Highlights from the 42nd EUCHEM Conference on Stereochemistry, Bürgenstock, Switzerland, April 2007

Matthew L. Maddess[a] **and Andreas F. M. Kilbinger**[b]

DOI: 10.1039/b707067p

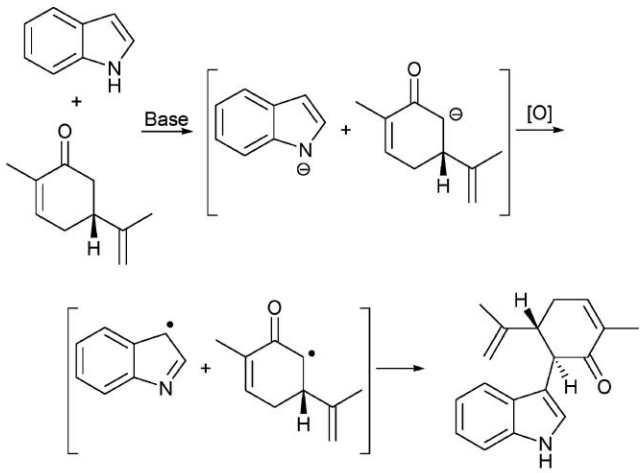
It was gloriously hot, the sort of day when nature seems to unbutton its waistcoat and put its feet up. Intent on keeping the 100-plus chemists from a record 23 countries around the world in the dark until the last minute, the conference program for the 42nd EUCHEM Conference on Stereochemistry in Bürgenstock was finally unveiled. However, this year, it was not quite business as usual. With the traditional site at Hotel Bürgenstock being renovated, the conference guests met in Hotel Fürigen, just a short—albeit steep—walk down the mountain. The organizing committee of **Francois Diederich** (ETH Zürich), **Peter Kündig** (Université de Genève), **Klaus Müller** (Hoffman–La Roche, Basel), **Philippe Renaud** (Universität Bern) and **Jay Siegel** (Universität Zürich), together with the President **Samir Zard** (Ecole Polytechnique, Palaisau), had once more put together a programme of exceptional international speakers covering the core disciplines of organic chemistry, as well as topics ranging from organic materials and polymers to bioorganic chemistry.

After welcoming the guests, the president introduced the guest of honour, **Rolf Huisgen**, who has been Professor Emeritus at the Ludwig-Maximilians-Universität in Munich for 19 years and is a pioneer in the field of 1,3-dipolar cycloadditions (for an excellent dissertation on his many accomplishments, see: C. Rüchardt *et al.*, *Helv. Chim. Acta*, 2005, **88**, 1154). As the president pointed out, it is the guest of honour's privilege to sit back and enjoy the scientific presentations. However, this did not apply to Rolf Huisgen, who was determined to play a far larger role in the proceedings, to the delight of all the conference attendees.

The inaugural presentation at the Hotel Fürigen to initiate the scientific proceedings was given by **Barry B. Snider** (Brandeis University, Waltham, USA), who provided a fascinating journey into the total synthesis of a number of novel natural products. To begin, an elegant 12-step synthesis of (±)-symbioimine featuring a highly constructive, intramolecular and stereospecific Diels–Alder reaction of an *N*-carboalkoxydihydropyridinium cation to form the tricyclic core was described, nicely setting the stage for a series of illustrative synthetic efforts of biologically-relevant compounds to come. Of particular note was the evaluation of possible biomimetic transformations to rapidly build complexity with stereocontrol, as seen in the successful completion of both (+)-Sch 642305 and berkelic acid. Also, a traditional role of total synthesis was exemplified in the revision of structures for the jenamidines in the course of their construction. A thoroughly enjoyable and lengthy question period was to follow, highlighting one of the very attractive features of this gathering, where ample time is allowed for discussion. Especially pleasing were Professor Huisgen's numerous pointed and elegantly-phrased questions, which were captivating and clearly demonstrated his enduring enthusiasm for science.

