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The 43rd EUCHEM Conference on Stereochemistry (Bürgenstock Conference 2008) Fürigen, April 12–18, 2008

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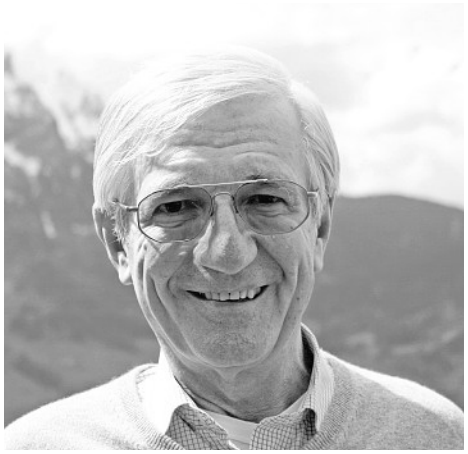
In an ever changing, metastable world of science and technology it is good to know of facts that will never change. For decades now, the Bürgenstock Conference in spring has been such an anchor-point, a week to step back and have a look at chemistry in its pure and applied forms. A week to be amongst people that speak the same language, a week to refocus one's view of current science.

This year's Bürgenstock conference has passed already, leaving the participants with the slightly melancholic impression of having been a part of an important event in chemistry.

Don Hilvert (ETH Zürich) presided over the symposium which attracted scientists from 22 countries. We all were curious what line-up of speakers the president had prepared together with vice-president *Ben L. Feringa* (University of Groningen) and his organizing committee: *François Diederich* (ETH Zürich), *E. Peter Kündig* (University of Geneva), *Klaus Müller* (F. Hoffmann-La Roche, Basel), *Philippe Renaud* (University of Berne), and *Jay Siegel* (University of Zürich). The dinner on Saturday evening was thus left with satisfied people looking forward to an exceptional week to come.

Don Hilvert

The first pleasant surprise was meeting this year's guest of honour, ***Dieter Seebach*** (ETH Zürich) one of the corner stones of current synthetic chemistry. Through his impressive list of contributions, he has helped to shape generations of chemists, planting the seed of curiosity deep within them together with an indestructible confidence in the power of organic synthesis.



Dieter Seebach

On an easy early spring Sunday morning – at nine o'clock sharp – Prof. *Schwarz* opened with Swiss 'Pünktlichkeit' the scientific part of the 43. Bürgenstock conference. The honor of the first lecture was given to ***Jérôme Lacour*** (University of Geneva), who set the standard for this meeting with a fulminant talk about chiral ions in asymmetric synthesis. He developed with his coworkers helical chiral phosphonate anions. As counter ion with metal salts they create a chiral environment, which Jérôme demonstrated in thoroughly designed NMR experiments. Application of his TRISPHAT counterion in the first asymmetric 1,2-Ste-

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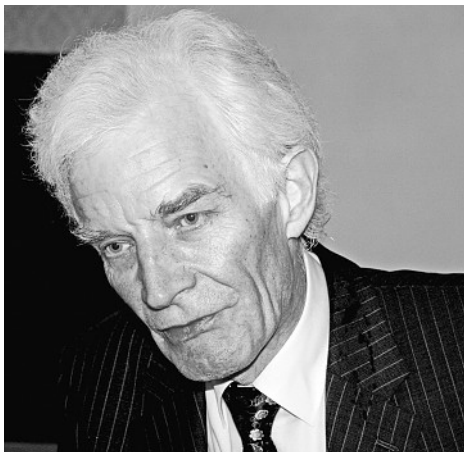
vens rearrangement proved that this is not just an exercise of theoretical intent. Additionally, he designed a highly selective catalyst for an asymmetric Carroll-rearrangement, based on a RuCp-complex in combination with chiral Schiff base ligands. An interesting observation on the aging of the catalytic species led Jérôme to discover new air stable catalysts that were easily separable by column chromatography on silica gel.

