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Heavy snow and rain falls could not discourage a large international community of scientists interested in chemistry related to biology to gather at the 1999 Lausanne Conference on Bioorganic Chemistry. The conference, which has taken place this year for the third time, has already established itself as one of the major events in the field in Switzerland, and it owns its radiation not only to the highly ranked lecturership from Europe and overseas, but also and primarily to the ample and well-appreciated opportunity for younger scientists to participate and communicate with those leaders of science in an interactive way. Thus, it was a pleasure for *Manfred Mutter*, who together with *Pierre Vogel* and *Gabriele Tuchscherer* organized the meeting, to welcome a particularly large and eager audience of well over 200 scientists in an auditorium generously decorated with forsythia.

At which stage and how generally can synthetic oligonucleotide derivatives recognize DNA and thereby interfere with gene expression? This was the topic of the opening lecture given by ***Claude Hélène*** from the Laboratoire de Biophysique, formally a department of the Muséum National d'Histoire Naturelle, Paris. And his approach is by no means destined to become a museum piece: he convincingly showed that double-helical DNA can be targeted by a third strand of an oligonucleotide wherever the target strand has a contiguous sequence of purines, and that the binding can effectively be enhanced by attachment of an intercalator at the site of the purine/pyrimidine junction in the target. The most recent generation of such oligonucleotide-intercalator conjugates consists of an N3' → P5' phosphoramidate oligonucleotide backbone with enhanced intrinsic binding affinity combined with intercalators of the benzopyridoindole or benzoquinoxaline type. The latter are known to enhance the binding constant of the oligonucleotide by an energetic equivalent of five to six base pairs, whereby the specificity of the recognition is effected by the oligonucleotide moiety of at least six base pairs in length. The triple-helical base pairing taking place in the major groove is of the *Hoogsteen*-type, which can be classified as 'non-natural' (of non-*Watson-Crick* type), as well as the intercalation by synthetic condensed aromatic heterocycles. However, a closer look at Nature's repertoire reveals that the latter are, of course, variants of cytotoxic substances produced by bacteria and microbial funghi, and that the former 'non-natural' types of base-pairing are found to occur at least in telomers bridging crucial events in the cell cycle. Combining such elements in stereochemical and thus functional compatibility with the parent molecular recognition pattern by the tools of synthetic organic chemistry renders our science instrumental to the development of highly efficient principles of action against crucial events in the life cycle of virally infected or cancerous cells.

The following lecture given by *Nobel*-laureate ***Jean-Marie Lehn***, Collège de France, Paris, and ISIS, Université Louis Pasteur, Strasbourg, was a brilliant 'tour d'horizon' covering major research themes in bioorganic supramolecular chemistry. Molecular recognition was again addressed in many-faceted examples. First, photochemically induced cleavage of nucleic-acid hairpin targets by bis-porphyrin macrocycles was presented to illustrate the conformation-dependent reactivity of nucleic acids and its chemical targeting. Then, artificial enzymes were mentioned, in particular carbonic anhydrase and the engineering of its active site. Various scaffolding as well as turn-over relays such as modified liposomes and tetrameric concanavalin have been constructed. Active-site optimization by molecular imprinting by the substrate ('substrate casting', 'receptor moulding') may reflect a process which has occurred over millions of years in evolution and can be accounted for in present-time generations of artificial antibodies; on the other hand, the normalization of substrates and products by a given catalytic system, as pointed out by Prof. *Lehn*, may have played an important role in the chemical evolution of the present enzyme substrates themselves – this is pure combinatorial chemistry performed in a biomimetic way! Prof. *Lehn* gave an impressive demonstration of what is possible by the channelling of general nature through the very special inventive nature of the human mind, to conclude with a boldly optimistic, but truly actual 1917 statement of *Emil Fischer*, that indeed we have gone much further by 'chemical synthesis' than by 'conventional breeding'.

