Highlights from the 41st EUCHEM Conference on Stereochemistry, Bürgenstock, Switzerland, April 2006

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Like the clouds surrounding the Bürgenstock hotels on the evening 120 chemists arrived for the 41st Bürgenstock Conference on Stereochemistry, an air of uncertainty surrounded the opening of this legendary meeting, with the possibility looming large that it might be the last due to an extended renovation! The local organizing committee of **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) together with the President **Bernhard Kräutler** (University of Innsbruck) had, yet again, assembled 14 mystery world class speakers, and with their identities revealed in time for the first of many delicious dinners, the clouds dissolved revealing a perfect conference environment overlooking Lake Lucerne within the mountains of central Switzerland. The President opened the meeting and welcomed guest of honour **Albert Eschenmoser** (ETH Zürich and Scripps Research Institute), and once Vice President **Samir Zard** (Ecole Polytechnique, Palaiseau) had assured us appropriate weather for the week had been arranged, all thoughts of gloom were banished as academic and industrial scientists from all over the world sat back and looked forward to the most delectable feast of lectures and discussions one can find on the subject of organic chemistry.

Peter H. Seeberger (ETH, Zürich, Switzerland) began the proceedings the following morning with a comprehensive summary of his research in the area of glycomics (an emerging area concerned with understanding and exploiting the role of carbohydrates in biology). The first stage of his group's research has necessitated development of novel rapid solid-phase and automated methods for oligosaccharide synthesis. In addition to developing Mukaiyama aldol routes to the building blocks and elaborating the peptide synthesizer concept for oligosaccharides, this has included extensive use of microreactor chips, which Seeberger refers to as the round-bottomed flask of the next century. Using these methods, oligosaccharides with well defined structure (like the Le^x–Le^y antigen) can now be produced in less than 24 h and in relatively high yields. This has made it possible to elucidate the role of carbohydrates in a plethora of biological processes (mediated by DNA/RNA–sugar, protein–sugar and sugar–sugar interactions) that have important roles in the immune response, metastasis and inflammation. In addition to identifying FGF-binding heparin fragments with microarrays it has ultimately allowed them to identify the toxin in the malaria pathogen and to develop a mortality neutralizing vaccine, with an HIV vaccine in the pipeline.

Antonio M. Echavarren (Institute of Chemical Research of Catalonia, Tarragona, Spain) then gave a talk on the use of gold I and platinum II salts as π-Lewis acid catalysts for ene–yne isomerisation reactions. The use of these simple salts as catalysts has been the subject of an explosion of interest in recent years. Professor Echavarren outlined how they work through binding of the metals to alkynes and described a number of proposed mechanistic pathways for this transformation, including the formation of cyclobutene intermediates. He then showed that this pathway is not necessary and impossible for the formation of certain dienes but that all products observed can be rationalized by careful consideration of the fate of the metal carbene intermediates.

In the afternoon, the first of two "appetizers" took place in which selected short presentations paved the way for an extended poster session. During these sessions a number of participants, including some of the 17 younger chemists whose attendance was financially supported by the Swiss Chemical Society (SCS) and various chemical industries, had an opportunity to present their work in an informal setting.

The final lecture of the day was given by **Rainer Herges** (Christian-Albrechts University, Kiel, Germany) who used literature, art, architecture and a string duet during his description of the first synthetic Möbius aromatic annulene. He first illustrated how a ring constructed by joining the ends of a rectangular strip together having given one end half a twist becomes one sided. Importantly for the molecular equivalent, it had been predicted that a hydrocarbon with a Möbius topology should be aromatic if it contains $4n$ rather than $4n + 2$ π electrons. Despite numerous calculations and attempts, the synthesis of such a compound had not previously been achieved because twisted cyclic molecules accumulate ring strain and suppress *p* orbital overlap favouring a Hückel topology. The problem was overcome by combining a normal aromatic structure (with *p* orbitals orthogonal to the ring plane) with a belt-like aromatic structure (with *p* orbitals within the ring plane). This belt-like motif was obtained from a bianthraquinodimethane motif that enforces pyramidalized

