EDSC
École Doctorale des
Sciences Chimiques

Université
de Strasbourg

JOURNEE DES DOCTORANTS EN CHIMIE 2024

Jeudi, 23 janvier 2025

Programme et Résumés

Collège Doctoral Européen
Campus de l'Esplanade

http://ed.chimie.unistra.fr/

AVANT-PROPOS

La Journée des doctorants en chimie en est à sa **18ème édition**.

Pour les doctorants déjà engagés dans le cursus doctoral, cette journée leur permet d'exposer leurs travaux de recherche.

Pour les doctorants de 1ère année, elle fait office de journée de rentrée et leur donne l'occasion :

- D'avoir un aperçu des recherches menées dans les laboratoires de chimie de l'Université de Strasbourg et du CNRS,
- De nouer des contacts avec les doctorants plus anciens, notamment ceux d'autres équipes et d'autres campus,
- De poser toutes les questions concernant le déroulement de la formation doctorale en chimie ainsi que l'après-thèse.

Je tiens à remercier toutes les personnes qui ont accepté de présenter leurs travaux de recherche lors de cette journée ainsi que celles qui ont fait des Journées précédentes un succès.

Mes remerciements vont tout particulièrement à Nathalie Kostmann pour sa contribution centrale dans l'organisation de la JDC 2024.

Gilles ULRICH

Directeur de l'EDSC

Journée des Doctorants en Chimie 2024

23 janvier 2025 - Amphithéâtre du CDE

PROGRAMME

	Programme de la matinée
8 h 00 - 8 h 15	**Ouverture** Exposé de rentrée de Gilles ULRICH, directeur de l'EDSC / Discussion avec les doctorants
8 h 15 - 8 h 25	**Présentation "programme de mentorat aux doctorant.es"** Exposé de Cécilia MENARD-MOYON
8 h 25 - 9 h 15	**Conférence** *"Capillary electrophoresis for the characterization of monoclonal antibodies: challenges and benefits for the patient "* **Pr. Yannis FRANCOIS**
9 h 15 - 9 h 25	**Présentation "SCF-ALSACE" et surtout du Réseau Jeunes dont il est le nouveau Président** **Exposé de Guillaume VOEGELI**
9 h 25 - 9 h 40	**BRAILLON Capucine**
9 h 40 - 9 h 55	**AUGE Anthony**
9 h 55 - 10 h 10	**BORG Antoine**
10 h 10 - 10 h 25	**ALEZ-MARTIN Lola**
10 h 25 - 10 h 40	**Pause Café**
	Communications orales
10 h 40 - 10 h 55	**CIOCCHETTI Fabiana**
10 h 55 - 11 h 10	**ECLANCHER Auguste**
11 h 10 - 11 h 25	**GHADDAR Ali**
11 h 25 - 11 h 40	**GUILMAIN Hugo**
11 h 40 - 11 h 55	**HEINRITZ Charlotte**
11 h 55 - 12 h 50	**Pause Repas**
12 h 50 - 13 h 05	**JUNG Eliott**
13 h 05 - 13 h 20	**LEFRANCOIS Léa**
13 h 20 - 13 h 35	**LETISSIER Léa**
13 h 35 - 13 h 50	**MAKHLOUF Wafa**
13 h 50 - 14 h 05	**OUADFEL Lydia**
14 h 05 - 14 h 20	**Pause Café**
14 h 20 - 14 h 35	**PHAM David-Jérôme**
14 h 35 - 14 h 50	**POUSSE Benoît**
14 h 50 - 15 h 05	**QIN Siyao**
15 h 05 - 15 h 20	**SCHUTZ Dorian**
15 h 20 - 15 h 35	**SHEN Xin**
15 h 35 - 15 h 50	**Pause Café**
15 h 50 - 16 h 05	**SINGH Akshita**
16 h 05 - 16 h 20	**STEINMETZ Maxime**
16 h 20 - 16 h 35	**TUAL Laurine**
16 h 35 - 16 h 50	**VOEGELI Guillaume**
16 h 50 - 17 h 05	**XIANG Shunyu**

TITRES DES

COMMUNICATIONS ORALES

LISTE DES COMMUNICATIONS ORALES

(1) Unveiling the Chemical Secrets of Ancient Remedies: Advanced HPLC-HRMS/MS approaches for a Modern Understanding

Capucine Braillon[*(a)], Elora Aubert[(a)], Régine Janel-Bintz[(b)], Véronique Pitchon[(c)], Pierre Fechter[(b)], Catherine Vonthron-Senecheau[(a)], Sergio Ortiz[(a)]

[(a)] Laboratoire d'Innovation Thérapeutique, LIT, CNRS UMR 7200
[(b)] Biotechnologie et Signalisation Cellulaire, BSC, CNRS, UMR 7242
[(c)] Archéologie et Histoire Ancienne : Méditerranée-Europe (ARCHIMEDE)

(2) New TURN-ON probes for the detection of bacteria in physiological fluids

Anthony Augé, Lucille Weiss, Julie Karpenko

Laboratoire d'Innovation Thérapeutique, UMR 7200 CNRS/Université de Strasbourg, Institut du Médicament de Strasbourg, 74 route du Rhin, 67401 Illkirch

(3) Development of glucose and biomass predictive models for real time monitoring of fermentation using Raman spectroscopy

Antoine Borg[1,2,3] *, Vincent Portaluri[1*], Mourad Elhabiri[2], Stéphane Le Calvé[3]

[1] Euroapi, 32 rue de Verdun, 76410 Saint-Aubin-lès-Elbeuf,
[2] LIMA and [3] ICPEES, 25 rue Becquerel, 67087 Strasbourg cedex.

(4) Pembrolizumab detailed charge variants characterization using capillary electrophoresis and tandem mass spectrometry

Lola Alez-Martin[1,2], Pascal Houzé[2], Rania Joomun[2], Nathalie Mignet[2], Yannis François[1], Rabah Gahoual[2]

[1] Laboratoire de Spectrométrie de Masse des Interactions et des Systèmes (LSMIS) UMR 7140 (Unistra-CNRS), Université de Strasbourg, France.
[2] Université Paris Cité, Unité de Technologies Chimiques et Biologiques pour la Santé (UTCBS), CNRS UMR8258, Inserm U1022, Faculté des sciences pharmaceutiques et biologiques, Paris (France)

(5) Non-équilibrium self-assembly of electroactive systems

Fabiana Ciocchetti[1*], Ahmad Bachir[1], Caterina Baccini[2], Cristian Pezzato[3], Giulio Ragazzon[1]

[1] University of Strasbourg, CNRS, Institut de Science et d'Ingénierie Supramoléculaires (ISIS) UMR 7006, 8 Allée Gaspard Monge, 67000 Strasbourg, France.
[2] University of Parma, Via Area Parco delle Scienze 17/A, 43124 Parma. 3University of Padova,Via Francesco Marzolo 1, 35131 Padova, Italy

(6) Guanidinium-porphyrin conjugates for antimicrobial photodynamic therapy

Auguste Eclancher[a], Nahid Sadeghi Alavijeh[a], Christopher Aisenbrey[b], Burkhard Bechinger[b], Philippe Lavalle[c] and Valérie Heitz[a]

[a] Laboratoire de Synthèse des Assemblages Moléculaires Multifonctionnels, UMR 7177, Institut de Chimie de Strasbourg, France
[b] Biophysique des membranes et RMN, UMR 7177, Institut de Chimie de Strasbourg, France
[c] Biomatériaux et bioingénierie, Inserm UMR-S 1121, Faculté de médecine de Strasbourg, France

(7) Development of analytical methods for characterization of Biogenic Volatile Organic Compounds (BVOCs) emitted by pest infested plants.

Ali Ghaddar[a,b], Damien Bazin[b], Stéphane Le Calvé[a]

[a] Institut de Chimie et Procédés pour l'Énergie, l'Environnement et la Santé (ICPEES, UMR 7515, CNRS/Unistra), 25 rue Becquerel, 67087 Strasbourg Cedex 2, France.
[b] Chromatotec, 1 Avenue Jean-Honoré Olibet, 33240 Saint-André-de-Cubzac, Bordeaux, France.

(8) Digital polymer synthesis using a fully orthogonal radical process

Hugo Guilmain, Jean-Louis Clément[*], Laurence Charles[*], Didier Gigmes[*] and Jean-François Lutz[**]

Université de Strasbourg, CNRS, UMR 7006, Institut de Science et d'Ingénierie Supramoléculaire (ISIS), 67000 Strasbourg (France)
Aix Marseille Université, CNRS, UMR 7273, Institut de Chimie Radicalaire (ICR), 13397 Marseille, France
28 rue de Thann

(9) Functionalized LnF3 nanoparticles as multimodal contrast agents for PET, MRI and Luminescence imaging

C. Heinritz[1], A. Ouadi[2], D. Brasse[2], C. Po[3], S. Bégin[4], M. Botta[5], F. Carniato[5], S. Harlepp[5], A. Detappe[5], C. Cheignon[1], L. Charbonnière[1], A. Nonat[1]

1 Equipe de Synthèse pour l'analyse, IPHC, CNRS, 67200 Strasbourg, FR
2 Equipe Imagerie Moléculaire et Radiobiologie, IPHC, CNRS, Strasbourg, FR
3 ICube - Laboratoire des sciences de l'ingénieur, de l'informatique et de l'imagerie, Strasbourg, FR
4 Chemical Engineering of Functional Nanomaterials, IPCMS, CNRS, Strasbourg, FR
5 Università del Piemonte Orientale, Alessadria, IT
6 ICANS – Institut de cancérologie, Strasbourg, FR

(10) Towards structurally complex aza-cyclic architectures merging 1-aza-spirocyclic and isoquinuclidine ring systems

Eliott Jung[1,2], Valérie Bénéteau[1], Patrick Pale[1], Stefan Chassaing[1*] and Christophe Gourlaouen[2*]

[1] COSyS, Institut de Chimie de Strasbourg, UMR7177, 4 rue Blaise Pascal, 67000, Strasbourg, FRANCE
[2] MSM, Institut de Chimie de Strasbourg, UMR7140, 4 rue Blaise Pascal, 67000, Strasbourg, France

(11) Acridinium receptors : π-π stacking and switchable properties

Léa Lefrançois[a], Johnny Hu[a], Jean-Marc Vincent[b], Valérie Heitz[a], Henri-Pierre Jacquot de Rouville[a]

[a] Institut de Chimie de Strasbourg, UMR 7177, Université de Strasbourg, 4 rue Blaise Pascal, 67000 Strasbourg, France
[b] Institut des Sciences Moléculaires, CNRS UMR 5255, Université de Bordeaux, 351 cours de la Libération, 33405 Talence, France

(12) Development of innovative analytical strategies based on Top-Down Mass Spectrometry (TD-MS) for characterizing bird hemoglobins and its active form

Léa Letissier[1,2], Turkan Nabiyeva[1,2], François Criscuolo[3], Fabrice Bertile[1,2,3], Christine Schaeffer[1,2], Sarah Cianférani[1,2], Oscar Hernandez-Alba[1,2]

[1] Laboratoire de Spectrométrie de Masse BioOrganique, Université de Strasbourg, CNRS, IPHC UMR 7178, 67087 Strasbourg, France
[2] Infrastructure Nationale de Protéomique ProFi – FR2048 CNRS CEA, 67087 Strasbourg, France
[3] Département d'écologie, physiologie et éthologie, Université de Strasbourg, CNRS, IPHC UMR 7178, 67087 Strasbourg, France

(13) Local Potential Functional Embedding Theory (LPFET)

Wafa Makhlouf, Emmanuel Fromager, Bruno Senjean

(14) Development of PROTAC targeting kinases for the treatment of cancers

Lydia Ouadfel, Frédéric Bihel, Martine Schmitt

(15) A Chiral [2 + 3] Covalent Organic Cage Based on 2,2'-BINOL Units

David-Jérôme Pham, Midhun Mohan, Pierre Mobian

UMR 7140, University of Strasbourg-CNRS, 4 rue Blaise Pascal, 67000 Strasbourg, France

(16) Synthesis of sequence-encoded morpholino oligomers

Benoit Pousse[1], Paul Baxter[1] and Jean-François LUTZ[1*]

Université de Strasbourg, CNRS, ISIS, 8 allée Gaspard Monge, 67000 Strasbourg (France)

(17) Multifunctional graphene-family nanomaterials for combined phototherapy and chemotherapy

Siyao Qin[1], Giacomo Biagiotti[2], Barbara Richichi[2], Yuta Nishina[3], Cécilia Ménard-Moyon[1], Alberto Bianco[1]

[1] CNRS, Immunology, Immunopathology and Therapeutic Chemistry UPR 3572, University of Strasbourg, ISIS, Strasbourg 67000, France
[2] Department of Chemistry "Ugo Schiff", University of Firenze, Via della Lastruccia 13, 50019, Sesto Fiorentino, FI, Italy
[3] Research Core for Interdisciplinary Sciences, and Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan

(18) Regio- and stereoselective azidation of activated N-allenamides : an entry to α, β, γ and δ-amido-azides

Dorian Schutz[‡], Maxime Hourtoule[‡], Laurence Miesch[*]

Équipe de Synthèse Organique et Phytochimie, Université de Strasbourg, CNRS-UdS UMR 7177, 4 rue Blaise Pascal CS 90032, 67081 Strasbourg, France

(19) Multi-scale Modeling of Charge, Mass and Heat Transfers in Anion Exchange Membrane Water Electrolysis

Xin Shen, Laurent Ruhlmann, Antoine Bonnefont and Gaël Maranzana

(20) Waste to Energy: A step towards circular economy

Akshita Singh[1,2*], Vimal Chandra Srivastava[2,3], Izabela Janowska[1]

