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The 42nd EUCHEM Conference on Stereochemistry (Bürgenstock-Conference 2007)

Fürigen, April 14–20, 2007

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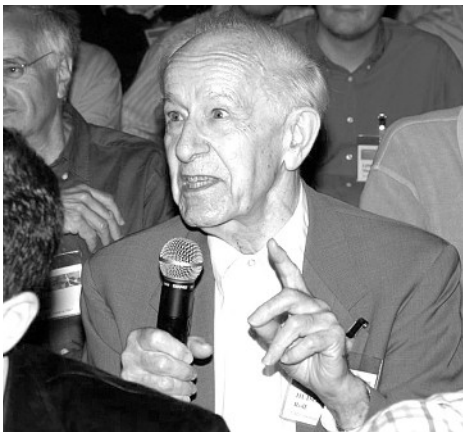
In 1291 the people of Nidwalden joined Uri and Schwyz to form an alliance that would in time go on to form the basis of the modern Swiss Confederation. Today, this idyllic part of central Switzerland continues to play host to gatherings of importance including the prestigious EUCHEM Bürgenstock Conference on Stereochemistry, now in its 42nd year. Almost 110 chemists converged on Bürgenstock in eager anticipation of a week of world-class science. In a departure from normality, the venue for this year's conference was the Hotel Fürigen, since the Bürgenstock hotels are currently undergoing a period of refurbishment. Surrounded by breathtaking mountain scenery and dominated by the might of Mount Pilatus, this region on the shores of Lake Lucerne continues to provide the perfect backdrop to this prestigious conference. In traditional fashion, the line-up of speakers was not revealed to the attendees prior to arrival, but the President ***Samir Zard*** (Ecole Polytechnique, Palaiseau), along with Vice-President *Don Hilvert* (ETH Zürich) and the Organizing Committee comprising *François Diederich* (ETH Zürich), *E. Peter Kündig* (University of Geneva), *Klaus Müller* (F. Hoffmann-La Roche, Basel), *Philippe Renaud* (Universität Bern) and *Jay Siegel* (Universität Zürich) had assembled a spectacular programme of scientists that promised to deliver a fascinating series of lectures. We were not disappointed. With this year's guest of honor being the legendary ***Rolf Huisgen*** (Ludwig-Maximilians-Universität Munich), who actively participated by asking questions in every session, and the Vice-President dutifully carrying out his responsibility to ensure that the entire Bürgenstock area was bathed in glorious sunshine for much of the week, the attendees were treated to an unforgettable conference. Next year's Vice-President has a lot to live up to…



Guest of Honor Rolf Huisgen

President Samir Zard

The excellence of the scientific program rapidly became clear when *Jean-Pierre Genét* introduced ***Barry Snider*** (Brandeis University) who described a series of impressive short stories covering his group's recent adventures into the synthesis of structurally interesting natural products. The

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underlying philosophy behind his research is to invent and discover new methods to assemble complex molecular architectures, and this was amply demonstrated during his lecture. Topics covered included: i) the total synthesis of (±)-symbioimine using a stereoselective intramolecular Diels-Alder reaction of an N-carboalkoxydihydropyridinium cation with a diene, ii) the formal synthesis of (±)-platensimycin using a radical cyclization of a vinyl bromide onto an enone to assemble a tricycle that could be readily converted into the tetracycle seen in the natural product, iii) the total synthesis of thallusin involving the Stille coupling of a stannylpyridine with a vinyl bromide (derived from sclareol oxide in only three steps) using a stoichiometric palladium source, iv) the total synthesis of (+)-Sch 642305 using a stereoselective transannular Michael reaction of a 14-membered macrolactone, v) the structural reassignment and total synthesis of jenamidines A1/A2 starting from an activated proline-derivative to assemble the bicyclic core, vi) the total synthesis of descurainin using a [5+2] cycloaddition and, vii) work towards berkelic acid. All in a one-hour lecture!

