Geneva chemistry & biochemistry days 2019

TH 17 January 2019, 08:30–17:35
FR 18 January 2019, 09:00–12:15
Sciences II – Auditoire A150 – quai Ernest-Ansermet 30 – 1205 Genève
No registration required

Prof. David J. Craik
The University of Queensland

Prof. Katharina M. Fromm
Prix Jaubert Lecture – Université de Fribourg

Prof. J. Justin Gooding
The University of New South Wales

Prof. Kai Johnsson
Max-Planck-Institut für Medizinische Forschung

Prof. Rasmita Raval
University of Liverpool

Junior Speakers:

Laura Akbal • Simona Angerani • Ani Baghdasaryan • Joseph S. Beckwith • Anna-Bea Bornhof • Alessandro Bosmani • Sophie Bravo-Veyrat • Léo Duchêne • Daniele Fiorito • Vladimir Girik • Bahman Golesorkhi • Alejandro Guarnieri Ibáñez • Sutida Jansod • Mateusz Kozak • Christoph Nançoz • Roberto D. Ortuso • Anna-Katharina Pfitzner • Michel Raetz • Annelies Sels • Lu Wang •

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 9th edition of its "***Geneva Chemistry & Biochemistry Days***".

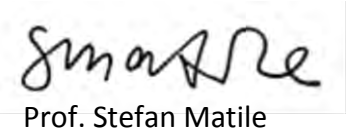
The vocation of the event is to give our students who are close to finishing their PhD studies the opportunity to present their research as attractive speed talks to an audience from academia and industry, and the steering committee is glad to welcome you in this context.

This year, five distinguished lecturers, amongst whom the recipient of the Prix Jaubert, 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 punchy 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 career, 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 *Responsable communication – Section de chimie et biochimie*

PROGRAMME – THURSDAY, 17 JANUARY

SESSION 1

Chair: **Prof. Eric Bakker** (Senior Lecture), **Prof. Sascha Hoogendoorn** (Junior speakers)

08:30- -08:35	**Prof. Stefan Matile**	Welcome message
08:35- -09:20	**Prof. J. Justin Gooding** The University of New South Wales	Diagnostic tools for the detection and treatment of cancer: From 3D cell culture to detecting single molecules
09:20- -09:35	**Lu Wang**	Hydrophobic solvatochromic dye based ion-selective optical sensors
09:35- -09:50	**Alejandro Guarnieri Ibáñez**	Synthesis of elaborate heterocycles and macrocycles *via* Rh(II)-catalyzed decomposition of α-imino carbenes
09:50- -10:05	**Anna-Katharina Pfitzner**	Unravelling the interplay between ESCRT-III sub-modules
10:05-	Coffee break	Hall of Sciences III
10:25- -10:40	**Roberto D. Ortuso**	Development of membrane force sensors
10:40- -10:55	**Sophie Bravo-Veyrat**	Short LC-differential mobility spectrometry-mass spectrometry for an increased throughput in bioanalysis
10:55- -11:10	**Daniele Fiorito**	Enantioselective metal-catalyzed borylation of 2-substituted 1,3-dienes
11:10- -11:25	**Ani Baghdasaryan**	Induced binding properties of post-functionalized Au_{25}
11:25- -11:40	**Bahman Golesorkhi**	Light-upconversion operating at the molecular scale: The pinnacle of miniaturization
11:40-	Photo (all speakers + all chairs + committee)	Hall of Sciences III
11:45-	Lunch (senior speakers + junior speakers)	Restaurant *Sole Mio*

SESSION 2

Chair: **Prof. Nicolas Winssinger**, **Prof. Karsten Kruse** (Senior), **Dr Alexandre Fürstenberg** (Junior)

14:00- -14:45	**Prof. David J. Craik** The University of Queensland	Discovery and applications of cyclic peptides in drug design
14:45- -15:00	**Sutida Jansod**	Tunable colorimetric readout for potentiometric responses with closed bipolar electrodes
15:00- -15:15	**Christoph Nançoz**	Bimolecular photoinduced electron transfer: Putting theory to the test
15:15- -15:30	**Mateusz Kozak**	Phase separation in the endocytic protein network
15:30-	Coffee break	Hall of Sciences III
15:50- -16:05	**Anna-Bea Bornhof**	Anion-π catalysis with NDI foldamers and carbon nanomaterials
16:05- -16:20	**Michel Raetz**	Data independent SWATH mass spectrometry for lipidomic analysis in *T. gondii* and plasma
16:20- -16:35	**Léo Duchêne**	A 3 V stable closo-borate electrolyte for all-solid-state sodium-ion batteries
16:35- -16:50	**Simona Angerani**	Luciferase-induced photoreductive uncaging of small-molecule effectors
16:50- -17:35	**Prof. Kai Johnsson** Max-Planck-Institut für Medizinische Forschung	Fluorescent and bioluminescent sensor proteins
17:35-	*Verre de l'amitié*	Hall of Sciences III
19:30-	Dinner (senior speakers + chairs + committee)	Restaurant *la Cantine des Commerçants*

PROGRAMME – FRIDAY, 18 JANUARY

SESSION 3

Chair: **Prof. Prof. Thomas Bürgi**, **Prof. Stefan Matile** (Senior), **Dr Thomas Hannich** (Junior)

09:00--09:45	**Prof. Rasmita Raval** University of Liverpool	What molecules do at surfaces
09:45--10:00	**Joseph S. Beckwith**	The products of photoinduced electron transfer – what can their excited states tell us?
10:00--10:15	**Laura Akbal**	Enhancing ionization in supercritical fluid chromatography – electrospray – mass spectrometry
10:15--10:30	**Vladimir Girik**	Specific targeting of sphingolipids to the yeast vacuole
10:30-	Coffee break	Hall of Sciences III
10:50--11:05	**Annelies Sels**	$Au_{25}(SR)_{18}$ cluster assembly in multiple dimensions
11:05--11:20	**Alessandro Bosmani**	Tröger bases: Enantiospecific functionalization and transformation to polycyclic indoline-benzodiazepines
11:20--12:05	**Prof. Katharina M. Fromm** Université de Fribourg	Prix Jaubert Lecture – How bacteria can cope with antibacterial silver: Molecular insights
12:05--12:10	**Prof. Marko Kaksonen**	Awards for the best oral presentations
12:10--12:15	**Prof. Stefan Matile**	Concluding remark

Discovery and applications of cyclic peptides in drug design

David J. CRAIK

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Naturally occurring cyclic peptides offer great potential as leads for drug design.[1,2]

This talk will focus on a class of cyclic peptides known as cyclotides,[3] which are topologically unique proteins in that they have a head-to-tail cyclised peptide backbone and a cystine knotted arrangement of disulfide bonds. This makes them exceptionally stable to chemical, thermal or enzymatic treatments and, indeed, they are amongst nature's most stable proteins.

They occur in plants from the Rubiaceae (coffee), Violaceae (violet), Solanaceae (potato), Fabaceae (Legume) and Cucurbitaceae (cucumber) families of plants. Their stability and compact structure makes them an attractive protein framework onto which bioactive peptide epitopes can be grafted to stabilize them.

More than two dozen examples have now been published where biologically active epitopes have been grafted onto cyclic peptide frameworks to produce lead molecules with potential in the treatment of cancer, cardiovascular disease, infectious disease, autoimmune disease (multiple sclerosis) and pain.

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1. Craik D.J. *Science* **2006**, *311*, 1561.
2. Craik D.J., Fairlie D.P., Liras S., Price D. *Chemical Biology & Drug Design* **2013**, *81*, 136.
3. Craik D.J. (Editor). Advances in Botanical Research, Volume 76. *Plant Cyclotides* **2015**. Series Editors J.P. Jacquot and P. Gadal. Elsevier, London UK (ISBN: 978-0-12-800030-4).

