

Complex Organic Synthesis: Structure, Properties, and/or Function?

George M. Whitesides^[a]

In 1956 – the year R. B. Woodward's famous Perspective^[1] was published – I was a senior in high school. The next year, when I started college and joined a research group, it was still all the (I thought, hopefully and in anticipation, “we”) organic chemistry graduate students talked about. The *vision* was so astonishing, and the ambition so grand, that it was transfixing. It clearly marked the transformation of the field of synthesis from one state into something entirely different – one marked by disciplined, elegant, complexity. I never actually *met* Woodward (other than secondarily, through one of his postdocs, to let me know of his intense displeasure at my use of his IR spectrometers in the middle of the night), but I did go to Woodward group seminars, where I learned humility, as well as new definitions of “endurance” and bladder control (these seminars were – or seemed – very, very long to someone who understood very little of what was going on). Still, it was impossible for me not to share the feeling of the birth of a new field.

I did not become a “synthetic organic chemist,” but almost all the research that my colleagues and I have done (and do) involves organic synthesis. The ability to put together molecules – bit-by-bit, simple or complex – is one of chemistry's great accomplishments, and a source of amazement to those in many other fields of science. More than one physicist has told me that s/he cannot believe that it is *possible* to manipulate bonds between individual atoms with the skill that organic chemists do. When I look at a complex structure assembled in a beautifully organized campaign, I also am amazed. That said, all fields of science morph with time. The phrase “organic synthesis” has come to mean “synthesis of structurally complex natural products”, or, perhaps, “synthesis of complicated molecules with pharmaceutical activity.” Nature, and relevance to healthcare, define the targets, and provide the utilitarian justification for the effort.^[2] Is there (or should there be) more to it than that?

Will this style of organic synthesis – a style that emphasizes technical proficiency and complexity rather than simplicity, breadth, and utility – persist? Natural products, and selected, specific types of transformations, provide endless technically interesting problems – in structure, in synthetic design, in development of reagents – but does their solution justify the effort that goes into them? Are there other types of problems that need the skills of experts in synthesis, and other types of opportunity than those that have historically been most exhaustively studied?^[3]

Aside from the technical focus, there is another issue. Much of complex organic synthesis goes on in universities. In

addition to performing research, university research groups have the important obligation to teach students what they need to know for their intended careers. Is the training that students currently receive in organic synthesis the one that best prepares them for their future (and which may possibly be entirely different than their research director's past)?

“Organic Synthesis:” What Is It?

The phrase “Organic Synthesis” is a complicated one, and means different things to different people. It is always risky, semantically, to use a single phrase to describe many different things. Arguably, the phrase “organic synthesis” is an umbrella that includes an enormous range of activities: the marvelously optimized processes used in production of fuels and commodity polyolefin film, the generation of monoclonal antibodies and of C₆₀, the synthesis of palytoxin, the manufacture of Simvastatin, the synthesis of the liquid crystals used in displays, and the many, many other types of organic compounds produced synthetically. It is *all* “organic synthesis”? Using a single phrase for everything risks ambiguity. For specificity in this Perspective, I propose to use a particular nomenclature: I will call the broad activity of synthesizing organic compounds at all scales, of all structural complexities, and by any methods – that is, without limit on target or method: the putting together of molecules – “organic synthesis,” and will specify the particular sub-activity of putting together *complex* structures – often (at least historically), natural products, in the style defined by Woodward, Barton, Eschenmoser, Stork, and others – as “Organic Synthesis.”

I suggest that it is appropriate – in light of the indisputable *past* successes of the field described by the phrase “Organic Synthesis” – to raise three questions about its future. i) Is the particular skill of synthesizing complex molecular structures a *science* (in the sense that it generates new concepts and new theory), an *art* (albeit one with an underlying aesthetic structure easily – but sometimes only – perceptible to experts, without regard to generality or utility?), or a *craft* (requiring great skill, but relying more on empirical expertise than on theory)? Fields of science tend to move toward “theory” as they mature. ii) Is Organic Synthesis better described as an invaluable enabling technology (making possible the synthesis

[a] G. M. Whitesides
Department of Chemistry and Chemical Biology
Harvard University

of new drugs and specialty chemicals), or as an intellectual structure within which to ask questions about the nature of molecular structure, the synthetic methods and designs needed to build them, and the purposes they can serve? iii) Should students understand all of it (or as much of it as humanly possible, since it encompasses an immense amount of empirical information), or just parts of what is now known, combined with ideas from other fields? Is “all of it” as presently practiced enough, or is there more – and different – that they should (or perhaps, *must*) know for the future?

The answers to these kinds of questions are never clear-cut, but important to the future of one of the most remarkable skills in science. The characteristics of scientists and engineers who are working on different parts of the synthetic spectrum are often quite specialized and almost non-overlapping. Complex Organic Synthesis has a large element of empiricism and pattern recognition, and experimental precedent is more important than theory: the details *count!* In designing large-scale industrial production facilities, both the product and the pathway to it are often already known, but the quantitative engineering detail is critical. In materials science, the design and production of a new photoresist (for example) requires knowledge of synthesis (*including* methods often *not* considered or included in Organic Synthesis), a deep understanding of mechanism, and an acute appreciation of the complex technical needs of those using the composition to prepare microchips. Although all are different – in fact, so different as to be almost unrecognizable as parts of the same field – all involve the formation of bonds between atoms in molecules, the designs of synthetic processes, and the execution of complex operations.