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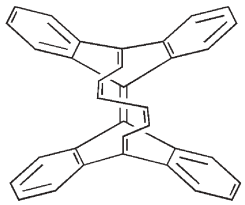
sp^2-hybridized atoms. Successive photocyclisations of this motif with *syn*-tricyclooctadiene gave five different isomers of which two were confirmed as having a Möbius topology and one as having Hückel topology. Such Möbius compounds with their interesting optical properties may serve as molecular building blocks of devices in the future.



A Möbius aromatic hydrocarbon

The second day saw a complete shift in focus towards nanotechnology and was opened by **Chad Mirkin** (Northwestern University, USA) who described two major topics of his research programme. Firstly he discussed the technique of dip-pen nanolithography. This method uses an AFM tip to deposit or write molecular species of virtually any type onto a surface including a nanoscale reproduction of R. B. Woodward! Recently this technique has been elaborated such that images can be written in parallel across large surfaces using a parallel DPN printer with a cantilever array of 55,000 pens. The second part of his talk was concerned with DNA-mediated assembly of gold nanoparticles. By appending oligonucleotides onto the surface of gold nanoparticles it is possible to aggregate them *via* DNA hybridization. This highly co-operative process which results in a sharper melting temperature upon disassembly of the duplexes gives a characteristic change in the resonance band of the gold nanoparticle that can be exploited in a variety of sensing applications. By tuning the specificity and selectivity of the assembly process and combining it with different methods of readout, methods of DNA, protein and even small molecule detection were described. Evidence was also presented for the use of nanoparticles in antisense therapy.

This was followed by a talk from **Colin Nuckolls** (Columbia University, New York, USA) on the use of smart surfaces for recognition, catalysis and electronics. In efforts to avoid the use of gold–sulfur bonds, Nuckolls presented new methods of attaching small molecules to surfaces. Precise gaps of 3–12 nm could be created between electrodes and then organic 'cruciform' molecules used to bridge the gap through imine forming reactions. In an alternative approach the use of ruthenium as a surface was explored due to its potential use in microelectronics. The use of carbenes to link to the surface of a ruthenium cluster was explored and exciting examples in which these carbene surfaces were used to grow polymers *via* olefin metathesis were presented. In a final approach, a method of connecting carbon nanotubes together was presented in which a gap in a carbon nanotube was created by burning the tube away. Oxidation followed by EDCI-mediated amide bond formation with bifunctional conducting molecules restored conductivity to the nanotubes.

The final talk of the day by **Hermann E. Gaub** (Ludwig Maximilian University, Munich, Germany) was introduced with images of two lovers being brought together and then pulled apart as an analogy to single-molecule force microscopy. With some introductory images of ATP rotors (some with defects) Prof. Gaub was able to highlight the advantages of studying individual molecules. His first demonstration of how pulling molecules apart by force could be used to derive molecular information focused upon Titin, a force-activated muscular enzyme that gives a saw tooth force extension as each domain is pulled apart, highlighting the unfolding process. He then moved on to the protein bacteriorhodopsin—a light-activated proton pump channel—and demonstrated how this technique could be used to study the unfolding of membrane-bound proteins; something difficult to do with any other technique. In his third topic he discussed the use of AFM devices as balances that could be used to measure differences in folding behaviour with duplex DNA as an example. Finally, on the premise that many future man-made devices are likely to be powered by light, Prof. Gaub discussed the exploitation of the photo-addressable *cis–trans* isomerisation of azobenzene to produce motor energy.

