Thoughts on organic chemistry

An interview with Victor Snieckus, Queen's University, Kingston, Ontario, Canada

What are the biggest challenges to be solved in organic chemistry in the next ten years?

Allow me to preface: I am addressing primarily the area of organic synthesis and I fondly reflect on an article by Nobelist John Cornforth whose theme, 'The Trouble with Synthesis' (*Austr. J. Chem.* **1993**, *46*, 157) which is timeless. Academic organic chemists are all in process of solving specific, self-inflicted problems; pharmaceutical industrials are provoked by laudable goals of human health and, more realistically, by company dictates. For academic synthetic organic chemists, the challenge is to avoid repetitive, me-too chemistry evident in the plethora of papers appearing of reactions that vary only in the conditions, catalysts, and ligands and pay little heed to showing that the reported method has advantages over previously published results from other and even their own laboratories. An ancillary challenge is to provide a mechanism that has real experimental evidence rather than reducing the understanding of a reaction to the results of 15–20 robotic screening experiments carried out during optimization. If me-too chemistry is avoided and fundamental mechanism is understood, serendipity will have a greater opportunity which, in turn, will lead to discovery of new chemistry.

To answer the title question without avoidance, the challenges are clearly at the chemistry-biology interface. Organic chemists must read the literature of the allied biological field and be in close collegial relationship with biologists to jump into opportunities that provide advances and solutions in major disease states.

What can organic chemists learn from biologists and *vice-versa*?

Here is a very worthy experiment that I witnessed at a major UK pharmaceutical company about 20 years ago: for one day, organic chemists were placed into a bioassay lab and biologists were taken into a synthetic lab and were told, respectively: today you will carry out a full set of bioassay experiments and today you are going to do a Grignard reaction AND work it up and purify the product. You can imagine, following this experiment, the improved respect each of the disciplines had for each other and how well they got along and communicated at coffee breaks. This was discontinued undoubtedly by management who were not scientists. For the uninitiated in the respective discipline, there is an immense language barrier replete with very different acronyms and visual elements. The biologist quickly grasps the beautiful ribbon structure of hemoglobin while the organic chemist sees, in his mind's eye, the three-dimensional structure of a steroid; the former knows the distances, the hydrophilic and hydrophobic pockets, the H-bonds, and the change of the shape in interaction with drugs; the latter can show how a molecule fits into a pocket or not and relates to the biologist in forms of understanding regarding the physical requirements for interaction. Bottom line: the two types of scientists must be able to translate their respective languages to each other. Courses and books help but the solutions are established at patient, lengthy, and regular interactions. Those that achieve the cross-communication stand out in meetings and conferences.

How close should academics' research be linked to the needs of industry?

The dictum that fundamental academic research is untouched and not influenced by industrial needs is the past. The past showed industrial chemists who were well-versed in academic work by virtue of literature reading, sitting around a table, and awarding grants to selected academic chemists to "use as you determine in the interest of your research programs." The present is increasingly the requirement of providing chemistry that is exactly required or adaptable for a given molecule/class of molecules of "great interest" to the company. This is not all to the bad. Depending on the philosophy of the company, a grant or contract from a company allows various levels of independence since the industrious med and process chemists know the literature well and have tried all the common suggestions of the academic whose students undertake the work. The academic is deflated but must know the previous work so as not to reinvent another aldol. New robust methods are required and, in the best of all worlds, the academic chemist and his students are given carte blanche to achieve them ... of course, with the gentle forewarning, that they are required yesterday.

Today, most current synthetic organic papers begin by a figure with structures of 3–4 bioactive or natural products which have imbedded

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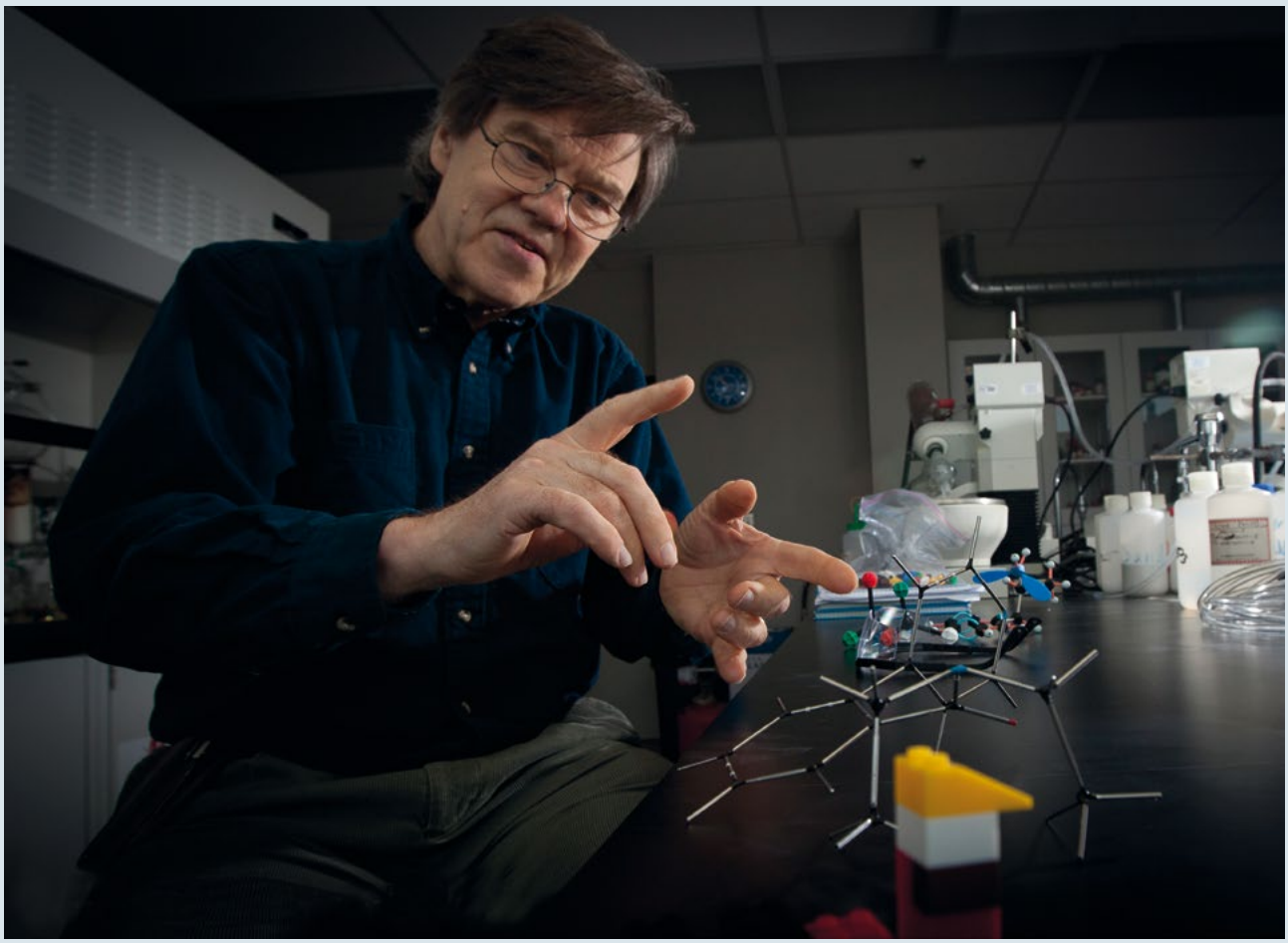

