Geneva chemistry & biochemistry days 2018

TH 18 January 2018, 09:00–17:00
FR 19 January 2018, 09:00–12:00
Sciences II – Auditoire A300 – quai Ernest-Ansermet 30 – 1205 Genève
No registration required

Prof. Ben Feringa
Rijksuniversiteit Groningen – Nobel Prize in Chemistry 2016

Prof. Laura Gagliardi
University of Minnesota

Prof. Bruno Lemaitre
École Polytechnique Fédérale de Lausanne

Prof. Luis Liz-Marzán
CIC biomaGUNE, San Sebastián | Ikerbasque, Bilbao

Junior speakers:

Sebastian Benz • Marta Brucka • Tianchi Cao • Nicolas Chuard • Ilaria Di Meglio • Nicolas Ecker • Léo Egger • Alexandre Homberg • Svilen Kozhuharov • Jorge Larios • Martin Magg • Hetty Manenschijn • Ciro Romano • Jacques Saarbach • Alexander Zech •

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FACULTÉ DES SCIENCES
SECTION DE CHIMIE ET BIOCHIMIE

UNIVERSITÉ DE GENÈVE

FOREWORD

The *Section de chimie et biochimie*, University of Geneva, has the pleasure to announce the 8th edition of its "***Geneva Chemistry & Biochemistry Days***".

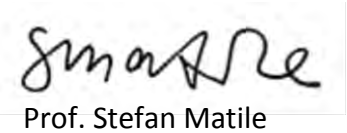
The vocation of the event is to give our students who are close to finishing their PhD studies the opportunity to present their research as short talks to an audience from academia and industry, and the steering committee is glad to welcome you in this context.

Four distinguished lecturers, amongst whom the Nobel Prize in Chemistry 2016, further enrich the programme. Our four departments have invited them, and they will illustrate the extent and the quality of top-level fundamental research in chemistry and biochemistry today.

Our BSc and MSc students are welcome to smell the very flavour of the research held in our School and abroad, and to learn a bit more about how to present results to a scientific audience.

We expect that the event will catalyse fruitful discussions between young and advanced researchers, and give our students an opportunity to get ready for their professional careers, yet offering our guests an overview of the quality of the fundamental research performed in our School.

Looking forward to meeting you at this event, we hope that you will enjoy the lectures and interactions!



Prof. Stefan Matile
Président de la Section de chimie et biochimie

Steering and organising committee

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Dr Didier Perret	didier.perret@unige.ch *Chargé de communication – Section de chimie et biochimie*

PROGRAMME – THURSDAY, 18 JANUARY

Senior chairman: **Prof. Michal Borkovec**
Junior chairwoman: **Prof. Charlotte Aumeier**

09:00--09:05	**Prof. Stefan Matile**	Welcome message
09:05--09:50	**Prof. Luis Liz-Marzán** CIC biomaGUNE + Ikerbasque	Chemistry and spectroscopy of noble metals at the nanoscale
09:50--10:10	**Ciro Romano**	Remote refunctionalizations by long-range isomerization of olefins
10:10--10:30	**Hetty Manenschijn**	The contribution of monomeric myosin motors to endocytic membrane bending
10:30--10:50	Coffee break Main hall of Sciences III	
10:50--11:10	**Léo Egger**	Synthesis of dioxepines, spiro ketals and pyrrolidines by CpRu-catalyzed decomposition of α-diazo-β-ketoesters
11:10--11:30	**Alexander Zech**	Modelling excited states in complex environments
11:30--11:50	**Marta Brucka**	Highly resolved pure shift 2D NMR experiments for fast spectral assignment
11:50--14:00	Lunch and photo (speakers + chairmen/women + steering committee) Restaurant *la Cantine des Commerçants*, boulevard Carl-Vogt	

Senior chairman: **Prof. Clément Mazet**
Junior chairman: **Dr Tatu Kumpulainen**

14:00--14:20	**Nicolas Ecker**	A phase-field approach for studying actin-wave driven cell migration
14:20--14:40	**Alexandre Homberg**	Synthesis and applications of chiral polyether macrocycles
14:40--15:00	**Tianchi Cao**	Heteroaggregation of oppositely charged particles in the presence of multivalent ions
15:00--15:20	Coffee break Main hall of Sciences III	
15:20--15:40	**Jorge Larios**	Endosomal recruitment of ESCRTs induced by the lipid-binding protein ALIX
15:40--16:00	**Sebastian Benz**	σ Holes in action for transport and catalysis
16:00--16:45	**Prof. Ben Feringa** Rijksuniversiteit Groningen	The art of building small
16:45-	*Verre de l'amitié* Main hall of Sciences III	

PROGRAMME – FRIDAY, 19 JANUARY

Senior chairmen: **Prof. Tomasz Wesolowski, Prof. Aurélien Roux**

Junior chairman: **Dr Gregor Trefalt**

08:30--09:15	**Prof. Laura Gagliardi** University of Minnesota	Computationally guided discovery of metal-decorated metal-organic frameworks active for catalysis
09:15--10:05	**Jacques Saarbach**	Kinase template abiotic reaction
10:05--10:25	**Ilaria Di Meglio**	Epithelial cell division under 3D constraint
10:25--10:45	**Svilen Kozhuharov**	Probing and manipulating polymer properties on the single molecule level
10:45--11:05	Coffee break Main hall of Sciences III	
11:05--11:25	**Martin Magg**	Raman optical activity of singe-walled carbon nanotube enantiomers
11:25--11:45	**Nicolas Chuard**	Strain-promoted thiol-mediated uptake: From disulfides to diselenides
11:45--12:30	**Prof. Bruno Lemaitre** École Polytechnique Fédérale de Lausanne	The foreign within: *Drosophila-Spiroplasma* interaction as a model of insect endosymbiosis
12:30--12:35	**Prof. Eric Vauthey**	Award of the best oral presentation
12:35--12:40	**Prof. Stefan Matile**	Concluding remark

The art of building small

Ben L. FERINGA – Nobel Prize in Chemistry 2016

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The fascinating molecular motors and machines that sustain life offer a great source of inspiration to the molecular explorer at the nanoscale. Among the major challenges ahead in the design of complex artificial molecular systems is the control over dynamic functions and responsive far-from-equilibrium behaviour. Chemical systems ultimately require integration of structure, organization and function of multi-component dynamic molecular assemblies at different hierarchical levels. A major goal is to achieve and exploit translational and rotary motion.

In this presentation, the focus is on the dynamics of functional molecular systems as well as triggering and assembly processes. We design switches and motors in which molecular motion is coupled to specific functions. Responsive behaviour will be illustrated in self-assembly and photopharmacology. The design, synthesis and functioning of rotary molecular motors will also be presented with a prospect toward future dynamic molecular systems.

References:

1. Information on http://benferinga.com.
2. Molecular Machines: *Nature* **September 2015**.
3. Molecular Switches: *Chemistry World* **June 2016**.

