

Control of supramolecular architecture by structural variation of self-assembling cyclodextrins

rebecca.churamani@sorbonne-universite.fr

Mickaël Ménand¹, Pierre-Alexandre Driguez², Matthieu Sollogoub¹

¹Sorbonne Université, Institut Parisien de Chimie Moléculaire, 4 place Jussieu, 75005 Paris, France

²Sanofi Vaccines, 13 Quai Jules Guesde, 94400 Vitry-sur-Seine, France

Gene therapy is a crucial scientific field we must further develop, and the Covid-19 crisis only confirms it. Viruses are known to be highly effective genetic material vectors. Among them, the *tobacco mosaic virus* (TMV) whose coat proteins can self-assemble in a cooperative hierarchical co-assembly with RNA, inspired our group to design a synthetic artificial virus based on cyclodextrins (CD).

We synthesized adamantyl-functionalized **CD 1** and demonstrated its ability to self-assemble into a supramolecular polymer. We then showed that **CD 1** could induce transfection of nucleic acids (NA).ⁱ To understand its mode of assembly we studied the **CD 1**/DNA mixture by CryoEM. To our surprise, we found that very long thin fibers were formed. We further proved that they contain many copies of double stranded DNA 18-mer, which are surrounded by self-assembled **CD 1** a structure highly reminiscent of TMV. Amazingly, a slight change of structure of **CD 1** into **CD 2**, where the adamantyl unit is positioned in the center of the cavity induces a drastic modification of the assembly: tubes were obtained instead of fibers. (Fig 1) Currently, we are studying this system and other CD variations with mRNA in terms of shape, size and pH to optimize transfection of mRNA.

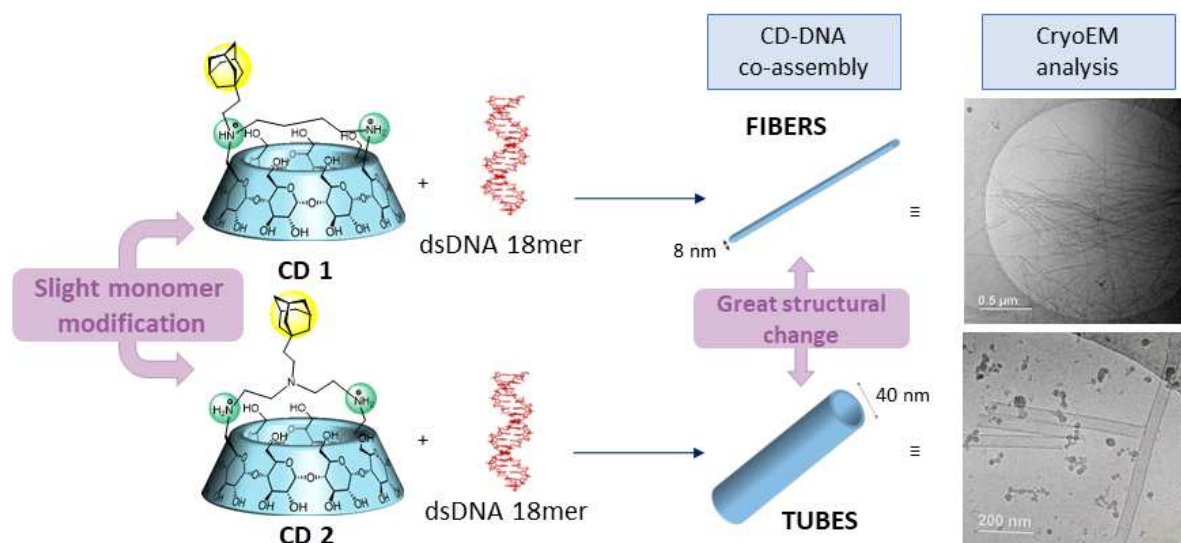


Fig 1 Control of the hierarchical co-assembly architecture built from CD 1 or 2 and double stranded DNA 18-mer

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ⁱ P. Evenou, J. Rossignol, G. Pembouong, A. Gothland, D. Colesnic, R. Barbeyron, S. Rudiuk, A-G. Marcelin, M. Ménand, D. Baigl, V. Calvez, L. Bouteiller, M. Sollogoub, *Angew. Chem. Int. Ed.* **2018**, 57, 7753-7758. PCT/EP2016/070892, 5th September **2016**, WO/2018/041377, 8th March **2018**