Next to take centre stage was **Phil S. Baran** (The Scripps Research Institute, La Jolla, USA), whose prestigious early publication record has firmly established him as a pre-eminent leader in the field of organic synthesis. In a beautifully crafted seminar, the common and ubiquitous use of protecting groups as a necessary strategy for building complex molecules was challenged; arguing rather that, at times, the innate reactivity of functional groups can be exploited to mitigate key bond-forming events. It was then shown how the adoption of this paradigm led to the extremely powerful direct coupling of either indoles or pyrroles with carbonyl compounds *via* oxidative radical

[a]*University of Cambridge, NSERC-PDF, Department of Chemistry, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: mlm46@cam.ac.uk*
[b]*Institut für Organische Chemie, Johannes Gutenberg-Universität Mainz, Duesbergweg 10-14, D-55099, Mainz, Germany. E-mail: akilbing@uni-mainz.de*



Oxidative Radical Dimerization of Indole and Carbonyl Compounds

dimerization. For instance, the addition of copper(II) 2-ethylhexanoate to an anionic mixture of carvone and indole results in their regioselective union at C3, providing a concise entry point to both the hapalindole and fischerindole alkaloid families. By the extension of these ideas, the remarkable protecting group-free total synthesis of both (+)-ambiguine H and (+)-welwitindolinone A were described. In the case of pyrroles, the locus of reactivity resides at C2 rather than C3, and coupling with carbonyl compounds at this centre affords equally efficient access to a whole new family of natural products, such as (*S*)-ketorolac. The same concept was also amenable to the intra- or intermolecular oxidative enolate heterocoupling of esters and amides, wherein natural electronic and steric differences were used to obtain selectivity in product formation.

With much food for thought provided by the morning talks, lunch was enjoyed overlooking the stunning vista of Lake Lucerne. A daily break in the afternoon schedule allowed the spectacular and unseasonably warm weather to be enjoyed through hiking along the numerous trails of the Bürgenstock, train excursions up the neighboring Mount Pilatus and Rigi, or ferry rides across the lake to the neighbouring city of Lucerne.

A series of short oral presentation tasters for the first poster session kicked-off the evening's events, which cumulated in an absorbing lecture, delivered by **Pierre Vogel** (EPFL Lausanne, Inst. Science and Ingénierie Chimiques, Lausanne, Switzerland), on the developing use of sulfur dioxide in organic chemistry. Starting with and in honour of the presence of Professor Huisgen, a series of insightful physical chemistry experiments were detailed that shed light on the mechanisms of SO_2 addition to 1,3-dienes, as well as the process by which SO_2 induces the isomerization of alkenes. For the latter, very convincing evidence was provided to suggest radical intermediates rather than the long-believed ene manifold. An improved mechanistic understanding of the chemistry of SO_2 was then used to facilitate the development of a number of very useful synthetic methods. For instance, polysulfones (SO_2 + methylidene cyclopentane) were shown to be useful solid organic catalysts for predictable alkene isomerization, allowing the selective deprotection of methyl-substituted allyl ethers under mild conditions. Furthermore, understanding the factors controlling the hetero-Diels–Alder (HDA) *vs.* cheleotropic cycloaddition of SO_2 to dienes has permitted a unique route leading to the rapid generation of polyfunctional sulfones *via* the tapping of intermediate zwitterionic intermediates generated from sultines in the presence of a Lewis acid. The versatility of this methodology was subsequently demonstrated through its application to a number of polyketide natural products, including the baconipyrones, rifamycin S and apoptolidin. To wrap things up, the emerging use of inexpensive and readily available sulfonyl chlorides in a variety of metal catalyzed cross-coupling reactions was described.