[1] Institut de Chimie et Procédés pour l'Énergie, l'Environnement et la Santé (ICPEES), CNRS UMR 7515-University of Strasbourg, 25 Rue Becquerel, 67087, Strasbourg, France

[2] Centre for Nanotechnology, Indian Institute of Technology Roorkee, Roorkee, 247667, India

[3] Department of Chemical Engineering, Indian Institute of Technology Roorkee, Roorkee, 247667, India

(21) Encapsulated Cationic Ruthenium and Rhodium Catalysts: Controlling The Catalytic Outcome By Confinement

Maxime Steinmetz, David Sémeril

Laboratoire de Synthèse Organométallique et Catalyse, Université de Strasbourg 4 rue Blaise Pascal, 67008 Strasbourg (France)

(22) Synthesis of medium-sized N,S-heterocycles by rhodium-catalyzed ring expansion

Laurine Tual, Romain Pertschi, Gaëlle Blond and Mihaela Gulea

Laboratoire d'Innovation Thérapeutique – LIT UMR 7200, Université de Strasbourg, CNRS – 67000 Strasbourg, France

(23) Photoallergic contact dermatitis: a novel EPR approach to assess xenobiotic-mediated radicals in UV exposed skin

Guillaume Voegeli

UMR 7177 Laboratoire POMAM

(24) Preparation and optimization of polymer/amino acid-based double network hydrogels for near-infrared light triggered drug release

Shunyu Xiang[1], Chloé Guilbaud-Chéreau[1], Paul Hoschtettler[2], Loïc Stefan[2], Alberto Bianco[1*], Cécilia Ménard-Moyon[1*]

[1] CNRS, Immunology, Immunopathology and Therapeutic Chemistry, UPR 3572, University of Strasbourg, ISIS, 67000 Strasbourg, France

[2] Université de Lorraine, CNRS, LCPM, 54000 Nancy, France

CONFERENCE

"Capillary electrophoresis for the characterization of monoclonal antibodies: challenges and benefits for the patient "

Pr. Yannis FRANCOIS,
Chimie de la matière complexe (UMR 7140)

Capillary electrophoresis for the characterization of monoclonal antibodies: challenges and benefits for the patient.

Yannis-Nicolas François

Laboratoire de Spectrométrie de Masse des Interactions et des Systèmes (LSMIS) UMR 7140 (Unistra-CNRS), Université de Strasbourg, France.

Monoclonal antibodies (mAbs) are demonstrating major success in various therapeutic areas such as oncology and the treatment of immune disorders. Over the past two decades, novel analytical methodologies allowed to address the challenges of mAbs characterization in the context of their production. However, after administration only their quantification is performed and insights regarding their structural evolution remain limited. For instance, clinical practice has recently highlighted significant inter-patient differences in mAbs clearance and unexpected clinical responses, without providing alternative interpretations.

Capillary electrophoresis (CE) has recently demonstrated to be particularly relevant for peptide separation. Indeed, the electrophoretic migration generated in CE enables the separation of analytes with different charge states in solution and/or different hydrodynamic radii. Thereby, CE is suitable for the separation of short or polar peptides, such as glycopeptides, in parallel with longer and more apolar ones in the same analysis. Therefore, the hyphenation of CE to mass spectrometry (MS) has recently proven to be particularly relevant for the characterization of the primary structure of mAbs, with the possibility to achieve 100% sequence coverage using a single analysis.

In this presentation, I will describe the challenges and solutions that analytical chemistry can provide for characterising mAbs, from production to administration to the patient.

RESUMES DES

COMMUNICATIONS ORALES

Unveiling the Chemical Secrets of Ancient Remedies: Advanced HPLC-HRMS/MS approaches for a Modern Understanding

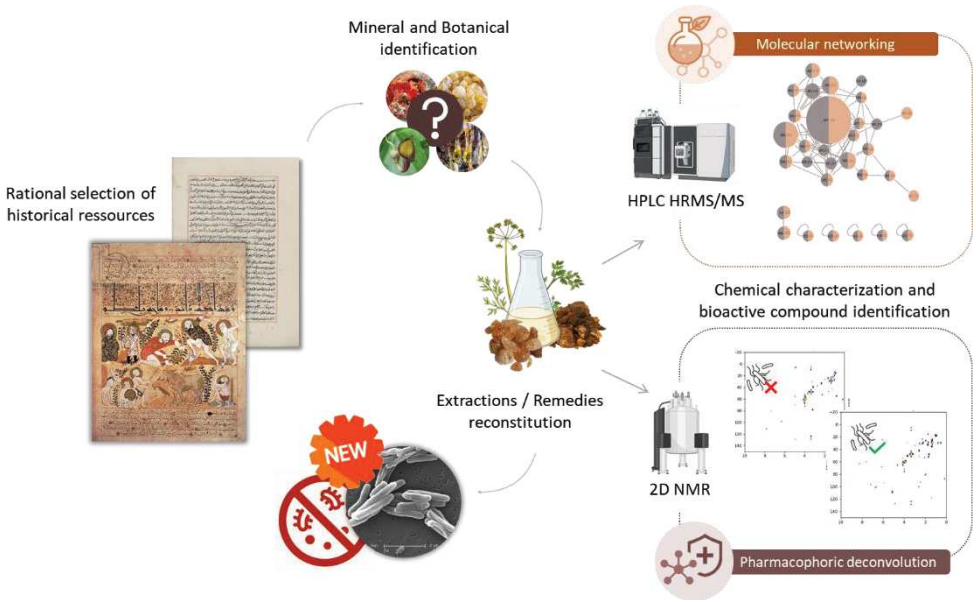
Capucine Braillon*[(a)], Elora Aubert[(a)], Régine Janel-Bintz[(b)], Véronique Pitchon[(c)], Pierre Fechter[(b)], Catherine Vonthron-Senecheau[(a)], Sergio Ortiz[(a)]

[(a)] Laboratoire d'Innovation Thérapeutique, LIT, CNRS UMR 7200
[(b)] Biotechnologie et Signalisation Cellulaire, BSC, CNRS, UMR 7242
[(c)] Archéologie et Histoire Ancienne : Méditerranée-Europe (ARCHIMEDE
* c.braillon@unistra.fr

The use of herbal medicinal preparation in bacterial infection fighting has been studied from traditional medicine and transmissions and holds significant potential for the discovery of novel bioactive compounds. Pharmacognosy leveraging historical sources which currently represents a novel source of innovative solutions, works toward this goal. A transdisciplinary project gathering researchers from biology, chemistry, humanities and informatics sciences, investigates old remedies from the Medieval Arabic Pharmacopeia to better understand their evolution, composition, and efficacy[1-2].

A rational selection process, supported by artificial intelligence[3], identified a promising remedy among numerous historical resources: a preparation combining plants and metals used over centuries (c. 9th –12th century) and across various geographical regions for the treatment of scrofula (mycobacterial cutaneous infection).

Preliminary *in vitro* anti-*Mycobacterium tuberculosis* highlighted promising plant extracts from *Ferula* species, Burseraceae family (*Commiphora*, and *Boswellia* species) and Pinaceae family (*Pinus* species). Their chemical composition is being analyzed using modern approach, including NMR, GC-MS/MS and HPLC-UV-HRMS/MS. Notably, HPLC-UV-HRMS/MS has enabled the detailed chemical characterization of bioactive extracts and facilitated the structural prediction of compounds with anti-Mycobacterial activity. These findings pave the way for a deeper understanding of historical remedies and the identification of innovative compounds to fight bacterial infections.



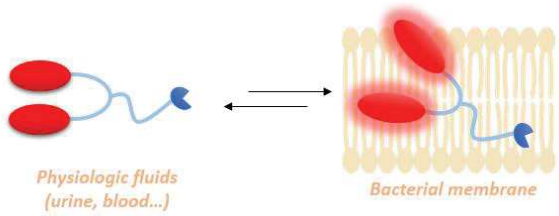
[1] Abdallah, B., *et al.* (**2022**) Past mastering of metal transformation enabled physicians to increase their therapeutic potential. *Journal of Trace Elements in Medicine and Biology*. Vol 71, 126926
[2] Falagas, M.E., Zarkadoulia, E.A., Samonis, G. (**2006**) Arab science in the golden age (750–1258 C.E.) and today. *The FASEB Journal*. Vol 20, 1581–1586.
[3] Fokou, V., *et al.* (**2024**) Exploring Old Arabic Remedies with Formal and Relational Concept Analysis. *Concepts 2024,* Cadiz, Spain. ffhal-04622852

New TURN-ON probes for the detection of bacteria in physiological fluids

Anthony Augé, Lucille Weiss, Julie Karpenko

Laboratoire d'Innovation Thérapeutique, UMR 7200 CNRS/Université de Strasbourg, Institut du Médicament de Strasbourg, 74 route du Rhin, 67401 Illkirch

Due to the spread of antibiotic-resistant pathogens, bacterial infectious diseases became one of first causes of mortality and morbidity in the world[1,2]. An early administration of an appropriate antibiotic reduces considerably the risk of mortality[3]. However, the current methods of clinical detection and identification of bacteria in physiological fluids (urine, blood…) are insensitive and time-consuming due to the bacterial culture step. In our team, we aim at developing rapid and direct next-generation methods for clinical diagnostics of bacterial infections.



We have recently developed a new concept of targeted fluorescent turn-on probes for bacteria, based on aggregation-caused quenching (ACQ)[4,5]. The probes are composed of bacteria-targeting vectors (antimicrobial peptides) and covalent dimers of far-red squaraine dyes. In an aqueous medium, the probes exist in the form of non-fluorescent π-stacked H-aggregates (OFF state). Upon binding to less polar components of bacterial cell envelope, the fluorescence of the probes is restored (ON state). We have successfully applied dimeric squaraine probes for the detection of bacteria in patient urine samples. However, the squaraine probes were not suited in blood, as they displayed strong fluorescence in the presence of serum albumins.

In order to reduce the non-specific opening of the dimer in the presence of albumins, we turned our attention to the hydrophobic highly planar dye Nile Red, which was expected to form strong intracellular dimers. Two dimers of Nile Red were synthesized and coupled to an antimicrobial peptide UBI^{29-41} known to interact with cell membranes of Gram-positive and Gram-negative bacteria[6]. Fluorescence studies demonstrated the ability to generate a strong fluorescence turn-on response when passing from an aqueous to a less polar medium. On the other hand, the fluorescence in the presence of serum albumins was greatly reduced. Unfortunately, the fluorescence staining of bacteria was less efficient compared to that of squaraine dimers. Finally, by synthesizing asymmetric dimers containing one squaraine and one Nile Red dye we have achieved low fluorescence in serum and efficient labeling of bacteria. Moreover, we demonstrated that the two covalently linked dyes formed a FRET pair with different FRET efficiency for Gram-positive and Gram-negative bacteria.

References

1. Ordonez, A. A. *et al.* Molecular imaging of bacterial infections: Overcoming the barriers to clinical translation. *Sci. Transl. Med.* **11**, eaax8251 (2019).
2. O'Neill, J. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. https://apo.org.au/node/63983 (2016).
3. Ferrer, R. *et al.* Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program*. *Crit. Care Med.* **42**, 1749–1755 (2014).
4. Karpenko, I. A. *et al.* Fluorogenic Squaraine Dimers with Polarity-Sensitive Folding As Bright Far-Red Probes for Background-Free Bioimaging. *J. Am. Chem. Soc.* **137**, 405–412 (2015).
5. Weiss, L. Développement de nouvelles sondes fluorescentes pour la détection et l'analyse de bactéries en milieux complexes. (Strasbourg, 2024).
6. Beiki, D. *et al.* (99m)tc-Ubiquicidin [29-41], a Promising Radiopharmaceutical to Differentiate Orthopedic Implant Infections from Sterile Inflammation. *Iran. J. Pharm. Res. IJPR* **12**, 347–353 (2013).

Development of glucose and biomass predictive models for real time monitoring of fermentation using Raman spectroscopy

*Antoine Borg[1,2,3] *, Vincent Portaluri[1] *, Mourad Elhabiri[2], Stéphane Le Calvé[3]*

[1] Euroapi, 32 rue de Verdun, 76410 Saint-Aubin-lès-Elbeuf, [2] LIMA and [3] ICPEES, 25 rue Becquerel, 67087 Strasbourg cedex.

* corresponding emails: antoine.borg@etu.unistra.fr, vincent.portaluri@euroapi.com

In 2004, the FDA issued a guidance document to encourage pharmaceutical industrial partners to develop and implement Process Analytical Technologies (PAT), i.e., technological means to monitor in quasi real time key parameters of an industrial process.[1] The benefits of this approach were clear: unlike historical offline analysis – collecting in-process samples , transporting them to the on-site laboratory, analyzing them and reporting the results – PATs are online by design. The analytical results are obtained in quasi real time 24 hours a day 7 days a week. Yet, the industry is slowly evolving. Twenty years later, PATs are still not universally adopted, particularly in the bioprocess field. Performing online analysis in a fermenter means dealing with a very complex matrix while avoiding direct contact that could cause contamination. Vibrational spectroscopies, such as Raman spectroscopy, enable data to be collected remotely and non-destructively, and are therefore a common technique in this field. They need to be coupled to powerful chemometrics tools to overcome the complexity of the matrix and generate results that meet industry standards for accuracy and robustness.[2]

In the context of industrial fermentation, two key parameters to monitor are the glucose concentration and the Optical Density at 600 nm (OD600), a common proxy for biomass concentration. Due to the technical challenges mentioned above, relatively few studies have reported the implementation of PATs dedicated to these key parameters in fermentation.[3-5] While producing seemingly functional tools, prior reports have lacked proper analysis with regard to the robustness of the tools in the context of long-term monitoring, which is crucial for their implementation in the full-scale industrial process.