Barry Snider

Phil Baran

The theme of natural product total synthesis driving new reaction discovery was continued with an impressive talk from ***Phil Baran*** (The Scripps Research Institute, La Jolla), who described a number of elegant and concise total syntheses carried out by his group. Very evident was Professor Baran's appreciation of the history of chemistry and his passion for the field of total synthesis. During his talk, he emphasized a number of general principles that should be applied to natural product synthesis to maximize brevity and efficiency. One of these principles is the minimization of oxidation state adjustments in a synthesis. A second ideal is to minimize or dispense with entirely the use of protecting groups in a synthesis. Professor Baran stressed the importance of embracing the natural reactivities of functional groups to avoid the use of protecting groups. A third ideal is to devise transformations that result in exponential, or at least linear increases in complexity as a synthesis progresses. These principles were demonstrated with a number of examples of total syntheses from the Baran lab. Chartelline C was prepared using a powerful ring-contraction and interesting decarboxylation of a chlorine-substituted vinyl carboxylic acid. Hapalindole Q was prepared employing a newly developed direct method to couple indoles with enolates under oxidative conditions. A similar strategy was employed to prepare hapalindole U, which was then converted into ambiguine H by an amazing sequence to install a required *tert*-prenyl group. Also described was methodology to cross-couple different enolate ions, which was exemplified in the synthesis of bursehernin. Racemic haouamine A was prepared using an intramolecular pyrone Diels-Alder reaction–decarboxylation sequence to form the bent aromatic ring, and a method to access enantiopure haouamine was also described.

The afternoon program consisted of the first of two poster sessions to provide opportunities for a number of the participants (some supported with generous financial assistance from the Swiss Chemical Society) to present their research in an intense but yet relaxed setting. Five of the 17 posters were selected for short oral presentations to serve as a pre-session 'appetizer': *Giorgio Columbo* (CNR, Instituto Chim. Riconosc. Molec., Milano, Italy, 'Imprint of Sequence and Structure on the Recognition and Self-Organisation Properties of Biochemical Systems: Insights from Molecular Simulations'), A*nja Hoffmann-Röder* (Johannes Gutenberg-University Mainz, Germany, 'Synthesis of Fluorinated Analogs of Tumor-Associated Carbohydrate Antigens: Novel Building Blocks for Cancer Vaccines'), *Hon Wai Lam* (University of Edinburgh, UK, 'Stereoselective Cobalt-Catalyzed Reductive Aldol Reactions'), *Véronique Michelet* (Ecole Nationale Supérieure de Chemie de Paris, France, 'Gold, Platinum and Iridium Catalysts: Novel Activities and New Opportunities'), *Michael J. Porter* (University College London, UK, 'Progress Towards the Sarain Core').

Continuing the synthetic organic chemistry theme, moderator *William B. Motherwell* introduced ***Pierre Vogel*** (EPFL Lausanne) as the final lecture of the first day. Professor Vogel described his group's studies into the development of cascade reaction sequences using sulfur dioxide as a reagent, and the incorporation of these cascades into the total synthesis of polypropionate natural products. At low temperatures, dienes react with excess sulfur dioxide to form sultines rather than sulfolenes. These intermediates may be used in a number of highly useful transformations under Lewis acidic conditions, for example reaction with carbon nucleophiles such as silyl enol ethers or allyl silanes. The resulting products are often valuable polyketide precursors. The absolute configurations of the products may be controlled by the use of a suitable chiral auxiliary on the diene, and this methodology was exemplified in a number of synthetic applications. For example, the chemistry could be applied to a one-pot four-component synthesis of polyfunctional sulfonamides, as well as one-pot three- and four-component syntheses of polyfunctional sulfones. The methodology was also applied in several natural product approaches, including the cyclohexanone subunit of baconipyrones A and B, the stereoheptad of rifamycin S, the C(1)-C(11)-polyene fragment of apoptolidin, and in work towards dolabriferol. Other topics covered included

Pierre Vogel

the use of polysulfones (obtained as a result of co-polymerization of sulfur dioxide with alkenes) in alkene isomerization reactions, a new bora-ene reaction with sulfur dioxide, and a new method for silylation.