The style and scope of modern organic synthesis stems from World War II, which had four lasting influences on organic synthesis. i) The first was the ability to carry out very large-scale conversions of petroleum to fuels. These conversions also produced a wide range of other molecules that became the starting materials for much of organic chemistry. ii) The second was the array of technologies that made possible the analytical methods (IR, UV, and NMR spectroscopies, mass spectrometry, and x-ray crystallography) without which Organic Synthesis would be impossible; iii) The third was an emphasis, within the broad area of capitalist healthcare, on end-of-life, symptomatic disease (especially cardiovascular disease and cancer) which provided one practical stimulus to develop strategies and methods capable of synthesizing molecules – whether natural products or purely synthetic entities – for use as pharmaceuticals, iv) The fourth was an enormous expansion of the chemical industry to provide the materials required to rebuild the world after the war. This industry made industrial chemistry a major part of the global economy, and provided jobs for students trained in chemistry.

Within this context, Organic Synthesis prospered as an academic discipline focused on developing new methods for the construction of complex structures. This discipline provided both enormous technical and intellectual challenges,

practical applications, and jobs for chemists and chemical engineers.

The situation has now changed. One can argue (or at least many skilled synthetic chemists have told me) that almost any natural product can be synthesized, given enough time and effort. Both the pharmaceutical industry and NIH – at least those parts that focused on oncology – have shifted their focus from cytotoxic agents (where synthetic chemistry had a very important role to play) to biopharmaceuticals (which are predominately proteins). At the other end of the scale (in terms of quantities required), the commodity and fine-chemical industries – with a few exceptions – turned away from new classes of products and from research (although they retained some interest in new processes). The resulting decline in innovation has been justified (or dictated) both by financial constraints and market opportunities. Companies that retained a strong interest in technical discovery (for example, DuPont) were unable to demonstrate that “Research and Development” was an *investment* (reflected in revenues and profits) rather than simply an expense.

Structure, Properties, or Function? Throughout this productive period, if one were to ask a synthetic chemist what she or he did, the answer would usually have been some form of “I make molecules.” That is, the intellectual emphasis was on molecular *structure*. In large-scale industrial chemistry, of course, properties (adhesion strength, corrosion resistance, tensile modulus) were often practically more important than structure. But for both, “function” – the ability of the molecules to *do* something – was largely left to others. A key question for the future of synthesis will be “is the target of the synthetic program a structure, a material with properties, or a solution to a problem in function?” If “function” is the objective, then the simplest (or perhaps simply least expensive) synthesis – not the most elegantly complicated – that provides this function will be the best. It is not what Woodward had in mind.

In a sense, this question of structure, properties, or function has always been one part of Organic Synthesis: that is, the balance between the aesthetics of natural product synthesis, and the potential utility of the methods it produces for the broader field of synthetic chemistry. And even with the complex natural products designed for programs in medicinal chemistry, the point was seldom just to make a specific compound. More often, that compound was the starting point for a program of structural variation designed to provide range of molecules for medicinal and clinical development, but the Organic Synthetic design and methods provided the engineering blueprint for this development, and the final product was often an abstraction of features from the starting natural product. (Also, of course, the *best* route to a pharmaceutical often involved “non-Organic Synthetic” methods. Antibiotics, where fermentation synthesis still plays a major role, is an obvious example.)

During this post-war period federal support for academic research was plentiful, and – perhaps more importantly – there was a remarkably productive interplay between activities in

universities and in industry. The simplified short-story version of this period suggested that academic synthesis developed new strategies and methods; and industrial R&D carried out the difficult and essential engineering development required to solve problems. In fact, the interaction between university and industry was very much a two-way street, both intellectually and practically. Far from being simple users of an intellectual structure developed in academia, industry provided both problems and, particularly importantly, discoveries: using catalysis as an example, almost all of heterogeneous catalysis originated in the petrochemical industry, the Shell triolefin process was the initial discovery on the path to olefin metathesis,^[4] transition metal-catalyzed asymmetric synthesis was jointly developed in industry and university, and most metal-catalyzed oxidation reactions of simple hydrocarbons were originally developed in industry.

The closest collaborations (science, technology, and training of students and professional chemists) connecting Organic Synthesis and industrial synthesis has always been in medicinal chemistry,^[5] where providing useful quantities of lead structures required practical synthesis of complex structures. Interestingly, as economics has become more important in the pharmaceutical industry, most of the largest volume (in terms of prescriptions) drugs are now molecules of only intermediate complexity. Examples (from lists of most-prescribed drugs) include Levothyroxine (Synthroid, and others), Rosuvastatin (Crestor), Albuterol (ProAir HFA, and other), Esomeprazole (Nexium), Fluticasone (Flonase Allergy Relief, and others), Lisdexamfetamine (Vyvanse), Pregabalin (Lyrica), Tiotropium (Spiriva), and Sitagliptin (Januvia). Examples of problematic products of organic synthesis (which also are societally important) are synthetic opioids (fentanyl, Oxycodone), and agricultural chemicals (neonicotinoids, organophosphorus insecticides).