In this work is reported the implementation of a tool that monitors glucose and OD600 during a type of fermentation. The tool was thoroughly tested on 14 fermenters, over 6 months and consistently produced analytical results significantly superior to the current state-of-the-art. Moreover, an easy-to-use interface was developed to help the fermentation operators to get the most of the analytical results.

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[1] Hinz, D. C. Process Analytical Technologies in the Pharmaceutical Industry: The FDA's PAT Initiative. *Anal. Bioanal. Chem.* **2006**, *384* (5), 1036–1042. https://doi.org/10.1007/s00216-005-3394-y.

[2] Gerzon, G.; Sheng, Y.; Kirkitadze, M. Process Analytical Technologies – Advances in Bioprocess Integration and Future Perspectives. *J. Pharm. Biomed. Anal.* **2022**, *207*, 114379. https://doi.org/10.1016/j.jpba.2021.114379.

[3] Hirsch, E.; Pataki, H.; Domján, J.; Farkas, A.; Vass, P.; Fehér, C.; Barta, Z.; Nagy, Z. K.; Marosi, G. J.; Csontos, I. Inline Noninvasive Raman Monitoring and Feedback Control of Glucose Concentration during Ethanol Fermentation. *Biotechnol. Prog.* **2019**, *35*. https://doi.org/10.1002/btpr.2848.

[4] Schalk, R.; Braun, F.; Frank, R.; Rädle, M.; Gretz, N.; Methner, F.-J.; Beuermann, T. Non-Contact Raman Spectroscopy for in-Line Monitoring of Glucose and Ethanol during Yeast Fermentations. *Bioprocess Biosyst. Eng.* **2017**, *40* (10), 1519–1527. https://doi.org/10.1007/s00449-017-1808-9.

[5] Müller, D. H.; Flake, C.; Brands, T.; Koß, H.-J. Bioprocess In-Line Monitoring Using Raman Spectroscopy and Indirect Hard Modeling (IHM): A Simple Calibration Yields a Robust Model. *Biotechnol. Bioeng.* **2023**, *120* (7), 1857–1868. https://doi.org/10.1002/bit.28424.

Pembrolizumab detailed charge variants characterization using capillary electrophoresis and tandem mass spectrometry

Lola Alez-Martin[1,2], Pascal Houzé[2], Rania Joomun[2], Nathalie Mignet[2], Yannis François[1], Rabah Gahoual[2]

[1] Laboratoire de Spectrométrie de Masse des Interactions et des Systèmes (LSMIS) UMR 7140 (Unistra-CNRS), Université de Strasbourg, France.
[2] Université Paris Cité, Unité de Technologies Chimiques et Biologiques pour la Santé (UTCBS), CNRS UMR8258, Inserm U1022, Faculté des sciences pharmaceutiques et biologiques, Paris (France)

Today, more than 130 different monoclonal antibodies (mAbs) have been approved for therapeutic use and more than 200 are currently in clinical trials. Those biomolecules used in the treatment of several diseases, are structurally complex molecules that can show microheterogeneities known as post-translational modifications (PTMs). Those modifications can change the charge and conformation of the molecules, creating charge variants, also potentially impacting the potency and pharmacokinetic of the mAb. Thus, it is an important to be able to characterize them. Capillary electrophoresis (CE) is particularly adapted for the analysis of charge variants as it can separate them. However, the specificity of the separation provided by the CE is not entirely understood. In order to understand better the separation seen in CE, mass spectrometry (MS) will be used to characterize precisely the modifications of the charge variants. **In this study, we developed a fraction collection strategy in CE-UV with fraction enrichment of the charge variants from pembrolizumab and an off-line CE-MS/MS characterization of the PTMs of each fraction collected.**
First results showed a specific separation of charge variants in CE-UV enabling the precise identification of an innovator and biosimilars of infliximab from the electropherograms. Enzymatic digestion of the mAbs with a carboxypeptidase-b enabled the identification of the origin of disparate charge variants coming from C-term Lys modifications. The same protocol was applied to pembrolizumab with two enzymes (carboxypeptidase-b and endoglycosidase), showing that no charge variants separated were due to dissimilarities in glycosylations pattern or C-Terminal Lys. Consequently, the fraction collection strategy was developed for PBZ to collect 5 fractions of the 5 charge variants separated in CE-UV (Figure 1). From fluidic calculations and migrations times, fractions were collected and enriched about fifty times. The charge variants collected were then digested into peptides and analyzed in CE-MS/MS for a precise characterization of PTMs. CE-MS/MS allowed the identification of variety of modifications such as asparagine deamidations, methionine oxidations and pyroglutamate formation. Moreover, the precise characterization of the succinimide intermediate from aspartic acid and asparagine was enabled. Results demonstrated that asparagine deamidations and succinimides formation were two prominent modifications observed, that could strongly impact the charge variant separation provided by CE-UV.

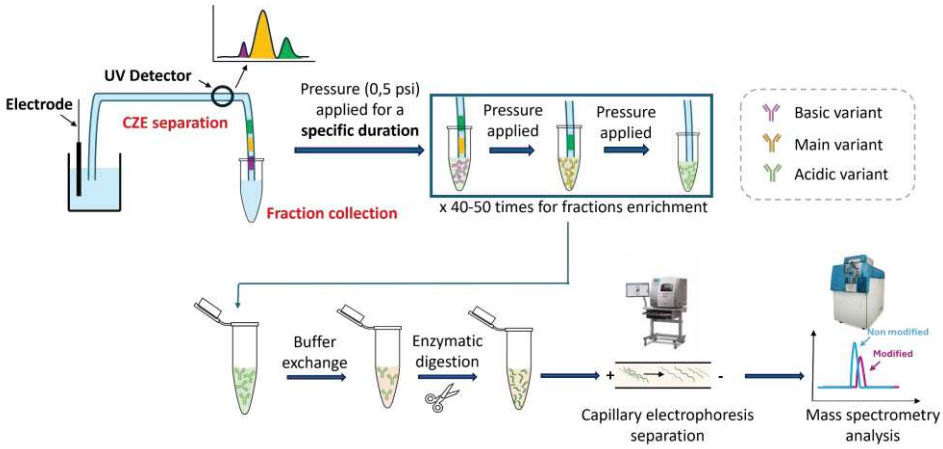


Figure 1: *Fraction collection strategy for the CE-UV and CE-MS/MS characterization of the charge variants from pembrolizumab.*

NON-EQUILIBRIUM SELF-ASSEMBLY OF ELECTROACTIVE SYSTEMS

Fabiana Ciocchetti[1*], *Ahmad Bachir[1], Caterina Baccini[2]*, Cristian Pezzato[3], *Giulio Ragazzon[1]*.

[1]University of Strasbourg, CNRS, Institut de Science et d'Ingénierie Supramoléculaires (ISIS) UMR 7006, 8 Allée Gaspard Monge, 67000 Strasbourg, France. [2]University of Parma, Via Area Parco delle Scienze 17/A, 43124 Parma. [3]University of Padova,Via Francesco Marzolo 1, 35131 Padova, Italy.

e-mail: ciocchetti@unistra.fr

Keywords: *Non-equilibrium systems ■ Interlocked structures ■ Redox-driven processes*

High-energy supramolecular interlocked structures have attracted considerable attention in recent decades, and they might offer unconventional strategies to harvest energy from various external sources (e.g., chemical, redox, or light inputs).[1] Fine-tuning the kinetic of a system is crucial and plays an important role in developing out-of-equilibrium systems. To this aim, pseudorotaxanes are ideal platforms because simple structural modifications can drastically modify the kinetics of their threading/dethreading processes.

Inspired by the seminal work of the Stoddart group,[1,2] we investigated kinetically trapped states upon alternating redox stimuli in systems composed of a derivative of the macrocyclic cyclobis(paraquat-*p*-phenylene) host and paraquat derivative guests. In particular, we used click chemistry to prepare multifunctional structures comprising either multiple guests or multiple hosts.[3] The formation of pseudorotaxanes, between these multifunctional hosts and guests, is expected to take place upon reduction of the two components, thanks to radical pairing interactions (Fig.1). The combination of spectroelectrochemistry, differential pulse voltammetry, and tailored cyclic voltammetry analysis, revealed peculiar effects of the different systems.

Our ongoing studies contribute to the development of redox-driven non-equilibrium systems

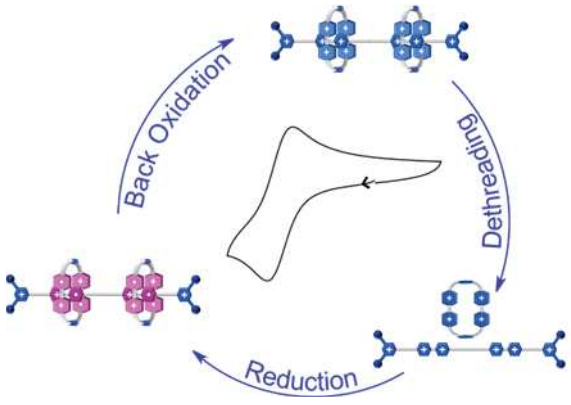


Figure 1: Schematic representation of an electrochemical reduction/oxidation cycle coupled with an assembly/disassembly of the host and guest molecules.

References

1 J. F. Stoddart, *Angew. Chem. Int. Ed.*, 2017, **56**, 11094–11125.

2 C. Cheng, P. R. McGonigal, W.-G. Liu, H. Li, N. A. Vermeulen, C. Ke, M. Frasconi, C. L. Stern, W. A. Goddard and J. F. Stoddart, *J. Am. Chem. Soc.*, 2014, **136**, 14702–14705.

3 A. Bachir, F. Ciocchetti, D. P. Couto, S. Di Noja, C. Pezzato and G. Ragazzon, *Eur. J. Org. Chem.*, 2023, **26**, e202300498.

GUANIDINIUM-PORPHYRIN CONJUGATES FOR ANTIMICROBIAL PHOTODYNAMIC THERAPY

Auguste Eclancher,[a] *Nahid Sadeghi Alavijeh,*[a] *Christopher Aisenbrey,*[b] *Burkhard Bechinger,*[b] *Philippe Lavalle*[c] *and Valérie Heitz*[a]

[a]Laboratoire de Synthèse des Assemblages Moléculaires Multifonctionnels, UMR 7177, Institut de Chimie de Strasbourg, France
[b]Biophysique des membranes et RMN, UMR 7177, Institut de Chimie de Strasbourg, France
[c]Biomatériaux et bioingénierie, Inserm UMR-S 1121, Faculté de médecine de Strasbourg, France

Correspondence: auguste.eclancher@etu.unistra.fr

Considered to be among the biggest threats for worldwide public health by the WHO, the emergence of resistance to antibiotics is generally attributed to their widespread and sometimes pointless use. Such resistant bacteria can target individuals of all ages and affect the agricultural, medical and veterinarian sectors among others.[1] Historically, almost all antibiotics have led to the development of resistance among different bacterial strains, highlighting the necessity of developing alternative antibacterial therapies. This is the backdrop of the development of antimicrobial photodynamic therapy (aPDT), which consists of the use of a photosensitiser that leads to the formation of cytotoxic oxygen species that kill bacteria once irradiated.[2,3]

Based on previous results obtained in the group,[4] we describe the synthesis and properties of two new porphyrin-based photosensitisers for aPDT (Figure 1). Both compounds exhibit guanidinium moieties to target bacterial membranes and to impart amphiphilic properties to the PS. They are connected to a π-conjugated porphyrin core to shift light absorption of the molecule in the optical therapeutic window to limit damage to endogenous chromophores and treat non-superficial infections.[5] One presents a bis-guanidinium symmetrical structure, and the other is vectorised by an antimicrobial peptide called PGLa, known for its ability to insert itself in bacteria membranes.[6] Difference studies to assess their affinity for bacteria membranes as well as antimicrobial activity at micromolar concentration have been conducted and will be presented.

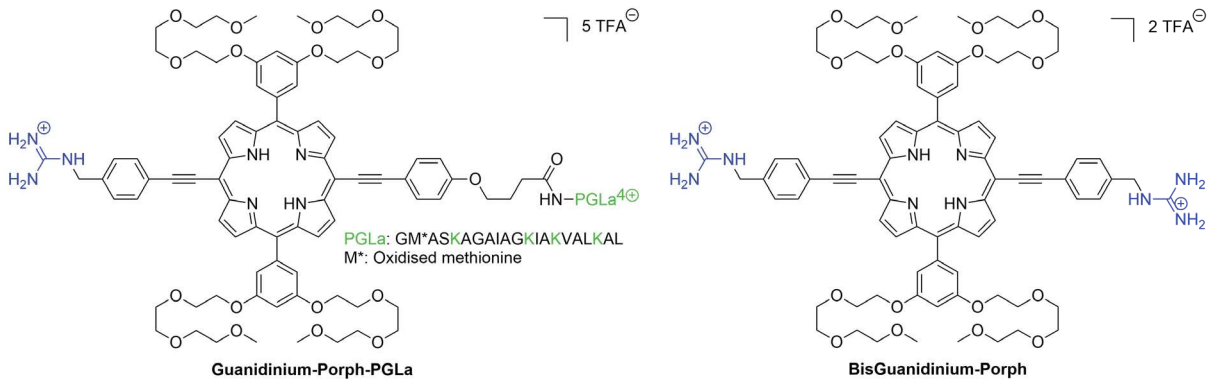


Figure 1: Targeted conjugates of interest for aPDT

[1] World Health Organization, M. C. Stuart, M. Kouimtzi, S. Hill, *WHO Model Formulary 2008*, World Health Organization, **2009**.
[2] J. H. Correia, J. A. Rodrigues, S. Pimenta, T. Dong, Z. Yang, *Pharmaceutics* **2021**, *13*, 1332.
[3] Y. Liu, R. Qin, S. A. J. Zaat, E. Breukink, M. Heger, *J. Clin. Transl. Res.* **2015**, *1*, 140–167.
[4] C. Gourlot, A. Gosset, E. Glattard, C. Aisenbrey, S. Rangasamy, M. Rabineau, T.-S. Ouk, V. Sol, P. Lavalle, C. Gourlaouen, B. Ventura, B. Bechinger, V. Heitz, *ACS Infect. Dis.* **2022**, *8*, 1509–1520.
[5] J. M. Dąbrowski, B. Pucelik, A. Regiel-Futyra, M. Brindell, O. Mazuryk, A. Kyzioł, G. Stochel, W. Macyk, L. G. Arnaut, *Coord. Chem. Rev.* **2016**, *325*, 67–101.
[6] E. S. Salnikov, B. Bechinger, *Biophys. J.* **2011**, *100*, 1473–1480.

