Geneva chemistry & biochemistry days 2015

TH 15 January 2015, 9.00–17.40
FR 16 January 2015, 9.00–12.30

Sciences II – auditoire P.F. Tingry A150
30, quai Ernest-Ansermet – 1205 Genève
No registration required

Dr Ludger Johannes
Institut Curie, Paris

Prof. Eric T. Kool
Stanford University

Prof. David A. Leigh, FRS
University of Manchester

Prof. Gustavo E. Scuseria
Rice University

Junior speakers: • **Mahshid Chekini** • **Axelle Cotte** • **Thibault Dutronc** • **Ivan Franzoni** • **Augustinus Galih** • **Valentina Galli** • **Harekrishna Ghosh** • **Matteo Granelli** • **Houhua Li** • **Mohsen Moazzami** • **Maria Romanova-Michailidis** • **Valentin Trofimov** • **Valentina Valmacco** • **Quentin Verolet** • **Mahesh Vishe** • **Antoine Wallabregue** • **Claudio Zambaldo** •

FACULTÉ DES SCIENCES
SECTION DE CHIMIE ET BIOCHIMIE

UNIVERSITÉ DE GENÈVE

Foreword:

2015 goes with the 5th edition of the "Geneva Chemistry and Biochemistry Days" organised by the *Section de chimie et biochimie*, University of Geneva, and the steering committee is glad to welcome you to this now traditional event.

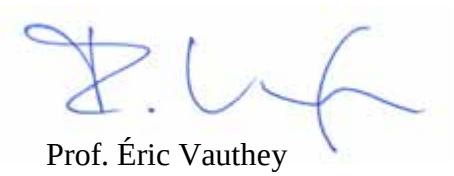
The "Geneva Days" are aimed at giving our students who are close to finishing their PhD studies the opportunity to present their research to a large audience from academia and industry. Our BSc and MSc students are also welcome to smell the very flavour of the research held in our School and learn a bit more about how to present results to a scientific audience.

Four distinguished lecturers will enrich the programme. They have been invited by the Departments of our School (*Département de chimie minérale et analytique, Département de chimie organique, Département de chimie physique, Département de biochimie*) and will seek to illustrate the breadth and quality of chemical and biochemical research in the world today.

This 1.5-day symposium is now the annual *Geneva rendez-vous* between chemists and biochemists from academia and the industry. The event will help stimulate fruitful discussions between young and advanced researchers, and give our students the opportunity to further prepare their professional careers.

We believe that it will give our guests an opportunity to appreciate the high quality of the different aspects of 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. Éric Vauthey
Président de la Section de chimie et biochimie

Steering and organising committee:

Prof. Jean Gruenberg	jean.gruenberg@unige.ch *Département de biochimie*
Prof. Nicolas Winssinger	nicolas.winssinger@unige.ch *Département de chimie organique*
Prof. Alan F. Williams	alan.williams@unige.ch *Département de chimie minérale et analytique*
Prof. Tomasz Wesolowski	tomasz.wesolowski@unige.ch *Département de chimie physique*
Prof. Eric Vauthey	eric.vauthey@unige.ch *Président de la Section de chimie et biochimie*
Dr Didier Perret	didier.perret@unige.ch *Chargé de communication de la Section de chimie et biochimie*

PROGRAMME – THURSDAY 15 JANUARY 2015

Session 1 – Morning Chairmen: **Prof. Tomasz Wesolowski + Dr Amalia Poblador Bahamonde**		
09:00- -09:15	**Prof. Eric Vauthey**	Welcome message Introduction
09:15- -10:05	**Prof. Gustavo E. Scuseria** Rice University	The strong correlation problem: A quantum chemistry perspective
10:05- -10:20	Coffee break Main hall of Sciences III	
10:20- -10:40	**Claudio Zambaldo**	Identification of a covalent bromodomain binder from a DNA display library of small molecule fragments
10:40- -11:00	**Valentin Trofimov**	Identification and characterization of novel antitubercular compounds
11:00- -11:20	**Valentina Valmacco**	Understanding forces acting between silica particles: Across ionic liquids and their mixtures with water
11:20- -11:40	**Antoine Wallabregue**	Modular synthesis of unprotected aziridines and chiral dyes and fluorophores using *N*-aminoacridinium cations
11:40- -12:00	**Maria Romanova-Michailidis**	Mechanism of Dpp gradient scaling in Drosophila wing imaginal discs

12:00- -14:00	Lunch (all senior lecturers + all junior lecturers) Restaurant-pizzeria Sole Mio, boulevard Carl-Vogt

Session 2 – Afternoon Chairmen: **Prof. Alan F. Williams + Prof. Kaori Sugihara**		
14:00- -14:20	**Harekrishna Ghosh**	Nanoparticle-polyelectrolyte composites: Enhanced IR absorption electron transfer upon visible light illumination
14:20- -14:40	**Mahesh Vishe**	Synthesis of functionalized polyether macrocycles
14:40- -15:00	**Valentina Galli**	Mechanistic studies on sequence-specific uptake of peptide nucleic acids by epithelial cells
15:00- -15:20	**Mohsen Moazzami Gudarzi**	Probing interactions between negatively charged colloidal particles in the presence of polyamine cations
15:20- -15:40	**Quentin Verolet**	Fluorescent flippers as membrane probes
15:40- 16:10	Coffee break Main hall of Sciences III	
16:10- -16:30	**Augustinus Galih**	Unraveling the roles of deoxysphingolipids in *C. elegans*
16:30- -16:50	**Houhua Li**	Tackling the steroid C-20 challenge by means of Ir-catalyzed selective isomerization
16:50- 17:40	**Prof. David A. Leigh, FRS** University of Manchester	Making the tiniest machines

17:40- 18:30	*Verre de l'amitié* Main hall of Sciences III
19:00-	Conference dinner (all senior lecturers + all chairmen + organisers)

PROGRAMME – FRIDAY 16 JANUARY 2015

Session 3 – Morning Chairmen: **Prof. Nicolas Winssinger + Prof. Jean Gruenberg + Dr Istvan Szilagyi**		
09:00- -09:50	**Prof. Eric T. Kool** Stanford University	Designer DNA bases: Probing molecules and mechanisms in biology
09:50- -10:10	Coffee break	Main hall of Sciences III
10:10- -10:30	**Ivan Franzoni**	Pd-catalyzed selective arylation of aldehydes
10:30- -10:50	**Matteo Granelli**	Chiral heteronuclear supramolecular dimers: Synthesis and magnetic properties
10:50 -11:10	**Mahshid Chekini**	Bottom-up fabrication of large scale plasmonic templates
11:10 -11:30	**Axelle Cotte**	From 2D to 1D homodecoupled proton NMR spectra
11:30 -11:50	**Thibault Dutronc**	Liquid crystalline and thermodynamic properties of methylated cyanobiphenyl derivatives
11:50- 12:40	**Dr Ludger Johannes** Institut Curie	Building endocytic pits without clathrin
12:40- 12:45	**Prof. Eric Vauthey**	Concluding remarks

Building Endocytic Pits Without Clathrin

Dr Ludger JOHANNES

Unité Compartimentation et Dynamique Cellulaires
Institut Curie – INSERM; Paris; France
ludger.johannes@curie.fr

Several endocytic processes do not require the activity of clathrin, and it has been a major question in membrane biology to know how the plasma membrane is bent and cargo proteins are sorted in these cases. Our recent studies have uncovered a novel mechanism: nanodomain construction by glycosphingolipid-binding toxins (Shiga and cholera toxins) and polyoma viruses (SV40) induces membrane curvature changes and drives the clathrin-independent formation of endocytic pits for the cellular uptake of these pathogens or pathogenic factors (Nature 450, 670-675; NCB 12, 11-18). We could show that actin polymerization on Shiga toxin-induced endocytic tubules is sufficient to trigger scission in a process that requires membrane reorganization (Cell 140, 540-553). Our data suggests that tubule membranes are poised such that an appropriate inducer can cause lipid segregation, thereby generating domain boundary forces that trigger line tension-driven squeezing of the tubule membranes leading to scission (Cell 142, 507). We are now analyzing how cortical actin dynamics contributes to glycosphingolipid clustering on active membranes, thereby facilitating the nucleation of endocytic tubules exploiting physical forces that had not been linked before to the membrane-mediated clustering of biomolecules. Another important aspect concerns the recruitment of cellular machinery for scission of uptake intermediates from the plasma membrane (Nature, in press), and targeting to and fusion with endosomes. Finally, we are studying cellular proteins that like the toxins use glycosphingolipids for endocytic membrane mechanics (NCB 16, 595), thereby regulating the cell surface dynamics of various markers with critical roles in cellular processes such as cell migration.

Our fundamental membrane biology research has incited us to explore the glycosphingolipid-binding B-subunit of Shiga toxin as antigen delivery tools for biomedical applications related to cancer immunotherapy (Science Translat Med 5, 172ra20). We are particularly exploring the mechanisms by which antigens are translocated across endosomal membranes to reach the cytosolic processing machinery.

Designer DNA Bases: Probing Molecules and Mechanisms in Biology

Prof. Eric T. KOOL

Department of Chemistry
Stanford University; Stanford, California; USA
kool@stanford.edu

Standard organic fluorophores have been highly useful in biology and medicine, but they exhibit physical properties that can limit their applications. For example, common dyes have relatively short Stokes shifts and each has its unique excitation wavelength; these properties make it difficult to image multiple biological species simultaneously, especially in moving systems, and make instrumentation more complex and expensive than it needs to be.