The second day of lectures focused on polymers and materials, and started with a talk given by **Eiji Yashima** (Nagoya University, Japan) on helical polymers and oligomers. In the first part of his talk, he focused on single helices based on poly(phenylacetylene)s. Importantly, a solvent vapour technique, which facilitated the self-assembly of monomers on a graphite surface, allowed the resulting helical conformations to be analyzed by both atomic force microscopy and X-ray diffraction. In this fashion, he could further demonstrate that non-covalent interactions, for example, between a polymer-bound carboxylic acid and a chiral amine, resulted in chirality amplification, which could be useful as amine configurational sensors. He also showed that, depending on the nature of the substituents, polymer helicity, as well as helical pitch, was affected by solvents, temperature or chiral guests. In the second half of his lecture, his group's latest efforts towards a rational design of double helices were described. Here, crescent shaped *meta*-terphenyl derivatives form helically-twisted dimers stabilized by salt bridges between chiral amidines and achiral carboxylic acids. Using the same non-covalent interaction, triple helices and cylindrical complexes could also be constructed. Most recently, the shape-persistent *meta*-terphenyl helix building blocks had been assembled *via* platinum acetylide complexes. In these cases, chiral ligands for the platinum complex allowed the formation of chiral helices, wherein the sense of the helix was "frozen-in", as substitution with achiral bidentate ligands maintained the chirality in a process ascribed to a memory effect.

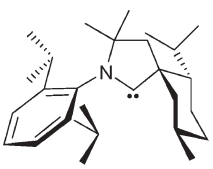
The next speaker, **Gero Decher** (Université Louis Pasteur, Strasbourg, France), presented a talk on the fast growing area of layer-by-layer self assembly, which he pioneered in the early 1990s. The principle of this technique is based on the sequential adsorption of oppositely-charged polyelectrolytes onto a charged substrate. In the early days, this was achieved by dipping substrates into different solutions of polyions. Preparing multi-layered structures in this way was, typically, a time consuming exercise. However, dramatic improvements are now realized by using a recently developed spray technique that speeds up the layer deposition time from minutes to seconds. Using more than two

different types of polyions allows the defined assembly of multi-layered structures, and, as Decher pointed out, ''layer-by layer deposition is analogous to a chemical reaction'', whereby a multi-layered film corresponds to a multi-step synthesis. However, this technique is not limited to polyion interactions. For instance, colloidal metal nanoparticles have been deposited in-between layers of polymers, as have biological systems! In addition, covalent layer-by-layer polymer depositions have been demonstrated, and the surface of a charged nanosphere was successfully modified using layer-by-layer adsorption, resulting in exceptionally stable nanoparticles. Decher's goal of ''functionalizing any surface with any ligand'' is certainly not far-fetched. A look at the growing number of applications that already use the technique confirms that the layer-by-layer method has survived the ups and downs of the hype-cycle and is nearing the plateau of productivity.

The last talk of the second day was given by **Deborah E. Leckband** (University of Illinois at Urbana-Champaign, USA) on how to make surfaces ''sticky''. After a brief introduction on the mechanisms of animal adhesion, she discussed single molecule force measurements to analyse protein–protein interactions. The cell surface adhesion glycoprotein NCAM is important for the development and stability of nerve tissue. To gain further insight into neural development, it is of particular interest to understand the homophilic binding between NCAM domains. The NCAM molecule is anchored to the cell membrane and contains five immunoglobulin (Ig) domains in its extracellular segment, which are necessary for NCAM–NCAM binding to occur. Atomic force microscope measurements on single molecules could reveal that NCAM can, in fact, form either of two homophilic bonds involving either the Ig1-2 domain for a weaker or the Ig-3 domain for a mechanically stronger bond. Moving on to a second system, the CD2-CD58 complex is known to be important for increasing the adhesion between T-cells and antigen-presenting cells, and thus the immune response. The importance of salt bridges, which were predicted by simulations, was subsequently confirmed using force measurements in solution. In summary, the surface force apparatus has provided a new and important tool for understanding some of nature's most complex and intimate associations.

