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« Synthesis : science or technology ? »
A few comments from an old-timer

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Introduction

In the mid-seventies I was invited to evaluate the merits of a colleague who had applied for a higher position in his institution. I knew the applicant, I liked his work which was interesting and well-done but , nevertheless, I felt somewhat embarassed when I was asked to evaluate his creativity. It turns out that, at that time, R.B. Woodward was visiting the University of Louvain. I expressed my concern about this evaluation. He had an amused smile and, with his typical dry wit, replied : *« Tell him to move to biology » !* I was amused but somewhat surprised by this reply. Then he went on by explaining the importance of synthetic probes for the discovery of biological targets and the elucidation of biological mechanisms, an area of research we now call « chemical biology ». He foresaw that this field would offer synthetic chemists ample and easier opportunities for creative research than « classical » synthesis. It turns out that, these days, many believe that synthesis has become a service technology arguing that almost any molecule could be synthetized by a competent synthetic chemist. As a result, the future of our science has been discussed extensively by major players in the field. I just wish to add a few personal comments to this much debated subject.

Comment 1 : Synthesis : science or technology ?

Fifteen years after my discussion with R.B. Woodward, Dieter Seebach, one of the most talented and productive synthetic chemist of the 20th century, wrote a review article entitled « *Organic Synthesis – Where Now* ?» which had raised some unrest within the community of synthetic chemists. Many felt that it gave a rather pessimistic view of the future of organic chemistry that was more and more considered by many as a mature science with little room for creativity. However those who carefully read this exceptionally lucid account of the state of our science realized that Seebach pointed out many new perspectives for creative research in organic synthesis resulting from the intrusion of chemistry into the material and biological sciences. Since this landmark publication many authoritative organic chemists have expressed their views[2] about what synthesis should be and will be and, in the present volume, Scott Denmark has provided a survey of his personal views of the past, present and future of organic synthesis.[3]

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It is obvious that synthesis will always remain a major endeaviour of chemists. In 1854 Auguste Laurent, an unfairly forgotten french organic chemist, wrote « la chimie est devenue aujourd'hui la science des corps qui n'existent pas ». Chemistry is indeed and will always be an unhexaustible source of new molecular structures and assemblies aimed at satisfying the ever-growing societal needs. The creativity of the chemist will be measured by his (her) ability to *design* but *also prepare* new molecules or molecular assemblies with the *desired properties* which will be further *engineered* and *produced* by industry for, hopefully, the benefit of mankind. However many view that, in this endeaviour, *synthesis* is merely a *technology* allowing to efficiently obtained the molecular targets. I see no problem at considering synthesis as « a molecular technology » requiring innovative thinking based on an excellent knowledge and understanding of the principles of physical organic chemistry . However I strongly believe synthesis is still a *science* since it is a unique source of *« discoveries »* of unprecedented behaviour of molecules in specific conditions (reagents, catalysts, temperature,….). In recent years a large majority of these *« discoveries »* have taken place in the field of organometallic catalysis as predicted in Seebach's 1990 paper. Many of these new chemical transformations could not have been predicted by the existing theories and thus have significantly contributed to our understanding of the behaviour of matter at the molecular and supramolecular level. These scientific discoveries led to the development of new technologies for the synthesis of molecules. Who would have predicted the *discoveries* which led to the technologies allowing to selectively activate C-H bond previously considered as « chemically inert » ? Recently we have also *learned* a lot about the factors controlling the mode of approach of two reactants allowing us to develop methods transforming achiral molecules into enantiopure products. These *scientific discoveries* and *inventions of new reactions* undoubtedly benefited from the availability of techniques allowing detailed analyses of chemical events.

