



Conference Report

The 44th EUCHEMS Conference on Stereochemistry
(Bürgenstock Conference 2009)

Brunnen, May 17–22, 2009

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This year's EUCHEMS Conference on Stereochemistry – the '44th Bürgenstock Conference' – had to relocate once more from the famous Bürgenstock Hotel that is still under renovation. Fortunately, the organization committee found an equally stunning venue with the Seehotel Waldstätterhof in Brunnen, located directly on the shore of Lake Lucerne. Fears that this lower location could impair the traditional excellence of the conference immediately disappeared when this year's outstanding program was finally revealed. The traditions of the Bürgenstock, with its secret program, extended question sessions, free afternoons and numerous social events create a unique atmosphere to build bridges between diverse fields in science and generations of researchers. In this respect, we are all indebted to president *Ben L. Feringa* (University of Groningen) and the organizing committee, *Donald Hilvert* (ETH Zürich), *Jérôme Lacour* (University of Geneva), *Reto Naef* (F. Novartis Pharma AG, Basel), *Philippe Renaud* (University of Bern), *Jay Siegel* (University of Zurich) and *Helma Wennemers* (University of Basel) who put together a top-notch line-up.

After the opening remarks of the president in royal manner from the gallery of the hotel and the dinner, the scientific part of the 44th Bürgenstock conference was opened by *Bernhard Kräutler* who introduced the speaker for the opening lecture on Sunday evening. This honor was given to *Ian Paterson* (Cambridge University). Professor Paterson gave an explosive lecture on natural product synthesis, starting with the microtubuli stabilizing marine polyketide dictyostatin. In addition to the synthesis itself, he presented hybrid structures between dictyostatin and discodermolide, another powerful anti-cancer natural product, and showed their biological properties. A second part of his lecture was dedicated to the total synthesis of spirastrellolide A. Spirastrellolide A is a highly complex polyketide, which shows specific inhibition activity of protein phosphatase 2A and therefore is a promising chemo-



Ben L. Feringa



Ian Paterson

therapeutic agent. Apart from the severe synthetic hurdles that had to be taken to reach the target, its exact three-dimensional structure had to be determined 'on-the-fly'. Without doubt, this is a tremendous achievement that opens the door to simplify the structure and to further explore the pharmacological profile of this compound class.

The second day started off with the two morning lectures under the moderation of *Stephen Mann*. *Joanna Aizenberg* (Harvard University) began with a fascinating talk on material sciences. She shared her admiration on how precisely nature can control biomineralization – the crystal growth of calcite – e.g. crystallographic orientation, crystal shape and size. Professor Aizenberg showed her efforts to exert such control in the crystal growth of calcite on SAMs (Self Assembled Monolayers) of different gold and silver supports. She found that the crystallographic orientation of the formed crystals is precisely defined by the orientation of the support, the SAM chain length (even, odd number of carbon atoms) and the acidic end group through impressive stereochemical recognitions between the organic/inorganic interfaces. In addition, the crystal size could be controlled by addition of ionic compounds, e.g. magnesium salts. She finished her talk by a short journey into the fabrication of bioinspired actuated nanostructures composed of a surface with spines, consisting of a polymeric hydrogel.



Joanna Aizenberg

The second morning speaker, *Lawrence Que* (University of Minnesota) opened his exciting lecture again with nature as an inspiration for reaction development, more precisely with non-heme iron oxidation chemistry. The selective oxidation of hydrocarbons under mild conditions constitutes a major challenge of modern chemistry. Professor Que pointed out that the right ligands for the iron center are necessary to control the formation of the desired active high-valent Fe^V(OH)O complex and to avoid destructive Fenton chemistry. He explained that under the optimized conditions, selective epoxidation or dihydroxylation of olefins succeeds, showing additionally that the whole process can be conducted in an enantioselective manner. He finished by presenting an iron catalyst system able to activate dioxygen. The oxidant formed by such an oxygenation of a biomimetic iron(II) α -ketocarboxylate complex is able to activate aliphatic C–H bonds, convincing the audience of the importance of powerful green oxidation chemistry.



Lawrence Que

In the afternoon, the first poster session was scheduled, kicking off with the oral poster appetizers from *Nicolai Cramer* (ETH Zürich), *Markus Kaiser* (MPI Dortmund), *Gerard Roelfes* (Goningen University), *Magnus Rueping* (RWTH Aachen), and *Giancarlo Terraneo* (Politecnico di Milano).