“Organic Synthesis” in Electronics Fabrication. In the context of industrially-relevant synthesis, it is, however, good to remember that there are also other kinds of “synthesis.” As one example of a technology even more important than that used by the pharmaceutical industry – microelectronics – the processes involved in the fabrication of chips – from Czochralski growth of crystalline silicon,^[6] through chemically amplified photoresist (originally developed by Willson and Frechet, then at IBM),^[7] to liquid crystals for display^[8] – are all “synthesis.” Shouldn’t these types of *functional* targets – targets based on functional design but requiring synthetic development – also be included in future directions for “Organic Synthesis?”

Innovation

One measure of the health of a scientific field is its ability to generate new ideas (as opposed to extensions of already established themes), and to reinvent itself. A familiar idea in discussions of innovation is that it comes in different forms: for example, innovation can focus on *new technology* (where

organic synthesis has tended to shine), or on *new processes* (where the most innovative work has often been done by process-development groups in industry), or *new business plans* (for example, the decision by China to make low-cost capital available for production of silicon-based solar cells – a decision that has been enormously important in accelerating the implementation of solar energy). The question facing organic synthesis is not “has the need for new methods of syntheses disappeared?” but rather “What *problems* – intellectual, empirical, or practical – most require new ideas in synthesis?” Is the future for more of the familiar – what Kuhn called “ordinary science”^[9] – or for something more radical, more important, more different fundamentally? (More, perhaps, having the audacity of what Woodward, Eschenmoser, and others suggested and demonstrated 50 years ago?)

Organic chemistry, of course, has continued to innovate, and this innovation has largely required some form of organic synthesis. There are, of course, also substantial structural changes occurring in the broad subject of organic synthesis. These changes are not, however, necessarily closely aligned with the style of Organic Synthesis as it has currently evolved. I sketch five examples:

Non-covalent Synthesis: A Simpler Route to Molecular Complexity. One new direction has shifted the focus of a form of synthesis away from forming *covalent* bonds, and toward *non-covalent* synthesis (also called, variously, “molecular self-assembly,” “supramolecular chemistry,” or “molecular recognition”). This interest is, of course, at least partially motivated by the strategy used repeatedly in living cells: that is, use of a limited set of highly efficient and high-yield catalytic reactions to make macromolecules, but then to involve, crucially, *non-covalent* processes to allow these biopolymers to fold, or associate, into functional structures. How important this still-developing field is (outside of biochemistry and biology), is a matter of perspective, but its interest is unquestionable.

There were three original motivations for studying self-assembly: i) *Biochemical processes*: Obvious examples are the complementary pairing of oligonucleotide sequences, folding of proteins, recognition of proteins by both small-molecule ligands and by other proteins, and formation of lipid bilayers. The fact that much of academic work in molecular self-assembly has been carried out in weakly solvating organic solvents simplifies the problem, but makes the research of doubtful direct relevance to biochemistry, or to *any* reactions in water. ii) *Familiar chemical processes*. Crystallization is the prototypical (and still poorly understood and unpredictable) example of self-assembly. The functional properties of detergents, emulsifiers, foaming agents, and surface-active molecules also all involve molecular self-assembly. Many of the properties of polymers (especially importantly, mechanical properties) reflect the same non-covalent interactions (e.g., formation of networks of hydrogen bonds in polyamides). iii) *Surface Science*. Formation and properties of liquid crystals have been examined extensively for liquid-crystal displays,^[10] and self-assembled monolayers (SAMs) are monolayer films

that form by quasi-crystallization of organic ligands on the surface of metals and metal oxides.^[11]

Modern interest in self-assembly started with studies of complexation of metal ions (especially potassium) by crown ethers and antibiotics such as Monensin, and other molecular aggregates organized around metal cations (e.g., cryptands) and has progressed to more elaborate studies: some organic systems (for example, melamine and cyanuric acid) are very attractive models.^[12–14] The original work by Pederson, Cram, and Lehn made the case that non-covalent chemistry could be used rationally to organize large aggregates of atoms,^[15] and subsequent studies (e.g., of SAMs) illustrate the ability to organize individual, easily synthesized molecules into structured (and enormous, by single-molecule standards) aggregates, with densities of $\sim 10^{14}$ molecules/cm² of surface, with little effort. Research in this area continues, with extension into 3D structures (e.g., metal-organic frameworks, or MOFs).^[16,17]

Although research in this area has demonstrated that self-assembly is a strategy that succeeds in making structured molecular aggregates much larger than is possible by classical covalent organic chemistry, and correlated structures of the aggregates with their properties, *new* functions of these aggregates have been slow to emerge. They nonetheless establish non-covalent reactivity as a method for assembling large, structured molecular aggregates, and their ubiquity in biology indicate that when it becomes possible to design function as easily as it is to design structure, this class of compounds will become very important.

Chemical Synthesis and Chemical Engineering: Fusion, or Separate Evolution?

