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The Legendary Bürgenstock 38th ESF/EUCHEM Conference on Stereochemistry

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Karl Gademann*

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The legendary Bürgenstock conference again attracted 120 scientists from over 20 countries worldwide to discuss stereochemistry in its broadest sense. The beautiful setting of the Bürgenstock Hotels and Resort with its majestic view over Lake Lucerne provided the perfect surroundings to spark stimulating discussions between chemists both from industry and academia and to contemplate future perspectives in chemistry. As the program and the names of all speakers were kept secret until the first evening, everyone eagerly awaited the start of the conference. Indeed, the President ***Jan-E. Bäckvall*** (University of Stockholm), the vice-president *Herbert Waldmann* (MPI Dortmund) together with the local organizing committee *Hans-Beat Bürgi* (University of Berne), *François Diederich* (ETH Zürich), *E. Peter Kündig* (University of Geneva), and *Klaus Müller* (Hoffmann-La Roche, Basel) succeeded in gathering 14 top-class speakers from all over the world. Moreover, thanks to support from the *European Science Foundation*, the *Swiss National Science Foundation* as well as from industry, the organizers were able to invite 15 promising young scientists from all over the world who presented their work in poster form. The first evening of the conference started with an opulent dinner in the grand ballroom of the Palace Hotel, where President Bäckvall gave a warm welcome to the guest of honor of the 2003 Bürgenstock conference, *Léon Ghosez* (University of Bordeaux).

Jan-E. Bäckvall (President)

Herbert Waldmann (Vice President) and Léon Ghosez (Guest of Honor)

*Correspondence: Dr. Karl Gademann
Laboratorium für Organische Chemie der ETH Zürich
ETH Hönggerberg, HCI G 337
CH–8093 Zürich
Tel.: +41 1 632 28 95
E-Mail: gademann@org.chem.ethz.ch

The privilege of the first lecture of the conference was given to ***Anthony G.M. Barrett*** (Imperial College, London) who shared with the audience his almost twenty-year-old 'obsession' with macrocyclic compounds. Indeed, he presented a journey on the chemistry and functionalization of porphyrazines leading to improved properties such as higher solubility or shift of the absorbance frequencies in UV/Vis spectra. The latter modification can lead to the use of such compounds as biomedical optical agents, as it is possible to selectively label human tumor cells *in vivo*. Moreover, Prof. Barrett showed impressive results from using such macrocycles in different areas such as ion sensors, sensitizing agents leading to the generation of singlet oxygen, as well as charge transfer complexes with fullerenes. As this lively multimedia presentation even included old video clips, it is no surprise that a long and intense discussion was sparked.

Anthony G.M. Barrett

T.V. RajanBabu (Ohio State University) followed with his presentation on 'Stereochemical Control in Inter- and Intramolecular Reactions of Olefins and Acetylenes'. As the driving force for his research program he defined the identification of new protocols for 'old' reactions. Of course, this includes a mechanism-based approach as well as the design of new ligands for asymmetric catalysis. The first part of his talk thus focused on the hydrovinylation of olefins, which, as he pointed out, is one of the oldest C–C bond forming reactions using asymmetric catalysts. His new protocols, however, using hemilabile phosphine ligands in connection with Ni(II) and non-coordinating counterions, resulted in improved selectivities and yields. Ligand design of a new class of hemilabile phosphine ligands further improved his method. The second part of his lecture demonstrated the use of $R_3Si\text{-}SNR'_3$ derivatives for the cyclization of diynes enabling rapid access to interesting cyclic structures.

T.V. RajanBabu

In the afternoon of the first day, the participants were given ample time for recreational activities at this marvelous place, before the first poster session started. The posters covered topics from areas as diverse as bioorganic chemistry and computational methods, materials science to analytical methods.