Jérôme Lacour

Equally young and enthusiastic, ***Benjamin List*** (MPI Mühlheim) presented his lecture about new strategies and concepts for catalysis. Without doubt he is one of the defining characters in the rejuvenated field of organocatalysis. In only a few years, he and his young group have developed asymmetric catalytic versions of a variety of classic reactions, like aldol, Mannich, Michael, *etc.* In the case of aldol condensations, he distinguished four modes of action: Intermolecular, intramolecular *endo–endo* and *endo–exo* and finally transannular. For the latter he recently published an organocatalytic asymmetric version, which he featured in the shortest asymmetric synthesis of (+)-hirsutene. He also solved one of the longstanding problems in organocatalysis using acetaldehyde in enamine catalysis. In the last part of his talk, Ben presented his new concept of asymmetric counterion directed catalysis (ACDC), which will not only 'rock' the organocatalytic community. He showcased the concept in, for example, an asymmetric epoxidation.

Benjamin List

As spectacular as the first day started it ended with a blooming presentation by ***Roman Kaiser*** (Givaudan) capturing the 'Scents of the Vanishing Flora'. For over 30 years, as stated by the moderator *Lia Addadi*, he has been tracking down the bouquet of Earth's remotest places. His latest project hunts down the odors of endangered plants, collecting samples of over 2500 species. In his lecture, he took an awed audience on a trip around the world of olfactory experiences, illustrated by distributed perfumers testing strips. We learned about *Dracula chestertonii* (that not only mimics the shape of a fungus, but also its smell), or the desert gold plant from Death Valley that produces chlorinated phenols originating from the soil's high salt concentration. The complexity of smelling was demonstrated by a scent sample of a Sauvignon Blanc Palliser Estate 2000, an ultimate challenge for anyone working in the field.



Roman Kaiser

With Don Hilvert as this year's president, the conference promised to also highlight recent advances in biology. Indeed, *Ilme Schlichting* chaired the Monday morning session on life's molecular machines. ***Lorena S. Beese*** (Duke University Medical Center) investigated the high-fidelity of DNA synthesis by analyzing an impressive number of crystal structures. Using a co-crystallization technique she was able to snapshot different stages of action of DNA polymerase I and the effect of the various nucleotide mismatches. Lorena further showed crystal structures with incorporated modified nucleosides (O6MeG and 8oxoG), noting the perfect fit into the natural DNA double helix, which explains their high carcinogenicity and the need for an additional proofreading mechanism in humans by *e.g.* MutSα. With the latter, Lorena crossed the bridge to human systems, opening new fields in cancer therapy.

Lorena S. Beese

Moving from DNA to peptide synthesis, ***Mohamed A. Marahiel*** (Philipps University Marburg) presented his latest results on non-ribosomal peptide synthesis (NRPS). Compared to the classical ribosomal peptide synthesis, the NRPS is able to introduce a larger variety of over 450 different building blocks, allowing much higher complexities. Molecules like bleomycin, surfactin, cyclosporin and vancomycin are just a few examples of the synthetic power of NRPS. In order to possibly exploit this natural assembly line for organic synthesis, a deep understanding of its architecture and function is needed. Mohamed impressively elucidated the modular structure of the surfactin biosynthesis cluster from crystals and NMR studies. From these results he was able to predict and modify the protein structure in order to incorporate specific amino acids during the peptide synthesis. Mohamed ended his talk with his inspiring vision of the architecture of a complete nonribosomal assembly line.

Mohamed A. Marahiel

The title of the evening promised a sweet lecture. After an introduction by *Peter Seeberger*, ***Ben Davis*** (University of Oxford) started a firework on sugar and protein chemistry. Glycosylation is one of the most important posttranslational modifications used by Nature to decorate proteins. Mimicking this process in the chemical laboratory will allow protein functions to be finetuned. Ben's first approach relied on a mixed sulfur-selenium reagent strategy to site-selectively couple sugars to proteins. He then went on to more complex systems, ultimately using PSGL-lacZ as an inflammation marker in a rat cortex. MRI active GNPs allow *e.g.* the visualization of inflammation in an *in vivo* stroke model. In order to selectively decorate proteins with different sugars, he developed new orthogonal strategies, such as methods to form sulfide bridges, cross-metathesis and click chemistry.