Computationally guided discovery of metal-decorated metal–organic frameworks active for catalysis

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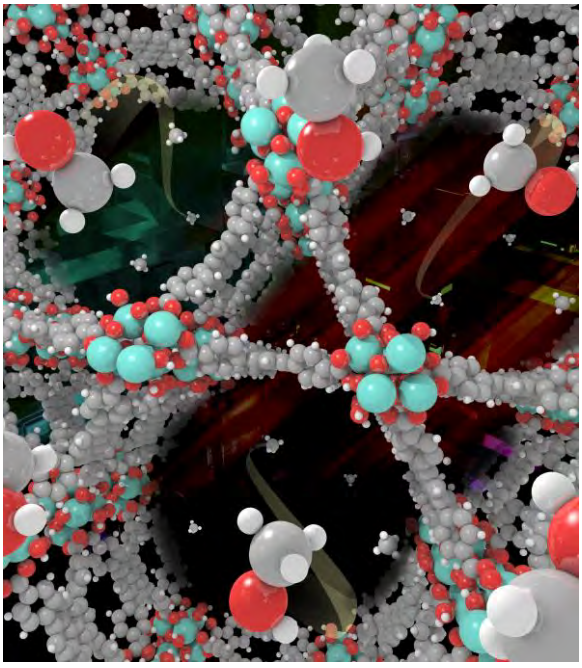
Metal-organic frameworks (MOFs) are attracting the attention of many scientists because of their high selectivity in gas separations, catalytic activity, and magnetic properties. We have combined theory and experiment to understand the activity of nickel, cobalt, and rhodium catalysts supported on Zr_6 nodes in metal–organic frameworks (MOFs) for reactions related to natural gas manipulation. For Ni and Co[1,2], computational studies provide important insights with respect to the catalytic mechanism(s) for observed ethylene dimerization after metal-decoration of the MOF NU-1000. Rh complexes have been installed on the Zr_6 nodes of not only NU-1000, but also the related metal–organic framework UiO-67, and the zeolite DAY; influences of the supports on ethylene hydrogenation and dimerization have been assessed[3]. A library of transition metals (TMs), ranging from first row TMs to noble metals, is now being screened computationally to search for optimal catalysts, and structure-function relationships are beginning to emerge from this theory-driven approach[4].



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2. Ye J., Gagliardi L., Cramer C.J., Truhlar D.G. *J. Catal.* **2017**, *354*, 278.
3. Bernales V., Yang D., Yu J., Gümüşlü G., Cramer C.J.,Gates B.C., Gagliardi L. *ACS Appl. Mater. Interfaces* **2017**. DOI: 10.1021/acsami.7b03858.
4. Simons M.C., Ortuño M.A., Bernales V., Cramer C.J., Bhan A., Gagliardi L. *submitted* **2017**.

The foreign within: *Drosophila-Spiroplasma* interaction as a model of insect endosymbiosis

Bruno LEMAITRE

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Virtually every species of insect harbors facultative bacterial endosymbionts that are transmitted from females to their offspring, often in the egg cytoplasm. These symbionts play crucial roles in the biology of their hosts. Many manipulate host reproduction in order to spread within host populations. Others increase the fitness of their hosts under certain conditions. For example, increasing tolerance to heat or protecting their hosts against natural enemies. Over the past decade, our understanding of insect endosymbionts has shifted from seeing them as fascinating oddities to being ubiquitous and central to the biology of their hosts, including many of high economic and medical importance. However, in spite of growing interest in endosymbionts, very little is known about the molecular mechanisms underlying most endosymbiont-insect interactions. For instance, the basis of the main phenotypes caused by endosymbionts, including diverse reproductive manipulations or symbiont-protective immunity, remains largely enigmatic. To fill this gap, we are dissecting the interaction between *Drosophila* and its native endosymbiont *Spiroplasma poulsonii*. This project will use a broad range of approaches ranging from molecular genetic to genomics to dissect the molecular mechanisms underlying key features of the symbiosis, including vertical transmission, male killing, regulation of symbiont growth, and symbiont-mediated protection against parasitic wasps. We believe that the fundamental knowledge generated on the *Drosophila-Spiroplasma* interaction will serve as a paradigm for other endosymbiont-insect interactions (ex. Wolbachia) that are less amenable to genetic studies.

Chemistry and spectroscopy of noble metals at the nanoscale

Luis M. LIZ-MARZÁN

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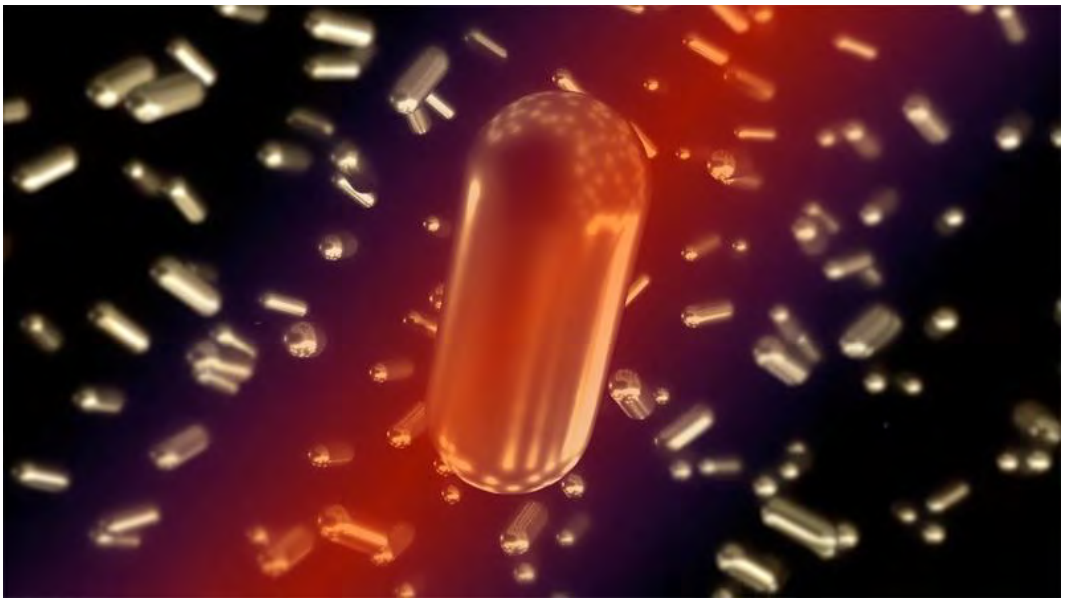
The response of noble metals to light changes dramatically when the size of the metal particles is reduced to the nanometer scale. The interaction of light with conduction electrons then results in coherent oscillations that can achieve resonance with certain electromagnetic frequencies. Such phenomena are called localized surface plasmon resonances (LSPRs), and can be finely tuned through the size and morphology of the nanoparticles, so that the whole visible and near-IR ranges can be covered. Exquisitely accurate synthetic methods have been devised toward the growth of metal particles with both spherical and anisotropic geometries, with narrow size distributions. Further tuning of morphological and optical properties can be achieved by post-synthesis chemical transformations, including the growth of sharp branches or the creation of internal holes and gaps, which offer advantageous application, *e.g.* in surface enhanced spectroscopy.

In this talk we shall discuss some ideas regarding the combination of anisotropic seeded growth and chemical transformations in metal nanoparticles, as well as some examples of their effects in different types of optical spectroscopy.