Another possible direction for the future evolution of Organic Synthesis is, in effect, to fuse (at least in part) with Chemical Engineering, and use the techniques of that area to simplify processes, to incorporate a broader range of reaction types (and thus to expand the range of *targets* for synthesis), and – crucially – to introduce the element of applied mathematics that may become an integral part of even routine organic synthesis. A number of groups are developing *Continuous Flow Synthesis*, in which sequences of reactions are optimized collectively, rather than individually, as continuous processes with little or no isolation of intermediates.^[18–23] This type of optimization is an interesting approach to improving purity and yield, and may contribute to smaller scale, production synthesis (for example, on-demand drugs).^[24] *Enzyme-Catalyzed Synthesis* has become firmly established – largely in process chemistry – for certain types of reactions.^[25] In three examples drawn from reactions at different scales, Wong has demonstrated the unique value of cofactor-requiring synthesis in complex carbohydrates,^[26] simple phosphatases are used in agricultural chemistry (for example, to hydrolyze the C–O–P bonds of inositol phosphate), and the conversion of acryloni-

trile to acrylamide by enzymatic hydrolysis is preferred over catalytic hydrolysis for its selectivity.^[27] Enzymes are also, of course, integral (albeit on small scales) to selective transformations of nucleic acids, and (on large scale) for processing of starch. These are transformations that are *important*, and entirely outside of the current scope of Organic Synthesis, as it is normally defined. Synthesis in genetically engineered living organisms is now possible for a broad range of compounds: propane-1,3-diol can be made on $> 10^6$ kg/year scale from glucose (DuPont), and a precursor to artemisinin on industrial scale, both using living cells. Fermenters – often using insect (and other eukaryotic) cells – are, of course, used routinely for production of the antibodies and other proteins (human insulin, erythropoietin, and many others) used in biopharmaceuticals.

The fact that biological processes have become a major part of synthesis – from research demonstrations to commodities is not new. What is interesting is that these methods have been largely ignored by the community of specialists interested in Organic Synthesis, but have been embraced by chemical engineers. As chemistry increasingly turns toward biology, and as broad classes of biologically derived molecules are synthesized using biological methods, it is not evident (to me) why *all* catalysts and processes are not worth exploitation in Organic Synthesis. Why is platinum on carbon a “legitimate” catalyst, and a phosphotransferase not?

Three other areas of synthesis have also been developed largely by chemical engineers. Electrochemistry is one;^[28] synthesis under “extreme” conditions (high temperatures and pressures) is a second;^[20,29] photochemistry is a third.^[30,31] All provide capabilities that cannot be achieved by conventional organic reactions, and each is relevant to a world in which more and more activity may focus on electrically driven transformations, and in which new approaches are needed for transformations of starting materials that have been largely ignored in the past (especially CO₂ and CH₄).

Materials: Pure Function

Materials science presents a class of problems to synthesis that are less far from fine-chemical synthesis than they might seem. Synthesis of commodity polymers is probably a solved problem, but new polymers with unusual properties is an exciting area at the border between chemistry and materials science. ATRP and ROMP have demonstrated that there *are* new approaches to the synthesis of polymers.^[32,33] Biological methods offer routes to all biopolymers. The flood of new methods in nanotechnology has relied on methods taken from self-assembly, supramolecular chemistry, and colloid and surface science to make structures of many previously unknown types. The full range of carbon-based structures – carbon black, carbon fiber, C₆₀, carbon nanotubes, graphene, and diamond – have all been synthesized, have all involved formation of C–C bonds, and have all used methods developed independently of Organic Synthesis.

Materials science has the stimulating feature that it is almost entirely focused on function rather than structure. As a result, it should allow synthetic chemists a very large range of opportunities to try new ideas.

Catalysis: Chemistry and Controlling Reactions

Catalysis is an exceptionally interesting problem. One can argue that chemistry is – in a sense – mostly catalysis, and “life” – as a dynamic, dissipative process – is almost *entirely* catalysis. Given its importance, it is astonishing how difficult it has been to discover fundamentally new classes of catalysts, and even to mimic and extend the structures already known. Heterogeneous catalysis remains almost entirely an empirical art, with mechanisms of action that are astonishingly complex (for an example, see the mechanism of the Sohio 21 catalyst,^[34] which catalyzes the conversion of propylene to acrylonitrile). The range of remarkable organic transformations buried in the industrial patent literature is enormous, and very little of it has made its way into academic synthetic practice (in part because it often involves unfamiliar reaction conditions, and catalysts that are not commercially available). This trove of exhaustive industrial empiricism is there to be discovered by enterprising academics! The field of homogeneous organometallic catalysis was also originally largely an industrial invention, although it has subsequently been the subject of enormous academic extension.

Although catalysis by metals has been a central theme in organic chemistry for decades, it has tended to focus on a limited number of subjects. There is still almost no progress in mimicking the characteristics of enzymes or ribozymes, and the broad field of catalysis in water is astonishingly underexplored. Larger-scale problems – catalysis in complex systems such as oceans and atmospheres – is not a part of organic synthesis, although much of the catalysis that is involved (reactions of hydrocarbons with oxidizing agents and sunlight) are certainly organic.

Synthetic Biology

This area is in a state that is, in a sense, the opposite of classic organic synthesis: It has unlimited opportunity, and a universal but constrained set of synthetic tools based on genetic engineering and metabolism.^[35,36] Organic Synthesis has a limited range of new opportunities, but great freedom to try new ideas. There *has* to be opportunity in between these subjects.

The central issue is that most of the molecules of current interest in synthetic biology – for cancer, and even more, for manipulation of the immune system – are proteins (especially antibodies, receptors, molecules in signaling pathways) – and genomic sequences. The techniques of this area are almost orthogonal to those used in Organic Synthesis, but are becoming more accessible (for example, CRISPR/Cas9 has

made gene editing dramatically easier, and site-specific mutagenesis is increasingly routine).^[37] That said, the current focus, (and one that will doubtless endure for the foreseeable future), is molecules targeting checkpoints in the immune response: for example, as inhibitors of CTLA4, PD1, and a rapidly-expanding group of similar entities).^[38] Are there small molecules effective in immunomodulation? Certainly, and some are known, but more would be valuable.