Development of analytical methods for characterization of Biogenic Volatile Organic Compounds (BVOCs) emitted by pest infested plants.

Développement de méthodes analytiques pour la caractérisation des composés organiques volatils biogéniques émis par les plantes infestées de parasites.

Ali GHADDAR [a,b], Damien BAZIN [b], Stéphane LE CALVÉ [a]

[a] Institut de Chimie et Procédés pour l'Énergie, l'Environnement et la Santé (ICPEES, UMR 7515, CNRS/Unistra), 25 rue Becquerel, 67087 Strasbourg Cedex 2, France.

[b] Chromatotec, 1 Avenue Jean-Honoré Olibet, 33240 Saint-André-de-Cubzac, Bordeaux, France.

ali.ghaddar@etu.unistra.fr, slecalve@unistra.fr, damien.bazin@chromatotec.com

One of the major binding goals of the Farm2Fork strategy is to halve the use and risk of pesticides by 2030[1]. However, controlling the invasions of new and currently-established pests seems to be offsetting this target due to climate change and the demanding increase in food production. Despite that several regulations were put in place to reduce the risk of the new pests' entry such as imposing a phytosanitary certificate on plants upon entry to Europe, many regional and international reports confirmed that the outcomes of these regulations have not been sufficiently effective[2]. Since the current detection diagnostics of the pests tend to be unreliable in terms of methodology and costs, the pesticides used to control the currently established pests are being misused, i.e., at the wrong time and to areas in the field where there are no pest attacks. This led to the establishment of the PurPest project (several partners in the EU).

The main objective of the PurPest project is to control serious plant pests during import and to detect them in a timely and non-invasive manner. The detection procedure follows the exploitation of specific volatiles released in low levels (ppt to ppb range) by plants or upon the infestation of these plants. As illustrated in Figure 1, the main goal of the project is to define the VOC signatures of pests and to develop a sensor system prototype (SSP) for detection of the VOCs combined with a reliable identification of target pests and that can easily be used in a field. Chromatotec leads the design of such portable and compact prototype. The first objective to do in the lab was to start synthesizing the required gas mixtures of target biogenic VOCs using permeation devices. The second objective was to evaluate already existing analyzers at Chromatotec and ICPEES such as TD-GC-FID/MS and µGC-PID. This allowed to characterize the targeted VOCs in the scope of the project.

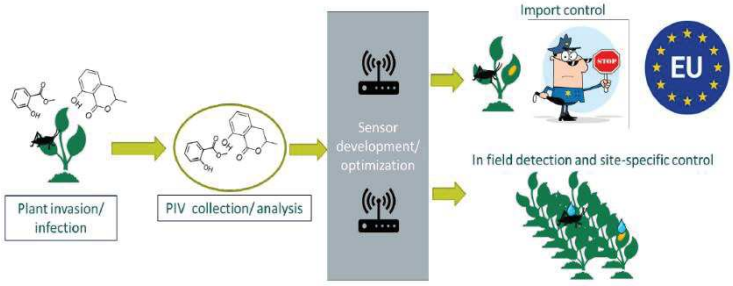


Figure 1: Illustration of the PurPest Concept

(1) European Commission, "Farm to Fork Strategy: For a fair, healthy and environmentally friendly food system," May 2020. [Online]. Available: https://ec.europa.eu/food/farm2fork_en#:~:text=The%20Farm%20to%20Fork%20Strategy%20is%20at%20the%20heart%2

0of,%2C%20healthy%20and%20environmentally%2Dfriendly.&text=The%20Farm%20to%20Fork%20Strategy%20aims%20to%20accelerate%20our%20transition,neutral%20or.

(2) Jung, T.; Orlikowski, L.; Henricot, B.; et al. A. Widespread *Phytophthora* Infestations in European Nurseries Put Forest, Semi-natural and Horticultural Ecosystems at High Risk of Phytophthora Diseases. *Forest Pathology* **2016**, *46* (2), 134–163.

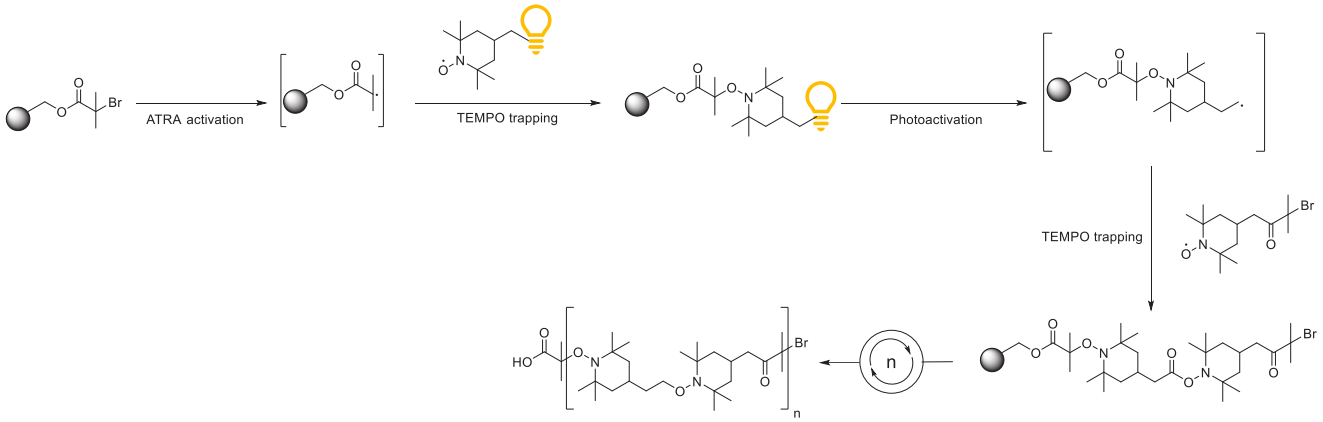
DIGITAL POLYMER SYNTHESIS USING A FULLY ORTHOGONAL RADICAL PROCESS

Hugo GUILMAIN, Jean-Louis CLEMENT*, Laurence CHARLES*, Didier GIGMES* and Jean-François LUTZ**

Université de Strasbourg, CNRS, UMR 7006, Institut de Science et d'Ingénierie Supramoléculaire (ISIS), 67000 Strasbourg (France)
Aix Marseille Université, CNRS, UMR 7273, Institut de Chimie Radicalaire (ICR), 13397 Marseille, France
28 rue de Thann, hugo.guilmain@etu.unistra.fr

We are currently facing a number of global challenges. One of the most important is data storage, which has an impact on the environment. According to several studies, it is responsible for over 2% of the world's annual energy consumption. This consumption is due to the cooling of spaces dedicated to computer servers. The main problem is that the amount of digital information to be stored increases every year. But over the last ten years, our group has found a way to store information on molecular scale, using poly(phosphodiester)s[1] or poly(alkoxyamine amide)s[2] . Those abiological approaches take advantage of the robustness and versatility of polymer chemistry for data storage. The problem now, is to achieve big data storage. Therefore, it is crucial to increase the speed of the synthesis.

In this context, radical chemistry has been investigated herein. In fact, this kind of chemistry is highly reactive and could hold great promise for the storage of voluminous data. The polymers are synthetized by stepwise synthesis on a solid support. The monomers are designed in three parts, the first being a persistent radical, the second a coding moiety and the third a radical initiator. To initiate a radical, two orthogonal activations are used. The first is a carbon-bromide bond activation by copper (I) (ATRA)[3] and the second is homolytic bond cleavage by photoactivation[4]. Due to the orthogonality of this method, the polymerization could be controlled by activation/coupling cycles.



Références.

[1] Lutz, J-F. Charles, L. Design of Abiological Digital Poly(phosphodiester)s, *Acc. Chem. Res.*, **2021**, 54, 7, 1791-1800

[2] Lutz, J-F. et al. Design and synthesis of digitally encoded polymers that can be decoded and erased, *Nat. Commun*, **2015**, 6, 7237-7245

[3] Matyjaszewski, K. Atom Transfer Radical Polymerization: From Mechanisms to Applications, *Isr. J. Chem*, **2012**, 13, 1700-1705

[4] Lalevée, J. et al. Effect of Decarboxylation on the Photoinitiation Behavior of Nitrocarbazole-Based Oxime Esters, *Macromolecules*, **2022**, 55, 2475-2485

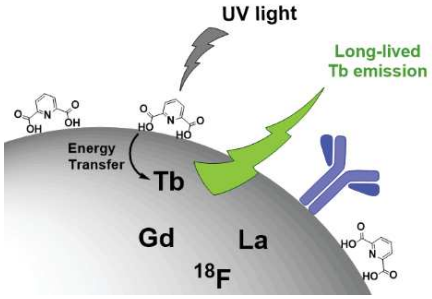
Functionalized LnF_3 nanoparticles as multimodal contrast agents for PET, MRI and Luminescence imaging

C. Heinritz,[1] A. Ouadi,[2] D. Brasse,[2] C. Po,[3] S. Bégin,[4] M. Botta,[5] F. Carniato,[5] S. Harlepp,[5] A. Detappe,[5] C. Cheignon,[1] L. Charbonnière,[1] A. Nonat[1]

[1] Equipe de Synthèse pour l'analyse, IPHC, CNRS, 67200 Strasbourg, FR
[2] Equipe Imagerie Moléculaire et Radiobiologie, IPHC, CNRS, Strasbourg, FR
[3] iCube - Laboratoire des sciences de l'ingénieur, de l'informatique et de l'imagerie, Strasbourg, FR
[4] Chemical Engineering of Functional Nanomaterials, IPCMS, CNRS, Strasbourg, FR
[5] Università del Piemonte Orientale, Alessadria, IT
[6] ICANS – Institut de cancérologie, Strasbourg, FR

Email address: charlotte.heinritz@etu.unistra.fr

Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI) and Luminescence Imaging being well employed techniques for medical diagnostics, interest in the development of multimodal contrast agents arises to facilitate the *in vitro* and *in vivo* detection in multimodal scanners. Our goal is the development of such trimodal agents based on Lanthanide Nanoparticles (Ln NPs).
The interesting spectroscopic and magnetic properties of Ln give rise to unique characteristics of the Ln NPs. Ln-containing compounds are used in probes for luminescence imaging and, especially in the case of Gd(III) for MRI.[1] The low intrinsic absorption of Ln and thus difficult photosensitization, can be overcome by indirect photosensitization through light-harvesting capping ligands (called antennae) on the NP surface, allowing exceptional high brightness of Ln NPs.[2]
We report here the microwave-based synthesis of $La_xGd_yTb_zYb_{1-x-y-z}F_3$ NPs and the characterization of these novel nano-objects in terms of size, stability, crystal structure, relaxation properties and composition. The dependence of the magnetic, luminescent and structural properties on the Ln ratio in the NPs is discussed. The brightness of the NPs after addition of antennae, the MRI images of phantom solutions as well as the PET images of phantom solutions after addition of radiotracers ^{18}F or ^{89}Zr during the NP synthesis present a proof-of-concept for the trimodality of the NPs. *In-* and *ex*-cellular TEM images of NPs are shown as well as modification trials to allow biological targeting *via* a NP-surface coordinated antibody. Advanced spectroscopic properties, such as anti-Stokes emission or 'upconversion' are also being developed with the aim to enlarge the application scope of these Ln NPs for imaging.



Scheme of a ^{18}F doped trimodal Ln NP surface-capped with photosensitizing antennae (dipicolinic acid) and antibodies for biological targeting.

