

---

# CONFERENCE REPORTS

---

*Chimia* 51 (1997) 248–249

© Neue Schweizerische Chemische Gesellschaft

ISSN 0009–4293

## 2nd Lausanne Conference on Bioorganic Chemistry, March 6/7, 1997

Institute of Organic Chemistry, University of Lausanne

A brilliant day of sun and fresh breeze received this year's scientific representatives from Europe and overseas in Lausanne to communicate and discuss the latest news in topics situated at the interface of chemistry and biology. Again more than 200 people were welcomed in the splendidly decorated auditorium by *Manfred Mutter*, who together with *Pierre Vogel* and *Gabriele Tuchscherer* was responsible for the organization of this one-and-half day meeting.

The initial talk by *Jean Chmielewski* from Purdue University (USA) focused on the investigation of DNA binding and its inhibition by transcription factors of the basic-helix-loop-helix (bHLH) and the leucine-zipper type. It is well established that proto-oncogenes such as *c-Fos* and *c-Jun* bind DNA with sufficient affinity to the major groove only in their dimeric form, therefore prevention of their dimerization might inhibit carcinogenesis. Significant secondary structural changes dependent on the aggregation state were evidenced by physicochemical techniques, such as size-exclusion chromatography followed by circular-dichroism spectroscopy. Her vivid presentation was followed by a firework of molecular modelling, organic synthesis and combinatorial lead-finding technologies presented by *Paul A. Bartlett* from the University of California at Berkeley (USA). Structure-based design of macrocyclic inhibitors of aspartic and zinc peptidases served as examples to illustrate the assessment of these strategies. Classical serial chemistry directed towards C-phosphonate-based tetrahedral transition-state mimetics was supported by nov-

el heterocyclization processes appropriate for the generation of combinatorial libraries. According to the nature of the inhibitor target, compounds of an essentially peptidomimetic type with variable degrees of conformational restriction emerged from the outlined highly advanced procedures.

A *novum* to international conferences, the contributions submitted as posters were announced by three-minute presentations of the responsible authors, thereby highlighting the manifold facets of this conference. Contributions ranged from novel techniques of Bio-NMR to highly elegant synthetic strategies for the synthesis of aminocyclitols; the chemical synthesis of enantiomeric RNA was treated as well as the conformational analysis of cyclopeptides, or the molecular design of synthetic redox proteins; anion receptors, chimeric peptides as biosensors, mimetics of neuropeptide Y, photocleavable DNA, inhibitors of porphobilinogen synthase as well as many more outstanding presentations ought to be mentioned and hopefully will encourage further full publications and the participation at future meetings. As in the preceding conference, all lectures – and also the poster presentations – were introduced and chaired by postdoctoral scientists of the Institute of Organic Chemistry.

The second day was opened fulminantly by *Steven A. Benner*, University of Florida (USA), whereby he described his ways of redesigning natural nucleic acids. He and his coworkers achieved to extend the molecular alphabet from four to 12 nucleobases, thus amplifying the potential information content of nucleic acids. Most

notably, many of the synthesized modified nucleotides are recognized and incorporated by natural polymerases. These approaches pave the way to a wealth of potential applications in diagnosis and genetic engineering. Further topics in nucleic-acid chemistry were addressed by *Robert Häner*, *Novartis* (Basel), who described recent advances in the field of antisense oligonucleotides. His core technology group (formerly belonging to the *Ciba* central research unit) was able to assemble sugar/phosphate-backbone-modified oligonucleotides resistant to natural nucleases, and, further, to enhance their action by covalently attaching a DNA-cleaving lanthanide complex to them. In certain naturally observed intron excision or self-cleaving processes, mismatched bulges play a crucial role; here this observation was used to enhance the RNA-cleaving efficiency within an 'RNAse H window' of the antisense oligonucleotide. Iron(III)protoporphyrin(IX) is found to be complexed in naturally occurring redox proteins by either histidine or cysteine side chains, the latter case being subject of an extended study by the group of *Wolf-D. Woggon* from the University of Basel. Structural information available from X-ray studies of different cytochromes P450 and chloroperoxidase served as a basis for the construction of face-protected iron porphyrins sheltering a catalytic site. The presented model compounds allow to study intermediates in the redox cycles of heme-thiolate proteins by classical physicochemical techniques. In the following lecture, *Mordechai Sheves* from the Weizmann Institute of Science (Rehovot, Israel) in-