In addition to drugs active against mammalian immune targets, there are at least two major classes of scientific problems dealing with microorganisms (problems concerning microbiomes and their interactions with the host,^[39] and the current race between antibiotics and the evolution of pathogen resistance^[40]).

The identification of biological targets, and the development of biologically-derived tools, probably have limited direct application in Organic Synthesis, but developing a new approach to the design and synthesis of small molecules active against these new classes of biological targets that would combine organic synthetic and biological tools, could create something genuinely new. And such techniques, almost incidentally, should make it easier for organic chemists without long experience in biology to engineer organisms to make intermediates (especially chiral intermediates, since chirality is of such interest to developers of new synthetic techniques). The truly dramatic work of Schultz demonstrating the expansion of the genetic code,^[41] and the demonstrations by Bertozzi of the usefulness of ordinary organic reactions in labeling living cells,^[42] provide examples.

Changes in the Environment for Organic Synthesis

Constraints on Future Synthesis. The evolution of Organic Synthesis is constrained, to an extent, by the evolution of the broader chemical industry. If synthesis is to have a chance of taking the step from an academic exercise to a practical process, it must deal with at least five important issues: i) Environmental concerns limit the types of solvents and catalysts (especially metal ions) that can be used. ii) The commoditization of even fairly demanding syntheses resulting from the global availability of skilled human resources (especially in the laboratories of fine-chemical and toll manufacturers in China and India) constrain the need for synthetic chemistry (and perhaps synthetic chemists!) in the U.S., Europe, and Japan. iii) The increasing pressure on prices for pharmaceuticals makes very complicated and very expensive structures less interesting commercially. iv) The societal and regulatory restrictions on the use of petroleum fuels raises questions for owners of refineries concerning the financial return on production of small-volume specialty products. v) Among the interests in large-scale chemistry is the possibility of new starting materials (e.g., glucose, cellulose, or CO₂, each for different reasons). This type of

chemistry has not historically been a focus of Organic Synthesis. vi) Social concern on even structurally simple compounds (Oxycontin, fentanyl, neonicotinoid insecticides and many others), and increasingly complicated requirements for registration of new (and old!) chemical entities makes commercialization of new specialty chemicals increasingly expensive and difficult, and thus unattractive commercially.

Are There New Ideas in “Organic Synthesis”?

This question is one that synthetic chemists are best qualified to answer. Certainly there is no question that some of the most important problems in Science, and in Chemistry, will require knowledge of organic synthesis and reactivity to answer. What are some?

Curiosity-Driven Research That Needs Organic Synthesis

Any list of this type is idiosyncratic. The following eight are among my favorites, but there are many others. i) *Origin of Life*. So far as we know, life started spontaneously on earth, probably by self-assembly (whatever that means in this context) of *reactions* (not necessarily molecules) occurring spontaneously in the prebiotic environment (with the supposition that geochemistry – chemical transformations occurring in water circulating through the sub-surface) catalyzed by minerals played an important role. How? We don't know. ii) *Sentience: How Do Reactions and Molecules become Thought?* Chemistry is only a part of this problem, but probably a very important part: the action of cells, including neurons, is based on molecular processes of a variety of sorts. But how this variety becomes sentience is again a problem with not even a hypothetical answer. iii) *High-throughput screening and Chemical Biology*. The values of high-throughput screens in genomics is clear, and the mixture of biochemical and chemical processes that make sequencing possible is flooding the world with genomic data. Proteomics, and especially the association of specific proteins with specific functions, is also making rapid progress. Interesting, high-throughput screening of small molecules – a strategy that originally seemed likely to produce useful information – has been more limited in its value. Why? Again, we don't know, but part of the issue may be that we have no theory suggesting how it should be done. How many different compounds, of how many different structural types, must be screened, to find – for example – a compound that would bind to an active site, or provide a starting point for further development toward a drug? Questions we presently cannot answer. iv) *Molecular Recognition in Water*. One of the enduring puzzles in molecular recognition and ligand design is why it continues to be so difficult to *design* ligands to bind in the active sites of proteins. Decades of effort by very competent modelers and

