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Fluorine in the Life Sciences
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«*I am not a fluorine chemist!*» I heard this laconic statement from several of the *ca.* 120 participants to the first International Symposium 'Fluorine in the Life Sciences' held on the Bürgenstock from 6th to 9th July, 2003. This avowal probably applies to most researchers both in academia and industry actively pursuing synthesis and applications of organofluorine compounds. The same researchers are very often faced with astonishing, unexpected, and unpredictable new properties that are precisely due to the incorporation of maybe even only a single fluorine atom into an otherwise 'well-behaved' molecule. Thus, while fluorine has become a sort of 'semi-empirical molecular tool', an interdisciplinary element par excellence, the above statement very much likely reflects the difficulties in understanding and explaining what fluorine substituents really do. The purpose of the Symposium, unique in its kind, was to try to gather state-of-the-art knowledge on this very topic.

The organizers of the Symposium – ***Karl-Heinz Altmann*** (ETH Zürich), ***Peter Maienfisch*** (Syngenta, Basel), ***Klaus Müller*** (Hofmann-La-Roche, Basel), and ***Manfred Schlosser*** (EPF Lausanne) – had indeed done a great job in putting together a very interesting program focusing more on the biological activity, structure, and properties, rather than primarily on the synthesis of fluoroorganic compounds. The Symposium encompassed ten plenary lectures, four topical workshops ('*Industrial Perspectives*', '*Structure and Properties*', '*Chemical Reactivity*', and '*Bioactivity*') with a total of sixteen 30-min lectures, as well as three poster sessions. The atmosphere of the meeting was typical 'Bürgenstock': Long discussions after each plenary lecture in the morning and after dinner as well as some time for pleasant recreation in a superb environment and/or more informal discussions after lunch time. In the following, I shall restrict my comments to key aspects as conveyed by the plenary lecturers.

The fundamental significance of fluorinated molecules for the life science industry was pointed out by several speakers representing both the agrochemical and pharmaceutical business sectors. It is important to realize that the number of commercialized fluorinated products has been steadily increasing in recent years reaching, for example, almost 20% of all compounds on the market in the case of crop protection agents. A systematic account on modern fluorine-containing crop protection ingredients was provided by ***P. Jeschke*** (Bayer CropScience AG) in one of the plenary lectures, whereas

Jack Dunitz, Bruce Smart, Dieter Seebach, Rolf Huisgen, Klaus Müller, and Manfred Schlosser

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F. Viani (CNR c/o Politecnico di Milano) gave a very exhaustive description of fluorine substitution effects in insect pheromones. Among the best selling prescription drugs, *i.e.* those with more than 1 billion US$ sales per year, at least four of them contain fluorine [1]. A very illustrative and exemplary presentation of the efforts carried out in medicinal chemistry concerning fluorinated drug derivatives was given by ***I. Ojima*** (State University of New York at Stony Brook) in an impressive evening lecture. His account, dealing mainly with fluorinated analogs of the taxanes, very well conveyed the interdisciplinarity of the endeavor necessary in this field before any breakthrough can be announced.

Dennis Curran discussing during the coffee break

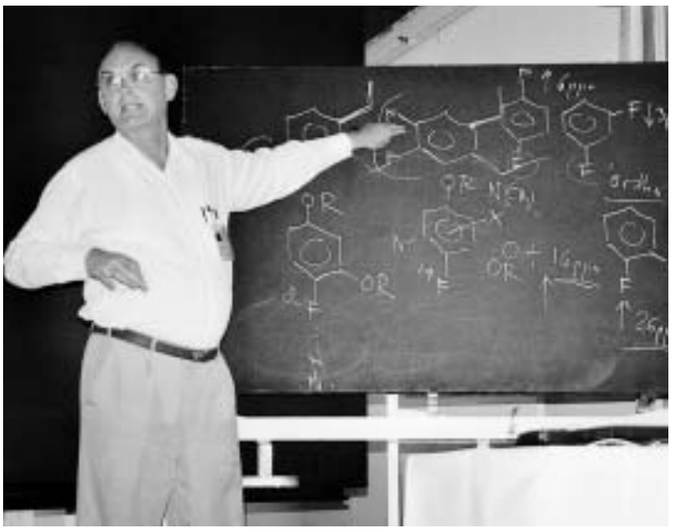
The selective fluorination of a bioactive compound can be generally beneficial in terms of a possible increased intrinsic activity, enhanced chemical and metabolic stability, and improved pharmacokinetics. However, once we have these desired benefits, does it also means that we understand the underlying new physico-chemical properties of the fluorinated bioactive compounds? Maybe the most important fundamental contribution to the discussion of these aspects was given by ***J. Dunitz*** (ETH Zürich). In his talk (chronologically the first plenary lecture), rich of insights as well as anecdotic material, he was able to convince pretty much everybody in the audience that *organic fluorine hardly ever makes hydrogen bonds* [2]. This is a very relevant point when trying to understand interactions of fluorinated compounds with *e.g.* enzymatic systems. Short non-bonded contacts between C-F groups and other functionalities, as observed for example in crystal structures, do not necessarily represent attractive relations, on the contrary, they mostly imply repulsive interactions. Here is probably a simple truism that we too often forget when interpreting geometric data of static structures. Dunitz also pointed out that, in order to fully understand the chemical behavior of fluorinated molecules, there is still a lot of fundamental – but alas not very attractive – work to be done, addressing *e.g.* their thermodynamic properties. Dunitz's thoughts kept recurring in the discussions following other lectures at the Symposium. If not hydrogen bonds, a C-F unit in a fluorinated compound appears to be able to undergo dipole–dipole interactions with carbonyl groups. An example of such an interaction has been found in an elegant work on thrombine inhibitors [3], as presented by ***H.-J. Böhm*** (Hoffmann-La-Roche) in another plenary lecture. Böhm also pointed out how fluorine substituents, in particular CF_3 groups, are able to increase the lipophilicity (the partition coefficient between water and octanol, often at defined pH), this being one of the 'easy' parameters, very often used to characterize fluorinated compounds. Furthermore, he illustrated that methoxy and trifluoromethoxy substituents will adopt drastically different conformations.