Monday's session began in entertaining fashion with *Nazario Martin* introducing ***Eiji Yashima*** (Nagoya University), who described his group's work on the preparation of helical polymers and oligomers. Professor Yashima has developed a neat method to induce helical chirality in poly(4-carboxyphenyl)acetylenes by the addition of chiral amines. Amazingly, this chirality can be 'memorized', even after complete replacement of the chiral amines with achiral ones. In other work, the chirality of cyclodextrin-containing polyphenylacetylenes may be inverted in response to various external stimuli, such as changing the solvent or varying the temperature, or by the addition of various achiral or chiral guest molecules. Professor Yashima also described the 2D crystallization of alanine-containing helical polymers on graphite, and the 2D crystal formation of helical polyisocyanides. A strategy to access artificial double helices using salt bridges between chiral diamidines and achiral dicarboxylic acids was also detailed. This general strategy was also applied to the preparation of cylindrical triple helices and complementary double helices where cross-linking of the strands is achieved using *trans*-Pd(II)-acetylide complexes. By judicious incorporation of pyridine residues, the synthesis of double-stranded metallosupramolecular polymers may be achieved.

Eiji Yashima

The next lecture entitled 'Self-assembly and Beyond' was given by ***Gero Decher*** (University Louis Pasteur). Professor Decher described the development and application of a technique to create multimaterial composites that display new and unusual properties and that potentially may be used in an enormous variety of applications. The technique is quite simple, and involves the layer-by-layer assembly of molecules from solution by adsorption. Although electrostatic interactions were mainly used at first, other types of non-covalent interactions can also be used. The range of molecules that may be used for making these multilayer composites is also broad, and includes proteins, DNA, polyelectrolytes and gold colloids. The paper in which this technique is described (entitled 'Fuzzy Nanoassemblies: Toward Layered Polymeric Multicomposites') has had a tremendous impact on the scientific community, having currently been cited over 2000 times! An example of a commercial application of this method is the Yasa sheet which, when wrapped around fruit and vegetables, prolongs their lifetime. Yasa sheets are made by the alternating layer-by-layer deposition of chitosan (a sugar-based ingredient of crab shells) and an enzyme-containing liquid obtained from bamboo. In an amusing twist, Professor Decher also referred to tremendous worldwide interest in layer-by-layer adsorption within the context of the Gartner Hype cycle, a model that is used widely in business environments to represent the maturity, adoption and application of new technologies. Specific phases within the Hype cycle include the 'Peak of Inflated Expectations' and the 'Trough of Disillusionment', followed by the 'Slope of Enlightenment' and the 'Plateau of Productivity'. Where exactly layer-by-layer deposition currently stands within the Hype cycle is anyone's guess, but there's no denying the power of this method.

Gero Decher

The scientific session on Monday concluded with *Kyoko Nazaki* introducing ***Deborah Leckband*** (University of Illinois at Urbana-Champaign), who provided a tutorial lecture on adhesive interactions in biology. Nature makes extensive use of adhesive interactions, for example in the 'sticky' feet of geckos to the suckers of octopus tentacles, to the powerful clinging ability of mussels. In her lecture, Professor Leckband focused on a number of case studies. The first of these described the Neural Cell Adhesion Molecule (NCAM), a glycoprotein that is implicated in cell–cell adhesion and neuronal outgrowth. NCAM consists of seven distinct domains, and there are two general models for the mechanism of binding of NCAM to another NCAM on adjacent cells that explain the observation that NCAM forms two bound states with different mechanical properties. The two models differ in the number of domains that are involved in the binding. The stronger bound state involves five domains, whereas the weaker bound state involves only two. The second case study described the adhesion between CD2, a transmembrane glycoprotein on T-cells with the counter-receptor CD58 that is found on a variety of target cells. The nature of adhesion may be studied using a number of methods, which suggest that the tensile strength of the protein–protein interaction is primarily determined by a number of discrete salt bridges.