References :

[1] C. Cheignon, A. A. Kassir, L. K. Soro, L. J. Charbonnière, *Nanoscale* **2022**, *14*, 13915

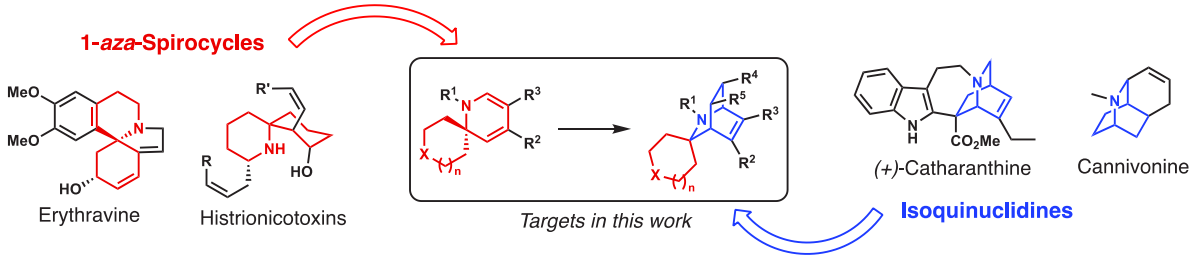
[2] J. Goetz, A. Nonat, A. Diallo, M. Sy, I. Sera, A. Lecointre, C. Lefevre, C. F. Chan, K.-L. Wong, L. J. Charbonnière, *ChemPlusChem* **2016**, *81*, 526

Towards structurally complex *aza*-cyclic architectures merging 1-*aza*-spirocyclic and isoquinuclidine ring systems

Eliott JUNG,[1,2] Valérie BÉNÉTEAU, [1] Patrick PALE, [1] Stefan CHASSAING,[1] and Christophe GOURLAOUEN[2*]*

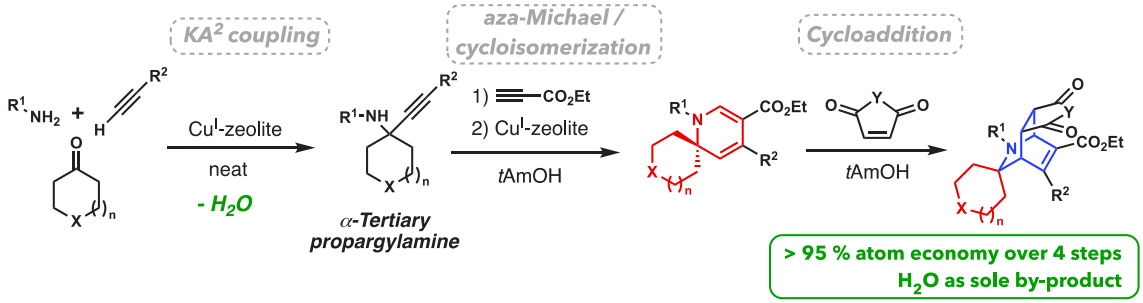
[1]COSyS, Institut de Chimie de Strasbourg, UMR7177, 4 rue Blaise Pascal, 67000, Strasbourg, FRANCE
[2]MSM, Institut de Chimie de Strasbourg, UMR7140, 4 rue Blaise Pascal, 67000, Strasbourg, FRANCE
eliott.jung@etu.unistra.fr

Constructing 3D *aza*-polycyclic architectures remains a big challenge in organic synthesis. In particular, much synthetic efforts have been devoted to 1-azaspirocyclic and isoquinuclidine ring systems, due to their presence in many natural products of biological relevance (**Scheme 1**).[1,2] Our goal is to go further in 3D structural complexity by accessing to unprecedented architectures merging these two *aza*-cyclic systems of high relevance.



Scheme 1

Herein, we wish to report our synthetic approach towards this complex azaspiro/isoquinuclidine hybrid skeleton from simple starting materials (**Scheme 2**). Our approach starts with a 3-step sequence, including 2 steps under Cu^{I}-zeolite catalysis (*i.e.,* KA^2 coupling and enyne cycloisomerization reactions)[3], that first furnishes 1-azaspirocyclic systems featuring a 1,2-dihydropyridine motif. The potential of the resulting 1,2-dihydropyridine motif as diene is finally exploited to construct the additional isoquinuclidine ring system *via* a formal cycloaddition process.[4] DFT calculations are conducted in parallel to rationalize the reaction mechanism and energetic pathway of the cycloaddition process. Noteworthy is that this methodology is highly atom and step economical, with water as sole by-product during the whole 4-step sequence.



Scheme 2

[1] K. Hiesinger *et al. J. Med. Chem.* **2021**, *64*, 150 ; F. Lovering *et al. J. Med. Chem.* **2009**, *52*, 6752 ; D. F. Veber *et al. J. Med. Chem.* **2002**, *45*, 2615.
[2] C. Lavaud *et al.* The Iboga Alkaloids. In: A. Kinghorn *et al. Progress in the Chemistry of Organic Natural Products*. Cham : Springer, **2007,** *105*, 89. ISBN : 978-3-319-49711-2.
[3] F. Schlimpen, PhD Thesis, Université de Strasbourg, **2022** ; F. Schlimpen *et al. J. Org. Chem.* **2021**, *86*, 16593.
[4] T. Wayama *et al. J. Org. Chem.* **2022**, *87*, 5938 ; P. Ramaraju *et al. J. Org. Chem.* **2019**, *84*, 12408 ; R. M. Martin *et al. Org. Lett.* **2013**, *15*, 444 ; N. Satoh *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 5734.

Acridinium receptors: π-π stacking and switchable properties

Léa Lefrançois,[a] Johnny Hu,[a] Jean-Marc Vincent,[b] Valérie Heitz,[a] Henri-Pierre Jacquot de Rouville[a]

[a]Institut de Chimie de Strasbourg, UMR 7177, Université de Strasbourg, 4 rue Blaise Pascal, 67000 Strasbourg, France
Email: lea.lefrancois@etu.unistra.fr
[b]Institut des Sciences Moléculaires, CNRS UMR 5255, Université de Bordeaux, 351 cours de la Libération, 33405 Talence, France

Abstract

Over the past decades, acridinium moieties gained interest as recognition units in artificial supramolecular receptors.[1] Their electro-deficiency allows interactions with electron-rich aromatic guest molecules. In addition, bis-acridinium receptors exhibit switchable properties through the application of stimuli (chemical, redox) as they can be converted to their acridane analogues and be reduced.[2,3]

In this work, the interaction between a functionalized proflavine and two macrocycles both incorporating acridinium units led to a significant difference in behavior (Figure 1). In one case, proflavine interacts with the acridinium moieties through π-donor/π-acceptor interactions (K_a = 660 ± 36 L mol^{-1} in CD_2Cl_2). The resulting host-guest interaction was further altered by exploiting the chemochromic properties of both host and guest. In a second scenario, the formation of bis-acridane derivative was detected by ^{1}H NMR and UV-visible spectroscopy upon addition of proflavine. These two different responses can be seen as two distinct detection modes, namely direct with the formation of a classical host-guest complex and indirect with proflavine acting as a reagent in the conversion of the macrocycle.

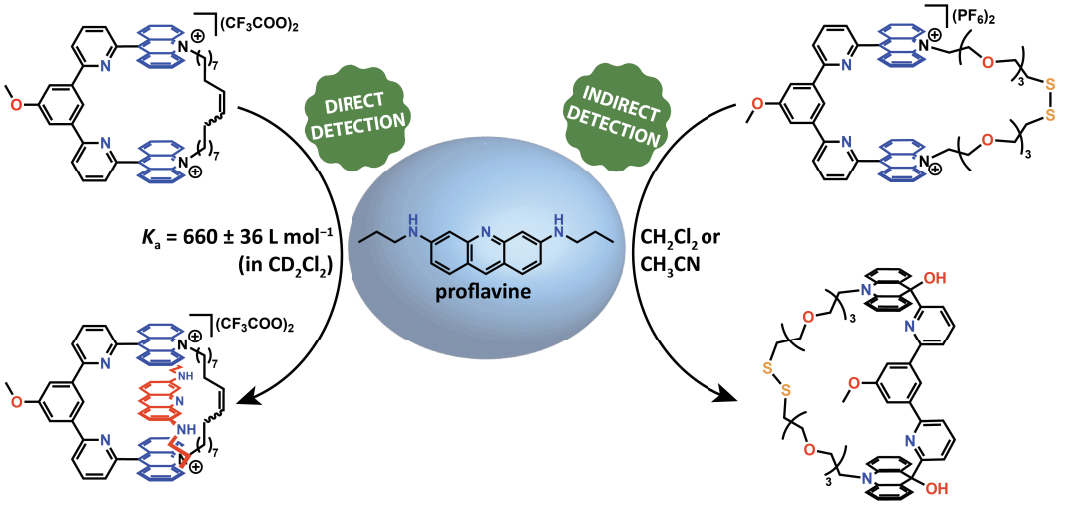


Figure 1: *Direct and indirect detection of proflavine, depending on the macrocycle used.*

References

[1] Jacquot de Rouville, H.-P.; Hu, J.; Heitz, V. *ChemPlusChem* **2021**, *86* (1), 110–129.

[2] Hu, J.; Ward, J. S.; Chaumont, A.; Rissanen, K.; Vincent, J.-M.; Heitz, V.; Jacquot de Rouville, H.-P. *Angew. Chem. Int. Ed.* **2020**, *59* (51), 23206–23212.

[3] Hu, J.; Adrouche, S.; Gauthier, E. S.; Le Breton, N.; Cecchini, M.; Gourlaouen, C.; Choua, S.; Heitz, V.; Jacquot de Rouville, H.-P. *Chem. Eur. J.* **2022**, *28* (71), e202202840.

Development of innovative analytical strategies based on Top-Down Mass Spectrometry (TD-MS) for characterizing bird hemoglobins and its active form

Léa Letissier[1,2] (lea.letissier@etu.unistra.fr),
Turkan Nabiyeva[1,2], François Criscuolo[3], Fabrice Bertile[1,2,3], Christine Schaeffer[1,2], Sarah Cianférani[1,2], Oscar Hernandez-Alba[1,2]

[1]Laboratoire de Spectrométrie de Masse BioOrganique, Université de Strasbourg, CNRS, IPHC UMR 7178, 67087 Strasbourg, France
[2]Infrastructure Nationale de Protéomique ProFi – FR2048 CNRS CEA, 67087 Strasbourg, France
[3]Département d'écologie, physiologie et éthologie, Université de Strasbourg, CNRS, IPHC UMR 7178, 67087 Strasbourg, France

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Hemoglobin is the protein responsible for the blood oxygen transport[1] in many vertebrates. Any abnormalities in hemoglobin structure, such as glycation, can lead to serious health outcomes[2,3]. This is why characterizing hemoglobin under native conditions is essential to access to its native structure and therefore understand better its functions[4] and interactions. For now in the literature, avian hemoglobin has not been characterized at the native intact level and this information will be critical for a better understanding of adaptive process, oxygen affinity of different bird species, and other hemoglobin-related metabolism. Also, it has also been shown that some bird species have three tetramers[5], rather than a single one as in humans. Consequently, this makes it impossible to use direct infusion, as is often the case in analyses of human hemoglobin.

Top-down mass spectrometry[6] (TD-MS) entails the fragmentation of intact biomolecules to cross-correlate the intact mass with the modifications of the aminoacids for an accurate proteoform description. This strategy can be taken one step further in combination with native MS (nMS) [7] connecting structural information about the tertiary and quaternary structure of proteins with their sequence, bridging the gap between proteomics and structural biology. In this context, we combined size exclusion chromatography (SEC) with TD-MS using various fragmentation methods in native conditions to develop an innovative complex-down strategy to unveil for the first time the structure of Zebra Finch hemoglobin.

SEC separation put in evidence the co-existence of three tetrameric structures within the Zebra Finch hemoglobin sample. The subunit release of the complex was performed by increasing the voltage in the source of the mass spectrometer, pinpointing that structural differences between the three tetramers stemmed from the substitution of the a^A to the a^D globin unit. Further isolation and fragmentation of the subunits based on collisions (HCD), electron transfer (ETD), and photodissociation (UVPD) led to a near complete sequencing providing more than 90% of sequence coverage.

This study highlights the perfect suitability of complex-down workflows in combination with non-denaturing liquid chromatography separations to characterize different biologically-relevant systems, allowing to unravel structural insights that can be crucial for a better understanding of the structure-function relationship.

References:

[1] Weber, R. E.; and Fago, A. *Respir Physiol Neurobiol*, **2004**, *144* (2–3), 141–159.
[2] Inzucchi, S. E. N *Engl J Med*, **2012**, *367* (6), 542–550.
[3] López-Otín, C. et al. *Cell*, **2013**, *153* (6), 1194–1217.
[4] Sotomayor-Vivas, C. et al. *PLoS One*, **2022**, *17* (1), e0261829.
[5] Brun, C. et al. *Exp Gerontol*, **2022**, *164*, 111811.
[6] Zhou, M. et al. *Chem Sci*, **2020**, *11* (48), 12918–12936.
[7] Barth, M.; and Schmidt, C. *J Mass Spectrom*, **2020**, *55* (10), e4578.

Local Potential Functional Embedding Theory (LPFET)

Wafa MakhloufSupervisors: Emmanuel Fromager & Bruno Senjean

Abstract: Solving the electronic structure problem (N-body problem) governed by the Schrodinger equation is the main challenge in molecular and materials science, as it scales exponentially with the size of the system. Solving this problem exactly with wavefunction theory (WFT) is exponentially costly and is restricted to systems with a very small number of electrons. However, while Full Configuration Interaction (FCI) exhibits exponential costs, other WFT methods incur polynomial costs, but at the expense of approximations. Quantum computers are expected to reduce this scaling from exponential to polynomial and allow us to treat much larger systems, which is why they are considered a technological revolution. Building such algorithms necessitates a complete translation of our knowledge of classical computers to the new language and architecture of quantum computers. In this context, the extension of the Local Potential Functional Embedding Theory (LPFET) method represents a significant advancement. By addressing finite and non-uniform model systems, such as Hubbard molecules and quantum chemical systems described on a localized orbital basis, this research aims to bridge the gap between classical and quantum computational methodologies. The key objective is to establish a precise relationship between the exchange-correlation (Hxc) potential of the full system and the optimized chemical potentials within different embedding clusters. Crucially, the LPFET algorithm is integrated with quantum algorithms, facilitating the solution of self-consistent Kohn-Sham Density Functional Theory (KS-DFT) equations and Schrodinger equations for clusters. Thus, this research not only contributes to advancing our understanding of electronic structure but also exemplifies the hybridization of classical and quantum computational approaches in tackling complex scientific challenges .