Acknowledgements:

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Prix Jaubert Lecture – How bacteria can cope with antibacterial silver: Molecular insights

Katharina M. FROMM

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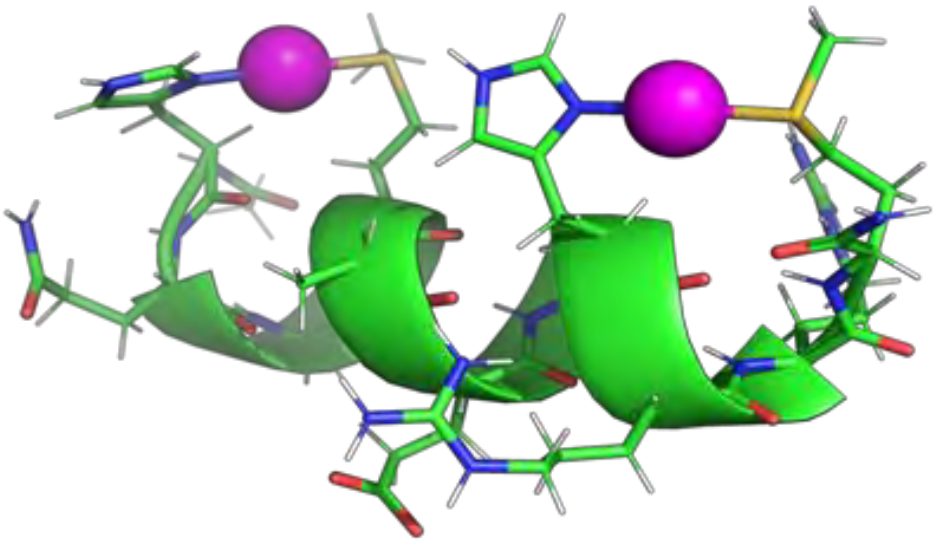
That silver is beneficial for human health is known since a very long time. Hence, today, it is used in medical applications such as eye drops, burn creams or wound pads. However, some bacteria have learned to cope with high concentrations of silver, either by exporting the heavy metal ion via an efflux pump, or by reducing the silver ions to silver nanoparticles.

The silver efflux pump of certain Gram-negative bacteria comprises a unique protein whose role used to be unclear. We have studied the binding properties of this protein with the help of model peptides and could contribute to the elucidation of its structure-function property. The second part of the talk will give insights into the silver ion reduction process by anaerobic bacteria.



Diagnostic tools for the detection and treatment of cancer: From 3D cell culture to detecting single molecules

J. Justin GOODING

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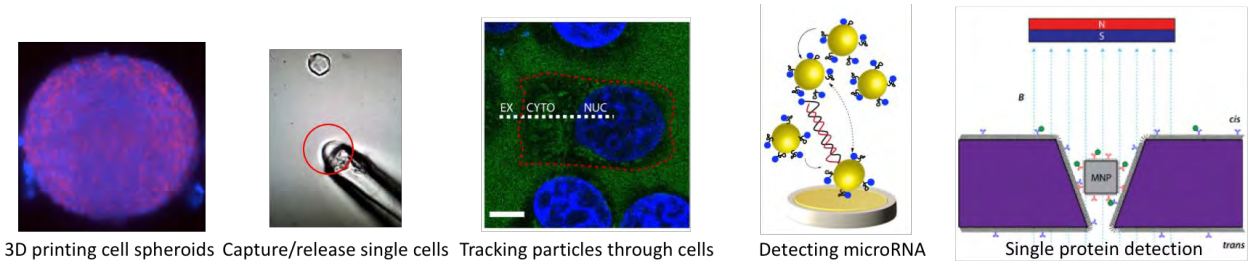
Diagnostic tools are required by the entire spectrum of cancer diagnosis and treatment. The different diagnostic tools however work on very different length scales from 3D cell cultures to the detection of single molecules. In this talk, we will cover a range of diagnostic technologies we are developing that cover the lengths scales required for evaluation of drug treatments to the early detection of cancer.

Starting from the larger size scale, the talk will describe our bespoke 3D bioprinter for producing in vitro 3D cell spheroid cancer models. The types of 3D cell biology assays will be described including our initial work on primary cell tumoroids for personalised medicine. We will then progress to technologies that allow us to capture rare cancer cells and then release single cells for further investigation on demand.[1] Methods of evaluating the drug tolerance of these single cell prior to release will then be discussed.[2] Next microscopy methods we have developed for tracking and quantifying the movement of nanoparticles carrying anticancer drug payloads through cells to the nucleus will be discussed.[3] We will then switch the emphasis to diagnosis and ultrasensitive biosensors that can detect just a few microRNA molecules for early cancer diagnostics.[4] Finally approaches to developing quantitative biosensors that can detect single molecules will be discussed.[5]



3D printing cell spheroids | Capture/release single cells | Tracking particles through cells | Detecting microRNA | Single protein detection

Decreasing length scale

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2. Yang Y., Botia M.C., Gonçales V.R., Gooding J.J., Bakker E. *Angew Chem Int. Ed.* **2018**, in press.
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Fluorescent and bioluminescent sensor proteins

Kai JOHNSSON

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The topic of my presentation will be how a combination of protein engineering and synthetic chemistry can be exploited to generate fluorescent and bioluminescent probes for live-cell imaging.

Specifically, I will talk about our attempts to introduce a new class of fluorescent sensor proteins that permit to visualize drug and metabolite concentrations in living cells with high spatial and temporal resolution. I will also discuss how these sensor proteins can be utilized for point-of-care therapeutic drug monitoring.

What molecules do at surfaces

Rasmita RAVAL

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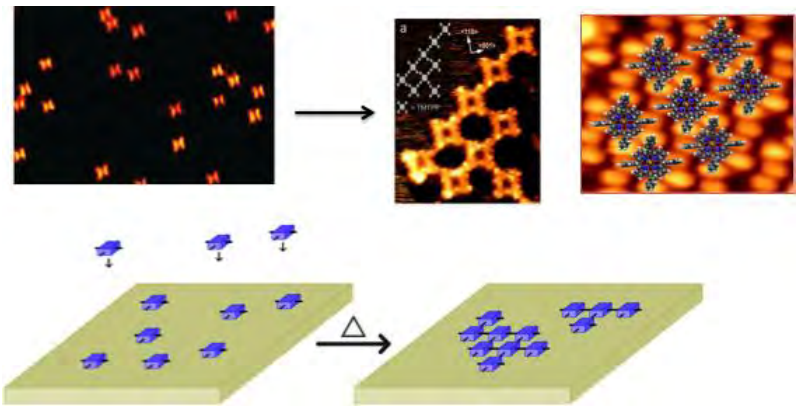
Molecules represent the most versatile, functional entities available in Nature and are central components in the machinery of life. This has inspired scientists to translate molecular systems to surfaces and interfaces in order to engineer 21st century nanotechnology. In both cases, a critical transition from a simple isolated molecule to a complex molecular collective is required for function. This talk will outline the pivotal role of scanning probe microscopy, surface spectroscopies and periodic density functional theory in mapping the nanoscale details of how organic and biological molecules come together and create supramolecular organisations at surfaces. In addition, the surface provides a reactive environment in which molecules can couple covalently to create complex organic matter, with the direct emergence of structural and topological complexity. In a number of cases, new types of molecular materials are created, which cannot be realised via normal synthetic routes. Such supramolecular and covalent assemblies give rise to complex functions at surfaces like homochirality, molecular recognition, stimuli-responsive behaviour and provide a platform for simple molecular machines.



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Enhancing ionization in supercritical fluid chromatography – electrospray – mass spectrometry

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Supercritical fluid chromatography (SFC) is a chromatographic separation technique using a fluid at the supercritical state as mobile phase. CO_2 is commonly used due to its easily reachable critical point (31°C and 74 bars) and which present several advantages such as its low toxicity, its cost, its low viscosity or its high compressibility. SFC has experienced a renaissance in the last decade with the commercialization of new hardware. The hyphenation of SFC with atmospheric pressure ionization is straightforward but limited data regarding the effects of the supercritical fluid on the ionization performance are available. In liquid chromatography (LC), the ionization conditions are predominantly dictated by the mobile phase composition. Whereas in SFC-ESI/MS, the ionization can be tuned using a post-column addition of a liquid make-up, which is independent of the chromatographic conditions. This work investigates the influence of the make-up (flow, pH, buffer concentration) for various SFC conditions and various analyte classes (pKa, log P).

SFC analyses were carried out on the Nexera UC system (Shimadzu Corporation, Kyoto, Japan). A triple quadrupole mass spectrometer LCMS-8060 (Shimadzu Corporation, Kyoto, Japan) was operated using Electrospray Ionization source (ESI). HIV protease inhibitors, beta-blockers, steroids and metabolites were used as reference classes for pharmaceutical and metabolomics applications.