Deborah Leckband

Chaired by *Shu Kobayashi*, Tuesday's lectures began with an impressive talk by ***Stephen K. Hashmi*** (Universität Heidelberg) on the use of homogeneous gold catalysis, currently a hot topic in organic synthesis. The last few years have witnessed an explosion in the number of publications that detail the use of gold catalysts to mediate novel transformations, and Professor Hashmi's self-confessed love of gold was clearly apparent as he gave a detail-packed lecture that described his group's numerous contributions. Gold salts have a high ability to bind unsaturated species such as allenes and alkynes, and activate them towards attack by various nucleophiles to form a large variety of products. Reactions that were described included the formation

of polysubstituted furans by cyclization of allenyl ketones and propargyl ketones, and the synthesis of polyfunctional phenols by the rearrangement of ω-alkynalfurans. The complex mechanism of the latter transformation is thought to involve the intervention of arene oxide intermediates. Strong evidence for the mechanism comes in the form of trapping of the arene oxide intermediate in an intermolecular Diels-Alder reaction. Professor Hashmi also described application of the phenol synthesis to a natural product, and preliminary efforts towards rendering the phenol synthesis enantioselective, offering an exciting look at Noble metal catalysis in a field where all that glitters really is gold.

Stephen K. Hashmi

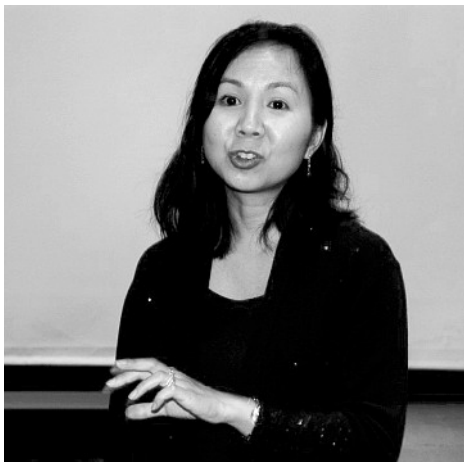
Guy Bertrand (University of California, Riverside) was up next, and described his group's explorations into the synthesis and reactivity of stable carbenes. The Bertrand group have over the years prepared a number of stable carbenes of varying structure, that include acyclic carbenes, carbenes that are stabilized with either one or two heteroatoms, cyclic carbenes of varying ring sizes, and even a cyclic three-membered non-heteroatom-substituted carbene! The middle part of Professor Bertrand's lecture focused on the preparation of cyclic (alkyl)(amino)carbenes (CAACs) and their use as ligands for transition metals. CAACs have been found to be highly effective ligands for the palladium-catalyzed α-arylation of carbonyl compounds with aryl chlorides. New methods to form CAACs using intramolecular hydroiminiumation and amidiniumation reactions were also described. The final part of the lecture described the reactions of stable CAACs with other molecules, such as the formation of ketenes by reaction with carbon monoxide, the nucleophilic activation of dihydrogen and ammonia, and reaction with phosphines, boranes and silanes.

Guy Bertrand

There was no lecture on Tuesday evening. Instead, the participants were treated to a delightful concert of chamber music by the *Aura String Quartet*. The programme comprised works by Ludwig van Beethoven, Anton Webern and Claude Debussy.