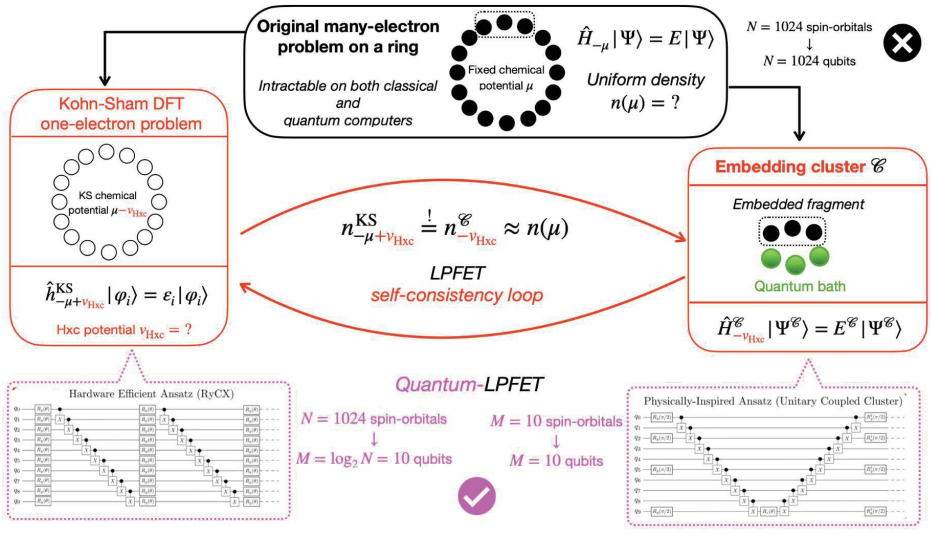


Figure: LPFET and its quantum implementation sketched for a uniform Hubbard lattice.

Quantum Science and Nanomaterials
23, rue du Loess, F-67034 Strasbourg

[1] Kohn, W. and Sham, L. J. Phys. Rev. **140**, A1133–A1138 (1965).
[2] K. Gerald, G. Kin-Lic Chan. Phys. Rev. Lett. **109**,186402 (2012).
[3] S. Sekaran, M. Saubanère, and E. Fromager, Computation. **10**, 45 (2022).
[4] S. Sekaran, M. Tsuchiizu, M. Saubanère, and E. Fromager, Phys. Rev. B. **104**, 035121 (2021).
[5] S. Sekaran, O.Bindech and E. Fromager, J. Chem. Phys. **159,** (2023).
[6] E. Fromager, Molecular Physics. **113**, 419–434 (2015).
[7] Mordovina U, Reinhard TE, Theophilou I, Appel H, Rubio A. J. Chem. Theory Comput. **15**, 5209–5220 (2019).
[8] F. Cernatic, E. Fromager, and S. Yalouz, J. Chem. Phys. **161**, 124107 (2024).
[9] S. Yalouz, "Quantnbody," https://github.com/SYalouz/QuantNBody (2022).
[10] S. Yalouz, M.R. Gullin and S. Sekaran. **7(80)**, 4759, (2022).

Development of PROTAC targeting kinases for the treatment of cancers

Lydia Ouadfel, PhD supervisors: Dr.Frédéric Bihel, Dr.Martine Schmitt

Cancer is a major public health issue worldwide. In France, it is considered as the leading cause of mortality in men and the second in women.[1,2] This high incidence is primarily attributed to metastases, which account for 90% of cases and posing significant treatment challenges.[3,4] Recent studies in the literature have demonstrated the involvement of CDK5 in tumors, with functions ranging from metastasis to angiogenesis. The inactivation of this kinase in melanoma cell lines has been shown to reduce cell motility in vitro, as well as the formation of lung and liver metastases in vivo in a human melanoma mouse model. CDK5-mediated cell motility thus represents an underlying driver of cancer metastasis[5,6,7.] Several orthosteric kinase inhibitors have already been used clinically; however, they exhibit relatively low selectivity due to limitations associated with their mechanism of action, which involves binding to the ATP pocket. To date, few allosteric inhibitors of protein kinases have been reported in the literature.[8,9] A promising new strategy involves the Ubiquitin-Proteasome System (UPS) degradation machinery, specifically Proteolysis-targeting chimeras (PROTACs), which represent an emerging therapeutic area. PROTACs are hetero-bifunctional molecules composed of a ligand for the protein of interest (POI) connected via a linker to a ligand for the E3 enzyme of the UPS system (Figure 1).

This thesis project focuses on the design and synthesis of PROTACs targeting either the orthosteric or allosteric pocket of CDK5. In our laboratory, potential allosteric modulators of CDK5 (unpublished data) have been identified, but establishing a definitive link between their cellular phenotypic effects and an allosteric mechanism on CDK5 remains a significant challenge. To address this, the PROTAC system is employed with two primary objectives: (1) to selectively degrade CDK5 using orthosteric or allosteric PROTACs, and (2) to validate the mechanism of action of these allosteric modulators. By inducing targeted protein degradation, PROTACs allows to visualize CDK5 degradation at the cellular level, providing insights into the relationship between protein loss and observed phenotypic effects. This innovative approach not only confirms the allosteric mechanism but also serves as a powerful pharmacological tool to elucidate the biological functions of CDK5, particularly its role in cancer cell migration.

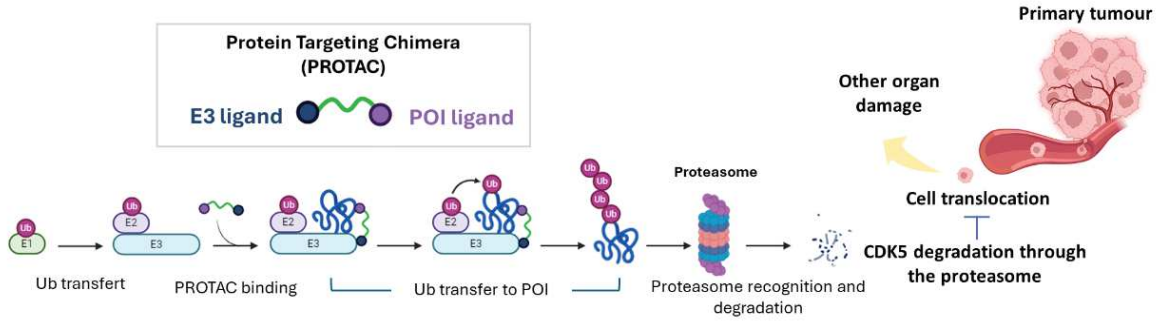


Figure 1:*Mechanism of CDK5 degradation by UPS machinery to block cell migration in tumor metastasis*

[1] R.L. Siegel; *et al. CA Cancer J Clin*. **2023**, 73(1), 17-48
[2] Globocan 2020, http://gco.iarc.fr/
[3] C.L. Chaffer; R.A. Weinberg. *Science.* **2011**, 331,1559-1564.
[4] S.A. Brooks ; *et al. Acta histochem*. **2010**, 112, 3—25
[5] A. Shupp; *et al*. Oncotarget. **2017**, 8, 17373-17382.
[6] M. Peyressatre; *et al*. *Cancers*. **2015**, *7*, 179-237.
[7] S. Sharma, *et al. PNAS*. **2020**, 117 (14), 8001-8012
[8] X. Lu; *et al. Angew. Chem. Int. Ed*. **2020**, 59 (33), 13764–13776
[9] A. Laure; *et al. ACS Pharmacol. Transl. Sci*. **2024**, 7, 5, 1377–1385

A Chiral [2 + 3] Covalent Organic Cage Based on 2,2'-BINOL Units

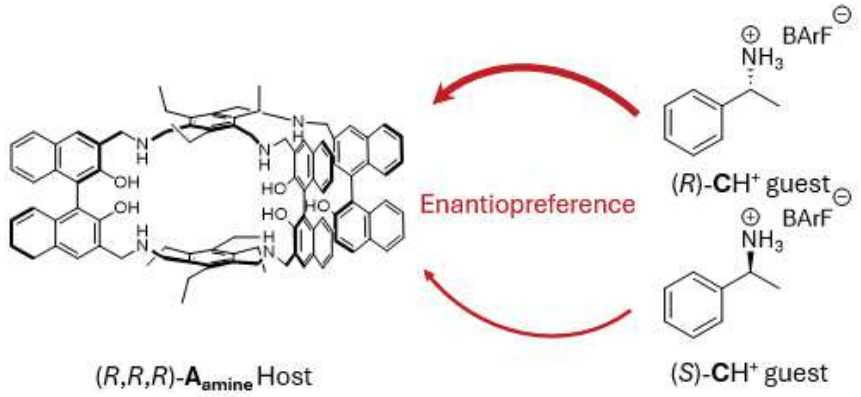
David-Jérôme Pham, Midhun Mohan, Pierre Mobian

UMR 7140, University of Strasbourg-CNRS, 4 rue Blaise Pascal, 67000 Strasbourg, France

david-jerome.pham@etu.unistra.fr

Keywords: covalent organic cage, self-assembly, chirality

Chiral covalent organic cage is an emerging class of architectures with various applications such as gas separation, chiral separation, and catalysis.[1] Combining dynamic covalent chemistry and chiral building blocks, self-assembly of chiral cages can be achieved.[2] In this contribution, a [2+3] enantiopure covalent organic cage ($\mathbf{A}_{\mathbf{imine}}$) was synthesized through the condensation between a 3,3'-diformyl 2,2'-BINOL unit with a triamino spacer in near quantitative yields.[3] Chiral self-sorting of cage **A** was performed, and its properties were compared with a homologous cage $\mathbf{B}_{\mathbf{imine}}$ containing biphenol units. Then, the reduction of the imine bonds of cage $\mathbf{A}_{\mathbf{imine}}$ into irreversible amine bonds to increase stability permitted binding studies of cage $\mathbf{A}_{\mathbf{amine}}$ with enantiopure phenylethylammonium cations (**C**H$^+$) through UV and DOSY NMR. A higher binding constant between (*R*)-**C**H$^+$ and (*R*,*R*,*R*)-$\mathbf{A}_{\mathbf{amine}}$ compared to (*S*)-**C**H$^+$ was found which is also in agreement with molecular dynamics simulation.



Enantiopreference for the binding of (*R*,*R*,*R*)-$\mathbf{A}_{\mathbf{amine}}$ with (*R*)-**C**H$^+$ related to (*S*)-**C**H$^+$

1. Montà-González, G.; Sancenón, F.; Martínez-Máñez, R.; Martí-Centelles, V. *Chem. Rev.* **2022**, *122*, 13636–13708
2. Ono, K.; Iwasawa, N. *Chem. Eur. J.* **2018**, *24*, 17856–17868
3. Mohan, M.; Pham, D-J.; Fluck, A.; Chapuis, S.; Chaumont, A.; Kauffmann, B.; Barloy, L.; Mobian, P. *Chem. Eur. J*. **2024**, *23*, e202400458

Synthesis of sequence-encoded morpholino oligomers

Benoit POUSSE,[1] Paul Baxter[1] and Jean-François LUTZ[1*]
Université de Strasbourg, CNRS, ISIS, 8 allée Gaspard Monge, 67000 Strasbourg (France)

DNA has been storing our genetic code since the beginning of life on Earth. The industrial process of storing data in DNA has been studied for decades but many problems still remain. For over ten years, the Lutz group has demonstrated that it is possible to store information in abiological polymers.[1,2] Coded polyphosphodiesters are synthesized using phosphoramidite chemistry. Each step of the iterative cycle has been optimized for decades however, the general cycle can be improved by removing one step. Indeed, pioneers of this technique worked with Phosphorus (III) because it was the most reactive phosphorus species at this time. Nowadays, new synthesis of nucleic acids are growing by using Phosphorus (V) chemistry. This chemistry could be promising for increasing the writing speed of digital polymers. Phosphorodiamidate oligomers with a morpholino scaffold were synthesized by Summerton & Weller[3] at the beginning of the century to create antisens molecules. The aim of this project is to transfer this technology to abiological digital morpholinos to store data.

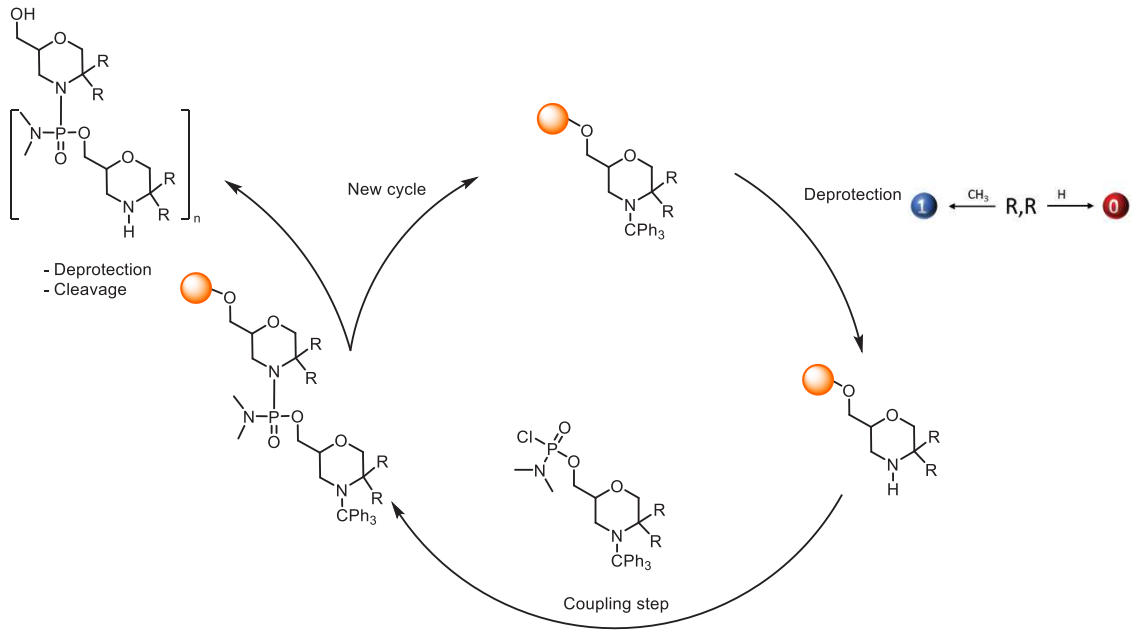


Figure 1 : multi step-growth polymerisation cycle

Références

[1] - Al Ouahabi, A.; Charles, L.; Lutz, J.-F. *J. Am. Chem. Soc.* **2015**, *137*, 5629–5635.
[2] - Charles, L.; Lutz, J.-F. *Acc. Chem. Res.* **2021**, *54*, 1791–1800.
[3] - Summerton, J.; Weller, D. *Antisense and Nucleic Acid Drug Development* **1997**, *7*, 187–195.