Photosensitive Bimetallic Catalyst based on Cyclodextrin

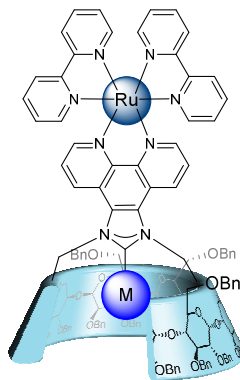
yupeng.fu@sorbonne-universite.fr

Matthieu Sollogoub, Yongmin Zhang, Sylvain Roland

Glycochimie Organique Biologique et Supramoléculaire (GOBS)

4 Place Jussieu, 75005 Paris, couloir 42-43 5ème étage

Bimetallic ruthenium complexes have been developed as photosensitive catalysts along with other transition metals^{1,2}. These types of compounds could be applied in a number of realms, exhibiting promising prospects^{3,4,5}. Previously our group reported series of NHC-modified cyclodextrins (CD) and their steric-selective catalytic effect which derives from the size of CD^{6,7,8,9}. Thus, we assume that the irradiation towards ruthenium and electron communication between ruthenium and transition metal which is connected with through a conjugated bridge may influence the catalytic process of the transition metal center situated inside the CD cavity. In this project, we want to combine the photosensitivity of ruthenium complexes and the steric selectivity of the CD, synthesizing complexes to evaluate how irradiation, CD size and electron communication influence the catalytic process of transition metals.



Scheme: Module molecule

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Selective C-H Functionalization at C3, C4 and C5 of furfural and HMF

alessia.mori@sorbonne-universite.fr

Dr. Julie Oble

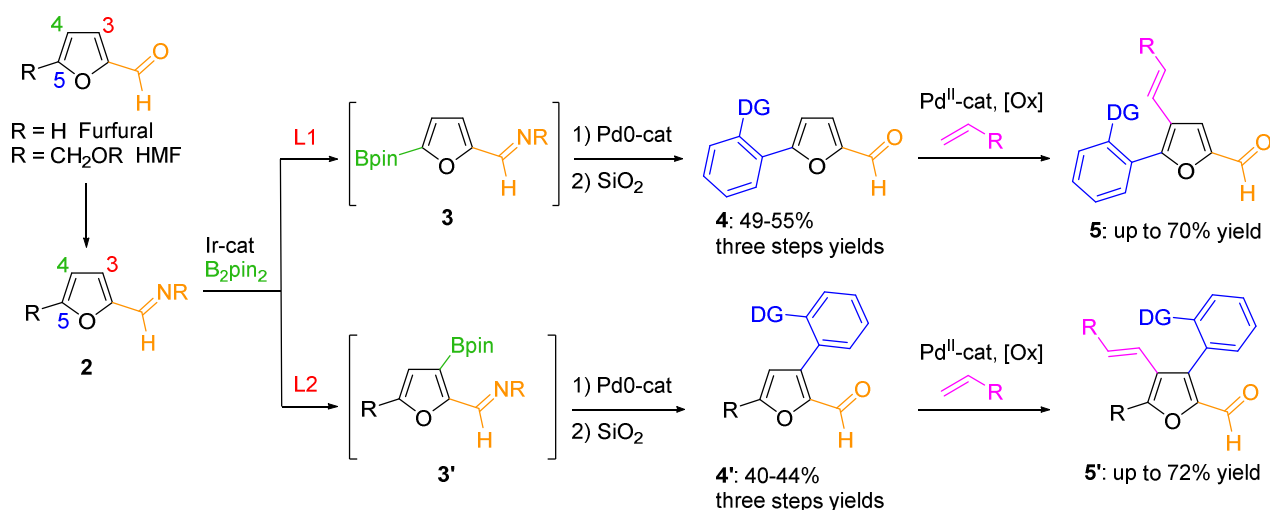
Equipe ROCS - IPCM – Sorbonne Université, 75005 Paris – France

Furfural and 5-hydroxymethylfurfural (HMF) are promising renewable products derived from lignocellulosic biomass, which are raw materials for sustainable production of high value-added chemicals. Their selective functionalization is currently an emerging field and subject of many research efforts.¹ A special quest for stabilizing substituents at C3 and/or C4 positions of furanic platforms is essential to improve chemical and thermal stability of the furanic core.