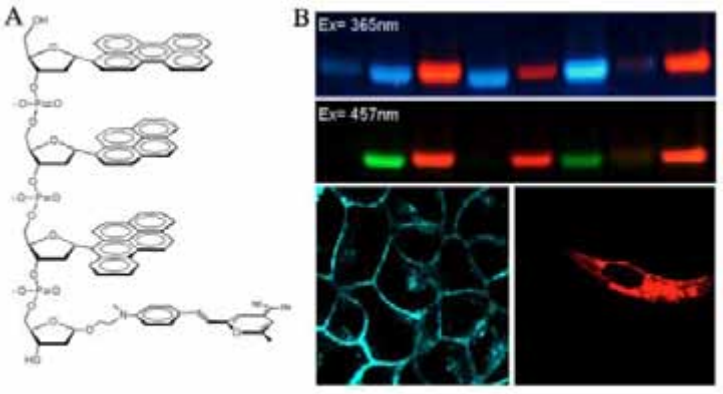


Figure 1. (A) Example of DNA-polyfluorophore. (B) Genetically encoded multispectral protein labeling in vitro and in live cells.

We have been investigating a new approach for construction of fluorescent labels, by assembling single chromophores into short DNA-like oligomers built on a DNA backbone. The oligomers are termed oligodeoxyfluorosides (ODFs). The close proximity of dyes (Fig. 1) results in multiple forms of energy and excitation transfer, yielding complex, emergent emission properties. The repetitive DNA synthesis cycle allows us to combine monomeric fluorophores in thousands of combinations in relatively low-molecular-weight structures (typically tetramers) that can be readily conjugated both to small molecules and large biomolecules[1-3]. Screening libraries of ODFs has enabled us to identify sets of dyes that can be excited at a single wavelength but emit in colors across the visible spectrum. Such ODFs have large Stokes shifts and high quantum yields, and can be used in real-time imaging of moving biological systems. ODFs can be cell permeable on their own, or they can be delivered intracellularly with DNA uptake reagents such as cationic lipids. We have further developed methods for conjugating them to antibodies, and using genetic encoding methods, to other proteins of interest in living cells[2,3].

ODF dyes can show static fluorescence properties, or they can change in response to molecular stimuli. Screening libraries of such ODFs has allowed us to identify sequences that respond with changes in fluorescence to organic and inorganic species in the air and in water[4-6].

References

1. Y.N. Teo, J.N. Wilson, E.T. Kool. *J. Am. Chem. Soc.* **2009**, *131*, 3923-
2. J. Guo, S. Wang, N. Dai, Y.N. Teo, E.T. Kool. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 3493-
3. V. Singh, S. Wang, E.T. Kool. *J. Am. Chem. Soc.* **2013**, *135*, 6184-
4. C.-K. Koo, S. Wang, R.L. Gaur, F. Samain, N. Banaei, E.T. Kool. *Chem. Commun.* **2011**, *47*, 11435-
5. L.H. Yuen, R.M. Franzini, S. Wang, P. Crisalli, V. Singh, W. Jiang, E.T. Kool. *Angew. Chem. Int. Ed.* **2014**, *53*, 5361-
6. T. Ono, S. Wang, C.K. Koo, L. Engstrom, S.S. David, E.T. Kool *Angew. Chem. Int. Ed.* **2012**, *51*, 1689-

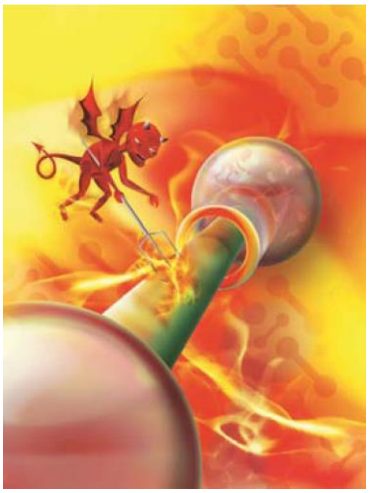
Making the Tiniest Machines

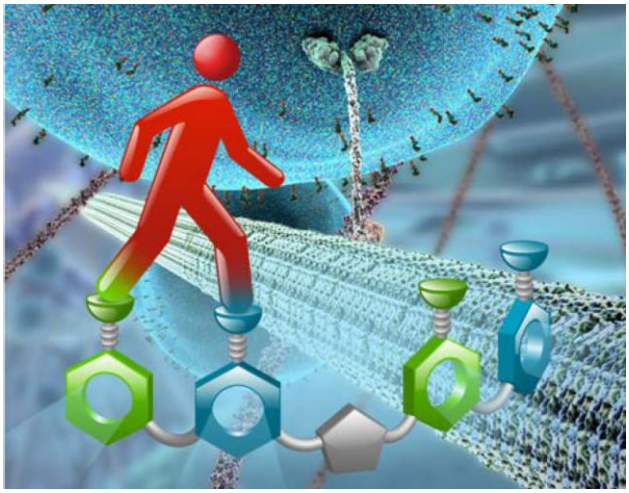
Prof. David A. LEIGH, FRS

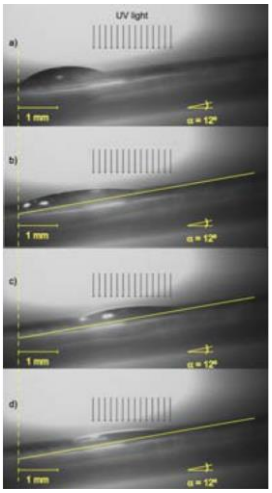
School of Chemistry
University of Manchester; Manchester; UK
david.leigh@manchester.ac.uk

Over the past few years some of the first examples of synthetic molecular level machines and motors —all be they primitive by biological standards— have been developed. These molecules respond to light, chemical and electrical stimuli, inducing motion of interlocked components held together by hydrogen bonding or other weak molecular interactions.

Perhaps the best way to appreciate the technological potential of controlled molecular-level motion is to recognise that nanomotors and molecular-level machines lie at the heart of every significant biological process. Over billions of years of evolution Nature has not repeatedly chosen this solution for achieving complex task performance without good reason. In stark contrast to biology, none of mankind's fantastic myriad of present day technologies exploit controlled molecular-level motion in any way at all: every catalyst, every material, every polymer, every pharmaceutical, every chemical reagent, all function exclusively through their static or equilibrium dynamic properties. When we learn how to build artificial structures that can control and exploit molecular level motion, and interface their effects directly with other molecular-level substructures and the outside world, it will potentially impact on every aspect of functional molecule and materials design. An improved understanding of physics and biology will surely follow.







Selected papers

"Sequence-Specific Peptide Synthesis by an Artificial Small-Molecule Machine". *Science* **2013**, *339*, 189-193. • "A Single Synthetic Small Molecule that Generates Force Against a Load". *Nature Nanotech.* **2011**, *6*, 553-557. • "A Synthetic Small Molecule That Can Walk Down a Track" *Nature Chem.* **2010**, *2*, 96-101. • "Operation Mechanism of a Molecular Machine Revealed Using Time-Resolved Vibrational Spectroscopy". *Science* **2010**, *328*, 1255-1258. • "Hybrid Organic-Inorganic Rotaxanes and Molecular Shuttles". *Nature* **2009**, 458, 314-318. • "A Molecular Information Ratchet". *Nature* **2007**, *445*, 523-527. • "Macroscopic Transport by Synthetic Molecular Machines". *Nature Mater.* **2005**, *4*, 704-710. • "A Reversible Synthetic Rotary Molecular Motor". *Science* **2004**, *306*, 1532-1537. • "Unidirectional Rotation in a Mechanically Interlocked Molecular Rotor". *Nature* **2003**, *424*, 174-179.

The Strong Correlation Problem: a Quantum Chemistry Perspective

Prof. Gustavo E. SCUSERIA

Department of Chemistry
Rice University; Houston, Texas, USA
guscus@rice.edu

Computational quantum chemistry is a very successful field. However, 85 years after Schrodinger's equation, strongly correlated systems remain outside the realm of accurate calculations. The reigning wavefunction paradigm, coupled cluster (CC) theory with single and double excitations, accurately describes weak electron correlation but is known to fail in cases of strong correlation. The same is true for density functional approximations. This talk will address recent efforts in our research group to deal with strongly correlated systems, including bulk systems, using first principles wavefunction methods. Our models make extensive use of similarity transformed Hamiltonians and the concept of pairing, but they do so utilizing two different bases: one is defined by the traditional reference determinant and the other one by the correlator themselves. Using these models as impurity solvers, we can study bulk systems using quantum embedding theories. This talk will present a pedagogical description of the strong correlation problem and discuss how quantum chemistry inspired tools can address its challenge.

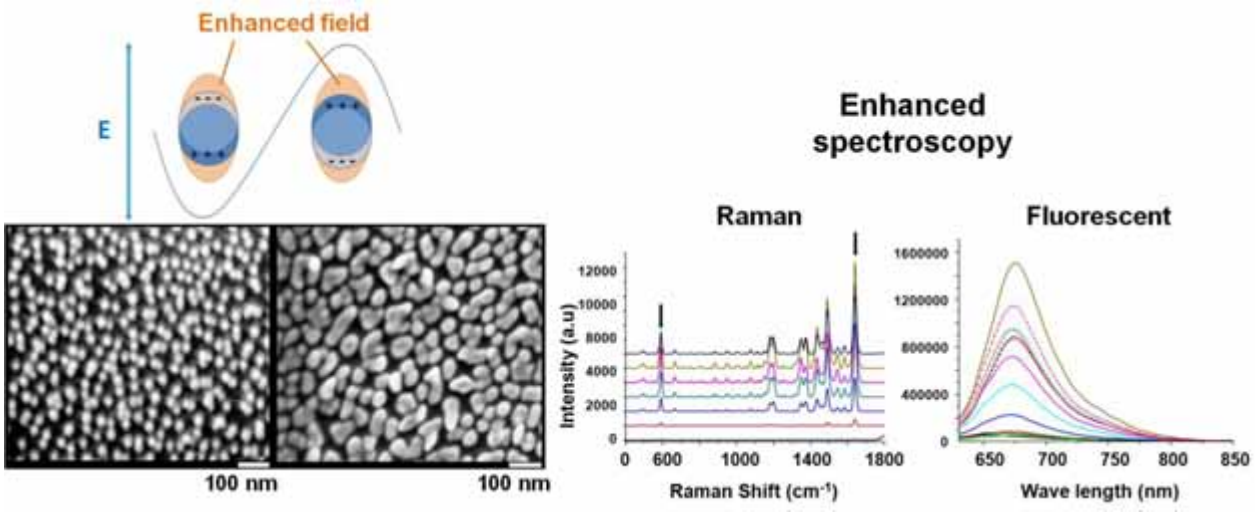
Bottom-up Fabrication of Large Scale Plasmonic Templates

