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The 41st EUCHEM Conference on Stereochemistry

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Trying to persuade around 120 chemists from all over the world to attend a conference where they are not told who the speakers are in advance might at first glance seem like quite a challenge. However, such is the history and prestige of the Bürgenstock Conference on Stereochemistry, coupled with its idyllic location in the Bürgenstock Hotels overlooking Lake Lucerne, that those who attend know they will be guaranteed a feast of chemistry in an environment conducive to discussion and interaction with scientists from academia and industry from all over the world. This year was no exception, with the President **Bernhard Kräutler** (University of Innsbruck), the Vice President **Samir Zard** (Ecole Polytechnique, Palaiseau), and the local organizing committee **Hans-Beat Bürgi** (Universität Bern), **François Diederich** (ETH Zürich), **E. Peter Kundig** (University of Geneva), **Klaus Müller** (Hoffmann-La Roche, Basel), **Philippe Renaud** (Universität Bern) and **Jay Siegel** (Universität Zürich) putting together a programme of fourteen world class speakers. Guest of honour **Albert Eschenmoser** (ETH Zürich



Bernhard Kräutler, President of the conference

and Scripps Research Institute) was welcomed by the President on the first night as participants relaxed over the first of many sumptuous dinners enjoyed throughout the week.

The scientific proceeding started the next morning with the impressive presenta-



Albert Eschenmoser, Guest of Honour

tion of **Peter H. Seeberger** (ETH Zürich), who described his efforts in the development of automated solid-phase oligosaccharide synthesis, based on a strategy analogous to peptide synthesis. These included new methods to produce the necessary building blocks, such as the Mukiyama aldol condensation, and the development of an oligosaccharide synthesizer. Prof. Seeberger spiced up his talk with examples of synthetically challenging oligosaccharides (like the Le^x-Le^y antigen), produced in less than 24 h and in relatively high yields, as well as the applications of his synthetic oligosaccharides in the understanding of heparin-related diseases and the development of carbohydrate vaccines against



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human pathogens such as anthrax and malaria parasites. The use of microreactors in organic synthesis was also introduced (and the application in glycosylation reactions), a subject further addressed in other talks throughout the conference.

The second talk was given by **Antonio M. Echavarren** (Institute of Chemical Research of Catalonia ICIQ). Professor Echavarren is at the forefront of the recent explosion in interest in the application of simple gold ^I and platinum ^{II} salts as catalysts for ene-yne isomerization reactions triggered by the interaction of these metals with alkynes. A number of mechanistic pathways can be conceived for this transformation, including the formation of cyclobutene intermediates. Prof. Echavarren showed that this pathway is not necessary and indeed is inaccessible for the formation of certain dienes. Instead, all products observed can be rationalized by careful consideration of the fate of the metallocyclopropane carbene intermediates.



Antonio M. Echavarren

In the afternoon, the first of two intensive poster sessions gave the opportunity for a number of participants, including some of the 17 younger chemists being financially supported by the Swiss Chemical Society (SCS) and various chemical industries, to present their work in an informal setting.

The final talk of the first day was given by **Rainer Herges** (Christian-Albrechts University Kiel). In a fascinating lecture that incorporated elements of mathematics, literature, architecture, art and even a musical demonstration, the subject of how to assemble a molecular Möbius strip was addressed. Chemists familiar with the Hückel criteria for aromaticity of $4n+2$ electrons will be perhaps surprised to learn



Rainer Herges

that a Möbius strip is aromatic when a $4n$ electron delocalised system is obtained. Through the integrated use of theory and experiment, the first synthesis of a Möbius aromatic hydrocarbon was achieved, truly a synthetic tour de force.

Monday's session was started by **Chad A. Mirkin** (Northwestern University), who reported some of the ground-breaking research done in his lab with a lecture entitled 'Nanostructures in Chemistry and Biomedicine'. He started by demonstrating the uses and potential of Dip-Pen Nanolithography (DPN), a technique he pioneered, showing a digitized photograph of R.B. Woodward printed at the nanometer scale to remarkable definition. New achievements included the development of a parallel DPN printer with a cantilever array of 55,000 pens. The second part of his talk focused on biomolecule directed assembly, in particular DNA-linked nanoparticles. These have a variety of interesting properties, including the formation of nanoparticle aggregates



Chad A. Mirkin

and a sharper melting temperature. When conjugated with the recognition potential of DNA these constructs have immense applications in biosensors, specific DNA detectors, screening of small-molecule DNA intercalators, or protein detection with antibody-linked nanoparticles containing a DNA bio-bar code.