The after-dinner speaker **Alan Rowan** (Radboud University Nijmegen) was introduced by **Helmut Ringsdorf**. Professor Rowan took us to an intriguing journey into supramolecular chemistry with catalysis and motion, again taking nature with its processive enzymes like DNA polymerases as an inspiration. He presented a mono-cavity manganese porphyrin catalyst that allows the epoxidation of butadiene polymers *via* a pseudo-rotaxane mechanism. Such reactions can help to understand the translocation and the threading behavior of biopolymers through pores and channels. He pointed out that the threading of polymers involves a kinetically favorable ‘entron’ effect, which is associated with the initial filling of the cavity by the end of the polymer. Furthermore he showed that a pre-association between the outer sphere of the macrocycle and the polymer induces a looping mechanism that results in accelerated threading rates and unidirectional motion. Such observation is reminiscent of the protein translocation through membrane pores.



Alan Rowan

The morning session of the third day was chaired by the vice president **Peter Kündig**. **Christina White**'s (University of Illinois) big theme of the presentation was to streamline organic synthesis by cleverly exploiting C–H bonds as latent functional groups. Professor White demonstrated that an iron-based catalyst that uses hydrogen peroxide is able to oxidize tertiary C–H groups of a broad range of substrates into tertiary alcohols. A predictable selectivity of different C–H groups is achieved by either electronic or steric properties or directing groups, so that the method can be applied to selectively oxidize even complex natural products such as artemisinin and tetrahydrogibberellic acid. Her second topic involved functionalizations of allylic C–H bonds of terminal olefins promoted by a palladium(II)(sulfoxide) catalyst with benzoquinone as the bulk oxidant. The resulting π -allyl-Pd complex can be trapped with nitrogen nucleophiles to form linear allylic amines derivatives. In contrast, addition of a chiral Cr(III)(salen) Lewis acid co-catalyst promotes enantioselective allylic C–H oxidation, now forming branched allylic acetates. She also gave first applications of this methodology in the context of lactonization reactions in natural product synthesis, circumventing the need for lengthy functional group protections/deprotections sequences.



Christina White

The second speaker of the morning, **Dirk Trauner** (Ludwig-Maximilians-Universität München) served us a brilliant mélange of organic chemistry and biochemistry in the context of neurosciences. He spoke about functional reengineering of ion channels by attaching synthetic switches that respond to a diverse array of input signals. The central element of these switches is a light-isomerizable azobenzene derivative that can be triggered with 380 nm and 500 nm wavelength light pulses. Attachments of glutamate surrogates to the switch allows the use of glutamate receptor gated ion channels as light actuated channels. These manipulated ion channels can



Dirk Trauner

be inserted into excitable cells, *e.g.* neurons, to control neuronal firing. Such neurons are now sensitive to optical stimuli, raising the hope of restoring vision.

On the afternoon, a president's special session on ‘Chirality on the origin of life’ was opened by Ben Feringa. **Bernard Kaptein** (DSM Pharmaceutical Products B. V.), **Günter von Kiedrowski** (Ruhr Universität Bochum), **Meir Lahav** (Weizmann Institute of Science), **Stephen Mann** (University of Bristol) and **Jay S. Siegel** (University of Zurich) contributed with short presentations on their research in this exciting area and guaranteed a passionate afternoon.

The evening speaker, **Nadrian C. Seeman** (New York University) was introduced by **Günter von Kiedrowski**. Professor Seeman gave a splendid lecture on DNA as a nanoscale object, convincing the audience that DNA is much more than the encoding molecule of life. He illustrated the possibility to create two- and three-dimensional engineered nano-objects from DNA with sticky ends and Holliday junctions. He introduced fascinating structures going from cube and truncated octahedron-like scaffolds to complex systems such as Borromean rings, which all have been visualized by beautiful X-ray crystal structures. He further demonstrated that DNA can be used to control molecular topology, as exemplified by a nanomechanical device operating by the conversion of B-DNA to Z-DNA. He finished with impressive illustrations of an autonomous DNA bipedal walker that coordinates the action of its two legs by cyclically catalyzing the hybridization of metastable DNA fuel strands.