Mahshid CHEKINI

mahshid.chekini@unige.ch

Metallic nanoparticles can support collective oscillations of conduction electrons which are called localized surface plasmon resonances (LSPR). For noble metal nanoparticles these resonances are placed in the visible region of the electromagnetic spectrum and as a result they present vivid and stable color which originates their earlier usage as a staining agent in ancient glass artifacts. In recent years their potential application as an efficient source of light, heat and energetic electrons at the nanoscale regime attracts a lot of attention and lead to their extensive study. Nanoparticles' plasmon resonances can be tuned by altering their size, shape, surrounding medium and even their assemblies and spatial arrangement. Their unique light interaction and advances in their syntheses and application paved the way toward their use in chemical, biological and therapeutics fields. Their strong interaction with light (absorption, scattering and electromagnetic field confinement in their vicinity) found application in sensing, detection and enhanced spectroscopy. These particles can work as a nanoantenna to enhance luminescence, fluorescence and Raman scattering signals[1,2].

Here we present our attempts to design and fabricate nano-structured templates. We further investigate their potential in electromagnetic field engineering and as a result their application in sensing and spectroscopy. We used facile bottom up approaches, mainly charge driven assemblies of these nanoparticles on different functionalized surfaces. These structures were modified by LBL (layer by layer) and seeded growth methods to enhance their ability in surface enhance Raman and fluorescence spectroscopy.



References

1. P.K. Jain, X. Huang, I.H. El-Sayed, M.A. El-Sayed. *Acc. Chem. Res.* **2008**, *41*, 1578-
2. J.R. Lakowicz, K. Ray, M. Chowdhury, H. Szmacinski, Y. Fu, J. Zhang, K. Nowaczyk. *Analyst* **2008**, *133*, 1308-

From 2D to 1D Homodecoupled Proton NMR Spectra

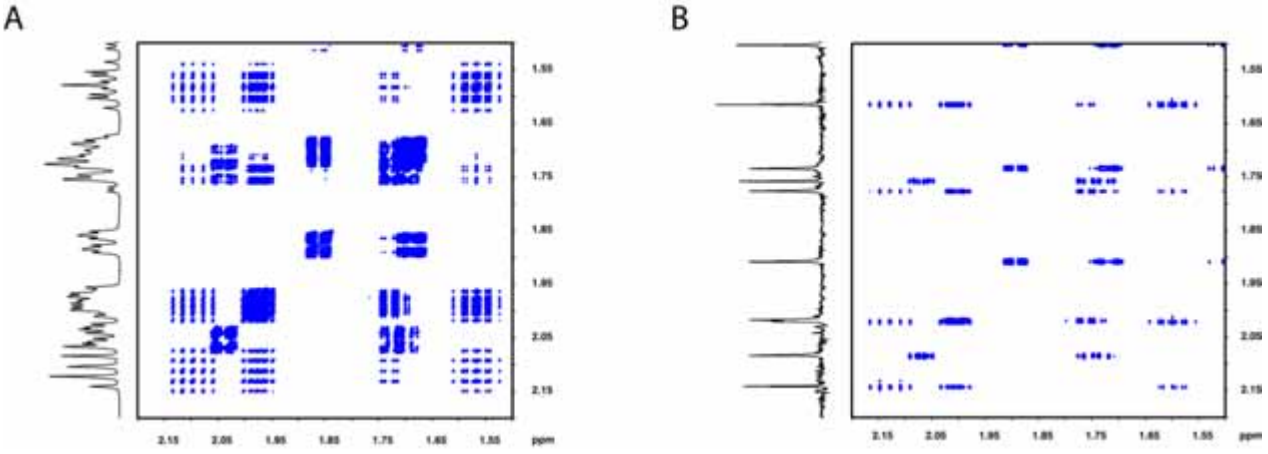
Axelle COTTE

axelle.cotte@unige.ch

In proton spectra, the coupling structures due to homonuclear scalar coupling often cause signal overlap making it difficult to exploit one- and two-dimensional spectra. To simplify the collection of NMR information, a well-known solution is to apply a decoupling method. The obtaining of proton spectra where multiplets are collapsed into singlets is therefore a quite interesting decades-old challenge[1-4].

We propose here a new approach based on spatial encoding[5] and spectral aliasing[6] to quickly obtain high-resolution 2D spectra leading to homodecoupled 1D proton spectra[7].

The Zangger-Sterk[5] decoupling element has been introduced in the t_1 evolution time of the 2D experiment. Combined with spectral aliasing, it allows an enhancement of the spectral resolution and a reduction of the experimental time proportional to the reduction of the spectral window in the F1 dimension. This factor can reach two orders of magnitude and leads to the separation of signals of protons less than 2 Hertz apart.



(A) 1D and 2D spectra recorded with high-resolution (B) 1D and 2D homodecoupled spectra.

References

1. M. Woodley, R. Freeman. *J. Magn. Reson. Ser. A* **1994**, *109*, 103-
2. A.J. Pell, R.A.E. Edden, J. Keeler. *Magn. Reson. Chem*. **2007**, *45*, 296-
3. A.J. Pell, J. Keeler. *J. Magn. Reson*. **2007**, *189*, 293-
4. J.A. Aguilar, S. Faulkner, M. Nilsson, G.A. Morris. *Angew. Chem. Int. Ed*. **2010**, *49*, 3901-
5. K. Zangger, H. Sterk. *J. Magn. Reson*. **1997**, *124*, 486-
6. D. Jeannerat, in *Encyclopedia of Magnetic Resonance*; G.A. Morris, Ed.; John Wiley, Chichester, **2011**
7. A. Cotte, D. Jeannerat. *Submitted*

Liquid Crystalline and Thermodynamic Properties of Methylated Cyanobiphenyl Derivatives

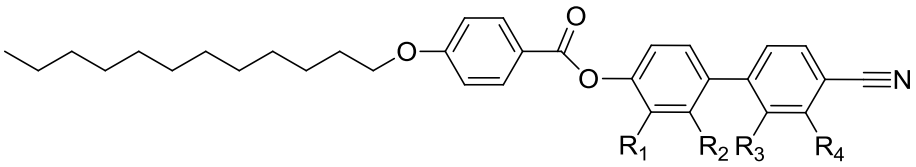
Thibault DUTRONC

thibault.dutronc@unige.ch

Intermolecular interactions are the main concern when designing new liquids crystalline materials[1]. Focussing on lanthanidomesogens[2] or simpler organic molecules[3], methylated cyanobiphenyl groups are known to induce great variability in terms of intermolecular interactions, phase sequences and thermodynamic parameters. Eight new amphiphilic compounds (Image below) were designed to study the effects of methyl perturbations in both solid and liquid crystal states. These methylated compounds, as well as six reference compounds of variable chain lengths, were synthetized and studied via XRD, SA-XRD, DSC and PLM.

The 4'-cyano-[1,1'-biphenyl]-4-yl 4-(dodecyloxy)benzoate reference compound exhibits a stable smectic phase and its isotropization occurs at 220°C. Iterative methylation greatly disturbs the phase sequence while gradually lowering the clearing points. The effects of methyl perturbations on the crystal structures, the intermolecular interactions, the phase transition thermodynamics (ΔH_{tr} and ΔS_{tr}), and the nature of the observed mesophases, will be discussed.

In an attempt to correlate structural variations with thermodynamic parameters, our results will be considered within the frame of enthalpy/entropy compensation and compared with those of the 4'-cyano-[1,1'-biphenyl]-4-yl 4-(*n*-alkoxy)benzoate family. Recent works highlighted a linear correlation between cohesion free energy densities (*cfed*)[3,4] and melting temperature which will also be investigated in these compounds.



$RCB_{Ø}$: $R_1 = R_2 = R_3 = R_4 = H$

RCB_1 : $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$

RCB_2 : $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$

RCB_3 : $R_1 = R_2 = R_3 = H$, $R_4 = CH_3$

RCB_3 : $R_1 = R_2 = R_3 = CH_3$, $R_4 = H$

RCB_5 : $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$

RCB_6 : $R_1 = R_3 = CH_3$, $R_2 = R_4 = H$

RCB_7 : $R_1 = R_3 = H$, $R_2 = R_4 = CH_3$

RCB_8 : $R_1 = R_4 = CH_3$, $R_2 = R_4 = H$

This work couldn't have been carried out without the invaluable contributions of E. Terazzi, L. Guénée, K.-L. Buchwalder and C. Piguet.