C3–H borylation was only reported on C5-substituted furfural derivatives to overpass the natural selectivity for the C–H bond α to the oxygen atom.² We developed a method to achieve a ligand-control selective borylation at C3 or C5 position of non-substituted furfural **1** by transition metal-catalyzed C–H activation exploiting the aldehyde function to install an imine as directing/protecting group. This strategy provide access to borylated reagents (**3** and **3'**) with high versatility that can be used *in situ* as nucleophilic partners in Suzuki-Miyaura cross-coupling reactions affording ortho substituted heterobiaryl compounds (**4** and **4'**) after removal of the imine group.

Finally, the installation of a second directing group in *ortho* of the new aryl moiety both in position C5 or C3 open the path for transition-metal-catalyzed C4-H functionalizations, such as Fujiwara-Moritani olefination, with the formation of **5** and **5'** from moderate to good yields.³

This C3/C4-H functionalization strategy is compatible with the employment of suitably protected HMF as starting material, providing the synthesis of the first example of tetrasubstituted furaldehyde.



Scheme 1. C5/C4-H or C3/C4-H functionalization of furfural and HMF

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Novel hydrogel-modified electrode for improvement bio-receptors immobilization and electrochemical detection of emerging pollutants

jie.sun@chimieparistech.psl.eu

PhD advisor(s): Cyrine SLIM, Sophie GRIVEAU, Yvette TRAN

¹Institute of Chemistry for Life and Health Sciences (i-CLeHS); SEISAD group; Chimie ParisTech, 11 Rue Pierre et Marie Curie, 75005, Paris

Although diclofenac (DCF), belongs to the most frequently detected pharmaceutically active compounds in the water-cycle¹ and can cause critical side effects, until now, DCF detection mostly rely on conventional techniques, such as HPLC-MS and GC/MS². These analytical techniques are time-consuming, expensive, and require experts. Overcoming these limitations, electrochemical biosensors for the detection of environmental pollutants have received considerable attention in recent years³, especially in trace level contaminants detection within different matrices, such as in natural and treated water samples. Electrochemical biosensors are attractive owing to their advantage of simple configurations, low cost, high sensitivity, and selectivity. Thus, engineering the bio-electrochemical sensing interface is crucial for further improving specific performance especially the bioreceptor immobilization procedure which remains one of the technological bottlenecks that critically affect the efficiency of biosensors. Additionally, cheap electrode materials exploitation, such as carbon, is appealing for the conception of low-cost sensing surface. Our work is thus oriented towards the conception of hydrogel-modified carbon electrodes for the stable covalent immobilization of aptamers as bio-element and application of impedimetric aptasensors for the DCF detection in water.

Our strategy is based on the covalent immobilization of aptamers onto surface attached hydrogel, the poly(acrylic acid) (PAA) hydrogel functionalized on carbon electrode. The immobilization of PAA hydrogel onto the carbon surface is based on a two-steps process involving first the carbon surface electrochemical functionalization by thiol groups and then a thiol-ene click chemistry strategy⁴. The hydrogel matrix covalently attached to the surface provides an excellent environment for the aptamer to preserve its active and functional structure. The covalent immobilization of the aptamer is based on the formation of amide bonds *via* the activation of the carboxylic acid groups of the PAA hydrogel thin film. Different steps of electrochemical biosensors fabrication are characterized by cyclic voltammetry (CV), SEM, AFM, ATR-FTIR, and water contact angle (WCA). The preliminary results for the electrochemical biosensors in DCF determination at trace concentration are probed by electrochemical impedance spectroscopy (EIS).

The performance of the designed aptasensor will then be compared to that obtained with a gold surface functionalized sensor using a similar strategy⁵.