The third day of the meeting began with a talk by **Donald Hilvert** (ETH Zurich, Switzerland), who discussed the use of molecular diversity in exploiting biocatalysts. In the first part, Prof. Hilvert outlined how the immune system could produce and optimize catalytic antibodies to catalyze a non-natural Diels–Alder reaction. Noting that most catalytic antibodies are limited by the availability of suitable transition state analogues, limited structural diversity, product inhibition or modest hapten affinity, he demonstrated how the 1E9 antibody could be evolved using yeast surface display and flow cytometry such that it optimized electrostatic interactions and surface complementarity to the hapten, resulting in higher affinity and greater catalytic activity. The second part of the talk focused on topologically re-engineering chorismate mutase from a dimer to a monomer. This was done by introduction of a randomized 6 amino acid loop and genetic selection of active variants. A series of H/D exchange experiments demonstrated that although the 'evolved' protein possessed near identical catalytic activity, it was disordered (less stable) in the absence of substrate, indicating the importance of structurally non-optimal molten globule type proteins as important intermediates on the evolutionary pathway.

This was followed by a talk from **Morten Meldal** (Carlsberg Laboratory, Denmark) on integrating the process of combinatorial chemistry, catalysis and molecular recognition into one platform for identification of molecules with the desired properties, either as drugs or catalysts. This addresses the screening and analysis bottleneck that currently limits the impact of large libraries obtained through combinatorial chemistry. A highly efficient 'scaffold-diversifying' intramolecular *N*-acyliminium Pictet–Spengler cyclisation on a solid support was described. Further particularly impressive highlights included a bead sorter that identifies cell adhesion receptors and bisoxazoline or *N*-linked phosphine ligands for palladium catalysed reactions that effect transformations with efficiency comparable to that of the same compounds 'off-bead'.

At this, the half-way point of the meeting, a special conference dinner took place in the Bürgenstock Club and the evening was devoted to a stunning performance of chamber music by Schubert, Shostakovich and Dvořák

selected by the President and Guest of Honour and performed by the Aura String Quartet.

Day four of the meeting saw a return to synthesis with talks focused on catalysis, methodology and mechanism. After a brief summary of the metal-catalysed transformations developed in his group, **Shengming Ma** (Shanghai Institute of Organic Chemistry, China) delivered the first of these on the control of regio- and stereoselectivity during electrophilic addition reactions of allenes. He described a wide variety of transformations initiated by electrophilic attack on sulfur-substituted allenes with impressive levels of regio- and stereocontrol, with particular emphasis on exploiting neighbouring group participation of sulfoxides. This provided continual mechanistic challenges for the audience to consider.

This was followed by a talk by **Ilan Marek** (Technion-Israel Institute of Technology, Israel) on new methods for the preparation of chiral quaternary centres. He started his lecture by highlighting how difficult it is to generate stereochemically pure quaternary centres using aldol type or allyl metal complex chemistry because making stable stereochemically pure intermediates is problematic. His group has addressed the metallotropic rearrangement problem using chiral sulfoxides which co-ordinate the metal ion and simultaneously effect stereocontrol. In a further development, these reactions could be carried out in one pot starting from alkynyl sulfoxides and reacting them first with an organocopper reagent and then a dialkyl zinc carbenoid. The methodology was shown to be so good that it was possible to differentiate between the smallest difference in size between two stereogenic centres, *i.e.* $^{12}CH_3$ and $^{13}CH_3$! Further synthetic utility was gained through sulfoxide–metal exchange to form vinyl lithium or vinyl zirconium species whilst the use of alkynyl ethers, dialkyl amines and carbamates in place of the sulfoxides was tolerated.

The final talk of the day by **Donna Blackmond** (Imperial College, UK) focused on the use of kinetic methods to understand non-linear effects in synthetic transformations, in particular, asymmetric amplification of chirality and the origins of biological homochirality. Prof. Blackmond demonstrated how reaction calorimetry which measures heat flow as a reaction progresses (and thus allows determination of reaction rates and thermodynamic parameters) can be used to study non-linear effects in a variety of remarkable reactions. In the first example, the Soai reaction in which a dialkyl zinc is added to a pyrimidine aldehyde moiety, she was able to show that the spontaneous amplification of chirality can be rationalised on the basis of homochiral aggregated structures reacting more quickly than monomeric intermediates or racemic aggregates. In the second example, she demonstrated that non-linear effects in the proline catalysed aldol reaction could be ascribed to the phase behaviour of the organocatalyst. It was shown that because the catalysts often have poor solubility in the reaction media, the enantiopurity of the catalysts in solution where the reaction takes place depends upon its preferred method of crystallisation.