σ Holes in action for transport and catalysis

Sebastian BENZ

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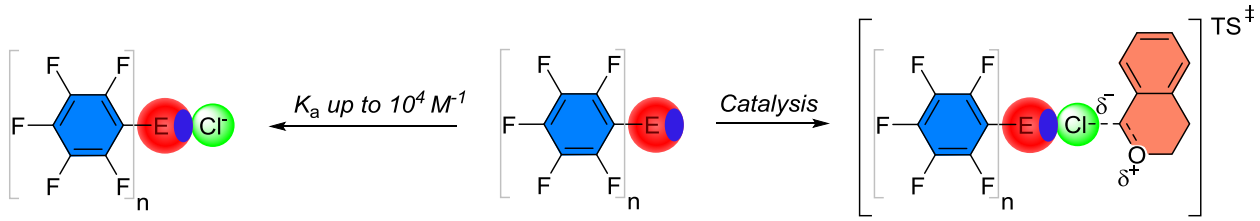
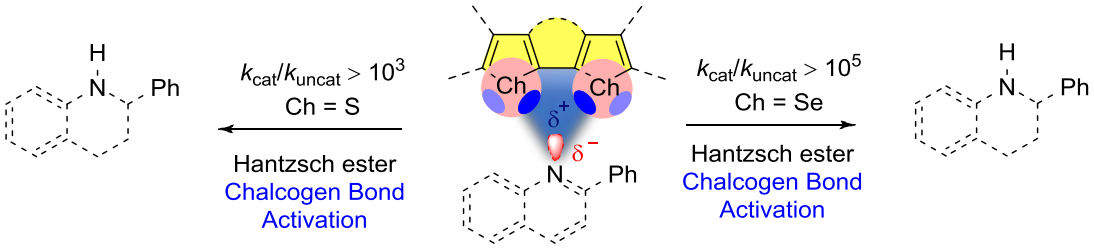
Weak noncovalent interactions are the key to understanding how complex chemical systems can be tailored to realize a specific function. Our most recent efforts geared towards expanding the toolbox of noncovalent interactions resulted in an in-depth study of halogen, chalcogen, pnictogen and tetrel bonds. These bonds arise when electron deficient σ* orbitals on main group elements interact with a lewis-basic partner. Binding of conceptually simple pentafluorophenyl derivatives of Br, I, Se, Te, P, As, Sb, Ge and Sn with Cl^- in solution and correlating activity in halide binding catalysis was studied. Depending on the intrinsic polarizability of the atom and specific geometry, K_a's of up to 10^4 M^{-1} with TBACl in THF were observed together with high catalytic activity.



E = I, Br with n =1
E = Te, Se with n =2
E = Sb, As, Sb with n =3
E = Sn, Ge with n =4

More sophisticated architectures have recently enabled bidentate chalcogen bonding with sulfur-based Dithieno[3,2-b;2',3'-d]thiophenes (DTTs) and their application in transmembrane transport[1] and catalysis[2]. Introduction of more polarizable selenium improved catalytic activity further[3].



Taken together these results showcase the power of organo maingroup born "σ-hole" interactions and predict a bright future for this underappreciated noncovalent interactions in functional systems particularly in catalysis.

References:

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Highly resolved pure shift 2D NMR experiments for fast spectral assignment

Marta BRUCKA

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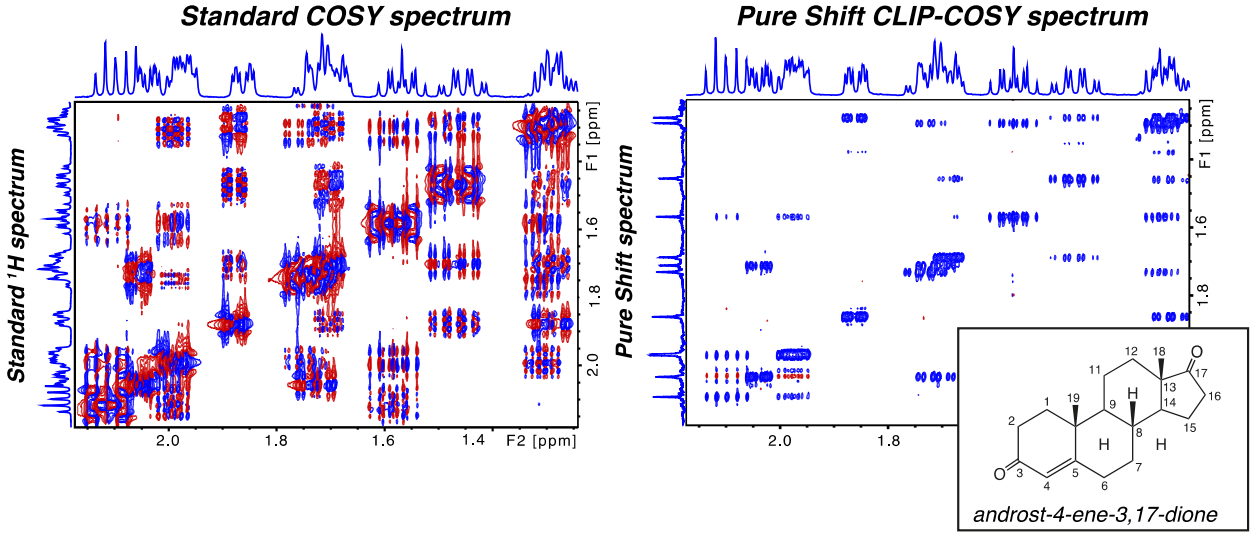
The analysis of complex NMR spectra poses a real challenge for an organic chemist. Simplification and improved resolution of 1D and 2D proton spectra is highly desired to facilitate the spectral analysis hampered by severe signal overlap over a narrow range of chemical shifts. Recent developments in the NMR methodology and in particular the "pure shift" techniques[1] provide an easily applicable solution that should facilitate the efforts of chemists seeking to structurally characterize their compounds.

The presence of the $J_{H,H}$ scalar couplings, even though indispensable for the structure elucidation, causes signal splitting and greatly contributes to the complexity of the spectra. Homonuclear decoupling applied to proton spectra allows to generate "pure shift" spectra where multiplets are reduced to singlets as in ^{13}C 1D spectra.

In order to take advantage of the information carried by the J scalar couplings but at the same time profit from the high resolution ensured by the homonuclear decoupling, we collapse the multiplets only in the indirect (vertical) dimension of various 2D homonuclear experiments: 2D DIAG[2], CLIP-COSY[3] and TOCSY, while preserving the coupling structure in the direct (horizontal) dimension.



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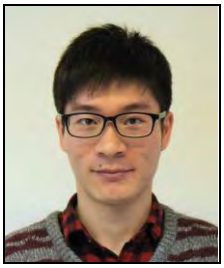
Heteroaggregation of oppositely charged particles in the presence of multivalent ions



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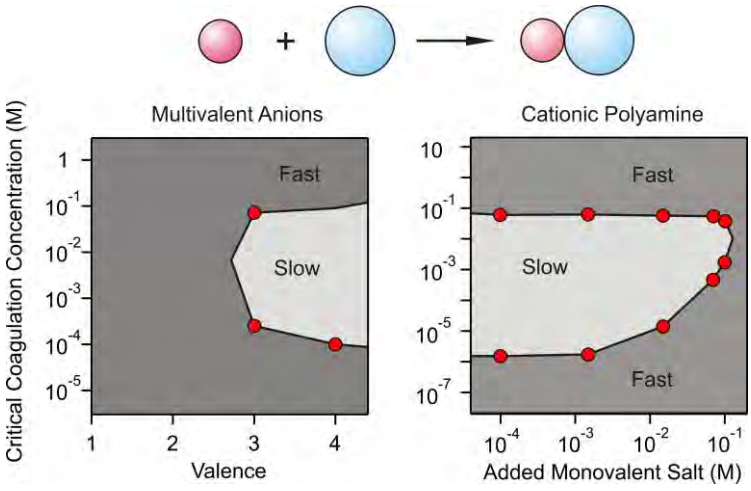
Particle aggregation in colloidal suspensions is an important process in many systems and phenomena, such as papermaking and wastewater treatment. The classical Derjaguin, Landau, Verwey, and Overbeek (DLVO) theory states that the aggregation of particles induced by increasing the salt concentration follows the mechanism of slow and fast aggregation regimes. The transition between these two regimes occurs at a certain concentration, referred to as the critical coagulation concentration (CCC). Particle aggregation can be categorized into homoaggregation and heteroaggregation due to the identity of particles involved. Homoaggregation between the same particles has been well-studied. Researchers already have a reasonably good understanding of homoaggregation by proposing Schulze–Hardy rule and inverse Schulze–Hardy rule[1]. However, heteroaggregation involving particles with different size and properties is understood to a much lesser extent.