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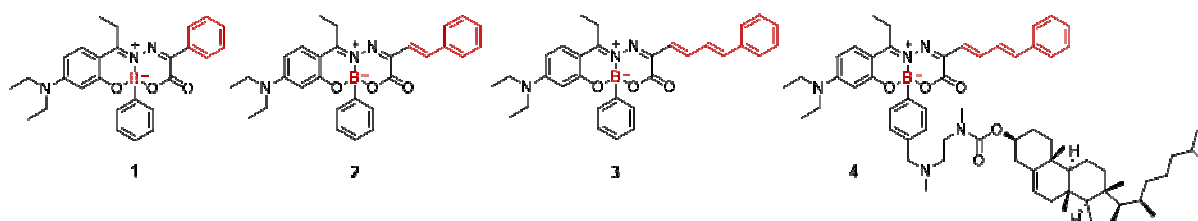
Rationally Designed Lipid Droplet-targeting BASHY Photosensitizers induce Ferroptosis upon Light Irradiation

e-mail address: yiyi.zhang@chimieparistech.psl.eu

PhD advisors: Prof. Gilles Gasser; Dr. Bich-Thuy Doan

Laboratory: Chimie Paristech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, Teams ICB & SEISAD, 75005 Paris

Ferroptosis is an iron-dependent lipid peroxidation-driven mechanism of cell death and a promising therapeutic target to eradicate cancer cells. Photodynamic therapy (PDT) has emerged as a potential strategy to induce ferroptosis selectively in cancer cells. In this study, we developed a series of boronic acid salicylidenehydrazone (BASHY) dyes as photosensitizers (PSs) for PDT-mediated ferroptosis. The dyes exhibited efficient population of the excited triplet state, generating singlet oxygen. Furthermore, the BASHY dyes showed selective accumulation in lipid droplets (LDs), cytoplasmic organelles rich in lipids, which play a crucial role in cancer cell metabolism. Among the dyes tested, BASHY dye **3** demonstrated the highest phototoxicity against cancer cells, with an IC_{50} of 4.40 nM, and a phototoxicity index (PI) >22,700. Importantly, the accumulation of dye **3** in LDs was found to be essential for its enhanced phototoxicity and induction of ferroptosis. In contrast, a dye variant (dye **4**) with limited LD accumulation showed reduced phototoxicity and ferroptotic cell death. These findings highlight the potential of BASHY dyes, particularly dye **3**, as effective PSs for PDT-induced ferroptosis in cancer cells through targeted lipid peroxidation in LDs.



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Mixed [Anti]Aromaticity unorthodox interactions and topologies

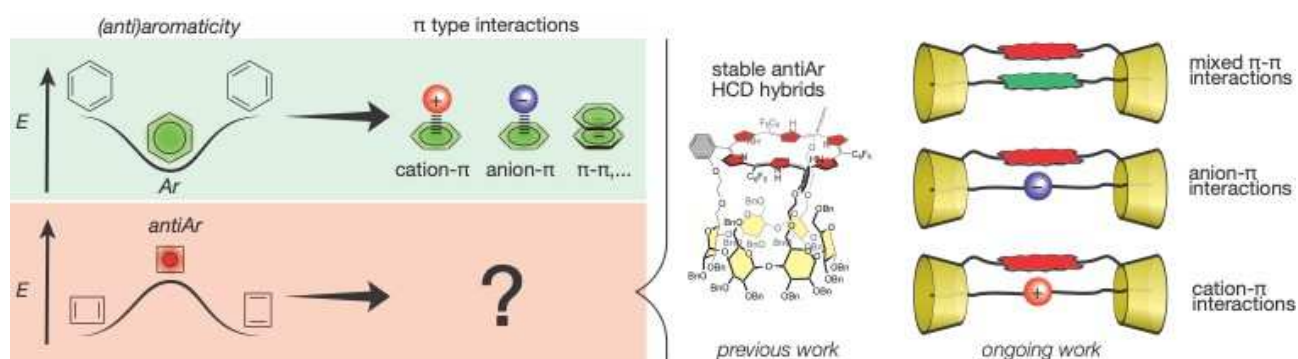
Thanaphon Khruewatthanawet,¹ Alexandre Porcheron,¹ Mathieu Mesnard,¹ Stéphane Le Gac,² and Mickaël Ménand¹

¹ Institut Parisien de Chimie Moléculaire (IPCM), CNRS — UMR 8232, Sorbonne Université, 4 place Jussieu, 75005 Paris, France