The theme of evolution crossed over into the final day of lectures concerned with biochemistry. Firstly **Ronald Breaker** (Yale University, USA) gave a talk on genetic expression with riboswitches; in particular the well-structured domains found in noncoding regions of certain bacterial mRNAs which control intracellular metabolite concentration. Prof. Breaker highlighted their potential as drug targets due to their role in binding specific metabolites, and regulating gene expression (*e.g. via* a change in conformation). Examples presented of natural metabolite-binding riboswitches included FMN-, guanine-, and SAM-regulators, and a special self-destructing GlcN6P-binding riboswitch, which upon binding its ligand hydrolyses and switches off gene-expression. Prof. Breaker demonstrated that it is possible to engineer these riboswitches by swapping and combining their modular components, *e.g.* by modifying a guanine riboswitch so that its ligand-binding domain recognised adenine. Similarly multiple recognition domains could be built into the riboswitch such that molecular logic could be performed.

This was followed by a talk delivered by **Gerald Joyce** (Scripps Research Institute, USA) who described the directed evolution of nucleic acid enzymes. Using the Darwinian process of evolution as the basis for molecular evolution, his talk centred on developing methods of mutating, selecting and amplifying RNA molecules that can perform the essential molecular processes of life. Using isothermal RNA amplification and mutagenic or hypermutagenic PCR as tools, together with microfluidic devices to facilitate continuous *in vitro* evolution making experiments faster and more consistent, Prof. Joyce was able to discuss a remarkable selection of evolved RNA biopolymers. A selection system for RNA ligase activity allowed evolution of an RNA ligase ribozyme from a random sequence, and further rounds of mutation and selection were able to convert it into an RNA polymerase. It was also possible to evolve RNA ligase ribozymes consisting of only three and even two nucleotide

bases, and also convert them into DNA equivalents.

This brought us to the final talk of the meeting by **Robert Stroud** (University of California at San Francisco, USA) who described a two billion year old tale of membrane transport. The talk focused on using X-ray crystallographic methods to uncover the structures, selectivity and mechanisms of channel proteins. First, crystal structures of water channels, notably GlpF, were described and used to rationalize why water and ethylene glycol are transported through water channels. The Grothus mechanism of transport was confirmed as the channels had water molecules oriented *via* hydrogen bonding from one end of the channel in one direction to the centre where a single bridging water reversed the orientation of the remaining water molecules which were also oriented in one direction through H-bonds. Polyols such as ethylene glycol could thus be substituted for water but transport of protons or other cations was prevented. The later part of the talk was concerned with the transport of ammonia across membranes by AMT channels. An amazing structure pointed towards the channel recruiting an ammonium ion through cation–π interactions and then deprotonating it to allow transport through a central hydrophobic region of the channel and to the other end where it interacts *via* cation–π interactions as it becomes reprotonated.

Finally, following the news before the final lecture that the Bürgenstock meeting would indeed continue on a temporary basis for at least the duration of the current renovation, **Klaus Müller** was able to happily sum up in the traditional manner with a selection of amusing comments on the week's proceedings. Thus for the next three years the hotel at Fürigen "down the hill" will cater for the guests, with the first of these meetings, the 42nd EUCHEM Conference on Stereochemistry, to take place from 14–20th April with **Samir Zard** as President and **Donald Hilvert** (ETH Zürich) as Vice President. This unique opportunity for scientists to embrace chemistry beyond their immediate knowledge comes highly recommended!

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