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## 1st Lausanne Conference on Bioorganic Chemistry, March 7/8, 1996

Institute of Organic Chemistry, University of Lausanne

On the occasion of the inauguration of their new chemistry building by the shores of Lake Geneva, the Institute of Organic Chemistry of the University of Lausanne established the Lausanne Conference on Bioorganic Chemistry. The goal of the meeting was to outline the state of the art in this interdisciplinary field and to offer especially to young scientists the opportunity to meet at the interface of physical, synthetic, and medicinal organic chemisiry, biochemistry, and structural and molecular biology. Prof. *Manfred Mutter*, who together with Prof. *Pierre Vogel* initiated the conference, welcomed more than 230 participants from seven European countries and the USA to attend a representative series of lectures and poster presentations spread over two days.

The opening lecture given by Prof. *Barbara Imperiali* from the California Institute of Technology, featured a marvellous demonstration of the use of modern research tools for the design, synthesis, and analysis of compact supersecondary peptide structural motifs of 20–40 amino acids. Choosing the well-known $\beta\beta\alpha$-motif found in DNA-recognising zinc fingers, she showed how by appropriate design it is possible to evolve such a structure into a system which is uniquely folded without the presence of a zinc ion and which can serve as a template for the construction of new functional molecules. One such system derived from a zinc finger framework and extensively characterised by multidimensional NMR incorporates a fluorophore which is sensitive to the large conformational change induced by metal binding and so holds promise for the development of novel metal ion sensors. This was followed by an impressive presentation from Prof. *Robin Offord* of the University of Geneva of recent progress made in the linking of larger protein fragments to produce protein-protein chimera. Prof. *Offord* described how ligation techniques based on oxime or hydrazone bond formation allow one to link protein fragments to each other, to non-protein macromolecules or to low molecular weight compounds to give chimeric derivatives with a single continuous backbone chain. In the context of non-protein macromolecules, peptide-polyethylene glycol conjugates (linear or branched) are particularly valuable as drug delivery systems, while one of the more remarkable achievements from Prof. *Offord*'s laboratory is the synthesis of an $F_{ab}$ trimer which has useful *in vivo* properties. Prof. *Michael Göbel*, one of the youngest faculty members at the University of Geneva, next gave a lucid account of the design of a synthetic phosphodiesterase based on the structural elements of bisguanidinium compounds which are capable of complexing the trigonal-bipyramidal transition state for phosphate ester hydrolysis. The catalytic element is complemented by an acridine intercalator and is incorporated as a modified arginine residue into the HIV-1 TAT sequence. In this way, encouraging preliminary results on TAR cleaving activity have already been obtained. The last speaker of the day was Prof. *Martin Karplus* of the Université *Louis Pasteur*, Strasbourg, and Harvard University, who introduced the audience to some of the concepts of the treatment of molecular recognition phenomena by theoretical methods. As an example, Prof. *Karplus* discussed the analysis of the substrate binding properties of a Tyr to Phe mutant of tyrosyl-$^t$RNA synthetase, showing how free energy simulations can aid our understanding of the forces involved in ligand-receptor interactions. He then went on to show how such information may be used predictively in the new field of combinatorial ligand design, wherein a region of interest in a receptor target is first scanned for functional group binding sites, and then functional groups from representative structural databases are matched and combined to form molecules that fit the receptor according to this map. Interlinking this computational approach with synthesis in the laboratory should help guide the composition of libraries to be prepared and so enhance the efficiency of compound searches.

The second day of the conference started with a lecture by Prof. *Jean-Jacques Périé*, of the Université *Paul Sabatier*, Toulouse, on mechanistic studies of glycolytic enzymes and their inhibition for the chemotherapy of diseases such as sleeping sickness. This is caused by the parasites trypanosoma and leishmania which rely exclusively on glycolysis as a source of energy. Consequently, constituent enzymes such as GADPH can be targeted by irreversible inhibitors introduced into the cell by the glucose transporter pathway. Glycopeptides and neoglycoproteins were the subject of the next lecture given by Prof. *Horst Kunz* of the University of Mainz, in which he detailed some of the new methodologies developed in his laboratory for the synthesis of such glycoconjugates. These compounds play important roles in many biological recognition processes such as immunodifferentiation, infection, cell adhesion and intercellular communication. Among other examples, Prof. *Kunz* described the synthesis by a combined solid phase and solution strategy of some particularly challenging mul-