The second day of the conference was opened by ***Alois Fürstner***, *Max-Planck* Institut für Kohlenforschung, Mülheim, who gave a lucid account on synthetic studies in the field of pyrrole alkaloids. Since the pyrrole nucleus accommodates six π-electrons on five ring atoms, it is an electron-excess aromatic heterocycle with enhanced reactivity and, therefore, requires a specially tuned armamentarium for its synthesis and functionalization. One of the recently introduced tools is the titanium-induced oxo-amide coupling reaction, which served as the key step in the pyrrole-ring synthesis of lukianol A, a metabolite of marine origin with activity against human epidermatoid carcinoma cell lines. Functionalization of the keto group in the 2-aza-8-oxo-1,2,3,4,5-pentadehydrobicyclo[3.3.0]octane skeleton representing the core moiety of the antitumor agent roseophilin and related pyrrole alkaloids should be possible without particular prob-

lems, since a favorable conjugation to an azafulvene system can be exploited – however, when substituents in positions 6 and 7 are present and oriented *trans*, as in the target molecule, such an attempt will be thwarted by the stereochemical disposition of those substituents in the *Bürgi-Dunitz* trajectory. Therefore, it was necessary to search for completely new alternatives, a search that was rewarded by the emergence of an unprecedented manifold of palladium-catalyzed *de novo* cyclizations to the particularly required substitution type of the pyrrole nucleus.

Molecular recognition of peptides and proteins has a scope wide enough to provide the basic theme for more than one prominent research group in the Swiss academic landscape, so it comes as no surprise that ***John A. Robinson*** from the University of Zürich has found a highly interested audience here in Lausanne (for an overview of the research activities in the various Swiss research centers, the reader is referred to this year's account 'Peptide Research at Swiss Universities' in *The European Peptide Society Newsletter,* Issue Nr. 20, 1 January 1999). Prof. *Robinson*'s outline emphasized the special role of aromatic amino acids in the recognition of the extracellular domain of the interferon-gamma receptor. No less than 13 aromatic residues (six tyrosines, six tryptophanes and one histidine) play an essential role in the recognition of this surface by the neutralizing antibody A6. These aromatic residues can be part of a complexation network consisting not only of non-bonding aromatic stacking interactions but also of hydrogen bond donor-acceptor as well as charge-compensation relays. In the second part of the talk, he presented a very valuable and concise approach to stabilize a series of functional CDR hairpin loops spanned by a D-pro-L-Pro(β-type-II')-locked dipeptide template. Structural studies involving 2D-NMR confirmed the cyclopeptides to consist of homogenous conformational types for most of the hairpins in their canonical conformation, a feature which is a prerequisite for faithful molecular recognition.

Signal transduction can be studied by covalently modified membrane-protein fragments, as has been demonstrated by ***Herbert Waldmann*** from the University of Karlsruhe. He chose as his research objective one of the most important examples in signal transduction, namely the *ras* pathway which controlls cell growth in mammals and many other organisms. By employing highly specific enzymatic protecting-group techniques, it was, for instance, possible to construct the (*S*)-palmitoylated and (*S*)-farnesylated C-terminal heptapeptide of the human N-*ras* protein tagged with a fluorescent label. Such compounds can serve as reporter groups in membrane-fusion and microinjection experiments. Further, the enzymatic lipidation approach has been applied to *rab* proteins and complemented by chemical synthesis of the neo-*ras* lipoprotein in order to allow studies by surface plasmon resonance. A remarkable take-home lesson for the organic chemist is the use of enzymes to orthogonally protect sensitive functional groups in low-molecular-weight peptides.

The following hard-core structurally oriented lecture presented by ***Bernard P. Roques*** from the Laboratoire de Pharmacochimie Moléculaire et Structurale, INSERM-CNRS, Paris, shed more light on extra-membraneous domains of regulatory proteins associated with the *ras*-dependent signalling pathway. In particular, his group studied the inhibition of phosphorylation by MAP kinase by a proline-rich *h-sos*-derived peptidimer, which has the significant property to bind to the Grb2 SH3 domain. Part of the multidisciplinary approach is the chemical synthesis of large peptide domains (60–120 amino acids) on solid phase. Then, structural studies by X-ray as well as NMR and molecular-modelling experiments allow to determine the mechanisms of binding and information transfer. Besides zinc metallopeptidases including important approaches towards their specific inhibition by aminophosphinic inhibitors, a further very deeply studied example was the tandem zinc-finger peptide which encapsidates the reverse transcription of viral genomic RNA of HIV-1. The nucleocapsid protein NCp7 features a non-classical tandem zinc-finger motif with three cysteine and one histidine residues complexation, whereby the two nucleic-acid-binding domains are linked by a proline-containing spacer. Substitution of the histidine ligand by a fourth cysteine resulted in the widening of the structure; similarly, the substitution of L-Pro at position 31 of the native spacer-unit by D-pro leads to significant changes in the overall shape of the retro-transcription factor. Again, the tools of synthetic peptide chemistry allowed to discriminate between fortuitous and essential features of a given functional unit.