Thanks to the pioneering work of ***D. Seebach*** (ETH Zürich) β-peptides are being recognized as potentially important proteomimetics. These compounds are not cleaved by proteases and peptidases and display very different folding properties with respect to their α-peptidic counterpart. Seebach and co-workers have carried out a systematic study on the effect of α-fluoro-, α-hydroxy-, and α,α-difluoro substitution on the folding and reactivity properties of β-peptides [4a]. In his presentation (chronologically the concluding plenary lecture of the Symposium) Seebach, after outlining the synthesis of the fluorinated derivatives, addressed the question of whether fluorine can still be tolerated in so-called forbidden axial positions of a β-peptidic 3_{14} helix. The CD spectra of the corresponding derivatives all show the typical pattern that could be assigned to a 3_{14}-helix. This is, however, very puzzling and justifies once more the use of the term *flustrates*, originally coined by Seebach [4b] when expressing a certain degree of frustration about the often unpredictable properties of fluorinated derivatives.

S.G. DiMagno's lecture (University of Nebraska) was concerned with the subtle structural changes of porphyrines deriving from the introduction of fluorine substituents and the consequences in terms of electronic transition energies and redox potentials. He also talked about the concept of 'polar hydrophobicity' that could be a possible strategy to improve transport and recognition of bioactive molecules.

The presentations by ***D.P. Curran*** (University of Pittsburgh) and ***T. Hiyama*** (Kyoto University) were, among the plenary lectures, very much synthesis-oriented. The former lecture was an inspiring demonstration of the creative and innovative use of so-called fluorous phases in synthesis [5]. Fluorous tags incorporated into reactive molecules, including catalysts, control the separation properties either in liquid–liquid or solid–liquid techniques, while not influencing significantly their reactivity. Thus, fluorous separation techniques are acquiring an important strategic value in synthesis, as illustrated by the many examples given in superbly didactic manner by Curran in his talk. Hiyama's lecture, on the other hand, focused on methodologies for the introduction of fluorine substituents. Oxidative desulfurization-fluorination reactions allow, for example, the efficient conversion of aryl dithioesters to trifluoromethyl derivatives. New nucleophilic perhalogenated zinc reagents (fluoro carbenoids) can be added to aldehydes; further elaboration of the intermediate products afford fluoro olefins with control of stereochemistry. Another interesting synthetic aspect regarded the preparation of trifluoromethylated divinyloxiranes, able of undergoing Cope rearrangements affording 2-CF_3-4,5-dihydro-oxepins.

Fluorine ranks thirteenth in the series of most abundant elements in the earth crust. However, in the oceans it is much less abundant than the other halogens. In other words, the element is 'buried' in Nature in form of insoluble minerals. This partly explains why naturally occurring fluoroorganic compounds are so rare (not much



Klaus Müller's enthusiastic discussion at the blackboard

more than a dozen known to date, as opposed to *ca*. 3500 disparate derivatives containing one or more of the other halogens). Fluoroacetic acid, a very toxic compound, is produced by several plants and bacteria, though its biosynthesis was unknown until about a year ago. ***D. O'Hagan*** (University of St. Andrews) recently discovered and studied the enzymatic pathway leading to fluorination in the bacterium *Streptomyces cattleya* [6]. His lecture told us a very nice and complete story, very much detective-like, on these investigations at the border between chemistry, biochemistry, and molecular biology. O'Hagan disclosed also some still unpublished material concerning the crystal structure of the first *fluorinase* enzyme. The fluorination step is an S_N2 reaction in the course of which fluoride reacts with S-adenosylmethionine generating methionine and 5'-fluoro-5'deoxyadenosine as the primary fluorinated product. Further, still unknown steps generate fluoroacetaldehyde and subsequently fluoroacetate and 4-fluorothreonine. When fluoride is the nucleophile an immediate question must be asked: How does the enzyme get fluoride 'stripped' of its solvating water shell and what is the counterion? In view of the very strong hydrogen bonds formed by fluoride, this is not an irrelevant question. The probable fluoride-binding site in the enzyme is characterized by two hydroxyl groups and a hydrophobic leucine residue. Is this the answer?

As a conclusion I want to add only this: I personally entered the field of organofluorine chemistry only recently, from a homogeneous catalysis perspective and I have been asked if this is only a …*flirt*. I must say that no other element has ever fascinated me more than fluorine. The Symposium, from which I learned a lot, has contributed considerably in strengthening this fascination. Is 'Fluorine-Bürgenstock' going to become a new legendary Bürgenstock-series? The start has been most favorable.

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