Due to the specific nature of gaseous CO_2, the tuning of the make-up conditions in electrospray becomes an important factor and can be used to tune analyte sensitivity. Neither a dilution effect (loss of signal) nor a relevant degradation of chromatographic performances is observed with the addition of a make-up at various flow-rates, up to 0.7 mL/min. From supercritical conditions (1 mL/min at 40°C and 150 bar) to gaseous state (room temperature, atmospheric pressure), the CO_2 expands around 430 times, contributing to almost 5% of the nebulizing process. In positive mode, the presence of ammonium ions either in the mobile phase or in the make-up did significantly increase the MS signal, even at basic apparent pH due to a Wrong-Way-Round ionization mechanism. The ionization performance of electrospray is influenced by the acidic buffer power of the carbon dioxide, and was found to be restricted in the apparent pH range of 3.8–7.2 in the various conditions investigated. This may challenge sensitive detection in negative mode, as illustrated for bosentan. Finally, the optimization of make-up composition leads to an enhancement up to a factor of 70 on the electrospray MS response signal, for the SFC-SRM/MS analysis of HIV protease inhibitors in plasma extracted from Dried Plasma Spots.[1]

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Luciferase-induced photoreductive uncaging of small-molecule effectors

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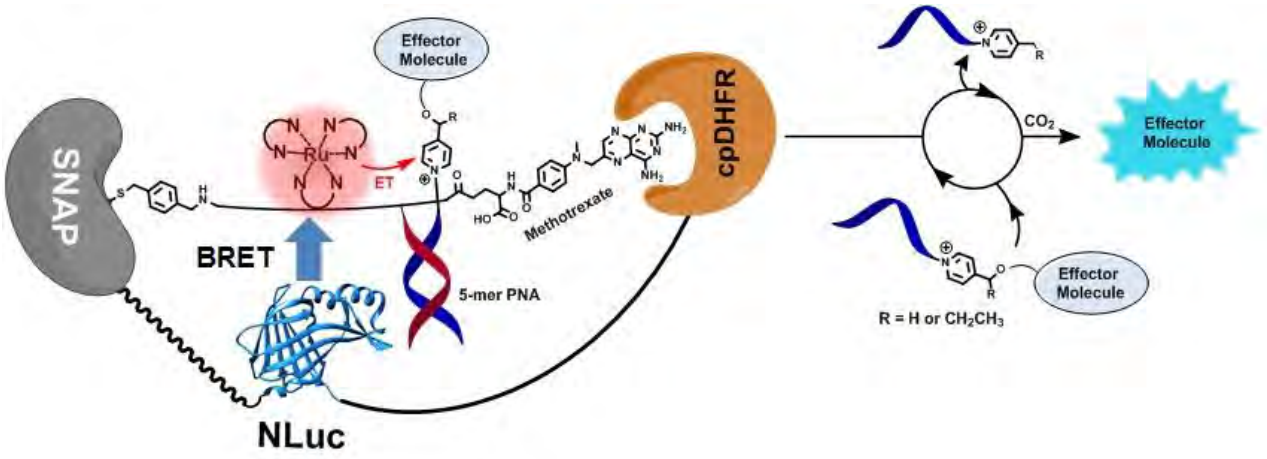
Bioluminescence resonance energy transfer (BRET) is extensively used to study dynamic systems and has been utilized in sensors for studying protein proximity, metabolites, and drug concentrations.[1,2,3] We demonstrate that BRET can activate a ruthenium-based photocatalyst which performs bioorthogonal reactions. BRET from luciferase to the ruthenium photocatalyst was used to uncage effector molecules with up to 64 turnovers of the catalyst, achieving concentrations > 0.6 μM effector with 10 nM luciferase construct. Using a BRET sensor, we further demonstrate that the catalysis can be modulated in response to an analyte, analogous to allosterically controlled enzymes. The BRET-induced reaction was used to uncage small-molecule drugs (ibrutinib and duocarmycin) at biologically effective concentrations *in cellulo*.[4]



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Induced binding properties of post-functionalized Au_{25}

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Nowadays, considerable effort is devoted to exploring the host-guest interactions based on molecular recognition events at the nanoscale. However, the investigation of the binding properties of atomically precise clusters is still in their infancy.[1,2] Herein, we have demonstrated the capability of post-functionalized Au_{25} cluster to bind multivalent metal cations in aqueous solutions. The ligand exchange reaction between $Au_{25}(2\text{-PET})_{18}$ cluster and dithiolated-18C6 crown ether was aimed to post-functionalize the cluster with ion binding properties (Fig.1). The reaction was followed in situ by UV-vis, ^{1}H NMR and HPLC. MALDI mass analysis reveals the existence of up to four exchange species. ATR-FTIR spectroscopic studies using 5000 ppm aqueous solutions of K^+, Cs^+, Ba^{2+}, Mg^{2+}, Gd^{3+} and Eu^{3+} show noticeable signal changes at ~1100 cm^{-1} which corresponds to the C-O stretching vibration. The red shift of corresponding frequency over time indicates ion encapsulation into the crown ether cavity. Similar low frequency shift was also observed using very low concentrations of metals in solution. Thus, post-functionalized $Au_{25}(2\text{-PET})_{18}$ cluster can be used to sense even traces of cations present in aqueous solutions.

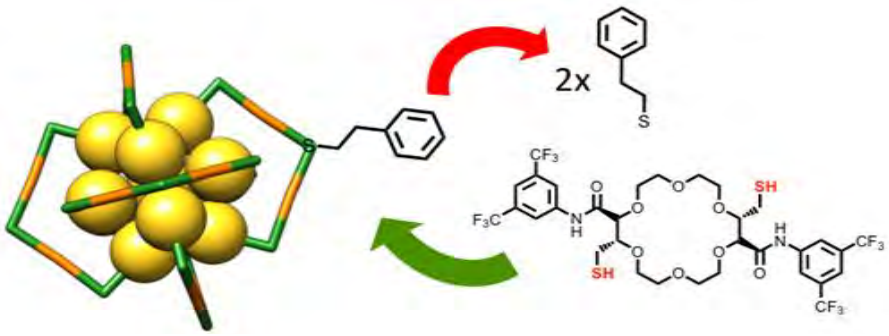

Figure: Schematic representation of the ligand exchange reaction between Au25 cluster and dithiolated 18C6 ligand.

Moreover, the cooperative binding behaviour of enantiopure crown-functionalized Au_{25} cluster with chiral 3,3-dimethyl-2-butylamine has also been studied. Titration experiments were performed to follow the binding of the amine to the crown cavity using NMR spectroscopy. Later, data fitting with a nonlinear regression algorithm derived the binding affinities and the cooperativity coefficients for the interaction. By changing the number of the crown ether ligands on the cluster surface, the binding affinity can be changed, and the allosteric effect can be switched from positive to negative in a controlled manner.

References:

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The products of photoinduced electron transfer – what can their excited states tell us?

Joseph S. BECKWITH

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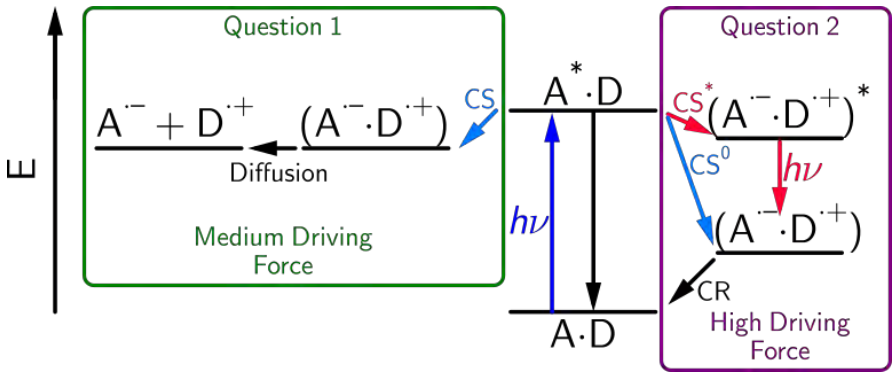
Electron transfer is one of the most fundamental and ubiquitous chemical reactions, yet there are still swathes of it that remain ill-understood. Here, two ultrafast spectroscopic techniques have been used to investigate what the excited states of the products of electron transfer (*i.e.* radical ions) may tell us about photoinduced bimolecular electron transfer.

An open question in the field is that of how the ion pair evolves after it is photoproduced. We would anticipate that there is a difference between when the ion pair is initially produced, in close contact (a "tight ion pair") to after the ions have diffused apart and the ions are "free".[1] Here we will use pump-pump-probe transient absorption spectroscopy to interrogate how the anion excited state behaves at different times after the electron transfer reaction, and what that can tell us about the distribution of distances between the anion and cation (Question 1 in the figure below).