tiple sialyl *Lewis*$^X$ *N*-glycopeptides, which are high-affinity ligands for selectins in cell adhesion. The use of highly selective chemical or enzymatic procedures was indeed a recurring topic throughout this talk, especially the application of novel allylic anchoring principles or protecting group techniques. Returning to the themes of the previous day's opening lecture, Prof. *Klaus Müller*, head of the department of 'New Technologies' in preclinical R&D of *F. Hoffmann-La Roche AG*, Basel, next presented some major highlights from the design and synthesis of new building blocks for $\alpha$-helix and $\beta$-turn conformations in small peptides. This included the development of some novel macrocyclic $\alpha$-helix capping units as well as '$\alpha$ chimeras', which are $\alpha$-substituted amino acids that bear the side chains of two proteinogenic amino acids. These may also be used to stabilise specific peptide conformations, for switching between different types of $\beta$-turn. Significantly, conformational predictions for such building blocks derived from modelling studies with the *Roche* 'in-house' program MOLOC (introduced at the University of Lausanne by one of the commentators), were shown by Prof. *Müller* to be confirmed in many cases by 2D NMR, CD spectroscopy, and an array of X-ray structures. The morning session was concluded on a slightly different note by Prof. *Bernhard Kräutler* of the University of Innsbruck, who outlined the state of current knowledge concerning the early steps of chlorophyll transformation in senescent leaves. Together with coworkers in Zürich, Prof. *Kräutler*'s group have succeeded in tracing a coherent pathway for the formation of a number of colourless tetrapyrolic chlorophyll metabolites in this hitherto poorly understood process. The structural elucidation of these molecules by an impressive combination of partial synthesis and spectroscopic techniques formed a major part of Prof. *Kräutler*'s very interesting contribution.

The afternoon proceedings were begun by Prof. *Andrée Marquet* from the Université *Pierre et Marie Curie*, Paris, speaking on the mechanism-based design of inhibitors of cytochrome $P_{450 11\beta}$, the enzyme responsible for the last steps of aldosterone biosynthesis. She described the synthesis and evaluation of some C(18)-modified progesterone derivatives which are potent irreversible inhibitors *in vitro*, then went on to discuss the agonist and antagonist properties of these derivatives towards the recombinant human mineralcorticoid receptor. In particular, the interactions of compounds of these classes of compounds with the human receptor are now being studied with the aid of photoaffinity labelling probes. The next lecture was once again an elegant demonstration of the power of computational methods for tackling problems in bioorganic chemistry. Prof. *Frieder Lichtenthaler* of the Technische Hochschule, Darmstadt, presented the results of extensive molecular modelling studies on various saccharides such as sucrose, cyclooligosaccharides and the amylose portion of starch. These consisted of molecular contact surfaces derived from extensive force field analysis (MolCAd) of their conformational features, upon which molecular electrostatic potential (MEP) profiles and lipophilicity patterns (MLPS) are projected in colour-coded form. Prof. *Lichtenthaler* showed how these detailed analyses allow one not only to rationalise differences in the reactivity of certain hydroxyl groups, but also to identify which functional groups in sucrose and other sweeteners may conceivably interact with the sweetness receptor, and to rationalise the capacity of cyclooligosaccharides to act as molecular hosts. Prof. *Christian Leumann* of the University of Bern also drew on the results of detailed conformational analyses in his subsequent presentation of the design, synthesis, and characterisation of bicyclo-DNA analogues. Introduction of an ethylene bridge between the 5'- and 3'-positions of the pentose unit of DNA constrains two out of six of the torsion angles associated with the sugar-phosphate backbone, resulting in a preference in bicyclo-DNA for the alternative *Hoogsteen* base-pairing mode. This was convincingly demonstrated by Prof. *Leumann* with the results of UV-melting curve analyses and CD spectra. The final lecture of the conference was given by Prof. *Robert Fischer*, formerly of *Sandoz Pharma AG*, Basel, in his capacity as Consultant to the Federal Office of Public Health and the Swiss Society of the Chemical Industry. In his talk entitled 'Psychedelic Chemistry', which brought to the discussion forum topics of an ethical nature, Prof. *Fischer* first explained the different classes of neuropsychotropic substances (analeptica, cataleptica, and dysleptica), then pointed out the difference between these compounds and analogy products prepared by underground chemists (so-called designer drugs). He then went on to highlight the current response of the United Nations International Drug Control Programme (UNIDCP) to this problem, namely the global control of chemicals required for the synthesis of illegal substances, which is implemented in Switzerland through close cooperation between the federal and cantonal authorities, industry and commerce.

The high quality and interest in the presentations was reflected by lively discussions after each lecture chaired by younger staff members from the Institute. Furthermore, the meeting was the forum for 40 well-presented posters from local and non-resident participants which covered a broad spectrum of bioorganic chemistry to round off the range and scope of the conference.

During the various breaks, the participants had the opportunity to visit the new chemistry building and to get 'on-site' an idea of the various research activities now in progress. These range from the synthesis of carbohydrate analogues and DNA-intercalating compounds to the study of the 'physiological size' of fluorine in biologically important molecules, as well as the design and synthesis of novel peptides and proteins.

With this type of conference a gap was filled and the very positive response has encouraged the organizers to continue in an annual fashion. The '2nd Lausanne Conference on Bioorganic Chemistry' will take place on March 6/7, 1997.

Dr. Ian Eggleston
Dr. Christian Lehmann
Institute of Organic Chemistry
University of Lausanne