simulators has produced results that are interesting but not usefully predictive. Why? The answer is not known, but one strong possibility is that almost all such calculations omit water, in other than crude approximations. The hydrogen bonding networks in water are unique, and give it unique properties (especially in its balance of entropy and enthalpy). Understanding the interactions of water with the hydrophobic surfaces, and understanding enthalpy/entropy compensation, may be necessary steps in learning how to design and synthesize ligands to bind to active sites. v) *Sequence-specific polymers*. One of the marvels of biology is its strategy for storing and using information as a specific sequence of bases in DNA or RNA, and of generating the precisely controllable catalysis of enzymes (as sequences of amino acids). Learning how to make long polymers (500 to 1000s of monomeric units) with perfect control of sequence would open the door to exploring both non-biological information storage and catalysis.^[43] vi) *Chemistry of CO₂, CH₄, N₂, HCN and Other “Simple” Molecules*. These molecules have moved from being irrelevant to being centrally important. Carbon dioxide and methane are the major C₁ sources of carbon, and crucial parts of environmental maintenance. N₂ is an example of an important molecule with (aside from the Haber-Bosch process) little synthetic chemistry. It is also the source (as the precursor for ammonia) of most nitrogen chemistry. The work by Eschenmoser,^[44] and also by Sutherland and others,^[45–47] has demonstrated the extraordinary variety of molecules that can be made with HCN. The conversion of very simple molecules to complex ones has thus been reopened. vii) *Functional, Biocompatible Materials*. One of the exciting, emerging areas of complex systems is systems that fuse living and non-living components. Early work on this area has produced some remarkable successes (deep-brain stimulation,^[48,49] implanted insulin pumps,^[50] lens-,^[51,52] and tooth replacements,^[53] and so on). The materials science of materials intended for long-term residence in the body – particularly as *functional* components of devices and structures – is barely out of its infancy. viii) *Antibody-mimetics*. Antibodies remain among the most useful classes of proteins. The function for which they are often used is molecular recognition (although they have another activities), and the design and synthesis of molecules with the variety and structure to provide almost universal binding to proteins (especially) *in water* would be enormously useful. Why is it so difficult to design and synthesize structure-specific binding sites that function in water? We don't know, but this problem is one whose solution would be both instructive and very useful.

Computer Synthesis and Artificial Intelligence (AI): Promise and Threat. There is a final issue that may (or, I entirely believe, will) be important for Organic Synthesis, and especially for young synthetic chemists: that is, the role of computer systems, information technology, and automation in future synthetic chemistry.^[54,55] Synthetic chemists *are* expert systems: their skill in pattern recognition, and in ability to remember precedent, is phenomenal. It is, however, exactly

these sort of skills that are now developing in AI. How will this development change Organic Synthesis?

A number of efforts to develop computer-assisted synthetic methods have, of course, taken place in the past,^[56–59] but all were efforts based on organic chemists trying to codify what they knew. None has been particularly successful.

The recent effort by Grzybowski to develop a route-tracing program *does* seem to be useful in its ability to search enormous amounts of literature information for paths connecting reactants and products;^[60–62] whether (or how rapidly) it can be extended to “creative” synthetic design is unclear, but if AI systems can be creative in the games of Chess, and Go, and in medical diagnostics, handwriting recognition, and face analysis, and in many other complex areas, I am sure they will be creative in synthesis.

Why has it not already happened? Part of the problem is that it has not been worth the effort by the AI community to build the required databases. A bigger part is the supposition by organic synthetic chemists that they are the ones best qualified to design programs for organic synthesis. Not so! Although they are the “experts,” effective AI usually emerges from the work of skilled coders (*using* information from databases and experts), and not from experts who have tried to learn how to code. Perhaps as a result, or perhaps just through unfamiliarity with the explosive growth of AI in other areas, synthetic chemists are largely unaware of the promise (and perhaps threat to the established order) that it represents. The implicit argument is that “Computers will never replace us synthetic chemists. We know so much detail, and have such exceptional pattern recognition, that it just will not happen.” But, of course, what well-constructed AI systems do is recognize patterns and manage detail. And recent history suggests the tide is already coming in. AI, in combination with automation, is displacing pilots from airplanes, and drivers from cars, and doctors from diagnosis. They are agnostic about methods, can manage multiple fields, and access all the empirical data of the past.

This evolution – guided by experts in artificial intelligence more than by experts in synthesis – raises a very important point for students: *viz.*, for the future, will it be more important to understand AI than to be able to recall all the methods for introducing chiral centers (or other transformation of choice) from human memory? How should one balance computer skills and empirical synthetic skills?

My (Obviously Personal) Conclusions

Synthesis – Including Organic Synthesis – Remains an Essential Part of Chemistry, and of Science and Technology. The trick will be to find classes of problems that return complex synthesis (Organic Synthesis, perhaps in an evolved and more expansive and ambitious form) to a central role in the future of the field, rather than having it become an extraordinary specialty or craft, admired but occupying an increasingly isolated place as the rest of synthesis moves on.

The argument that complex synthesis, by itself, is *beautiful* is doubtless true, but also dangerous. Most societies have valued beautiful products of human imagination and skill, but paying to support the artists who produce them has been another matter entirely. And, unfortunately, the beauty of Organic Synthesis is not something that most non-synthetic-chemists can understand.

Technical expertise is not, by itself, enough to sustain a field (consider mechanical watchmaking or glass-blowing). To prosper, Organic Synthesis must also solve recognizable problems.

Natural Products Synthesis Is a Highly Developed Artform. It could be more. The same skills – applied to types of problems other than a limited class of natural products, and structurally similar molecules – could be revolutionary. Why not DNA-mimetics? Why not organic ferromagnets? Every area of science has to answer the simple question “Who cares?”

In the Future, Function Will Provide the Most Stimulating Scientific Directions, Not Structure. Organic Synthesis has focused on making structures. It is, admittedly, astonishing that it is possible to synthesize the structures that it has, but they are still often without value beyond their illustration of “What is possible.” Adding the requirement of “function” to aesthetic design and execution – or even making function the *primary* concern – would add a breadth and universality to Organic Synthesis that would move it back toward the center of chemical sciences and technology, and make it more broadly interesting – both to the practitioner and to the admiring observer. Learning something new is always stimulating.