References

1. A. Levine, In *Introduction to Liquid Crystals*; E.B. Priestley, P. Wojtowicz, P. Sheng. Springer US, **1975**, 15-
2. T.B. Jensen, E. Terazzi, K.-L. Buchwalder, L. Guénée, H. Nozary, K. Schenk, B. Heinrich, B. Donnio, D. Guillon, C. Piguet. *Inorg. Chem.* **2010**, *49*, 8601-
3. T. Dutronc, E. Terazzi, L. Guénée, K.-L. Buchwalder, A. Spoerri, D. Emery, J. Mareda, S. Floquet, C. Piguet. *Chem. Eur. J.* **2013**, *19*, 8447-
4. T. Dutronc, E. Terazzi, C. Piguet. *RSC Advances* **2014**, *4*, 15740-

Pd-Catalyzed Selective Arylation of Aldehydes

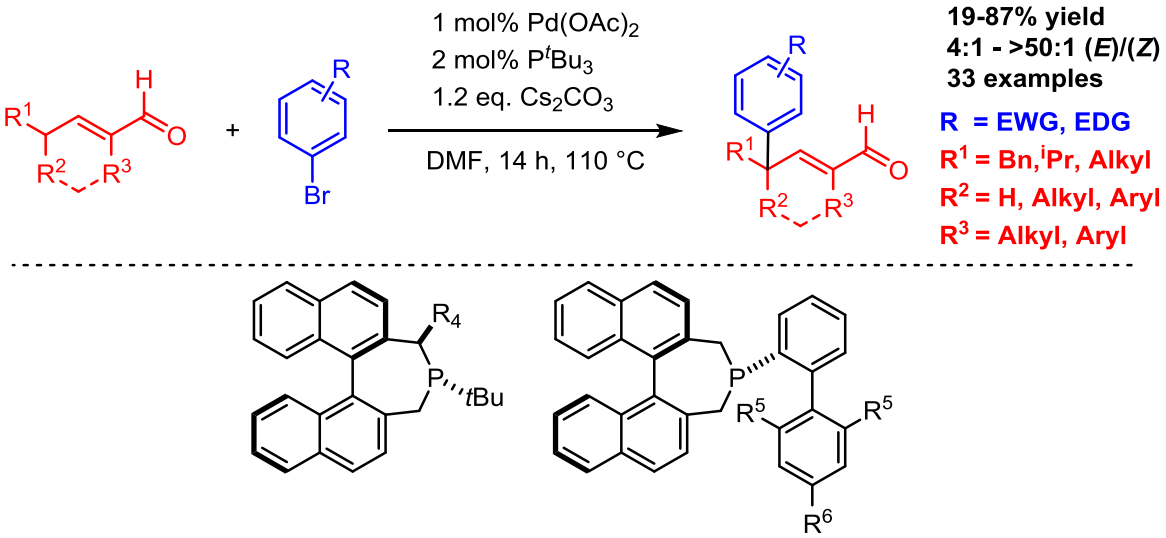
Ivan FRANZONI

ivan.franzoni@unige.ch

In the last two decades, the α-arylation of enolizable carbonyl compounds had advanced with significant strides[1]. In this context, aldehydes have revealed particularly challenging substrates[2]. Our group has recently reported an enantioselective intramolecular α-arylation of α-branched aldehydes using novel chiral (P,N) ligands[3]. In a direct continuation of this work, and based on the vinylogous analogy[4], we developed a perfectly regio- and stereoselective intermolecular γ-arylation of γ-branched α,β-unsaturated aldehydes using commercial ligands and palladium precursors[5]. In addition to the γ quaternary center, the products of this remote coupling bear substantial synthetic potential as derivations are possible both at the olefinic position and the aldehyde functionality.

We next set out to develop an enantioselective version of this reaction. We present herein our results in this direction. This includes the design and the stereoselective synthesis of a novel class of monodentate chiral phosphine ligands as well as their evaluation in this challenging cross-coupling reactions[6].

Preliminary results on the biological activity of these coupling products will be also disclosed.



References

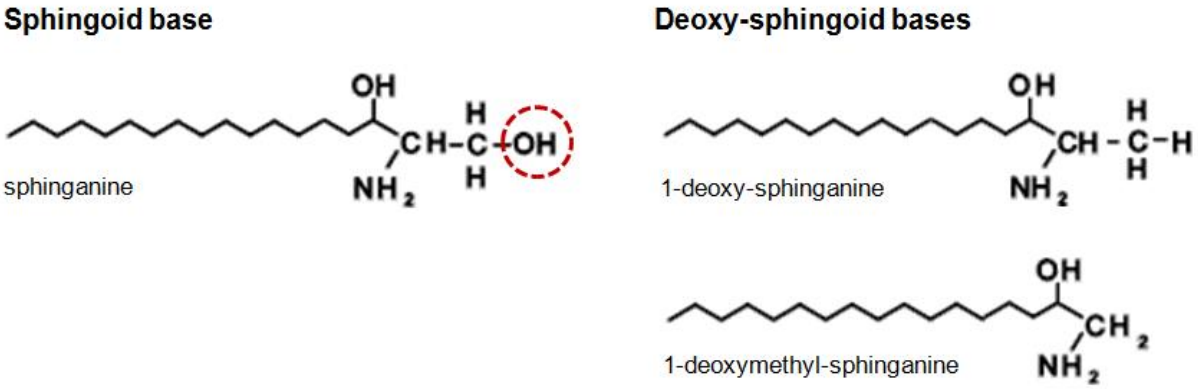
1. (a) C.C.C. Johansson, J.T. Colacot. *Angew. Chem. Int. Ed.* **2010**, *49*, 676-. (b) F. Bellina, R. Rossi. *Chem. Rev.* **2010**, *110*, 1082-. (c) C. Mazet. *Synlett.* **2012**, *23*, 1999-
2. (a) Y. Terao, Y. Fukuoka, T. Satoh, M. Miura, N. Nomura. *Tetrahedron Lett.* **2002**, *43*, 101-. (b) G.D. Vo, J.F. Hartwig. *Angew. Chem. Int. Ed.* **2008**, *47*, 2127-. (c) J. Garcia-Fortanet, S.L. Buchwald. *Angew. Chem. Int. Ed.* **2008**, *47*, 8108-
3. P. Nareddy, L. Mantilli, L. Guénée, C. Mazet. *Angew. Chem. Int. Ed.* **2012**, *51*, 3826-
4. (a) R.C. Fuson. *Chem. Rev* **1935**, *16*, 1-. (b) Y. Terao, T. Satoh, M. Nomura, M. Miura. *Tetrahedron Lett.* **1998**, *39*, 6203-
5. I. Franzoni, L. Guénée, C. Mazet. *Chem. Sci.* **2013**, *4*, 2619-
6. I. Franzoni, L. Guénée, C. Mazet *Tetrahedron* **2014**, *70*, 4181-

Unraveling the Roles of Deoxysphingolipids in *C. elegans*

Augustinus GALIH

augustinus.galih@unige.ch

Sphingolipids are exceptionally versatile biomolecules that serve essential roles as structural components of cellular membranes and as signaling molecules in a wide range of physiological and pathological processes. The first step of the sphingolipid biosynthesis pathway is the condensation of serine with palmitoyl-coA, catalyzed by serine palmitoyltransferase (SPT), generating a sphingoid base, sphinganine. Besides serine, SPT is also able to use alanine or glycine at much lower frequencies to produce two deoxysphingoid bases, 1-deoxy-sphinganine and 1-deoxymethyl-sphinganine, respectively[1] (Figure below).



Different from sphingoid bases, deoxysphingoid bases lack a hydroxyl group at the first carbon atom. The hydroxyl group is required for their conversion to complex sphingolipids and for their degradation. Therefore, deoxysphingoid bases have limited conversion possibilities and tend to accumulate in the cell. In human, the accumulation of deoxysphingoid bases is associated with a neurological disease named Hereditary Sensory and Autonomic Neuropathy type IA (HSAN IA)[2].

In the roundworm *C. elegans*, sphingolipids are involved in anoxia resistance[3]. We propose a mechanism by which deoxysphingolipids cause *C. elegans* susceptibility to anoxia by using a chemically-synthesized deoxysphingolipid and a *C. elegans* model of HSAN IA. In addition, we will exploit the *C. elegans* model to unravel the roles of deoxysphingolipids in normal and pathological conditions.

References

1. A. Penno, M.M. Reilly, H. Houlden, M. Laurá, K. Rentsch, V. Niederkofler, E.T. Stoeckli, G. Nicholson, F. Eichler, R.H. Jr Brown, A. von Eckardstein, T. Hornemann. *J Biol Chem.* **2010**, *285*, 11178-
2. A. Rotthier, J. Baets, V. Timmerman, K. Janssens. *Nat Rev Neurol*. **2012**, 8, 73-
3. V. Menuz, K.S. Howell, S. Gentina, S. Epstein, I. Riezman, M. Fornallaz-Mulhauser, M.O. Hengartner, M. Gomez, H. Riezman, J.-C. Martinou. *Science* **2009**, *324*, 381-

Mechanistic Studies on Sequence-Specific Uptake of Peptide Nucleic Acids by Epithelial Cells

Valentina GALLI

valentina.galli@unige.ch

Peptide nucleic acids (PNAs) are artificially synthesized molecules that mimic DNA in which the phospho-deoxyribose backbone is substituted by a pseudo-peptide backbone[1]. They are being studied as biomolecular tools such as antisense agents, molecular probes and biosensors since they are more stable than DNA and RNA molecules[2].

From a cell-uptake screening of 10'000 different PNA sequences of Serine-modified 14mers we found evidence of sequence specific uptake of PNAs, where some sequences were entering HeLa cells more efficiently then others.

We identified by mass spectrometry a possible candidate that could provide the means for the cell to discriminate between PNAs: Caprin-1, a protein known to bind nucleic acids that is up-regulated in highly proliferating cells[3].

In pull-down experiments, Caprin-1 is co-precipitating with PNAs in a sequence-specific manner that recapitulates the specificity we observed in cells. We also show that Caprin-1 overexpression is increasing cell uptake of PNAs, again in a sequence-specific fashion.

Currently we are confirming the involvement of Caprin-1 in cell uptake of PNAs and we plan to study how the sequence-specificity is achieved.