In the present work, heteroaggregation processes in the presence of multivalent ions were studied by time-resolved dynamic light scattering for the first time[2]. We investigated here binary suspensions of positively charged amidine and negatively charged sulfate latex particles. The two types of particles are oppositely charged in the presence of monovalent salt. However, in the presence of multivalent ions, the charge of one particle type becomes neutralized and then charge reversal occurs, while the other particle type remains highly charged. In this region, the heteroaggregation stability ratio goes through a maximum when plotted versus concentration. This region of slow heteroaggregation is wider than the one in homoaggregation. Furthermore, the calculated stability ratios for heteroaggregation based on DLVO theory sensitively depend on the boundary conditions used to calculate the double layer force.



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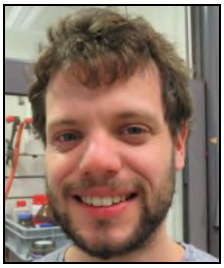
Strain-promoted thiol-mediated uptake: From disulfides to diselenides



Nicolas CHUARD

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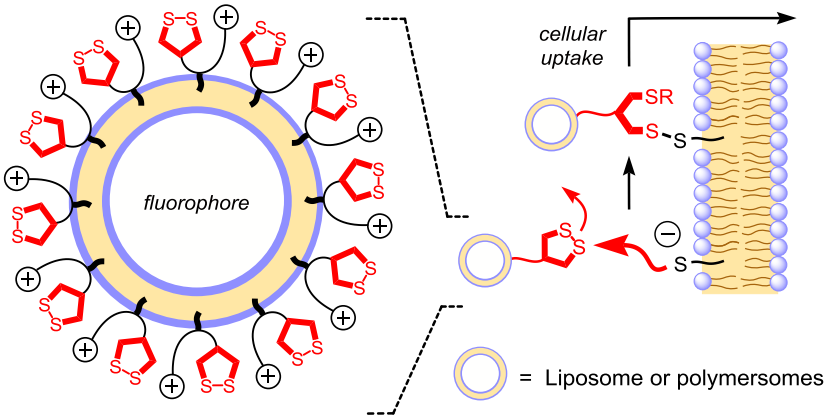
The successful cell delivery of substrates remains one of the main challenges in chemistry and biochemistry. In order to cross the plasma membrane, cell-penetrating peptides (CPPs) and their counterion activators have been extensively studied to deliver efficiently various compounds into cells[1].

Our group has adopted a similar system taking advantage of CPPs entry mechanism, while eliminating their main drawback: cytotoxicity. Cell-penetrating poly(disulfide)s (CPDs) are indeed quickly degraded when they reach the reducing environment of the cytosol[2]. This new transporters are efficiently uptaken by a combination of electrostatic interactions and thiol-mediated uptake.

This uptake mechanism takes advantage of the thiols exposed by proteins at the surface of the cellular membrane to perform disulfide exchange with substrates containing disulfides. Using CPDs or smaller strained cyclic disulfides (SCDs), various compounds have been delivered, from small fluorophores and peptides[3] to quantum dots[4] and entire vesicles[5].



The successful delivery of compounds using SCDs called for a move from sulfur to selenium. The uptake of fluorescent probes linked to diselenolane shows a homogenous staining of the whole cell without organelle specificity except the exclusion of nucleoli[6].

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Epithelial cell division under 3D constraint

Ilaria DI MEGLIO

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From very early on in development, the formation of organs and tissues in all stages of development is characterized by profound changes in the shape and form of tissues. Processes like gastrulation, vilification and neurulation involve invagination of a continuous sheet of epithelial cells that will give rise to the gut and the neural tube of the organism. These and other examples illustrate the physical basis of morphogenesis; tissues must deform, fold and push to give rise to organs of defined shapes and sizes. This change in form, occurring at the tissue level, is due to changes that occur at the cellular level, such as cell proliferation, cell shape changes, cell rearrangement and cell death. These cellular processes will (I) ultimately define the shape of the tissue and (II) give rise to forces that are propagated within and between tissues. Once the tissue has fully formed, cells also encounter a range of different geometrical conditions (such as lower/higher substrate curvature or softer/stiffer substrates). Forces that arise during development and that are present during tissue homeostasis must be tightly regulated, yet our understanding of the mechanisms underlying this regulation remains elusive.

With the goal of better understanding the coupling between mechanical forces and cellular processes, mainly cell proliferation, we are using an *in vitro* model[1,2] consisting of epithelial cells encapsulated inside hydrogel hollow microspheres. The shell constrains the growth of the monolayer and thus allows us to investigate the effect of mechanical forces, such as compression, while the spherical shape allows us to investigate the effect of curvature, on cell growth.

References:

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A phase-field approach for studying actin-wave driven cell migration

Nicolas ECKER

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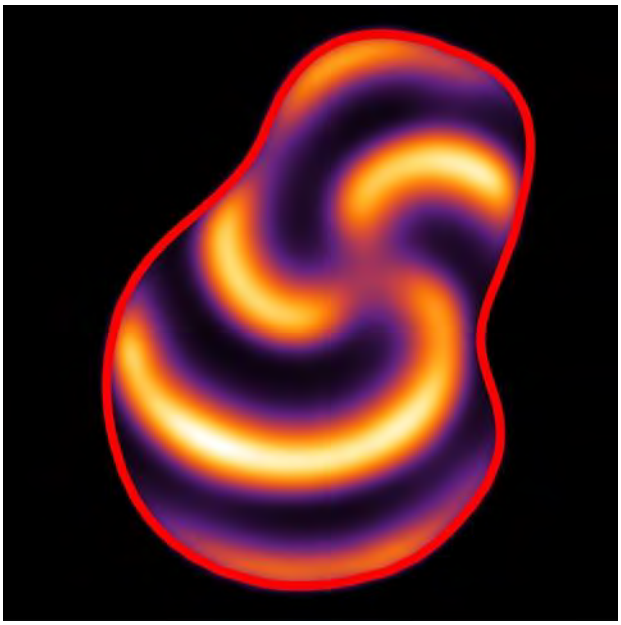
Cells migration is an important part of their search for nutrients, of immunological responses, and of developmental processes among others. It is driven by the actin cytoskeleton a network of actin filaments, molecular motors, and other actin-binding proteins. Although many important factors involved in actin-driven cell motility have been identified and characterized in amazing detail, it is still poorly understood how the network is organized in this process. Spontaneous actin waves have been observed in a large number of different cell types and present an attractive concept to understand orchestration of the cytoskeleton during migration. We introduce a mean-field description of spontaneous actin waves. The actin network is confined to an evolving cellular domain by means of a phase field. We numerically solve the dynamic equations and obtain the corresponding phase diagram. In particular, we find erratic motion due to the formation of spiral waves. We compare these findings to experiments and discuss possible physiological consequences.