Stephen K. Hashmi (University of Stuttgart, Stuttgart, Germany) got day three under way by disclosing his love affair with gold. In a convincing presentation, Professor Hashmi proceeded to outline a number of unique reactivity patterns and advantages of this relatively inexpensive metal. To begin with, allenyl ketones in the presence of α,β-unsaturated ketones and a small amount of a soluble gold catalyst were shown to form functionalized furans *via* a C–O/C–C cycloisomerization/hydroarylation process. These observations lead to the subsequent development of a useful phenol synthesis, which can occur in either an inter- or intramolecular sense, allowing access to 5- or 6-ring annulated arenes, as well as benzofurans. Importantly, these transformations do not exhibit significant steric limitations and thus permit access to congested compounds such as 8-hydroxytetrahydroisoquinolines that would be difficult to obtain by other means. Description of an intriguing series of mechanistic experiments proved the intermediacy of arene oxides in these reactions, while practical application to the total synthesis of jungianol (without the use of any protecting groups) provided an example of its utility.

Guy Bertrand (University of California-Riverside, Riverside, USA) was next to speak, and gave a stimulating account of the synthesis of an array of mesmerizing structural motifs. Especially pleasing was the apparent rational thought and design implicit in the preparation of these challenging targets, such as the subtle arrangement of phosphorus and boron atoms that permitted the construction of a localized singlet diradical, indefinitely stable at room temperature both in solution and in the solid state. Approaches to a number of novel carbenes were then discussed, where, for example, exploiting the concept of push–pull stabilization extended the lifetime of a (phosphanyl)(trifluoromethyl)carbene from nanoseconds to weeks. Other highlights included a fragmentation method of *C*-amino phosphorus ylides as a unique entry point to amino carbenes, the synthesis of electronically-tunable *N*-heterocyclic carbenes (NHC) built upon a boron skeleton and the preparation of remarkably stable cyclopropenylidenes. To conclude, recent work on the synthesis, properties and potential applications of cyclic (alkyl)(amino)carbenes (CAACs) was presented. Readily available through the intramolecular hydroiminiumation or hydro-amidiniumation of alkenes, these highly versatile carbenes hold much promise as ligands for transition metals, being stronger σ-donors than NHCs. For instance, a CAAC–Pd complex has been shown to allow the α-arylation of ketones and aldehydes with unactivated aryl-chlorides at room temperature. Importantly, as the CAACs possess a quaternary carbon in the α-position to the carbene centre, their structures are highly tunable and asymmetric variants are readily prepared. Nucleophilic (alkyl)(amino)carbenes of this type, possessing a lone pair of electrons and an accessible vacant orbital, were shown to be able to mimic the chemical behavior of transition metals, successfully splitting both hydrogen and ammonia! This raised the exciting prospect of potentially performing such tasks as hydrogenation and hydroamination/boration/silylation mediated by a free carbene.



An Enantiopure CAAC

Following an enjoyable evening of chamber music provided by the Aura Quartett, the participants awoke eager for the new day, wherein bio-organic chemistry was the dominant theme. The first speaker was **Linda C. Hsieh-Wilson** (California Institute of Technology, Pasadena, USA), reporting on chemical approaches to neurobiology. In the first part of her talk, she discussed chondroitin sulfate (CS) glycosaminoglycans, which are sulfated polysaccharides. These sulfated sugar chains play an important role in neural growth, as was demonstrated for a model tetrasaccharide. The tetramer appeared to be the smallest motif required, and the sulfatation pattern on the oligomer was crucially important for biological

activity. She further showed that the sulfated tetrasaccharide, exhibiting the so-called CS-E motif, stimulated the growth of neurons. In order to identify the proteins responsible for CS-binding, Hsieh-Wilson created an analytical microarray. The major sulfatation motifs found in nature were displayed on immobilized tetrasaccharides, and rapid screening allowed identification of the critical CS-binding proteins. Protein glycosylation, the molecular sugar coating that is responsible for many fundamental biological processes, was a further topic of Hsieh-Wilson's lecture. She discussed the post-translational modification of proteins with β-*N*-acetylglucosamine (*O*-GlcNAc) as a means of regulating transcription factors such as CREB (cyclic AMP-responsive element-binding protein), and showed a highly sensitive and fast strategy to detect *O*-GlcNAc modifications in proteins.