References

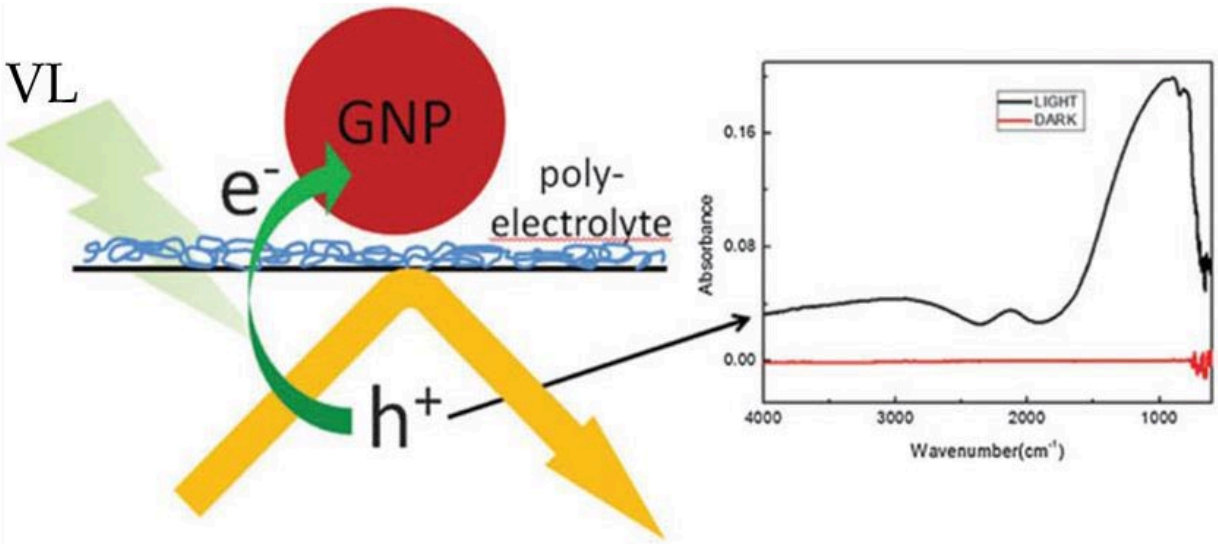
1. P.E. Nielsen, M. Egholm, R.H. Berg, O. Buchardt. *Science* **1991**, *254*, 1497-
2. P.E. Nielsen, M. Egholm. *Curr. Issues Mol. Biol.* **1999**, 89-
3. B. Grill, G.M. Wilson, K. Zhang, B. Wang, R. Doyonnas, M. Quadroni, J.W. Schrader, *J. Immun.* **2004**, 2389-

Nanoparticle – Polyelectrolyte Composites: Enhanced IR Absorption Electron Transfer upon Visible Light Illumination

Harekrishna GHOSH

harekrishna.ghosh@unige.ch

Attenuated total reflection infrared (ATR-IR) spectroscopy and scanning electron microscopy (SEM) are used to study the formation and the properties of nanoparticle-polyelectrolyte composites on a Ge internal reflection element. First the Ge ATR crystal is functionalized by a positively charged polyelectrolyte poly (allylamine hydrochloride) (PAH). Then negatively charged citrate-stabilized nanoparticles (gold, silver) are adsorbed onto the modified Ge ATR crystal. The layer-by-layer growth of polyelectrolytes (PAH and PSS; poly (sodium 4-styrenesulfonate)) on top of the nanoparticles is followed in situ. Enhancement of polyelectrolyte signal is observed and is more pronounced very near to the nanoparticles surface. Stronger enhancement is observed from bigger nanoparticles and when their coverage on the surface is high. This shows that the inter-particle distance plays a crucial role for the enhanced infrared absorption. Silver nanoparticles show much stronger enhancement than gold nanoparticles, which allows to detect submonolayers of adsorbed molecules. Upon illumination of gold nanoparticles adsorbed on PAH-functionalized Ge with visible and near infrared light, a strong infrared absorption has been observed, which can be traced to intervalence band transitions in Ge. This reveals the existence of holes in the Ge near its valence band edge (Figure below). The effect develops with a peculiar kinetics, which may indicate the development of an interfacial layer between germanium and gold that allows efficient electron transfer upon illumination.



References

1. H. Ghosh, T.J. Bürgi. *Phys. Chem. C* **2013**, *117*, 26652-
2. H. Ghosh, A. Bouhekka , T.J. Bürgi. *Phys. Chem. Chem. Phys*. **2014**, *16*, *19402-*

Chiral Heteronuclear Supramolecular Dimers: Synthesis and Magnetic Properties

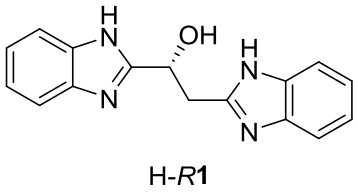
Matteo GRANELLI

matteo.granelli@unige.ch

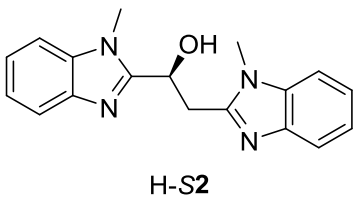
Tridentate chiral bis-benzimidazol ligands[1,2] are readily prepared and coordinated to octahedral transition metals (Figure 1). They can form complexes of the type [M**L**$_2$] as *cis*-or *trans*- isomers or heterocubane complexes[2,3] containing a central [M$_4$**L**$_4$] core. With M(III) ions alcohol functions on the ligands are deprotonated while with M(II) ions they can be deprotonated in slightly basic solution.

cis-[M**L**$_2$] complexes crystallise as supramolecular dimers: the connection between two [M**L**$_2$] subunits is by hydrogen bonding. In the M(II) – M(II) dimers one alcohol function is protonated while the other is not, in this way two [M(H-**L**)**L**] subunits are linked by two hydrogen bonds. In the M(III) – M(II) dimers the ligands in the M(II) subunit are protonated while the ligands in the M(III) subunit are not, giving two hydrogen bonds as a result (Figure 2).

In both M(II) – M(II) and M(III) – M(II) supramolecular dimers, the short O ··· O distance (2.5 Å) is indicative of strong hydrogen bonding. Due to this spatial proximity, magnetic exchange between the metal centres is allowed, being antiferromagnetic or ferromagnetic depending on the nature of the metals involved.



H-*R***1**



H-*S***2**

Figure 1: ligands (H-**L**)

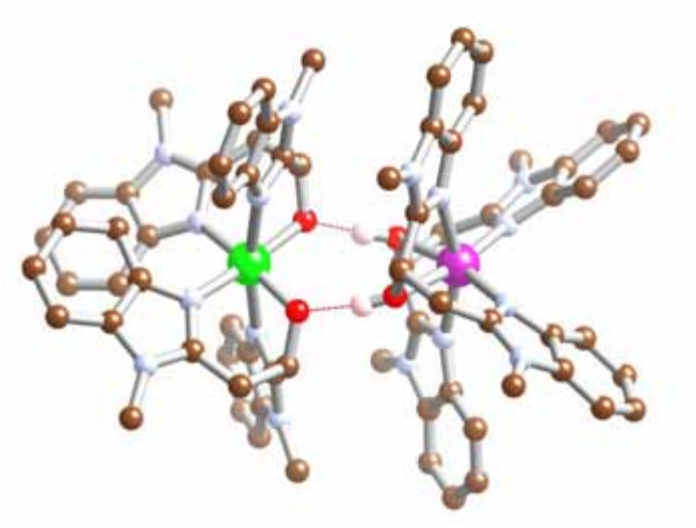


Figure 2: the complex [Mn^{III}(*S***2**)$_2$:Mn^{II}(H-*S***2**)$_2$]$^{3+}$

References

1. G. Van Albada, J. Reedijk, R. Hämäläinen, U. Terpeinen, A.L. Spek. *Inorg. Chim. Acta*, **1989**, *163*, 213-
2. C. Deville, A. Spyratou, P. Aguirre-Etcheverry, C. Besnard, A.F. Williams. *Inorg. Chem.*, **2012**, *51*, 8667-
3. C. Deville, M. Granelli, A.M. Downward, C. Besnard, L. Guenée, A.F. Williams. *Dalton Trans.*, **2014**, *43*, 12917-

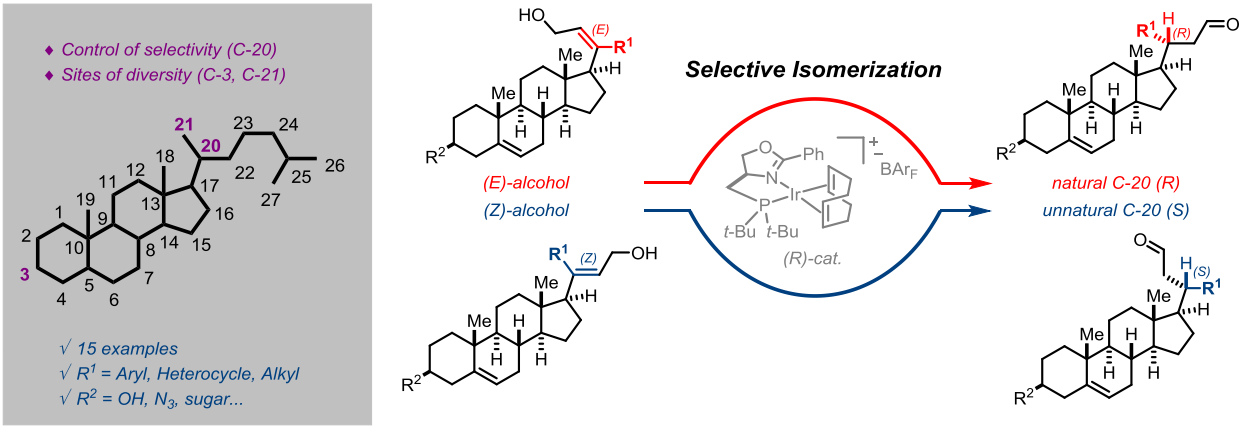
Tackling the Steroid C-20 Challenge by Means of Ir-Catalyzed Selective Isomerization

Houhua LI

houhua.li@unige.ch

The discovery and investigation of steroids have not only left a lasting impact on many aspects of chemistry, biology, medicine but also on our society[1]. Steroids are characterized by a prototypical cyclopentenophenanthrene ring system and a side chain attached to this polycyclic framework at C-17. Driven by the distinguished biological activity differences between C-20 (*R*) and C-20 (*S*) isomers, the specific stereocontrolled construction of this exocyclic stereocenter is recognized as one of the most difficult challenges in the field[2]. While numerous methods have provided access to steroids having the 'natural' C-20 (*R*) configuration, access to the corresponding C-20 (*S*) epimers remains problematic[3]. In addition, it is widely appreciated that the ideal strategy to tackle this challenge should be modular and flexible to achieve the requisite structural diversity for subsequent therapeutic applications[4].