Synthesis of dioxepines, spiro ketals and pyrrolidines by CpRu-catalyzed decomposition of α-diazo-β-ketoesters

Léo EGGER

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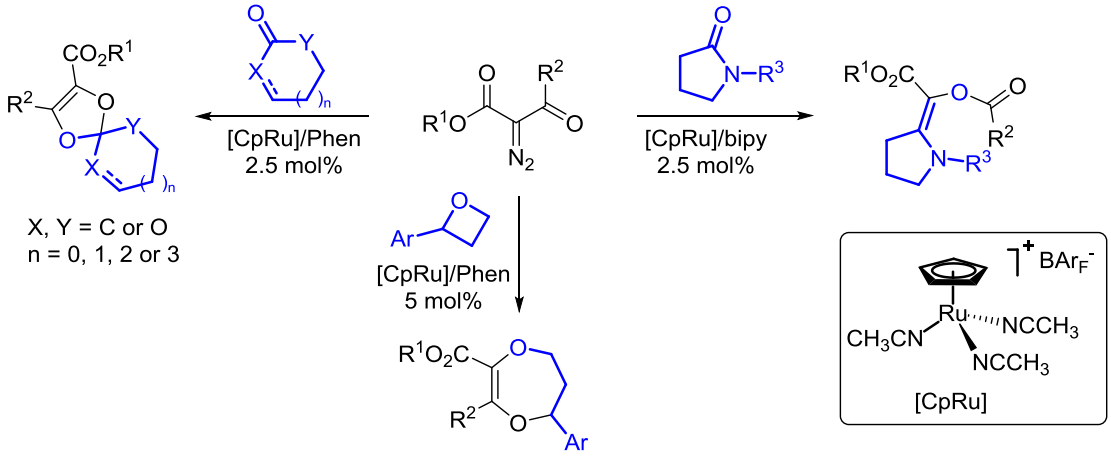
Recently, combinations of [CpRu] and diimine ligands were found to catalyze several types of transformations such as allylic substitutions and Carroll rearrangements among others[1]. These complexes can also promote diazo decompositions; their reactivity being complementary to copper and dirhodium catalysts[2].

Herein, we report that the combination of $[CpRu(CH_3CN)_3][BAr_F]$ and diimine catalyzes the decomposition of α-diazo-β-ketoesters, allowing, in presence of cyclic ketones, lactones and carbonates the formation of spiro bicyclic ketals, orthoesters and orthocarbonates respectively[3]. Interestingly, these reactions seem to be the first examples of intermolecular condensations of electrophilic Fischer carbenes with esters and carbonates. Moreover, in presence of γ-lactams, Brook-*like* rearrangement is observed. The favored 1,2-acyl migration yields the olefination product as single regioisomer.

Finally, the same catalytic combination allows the reaction of α-diazo-β-ketoesters with cyclic ether moieties[4]. In the case of oxetane, the direct formation of dioxepine motif is observed with retention of configuration[5]. This process is only possible with [CpRu] complexes as under Rh(II) catalysis macrocyclisation reactions occur[6].



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Synthesis and applications of chiral polyether macrocycles

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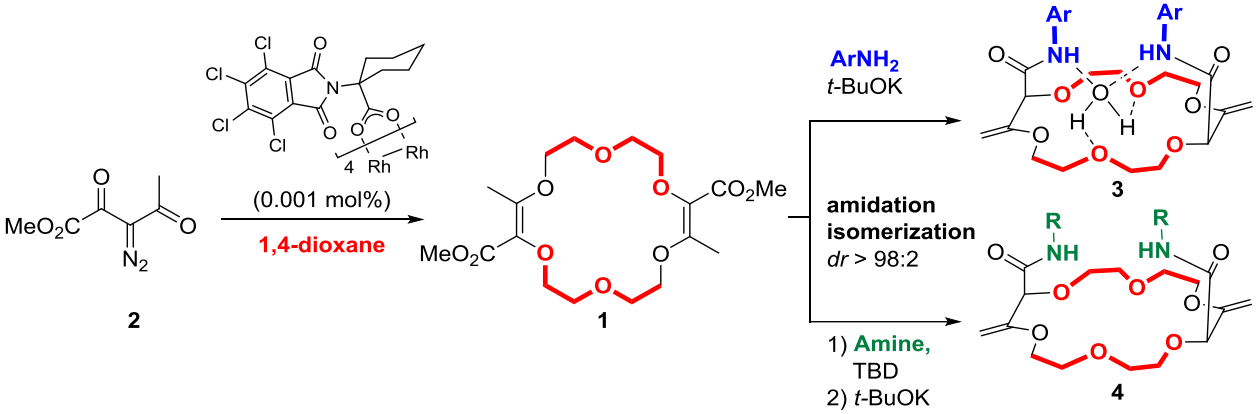
Previously, our group reported the synthesis of polyether macrocycles **1** by [3+6+3+6] condensations of α-diazo-β-ketoester **2** and 1,4-dioxane under dirhodium catalysis at 0.6 *M* concentration[1]. The reactions of **1** with aromatic amines under basic conditions lead to chiral crown ethers **3** (*dr* > 98:2) in a single step by tandem amidation / olefin transposition[2]. However, at the start of this PhD, this rearrangement was strictly limited to aniline nucleophiles. For the introduction of aliphatic amines, it is necessary to form conjugated amides in a first step and then proceed to the transposition in basic conditions to form crown ethers of type **4** (*dr* > 98:2). Moreover, with enantiopure amines, chiral (diastereomeric) crown ethers are obtained which reveal to be efficient catalysts in asymmetric phase transfer catalysis.

When certain fluorescent aromatic amides (pyrene, perylene, NMI, fluorene) are used the molecule display a strong excimer fluorescence due to the spatial proximity of the arenes[3]. The CSP-HPLC resolution of the fluorescent crown ethers allows the access to enantiopure materials displaying effective ECD/CPL properties than can be switched on-off upon cation binding. Finally, late-stage functionalization of crown ethers of type **3** can afford cryptands in one-step. ^{1}H NMR spectroscopy and solid-state structure analysis demonstrated a ditopic character of these new receptors with sodium salts and linear anions in particular.



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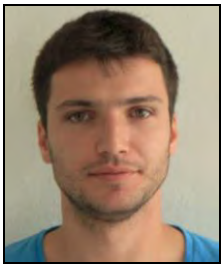
Probing and manipulating polymer properties on the single molecule level



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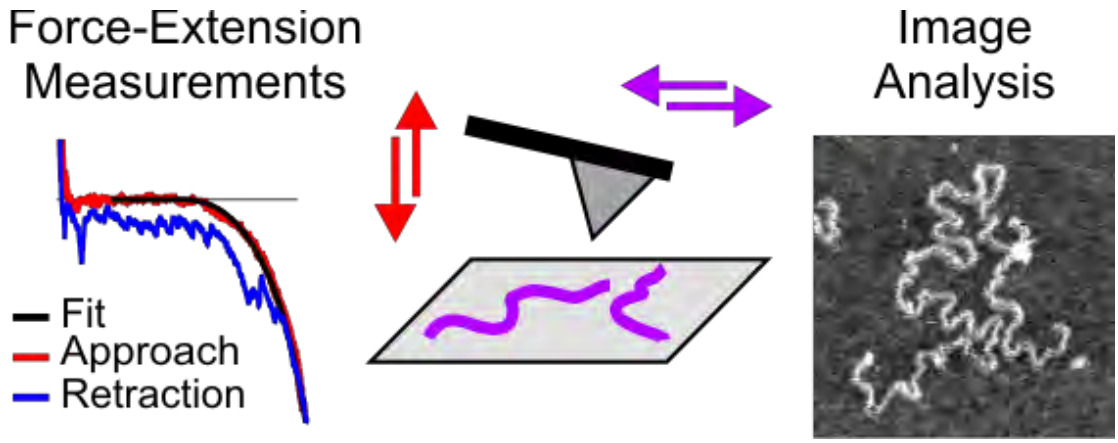
Over the last few decades there has been substantial interest in investigating the properties of biological polymers, such as: various proteins[1] and DNA[2], but also of simple and complex synthetic polymers, such as: polyelectrolytes[3] and dendronized polymers[4], respectively. Here we present a study of single molecules of *poly(vinylamine)* (PVA), analyzed in the adsorbed state by atomic force microscopy (AFM) in two different ways. First, high-resolution images of individual adsorbed polymers were recorded in monovalent electrolyte solutions and the directional correlation function and internal mean square end-to-end distance were evaluated with the worm-like chain (WLC) model. Second, individual polymer chains were picked up from the surface and their force-extension behavior recorded in the same electrolyte solutions. These force profiles were also analyzed with the WLC model, whereby the elastic contribution was also included in the model. Both techniques yield the *persistence length* of the configurational ensemble. From imaging experiments, a persistence length of about 1.6 nm is obtained, while the value of the persistence length derived from force experiments is around 0.25 nm; approximately 7 times smaller. It is the goal of this study to shed some light on the discrepancy between these two persistence scales.