A second question is that of highly exergonic reactions – why are they considerably faster than theory would predict?[2] One hypothesis is that, when the reaction is highly exergonic, the charge separation step may proceed directly to the electronically excited ion products (Question 2 in the figure below) – a hypothesis recently boosted by transient infrared measurements.[3] Here, we will present broadband time-resolved fluorescence measurements (a technique we have already applied to observe intramolecular charge transfer processes[4]) where the fluorescence of the excited ion product appears to be directly observable at early times in highly exergonic reactions, a considerably clearer marker of the excited ion's presence.



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Anion-π catalysis with NDI foldamers and carbon nanomaterials

Anna-Bea BORNHOF

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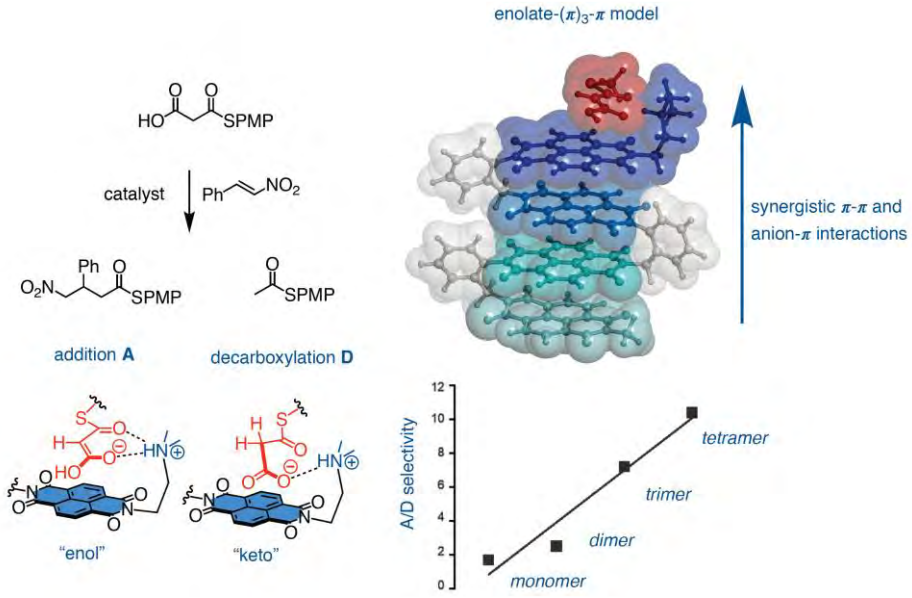
In a conceptually new approach we show that combining π-π stacking and anion-π interactions in π-stacked naphthalenediimide (NDI) oligomers reaches selectivities that exceeded previous anion-π catalysis with NDIs.[1] A series of up to four covalently bound NDI units that stack in a face-to-face manner was designed and synthesized. The stacked conformation and electronic communication of the foldamers was confirmed by NMR analysis, UV absorption spectroscopy, cyclic voltammetry, steady-state and transient absorption spectroscopy. The biologically important reaction of a malonate half thioester with an enolate acceptor was used to probe the catalytic activity of the oligomers. The chemoselectivity for the addition rather than the decarboxylated product increases linearly with the number of NDI units stacked while ratiomeric changes in absorption and decreasing energy of the LUMO show sublinear trends.



The number of NDI units stacked correlates with surface potentials, chloride binding energies, and the distances between chloride and π surface. Increasing numbers of NDI units show increasing binding energies with the planar "enol" tautomer on π acidic surfaces that corroborates discrimination on the level of tautomers proposed in earlier work. The experimental results are thus confirmed except for the extraordinary violation of the oligomer's law of diminishing returns. The results show that polarizability plays an important role in anion-π interactions so the next step is going towards larger and larger π-surfaces. On that account we started investigating pristine and functionalized nanographenes that show promising results as heterogenous anion-π catalysts and can be used as electrodes controlling catalysis by an external electric field to induce stronger macro dipole moments and increase anion-π interactions.

References:

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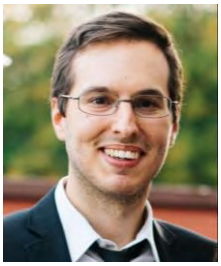
Tröger bases: Enantiospecific functionalization and transformation to polycyclic indoline-benzodiazepines



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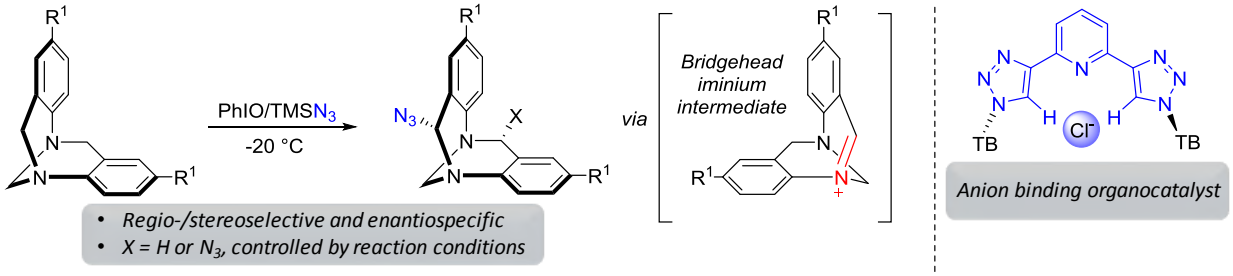
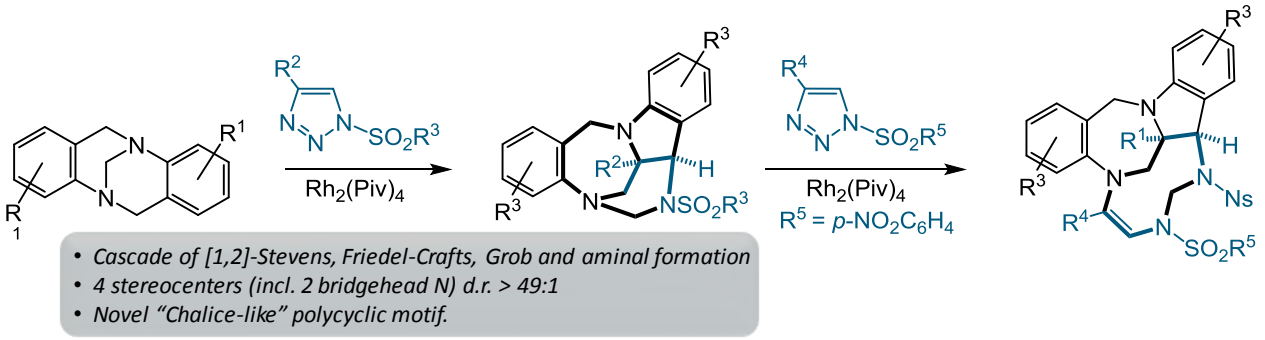
Tröger bases (TB) are chiral bicyclic heterocycles with a large range of applications, from analytical to material sciences.[1] Late-stage functionalizations at benzylic positions are rare, and an access to new derivatives *via* an oxidative process was investigated. As a consequence, highly regio and stereoselective azidations were achieved using combinations of PhIO and $TMSN_3$.[2] The process occurs with high enantiospecificity (*es* 96–99%) and *via* bridgehead iminium intermediates. Bis-triazoles derivatives were also prepared in high yields and enantiospecificity. This class of compounds revealed some potential as anion binding organocatalysts and were used for the tritylation of amines and alcohols.



In TB chemistry, our group has previously reported the addition of electrophilic carbenes to methano-TB, that leads to the expansion of the methanodiazocine bridge, and hence to ethano-TB.[3] In a new development, polycyclic indoline-benzodiazepines were obtained when methano-TB were reacted with α-imino carbenes; intermediates generated *in situ* by the reactivity of *N*-sulfonyl-1,2,3-triazoles in presence of Rh(II) catalysts.[4] The process occurs *via* a cascade of [1,2]-Stevens, Friedel-Crafts, Grob and aminal formation reactions to yield the heterocycles as single isomers. Further ring-expansion by insertion of a second α-imino carbene leads to elaborated polycyclic 9-membered ring triazonanes.