Starting from either (*E*) or (*Z*) primary allylic alcohols and based on the Ir-catalyzed isomerization developed in our laboratories[5], we present herein a new strategy which enables access to a structurally diverse collection of both C-20 (*R*) and C-20 (*S*) steroid analogues with high levels of selectivity and broad functional group tolerance[6].



References

1. K.C. Nicolaou, T. Montagnon. *Molecules that Changed the World*, Wiley-VCH:Weinheim, 2008.
2. Y. Zhang, S.J. Danishefsky. *J. Am. Chem. Soc.* **2010**, *132*, 9567-
3. B.B. Shingate, B.G. Hazra. *Chem. Rev.* **2014**, *114*, 6349-
4. H. Renata, Q. Zhou, P.S. Baran. *Science* **2013**, *339*, 59-
5. a) For a recent review, see: L. Mantilli, C. Mazet. *Chem. Lett.* **2011**, *40*, 341-. b) For seminal work, see: L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet. *Angew. Chem. Int. Ed.* **2009**, *48*, 5143-. c) H. Li, C. Mazet. *Org. Lett.* **2013**, *15*, 6170-
6. H. Li, C. Mazet. *Unpublished results*

Probing Interaction Between Negatively Charged Colloidal Particles in the Presence of Polyamine Cations

Mohsen MOAZZAMI GUDARZI

mohsen.moazzami@unige.ch

The aim of this study is to shed a light on surface forces between colloidal particles interacting through aqueous medium containing polyamine cations (mono to hexamers). Colloidal probe force microscopy was employed to measure forces between two polystyrene latex particles bearing solfunated groups on the surfaces[1].

In line with classical expectation, surface potential is lower for lower valence oligomers and for tetra, penta and hexamer inversion of charge from negative to positive is observed due to ion adsorption. The adsorption of ions is reversible and no saturation level in charge inversion is detected in the case of high valence oligomers, even at concentration of four orders magnitudes higher than charge reversal point. The colloidal forces between the particles at large separation distance (typically >5nm) are predicted well by DLVO theory considering constant regulation parameter (RP). The measured Debye length is in very good agreement with theoretical value expected from bulk concentration of oligomers. The cornerstone of this finding is that multivalent ions screen the electrical double layer similar to what predicted by Poisson-Boltzmann equation, whether as counter ions or coions.

References

1. M. Borkovec, I. Szilagyi, I. Popa, M. Finessi, P. Sinha, P. Maroni, G. Papastavrou. *Adv. Colloid Interf. Sci.* **2012**, *179-182*, 85-

Mechanism of Dpp Gradient Scaling in Drosophila Wing Imaginal Discs

Maria ROMANOVA-MICHAILIDIS

maria.romanova@unige.ch

The growth of wing imaginal discs in Drosophila melanogaster is controlled by morphogens, like Decapentaplegic (Dpp), that form graded concentration profiles[1,2]. The width of the Dpp gradient adjusts to the growing size of the tissue[3,4]. This phenomenon is termed scaling. Previous studies have shown that the change in time of the width of the gradient depends on the degradation rate of Dpp[3]. The concept of scaling can be therefore seen as Dpp degradation rate adjusting to the size of the tissue. The goal of our project is to understand the mechanism of scaling at the cellular and molecular level.

Pentagone has been shown to be essential for scaling[5]. It has also been shown that Dally binds Pentagone[5], and we showed that, indeed, Dally is also essential for scaling. To study whether Pentagone and Dally act on scaling through regulation of Dpp turnover, we have developed a novel assay to robustly measure the kinetic parameters of Dpp transport (degradation and diffusion) from its steady-state spatial distribution. The dependence of these parameters on Dally and Pentagone could then be determined. This assay involves Dpp fused to tandem fluorescent timers: tandem fusion of two fluorescent proteins that mature with different kinetics[6].

To understand how Pentagone and Dally could regulate Dpp turnover, we have generated transgenic flies with fluorescently tagged endogenous Dpp receptor and Dally using the protein trap MIMIC approach[7]. With these transgenic flies, we will perform internalization assays to study Dpp endocytosis, lysosomal degradation and recycling as well as its dependence on Pentagone and Dally. Our hypothesis is that the mechanism of scaling by Pentagone and Dally involves regulation of Dpp turnover by tuning the ratio between lysosomal degradation and recycling of Dpp.

References

1. M. Affoler, K. Basler. *Nat. Rev. Genet.* **2007**, *8*, 663-
2. O. Wartlick, A. Kicheva, M. Gonzalez-Gaitan. *Cold Spring Harb. Perspect. Biol.* **2009**, *1*, a001255
3. O. Wartlick, P. Mumcu, A. Kicheva, T. Bittig, C. Seum, F. Julicher, M. Gonzalez-Gaitan. *Science* **2011**, *331*, 1154-
4. F. Hamaratoglu, A.M. de Lachapelle, G. Pyrowolakis, S. Bergmann, M. Affolter. *PloS Biol.* **2011**, *9*, e1001182
5. R. Vuilleumier, A. Springhorn, L. Patterson, S. Koidl, M. Hammerschmidt, M. Affolter, G. Pyrowolakis. *Nat. Cell Biol.* **2010**, *12*, 611-
6. A. Khmelinskii, P.J. Keller, A. Bartosik, M. Meurer, J.D. Barry, B.R. Mardin, A. Kaufmann, S. Trautmann, M. Wachsmuth, G. Pereira, W. Huber, E. Schiebel, M. Knop. *Nat. Biotechnol.* **2012**, *30*, 708-
7. K.J.T. Venken, K.L. Schulze, N.A. Haelterman, H. Pan, Y. He, M. Evans-Holm, J.W. Carlson, R.W. Levis, A.C. Spradling, R.A. Hoskins, H.J. Bellen. *Nat. Meth.* **2011**, *8*, 737-

Identification and Characterization of Novel Antitubercular Compounds

Valentin TROFIMOV

valentin.trofimov@unige.ch

Over one third of the world population is infected by *Mycobacterium tuberculosis*, resulting in 2 million deaths and 8 million newly infected people every year. In addition, the efficiency of the existing therapies is threatened by the dramatic increase of multi-drug resistant strains. Many drug candidates identified by *in vitro* screens on *M. tuberculosis* fail when tested *in vivo* systems. Therefore, novel strategies, including phenotypic screenings directly in a host-pathogen system, are needed to discover antibacterial activities with high *in vivo* potency.

Amoebae such as *Dictyostelium discoideum* and *Acanthamoeba castellanii* allow performing convenient medium to high-throughput drug screenings. We developed assays to monitor the impact of chemicals and intracellular factors on bacteria health, growth, and virulence mechanisms as well as on intrinsic host defenses. We used mCherry and GFP fluorescent reporters for *M. marinum*, *Dictyostelium* and *Acanthamoeba*, respectively. We validated the system using known first and second line antimycobacterial drugs, including isoniazid, rifampicin pyrazinamide, ethambutol, streptomycin, amikacin, kanamycin, confirming the fluorescence measurements by visual inspection. High-content microscopy assays were developed for subsequent validation in a mammalian cell line system.

We first performed a medium-throughput screening with 1224 compounds from a library designed by the group of Prof. Scapozza (University of Geneva), with a final hit rate of about 1.7%. Both anti-infective and pro-infective activities were identified. Identified compounds were validated and dose-dependent curves were generated. The hits were validated in infected *Dictyostelium* and mammalian microglial cells by high content microscopy. We have started to investigate structure-activity relationships (SAR) and have also screened additional chemical libraries, such as the GlaxoSmithKline TB set, the Malaria box and the Prokinase library.

Understanding Forces Acting Between Silica Particles Across Ionic Liquids and Their Mixtures With Water

Valentina VALMACCO

valentina.valmacco@unige.ch

Ionic Liquids (ILs) are salts with a melting point below 100°C. In the last decade, they have attracted considerable interest in account of their unique physicochemical properties and have appeared to be great candidates for several applications such as solar cells, fuel cells and batteries, dispersants, solvents for organic synthesis, catalysis and nanoparticle synthesis. The greatest advantage of this class of compounds is the possibility to tune their properties by systematic variation of cation's and anion's molecular structure and combination, allowing the design and development of task-specific solvents[1].

The behavior of particle suspensions in ILs and the IL-solid interface have also been studied[2,3], but the overall picture is still controversial and incomplete, especially for what concerns their mixtures with water. Our work is addressed to characterize forces between particles in the whole dilution range of IL-water mixtures and in pure ILs, giving a quantitative interpretation of the data acquired.

Forces between 5 μm silica particles have been measured using Atomic Force Microscopy (AFM) colloidal probe technique[4] in three different imidazolium based ILs. At very low IL concentrations (up to 10mM), the forces are of electrostatic nature and the double layer repulsion decreases with the IL concentration. The fitted Debye length can be predicted by the Poisson-Boltzmann theory, suggesting that ILs behave like classical electrolytes within this concentration range. Increasing further the IL concentration, the resulting force is attractive due to dispersion forces. In pure ILs, step-like force profiles are observed, showing layering of IL molecules on the surface, whose order decreases going from the surface to the bulk.