Nadrian C. Seeman

The morning of the fourth day was dedicated to biological chemistry, under the moderation of **Don Hilvert**. **Chaitan Khosla** (Stanford University, currently on sabbatical at ETH Zürich) first revealed the secrets of polyketides biosynthesis. The modularity of the synthesis of polyketides incorporating a succession of enzymes clusters is now well-established, but the elucidation of the detailed mechanism of activation and regulation on the molecular level still constitutes a formidable challenge, even for the minimal module (composed of a Ketosynthase (KS), an Acyltransferase (AT) and an Acyl Carrier Protein (ACP)). Professor Khosla gave a more detailed impression of the complexity of this biological system based on a combination of structural biology using NMR and X-Rays techniques and systematic modifications of the proteins and the growing polyketide chain. He discovered that substrate specificity was not only dependent on direct enzyme–substrate interactions, but also on inter-protein recognition, notably in homodimer structures. Furthermore, proteins not involved directly in the polyketide elongation were also important for the efficiency of the synthesis and cannot be neglected anymore to achieve Khosla's ultimate goal: The engineering of polyketides synthases to access non-natural polyketides with increased bioactivity.



Chaitan Khosla

Engineering biological systems to solve chemical problems is also the driving force for the research of **Hiroaki Suga** (Tokyo University), the second speaker of the morning. His very ambitious goal encompasses the reprogramming of the genetic code for the introduction of non-natural amino acids into peptides. Whereas current techniques are often limited to the use of stop

codon, he developed a system to use any codon for the introduction of non-natural amino acids. He introduced new RNA transferases (Flexizymes) dedicated to specific non-natural amino acids. These new 'RNAs' were indeed tolerated by the ribosomal system and lead to the synthesis of libraries of non-natural peptides with up to twelve residues. He then demonstrated the power of this approach for the introduction of electrophilic functional groups, such as vinyl glycine and chloro-acetate terminating groups, which allowed intramolecular cyclization with cystein residues to form stable cyclic peptides. As cyclic non-natural peptides constitute an important class of bioactive compounds, the developed methodology will be useful for the fast identification of new drugs.



Hiroaki Suga



Asasello Quartet (Source: Asasello Quartet; photo by Wolfgang Burat, Köln, 2008)

After a relaxing afternoon enjoying the great weather on the Lake Lucerne or on top of the mountains near Brunnen, it was time for the traditional chamber music evening by the **Asasello Quartet** from Basel (*Rostislav Kojevnikov, Barbara Kuster, Justyna Śliwa and Andreas Müller*). The guest of honor, *Klaus Müller*, picked an excellent assortment of compositions from Paul Hindemith, Fanny Hensel-Mendelssohn, Dmitri Shostakovich, Alexander Borodin and Sulchan Tsintsadze that rounded out this evening.

Under the moderation of *Lee Cronin*, the fifth day of the conference began with a journey through the secrets of surface sciences. **Karl-Heinz Ernst** (EMPA, Nano-scale Materials Science) demonstrated the power of modern techniques such as STM (Scanning Tunneling Microscopy) or LEED (Low Energy Electron Diffraction) for the study of chiral molecules on surfaces. He showed how the influence of the chirality of small molecules on extended two-dimensional structures could be observed easily on the Cu(111) surface for the examples of heptacene and tartaric acid. Long-range chiral motifs were formed and spontaneous symmetry breaking was possible for prochiral



Karl-Heinz Ernst

molecules. Interestingly, he pointed out that small amount of chiral impurities led to homochirality in the molecular lattice *via* cooperative amplification and that achiral molecules can become chiral when bound to surface due to the loss of symmetry. He finished his lecture by presenting future important areas of research: the study of multi-layer systems *en route* to tridimensional crystals and the monitoring of reaction on surfaces, for example using IETS (Inelastic Electron Tunneling Spectroscopy).

After the break, **Rustem F. Ismagilov** (University of Chicago) held a stunning lecture on the importance of space confinement in complex chemical and biological systems. The process of blood coagulation is essential for life and exquisitely complex, with more than 80 chemical reactions involved. Using simplified model systems, Professor Ismagilov demonstrated the importance of threshold kinetics. He pointed out that not only the medium concentration of activator molecules in the system was important, but also their exact space distribution. Once a certain cluster size and local concentration was reached, an irreversible clotting process began, whereas diffusion process prevented smaller activator clusters to initiate clotting. He then showed that space confinement also plays an essential role in bacterial quorum sensing. Confined in smaller containments, even single bacteria were able to activate the metabolism for colony growth, which can be very important for a faster access to bacteria cultures. Separating bacteria in space but still allowing chemical communication allowed engineering multi-step chemical reactions. Finally, he presented the development of miniaturized analytical sensors to study chemical flow in biological systems (the '*chemistrode*').