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Endosomal recruitment of ESCRTs induced by the lipid-binding protein ALIX

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The regulation of membrane dynamics in eukaryotic cells is vital for numerous cellular functions. Proteins belonging to the endosomal sorting complexes required for transport (ESCRT) are known as membrane remodeling factors, which regulate events such as cytokinesis, virus budding and multivesicular endosome (MVE) formation, among others. In the endocytic pathway, ESCRTs play a crucial role in the sorting of activated, ubiquitinated receptors into MVE intraluminal vesicles (ILV), which are then transported to lysosomes for their degradation. In addition, ESCRT complexes, in particular the CHMP proteins, are also thought to mediate the membrane deformation and scission processes, leading to ILV formation.

The ESCRT-associated protein ALIX, a binding partner of CHMP4, is recruited to late endosomes by its interaction with LBPA and facilitates membrane deformation[1]. Even though ALIX and ESCRTs play a role in MVE formation, the functional link between both remains elusive. Here, we show that ALIX recruits CHMP4 to late endosomal membranes containing CD63 and LBPA. This recruitment depends on the interaction of ALIX with CHMP4B and LBPA, but is independent of other ESCRT proteins. In-vitro experiments demonstrate that recombinant ALIX recruits CHMP4B to artificial membranes containing LBPA, reinforcing our results obtained in cells.

These results suggest that in mammalian cells, ALIX, together with its binding partner LBPA, induce the redistribution of CHMP4 from the cytosol to endosomal compartments.

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Raman optical activity of singe-walled carbon nanotube enantiomers

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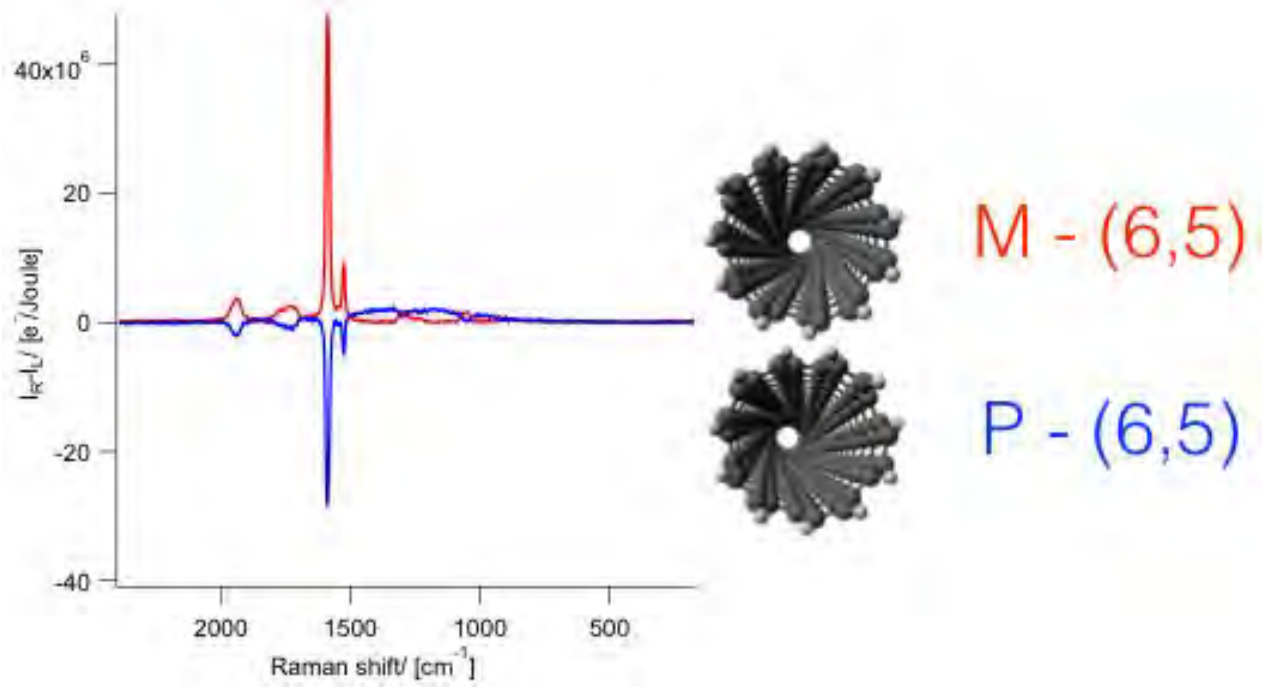
Raman optical activity (ROA) is known to be a sensitive technique to determine the absolute configuration and to investigate the conformation of chiral molecules in solution. ROA has been applied to small organic molecules as well as to larger structures, such as proteins. In recent years, there has been a growing interest in chiral extended nanostructures. Due to their unique optical and electronic properties, Single-Walled Carbon nanotubes (SWCNT) are amongst the most studied novel materials. Synthesised SWCNTs come as a mixture of many different structures characterized by a roll-up vector, typically denoted by two integers **n**, **m**. Most of (**n**,**m**)-SWCNTs are helically chiral structures, and thus exist as two enantiomers.

In my work, I have focussed on the investigations of SWCNT enantiomers by ROA. Due to the resonance enhancement of SWCNTs, we found strong signals of the G-band and large ROA-to-Raman ratios. Since Raman scattering is a two-photon process, there are four different ways to combine the circular polarised components. Besides our scattered circular polarised setup (SCP), we have also realised a dual circular polarised setup (DCP). DFT calculations of resonance ROA on small fragments of SWCNTs were furthermore used to gain better insight.