Maintaining a leadership in creating new products to meet societal needs will ***only*** be possible if we keep investing in these fundamental studies which will provide the knowledge required to invent pratical syntheses of even the more complex molecules. I have often noticed that some industrial projects were dropped off simply because the synthesis of the target molecules appeared too complex or too long to be economically viable. This just reveals that there is still a great need for new efficient and productive synthetic methods which meet economical constrains and the growing challenges imposed by the protection of health and environment . However designing the « ideal » synthetic route in the laboratory will not be sufficient. The syntheses will have to be adaptable to large scale productions. Process chemists in industry have been particularly good at transforming an « academically-discovered » laboratory synthetic route into a practical industrial synthesis. In recent years some academic groups have been much concerned by our way of doing synthesis in the laboratory. Our present way to do synthesis is indeed labour intensive (most tasks are manual), often not very safe (the « kamikaze » approach is no longer tolerated !), and certainly not very productive. Automated synthesis has already invaded many industrial laboratories especially when repetitive work (*eg* building libraries of compounds) is concerned. Several academic groups around the world had brought about punctual improvements of some operations in the laboratory but it was S. Ley and his group at Cambridge who really took the lead of what could be a genuine revolution in the way synthetic chemists do experiments in the laboratory[4]. Even an old-timer can see the advantages of having machines and computers controlling the unit operations presently done with our « hands ». We are still doing experiments like farmers pulling the plow or a disk harrow : it is time for buying

tractors or , at least, horses or oxen, isn't it ? *Thus it is also time to engineer chemical synthesis.* Thas is indeed technology but still it will require creative minds.

Comment 2 : more natural product chemistry ?

This comment is inspired by a international meeting I recently attended : the selection of speakers made by a brilliant young synthetic chemist was superb but I noticed that, like in the past, a majority of talks dealt with natural product syntheses.
I was asking myself : why so many synthetic chemists including brilliant scientists of the young generation are still involved in natural products synthesis ?

Small organic natural products mostly derived from secondary metabolism have continuously fascinated and inspired the community of synthetic chemists. In the early days the main goal was to isolate, purify and establish the structure of molecules found in nature. Some were known and eventually found to exhibit interesting biological activities which provided further incentive for their studies and the development of analogs for therapeutic or agrochemical applications. For several years the ultimate proof of structure rested upon the total synthesis of the molecule and the comparison of the synthetic product with an authentic sample. Nowadays the all process isolation-purification-structure proof can be done rather easily in laboratories equipped with the appropriate analytical and spectroscopic tools. Nowadays synthesis seldom plays an important role in this endeaviour.

Synthetic chemists of my generation have been fed by elegant and imaginative total syntheses of increasingly complex natural products. These endeaviours which require a unique combination of imagination, mastering of chemical reactivity and experimental skill have been at the root source of modern structural theories,
development of new synthetic methods. and even our understanding of biogenesis. That only would provide ample justification for the major investments in manpower often required by these ambitious research projects. Also many will probably agree that a project aiming at the total synthesis of a complex natural product is an unrivaled tool for training young organic chemists and stimulating their creativity and imagination.

Still critical minds will object that, in spite of this huge effort in « making » complex natural products, many total syntheses are too long, too expensive and unpractical for large scale preparation of these complex molecules. Many total syntheses have indeed never been reproduced outside the « original » laboratory ! Thus while these synthetic studies have been extraordinality efficient in generating knowledge, they have not been as successful in making efficiently and economically the target products in amounts suitable for further studies and applications in biology or material sciences. Rewardingly the young generation of synthetic chemists has become aware of this extremely challenging task. Let me quote here Phil Baran who is a tireless crusader on this subject : **«** *but before one declares the science of synthesis an endeavor in engineering, one only needs to reflect on the inspiring ease with which Nature crafts large quantities of her most complex molecules (e.g. vancomycin and taxol). Total synthesis in this century must therefore be keenly aware of this ultimate challenge – to be able to provide large quantities of complex natural products with a minimum amount of labor and material expenses ».*[2b,5,]
Clearly nowadays total synthesis of natural products can no longer be a pure intellectual and educational endeaviour but should take more into account what synthesis is for : making compounds whathever their complexity in a practical and economical way for the benefit of mankind. Progresses are made but the route toward the "ideal synthesis" is still long.