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Short LC-differential mobility spectrometry-mass spectrometry for an increased throughput in bioanalysis

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Liquid chromatography coupled to mass spectrometry using the selected reaction monitoring mode (LC-SRM/MS) has become the gold standard in quantitative bioanalysis. For accurate quantification the analysis time are typically in the range of five to ten minutes, which challenges its use for high-speed analysis. A LC-DMS-SRM/MS platform was developed to improve samples throughput combining trap/elute sample preparation and improved selectivity using differential mobility spectrometry (DMS) and was applied for quantitative high throughput analysis in less than 1.5 minute of oxidized and reduced form of glutathione respectively GSH and GSSG.

GSH was derivatized prior analysis with N-ethylmaleimide (NEM). The derivatization of GSH was required for its stabilization during sample preparation and for analysis by enhancing the electrospray (ESI) signal by at least 1000-fold. A short 10 mm C18 column was used in trap/elute mode enabling firstly a shorter sample preparation time thanks to the sample pre-cleaning occurring in it, and secondly improving the sensitivity of both GSH and GSSG thanks to the focusing effect of the backflushing elution.

A second separation dimension was added using the recently introduced modifier-assisted differential ion mobility spectrometry device (DMS, SelexIon). The DMS technology was found to be essential to increase the selectivity, acting like a filter based on the different mobility of the compounds to remove interferences. The nature of the modifier was an additional important parameter to improve further the selectivity, modifying the ion's mobility depending on the type of modifier used. Here N_2, methanol, toluene, ethanol, acetonitrile, and isopropanol were tested as modifier to tune the assay selectivity. The quantification performances of a reference LC (Hypercarb column, 50 mm)-SRM/MS method[1] were compared to this short 10 mm LC-DMS-SRM/MS method.[1]

These results show that the hyphenation of a short 10 mm column in trap/elute mode with the modifier assisted differential mobility spectrometry gives the opportunity to quantify simultaneously both GSH and GSSG, reducing the analysis time from 15 minutes (with the reference LC-SRM/MS method)[2] to 1.5 minute with good precision and accuracy. The throughput could be increase to 400 samples analyzed in 10 hours with the short LC-DMS-SRM/MS platform showing promising results for other analytes.

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A 3 V stable closo-borate electrolyte for all-solid-state sodium-ion batteries

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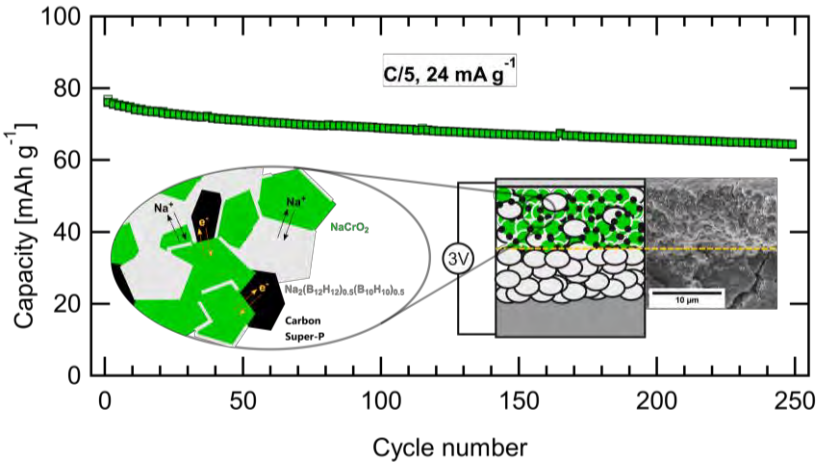
All-solid-state sodium-ion batteries promise to simultaneously yield higher energy density, improved safety, and lower cost as compared to state-of-the-art lithium-ion technologies based on organic liquid electrolytes. A competitive all-solid-state battery requires a solid-state electrolyte with high ionic conductivity near room temperature combined with high thermal and electrochemical stability. Meeting these three requirements simultaneously represents a major challenge.

In this regard, we present a new sodium-ion conductor, namely $Na_2(B_{12}H_{12})_{0.5}(B_{10}H_{10})_{0.5}$, that simultaneously offers high sodium ion conductivity of 0.9 mS cm^{-1} at 20 °C comparable to that of liquid electrolytes, excellent thermal stability up to 450 °C, and importantly a large electrochemical stability window of 3 V including stability versus metallic sodium enabling long term striping and plating and the use of a sodium metal anode.[1] Using an innovative solution-based impregnation method to create a stable contact at the interface between cathode material and solid-state electrolyte we demonstrate that $Na_2(B_{12}H_{12})_{0.5}(B_{10}H_{10})_{0.5}$ can be implemented in a 3 V all-solid-state sodium-ion battery consisting of a sodium metal anode and a $NaCrO_2$ cathode. The cell shows high cycling stability and good rate performance with more than 85% capacity retention after 250 cycles at C/5.[2] Finally, new insights into the origin of the peculiar, non-Arrhenius conduction mechanism for this class of electrolyte will be discussed.

Our results prove the importance of interface optimization for solid-state batteries and that owing to their high stability and conductivity closo-borate based electrolytes can play a significant role for the development of a competitive solid-state battery technology.



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Enantioselective metal-catalyzed borylation of 2-substituted 1,3-dienes

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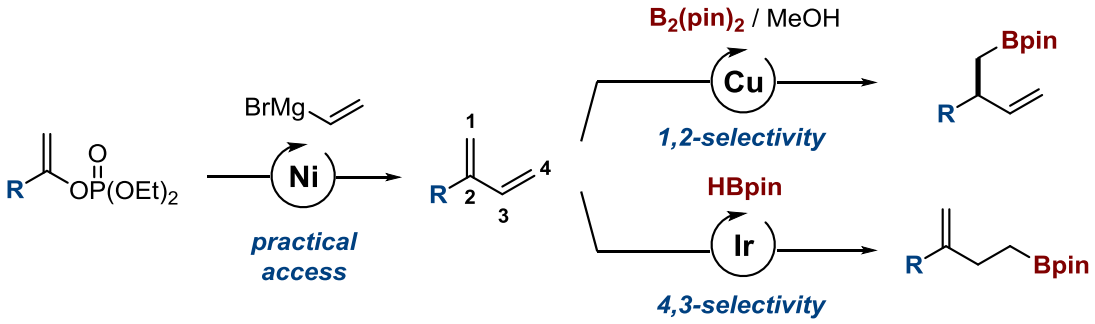
Conjugated 1,3-dienes represent a particularly attractive platform for selective functionalization. They find widespread use as building blocks for organic synthesis as well as in polymerization processes. From a selectivity standpoint, functionalization of 1,3-dienes poses a significant challenge due to the numerous coordination and insertion modes conceivable for a transition metal catalyst.[1] In recent years, efforts to develop selective catalytic transformations have been essentially focused on *linear* 1,3-dienes (*i.e.* 1-substituted 1,3-dienes).[2] Until recently, the limited synthetic accessibility of *branched* 1,3-dienes (*i.e.* 2-substituted 1,3-dienes) has severely limited their use in the development of selective transformations.[3] Within this context, our laboratory recently reported a general Ni-catalysed protocol which streamlines access to 2-substituted 1,3-dienes from readily available synthons.[4]



Herein we describe our results in the selective hydroboration and protoboration of this underexplored class of conjugated olefins. An enantioselective Cu-catalyzed protoboration of 2-substituted 1,3-dienes has been developed. The use of a chiral phosphanamine ligand is essential in achieving high chemo-, regio- and enantioselectivity, providing rapid access to a variety of synthetically relevant homoallylic boronates/ alcohols.[5] A complementary approach based on iridium catalyzed hydroboration of dienes affords 4,3-selectivity, providing valuable homoallylic boronates with a 1,1-disubstituted olefin.[6] Overall, we present two catalytic strategies that address critical challenges posed by conjugated dienes both in terms of *reactivity* (mono- *vs.* di-functionalization, parasitic reduction, competing isomerization) and *selectivity* (chemo-, regio- and enantioselectivity).

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Specific targeting of sphingolipids to the yeast vacuole

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Sphingolipids are a subclass of lipids containing an aliphatic amino acid alcohol backbone (long-chain base) and have been shown to play a crucial role as signalling molecules besides being essential structural components of cell membrane. Baker's yeast, *Saccharomyces cerevisiae*, is a unicellular eukaryotic model organism that has been extensively utilized for fundamental studies of lipid metabolism owing to its ease of handling, genetic tractability and to the large number of genes conserved from yeast to humans.[1] Recent advances in lipid biochemistry have revealed an underestimated network of direct inter-organelle lipid transport through membrane contact sites.