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The contribution of monomeric myosin motors to endocytic membrane bending

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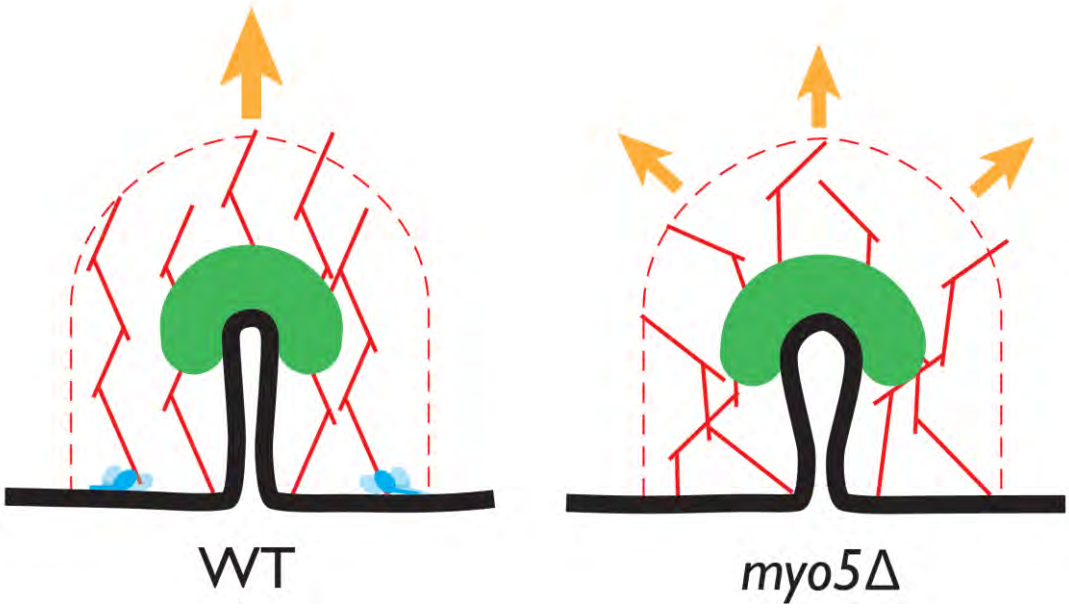
Endocytosis involves bending and reshaping of the plasma membrane, resulting in the formation of a small vesicle. Cells use endocytosis to retrieve extracellular material and to regulate plasma membrane composition. In yeast, endocytosis is strictly dependent on the construction of a transient, branched actin scaffold[1]. This actin network produces the force required to bend the membrane against the turgor pressure. In yeast, two type-I myosins - Myo3 and Myo5 - are essential components of the endocytic actin network[2,3], yet their precise roles in the endocytic machinery remain unclear. By combining genetic perturbations of these myosins with quantitative microscopy techniques we aim to elucidate their function. We show that Myo3 and Myo5 are recruited to endocytic site in a concentration-dependent manner independently from each other, suggesting that they do not compete for binding sites. Live-cell imaging showed that deletion of Myo5 reduces the rate of growth of endocytic membrane invaginations, while correlative electron microscopy indicated that endocytic invaginations in Myo5-deletion cells have wider heads. These results suggest that monomeric myosins structure the actin network in a way to optimize force transfer.



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Remote refunctionalizations by long-range isomerization of olefins

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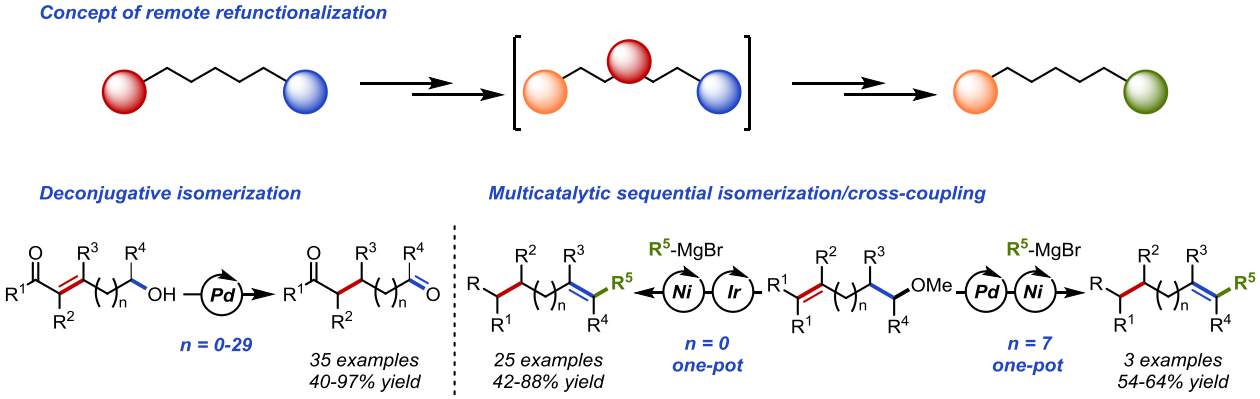
The long-range isomerization/refunctionalization of olefins has emerged as an effective method for the construction of functionalized molecules starting from readily available precursors[1].



Building on previous studies from our group[2], we identified two Pd catalysts for the deconjugation of α,β-unsaturated carbonyls bearing a remote alcohol functionality to the corresponding α,ω-dicarbonyl compounds[3]. Isomerization of di-, tri- and tetra-substituted olefins to aldehydes and ketones was achieved regardless of the chain length connecting both end groups (up to 31 carbon atoms). Preliminary results of the enantioselective variant of the reaction and some mechanistic studies will also be presented.

We found that isomerization was not restricted to alkenyl alcohols but could also be extended to alkenyl methyl ethers. Thus, two complementary multicatalytic sequential processes enabling the preparation of substituted alkenes by merging isomerization and cross-coupling were developed[4]. First, a cationic iridium catalyst was found to be suitable for the stereoselective isomerization of allyl methyl ethers into methyl vinyl ethers. It was also shown to be compatible with a nickel catalyst for the subsequent cross-coupling using Grignard reagents – sequence that was run in a single reaction flask. The development of a highly enantioselective variant of this [Ir/Ni] sequence was achieved using a chiral iridium precatalyst. Next, a complementary [Pd/Ni] sequence was optimized for the long-range isomerization/cross-coupling of alkenyl methyl ethers with a distal C=C bond. The methodology enabled the formation of C(sp^2)-C(sp^2) and C(sp^2)-C(sp^3) bonds and afforded substituted alkenes that would be otherwise difficult to access.

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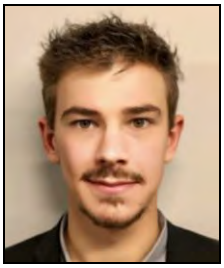
Kinase template abiotic reaction



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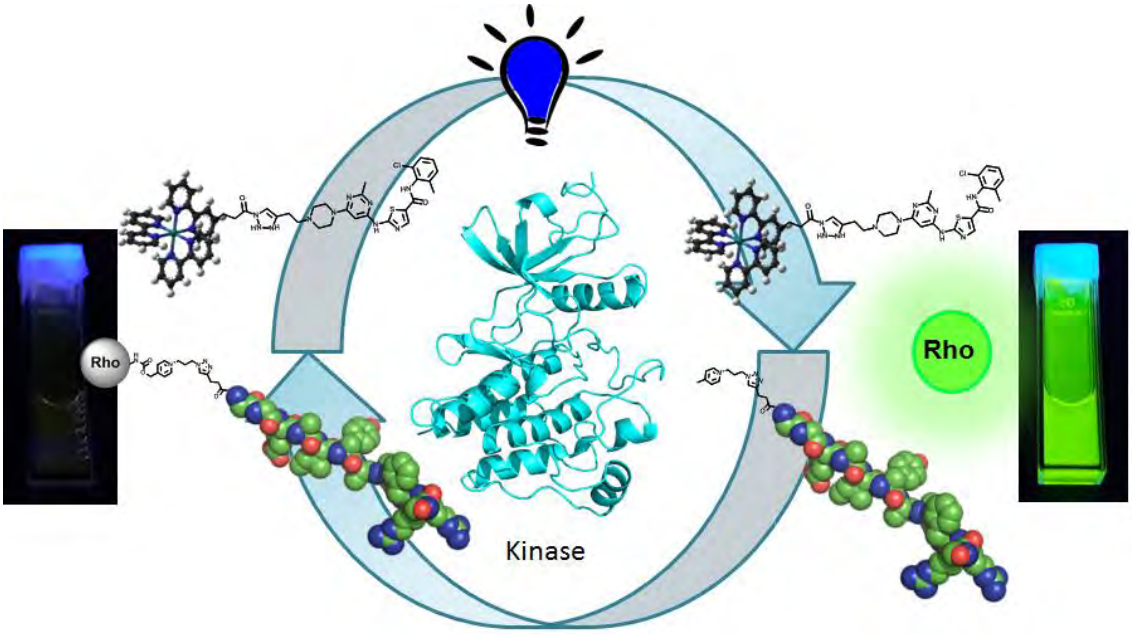