Colin Nuckolls (Columbia University) continued the materials theme with a lecture entitled 'Recognition, Catalysis and Electronics from Smart Surfaces'. Bridging the gap between electrodes with organic molecules to complete electronic circuits requires a method of attachment to surfaces, a technique which remains heavily reliant on the gold-sulfur bond. In moving beyond such systems, new electrodes have been developed with precise gaps of 3–12 nm based on alumina swelling. Such gaps can be bridged by readily functionalized cruciform-shaped molecules termed 'cruciforms'. Polymer growth using the olefin metathesis from a ruthenium metallocarbene on a ruthenium surface, and selectively functionalized carbon nanotubes were also described as complementary approaches towards the same goal.



Colin Nuckolls

The evening lecture on 'Single-Molecule Force Microscopy' (SMFM) was presented by **Hermann E. Gaub** (LMU, München), who introduced his topic through an analogy with a kiss between two lovers, where the strength of their relationship could be determined by the force necessary to pull them apart. Prof. Gaub described the application of this technique to more 'molecular' problems, such as the study of titin kinase, a force-activated enzyme present in muscle tissue as a domain of titin. Titin kinase is naturally activated by stretching (C- and N-termini pulled in opposite directions) of the



Hermann E. Gaub

muscle, and SMFM was used to mimic this effect *in vitro*. Another creative application of SMFM involved the sequential unfolding of bacteriorhodopsin, which showed the unfolding energy barriers of this membrane-bound protein. This method was also applied in a scale-like system where binding energies of annealed DNA strands were determined by comparison with a reference, and finally in the use of azobenzene's two photoinducible conformations to produce motor energy.

The Tuesday session started with a lecture by **Donald Hilvert** (ETH Zürich) on 'Molecular Diversity and Catalysis', where the audience was treated to a wonderful overview on the evolution of biocatalysis. In the first part of his lecture, Prof. Hilvert described his efforts to explore the versatility of the immune system to produce and optimize catalytic antibodies. Particularly the studies performed on the 1E9 antibody, which catalyzes a non-natural Diels-Alder



Donald Hilvert

reaction, showed how surface complementarity and electrostatic interactions were essential to hapten binding and catalysis. Evolution of 1E9, using yeast surface display and flow cytometry, resulted in a new catalyst with significantly improved hapten binding and Diels-Alder activity. The second part of the lecture was devoted to the topological redesign of chorismate mutase (CM), where a dimeric CM was re-engineered with the introduction of a randomised six amino-acid loop and genetic selection, forming a monomeric CM. Although the structure of this monomeric CM is severely disordered (molden globule), as shown by NMR studies, there is no significant decrease in catalytic activity from the fully-ordered natural dimeric enzyme.

The initial promise of combinatorial chemistry in drug discovery has failed to materialize, yet this technology offers huge possibilities for the rapid synthesis of large numbers of new molecules. The problem here is as much in the analysis as in the generation of large libraries of compounds. **Morten Meldal** (Carlsberg Laboratory) described an approach to combinatorial chemistry where the design of the solid phase compound library, the selection criteria and compound analysis are all integrated. Towards this goal a highly efficient intramolecular N-acyliminium Pictet-Spengler reaction on solid phase was described. The audience was particularly interested in the integration of solid phase combinatorial chemistry with the search for new catalysts. Solid supported peptides modified with N-linked phosphines act as ligands for palladium and ultimately catalysts for transformations with efficacies matching that obtained for the same compounds 'off-bead'.



Morten Meldal

After a relaxing afternoon and a conference dinner at the Bürgenstock club, an evening concert of chamber music by Schubert, Shostakovich and Dvorák was performed by the *Aura String Quartet*, in a programme chosen by the President himself.



Aura String Quartet

The fourth day of the conference was directed towards organic synthesis and catalysis. After starting his talk with a brief overview of metal-catalyzed transformations developed in his group, **Shengming Ma** (Shanghai Institute of Organic Chemistry/Chinese Academy of Sciences) went on to describe a wide variety of transformations initiated by electrophilic attack on sulfur-substituted allenes. An impressive array of regio- and stereoselective transformations can be achieved with this chemistry, which provided continual surprises to challenge the audience in terms of mechanistic understanding.