For Students

What will be needed for future careers in synthesis? It is always difficult to predict where an already mature field will go, as it reaches for another direction. Newtonian physics become quantum physics. Empirical biology became genomics, immunology, and many other subfields. Where will synthetic chemistry go? What will be needed for future careers in synthesis?

My first hypothesis is that the skill of synthesis will always be invaluable, but the way in which it is used will determine its scientific impact. High-level Organic Synthesis is elegant, difficult, and esoteric. Adding “function” to the list of characteristics that a synthetic chemist should know – in whatever area, from electronics to medicinal chemistry – will make it more interesting and important to others, and also both require and allow learning new areas (some quite different than anything now considered a part of chemistry): electronics, materials science, biology, environmental science, economics, complex systems, geochemistry. It will add a requirement for breadth, perhaps at the cost of technical depth (since the mind, and memory, and attention, are limited resources).

And the prospect that synthesis (not just complex organic synthesis) may become a field that requires understanding – not just of function – but of appropriate forms of artificial intelligence, will paint the field in a new color. Will synthetic methods be recalled from memory, or will they live in look-up tables residing in the Cloud? Obviously, I don't know. But synthesis has often been taught on the "Apprentice" model – that is, a skilled senior chemist helps to train more junior chemists in a set of skills already familiar to him or her. This method has worked reasonably well in chemistry for several centuries, but changes across science – from cell biology and sociology to physics and astronomy – that demonstrate that the skills of the master are not the skills needed by the student are unlikely to leave chemistry untouched. Students may want to consider rethinking their education (especially advanced education) to include less synthetic depth and more non-synthetic breadth.

Acknowledgements

Drs. Brian Cafferty, Michael Fink, Lee Belding, and Amit Nagakar contributed to the development of this manuscript. It was supported by Mr. Chris Flowers, through the Woodford L. and Ann A. Flowers University Professorship.