² Institut des Sciences Chimiques de Rennes (ISCR), CNRS - UMR 6226, Université de Rennes, 263 Av. Général Leclerc, 35000 Rennes, France

Hückel aromaticity stabilize cyclic molecules containing $[4n+2]$ delocalized π electrons,^[1] leading to several π -type interactions (π stacking, cation- π , anion- π or C-H π) that largely contribute to the development of aromatic compounds in various fields of application.^[2] In contrast, Hückel antiaromaticity destabilize cyclic molecules containing $[4n]$ delocalized π electrons leading to an inherent instability hampering their synthesis.^[3] As a consequence, very little is known on antiaromatic π -type interactions. However, porphyrinoid macrocycles such as norcorrole^[4] or hexaphyrin^[5] are able to stabilize antiaromaticity allowing to explore antiaromatic nanospace^[6] or antiaromatic molecular junction.^[7]

Recently, we also developed hybrid structures made of a cyclodextrin (CD) coupled to an hexaphyrin (H) unit stabilizing both aromatic and antiaromatic states.^[8] We now wish to use these hybrids to study antiaromatic π -type interactions through the design of bis-CD Hexaphyrin hybrids. The corresponding hybrids would allow to bind different guests ((anti)aromatic compounds, cations, anions, ...) and bring them in close proximity with an antiaromatic core affording an efficient tool to study antiaromatic π -type interactions.



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Gold catalysis under visible light

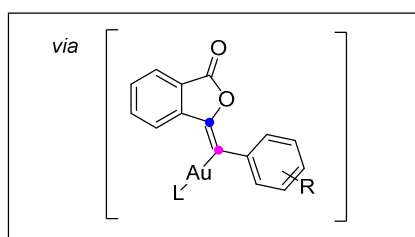
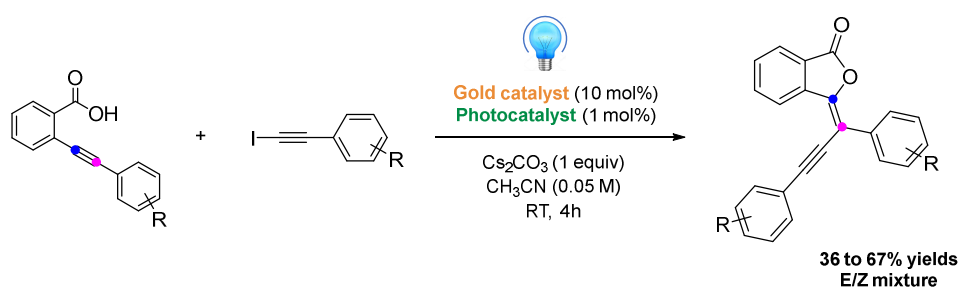
maria.ballarin_marion@sorbonne-universite.fr

PhD advisor(s): Louis Fensterbank, Virginie Mouriès-Mansuy, Cyril Ollivier

Laboratory: Institut Parisien de Chimie Moléculaire (team MACO)

Gold(I) catalysis is an efficient method of activating π -bonds and generally leads to products resulting from the protodeauration of the organogold intermediate. In situ post-functionalization of the organogold intermediate is desirable, for instance via cross-coupling reactions. This implies a Au(I)/Au(III) cycle which is difficult to establish as Au(I) complexes are remarkably reluctant to oxidative additions due to the high redox potential of the Au(III)/Au(I) couple ($E^0 = 1.41$ V). In 2019, our team developed a new type of dual catalysis (gold/photocatalysis) that involves energy transfer from an excited iridium photocatalyst to the vinylgold intermediate to form *o*-alkynylbenzofurans.¹ More recently, we synthesized 2,3-disubstituted indoles from *o*-alkynyl anilines via photosensitization of the vinylgold intermediate in the absence of a photocatalyst, thanks to the emissive properties of the potassium sulfonide amide aggregates formed in situ.²

Here, we have applied this dual gold/photocatalysis to *o*-alkynyl benzoic acids, which readily form disubstituted isobenzofuranones *via* the 5-exo dig cyclization pathway. In this case, the triplet state of the ruthenium photocatalyst triggers by energy transfer the excitation of the vinylgold intermediate, which is able now to undergo oxidative addition of the alkynyl iodide.