The Aura String Quartet

A more biological flavour was imparted to Wednesday's lectures, which began with *Don Hilvert* introducing a presentation from ***Linda Hsieh-Wilson*** (California Institute of Technology) entitled 'Chemical Approaches to the Neurobiology of Carbohydrates'. The first part of the lecture was concerned with chondroitin sulfate (CS) glycosaminoglycans, a family of sulfated sugar chains that are thought to play important roles in neuronal development and cell division. CS glycosaminoglycans have a repeating disaccharide structure and extremely diverse patterns of sulfation, and it is this diversity which can often inhibit the study of the structures and functions of these molecules. Professor Hsieh-Wilson described a synthetic route to a CS tetrasaccharide which was found to stimulate the growth and differentiation of hippocampal neurons. In addition, these studies established that a tetrasaccharide is the minimum structural requirement for biological activity and that sulfation is crucial. A 'sulfation code' hypothesis was put forth which assumes that the nature of the sulfation pattern is directly responsible for the precise bioactivity, much in the same way that DNA encodes information. In a second area, the post-translational modification of serine and threonine residues of proteins in the brain with N-acetylglucosamine (GlcNAc) was described. A protein of particular interest is the cAMP response element binding protein (CREB), a transcription factor that plays critical roles in memory and learning. This was highlighted in spectacular fashion with fruit flies genetically engineered to have the CREB gene permanently 'switched on'. Such 'superflies' were found to have photographic memories. In related work, glycosylation of CREB was shown to inhibit its ability to bind to basal transcription machinery, thereby repressing its transactivation ability, and contributing to pancreatic β-cell death.



Linda Hsieh-Wilson

The biological theme was continued by ***Benjamin Cravatt*** (The Skaggs Institute for Chemical Biology), who described the use of chemical proteomics and metabolomics to study enzyme pathways in human diseases. A key principle is that it is the activity of an enzyme (rather than its abundance) that is ultimately responsible for its role in cell physiology, and the Cravatt group have developed a series of technique called activity-based protein profiling (ABPP) that enable direction quantification of activity. ABPP has been used to discover several novel cancer targets, such as the membrane hydrolase KIAA1363. It has been found that levels of KIAA1363 are elevated in invasive cancers, and that overexpression of KIAA1363 increases the pathogenic properties in ovarian cancer cells. Using competitive ABPP, the Cravatt group has identified a small molecule named AS115 that strongly inhibits the activity of KIAA1363.

AS115 was found to reduce the levels of a class of lipids known as the monoalkylglycerol ethers, which are products of a KIAA1363-catalyzed reaction. These data place KIAA1363 at an important junction in an ether signaling network. In discussing the future of this technology, Cravatt emphasized that there are more than seven dozen other enzyme classes waiting to be investigated.

Benjamin Cravatt

The afternoon was devoted to the second of the two poster sessions. Again, five of the 17 posters were selected for short oral presentations: *Stephen J. Connon* (Trinity College Dublin, Ireland, 'A Reductase-Mimicking Thiourea Organocatalyst Incorporating a Covalently Bound NADH Analogue: Efficient 1,2-Diketone Reduction with in situ Prosthetic Group Generation and Recycling'), *Chiara Monti* (Universita degli Studi di Milano, Italy, 'Synthesis of the C10-C23 Fragment of Dictyostatin Using a Highly Stereoselective Carreira Alkynylation'), *Gwénaél Rapenne* (Université de Toulouse, France, 'Design and Synthesis of a Family of Molecular Motors'), *Andràs Kotschy* (Eötvös Lorand University Budapest Hungary, 'Sensor Design Based on Conformational Dynamics'), *Dieter Vogt* (Eindhoven Institute of Technology, Netherlands, 'Asymmetric Hydrocyanation: The Enantioselective Step').