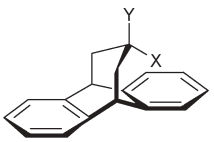
This was followed by the second lecture of the day, given by **Benjamin F. Cravatt** (The Skaggs Institute for Chemical Biology, La Jolla, USA), on activity-based protein profiling (ABPP). This technique allows the *in vivo* labelling of active enzymes using activity-based probes (ABPs). Cravatt showed how ABPP was used to identify enzymes in aggressive human cancer cells, and revealed a hydrolase (KIAA1363) that had previously not been associated with cancer. In order to assign function to the enzyme and identify metabolites, enzyme inhibitors had to be found, which again could be achieved using the ABPP technique. With the inhibitor in-hand, the metabolites of KIAA1363 could be identified as monoalkylglycerol ethers (MAGEs). However, as Cravatt stated, the metabolome is larger and more complex than the proteome and has no direct link to the genetic code, which makes metabolite analysis more complicated. Using a recently developed method called metabolite enrichment, by tagging and proteolytic release (METPR), Cravatt could demonstrate that the immobilisation of entire classes of small molecules can help enrich and profile metabolites.

The after-dinner speaker on day four was **Michael A. Marletta** (University of California Berkeley, USA) who, before moving on to his presentation, told the story of how he received the president's invitation to Bürgenstock, with a request to keep it a secret. He then confessed that he had broken the Bürgenstock code of honour and told his wife, wondering how other speakers managed to sneak away for a week without telling people at home where they would be… Moving on, he proceeded to unveil some of nature's tricks in sensing oxygen and nitric oxide with structurally very similar "enzyme detectors". NO is used in nature in two fundamentally different ways. While at higher concentrations macrophages use it for killing cells, much lower concentrations are required for its function as a signalling agent. A known signalling pathway starts with NO binding to the heme group in soluble guanylate cyclase (sGC), which subsequently produces higher levels of cyclic guanosine monophosphate (cGMP). Interestingly, the heme group, typically known for its O_2 affinity, can discriminate between O_2 and NO, and selectively binds the latter. Marletta showed that the heme-NO/O_2 binding domain (H-NOX) binds O_2 in anaerobic prokaryotic cells and excludes O_2 in all others. In order to find the specific amino acid differences that cause the difference in affinity, mutation studies were carried out on a protein (*Tt* H-NOX), of which the crystal structure was known. The results of these studies clearly demonstrated that on a molecular level, a single tyrosine residue is responsible for O_2/NO discrimination.

The last day of the conference got off to a rousing start when **Sunggak Kim** (Korea Advance Institute of Science and Technology, Daejeon, Republic of Korea) presented a summary of his group's search for new C–C bond-forming reactions based on a radical manifold. *N*-Aziridinyl imines were shown to be useful radical acceptors, permitting convenient access to 5-*endo* cyclization products not easily accessed otherwise. Moreover, this methodology is readily amenable to tandem bond forming processes, as illustrated by elegant total syntheses of both α-cedrene and the propellane *dl*-modhephene. A study of a second functional group combination, namely carboxylic imides, was equally successful, leading to a method for the radical-mediated alkylations of carboxylic acid derivatives under tin-free conditions with a variety of activated alkyl halides bearing an α-electron withdrawing group. A number of other novel and useful transformations were then described, such as the radical alkylation of bis(silyloxy)enamine derivatives of organic nitro compounds, tin-free carbonylations leading to thiol esters using alkyl allyl sulfones and the radical-mediated γ-functionalization of α,β-unsaturated carboxylic amides. Finally, and in keeping with the Bürgenstock theme of stereochemistry, recent results of an enantioselective conjugate radical addition to α′-hydroxy enones were provided. The use of the Ph-Box ligand in the presence of $Mg(NTf_2)_2$ was found to be the optimal combination, leading to good yields and high ees of the desired conjugate addition products.