Acknowledgments:

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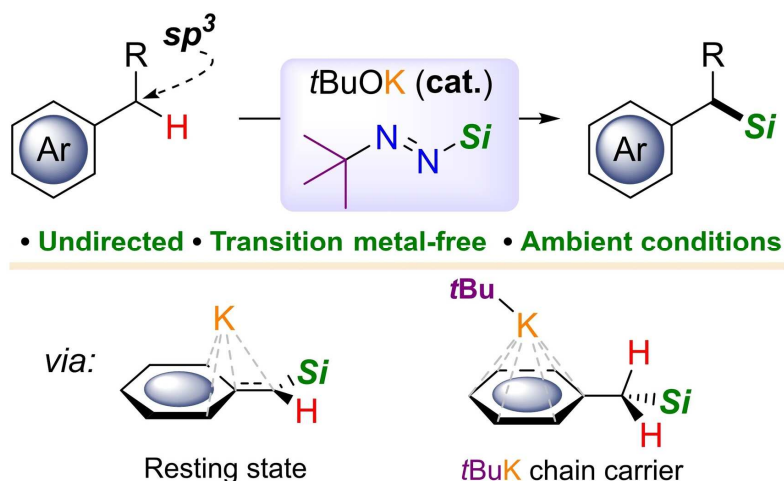
Organopotassium-Catalyzed Silylation of Benzylic C(sp³)-H Bonds

baptiste.neil@sorbonne-universite.fr

PhD advisor: Clément Chauvier

Laboratory: MACO Team, IPCM, 4 Place Jussieu, Paris.

Benzylsilanes have found increasing applications in organic synthesis as bench-stable synthetic intermediates, yet are mostly produced by stoichiometric procedures. Catalytic alternatives based on the atom-economical silylation of benzylic C(sp³)-H bonds remain scarcely available as specialized directing groups and catalytic systems are needed to outcompete the kinetically-favored silylation of C(sp²)-H bonds. Herein¹, we describe the first general and catalytic-in-metal undirected silylation of benzylic C(sp³)-H bonds under ambient, transition metal-free conditions using stable *tert*-butyl-substituted silyldiazenes (tBu-N=N-SiR₃) as silicon source. The high activity and selectivity of the catalytic system, exemplified by the preparation of various mono- or *gem*-bis benzyl(di)silanes, originates from the facile generation of organopotassium reagents, including *tert*-butylpotassium.



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TURNING REGIOSELECTIVITY TO PSEUDO-ENANTIOMERY: ASYMMETRIC SHAPING OF CYCLODEXTRIN CAVITIES

clara.testard@sorbonne-universite.fr

PhD advisor(s): Matthieu Sollogoub & Yongmin Zhang

Laboratory: Institut Parisien de Chimie Moléculaire, Sorbonne Université, 4 place Jussieu, 75005 Paris, FRANCE

Building only from a pool of L-amino acids, Nature makes proteins capable of great enantio-discrimination. Following a precise folding scheme, the asymmetric shape of the active site is dictated by the 3D-positioning of amino-acids relative to one another. As organic chemists, can we build a similar system using only D-sugars such as cyclodextrins (CDs) and achieve shape-directed enantio-discrimination ?

Our group previously developed NHC-bridged CDs that complex transition metals inside their cavity.ⁱ These complexes are active in catalysis, with interesting chemo-, regio-, and stereo selectivities.^{ii,iii,iv} We found that the 2-point bridging of a CD induce a helicoidal distortion of its cavity into an M-helix, that accounts for the observed selectivities. However, only the distortion into an M-helix is accessible from this functionalization pattern, and no control over the catalysis stereoselectivity was possible. Pushing the concept forward, we want to gain control over the distortion of the cavity and access pseudo-enantiomeric shaped cavities from 3-point bridging.

Based on known synthetic methodologies from our team, we now propose the synthesis of 2 regioisomers with mirror-image anchoring patterns using tripodal moieties such as tren groups (**Figure 1**). Delightfully, we found that corresponding Cu(II) complexes of those regioisomers behave like enantiomers, as observed from the opposite circular dichroism spectra. Furthermore, we performed the UV-vis titration of each enantiomer of a pair of a chiral carboxylate with both regioisomers and found opposite enantioselectivities thus proving the efficiency of those compounds for chiral recognition in water.