Ben Davis

The Tuesday session was chaired by *Ben Feringa*, preparing the grounds for two lectures on polymer chemistry. ***Geoffrey W. Coates*** (Cornell University) opened our eyes to the importance of stereochemistry not only in drugs, but also in the polymer bottle, in which the pill is packaged. He uses a C_2-symmetric α-diimine Ni-catalyst to induce a living polymerization of propylene to form thermoplastic elastomers. A project dear to Geoffrey's heart is the development of biodegradable and environmental friendly polymers based on CO_2 monomers. He showed that Zn- and Co catalysts can form poly(propylene)carbonates. In the course of his research on poly(β-hydroxybutyrates) he discovered an intriguing insertion reaction of CO into cyclic ethers to form lactones.

Geoffrey W. Coates

After this splendid start ***Kyoko Nozaki*** (University of Tokyo) stepped into her father's footsteps, who gave a lecture at the 15. Bürgenstock Conference in 1979. She presented her work on olefin–CO co-polymerization catalyzed by Pd(II)-(*R*,*S*)-BINAPHOS. By carefully combining experimental and theoretical data she elucidated the stepwise chain propagation mechanism. A thorough analysis of the 3D structure of these polymers revealed an equilibrium between a polyketone and a polyspiroacetal form. Using a phosphine-sulfate based ligand on a Pd-catalyst she demonstrated the first coordination polymerization of vinylacetate. She finished her lecture with excerpts from her studies on boron nucleophiles and double arylation of primary amines.

Kyoko Nozaki

The spectacular site over the lake Lucerne was the perfect setting for the evening's traditional chamber music evening. After the insightful introduction by *Klaus Müller*, we were taken back in time to the founder of modern string quartets, Joseph Haydn. His String Quartet C Major (Op. 54/2) opened the concert by the *Asasello Quartet* from Basel. The program continued with Five Pieces for String Quartet by Erwin Schulhoff which underlined the virtuosity of the four young musicians. The evening was concluded by Beethoven's String Quartet 'Rasumowsky' in C Major (Op. 59/3) and a short traditional piece from Georgia.

The fourth science day of the meeting, moderated by *Beate Koksch*, was again under the stars of biochemistry. The first lecture by ***Frances H. Arnold*** (California Institute of Technology) dealt with her 'favored chemist', Nature's cytochrom P450 heme-mono oxygenase. Probing into the vast sequence space she was able to decouple the enzyme from its biological context. She changed the function of cytochrom P450 BM3 from subterminal oxidation of fatty acids to the oxidation of propane using directed evolution, a technique pioneered in her laboratory. She experienced the fine line between optimizing turnover numbers and stability of the protein. The knowledge obtained in that process was applied to the oxidation of other alkanes by enzymes, as well as the selective deprotection of permethylated sugars. A now commercially available plate with 120 mutants of P450 was used in her laboratory to create milligram quantities of dozens of metabolites of drug candidates in one week.

Frances H. Arnold

After the break ***Homme W. Hellinga*** (Duke University) stunned the audience with his results on computational protein design. Using *in silico* methods he re-engineered ligand binding sites of proteins.

Homme W. Hellinga

By modifying the enzyme thioredoxin to contain a Zn^{2+} binding site he was able to prepare an ATP-driven nanomotor. In the following, Homme showed an various biosensors ranging from immobilized GSP for continuous *in vivo* glucose monitoring to detectors for warfare agents and explosives. The latter he was even able to engineer into plants. Recently, he developed an automated 'Protein Writing' robot that dramatically shortens the synthesis time of proteins.