The second lecture of the day, and the penultimate of the conference, was delivered by **William B. Motherwell** (University College London, London, UK), who provided some entertaining tales of a curious chemist. Initially, the development of a practical cyclopropanation method employing the direct generation of organozinc carbenoids from carbonyl compounds was described. The original procedure of treating aryl or α,β-unsaturated aldehydes and ketones with zinc and 1,2-bis(chlorodimethylsilyl)ethane was subsequently revised to the more user friendly use of orthoformates with $ZnCl_2$ and TMSCl. Importantly, direct access to aminocyclopropanes could also be achieved by the use of *N*-diethoxymethyl amides, wherein the use of an electron withdrawing group on nitrogen was found to be necessary for the reaction's success. Extension to an asymmetric version through the incorporation of an oxazolidinone controller was also discussed, and the methodology was demonstrated by its application to the synthesis of Belactosin A. In the second part of his talk, Professor Motherwell described the engineering of an ingenious system to help quantify various non-covalent interactions. Through the appendage of various competing functional groups (*e.g.* X *vs.* Y) upon a bicyclic spacer separating two aromatic rings, analysis of the preferred ring conformation by NMR provides a tool that is beginning to shed some light on the relative magnitude of non-covalent interactions with aromatic rings. Further

work is this area should provide knowledge of fundamental importance.



A System for Study of Non-covalent Interactions

The last scientific talk of the 2007 Bürgenstock meeting was given by **Perry Frey** (University of Madison, USA) and focused on free radicals as intermediates in enzymatic catalysis. As he pointed out, the number of radical mechanisms found in enzymatic transformations have been steadily growing over the last decade. In his lecture, Perry Frey started off with a group of enzymes that share the adenosylcobalamine co-factor, ribonucleoside triphosphate reductase (RTPR) and dioldehydrase. RTPR catalyses the reduction of ribonucleoside triphosphates to deoxyribonucleotide triphosphate. In this particular case, radical formation *via* cleavage of the Co–C bond is followed by hydrogen abstraction of a thiol, generating a thiyl radical. However, the presence of the thiol is not necessary for Co–C bond cleavage, as could be shown using enzyme variants lacking the cysteine residue. Another enzyme discussed by Perry Frey was lysine 2,3-aminomutase (LAM). This enzyme allows a 1,2-amino group migration from α-lysine to β-lysine, a rather intriguing reaction from a synthetic chemist's point of view. Through a series of elegant experiments, Professor Frey was able to demonstrate that a pyridoxal-5′-phosphate (PLP), normally associated with stabilizing carbanions in enzymatic reactions, appears to facilitate the rearrangement of a substrate radical. The amazing story of the successful search for the most fleeting and reactive of species in highly complex biological systems, and against conventional thinking, was a most fitting way to end a spectacular week on the Bürgenstock.

Following the last scientific contribution, **Klaus Müller** gave his traditional and highly amusing wrap-up presentation of the conference proceedings. Finally, next year's president, **Don Hilvert** (ETH Zürich), was confirmed and the new vice-president, **Ben Feringa** (University of Groningen, The Netherlands), announced. Next year's programme and list of speakers will, of course, only be revealed to a select few fortunate enough to attend, so watch out for next year's conference report in *ChemComm*. And, if you do get invited, make sure you don't tell a soul…

The 43rd Conference on Stereochemistry is scheduled for April 12–18, 2008 under the presidency of Don Hilvert (ETH, Zürich). See http://www.stereochemistry-buergenstock.ch/ for details.

The authors thank A. Stephen K. Hashmi for kindly providing a photograph of the conference location, the conference's organizing committee and the Swiss Chemical Society for generous financial support to attend the meeting.