References

- [1] R. B. Woodward, In *Perspectives in Organic Chemistry*; Todd, A. R., Ed.; Interscience Publishers: **1956**, p 155.
- [2] K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem. Int. Ed.* **2000**, *39*, 44.
- [3] G. M. Whitesides, *Angew. Chem. Int. Ed. Engl.* **2015**, *54*, 3196.
- [4] W. Keim, *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 12492.
- [5] Q. Michaudel, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* **2015**, *48*, 712.
- [6] J. Czochralski, *Z. Phys. Chem.* **1918**, *92*, 219.
- [7] H. Ito, *IBM J. Res. Dev.* **1997**, *41*, 119.
- [8] H. Kawamoto, *Proc. IEEE* **2002**, *90*, 460.
- [9] T. S. Kuhn, *The Structure of Scientific Revolutions*; University of Chicago Press, **1962**.
- [10] T. Uchida, *Jpn. J. Appl. Phys.* **2014**, *53*, 03CA02.
- [11] J. C. Love, L. A. Estroff, J. K. Kriebel, R. G. Nuzzo, G. M. Whitesides, *Chem. Rev.* **2005**, *105*, 1103.
- [12] Z. Liu, S. K. M. Nalluri, J. F. Stoddart, *Chem. Soc. Rev.* **2017**, *46*, 2459.
- [13] D. Aowicki, A. Huczynski, *Biomed. Res. Int.* **2013**, *2013*, 742149.
- [14] G. M. Whitesides, E. E. Simanek, J. P. Mathias, C. T. Seto, D. Chin, M. Mammen, D. M. Gordon, *Acc. Chem. Res.* **1995**, *28*, 37.
- [15] J. M. Lehn, *Chem. Soc. Rev.* **2017**, *46*, 2378.
- [16] O. M. Yaghi, H. Li, *J. Am. Chem. Soc.* **1995**, *117*, 10401.
- [17] J. J. Perry IV, J. A. Perman, M. J. Zaworotko, *Chem. Soc. Rev.* **2009**, *38*, 1400.
- [18] K. F. Jensen, *Chem. Eng. Sci.* **2001**, *56*, 293.
- [19] K. D. Nagy, B. Shen, T. F. Jamison, K. F. Jensen, *Org. Process Res. Dev.* **2012**, *16*, 976.
- [20] B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688.
- [21] J. C. Pastre, D. L. Browne, M. O'Brien, S. V. Ley, *Org. Process Res. Dev.* **2013**, *17*, 1183.
- [22] R. M. Myers, D. E. Fitzpatrick, R. M. Turner, S. V. Ley, *Chem. Eur. J.* **2014**, *20*, 12348.
- [23] S. Kobayashi, *Chem. Asian J.* **2016**, *11*, 425.
- [24] A. Adamo, R. L. Beingessner, M. Behnam, J. Chen, T. F. Jamison, K. F. Jensen, J.-C. M. Monbaliu, A. S. Myerson, E. M. Revalor, D. R. Snead, T. Stelzer, N. Weeranoppanant, S. Y. Wong, P. Zhang, *Science* **2016**, *352*, 61.
- [25] U. T. Bornscheuer, G. W. Huisman, R. J. Kazlauskas, S. Lutz, J. C. Moore, K. Robins, *Nature* **2012**, *485*, 185.
- [26] K. M. Koeller, C. H. Wong, *Nature* **2001**, *409*, 232.
- [27] H. Yamada, M. Kobayashi, *Biosci. Biotechnol. Biochem.* **1996**, *60*, 1391.
- [28] M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230.
- [29] D. Cantillo, H. Sheibani, C. O. Kappe, *J. Org. Chem.* **2012**, *77*, 2463.
- [30] N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052.
- [31] M. H. Shaw, J. Twilton, D. W. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898.
- [32] K. Matyjaszewski, *Macromolecules* **2012**, *45*, 4015.
- [33] C. W. Bielawski, R. H. Grubbs, *Prog. Polym. Sci.* **2009**, *297*.
- [34] M. Jacobs, *Chem. Eng. News* **1996**, *74*, 40.
- [35] J. D. Keasling, *ACS Chem. Biol.* **2008**, *3*, 64.
- [36] M. J. Smanski, H. Zhou, J. Claesen, B. Shen, M. A. Fischbach, C. A. Voigt, *Nat. Rev. Microbiol.* **2016**, *14*, 135.
- [37] F. Jiang, J. A. Doudna, *Annu. Rev. Biophys.* **2017**, *46*, 505.
- [38] A. H. Sharpe, *Immunol. Rev.* **2017**, *276*, 5.
- [39] I. Cho, M. J. Blaser, *Nat. Rev. Genet.* **2012**, *13*, 260.
- [40] J. M. Blair, M. A. Webber, A. J. Baylay, D. O. Ogbolu, L. J. Piddock, *Nat. Rev. Microbiol.* **2015**, *13*, 42.
- [41] L. Wang, A. Brock, B. Herberich, P. G. Schultz, *Science* **2001**, *292*, 498.
- [42] E. M. Sletten, C. R. Bertozzi, *Acc. Chem. Res.* **2011**, *44*, 666.
- [43] J. F. Lutz, M. Ouchi, D. R. Liu, M. Sawamoto, *Science* **2013**, *341*, 1238149.
- [44] A. Eschenmoser, *Angew. Chem. Int. Edit* **2011**, *50*, 12412.
- [45] B. H. Patel, C. Percivalle, D. J. Ritson, C. D. Duffy, J. D. Sutherland, *Nat. Chem.* **2015**, *7*, 301.
- [46] C. Butch, E. D. Cope, P. Pollet, L. Gelbaum, R. Krishnamurthy, C. L. Liotta, *J. Am. Chem. Soc.* **2013**, *135*, 13440.
- [47] J. Oró, *Biochem. Biophys. Res. Commun.* **1960**, *2*, 407.
- [48] G. Hong, X. Yang, T. Zhou, C. M. Lieber, *Curr. Opin. Neurobiol.* **2018**, *50*, 33.
- [49] J. Liu, T.-M. Fu, Z. Cheng, G. Hong, T. Zhou, L. Jin, M. Duvvuri, Z. Jiang, P. Kruskal, C. Xie, Z. Suo, Y. Fang, C. M. Lieber, *Nat. Nanotechnol.* **2015**, *10*, 629.
- [50] J.-L. Selam, P. Micossi, F. L. Dunn, D. M. Nathan, *Diabetes Care* **1992**, *15*, 877.
- [51] F. J. Ascaso, V. Huerva, *Optom. Vis. Sci.* **2016**, *93*.
- [52] J. Pandey, Y. T. Liao, A. Lingley, R. Mirjalili, B. Parviz, B. P. Otis, *IEEE Trans. Biomed. Circuits Syst.* **2010**, *4*, 454.
- [53] M. Oshima, K. Inoue, K. Nakajima, T. Tachikawa, H. Yamazaki, T. Isobe, A. Sugawara, M. Ogawa, C. Tanaka, M. Saito, S. Kasugai, T. Takano-Yamamoto, T. Inoue, K. Tezuka, T. Kuboki, A. Yamaguchi, T. Tsuji, *Sci Rep. Uk.* **2014**, *4*, 6044.
- [54] A. Aspuru-Guzik, R. Lindh, M. Reiher, *ACS Central Science* **2018**.
- [55] S. V. Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio, R. J. Ingham, *Angew. Chem. Int. Ed. Engl.* **2015**, *54*, 10122.
- [56] E. J. Corey, W. J. Howe, D. A. Pensak, *J. Am. Chem. Soc.* **1974**, *96*, 7724.

- [57] D. E. Lushnikov, N. S. Zefirov, *J. Chem. Inf. Comput. Sci.* **1992**, 32, 317.
- [58] A. K. Long, J. C. Kappos, S. D. Rubenstein, G. E. Walker, *J. Chem. Inf. Comput. Sci.* **1994**, 34, 922.
- [59] W. Zhang, M. Binns, C. Theodoropoulos, J.-K. Kim, R. Smith, *Ind. Eng. Chem. Res.* **2015**, 54, 4603.
- [60] C. M. Gothard, S. Soh, N. A. Gothard, B. Kowalczyk, Y. Wei, B. Baytekin, B. A. Grzybowski, *Angew. Chem. Int. Ed.* **2012**, 51, 7922.
- [61] M. Kowalik, C. M. Gothard, A. M.; Drews, N. A. Gothard, A. Weckiewicz, P. E. Fuller, B. A. Grzybowski, K. J. M. Bishop, *Angew. Chem. Int. Ed.* **2012**, 51, 7928.
- [62] P. E. Fuller, C. M. Gothard, N. A. Gothard, A. Weckiewicz, B. A. Grzybowski, *Angew. Chem. Int. Ed.* **2012**, 51, 7933.

Received: February 12, 2018

Accepted: February 12, 2018

Published online on February 20, 2018