Understanding the mechanisms which have led to the evolution of an enzymatic function may provide a clue to direct multiple cycles of mutation, selection and amplification in the laboratory towards the bio-synthesis of macromolecules with tailored activities. This is the major objective persued by ***Donald Hilvert*** from the Laboratorium für Organische Chemie at ETH Zürich. By a molecular genetic-diversity approach which has its conceptual parentage in the generation of diversity in the contemporary immune-response cycle, his research team was able to virtually attain native activity with a monomeric multiply point-mutated and amplified four-helical bundle chorismate mutase. If scaffolding is altered and taken over from different classes of proteins, *e.g.*, the heavy-chain variable domain v_H of the IgG class, the enzyme topology can even be changed and directed to new classes of biocatalysts. Due to the high stability of those scaffolds, which remain the same even while presenting a high variability in their prosthetic groups, it is prospected to achieve a tailored substrate specificity with optimal catalytic stability.

Highly systematic and complementary approaches on the low-molecular-weight scale were presented by ***Daniel H. Rich*** from the Department of Chemistry and School of Pharmacy, University of Wisconsin-Madison, USA. He succeeded to span a bridge between the two currently applied techniques of inhibitor development: rational design based on mechanistic and structural insight into the catalytic center of an enzyme to be inhibited, contrasted by combinatorial synthesis of a manifold of potential inhibitors to be screened by a suitably established enzymatic assay. The relatively straightforward and rationally guided development of protease inhibitors in the last decade led to the statement that it is, in most cases, possible without major obstacles to find an inhibitor to a given target enzyme. An inhibitor is, however, not yet generally acceptable as a drug, since a number of very high benchmarks concerning its toxicity and bioavailability have to be met. Therefore, it is indispensable to apply systematic variation principles to a peptidic lead to transform it into a non-peptidic and thus non-degradable ligand or transition-state mimetic which may be adequate as the active principle of a drug formulation. Several computer programs are now ready to assist the medicinal chemist not only in rational inhibitor design, but also in the systematic generation of new constitutions which have the potential to further develop the lead structure into a suitable drug. Prof. *Rich* has developed together with Drs. *Bohacek* and *McMartin* (*No-*

vartis) the program *GrowMol* which is capable to propose a well-balanced manifold of variant constitutions for examination to the medicinal chemist. Most notably, the program is so well 'calibrated' with present state of the art in medicinal chemistry, that 25% of the proposed structures correspond to already known compounds, 25% to similar variants and 50% to completely new but reasonably stable constitutions. The presented results convincingly illustrated how 'combinatorial design' coupled with 'combinatorial synthesis' can lead to novel scaffolds for inhibitor development.

The last session block took up thematically with the opening lecture: ***Bernard Cuenoud*** from the *Novartis* Horsham Research Center, England, featured triple-helix formation as a valuable principle to target double-stranded DNA in the major groove. Generally, the need for chemically modified oligonucleotides with enhanced affinity and nuclease resistance is of paramount importance for their biological activity. In their present approach, the *Novartis* research team proposes 2'-aminoethoxy-modified oligonucleotides to achieve this goal. Not only does this 2'-modification enhance the overall affinity due to the positive charge of one ammonium functionality per negatively charged phosphate group, but also because the resulting intermolecular hydrogen-bond network is furcated from a well-defined oligo-homogenous (+)-*gauche* conformation of the two electronegative bonds in the 2'-substituent. The approach convinces with its very reasonable ratio of effect *vs.* complexity, and the clear and competent presentation left no major question on synthesis or physical characterization of the molecular recognition principle actually exploited.