The Wednesday evening lecture, chaired by *Wolf-Dieter Woggon* was delivered by ***Michael Marletta*** (University of California, Berkeley). Marletta began in comical fashion by commenting on the conference's tradition of not making the program known prior to registration. Upon receiving his initial invitation and enquiring to his wife as to why this was so, he was simply told "Maybe they are worried no-one will come if they know you are on it". Nothing could be further from the truth! Marletta's theme was the biological generation, role and application of nitric oxide. It is now well established that nitric oxide plays important roles in signal transduction, and in the response of a host organism to infection. Just one example of a medical application is in the treatment of pulmonary hypertension in infants, where the administration of nitric oxide dilates the airways. The enzyme nitric oxide synthase (NOS) catalyzes the conversion of L-arginine to nitric oxide and citrulline, and Professor Marletta described the results of in-depth investigations into several aspects of structure and catalytic action of NOS. He then moved on to discuss H-NOX (heme-nitric oxide and/or oxygen) binding domains in proteins. In facultative aerobic prokaryotes, H-NOX domains bind nitric oxide but not oxygen, however, in obligate aerobic prokaryoates, H-NOX domains bind nitric oxide and oxygen. The question is then, how does discrimination between nitric oxide and oxygen occur? Through mutation studies, it has been found that substitution of phenylalanine to tyrosine 'turned on' oxygen binding in facultative aerobic prokaryoates, which suggests that hydrogen bonding may play a critical role in binding to oxygen ligands. Marletta concluded with a masterclass in 'worm science' demonstrating that the 'clumping and bordering' behaviour of *C. elegans* could be rationalized by the response of H-NOX domains to changing NO/O_2 levels.

Michael Marletta

The final day kicked off on a radical note with *Trøls Skrydstrup* introducing ***Sunggak Kim*** (Korea Advanced Institute of Science and Technology), who described the development of new synthetic methodologies based around the use of radical chemistry. Cyclization of carbon radicals onto N-aziridinylimines was shown to result in the production of new five- and six-membered ring radicals. This process may be incorporated into a wide variety of domino sequences that produce polycyclic products, and a number of impressive applications to natural product synthesis (including zizaene, pentalenene, and hirsutene) were described. The discussion then moved onto the alkylation of carboxylic amides by reaction of carbon radicals (activated with an adjacent electron-withdrawing group) with silylketene N,O-acetals. The initially developed α-alkylation may be extended to the γ-alkylation of α,β-unsaturated amides. A tin-free radical carbonylation procedure using alkyl allyl sulfone precursors, carbon monoxide and phenyl benzenethiosulfate was described next, which allows preparation of a wide variety of thioesters. The last part of the lecture covered enantioselective conjugate radical additions onto α,β-unsaturated carbonyl compounds. Using a phosphonate ester as an achiral template in conjunction with a zinc-bis(oxazoline) complex, high enantioselectivities may be achieved. The phosphonate ester serves as a functional handle in the products to allow elaboration to a variety of structures.

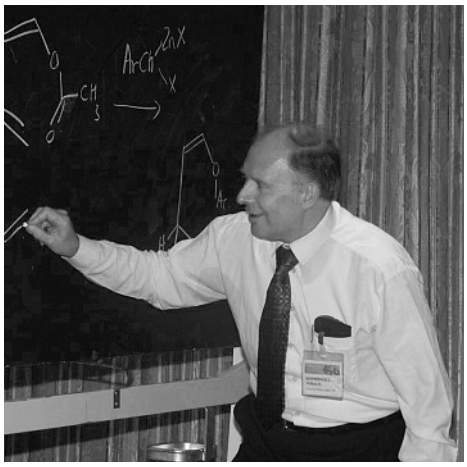
Sunggak Kim

The penultimate lecture of the conference was delivered by ***William Motherwell*** (University College London) in his own unique and humorous style. Describing the history of zinc chemistry Motherwell entertained with the tail of Sir Edward Frankland's preparation of the first alkylzinc reagent (Et_2Zn) in 1849 in which H_2 was used as an inert chemical atmosphere rather than Ar or N_2 as is commonly used today. The preparation of Et_2Zn was subsequently used by Frankland as a simple test for incoming coworkers who, if they survived the process, were welcomed into the group. In moving to his own research, Motherwell described in the first half of the lecture a rather underutilized method for generating zinc carbenoids from carbonyl compounds, or acetals, using zinc metal and trimethylsilyl chloride. Zinc carbenoids generated in such a fashion undergo cyclopropanation reactions with alkenes, and by using ortho-