The afternoon poster session began with short appetizer presentations by *Chien-Tien Chen* (National Taiwan Normal University), *Lee Cronin* (University of Glasgow), *Emmanuel Lacôte* (Université Pierre and Marie Curie) and *Oliver C. Trapp* (Ruprecht-Karls-Universität Heidelberg) and was followed by two hours of passionate discussions at the posters.

After the poster session, the evening lecture in biochemistry was moderated by *David N. Reinholdt*. **Xiaoliang Sunney Xie** (Harvard University) presented his impressive work on new analytical tools to monitor important biological process directly in the living cell. He showed how the behavior of single molecules in the cell could be examined using fluorescence-labeled proteins. One major issue for single molecule detection is the relatively fast diffusion in the cytoplasm, which diminishes the resolution. He presented elegant solutions to this problem either by studying proteins that are specifically localized in the cell (for example yellow fluorescent proteins in the membrane) or by using very short laser pulses for detection. Gene expression could be monitored using fluorescence. He found that gene expression was stochastic in several cases due to the small number of molecules involved. This constitutes a first step in understanding why organisms with the same genotype can lead to different phenotypes. Finally, he introduced Coherent Anti-Stokes Raman Scattering (CARS) as a promising non-invasive imaging method to detect molecule in the cell without the need of covalent labeling.



Rustem F. Ismagilov



Xiaoliang Sunney Xie

As it had begun, the conference concluded on the sixth day with a synthetic organic chemistry festival under the direction of *Hélène Lebel*. The importance of total synthesis to drive progress in chemistry was demonstrated in the first lecture by **Erik J. Sorensen** (Princeton University). Beginning with the famous Feynman citation: “*What I cannot create, I cannot understand*”, Professor Sorensen reminded the audience of important landmarks in the history of total synthesis, such as Robinson’s tropinone synthesis and the Woodward-Eschenmoser Vitamin B12 synthesis. He then smoothly continued with his own work, characterized by elegantly orchestrated cyclization–cycloaddition events to construct complex polycyclic structures. In particular, he demonstrated the use of an impressive transannular Diels-Alder-hetero-Diels-Alder cascade for the efficient synthesis of FR182866 and showed how the core of abyssomicin C could be accessed *via* an intramolecular Diels-Alder reaction. Finally, he presented his current work on the core of hirsutellone, a promising new lead compound against tuberculosis, using an intramolecular *retro*-Diels-Alder-Diels-Alder-acylketene-trapping sequence.

After these masterpieces in total synthesis, new methodological tools for organic chemistry were presented by **Dean Toste** (University of California, Berkeley). Professor Toste has largely been recognized as one of the leaders in what has been called the ‘*gold rush*’ in organic chemistry. He began his lecture by introducing the unique properties of gold due to the strongest relativistic effect in the periodic table. He showed how the high π -acidity of gold could be used for the activation of acetylenes towards nucleophilic attack. He then emphasized that



Erik J. Sorensen



Dean Toste

this constituted only one of the multiple reactivity pattern that could be accessed. Particularly important is the capacity of gold to stabilize cationic intermediate in the α -position. This stabilizing effect led to a carbenoid character of the intermediate, the amount of which has been a matter of considerable debate in the recent literature. He demonstrated that carbene-like chemistry was indeed possible, such as cyclopropanation or oxygen transfer from diphenylsulfoxide. Following these initial successes, he deeply impressed the audience by the amazing number of reactions that could be catalyzed by gold, such as pyrrole synthesis, Rautenstrauch rearrangement, Stevens rearrangement, [2+2] cycloaddition and intramolecular cyclization reaction with nitrogen and oxygen. He concluded his lecture with a breakthrough: the development of an asymmetric method using chiral counter anions for asymmetric induction.

The Bürgenstock Conference 2009 ended with enthusiastic concluding remarks by the president, *Ben Feringa* and the guest of honor, **Klaus Müller**. In the name of the organization committee, *Philippe Renaud* then gave some preliminary information on the 45th Bürgenstock Conference, which will be held again in Brunnen in May 2–7 in 2010. The presidency will be held by *Peter Kündig* supported by the vice-president *Jeremy Sanders*. The stage is ready again for an outstanding meeting across the fields of chemistry and related sciences!

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Klaus Müller

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