An interesting development of natural products chemistry which has been pioneered by the groups of Danishefsky , Waldmann and a few others including our own group results from the use of natural products as templates for the design of molecules of therapeutic interest.[6] Small natural products are indeed the results of long-term co-evolution within biological communities : interacting organisms generated compounds which could act on biological processes of other organisms. If profitable, natural selection will retain and improve them throughout the course of evolution. Thus, eventually, the *chemical descriptor* of a natural product should be ideal for interaction with a biological target. The *complexity* of NPs makes them able to target biological macromolecules in a highly selective fashion. The strategy consists in designing a privileged scaffold retaining selected structural and stereochemical features which are thought to be essential for the interaction with a biological target. An additional criterion for the selection of the scaffold will be its availability in multigram quantities : the challenge of the synthetic chemist will then be to implement short, practical and productive sequences of reactions leading to these scaffolds. Eventually the scaffolds will be transformed into libraries of "analogs" of the natural product by simple chemical transformation. To me this represents a more powerful tool for the discovery of molecules of therapeutic interest than the total synthesis of a particular natural product.

Comment 3 : what about catalysis ?

I would like to add a brief comment about catalysis which is often considered as the ultimate goal in the development of a new synthetic method. In the abstract of his prophetic paper, D. Seebach wrote that « the primary center of attention for all synthetic methods will continue to shift toward catalytic and enantioselective variants ». Later , in the text, he mentioned : « It is easy to predict that by the year 2000 this flurry of activity will have provided us with all of the following: a) simple approaches to the synthesis of enantiomerically pure chiral compounds representing all the known classes of substances; b) catalytic variants for every reaction in which achiral precursors lead to at least one element of chirality; c) corresponding methods suitable for industrial use on any desired scale; and d)much wider understanding of intermolecular interactions and the detailed course of reactions ». This was clearly over-optimistic. We all agree that the extraordinarily development of organometallic catalysis and the rediscovery of organocatalysis by exceptionally creative chemists has not only provided us with catalytic variants for many known reactions but also with a wealth of *new transformations* synthetic chemists could not have dreamed of. The recent discovery of selective catalytic C-H activation is a striking illustration of this spectacular development of organic synthesis.

At the same time enantioselective variants of these reactions have been discovered allowing chemists to compete successfully with nature in preparing natural products but also a huge collections of unatural enantiopure molecules. Some enantioselective catalytic processes (*eg* epoxidation or hydrogenation*)* are not very far from the ultimate goals of the « ideal synthesis » and have been applied industrially. This is not true for most of the even very best catalysts used in organic synthesis. Synthetic chemists have indeed been outstanding in designing chiral catalysts which lead to very high stereoselectivity but they have often neglected an essential feature of catalysis which is linked to the molecular weight of the catalyst and its turn-over frequency. Most of these catalysts have a high molecular weight and their turn-over frequency is too low. Recently I asked a student to prepare 3 grams of an enantiopure intermediate using a catalytic process involving a « well established » catalyst described in a « high impact

journal (apparently a new criterion of scientific excellence)». He came back and told me : do you realize that I shall need a 5l. flask to prepare these few grams ? The molecular weight of the catalyst was indeed 5 times that of the reactant and it was poorly soluble. Often this practical aspect of enantioselective catalysis is considered as being « *technological »* and therefore not of much interest for an academic chemist. I disagree with this and I am convinced that this challenge of finding more productive catalysts will require much creativity from the future generation of chemists.

Another drawback of many « asymmetric » catalysts results from their poor functional tolerance. Therefore they cannot be applied to the synthesis of highly functionalized molecules which usually exhibit the most interesting properties. Clearly, in most cases, there is still some way to go before we reach the « ideal catalytic enantioselective reaction »

Comment 4 : Apologies !