Shengming Ma

The use of sulfoxides as chiral control elements in asymmetric transformations was also exploited by **Ilan Marek** (Israel Institute of Technology) in combination with a dazzling array of organometallic species in methodology directed towards the synthesis of quaternary carbon stereo-



Ilan Marek

centres in enantiomerically enriched form. Further synthetic utility was gained through sulfoxide–metal exchange to form vinyl lithium or vinyl zirconium species. Other applications of metals in organic synthesis made a convincing case for the remarkable transformations that can only be achieved in this manner.

The evening lecture was given by **Donna G. Blackmond** (Imperial College, London). Prof. Blackmond provided a convincing case for the use of reaction calorimetry for the determination of kinetic parameters. In this technique, heat flow is directly proportional to reaction rate. In a remarkable re-evaluation of a number of asymmetric transformations reported to display non-linear effects, the crucial role of the physical behaviour of the reactants and catalysts was shown. The audience was left in no doubt as to the importance of this work in future kinetic studies.



Donna G. Blackmond

The last day of the conference was devoted to the more biological areas of chemistry. In the first lecture, **Ronald R. Breaker** (Yale University) guided the participants in an exciting journey to the world of gene expression control. Prof. Breaker's talk focused on riboswitches, in particular the well-structured domains found in noncoding regions of certain bacterial mRNAs. These bind specific metabolites, regulating gene expression and therefore intracellular metabolite concentration, and are recognised as possible drug targets. Examples of natural metabolite-binding riboswitches included FMN-, guanine-, and SAM-regulators, and a special GlcN6P-binding riboswitch, which acts as a self-destruct system and controls gene expression via ligand-induced RNA-cleaving. These natural examples served as a basis to engineer new riboswitches, either by swapping and combining the ligand-binding domains in a modular way, or through modification of the binding domain of a guanine riboswitch to recognise adenine.



Ronald R. Breaker

Moving from riboswitches to ribozymes and evolution, the second talk of the day was given by **Gerald F. Joyce** (Scripps Research Institute) on 'Directed Evolution of Nucleic Acid Enzymes'. His talk described the basis of directed evolution and the search for catalytic activities in RNA molecules, ribozymes, thought to be the primary catalysts in a primordial RNA world. The development of a selection system for RNA ligase activity allowed the evolution of a RNA ligase ribozyme from a random sequence, and further rounds of mutation and selection were able to convert it into a RNA polymerase. Using this system it was possible to evolve

RNA ligase ribozymes consisting of only three and even two nucleotides bases, and also convert it into a deoxyribozyme. The final part of the talk was devoted to the concept and methods of continuous *in vitro* evolution, and the application of microfluidics to design such systems.



Gerald F. Joyce

The honour of presenting the last lecture of the conference belonged to **Robert M. Stroud** (UC San Francisco), entitled 'A Two Billion Year Old Tale of Membrane Transport'. His fascinating talk described the study of two membrane transport systems, one involved in water and glycerol transport, and the other an ammonia channel. Solving the crystal structure of the water/glycerol channel GlpF was crucial to understand its selectivity and transport mechanism. This involves the formation of a polarized line of waters along the channel, where glycerol can be inserted, which allow transport while preventing the leak-



Robert M. Stroud

age of protons from the cell. A molecular mechanics simulation of the movements in the water line illustrated this mechanism. The second part of the lecture centred on the mechanism of ammonia transport by Amt channels. These channels are clearly distinct from the GlpF, and structural determination showed a recruitment site for ammonium cations towards the exterior of the membrane and a hydrophobic channel that promotes the passage of neutral ammonia. The contrasts between these two transport systems are a wonderful remainder of nature's versatility.

The conference ended with the now customary and much anticipated 'overview' of the week's proceedings given by **Klaus Müller**, delivered in his own inimitable style.



Klaus Müller



Samir Z. Zard

With **Samir Zard** as President and **Donald Hilvert** (ETH Zürich) as Vice President, the 42nd EUCHEM Conference on stereochemistry will take place 14–20th April 2007. The future of this unique meeting, which challenges all those involved to understand chemistry beyond their immediate knowledge, is in safe hands.

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