.*, **2016**, 138, 4908. 4) Sonnendecker C., Thürmann S., Przybylski C., Zitzmann F.D., Heinke N., Krauke Y., Monks K., Robitzki A.A., Belder D., Zimmermann W., *Angew. Chem. Int. Ed.,* **2019**, 58, 6411. 4) Przybylski C., Benito Juan M., Bonnet V., Ortiz Mellet C., García Fernández José M. *Anal. Chim. Acta.*, **2018**, 1002, 70 5) Przybylski, C., Bonnet, V., Jarroux, N. *ACS Macro Lett.*, **2012**, 1, 533.