The relaxed poster session

The evening lecture belonged to the director of the Max-Planck Institute für Kohlenforschung, ***Manfred T. Reetz,*** who gave a fascinating lecture on 'Evolutionary and Combinatorial Methods in Enantioselective (Bio)Catalysis'. Starting off with the traditional transition metal catalysis of Rh-catalyzed hydrogenation using monodentate phosphites and phosphonites introduced by his group only recently, he presented a combinatorial approach leading to high enantioselectivity. Interestingly, as mechanistic evidence points to the fact that two ligands are coordinated to the Rh in the transition state, he observed that using heterodimers consistently gave higher *ee* than homodimers! This spectacular observation could be exploited by using small combinatorial libraries of mixing phosphites and phosphonites leading to unprecedented high *ee* values. In a second part of his talk, Reetz demonstrated that evolutionary methods can be used to tune the enantio-

Manfred T. Reetz

selectivity of enzymes for a given reaction to high levels using standard techniques such as DNA shuffling or error-prone PCR. Several rounds of mutation and selection yielded highly stereoselective enzymes. Even a 'Bayer-Villigerase' was the target of his research and the preliminary results look promising. Last, he introduced a fascinating new concept for the generation of enzyme-transition metal hybrids. Using this strategy, a metal complex would be covalently linked to an enzyme and both parts could be optimized by combinatorial or evolutionary methods.

The first talk on Monday morning was given by ***Klaas Martinus Pos*** (ETH Zürich): 'On the Structure and Function of Bacterial Pumps and Bacterial N-Glycosylation'. The interest in the mechanism of the bacterial resistance to known anti-infectives is rising, as is the number of bacteria developing resistance. One pathway of bacterial resistance is the extracellular excretion of antibacterials by specialized channels. The speaker was able to grow crystals of the acrB protein, which is expressed by multi drug resistant bacteria, and to solve its X-ray structure. A thorough structural analysis led to a postulate for the mechanism of action. In a second short part, he presented preliminary data on bacterial N-glycosylation by *Campylobacter jejuni*. Until now, this type of protein modification was only observed in eukaryotes and archae, and the results presented by the speaker shed some light on this important process performed by *C. jejuni*.

Klaas Martinus Pos

Jeffery W. Kelly (The Scripps Research Institute) presented his group's research on 'The Chemistry and Biology of Misfolding Diseases' thus discovering new therapeutic strategies for amyloid diseases. Among these, misfolding of the transport thyroxine retinol binding protein (TTR) leads to diseases such as senile systemic amyloidosis, of which *ca.* 15% of the age group above 80 suffer. His group performed many kinetic and thermodynamic studies on TTR thus elucidating the mechanism of folding. This detailed understanding of the misfolding even led to the identification of small molecules as potential therapeutics. One FDA approved compound for arthritis, *diflunisal*, shows great efficacy in preventing TTR misfolding!

Jeffery W. Kelly

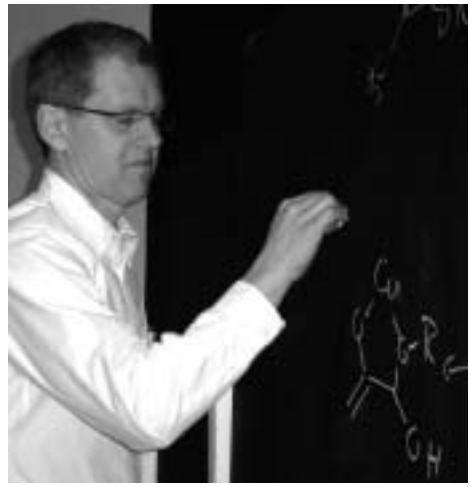
The next recreational event, a fondue dinner, gave the participants the opportunity to taste some typical Swiss food and Swiss culture. This pleasant experience was made by *Tim Swager* (MIT), who lost his bread twice in the fondue and thus was forced to buy several rounds of wine by his colleagues, *Karl Anker Jørgensen* and *David W.C. MacMillan*.