Ehud Keinan welcomed the evening lecturer ***Kai Johnsson*** (EPF Lausanne), who is working on observing and manipulating proteins and their function in living cells. In this context, his group developed a fusion protein assay allowing to label proteins *via* an O^6-alkylguanine DNA alkyltransferase. This SNAP-tag technology is now becoming a standard biological technique. Kai showed time-dependent dual labeling techniques and experiments and differentially colored the evolving segments of budding yeast. He took his method to the next level by presenting an orthogonal CLIP-tag based on a pyrimidine base. A cunningly designed experiment, combining SNAP and CLIP fusion proteins allowed the monitoring of protein–protein interactions, *e.g.* between p53 and Mdm2.

Kai Johnsson

The last day of science was opened by *Samir Z. Zard*, welcoming ***Goverdhan Mehta*** (Indian Institute of Science, Bangalore), who gave a vivid lecture on natural product synthesis. In his opinion, natural products have a locked-in co-evolutionary memory and are still the most important inspiration for drug discovery. He highlighted his contribution on the synthesis of polyprenylated acylphloroglucins (PPAPs). Starting from simple cyclohexadiones he accessed a number of members of the PPAPs in an elegant and efficient way. Another class of neurotrophically active compounds Goverdhan was interested in were the *seco*-prezizaane sesquiterpenes. He prepared merrilactone A in 26 linear steps. He also developed a global route to epoxyquinones which he used to prepare 22 natural products in just four years.

Goverdhan Mehta

The second talk of the morning was delivered by ***Justin du Bois*** (Stanford University). He gave the audience an idea about the power of modern organic synthesis by showing a very elegant amination reaction of unfunctionalized C–H bonds. Carbamates as well as sulfonamides are suitable substrates for his insertion reaction catalyzed by a Rh catalyst. The products obtained are useful building blocks for a variety of functionalities (*e.g.* diamines) as well as starting materials for further reactions (*e.g.* cross-coupling reactions). He continued his presentation with a meticulous study on the mechanism of this reaction. From those results he was able to greatly improve the catalyst, concerning its stability, reactivity as well as selectivity. He could even show first results towards an asymmetric version of the reaction.

Justin du Bois

The grande finale of this year's Bürgenstock Conference was delivered by ***David R. Liu*** (Harvard University), introduced by *Helma Wennemers*. David's lecture on DNA-templated organic synthesis nicely summarized the main topics of the meeting – Biochemistry and Organic Synthesis. He encodes a specific reactivity by attaching a DNA fragment to his starting materials. Matching DNA strands will bring the reactive sites in close proximity increasing the effective molarity by several magnitudes. With this concept he could, for example, conduct multi-step syntheses in one pot. His method also revolutionizes the way of discovering new reactions and reactivities by combinatorially combining a multitude of reactants under different reaction conditions. In the last part of his talk he investigated if Nature also uses this concept of DNA or RNA templated synthesis. For this reason he developed a methodology to extract conjugates of RNA with small molecules, identifying a variety of structures, *e.g.* RNA bound CoA, a promising result to prove his theory.

David R. Liu

The Bürgenstock Conference 2008 ended with a humorous summary by ***Klaus Müller*** (F. Hoffmann-La Roche) picking up on the themes of the symposium and delivering subtle stings. President Don Hilvert closed the sessions by revealing key features of the 44th EUCHEM conference of Stereochemistry that will be held in the Seehotel Waldstätterhof in Brunnen (the Bürgenstock Hotel will undergo extensive renovations until 2011). Next year's president *Ben L. Feringa* will be supported by the vice-president *E. Peter Kündig* and the guest of honor, *Klaus Müller*. This will be a very special thank you to the two researchers who resigned from the organization committee (together with *François Diederich*) after a combined service of almost five decades! The new organization committee will consist of *Helma Wennemers* (University of Basel), *Jérôme Lacour* (University of Geneva), *Reto Näf* (Novartis), *Don Hilvert* (ETH Zürich), *Philippe Renaud* (University of Berne) and *Jay Siegel* (University of Zürich). This lineup in the committee promises again an outstanding meeting with excellent science!

Acknowledgments

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