CONFERENCE REPORT

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Highlights from the 38th ESF/EUCHEM Conference on Stereochemistry, Bürgenstock, Switzerland, April/May 2003

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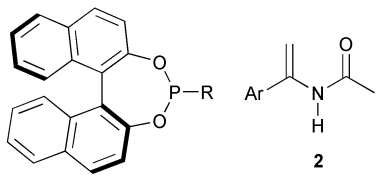
Some 120 chemists assembled at the spectacular Bürgenstock overlooking Lake Lucerne in Switzerland at the end of April 2003 to participate in the 38th ESF/EUCHEM Conference on Stereochemistry. The President for 2003, **Jan-E. Bäckvall** (University of Stockholm), and the Organising Committee (**Hans-Beat Bürgi** (University of Bern), **François Diederich** (ETH Zürich), **E. Peter Kündig** (University of Geneva) and **Klaus Müller** (F. Hoffmann-La Roche, Basel)) put together an exciting programme of innovative and fascinating chemistry, highlights of which are presented in this account.

The scientific part of the meeting commenced with a presentation from **Anthony Barrett** (Imperial College, London) who confessed to having an obsession with macrocycles. The extent of his obsession was soon confirmed in a dazzling account of the synthesis, metal complexation and photophysics of porphyrazines. Included in the journey was some remarkable old film footage illustrating the aromaticity and preparation of the earliest examples of this rather unique class of macrocycles. A key feature of the talk was how a chance side reaction of a porphyrazine with air had opened the door to the preparation of a whole new series of seco-porphyrazine compounds which are significantly more photosensitizing than the original porphyrazines. This property engenders significant potential for the development of novel photodynamic agents for medical diagnosis and therapy. The audience was left in no doubt as to the vigour with which this aspect was being pursued.

Switching the focus of the remainder of the day to catalysis, **T. V. RajanBabu** (Ohio State University) discussed asymmetric alkene hydrovinylation. This reaction involves the net formal addition of a =C–H unit of an alkene, across the C=C unit of another, and makes serious demands on a catalyst's ability to precisely control the orientation and relative reactivities of the alkene partners, in order to avoid poor regioselectivity, homocoupling and polymerisation. A series of Ni-based catalysts were presented which offer remarkable rates and selectivities for the asymmetric addition of ethylene to styrenes. The resulting enantiomerically enriched 3-arylbutenes have an obvious connectivity through oxidative C=C cleavage to a range of NSAIDs (nonsteroidal anti-inflammatory drugs). Key to attaining the selectivity is the control of catalyst activation and each step of its subsequent propagation. A mechanistic rationale involving the generation of a Ni–H species and the importance of ligand hemi-lability, η^3-benzyl type intermediates and the use of non-interactive counter-ions was presented.

With a foot in either camp, **Manfred Reetz** (Max Planck Institute, Mülheim) described his recent developments in 'combinatorial' enantioselective catalysis by both biological and synthetic systems. Starting with the recent resurgence of interest in monodentate ligands, such as biaryl-derived phosphonites (*e.g.* **1**), for Rh-catalysed hydrogenation reactions, he presented a range of truly remarkable synergistic ligand effects. For example, the asymmetric hydrogenation of a typical dehydroamino acid such as **2** proceeds in low or moderate selectivity with ligands **1a** and **1b** (78 and 3% *ee*, respectively). Detailed NMR, kinetic, non-linear and computational studies demonstrate that these reactions involve *bis cis*-monodentate ligation (*i.e.* [(**1**)$_2$Rh]). Mixing **1a** and **1b**, then allows the generation of a dynamic combination of the two original catalyst systems as well as a new hetero-ligand assembly '[(**1a**)(**1b**)Rh]'. Using this catalyst mixture, the hydrogenation proceeds in up to 97% *ee* and demonstrates that the synergism of the two ligands (the methyl group of **1a** 'docks' into the *tert*-butyl group of **1b**) results in the hetero-ligand complex being *both* more active and more selective.



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1a R = Me
1b R = *t*-Bu

Switching to enzymatic catalysis, the exertion of 'evolutionary pressure' for the development of highly selective asymmetric transformations was presented. Having invented a number of very high throughput screens for enantiomeric excess, steered or random mutagenesis expression then allows the generation of a spatially addressable library of new enzymes from which the best (rate and enantioselectivity) can easily be selected. Feedback then results in daughter libraries and the evolution of better and better catalyst systems.

The second day of the meeting saw a major shift in focus from synthesis to the physical and biological chemistry of the living cell. **Klaas Martinus Pos** (ETH, Zurich) described a long battle to elucidate the solid-state structure of acridine resistance protein B (AcrB), a protein involved in one type of cellular

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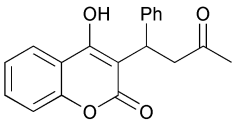
antibiotic resistance. Having successfully crystallised and analysed (synchrotron) the protein, a year was spent solving the diffraction pattern. With insufficient resolution, the process was repeated, this time using a heavy atom doped (Se) sample. With 95% of the structure solved, the group were scooped by the publication of the same structure by another group. The AcrB protein is a key component of the bacterial pump and thus of great interest in the search for the mechanisms by which cells can excrete materials across the cell wall and thereby protect themselves from undesired agents. The solid-state structural analysis of such proteins suggests that AcrC and AcrB combine to bridge the periplasm, with AcrB, in an α-helix arrangement, forming the inner unit. Loops then link three α-helix units together to form a conduit along which the undesired species are transported by means of a proton pump.