Tim Swager and David MacMillan tasting fondue

The evening lecture belonged to ***Ari Helenius*** (ETH Zürich). His talk on 'Quality Control during Protein Folding' demonstrated fascinating strategies of nature to correct the many errors made in protein manufacturing. Using the calnexin and calreticulin examples, his group was able to demonstrate how carbohydrate attachments are read by chaperones and, if misfolding occurs, it is immediately corrected in the endoplasmic reticulum.

Ari Helenius

The next day focused on asymmetric catalysis as the two speakers as well as Chairman *Carsten Bolm* were prominent members in this research area. ***Karl Anker Jørgensen*** (Aarhus Tech) started his talk on 'A Failed Reaction Leading to New Catalytic Asymmetric Transformations' with a lively presentation of over 2000 years old Danish music instruments, so-called lures. While the speaker demonstrated the deep tone of these instruments, he pointed out that they were found as an exact pair of enantiomers. As these instruments were made from copper, this metal, especially in conjunction with bisoxazoline (box) ligands, was also the metal of choice of the speaker. He presented the use of such complexes in a plethora of reactions ranging from Aza-Henry, Aza-Friedel-Crafts, and Aldol to the 1,4-addition of 1,3-diketo compounds to α,β-unsaturated ketones, all of which proceed with high yields and stereoselectivities. Using the last method men-



Karl Anker Jørgensen

tioned he showed a new synthesis of the old drug *warfarin* which over 1 million people in the U.S. are still using on a daily basis. Abandoning metals and turning towards 'organocatalysis', he showed the powerful methodology of this emerging field within catalysis with use of proline for direct aldol reactions.

It was one of the pioneers of the use of small organic molecules as catalysts, ***David W.C. MacMillan*** (Caltech) who immediately followed with a talk on 'Development of New Catalysis Concepts of Broad Utility to Chemical Synthesis'. In a fascinating presentation, he elaborated the design of chiral secondary amines as enantioselective catalysts for Diels-Alder and nitrone [3+2] cycloadditions. The most interesting reaction, however, was the 1,4-addition of aromatic compounds to α,β-unsaturated aldehydes resulting in useful products with high yield and selectivity. Using a chiral imidazolidinone pioneered by Dieter Seebach more than a decade ago for amino acid synthesis, he was able to further improve selectivity and rate of various reactions. The successful use of his methodology in complex natural product synthesis further proved its power.

David MacMillan

Tuesday evening, it was time for the traditional conference dinner at the Bürgenstock club. The delightful banquet was followed by lovely chamber music performed by the *Aura String Quartet* (Basel). The president himself selected the pieces from Jean Sibelius, Germaine Tailleferre, and Felix Mendelssohn, which touched the heart of many of the 'big brains' in the audience. After the last sounds had faded out in the mild spring night, a wine reception stimulated the participants to late-night discussions.

V.K. Aggarwal was happy to announce the Wednesday morning speaker**, *Pher G. Andersson*** (Uppsala Univ.), who presented his group's research, "Development and Application of a New Class of Chiral Ligands" for asymmetric catalysis. After he shared his first independent research experience as chalk talk, he quickly moved to a real success story employing bicyclic amine derivatives. These chiral auxiliaries can be used in reactions as diverse as Et_2Zn addition, transfer hydrogenation and enantioselective ring opening of epoxides. His statement that the real challenge in asymmetric catalysis is defined by rate and not by selectivity is certainly right. He elaborated that the Ru-catalyzed transfer hydrogenation using, for example Noyori's modified diamines, is not practical due to an inherently low rate. Andersson presented a modified aminoalcohol which displayed turnover frequencies of up to 8500 and substrate/catalyst ratios of 1000 in the transfer hydrogenation of ketones and azirines.