Future goals include to further characterize the Cu^{II}-complexes of tren-bridged CDs and assess their enantioselectivity towards a larger panel of chiral guests. Additionally, crystal structures and molecular modeling should give more insight on the relationship between the shape of the cavity and the chiral recognition properties.

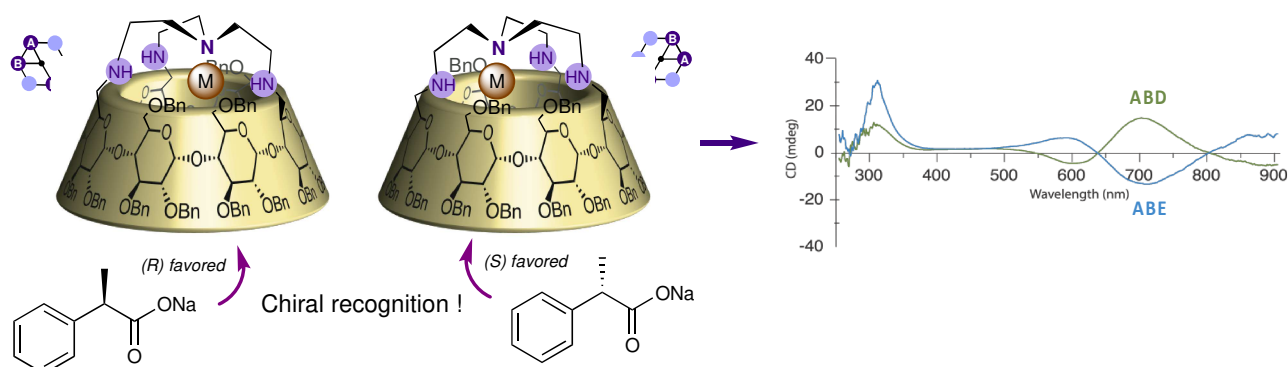


Figure 1. Schematic representation of tren-bridged CD regioisomers, the circular dichroism spectra of the corresponding copper acetate complexes, and their enantioselectivity towards chiral carboxylate.

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Graphene-based quantum dots as new generation of theranostic agents

e-mail address: zhihang.zhang@chimieparistech.psl.eu

PhD advisor(s): Anne VARENNE, Laura TRAPIELLA, Bich-Thuy DOAN, Fanny d'Orlyé

Laboratory: SEISAD, 11 rue pierre&Marie curie, 75005 paris, France

Due to their biocompatibility and photostability, carbon-based nanomaterials, such as the emergent graphene quantum dots (GQDs), are gaining increasing attention in the biomedical field.ⁱ⁻ⁱⁱⁱ The properties of GQDs are dependent on many factors (size, edge effects, functional groups at the surface, synthetic precursors, etc.). A greater understanding of the structure-property relationship can be attained by optimizing the synthetic process, undertaking a rational study under different conditions, and performing an exhaustive and in-depth characterization of the nanomaterial. Herein, we explored and optimized the methods of synthesizing GQDs via microwave-assisted processes using citric acid as the precursor.^{iv, v} After that, an exhaustive characterization has been made using conventional methods such as UV-Vis (UV), Dynamic light scattering (DLS), fluorescence spectrophotometry (FL), and new methodologies based on capillary electrophoresis.^{vi} In this sense, we have developed an electrokinetic method to help in the optimization of the synthetic process thanks to the possibility offered by this separation method to visualize the number of populations of nanomaterial synthesized as well as the polydispersity and the yield of conversion. . . However, one of the weaknesses of GQDs is their reduced spectral window (UV-VIS), which may restrict their applications. To elucidate and expand this spectral window, the surface properties of GQDs can be modified,^{vii} which could drastically alter their electronic characteristics and offer more active sites, thus producing new phenomena and unexpected properties. We are currently affording this step of GQDs modification by heteroatom doping (expanding the optical window and properties) and going further towards potential biomedical applications^{viii} by doing the surface functionalization with specific recognition ligands allowing for the development of in vitro assays and/or cell targeting.

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