At the end of this short paper, I feel somewhat guilty to have succumbed to the temptation of many old-timers to become « philosophers » at the end of their career ! I thus apologize to my many younger colleagues and friends who have written more comprehensive and probably more pertinent comments on the future of our science. I also apologize for have written for the first time a chemical paper without any formula.

Let me end these comments by quoting again R.B. Woodward :

« The unique challenge which chemical synthesis provides for creative imagination and the skilled hand ensures that it will endure as long as men write books, paint pictures and fashion things which are beautiful or practical ... or both ».

References

1. D. Seebach, *Angew. Chem Int. Ed. Engl.* **1990,** *29*, *1320-1367.*
2. See for example : (a) G.M. Whitesides, *Angew. Chem. Int. Ed. Engl*. **1990**, *29, 1209-1218 ;* (b) T. Gaich, P.S. Baran, J. *Org. Chem*. **2010**, *75*, *4657–4673 ;* (c) S.V. Ley, *Tetrahedron,* **2010**, *66, 6270-6292* ; (d) A. Mendoza, P.S. Baran, *Nature,* **2012**, *492, 188* ; *(e)* H. Mayr, *Isr. J. Chem*. **2016**, *56, 30– 37* ; (f) B. Giese, *Isr. J. Chem*. **2016**, *56, 91-92.*
3. S. Denmark, *Isr. J. Chem.* **2018,** to be completed by the publisher
4. Review : D.E. Fitzpatrick and S.V. Ley, *Tetrahedron,* **ASAP** ; see also articles published in this Tetrahedron Symposium-in-print (Guest Editor : S.V. Ley) to be published in 2018.
5. (a) C.A. Kuttruff, M.D. Eastgate, P.S. Baran, *Nat. Prod. Rep.* **2014**, *31, 419-432 ;* (b) I.S. Young, P.S. Baran, *Nature Chem.* **2009**, *1, 193-205 ;* (c) T. Newhouse, P.S. Baran, R.W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38, 3010-3021.*
6. See for examples : (a) R. Breinbauer, I.R.Vetter, H. Waldmann, *Angew. Chem.Int. Ed.* **2002,** *41***,** *2878–2890* ; (b)Y. Liao, Y. Hu, J. Wu, Q. Zhu, M. Donovan, Z. Yang, R. Fathi, C*urrent medicinal chemistry,* **2003**, *10*, *2285-2316* ; (c) M. Koch, L-O. Wittenberg, S. Basu, D.A. Jeyaaraj, E. Gourzoulidou, K. Reinecke, A. Odermatt, H. Waldmann, *Proc. Natl. Acad. Sci. USA,* **2004,** *101, 16721-16726*; (d)M.A. Koch, H. Waldmann, *Drug Discovery Today,* **2005,** *10, 471- 483*; (e) A. Reayi, P. Arya, *Current Opinion in Chemical Biology*, **2005**, *9, 240-247*; (f) M.A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, *Proc. Natl. Acad. Sci. USA,* **2005,** *102, 17272-17277*; (g) R.M. Wilson, S.J. Danishefsky, *J. Org. Chem*. **2006,** *71, 8329-8351*; (h) K. Huebel, T. Lessmann, H. Waldmann, *Chemical Society Reviews,* **2008,** *37, 1361-1374;* (i) Zhu, W.; Mena, M.; Jnoff, E.; Sun, N.; Pasau, P.; Ghosez, L.; *Angew. Chem. Int. Ed.* **2009**, *48, 5880-5883 ;* (j) R.M.

Wilson, S.J. Danishefsky, *Angew. Chem. Int. Ed.* **2010**, *69, 6032-6056 ;* (k) K.C. Morrisson, P.J. Hergenrother, *Nat. Prod. Rep.* **2014,** *31, 6-14 ;* (l) K. Gademann, *Acc. Chem. Res.* **2015**, *48, 731-739 ;* (m) P.A. Wender, R.V. Quiroz, M.C. Stevens, *Acc. Chem. Res.* **2015**, *48, 752-760.*