roduced a novel biophysical technology which allowed him to study light-induced conformational changes in bacteriorhodopsin-channelled membranes. The technology is based on kinetic atomic force sensing (AFS) and essentially reflects microdimensional changes of single membrane layers as a response to laser excitation. Various conformationally restricted retinal analogues were incorporated into the membrane protein and the AFS signals of the complexes observed. Induced polyene dipole moment changes were perceived as conformation-determining factor, rather than C<sub>13</sub>-C<sub>14</sub> isomerization. Foremost, conformational control of bioactivity was shown to be critically dependent on the influx and subsequent catalytic activity of water within the transmembrane protein.

In the afternoon session, *Antonello Pessi* from the Istituto di Ricerche di Biologia Molecolare P. Angeletti (IRBM, Roma) started with an interesting talk on combinatorial chemistry strategies followed in collaboration with the *Merck* Department of Cancer Research (USA) to discover inhibitors of farnesyl-protein transferase (FPTase). The latter is a key enzyme in cell transformation mediated by the Ras oncogene, since it catalyzes the transfer of the farnesyl moiety of farnesyl diphosphate to a cysteine thiol in the Ras protein substrate. FPTase inhibitors were optimized through combinatorial screening in the positional scanning format. The C-terminal carboxy group of those compounds were masked *via* a classical ester prodrug strategy. A different type of prodrug approach in antitumor therapy was further presented by *Claude Monneret* from the Institut Curie (Paris). His approach is based on tumor-antigen-specific monoclonal antibodies conjugated to a drug-releasing enzyme. The so-called ADEPT (Antibody-Directed Enzyme Prodrug Therapy) concept is realized in two steps, whereby first the mAb-enzyme conjugate (directed glucuronidase) is administered, followed in the second step by a glucuronide-based prodrug of an anthracycline antibiotic. Therapeutic effects superior to those of standard anthracycline chemotherapy evidence that the cytotoxic agent indeed reaches its target in a more selective way, presumably *via* penetration of the addressed tumor cell wall followed by intercalation of the tumor DNA. *Jane Richardson*, Duke University, North Carolina (USA), then gave a peerless lesson on protein design and structural analysis of protein conformation. She together with her coworkers has developed a computer tool to quantify and understand internal

side-chain packing. Contrary to conventional approaches, their surface analysis algorithm (component of program SCULPT) puts patches of dot surface only where two atoms are within 0.5 Å of *van der Waals* contact. The ultimate requirement for the inclusion of explicit hydrogen atoms in the detailed study of protein conformation was illustrated convincingly by giving reasons for the statistical occurrence of disulfide conformations. Further applications will include the optimization of docking procedures as well as ligand-receptor binding studies. Not less didactic – and an energetic highlight of the day – was the excursion of *Murray Goodman* from San Diego (USA) into design and synthesis of template-assembled triple-helical collagen mimetics. By applying very elegantly integrated biophysical studies including CD and NMR spectroscopy, he evidenced the successful triple helix nucleation of glycine-proline-hydroxyproline oligomers covalently attached to *Kemp's* triacid template. His best-seller in chemistry 'Organic Molecules in Action' is most well-known by almost every member of the chemical community, and it was delightful to see its author setting a highlight to a conference which encompassed the very same theme.

The conference participants will treasure the scientific contacts made this year in Lausanne, and the organizers are planning to continue exchanging new developments in this most fascinating interdisciplinary field on the occasion of the next 'Lausanne Conference on Bioorganic Chemistry' in March 1999.

*Christian Lehmann* and *Thomas Rückle*  
Institute of Organic Chemistry  
University of Lausanne