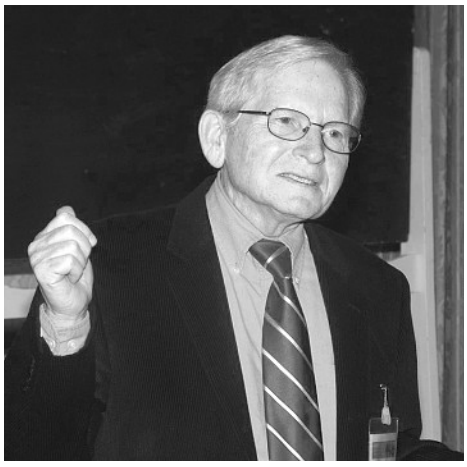
formates or acetal derivatives of amides as the precursors, this methodology may be employed to prepare oxygen- and nitrogen-substituted cyclopropanes respectively. An oxazolidinone chiral auxiliary may be used to effectively control the absolute stereochemistry of the cyclopropanation, and after hydrogenolytic cleavage of the auxiliary, enantiomerically enriched aminocyclopropanes are obtained. This methodology was illustrated in synthesis of a key fragment of the peptidomimetic immunosuppressant Belactosin A. The second half of the lecture described the use of an interesting system to probe the strength of non-covalent interactions of various functional groups with aromatic rings. The system was cleverly designed to set up a competition between two different substituents to sit directly above either one of two equivalent aromatic rings in the molecule. By measuring the position of equilibrium (mostly by determining time-averaged coupling constants), one can get an idea of the relative strengths of various functional group-arene interactions. The lecture was followed by a fruitful question and answer session that included a traditional blackboard discussion in which questioners were invited to illustrate their queries with chalk in hand. This was accompanied by Motherwell's friendly reiteration of Sir Derek Barton's statement that "words conceal, boards reveal".

Bernhard Kräutler introduced the last lecture of the conference. This honor was given to ***Perry Frey*** (University of Wisconsin, Madison), who dedicated his presentation to the memory of the late, great ***Frank Westheimer*** (Harvard University), who passed away on April 14th, 2007 aged 95. The topic of discussion was the identification and characterization of free radicals as intermediates in enzymatic pathways. Several case studies were presented. The adenosylcobalamin-dependent ribonucleoside triphosphate reductase (RTPR) catalyzes the reduction of ribonucleoside triphosphates to deoxyribonucleoside triphosphates. An observed epimerization at stereoselectively-deuterated carbon-5' of adenosylcobalamin by RTPR implicates the intervention of radical intermediates, which are generated by the action of a thiyl radical of Cys 408 of RTPR. Professor Frey also touched on the mechanism of diol dehydrase, which converts vicinal diols into aldehydes, and the action of lysine 2,3-aminomutase, which converts α-lysine into β-lysine. In the case of lysine 2,3-aminomutase, an iron-sulfur cluster is thought to be important, with S-adenosylmethionine playing an important role in mediating hydrogen transfer.

To conclude proceedings, ***Klaus Müller*** summed up the five days of lectures and discussions by providing a comprehensively abstract overview of the conference in his own unique and humorous style. The outstanding level of lectures and scientific discussion coupled with beautiful scenery and relaxed and friendly atmosphere has once again made the Bürgenstock conference a resounding success. With Don Hilvert (ETH Zürich) as next year's President, and the announcement that Ben Feringa (University of Groningen) will be next year's Vice-President, this meeting continues to have an extremely bright outlook.



William Motherwell



Perry Frey

Klaus Müller

Next year's President Don Hilvert

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