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structural components of the molecules whose synthesis is described. However, to the detriment of the authors (and the literature), they are immediately forgotten; with some exceptions, none of the figure molecules or even their fragments are synthesized. The conscientious chemist authors that complete such tasks do, in fact, contribute considerably since they provide a new cuisine for thought for the industrial med or process chemist.

Which modern methodologies and techniques are not being fully utilized?

The question deals with a function of availability. The industrial chemist who needs robotics, flow chemistry, multiwell reaction optimization apparatus proposes the equipment to his/her supervisor and, given that the case is well made, orders it the next day; the academic writes an equipment grant proposal and, today, is extremely fortunate if it is awarded in the 3rd year of continuing submission. A very obvious extension of hands by industrial and to the academic chemists. Based on this and other advantages of academic-industrial collaboration, increasing collaboration of this type, to some extent in progress by select pharma, is urgently required. The academic gains by showcasing the new chemistry as optimized, robust, scope-advantageous methodology; the industrial chemist adds to his tool box of reactions required by the various groups of colleague synthetic chemists and obtains a publication or two which enhances his and the company's visibility.

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Do reaction mechanisms need to be better investigated and understood?

This question has been partially answered above. Additional points to consider: academics are harassed by the need to publish (also below); almost unavoidable in a devil's bargain to obtain more funding, and therefore negate or at least hesitate to delve deeply into mechanisms; graduate students and especially postdocs harass the supervisor to publish since the review boards for job application increasingly counts and does not read papers or, shoddier, only use the italic titles of the top 5 CI journals in order to make decision of hire/reject; demise of courses in physical organic chemistry because of lack of training in this discipline makes students incapable to carry out kinetics, isotope effect measurements, and detailed analysis of reaction paths. Some departments are fortunate to have instrument managers that rapidly provide rate profiles and energy barriers which are then placed into papers by synthetic chemists, some without full understanding.

The question also needs to address calculations. Most synthetic chemists of previous generations have no training in DFT calculations and place pretty pictures of energy diagrams with only an appreciation of low and high numbers and the perhaps better appreciation of steric and electronic effects than those given by toy molecular models. Perhaps that is ok because those who DO understand DFTs will be able to gain knowledge which will be useful in the general pot of organic reaction mechanisms.

Does organic chemistry overlap with non-scientific fields, like art, architecture or philosophy?

As stated by many illustrious practitioners, most notably R.B. Woodward: *Synthesis is Art*. Constructing a molecule, no matter of complexity, involves thinking of where to brush to make or break a bond, what lightness or thickness the stroke should be, and what glorious colors quickly facilitate the appreciation of a retrosynthetic analysis. Synthesis is the assembly process and not only in a single multi-step way because all synthetikers know of multiple failures. On overlap with architecture and art: *Viewing the Taj Mahal*, a Klee or Mondrian work, the set hexagons in a cobblestone sidewalk – all may bring ideas for creating molecules and, on rare occasions, the Aha moment. On overlap with philosophy: the highly used metaphor is climbing Mt. Everest. Synthetic chemist in the lab are excited to create new compounds because "they are there" and because "they may be good drugs", i.e. give relief from ailments and cure diseases which continue to appear in different and, many times, in apparently impenetrable forms. The "they are there" molecules appearing on a page of a journal sometimes receives the comment: "what?, useless!") but we should not open our mouths having been proved wrong too many times, e.g., most recently, buckminsterfullerene. The "they may be good drugs" involves usually a 15 year journey by very dedicated chemists with a very low percent success rate whom we should champion, e.g. in current efforts to overcome dementia, Alzheimer's and Parkinson's, the obvious prevalent diseases of the 21st Century. But I turn you over to Roald Hoffmann who, with clarity, wit, and deep knowledge, has placed this question in perspective for all: *R. Hoffmann on the Philosophy, Art, and Science of Chemistry*, Oxford University Press, 2012.

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