Multifunctional graphene-family nanomaterials for combined phototherapy and chemotherapy

Siyao Qin[1], Giacomo Biagiotti[2], Barbara Richichi[2], Yuta Nishina[3], Cécilia Ménard-Moyon[1], Alberto Bianco[1]

[1]*CNRS, Immunology, Immunopathology and Therapeutic Chemistry UPR 3572, University of Strasbourg, ISIS, Strasbourg 67000, France*

[2]*Department of Chemistry "Ugo Schiff", University of Firenze, Via della Lastruccia 13, 50019, Sesto Fiorentino, FI, Italy*

[3]*Research Core for Interdisciplinary Sciences, and Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan*

Email: siyao.qin@etu.unistra.fr

Graphene oxide (GO), one of the most studied members of the graphene family materials, can be exploited as a photothermal agent to convert light energy into heat and cause hyperthermia, leading to thermal ablation of tumor cells [1]. In addition to this property, GO has a large specific surface area that allows many therapeutic drugs or photosensitizers to be loaded onto its surface by covalent and non-covalent methods [2]. Photothermal therapy (PTT) and photodynamic therapy (PDT) have shown great potential as effective treatments against cancer [3]. However, a single approach has some limitations, and the combination of PTT and PDT can lead to a synergistic effect with greater therapeutic efficiency [4]. In this context, we synthesized GO doubly functionalized with folic acid (FA) and a boron dipyrromethene (BODIPY) derivative for combined targeted PTT/PDT. The GO-FA-BODIPY conjugate was characterized by thermogravimetric analysis, Fourier-transform infrared spectroscopy and X-ray photoelectron spectroscopy. We will assess the capacity of the multifunctional GO to perform combined targeted PTT and PDT to induce the death of cancer cells.

References

[1] X. Cui, Q. Ruan, X. Zhuo, X. Xia, J. Hu, R. Fu, Y. Li, J. Wang, H. Xu, Photothermal Nanomaterials: A Powerful Light-to-Heat Converter, Chem. Rev., **2023**, 123, 6891–6952.

[2] S. Guo, S. Garaj, A. Bianco, C. Ménard-Moyon, Controlling covalent chemistry on graphene oxide, Nat. Rev. Phys., **2022**, 4, 247–262.

[3] X. Li, J. Lovell, J. Yoon, X. Chen, Clinical development and potential of photothermal and photodynamic therapies for cancer, Nat. Rev. Clin. Oncol., **2020**, 17, 657–674.

[4] Z. Gao, S. Qin, C. Ménard-Moyon, A. Bianco, Applications of graphene-based nanomaterials in drug design: The good, the bad and the ugly, Expert Opin. Drug Discov., **2023**, 1321-1332.

Regio- and stereoselective azidation of activated *N*-allenamides: an entry to α, β, γ and δ-amido-azides

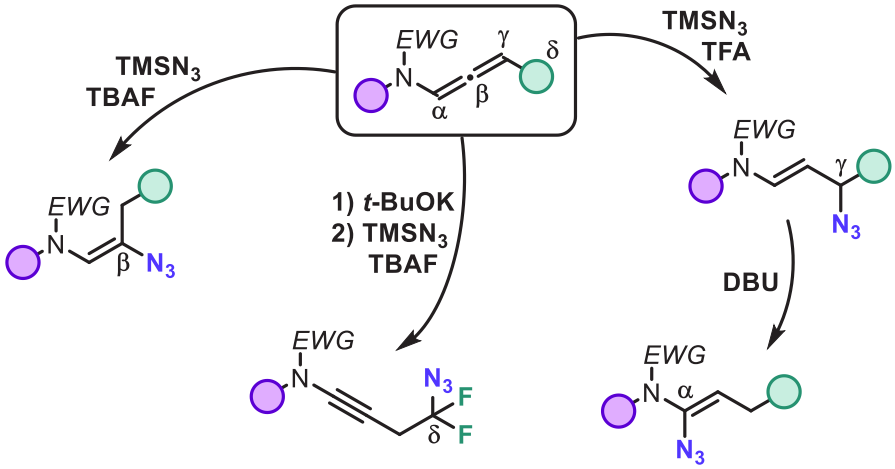
Dorian Schutz[‡], Maxime Hourtoule[‡], Laurence Miesch*

Équipe de Synthèse Organique et Phytochimie, Université de Strasbourg, CNRS-UdS UMR 7177, 4 rue Blaise Pascal CS 90032, 67081 Strasbourg, France

dorian.schutz@etu.unistra.fr, lmiesch@unistra.fr

Organic azides are versatile synthetic intermediates. Among them, the unique features of vinyl-azides have turned these compounds into critical building blocks for the construction of *N*-heterocycles. The remarkable properties of the azide group connected to an alkene moiety allow this functional group to act as an electrophile, an enamine-type nucleophile or a radical acceptor.[1] The multifaced reactivity of these highly versatile synthons have generated a great inspiring variety of intermediates such as iminodiazonium ions, nitrilium ions, iminyl radicals and metal enaminyl radicals upon heating-, metal-or light-induced processes.[2] Following our interest in the preparation of nitrogen-containing building blocks, we envisioned that *N*-allenamides would be ideal candidates to generate vinyl azides.

A totally controlled regiodivergent azidation of activated *N*-allenamides is presented. Using $TMSN_3$/TBAF, β-azidation of *N*-allenamides occurred exclusively, yielding vinyl azides. Conversely, employing a TFA/$TMSN_3$ mixture resulted solely in the formation of γ-azides. A subsequent azide shift of the latter with DBU produced α-amido vinyl azides. Additionally, δ-difluorinated azides featuring an ynamide were selectively synthesized from ene-ynamides.[3]



[1] J. Fu, G. Zanoni, E. A. Anderson, X. Bi, *Chem. Soc. Rev.* **2017**, *46*, 7208–7228.
[2] F. Gholami, F. Yousefnejad, B. Larijani, M. Mahdavi, *RSC Adv.* **2023**, *13*, 990–1018.
[3] D. Schutz, M. Hourtoule, L. Miesch, *Org. Chem. Front.* **2024**, DOI 10.1039/D4QO01802H.

Multi-scale Modeling of Charge, Mass and Heat Transfers in Anion Exchange Membrane Water Electrolysis

Xin SHEN, Laurent Ruhlmann, Antoine Bonnefont and Gaël Maranzana

e-mail: xin.shen@etu.unistra.fr

Abstract

Anion exchange membrane water electrolysis (AEMWE) is a sustainable hydrogen production technology that combines the advantages of proton exchange membrane and traditional alkaline water electrolysis. To optimize its operation, modeling of electrochemical and mass transport processes is essential. However, current studies primarily focus on macroscopic phenomena such as mass transfer, charge transport, and Butler-Volmer equations, while often neglecting the impact of local pH on the electrochemical reaction kinetics at the anode and cathode, which affects overall cell performance.

To address this limitation, we focuses on developing microkinetic models for the hydrogen evolution reaction (HER) at the Ni-based cathode and the oxygen evolution reaction (OER) at the Ni/Fe anode of AEMWE. These models will be coupled with a macroscopic electrolysis model incorporating mass transfer, charge transfer, and heat transfer. The simulations will be validated using experimental data from the Daemonhyc PEPR H2 project. Ultimately, the multiscale model will bridge microscopic and macroscopic scales, providing a deeper understanding of AEMWE processes and predicting optimal operating conditions and parameters.

We performed microkinetic modeling of the hydrogen evolution reaction (HER) on pure Ni metal and partially oxidized Ni electrode surfaces, based on the Heyrovsky and Volmer reaction steps. The model was validated against experimental data obtained from cyclic voltammetry (CV) measurements under pH 13 using a rotating disk electrode, successfully reproducing the experimental CV curves.

For the oxygen evolution reaction (OER), we developed a microkinetic model following the classical four-step reaction mechanism. To determine the optimal reaction parameters, we fitted the model to experimental data collected under varying pH conditions. However, the calculated results failed to consistently match the experimental curves, particularly in capturing the observed pH dependence of the reaction. To address this discrepancy, we decoupled the proton-coupled electron transfer (PCET) step in the typical mechanism into separate proton transfer and electron transfer steps and revised the microkinetic model accordingly. The simulation results, using a single set of reaction parameters, achieved good agreement with experimental curves across multiple pH conditions. This provides further insights into the complex reaction mechanisms underlying the OER process.

Waste to Energy: A step towards circular economy

Akshita Singh[1,2*], Vimal Chandra Srivastava[2,3], Izabela Janowska[1]

[1]Institut de Chimie et Procédés pour l'Énergie, l'Environnement et la Santé (ICPEES), CNRS UMR 7515-University of Strasbourg, 25 Rue Becquerel, 67087, Strasbourg, France
[2]Centre for Nanotechnology, Indian Institute of Technology Roorkee, Roorkee, 247667, India
[3]Department of Chemical Engineering, Indian Institute of Technology Roorkee, Roorkee, 247667, India
*Email: akshita.singh@etu.unistra.fr

Abstract: The World Bank's alarming estimate that biomass waste, industrial garbage, plastic garbage, and electronic waste make up over 60% of global waste production is a stark reminder of the urgent need for action (What a Waste 2.0. (2018)). One of the effective ways to address this crisis is to establish a circular economy and utilize these bulk wastes in the most pressing field today. While environmental preservation has become a global priority, the demand for sustainable energy, particularly high-capacity energy storage and portable backup power, is growing rapidly in the expanding electronic industries. Supercapacitors have the potential to serve as an energy source in hybrid vehicles, power grids, military industry, wind turbines, rail transit, etc.; however, they have not been incorporated to the full extent due to various limitations. In light of the fact that mankind is actively seeking out solutions for cleaner energy, the need of the hour is to augment the current research level for unfolding ways of waste utilization in the development of this device (Figure 1). Therefore, they must be subjected to thorough research, and in fulfilling this purpose, waste-derived materials like activated carbon, graphene, metal oxides, and their composites for supercapacitor electrodes are found to be very promising. The presented work consists utilization of carbon-black manufacturing industry waste and biomass waste for deriving suitable materials, along with their electrochemical performance analysis as supercapacitor electrodes (Singh et al., 2024).

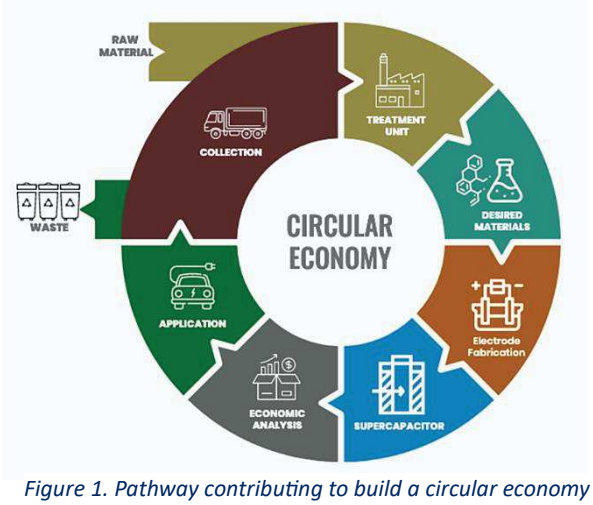


Figure 1. Pathway contributing to build a circular economy

Keywords: Waste to energy, Supercapacitor, Circular Economy, Sustainability

References

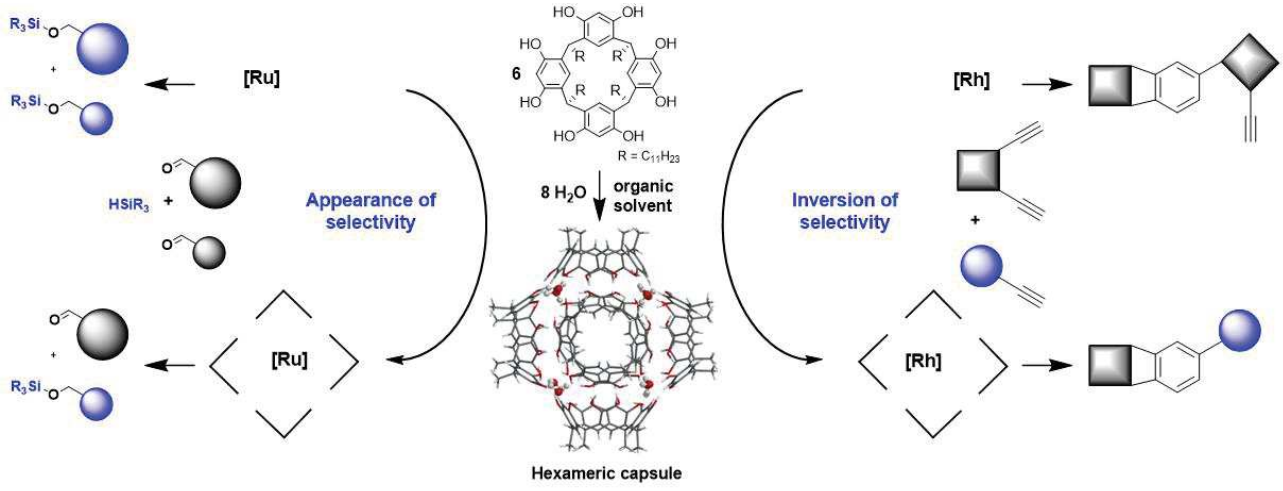
- Kaza, Silpa, et al. *What a waste 2.0: a global snapshot of solid waste management to 2050*. World Bank Publications, 2018.
- Singh, Akshita, Vimal Chandra Srivastava, and Izabela Janowska. "Utilization of carbon-black industry waste to synthesize electrode material for supercapacitors." *Energy Storage* 6.5 (2024): e677.