Pher G. Andersson

Similar small-ring organic compounds, more exactly cyclobutenes, were also in the focus of ***Masahiro Murakami*** (Kyoto University), who examined 'The Stereochemistry of Electrocyclic Reactions Dominated by Hyperconjugation Rather than Sterics'. He was able to show experimentally that Si-substituted cyclobutenes react differently than their C-atom counterparts. While the 1,2-dimethyl-cyclobutene opens under thermal conditions to the (*E,E*)-Diene, the corresponding Si derivative preferentially gave the (*Z,Z*) isomer! This is due to hyperconjugation of the σ*(C–Si) to the HOMO of the breaking C–C bond in the transition state, as DFT calculations showed. Interestingly, the Sn-derivate does not display the (*Z,Z*)-selectivity presumably due to the longer C–Sn bond. Murakami also gave two synthetic applications leading to interesting highly substituted dienes.

Masahiro Murakami

The Aura String Quartet

The conference organizers and *Franz Schmittchen* as moderator switched gears for the evening lecture as ***Chris A. Hunter*** (Univ. Sheffield, UK) presented fundamental results obtained by his group's 'Quantitative Approaches to Molecular Recognition'. This phenomenon is of utmost importance in many areas of science, and not surprisingly, exact measurements of the free energy contributions of, for example, solvation, dispersion, and electrostatic interaction are crucial for deeper understanding. Using synthetic self-assembly systems, Hunter was able to determine many of these parameters leading to interesting observations. The question as to what extent pKa values and H-bond donor abilities correlate, was intensively discussed after the presentation.

Chris A. Hunter

Traditionally one of the main areas in chemistry is the development of new materials. The last day of the 2003 Bürgenstock conference covered this subject broadly, as conference chairman *Peter Bäuerle* pointed out. The lecture by ***David A. Leigh*** (University of Edinburgh, UK) entitled 'Tooling up for Nanoworld: Hydrogen Bond Assembled Molecular Machinery' introduced the audience into the programmed synthesis of functional molecules. For example, he demonstrated the protection of a biologically active peptide by a rotaxane thus preventing attack by proteases. This could lead to interesting applications of rotaxanes as prodrugs. In another fascinating example, his group prepared a catenane where the motion of one ring was driven solely by light. This represents the first light-driven 'molecular machine', where the movement of atoms can be strictly controlled. However, this talk really became a magical experience by the many magic tricks that were performed by the speaker in order to exemplify the structure and chemistry of his molecules!

David A. Leigh

Takashi Kato (University of Tokyo) elaborated in his talk on 'Nanostructured Liquid Crystals: Supramolecular Self-Assembly of Soft Materials'. The speaker happily pointed out that he was the only 'nanoscientist' at this conference, thus allowing him to present to a wider community his scientific work. Indeed, from molecular shuttlecocks to thermotropic liquid crystal biomolecules, from ion conductive liquid crystals to liquid crystalline gels, he achieved impressive results from this important area of research.

Takashi Kato

The privilege of giving the last lecture of this conference was given to ***Tim M. Swager*** (MIT, Boston). His fascinating talk, entitled 'Polymer Electronics for Ultra-Sensitive Chemical and Biological Sensors', demonstrated how efficiently electronic polymers can be used to amplify sensory signals. The basic principle is the 'wiring' of chemical receptors in series along electronically conjugated polymers. If the analyte binds to the receptor, the transport properties of the system are perturbed by either electrical resistivity or fluorescence thus resulting in huge amplification of the sensory signal. For example, his research led to ultra-sensitive sensors for tri-nitro toluene (TNT). Although the vapor pressure of TNT is very low, his device is able to detect land mines hidden underground. The U.S. Army is currently evaluating this very innovative and life-saving technology.

With this lecture, another fascinating week of Bürgenstock chemistry was over. The blend of cutting-edge science and bright people from both industry and academia again demonstrate the vitality of organic chemistry. Moreover, it became clear how chemistry as the enabling science needs organic synthesis as its core discipline to generate new molecules and thus, to discover new function.

Tim M. Swager

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