Continuing the theme of protein structure, **Jeffery Kelly** (Scripps Research Institute) gave a fascinating account of the molecular origin of 'amyloid diseases'. This large collection of diseases, which include Parkinson's and Alzheimer's diseases, as well as familial diseases such as Finnish disease and cardiocongestion in African American males, were all suggested to arise from protein mis-folding. The quality control (QC) of protein folding in the cell acts as a protection mechanism. However, when QC fails, such amyloid diseases emerge. For example, transthyretin amyloid diseases arise from the formation of amyloid protein fibrils which accumulate in the cell. The folding of amyloid proteins has been found to involve a tetrameric assembly of amyloids. A physical organic study of the dissociation of such tetrameric species, led to the conclusion that dissociation leads to aggregation and, in the absence of effective QC, to fibrils. A clever outcome of the study was the design of small, non-symmetrical, rod-like molecules containing benzoic-acid-type binding units at either end. These species are able to link monomers within the tetramer and thereby strongly inhibit dissociation. These novel therapies are currently undergoing clinical study.

The mechanism by which the highly complex operation of QC of protein folding was the subject of the last speaker of the day, **Ari Helenius** (ETH, Zurich). A surprise to those in the audience familiar with NMR type studies on the rapid (≤1 s.) folding of isolated proteins, is the time scale of the process in the cell which can take up to four hours. During this time period, the protein undergoes a staggeringly complex series of folding/QC operations within the endoplasmic reticulum. The manufacture and export, *via* the Golgi apparatus, of folded proteins involves a diverse collection of vividly named associates such as chaperones, retention factors, escorts and guides—all of which can be 'public' or 'private' in nature. Focusing on the physical organic aspects of the operation, a remarkable relationship between the efficacy of secretion of the protein and the thermal stability (ΔG) of the folded (native) versus non-folded (non-native) states of the protein was described. Additionally, an elegant timing/logging mechanism is employed by the cell to track how far the protein is through the process and whether or not it should be allowed to continue. This mechanism involves a chain of glucose and mannose units, which undergo sequential 'trimming' from the protein and thereby allow the various QC mechanisms to compare how long the protein has been in the system and whether the correct stage of folding has been achieved. Amazingly, only a low percentage of proteins make it to the end of the process, with the bulk being degraded and recycled—at great energetic cost, yet ensuring fidelity.

Accompanied by the sounds of 2000-year-old Danish horns known as 'Lurs', **Karl-Anker Jørgenson** (Aarhus University) returned the meeting to the theme of catalysis. He described how an extensive range of reactions have been developed from a tin-catalysed ene reaction of cyclopentene with ethylglyoxalate, which failed to proceed as planned. Instead, an arylation reaction occurred between the ethylglyoxalate and the toluene that was employed as solvent. Using Cu cations as catalysts and the chiral diphosphine 'Tol-BINAP' as ligand, the reaction was improved upon until a synthetically useful process emerged. Continuing on this vein, the audience was then treated to a veritable firework display of asymmetric reactions, which moved from organometallic catalysis to 'organocatalysis' and ultimately led to the asymmetric synthesis of warfarin (**3**) from very cheap starting materials, namely benzylidene acetone and hydroxy-coumaric acid.



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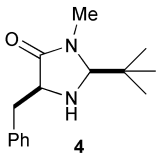
The theme of organocatalysis was continued by **David MacMillan** (California Institute of Technology) who delivered a tour de force of synthetic organic chemistry detailing many of the 18 reactions that could be catalysed enantioselectively by his imidazoline catalysts **4**. Cycloadditions, aryl and enol silane additions to enals generally proceeded with greater than 90% yield and e.e. Catalyst structure modifications enabled the e.e. of many reactions to be increased to >95%. Also highlighted was a catalytic direct aldol coupling between aldehydes **5** and **6** in excellent e.e. and good d.e. These reactions could be iterated before the process self-terminated by cyclising hemi-acetal formation thus opening a powerful and simple route to enantiopure pyranyl-sugar derivatives as well as highly functionalised polyketide molecules. The chemistry was showcased by application to a range of natural product structures thus demonstrating the efficacy of these reactions by the ease with which the complex molecular architectures could be assembled.