However, unravelling mechanisms of sphingolipid transport is challenging since these biomolecules are not genetically encoded, cannot be easily tagged with fluorescent proteins or detected by antibodies. Therefore, alternative strategies are required to enable the investigation of metabolism and inter-organelle transport of sphingolipids with high spatial and temporal resolution.[2] One of such strategies relies on synthesized organelle-specific "caged" molecules released upon UV illumination at the defined place in the cell. It has been recently demonstrated that one of the caged sphingolipids, sphingosine could be specifically delivered and released in mammalian mitochondria.[3]

We found out that mitochondria-targeted caged long-chain bases (mitoLCBs) labelled yeast vacuoles but not mitochondria. Other caged lipid molecules like oleic acid were also found in the vacuole. In contrast, mitoCholesterol could not be targeted to the vacuole. The delivery to the vacuole does not depend on endocytosis yet requires the presence of hydrophobic acyl chain. Disruption of membrane potential by treatment with the uncoupler CCCP did not affect mitoLCB delivery to the vacuole. Furthermore, we could see using LC-MS-MS that the caged biomolecules delivered to the vacuoles could be released by UV illumination and thus be used to get a glimpse into how spingoid bases are metabolized and transported from the vacuole to the endoplasmic reticulum through the nucleus-vacuole junctions (NVJs).

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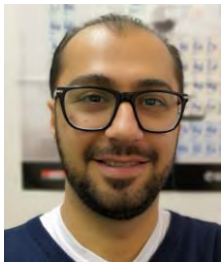
Light-upconversion operating at molecular level: The pinnacle of miniaturization



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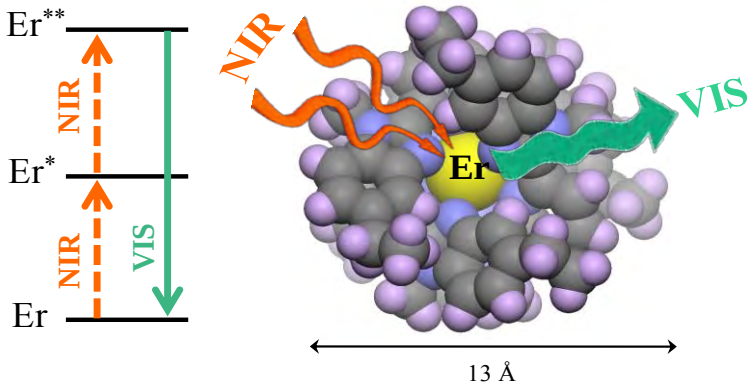
With the fast growth of lanthanide-containing luminescent nanoparticles during the last few years, linear light-upconversion, that is the conversion of near-infrared (NIR) light into emitted visible light by successive linear absorption of NIR photons, a phenomenon which was well-known in doped ionic solids and garnets, entered the nanoscale dimension. It led to unprecedented applications as optical devices in biology, medicine and analytical chemistry.[1] The next miniaturizing step aims at reaching linear light upconversion at the molecular level, a challenge highly wanted for benefiting from the toolbox of molecular chemistry for designing robust, tunable and reproducible upconverting devices. Achieving this goal however requires the piling up of low-energy near-infrared photons onto a single lanthanide center via excited state absorption (ESA) operating in molecular complexes. This represents an almost inconceivable tour de force in presence of the efficient non-radiative luminescence quenching processes provided by the closely located high-energy oscillators of the bound organic ligands.[2]

Taking advantage of the recent rational design of trivalent erbium complexes equipped for dual emission,[3] the present work reports the first example of a compelling single-center lanthanide linear upconversion process operating at the molecular level converting 801 nm and 966 nm NIR excitation light beam into 525 nm and 542 nm visible (blue-green) luminescence, which might open new avenues for pushing miniaturization towards 'sub-nanophosphors' (*i.e.* molecules) for light-upconversion.[4]



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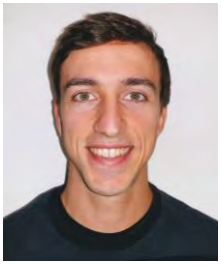
Synthesis of elaborate heterocycles and macrocycles *via* Rh(II)-catalyzed decomposition of α-imino carbenes



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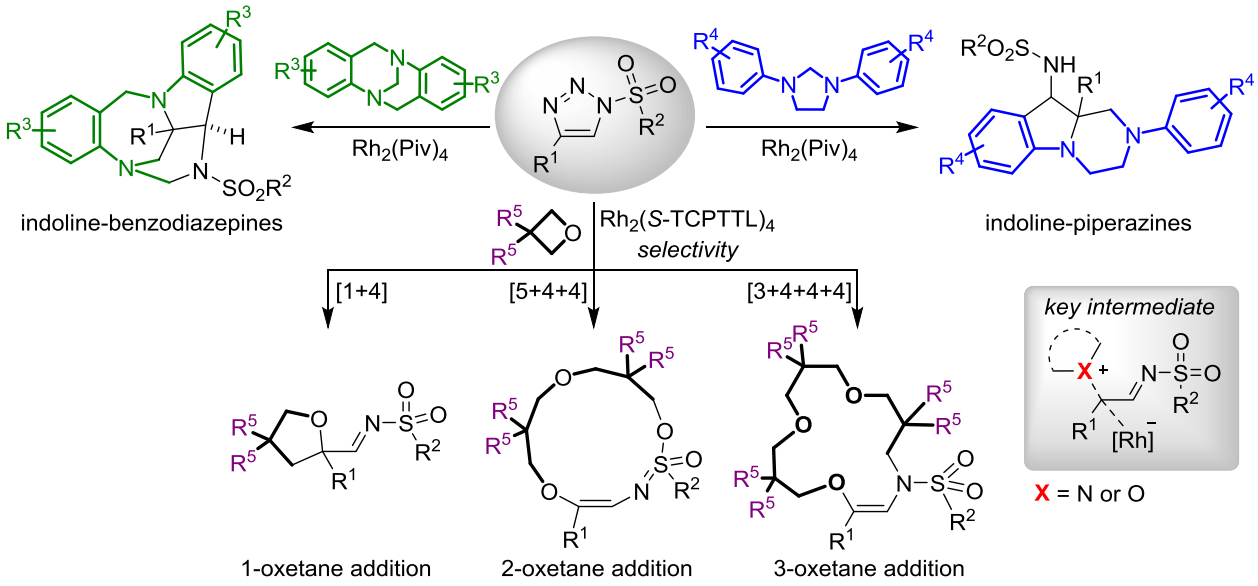
N-Sulfonyl-1,2,3-triazoles are known to decompose under metal catalyzed reaction conditions leading to electrophilic *α*-imino carbenes.[1] These intermediates undergo many original processes, from cyclopropanations to C-H insertion reactions, and subsequent transformations.[2] In the field of ylide generation and reactivity, processes involving *α*-imino carbenes have been less studied, either in oxygen or in nitrogen ylide chemistry. For instance and as a new development, the Rh(II)-catalyzed reaction of *N*-sulfonyl-1,2,3-triazoles with oxetanes was tested.[3] Depending on reaction conditions or substrate selection, 2-imino tetrahydrofurans, 13-membered sulfonimidates or 15-membered aza-macrocycles are generated selectively *via* formal [1+4], [5+4+4] and [3+4+4+4] condensations of α-imino carbenes and oxetanes, respectively.

Moreover, a straightforward access to novel polycyclic indoline-benzodiazepines with exclusive diastereoselectivity (*d.r.* > 49:1) was achieved using Tröger Bases as substrates.[4] Treatment of other stable aminals with *N*-sulfonyl triazoles was tested, and imidazolidines in particular. A direct formation of fused indoline-piperazines was achieved *via* subsequent ylide formation, [1,2]-Stevens and Friedel-Crafts reactions.