When the natural variation principle has been triggered by the generation of antibodies against synthetic transition-state analogues, it is of primary importance to detect the individual molecular responses by an efficient assay to concentrate further cloning efforts. ***Jean-Louis Reymond*** from the Department of Chemistry and Biochemistry, University of Bern, concluded the lecture series with a very attractive detection method based on a direct fluorescence assay which is entirely compatible with the environment in the cell culture. Thereby, in a retro-*Diels-Alder* reaction, nitroxyl (NO^-) is being released to leave a fluorescent chromophore covalently attached to the protein conjugate on the detector probe. A very respectable number of antibody types have so far been screened with the fluorescence assay, notably catalytic antibodies elicited for the enantioselective reduction of ketones, the kinetic resolution of chiral acetates, the stereoselective aldolization of polypropionate fragments and the *Diels-Alder* cycloaddition. Prof. *Reymond*'s presentation very well complemented the preceding lectures by the focused illustration of a diagnostic detection method employing combined bio-organic techniques to solve the only too frequently encountered 'needle in a haystack' problem being raised by any variational or combinatorial approach.

As mentioned in the beginning, there was provided ample opportunity for all of the participants to discuss their own work with the lecturers between the breaks and in the **poster sessions**. The more so, since two one-hour blocks for three-minute oral introductions of the 45 posters have been organized that were well appreciated by all participants. The posters covered a broad range of topics in bioorganic chemistry, including – amongst many others worth to be mentioned – the metabolism of chlorophyll and porphobilinogen synthase, dichloromethane conversion by glutathione transferase, a model for cobalamin-dependent methionine synthase, dendritic carbohydrate receptors, the synthesis of racemic RNA, conformation and pH-dependent hirudin phosphorylation, thioxo peptide bonds as sensitive molecular probes for backbone conformation, the importance of the β-turn type in topological templates as surface mimetics of ICAM-1, gramicidin-S as instructive template paradigm, differential surface mapping in four-helical protein cores, receptor mapping by small-molecule inflation, the determination of ψ-angles in proteins by measurements of cross-relaxation rates, a neuropeptide Y conjugate of daunorubicin as anticancer drug, a template *de novo*-assembled hemoprotein for bioelectric applications, the synthesis of new types of *C*-disaccharides, a highly elegant approach towards the synthesis of 1,3-polyol motifs found in macrolide antibiotics, as well as important progress towards the total synthesis of the C_{29}–C_{51} fragment of spongistatins. The group of *Kai Johnsson*, recently appointed assistant professor at the Institute of Organic Chemistry, presented itself with appealing poster contributions on a combinatorial approach towards an understanding of the structure-function relationship of peroxidases, reactions of isoniazid metabolites with NAD^+ and O^6-alkylguanine derivatives for the *in vitro* selection of novel DNA-repair enzymes.

Any approach in bioorganic chemistry can be examined according to its congruence with or divergency from Nature's way. The task of the bio-organic chemist consists first of all in understanding the natural paradigm to the best of the state-of-the-art of his science, then he will explore these limits by the tools of synthetic organic chemistry or molecular biological recombinant techniques to achieve better performance or to speed up a drug-discovery process. At the end, he might allow himself a glance backwards and find himself at the beginning: did he not consciously or unconsciously apply a principle which has already been active in the natural world, which he had, however, only understood partially and which was hidden by another veil Nature had left concealed? Many of the mentioned variational principles seem to be successful only because they are in a certain congruency with the natural way. Moreover, it is a delicate issue and an important challenge for the biostructurally oriented scientist to delineate those three-dimensional features in his artificially modeled constructs which he can define as recurring and canonical motifs, and which he will have to take as further and ever re-assessed basis for any biomimetic endeavor.

With the certainty that it is possible to learn from Nature's way through our own emulation of its principles on a molecular level, organizers as well as participants will treasure the scientific and personal enrichments of this meeting, and look forward to the next 'Lausanne Conference on Bioorganic Chemistry' to take place in early March 2001.

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