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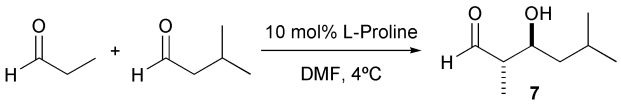
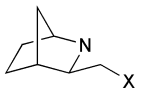


5 **6** **7**

88% yield, 97% ee
anti:syn 3:1

Ligands for metal catalysts and organocatalysts were used by **Pher Andersson** (Uppsala University) to perform a range of enantioselective reactions. Bridged bicyclic amino alcohols **8a** were the key to success to the development of an enantioselective transfer hydrogenation processes. A keen interest in the mechanistic side of reaction design enabled rationalisation of the mechanism and enantioselectivity of amino-alcohol controlled ruthenium catalysed reduction of ketones. Three alternatives were proposed, however a mechanism involving simultaneous transfer of metal-bound hydride and a proton from the amine to the ketone was shown to occur. Experimental studies of both rate and enantioselectivity were used to support the computational results. Finally, enantiopure allylic alcohols were produced from meso epoxides by a lithium amide catalysed rearrangement using diamine **8b**. Excellent enantioselectivities were obtained in many cases. Furthermore, kinetic resolution of racemic epoxides could be achieved using a similar system.



8a X = OH
8b X = pyrrolidine

Steering pericyclic reactions to the sterically unexpected outcome was the main theme of the talk by **Masahiro Murakami** (Kyoto University). He described how the ring

opening reaction of silyl-substituted cyclobutenes proceeds to form the *Z*-1-silylsubstituted dienes. In contrast, the corresponding *tert*-butyl or alkyl-substituted cyclobutenes formed the *E*-substituted dienes. The explanation for this outcome lay in a negative hyperconjugation wherein orbital interaction between the σ* orbitals of a distal C–Si bond and the breaking σ-bond of the cyclobutene ring controls the mode of rotation during the bond breaking event thus leading to the *Z*-diene product. This effect could be further enhanced by using an electron deficient aryl substituent on silicon in order to lower the energy of the σ* orbital thus enhancing the observed effect. Even the *Z*,*Z*-1,4-disilyl butadienes could be accessed from the appropriately substituted cyclobutene demonstrating the importance of often forgotten electronic factors in the stereochemical outcome of chemical reactions.

The size of molecules increased by an order of magnitude between the morning and evening sessions as **Chris Hunter** (University of Sheffield) began the molecular recognition and supramolecular section of the conference. He began by explaining how the strength of non-covalent interactions can be predicted in a variety of systems. The magnitude of these biologically important non-covalent interactions were quantified using a method called a chemical double mutant cycle that involved building non-covalently linked dimers that enabled the measurement of the strength of the interaction between the groups in question. Then by removing one of the units and measuring the change in strength of the complex, a means of quantifying the non-covalent interaction was made possible after the suitable controls were factored in. Thus experimental measurements allowed a quantifiable measure of non-covalent interactions that take place in molecular recognition events.

David Leigh (University of Edinburgh) brought his own individual flavour of chemical magic to the conference as he began the final day of the conference. He described his progress towards nanoscale molecules based on catenane and rotaxane molecular architectures. In a thoroughly entertaining lecture that was interspersed with an array of magical tricks we were led through new reliable methods to form catenanes and rotaxanes using alkene metathesis as the ring forming step. With the required synthetic tools to hand catenanes and rotaxanes were linked together that contained a number of binding sites. Using either chemical or photochemical activation the catenane rings could be made to move in a controlled manner around the central cyclic motif providing a 'molecular machine'. Audience participation was at a premium as a number of the more prestigious conference delegates were asked to help the magician do his work……

The nanotechnology and self-assembly theme continued as the conference drew to its close with **Takashi Kato** (University of Tokyo) describing his research on liquid crystals. He began by explaining that a thermotropic folic acid derivative can be changed from smectic phase liquid crystalline state to hexagonal columnar phase by the addition of alkali metal ions—a feature that could be useful as a readout in sensor application. This change was caused by the alteration of the intrinsic hydrogen bonded patterns of the folic acid derivatives induced by the polar metal ions. 2D conductive materials were also designed wherein alternating insulating and conducting layers could be assembled using traditional amphiphilic molecules in combination with either lithium salts or ionic liquids. In these polar layers efficient ion transportation was observed that could lead to the design of new battery materials. The application of electric fields across materials where micrometer scale droplets of thermotropic nematic liquid crystals are dispersed within polymer matrices lead to phase-segregated structures with electro-optical properties. These phase-segregated structures induce light scattering milky white states which can be switched to transparent states by the application of electric fields and have great potential as electro-optical display materials.

The final lecture of the conference was by **Timothy Swager** (Massachusetts Institute of Technology) and continuing the materials theme described the design, synthesis and application of his polymer materials towards detection of chemical warfare agents and explosives. He described the use of TNT sensing polymers that could be used for the detection of explosive material even at extremely low concentrations and are now used in landmine detection. Switching gears, liquid crystals were again on the agenda as we were shown how liquid crystal hosts can be used to dissolve electronic polymers to form conducting materials. Specially designed conjugated polymers form well-aligned, highly conjugated, chain extended structures in nematic liquid crystals that can be redirected with electric fields. These materials have applications to molecular electronic devices (wherein polymers are extended between two electrodes), electroluminescent devices and field effect transistors.

At the end of timetabled talks there was one last surprise as **Klaus Müller** provided a whirlwind summary of the week. This energetic and entertaining finale set the tone for the last evening in the bar where anticipation for the 39th meeting ran high.

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