Protein kinases are essential regulators of cellular signalling and have been at the centre stage of drug discovery for the past decade. The successful development of kinase inhibitors against Abl demonstrated that kinases were drugable and triggered tremendous research effort in this area towards the whole kinome. However, inhibitors developed so far often target the conserved ATP binding site of the protein and thus are lacking selectivity, and the more selective ones are targeting an inactive form of the protein. These features limit their use as chemical probes to sense kinase activity.

Herein we report a strategy based on two reacting probes targeting both nucleotide and substrate binding sites. The reaction used allows to use fluorescence readout to selectively sense Abl of Src kinase activity both in biochemical assays and fixed whole cell experiments.

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Modelling excited states in complex environments

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In the presence of an environment, molecular properties such as absorption/emission spectra, and sometimes even reactivity may change drastically. Thus, including environmental effects into quantum chemical calculations is necessary for an adequate description of these systems. However, the unfavorable scaling of accurate Quantum Chemistry methods renders any explicit treatment of the environment unfeasible, particularly for systems of biological interest. Multi-level methods reduce the computational cost by treating environment and target molecule(s) at different levels of theory. Among such methods, Frozen-Density Embedding Theory (FDET)[1,2] provides a formal framework in which the whole system is described by means of two independent quantities: the embedded wavefunction and the density associated with the environment.

The FDET approach can conveniently be combined with pertubative wavefunction methods, e.g. the Algebraic Diagrammatic Construction (ADC) scheme for the polarization propagator[3]. We present the new multiscale variant FDE-ADC[4,5] as a combination of FDET and ADC. The current implementation of FDE-ADC uses the Linearized FDET formalism[6], which in comparison to FDET, is significantly less expensive computationally and more importantly leads to self-consistency between the energy and embedding potential while simultaneously preserving the orthogonality of the embedded wave functions for each electronic state.

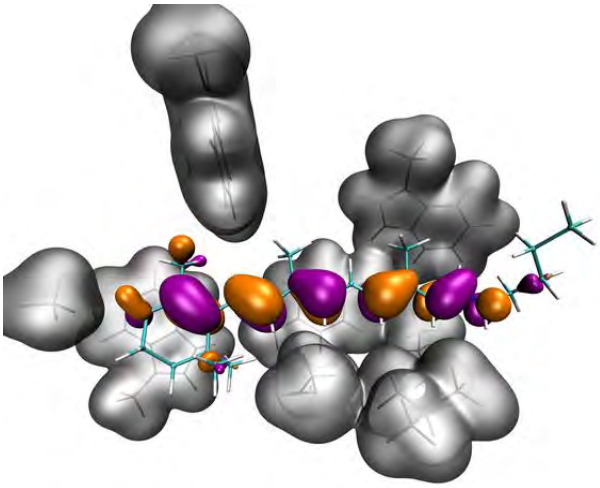

Fig. 1: Retinal wavefunction embedded in eight amino acid residues (cut at β-carbon positions)

A systematic study[7] of FDE-ADC excitation energies involving 50 molecular model systems with varying interaction strengths and application to a biological system (human cellular retinol binding protein II) are shown.

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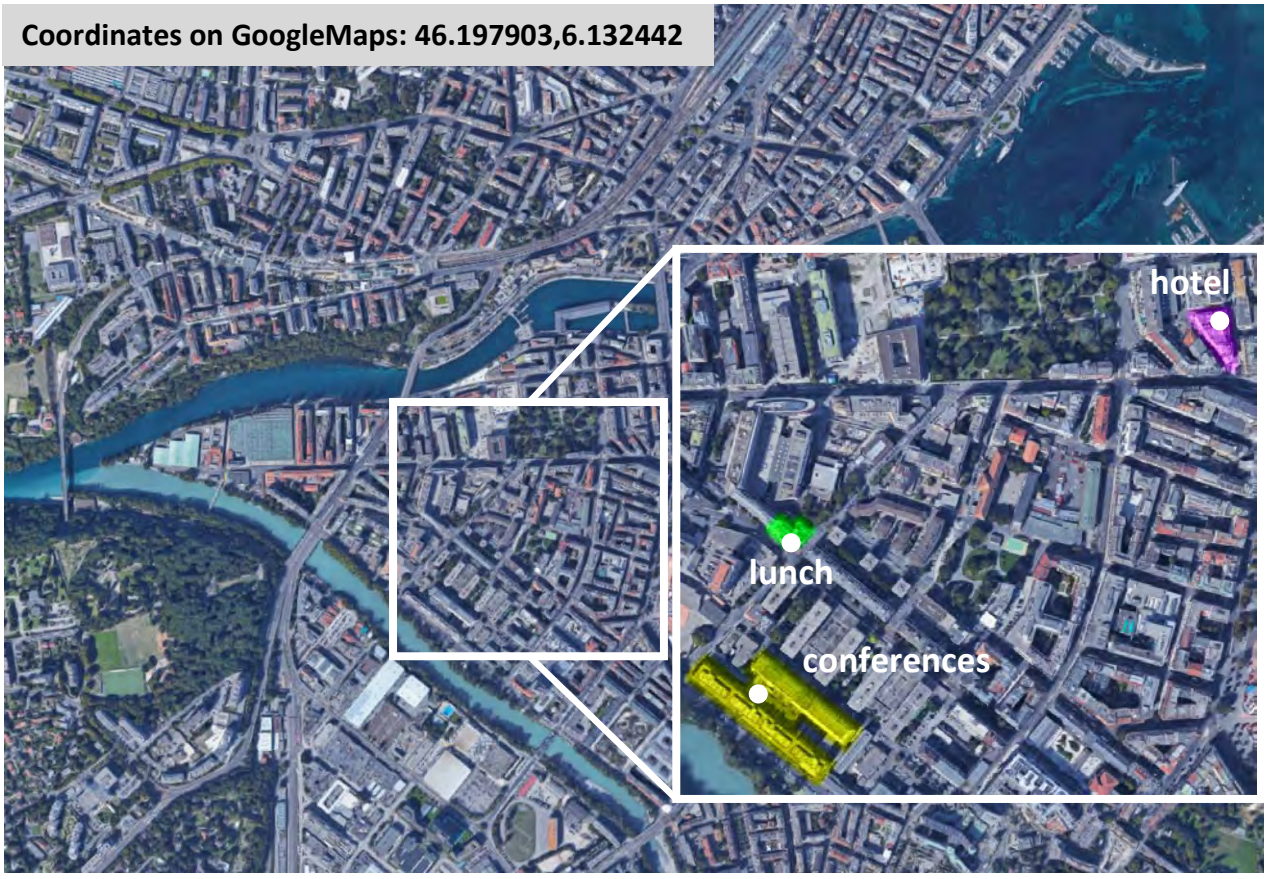

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