References

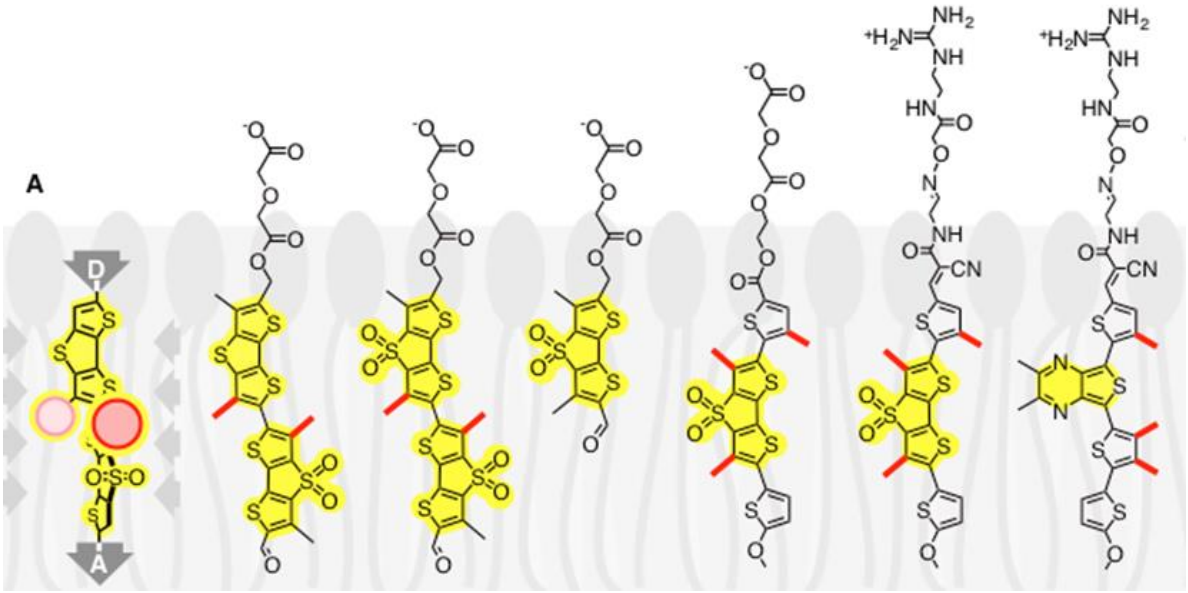
1. N. Plechkova, K.R. Seddon. *Chem. Soc. Rev*. **2008**, *37*, 123-
2. M. Mezger, H. Schröder, H. Reichert, S. Schramm, J. Okasinski, S. Schöder, V. Hokimäki, M. Deutsch, B.M. Ocko, J. Ralston, M. Rohwerder, M. Stratmann, H. Dosch. *Science* **2008**, *332*, 424-
3. J.A. Smith, O. Werzer, G.B. Webber, G.G. Warr, R. Atkin. *J. Phys. Chem C* **2010**, *114*, 19452-
4. W.A. Ducker, T.J. Senden, R.M. Pashley. *Nature* **1991**, *353*, 239-

Fluorescent Flippers as Membrane Probes

Quentin VEROLET

quentin.verolet@unige.ch

Fluorescent probes are nowadays the most promising tools to study biomembrane characteristics such as fluidity, lateral tension and polarity. Inspired by the chemistry of the impressive color variation observed in lobster pigmentation after cooking, our group proposed the use of a new class of fluorescent probes that exploits the combination of chromophore planarization and polarization as an environment reporter[1]. The innovative amphiphilic systems consist of a hydrophobic push-pull chromophore composed of several units connected by rotatable bonds, and a charged head to control the partitioning and the location of the probe inside the membrane. These probes respond to fluidity changes by the coplanarization of the scaffold units in the ground state, thus red-shift of the absorption (or excitation) maxima upon passage to a more rigid environment. After an extensive optimization of the first generation fluorophores based on oligothiophenes[2], a second generation containing a bright dithienothiophene S,S-dioxide unit is designed for higher mechanosensitivity and quantum yield. Indeed, their fluorescence properties observed in large or giant unilamellar vesicles confirmed our expectations[3].



References

1. A. Fin, A. Vargas Jentzsch, N. Sakai, S. Matile. *Angew. Chem., Int. Ed*. **2012**, *51*, 12736-
2. D. Alonso Doval, M. Dal Molin, S. Ward, A. Fin, N. Sakai, S. Matile. *Chem. Sci.* **2014**, *5*, 2819-
3. M. Dal Molin, Q. Verolet, A. Colom Diego, R. Letrun, E. Derivery, M. Gonzalez-Gaitan, E. Vauthey, A. Roux, N. Sakai, S. Matile. *J. Am. Chem. Soc.* **2015**, *in press*

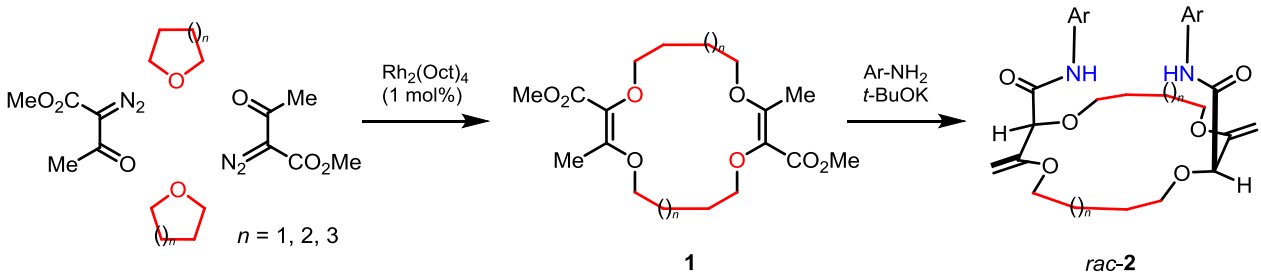
Synthesis of Functionalized Polyether Macrocycles

Mahesh VISHE

mahesh.vishe@unige.ch

Polyether macrocycles are generally synthesized from linear molecules using intramolecular reactions. Recently, our group has developed several one-step syntheses of medium sized rings and polyether macrocycles by multicondensation reactions of simple cyclic ethers and diazo reactants under high concentration and non-templated conditions (see below)[1]. Herein, we present a series of Rh(II)-catalyzed[2] reactions of diazocarbonyls and substituted tetrahydrofurans and tetrahydropyrans that afford densely-functionalized 16- to 18-membered macrocycles in a single step and yields up to 60 %[3]. A rather high functional group tolerance is exhibited. Mechanistic rationals for these macrocyclization reactions and a comprehensive analysis of the influence of the introduced functional groups on the macrocyclic geometries will be detailed.

Of particular importance, an unprecedented amidation-isomerization sequence is now presented that allows the formation of deconjugated crown ethers as single diastereomer (*dr* >99 : 1). These compounds of type **2** display unique cylindrical conformations resulting hence in interesting properties[4].



References

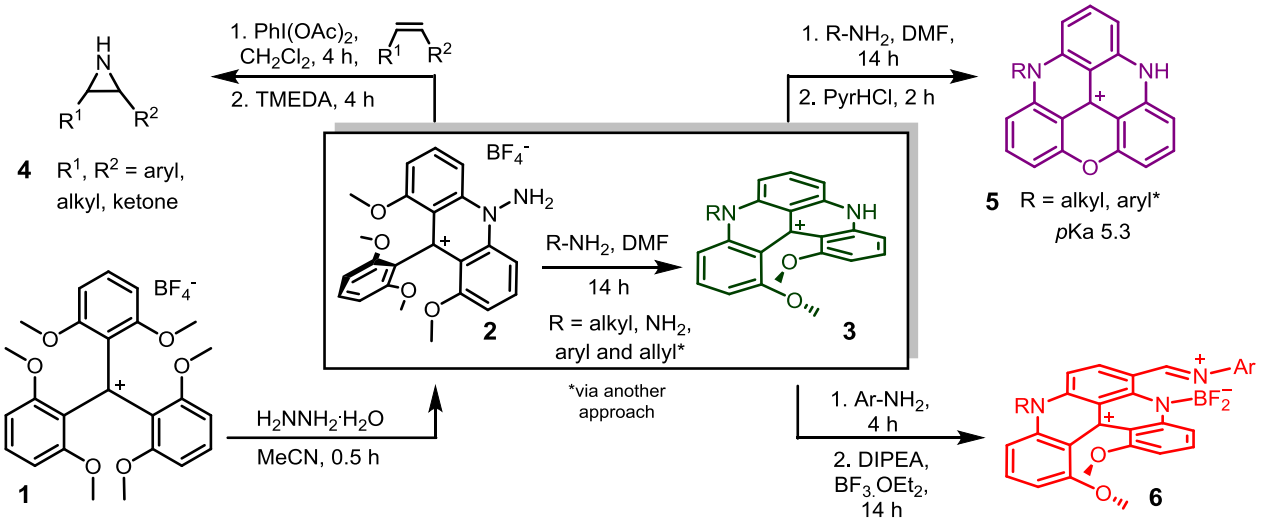
1. R. Ballesteros-Garrido, D. Rix, C. Besnard, J. Lacour. *Chem. Eur. J.* **2012**, *18*, 6626-
   D. Rix, R. Ballesteros Garrido, W. Zeghida, C. Besnard, J. Lacour. *Angew. Chem. Int. Ed*. **2011**, 50,7308-
   W. Zeghida, C. Besnard, J. Lacour. *Angew. Chem. Int. Ed*. **2010**, *49*, 7253-
2. P. Doyle, M.A. McKervey, T. Ye. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*. Wiley, New York. **1998**
3. M. Vishe, R. Hrdina, L. Guénée, C. Besnard, J. Lacour. *Adv. Synth. Catal*. **2013**, 355, 3161-
4. M. Vishe, R. Hrdina, C. Besnard L. Guénée, J. Lacour. *Submitted*

Modular Synthesis of Unprotected Aziridines and Chiral Dyes and Fluorophores using *N*-Aminoacridinium Cations

Antoine WALLABREGUE

antoine.wallabregue@unige.ch

Cationic helicenes and triangulenes are unusual dyes and fluorophores with a broad spectrum of applications[1]. They are readily prepared from tris(2,6-dimethoxybenzene)methyl carbenium **1** by sequences of nucleophilic aromatic substitutions with nitrogen nucleophiles and facile O-ring closures.