Encapsulated Cationic Ruthenium and Rhodium Catalysts: Controlling The Catalytic Outcome By Confinement

M. Steinmetz, D. Sémeril

Laboratoire de Synthèse Organométallique et Catalyse, Université de Strasbourg
4 rue Blaise Pascal, 67008 Strasbourg (France)
maxime.steinmetz@etu.unistra.fr

Catalysis with molecular containers is an emerging field due to its similarity with enzymes.[1] Two ways of making large assemblies exist: *i*) the formation of covalent cages or metallo-capsules but their synthesis require several steps, like in the case of the pallado-trimeric-resorcinarene, previously reported;[2] *ii*) supramolecular assemblies, which are easily achievable like the self-assembled capsule based on 2,8,14,20-tetra-undecyl-resorcin[4]arene discovered by Atwood.[3] By using this hexameric host, two new complexes of ruthenium and rhodium were encapsulated. The formation of inclusion complexes was deduced from UV/Vis and NMR (^{1}H, ^{31}P and DOSY) spectroscopies in the same way as in our previous example based on a neutral ruthenium catalyst.[4] The embedded ruthenium complex was evaluated in the competitive hydrosilylation of mixtures of aldehydes. With the encapsulated catalyst, the smaller aldehyde is converted faster than more sterically hindrance aldehydes. On the other hand, the rhodium complex was used to modify the catalytic outcome of the [2+2+2] cycloaddition. With the unencapsulated catalyst, we mainly observe the formation of the homocycloaddition product, while in the presence of the supramolecular assembly the heterocycloaddition product is favored. These two examples clearly show the benefic role played by the self-assembling capsule, which is able to select a reagent from a mixture of substrates or to modify the nature of the formed products.



[1] a) Bristi, O.; Reinaud, O. *Org. Biomol. Chem.* 2015*, 13*, 2849-2865; b) Xu J.; Cheng H.; Liang Z.; Chunying D. *Acc. Chem. Res.* 2019*, 52,* 100-109*;* c) Yang J.; Chatelet B.; Hérault D.; Dutasta J.P.; Martinez A. *Eur. J. Org. Chem.* 2018, 5618-5628.

[2] Steinmetz, M.; Schurhammer, R.; Gourlaouen, C.; Sémeril, D. *Molecules* 2024, *29,* 4910-4924.

[3] MacGillivray L.R.; Atwood J.L. *Nature*. 1997, *389*, 469-472.

[4] Hkiri, S.; Steinmetz, M.; Schurhammer, R.; Sémeril, D. *Chem. Eur. J.* 2022, *28*, e202201887.

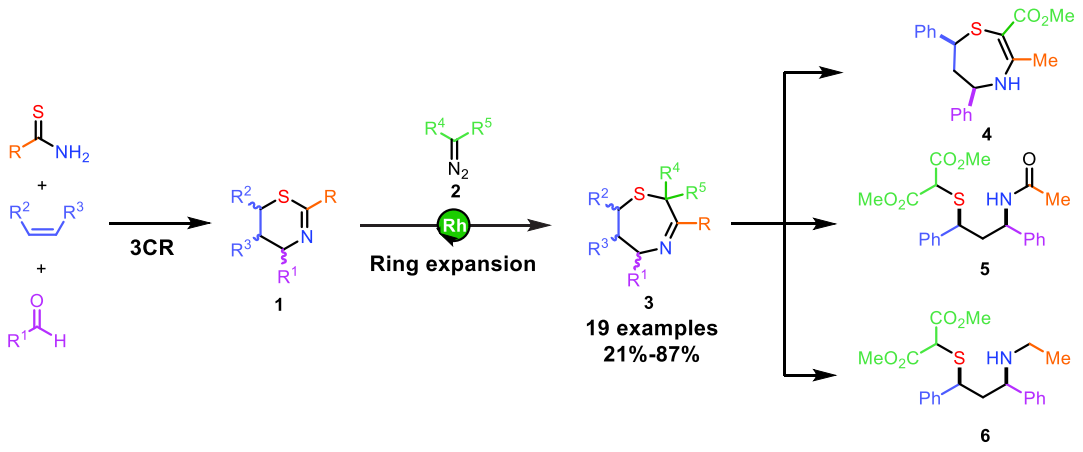
Synthesis of medium-sized *N,S*-heterocycles by rhodium-catalyzed ring expansion

Laurine Tual, Romain Pertschi, Gaëlle Blond and Mihaela Gulea

Laboratoire d'Innovation Thérapeutique – LIT UMR 7200,
Université de Strasbourg, CNRS – 67000 Strasbourg, France
Email : laurine.tual@etu.unistra.fr

The pharmaceutical industry is currently faced with the need for molecular diversity and structural originality to discover new drug candidates. Heterocycles play a key role in the structure of bioactive molecules.[1] Among them, mixed sulfur and nitrogen (*N,S*) heterocycles, especially 5- and 6-membered rings, have demonstrated their interest in medicinal chemistry and pharmaceutical industry (e.g. Amoxicillin, Chlorpromazin).[2] Medium-sized rings are however under-represented due to the difficulty of synthesis. In this context, the development of new synthetic routes is crucial to access complex and original (*N,S*) heterocyclic structures efficiently and in a minimum of steps.

Here we report a ring expansion of 6-membered (*N,S*)-rings leading to new diversified 7-membered (*N,S*) heterocycles. Starting from 1,3-dihydrothiazine precursors **1** obtained *via* a three-component reaction developed by our group,[3] the ring expansion proceeds *via* their reaction with a metallocarbene to yield 1,4-thiazepines **3**. The metallocarbene is generated *in situ* by decomposition of the diazo compound **2** in the presence of a rhodium(II) complex. After optimisation, the scope of the reaction was investigated by varying both the 1,3-dihydrothiazine **1** and the diazo partner **2**. Finally, the reactivity of the 1,4-thiazepines was explored and allowed to obtain new (*N,S*)-heterocycles **4**, amidothioethers **5** and aminothioethers **6**.



[1] R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem*. **2014**, 57, 5845–5859.

[2] a) A. Martinez, C. Gil, in Drug Discovery (Ed.: S. Bräse), Royal Society of Chemistry, Cambridge, **2015**, pp. 231–261. b) K. A. Scott, J. T. Njardarson, *Top Curr Chem* (Z) **2018**, 376, 5. c) E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem*. **2014**, 57, 2832–2842.

[3] F. Peudru, R. Legay, J.-F. Lohier, V. Reboul, M. Gulea, *Tetrahedron* **2012**, 68, 9016–9022.

Photoallergic contact dermatitis: a novel EPR approach to assess xenobiotic-mediated radicals in UV exposed skin

UMR 7177 Laboratoire POMAM
Guillaume Voegeli

Photoallergic contact dermatitis (PACD) is a common disease caused by the activation of the immune system after repeated contact of the skin with xenobiotics that are activated under sunlight exposure (UVA/B and or visible light). PACD occurs via two phases: (i) an initial sensitization phase produced after first contact with the chemical and (ii) an elicitation clinical phase occurring after new exposure of the individual to the same chemical, leading to eczema, itching, redness and/or swelling[1]. The first key step leading to skin photo-sensitization and further clinical expression of PACD is the binding of the chemical activated by irradiation to a skin protein, forming an antigenic complex that triggers the immune system. There is no treatment for PACD other than symptomatic. When the individual is sensitized to the photo-allergen, it is lifelong. This is why risk assessment of chemicals present in consumer goods continues to be essential to prevent PACD. In this context, understanding the chemical mechanism(s) of action of skin photo-sensitizers is necessary.

Ketoprofen (KP) is a non-steroidal anti-inflammatory drug that can be taken as a tablet or cream for topical use. It is also one of the most common photo-allergens, with numerous clinical cases reported[2,3]. As shown in Figure 1, KP presents a benzophenone (BP) core unit (red) with a side chain attached (blue). Moreover, KP can be at the origin of PACD to other common molecules containing BP units, such as octocrylene (OCT) and oxybenzone (OBZ), both used as UV-filters in sun tanning creams[4]. Indeed, it is often found in the literature that KP cross-reacts with these molecules. Patients sensitized to KP can develop symptoms of PACD when in contact with OCT and/or OBZ for the first time. Understanding how KP reacts in the skin may give insights to understand those cross-reactivities.

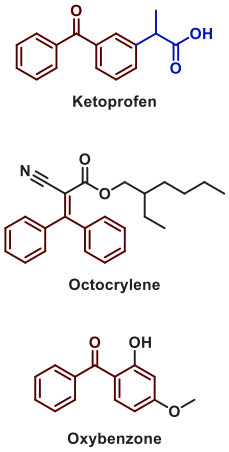


Figure 1: Molecular structures of KP, OCT, OBZ

BP derivatives as KP are thought to become reactive after sun exposure by formation of radical intermediates able to react with skin proteins through radical mechanisms (1+1 electron transfer)[5] although this has never been proved in the skin. To deepen our knowledge and thus help risk assessment procedures, electron paramagnetic resonance studies are carried out to investigate, from the test tube to further use of reconstructed human epidermis 3D models, if radicals are formed from these compounds in the skin.

References:

(1) Kimber, I.; Basketter, D. A.; Gerberick, G. F.; Dearman, R. J. Allergic Contact Dermatitis. *Int. Immunopharmacol.* **2002**, *2* (2), 201–211. https://doi.org/10.1016/S1567-5769(01)00173-4.

(2) Subiabre-Ferrer, D.; Esteve-Martínez, A.; Blasco-Encinas, R.; Sierra-Talamantes, C.; Pérez-Ferriols, A.; Zaragoza-Ninet, V. European Photopatch Test Baseline Series: A 3-year Experience. *Contact Dermatitis* **2019**, *80* (1), 5–8. https://doi.org/10.1111/cod.13118.

(3) Guenther, J.; Johnson, H.; Yu, J.; Adler, B. L. Photoallergic Contact Dermatitis: No Fun in the Sun. *Cutis* **2022**, *110* (5), 241–267. https://doi.org/10.12788/cutis.0651.

(4) Tanahashi, T.; Sasaki, K.; Numata, M.; Matsunaga, K. Three Cases of Photoallergic Contact Dermatitis Induced by the Ultraviolet Absorber Benzophenone That Occurred after Dermatitis Due to Ketoprofen-Investigation of Cosensitization with Other Ultraviolet Absorbers and Patient Background. *J. Cutan. Immunol. Allergy* **2019**, *2* (5), 139–147. https://doi.org/10.1002/cia2.12080.

(5) Nakajima, A.; Tahara, M.; Yoshimura, Y.; Nakazawa, H. Determination of Free Radicals Generated from Light Exposed Ketoprofen. *J. Photochem. Photobiol. Chem.* **2005**, *174* (2), 89–97. https://doi.org/10.1016/j.jphotochem.2005.03.015.

Preparation and optimization of polymer/amino acid-based double network hydrogels for near-infrared light triggered drug release

Shunyu Xiang[1], Chloé Guilbaud-Chéreau[1], Paul Hoschtettler[2], Loïc Stefan[2], Alberto Bianco[1], Cécilia Ménard-Moyon[1*]*

[1]CNRS, Immunology, Immunopathology and Therapeutic Chemistry, UPR 3572, University of Strasbourg, ISIS, 67000 Strasbourg, France

[2]Université de Lorraine, CNRS, LCPM, 54000 Nancy, France

Abstract: The high wettability of amino acid-based supramolecular hydrogels and their compatibility with biological tissues have attracted particular interest in drug delivery. Nevertheless, single amino acid hydrogels typically display weak mechanical properties and long gelation times, hindering their development for biomedical applications. Here, near-infrared (NIR) light-responsive double network (DN) amino acid-based hydrogels, containing different polymers (e.g., polyacrylamide, poly(*N*-isopropylacrylamide), agarose or low-gelling agarose) and photothermal agents were prepared. The hydrogels displayed a high mechanical strength and drug loading capacity. Increasing the concentration of the polymerization initiators significantly reduced the residual amount of acrylamide and *N*-isopropylacrylamide monomers. NMR and Fourier-transform infrared spectroscopy, as well as circular dichroism, proved that the polymers were present in the DN hydrogels and did not affect the self-assembly of the amino acids. Most importantly, adjusting the ratio of the binary amino acid mixture, namely Fmoc-Tyr-OH/Fmoc-Tyr(Bzl)-OH or Fmoc-Phe-OH/Fmoc-Tyr(Bzl)-OH, key constituents of the hydrogels, drastically shortened the gelation time of DN formulations at room and body temperature. Different photothermal agents (e.g., graphene oxide, carbon nanotubes, MoS_2 nanosheets or indocyanine green) and the drug baclofen, considered as the first-line molecule in the treatment of spasticity, were integrated into the DN hydrogels, and the drug release efficiency was evaluated under NIR light irradiation. Rheology and stability studies demonstrated that the different polymers significantly improved the mechanical strength of the amino acid hydrogels while maintaining a good stability in physiological conditions. These studies uncover novel hydrogel formulations with high mechanical strength and resistance, rapid gel formation and efficient NIR light-controlled drug release, providing new opportunities for biomedical applications.

Keywords: Carbon nanomaterials, 2D materials, photothermal agents, self-assembly