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Tunable colorimetric readout for potentiometric responses with closed bipolar electrodes

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A general platform is presented to translate potentiometric responses directly into a colorimetric readout by a closed bipolar electrode, where the optical detection compartment is physically separated from the sample. A constant electrical potential is imposed across the bipolar electrode by solution contact, any potentiometric signal change respecting to the reference electrode in sample compartment results in a change of the colorimetric redox indicator in detection compartment. The potential change at the sample side is compensated by the potential at the optical probe, triggering a ratio of colorimetric redox indicator until the new equilibrium is established. The approach is firstly introduced with an Ag/AgCl element as a model ion-selective for determination of chloride also a liquid membrane based calcium-selective probe doped in a high mobility of Celgard membrane.[1] This strategy is further extended in the traditional ion-selective PVC membrane electrodes which are doped with an inert electrolyte, ETH 500 to maintain a required current transient. The external applied potential can be tuned the optical response range as a function of ion activity. The sigmodal colorimetric calibration curves are greatly performed the quantitative analysis in a wide range of real-world samples, which are well-correlated with atomic emission spectroscopy and direct potentiometry.

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Phase separation in the endocytic protein network

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Clathrin-mediated endocytosis is a major pathway of vesicle biogenesis in eukaryotic cells. It has been extensively studied in our model organism, the budding yeast.[1] A complex machinery consisting of over fifty proteins assembles during this process to gather cargo molecules, build the eponymous clathrin coat, and trigger a burst of actin polymerization that drives membrane bending and vesicle formation. In yeast, the order and duration of each step is precisely controlled – we call this the modular design of endocytosis.[2]

The early phase of endocytosis regulates the timing, site selection and cargo clustering at the nascent endocytic site. The exact molecular mechanisms of site initiation are unknown, as the process is highly redundant and lacks a clearly defined starting point.[3] Many early phase proteins show dynamic behaviours and variable lifetimes, and, unlike clathrin, are not known to form defined structures. The proteins involved contain many linear interaction motifs as well as charged, intrinsically disordered regions – two hallmarks of proteins able to phase separate under physiological conditions.[4]

Ede1 is one of the earliest-arriving endocytic proteins. It is a key initiation factor that facilitates the organization of other early phase proteins into discrete sites. We have observed micron-sized clusters of endocytic proteins that form in the yeast cytoplasm when the concentration of Ede1 is increased, or its recruitment to the plasma membrane is weakened. These clusters exhibit liquid-like properties that resemble phase-separated organelles; we call them 'endocytic nuages'. The nuages recruit multiple coat and early proteins, but their formation depends on coiled-coil and low complexity domains of Ede1. They are sensitive to Ede1 concentration and physical factors such as osmolarity and temperature.

We investigate the possibility that phase separation of proteins at the plasma membrane plays a role in the initiation of endocytic events and clustering of cargo. Such mechanism could explain the flexibility seen in the early phase, and allow for rapid regulation of endocytosis.

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Bimolecular photoinduced electron transfer: Putting theory to the test

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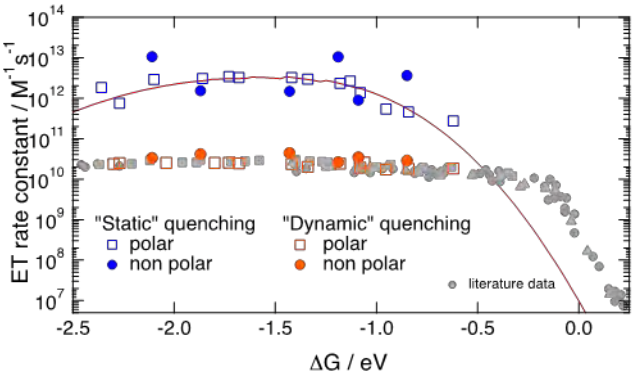
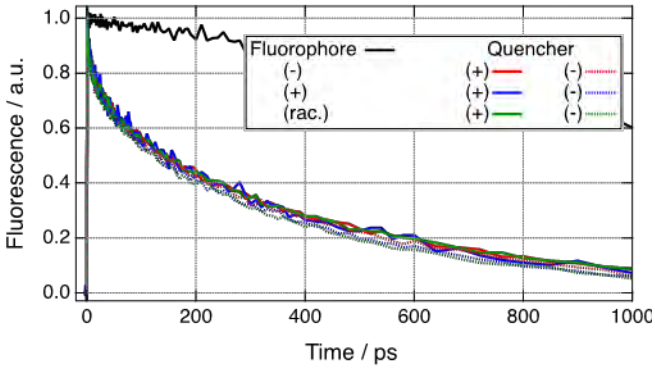
Electron transfer (ET) reaction is one of the simplest and at the same time, one of the most investigated photochemical reactions.[1] ET is usually rationalised in terms of Marcus theory, where the ET rate constant is expressed as a function of several parameters including the driving force, the reorganization energy and the electronic coupling.[2] Whereas the effect of driving force has been intensively studied, especially in polar solvents, the influence of the other parameters is less documented.

A study of the effect of the reorganization energy will first be presented. This energy includes contributions from the solvent (λ_s) and from intramolecular modes (λ_i). To investigate the effect of λ_s, we measured the ET dynamics in apolar solvents and compared them to previous results in polar solvent (left panel).[3] The effect of λ_i was explored using isotopic substitution.

In the second part, the influence on the ET rate constant of the chirality of the reactants (that should affect the electronic coupling) will be discussed. The ultrafast fluorescence quenching dynamics of the two enantiomeric forms of chiral fluorophores by chiral quenchers was compared to look for the presence of chiral selectivity in bimolecular photoinduced ET reactions (right panel).





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Development of membrane force sensors

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Membrane forces play pivotal roles in numerous physiological processes such as endocytosis, cell mutations and calcium signalling. Currently used characterization methods such as atomic force microscope (AFM) or optical tweezers allow for the controlled force application but not for the detection of the forces applied to the bilayers. Micro-aspiration of giant unilamellar vesicles (GUV) enables the quantification of surface tension, however, its conversion into local forces is difficult.

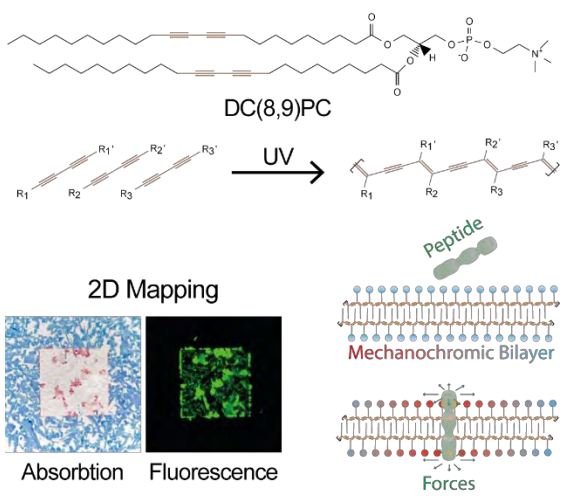

Figure: The chemical structure of DiynePC and polydiacetylene. Confocal microscopy image; outer part of the square blue state PDA, inner part red state PDA. The scheme shows the concept of the membrane force sensor we are developing.

We are developing a conductive[1] and mechanosensitive membrane probe that enables direct measurement of molecular forces applied within lipid bilayers. We employ a mechanochromic polymer polydiacetylene (PDA, Figure 1) that changes its colour and fluorescence intensity upon application of forces (Figure 2B).

As a first step, we studied in detail the polymerization process of the polymer with the use of infrared spectroscopy.[2] We then observed the reactivity of a biocompatible polymer against peptides, to discover that the developed assay proved also sensitive to mechanical stimuli.[3] An advantage that will allow us to incorporate the sensor within cellular membranes with minimal interference into the biochemistry of this with the surrounding environment. Its combination of sensitivity and the biocompatibility will allow us to incorporate this probe in live cells in future, providing us a further possibility to investigate force distribution during mitosis, cell migration, and interactions with medical implants. After a deep investigation into lateral force microscopy,[4] we finally probed the sensor against applied forces discovering a unique and unprecedented stimuli threshold.[5] The next and final step will be to apply it in the field of bio-cellular chemistry.

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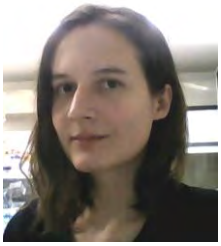
Unravelling the interplay between ESCRT-III sub-modules



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Membrane scission from the lumen of membrane structures is a geometrical challenge for the cell. This so-called inverted membrane fission is, however, required for crucial processes such as cytokinesis, plasma membrane repair and nuclear envelope reestablishment and repair. In eukaryotes, inverted membrane fission is uniquely performed by the ESCRT-III complex, which, in addition to its physiological functions, can also be hijacked by several viruses to help their exit from cells.

To shine light on the yet unknown mechanism of inverted membrane fission by ESCRT-III, we performed a detailed *in vitro* analysis of the dynamics, biochemical functions and membrane curvature preferences of ESCRT-III proteins and sub-modules.