Herein, in a new development, the synthesis of novel *N*-aminoacridinium salts **2** is reported. These derivatives can be used for the preparation of diaza [4]helicene dyes **3**[2] thanks to particularly facile N-N bond cleavage reactions and as nitrogen source for the stereospecific aziridination of unfunctionalized olefins under metal-free oxidative conditions[3]. The corresponding NH aziridines **4**[4] are then obtained using mild reductive or photoreductive conditions[5]. Moreover, compounds **3** can be used for the preparation of fluorophores of type **5** (pK_a 5.3) and chiral (helical) BODIPY derivatives **6**. Fluorophores **5** have been applied as specific stain for late endosome compartments (pH 4.8-6)[6].

References

1. (a) J. Bosson, J. Gouin, J. Lacour. *Chem. Soc. Rev.* **2014**, *43*, 2824-. (b) Y. Shen, C. Chen. *Chem. Rev.* **2012**, *112*, 1463-. (c) J. Hamacek, C. Besnard, N. Mehanna, J. Lacour. *Dalton Trans.* **2012**, *41*, 6777-. (d) C. Nicolas, J. Lacour. *Org. Lett.* **2006**, *8*, 4343-. (e) B. Laleu, M.S. Machado, J. Lacour. *Chem. Commun.* **2006**, 2786-. (f) B. Laleu, C. Herse, G. Bernardinelli, B.W. Laursen, J. Lacour. *J. Org. Chem.* **2003**, *68*, 6304-. (h) B.W. Laursen, F.C. Krebs. *Chem. Eur. J.* **2001**, *7*, 1773-. (i) B.W. Laursen, F.C. Krebs. *Angew. Chem. Int. Ed.* **2000**, *39*, 3432-
2. A. Wallabregue, P. Sherin, J. Gouin, E. Vauthey, J. Lacour. *Eur. J. Org. Chem.* **2014**, 6431-
3. (a) L.B. Krasnova, R.M. Hili, O.V. Chernoloz, A.K. Yudin. *Arkivoc* **2005**, *4*, 26-. (b) J. Li, J.L. Liang, P. Chan, C.M. Che. *Tetrahedron Lett.* **2004**, *45*, 2685-. (c) A. Wallabregue, J. Lacour. *Manuscript in preparation*
4. J.L. Lat, M.P. Paudyal, H. Gao, Q. Xu, M. Yousufuddin, D. Devarajan, D. Ess, J. Falck, L. Kürti. *Science* **2014**, *343*, 61-
5. (a) C.K. Prier, D.A. Rankic, D.W.C. MacMilan. *Chem. Rev.* **2013**, *113*, 5322-. (b) J. Narayaman, C.R. Stephenson. J. *Chem. Soc. Rev.* **2011**, *40*, 102-
6. A. Wallabregue, D. Moreau, J. Grünberg, J. Lacour. *Manuscript in preparation*

Identification of a Covalent Bromodomain Binder from a DNA Display Library of Small Molecule Fragments

Claudio ZAMBALDO

claudio.zambaldo@unige.ch

Regulation of transcriptional programs by epigenetic readers (bromodomains)[1] has been linked to the development of several pathologies.

Notably, it has been implicated in regulation of cellular growth and evasion of apoptosis, in cancer as well as in inflammation. The discovery of small molecule probes to dissect the role of bromodomains is thus important.

We demonstrate that specific cysteines conserved across the bromodomains can be harnessed for covalent trapping. We report the discovery of a small molecule probe that forms a covalent bond with conserved cysteines across the bromodomain family and demonstrate its utility for proteomic analysis of bromodomains.

References

1. P. Filippakopoulos, S. Knap. *Nature Rev. Drug Disc.* **2014**, 13, 337-

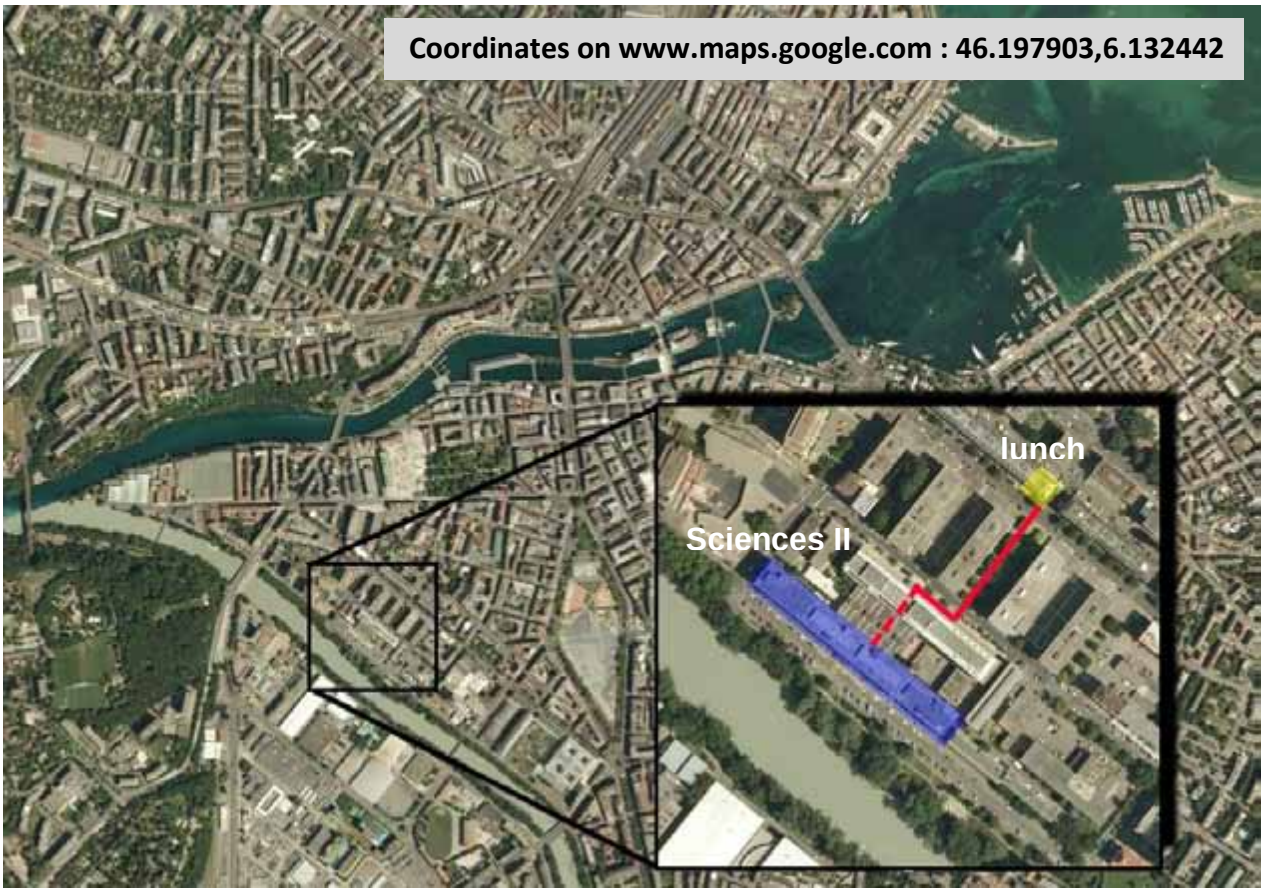
The School of chemistry and biochemistry:

The *Section de chimie et biochimie*, University of Geneva, offers a top tier training environment that results in a highly competitive expertise. An increasing number of diplomas (now *ca.* 65 per year) at the Bachelors, Masters and Doctoral level in chemistry and in biochemistry are being delivered to foreign and Swiss students.

The *Section de chimie et biochimie* plays host to the National Centre of Competence in Research "Chemical Biology" and produces about 200 publications per year. The research themes encompass most essential areas of fundamental molecular and biomolecular sciences:

- Development of highly selective and environmentally benign methods of organic synthesis.
- Elucidation and modelling of the behaviour of complex molecules on ever shorter time scales.
- Elaboration of new supramolecular architectures on the nanometre scale with promising microscopic and macroscopic properties.
- Development of analytical techniques surpassing today's frontiers of precision, in order to identify ultra-trace species in complex environments.
- Work towards an in-depth understanding of the biomacromolecules involved in the processes governing the living world at the interfaces between chemistry, biology and medicine.
- Development and optimisation of alternatives to fossil fuels as sources of energy.

Directions to the Geneva chemistry & biochemistry days:



Visit the *Chimiscope*, our platform for discovering and experimenting molecules
http://chimiscope.ch

The *Swiss National Centre of Competence in Research Chemical Biology*
is hosted at the School of chemistry and biochemistry
http://www.nccr-chembio.ch

Section de chimie et biochimie
Université de Genève
Sciences II
30, quai Ernest-Ansermet
CH-1211 Genève 4

Tel +41-22-3796024
Mail info-chimie@unige.ch
Web http://www.unige.ch/sciences/chimie/

UNIVERSITÉ DE GENÈVE
FACULTÉ DES SCIENCES
Section de chimie et biochimie

Imprimé à l'imprimerie de la Fondation Trajets,
active dans l'intégration sociale et professionnelle
http://trajets.org