Data independent SWATH mass spectrometry for lipidomic analysis in *T. gondii* and plasma

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Lipidomics approaches are generally conducted on triple quadrupole instruments (QqQ) using selected reaction monitoring (SRM) or on high resolution (HR) mass spectrometers with precursor quantification. Accurate quantification is one of the key points in a successful lipidomics study and more selective quantification on MS2 level (HR-SRM of any precursor) has so far not been fully exploited. A novel data independent workflow (SWATH/MS) was investigated to cover a large number of analytes for qualitative and quantitative analysis (QUAL/QUANT) of the lipidome of *T. gondii* and HFF cells to gain a better understanding of the mechanism of toxoplasmosis infection. As it is a close relative of the Plasmodium family potential cross links regarding Malaria infections might be drawn on a future stage.

The major difficulty in MS-based lipidomics is the complexity of the analytes as lipids are generally built up from building blocks (*e.g.* fatty acids and headgroups) which results in a large chemical space without main diversities within a lipid class. Therefore, data independent acquisitions have so far been restricted to MS1 quantification. Due to the large number of the selected precursors in a 25 unit SWATH approach, the resulting fragments cannot be assigned to any precursor which limits MS2 to a qualitative level used to support precursor identification. Using this approach >300 lipid sum compositions could be identified and quantified in *T. gondii* for various knock-outs in the lipid biosynthesis pathway. Significant changes within the sphingolipid pathway could be observed and can be used as an explanation of the phenotypes of the knock-outs.

Additionally, a unit mass SWATH/MS approach enabling the analysis of almost any ionizable lipid will be benchmarked against currently targeted methodologies (*e.g.* HILIC-SRM analysis, flow-injection differential ion mobility/SRM) to compare the performance and robustness of the different workflows for the analysis of phospholipids in human plasma.

The unit mass approach offers possibilities of precursor isolation while still retaining the full scan properties of TOF instrumentation. This allows for resolving isobaric species *(e.g.* Cl^- vs- OAc^-) on a fragment level. In contrary to SRM or MS1 quantification the resulting inaccuracies of absolute quantifications can be explained and bypassed due to flexible fragment choice. Compared to current MS1 quantification, the unit mass SWATH approach yields in up to 60% higher or lower concentration values when adduct related interferences are taken into account. For MS2 quantification on fatty acid level, increases in accuracy by up to 50% and precision by up 40% were observable.

$Au_{25}(SR)_{18}$ cluster assembly in multiple dimensions

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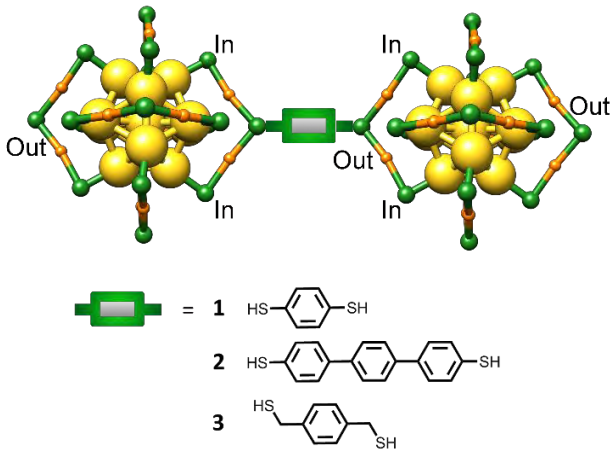
Designing new generations of superstructures by controlled self-assembly of nano-sized objects has great potential in applications such as molecular electronics or sensors. Monolayer protected gold clusters $Au_n(SR)_m$ are optimal building blocks due to their well-defined structure and high stability. Nanoclusters are a remarkable group of atomically precise structures in the field of noble metal nanoscience. A section of this group contains the 'magic clusters', owing their extreme stability due to the electronic configuration and robust Au-S bonds, where S originates from the thiolate ligands (SR). Their exceptional size-dependent physical, chemical and optical properties, related with their discrete molecular-like electronic structure make them a well-studied and rapidly growing topic.[1]



Scheme: $Au_{25}(SR)_{18}$ dimer linked by dithiol ligands 1-3.

Formation of superstructures without modification of the original clusters structure could however be a challenging task. Ligand exchange reactions are a valuable solution for this problem and frequently used methods to tailor the clusters properties towards required functions.[2] It involves the replacement on the $Au_n(SR)_m$ cluster surface of one of the protecting thiol (ligand) with a new entering ligand SR'. As bridging agent rigid linear aryl dithiols were chosen, replacing two original protecting ligands. The dithiol is expected to create a conducting system, which allows communication between the covalently bonded $Au_{25}(SR)_{18}$ clusters.[3] This formation of communicating clusters gives interesting perspectives for the creation of conducting two dimensional arrays. The development of these superstructures and their electrical properties is an important step towards the use of well-defined metal clusters in molecular electronics.

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Hydrophobic solvatochromic dye based ion-selective optical sensors

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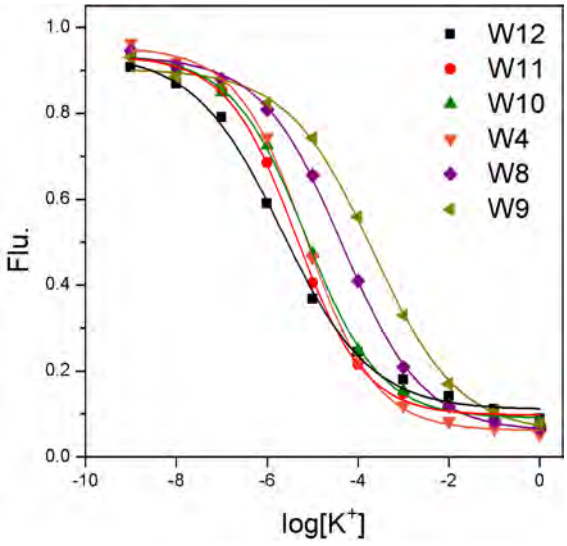
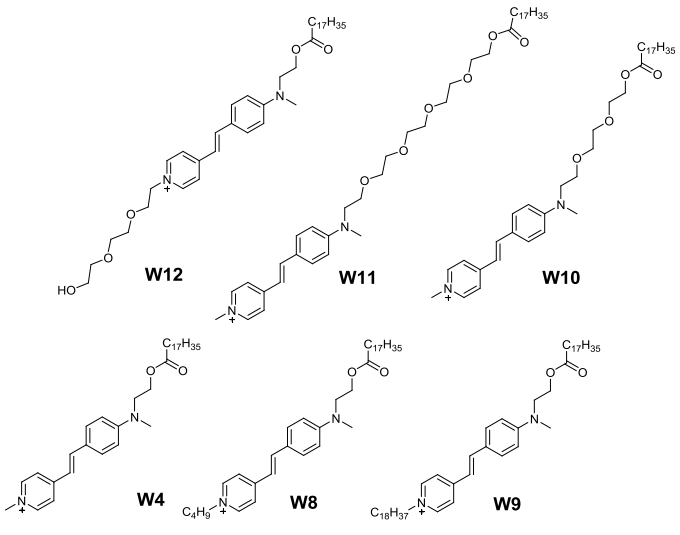
Miniaturized nano- and micro-particle ion-selective optodes have been extensively researched in the last few decades.[1] Typically, such ion optodes are composed of a polymeric phase containing a lipophilic or immobilized pH indicator (also called chromoionophore), an ion exchanger and an ionophore selective for the analyte which gives a cross response to sample pH changes.

Recently introduced ionic solvatochromic dyes (SD)[2,3] as transducer replace the pH indicator and renders the optical response independent of sample pH. However, water-soluble SDs are expelled to the aqueous phase during the ion-exchange progress, which is undesired. Hydrophobic SDs result in a localization of the ion-exchange process for ion-selective optodes and can avoid dye leakage. Based on this, a reversible nylon membrane based optical sensor was reported.[4] The ionic hydrophobic SD is also an amphiphilic molecule that is found to stabilize emulsified optical ion sensors without the help of added surfactant. Surprisingly, matrix-free emulsion sensor fabricated without any surfactant or plasticizer also exhibit functional response.[5]

Structural adjustment of SDs results in a range of lipophilicities. The functional response range can be successfully tuned by choosing the appropriate dye, making them potentially attractive for wider concentration range measurements.





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