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ILLUSTRATIONS BY DAVID PARKINS

Why synthesize?

Philip Ball ponders the many reasons that chemists make molecules, and weighs what is lost, and gained, when they don't.

Why do chemists make molecules? The obvious (and true) answer is: because we need them. That is why chemical synthesis is still vibrant, and will continue to supply the drugs, materials and commodities of the twenty-first century. Every year brings its bounty. In 2015, chemists published a new and elegant route to the anticancer drug paclitaxel (Taxol)[1], and syntheses of a nodulisporic acid that might act as an insecticide[2] and, in this journal, of an anti-HIV alkaloid[3].

There are also less utilitarian reasons for making molecules. One chemist might want to explore theoretical questions, such as what constitutes a bond. Another might delight in, and be curious about, the variety of shapes and structures that molecules can have. That diversity of purpose is how it should be. For at the root of the impulse to build molecules is a deep, cherished belief that arguably distinguishes chemistry from other sciences: that there is an art in making, worth nurturing for its own sake.

Chemical synthesis can entail many things — minor modification of existing molecular frameworks, for example, or making new materials. Total synthesis — the complete construction of a complex (often natural) molecule from simple reagents — has long been seen as the epitome of the art. But some say that the age of monumental projects to make complicated molecules is waning. These long and expensive procedures may produce tiny yields of the target molecule. And now there are automated methods that put molecules together; eventually, even the synthetic route might be planned automatically.

So, could bespoke, elaborate synthesis become a boutique rarity akin to the handcrafting of books in the age of e-readers and print-on-demand? And if synthesis is relegated to a routine, should chemists be worried?

Chemists periodically revisit (and revile) the argument over whether total synthesis is moribund, generally with more heat than light. It's the wrong argument. Both the methods and motives of chemistry are evolving fast. We should be focusing on how synthesis responds. That response may be driven partly by pragmatism. But synthesis also has pedagogical and — unusually in a core scientific discipline — aesthetic dimensions that must be factored into the equation. There are several possible reasons to make ▶

complex molecules by total synthesis. A century ago the aim was often to identify a molecular structure, as in Robert Robinson's classic work on the synthesis of strychnine in the 1940s: if you know what happens at each step, you know what the end result looks like. That motive has vanished, however, thanks to advances in structural analysis, especially crystallography and nuclear magnetic resonance spectroscopy.

Another reason that chemists synthesized natural products was because of their useful properties. Molecules could be cheaper to make from scratch than to extract painstakingly from rare organisms. The total synthesis of the dye indigo in the 1870s that led to the collapse of the cultivation of the indigo plant is a canonical historical example.

Today, most wholly synthetic routes to complex natural products are too complicated to be useful in themselves to the pharmaceutical industry. Even the celebrated total synthesis of paclitaxel in 1994 was never seriously expected to lead to a commercial route (it is now made semi-synthetically from a natural precursor, or by fermentation). But total synthesis of a natural product can give chemists access to non-natural derivatives that might have pharmacological effects — as, for example, in the discovery of new antibiotics.

What's more, the grounding in synthetic chemical methods provided by making a complex natural molecule from scratch is said to equip students with the practical skills that industry requires. Synthesis also cultivates an understanding of the basic principles of chemistry: how and why reactions occur, the relationships between molecular shape and function, and so on. An ability to synthesize molecules remains essential training for the next generation of chemists; it is simply part of the indispensable core of the subject. By the same token, a lack of drawing skill does not make an artist bad but it makes them limited.

Perhaps that's why chemists with synthesizing skills are often said to get jobs in the pharmaceutical industry most easily. What is less clear is whether these skills can be learnt only by tackling fiendishly complicated structures. Indeed, Derek Lowe at Vertex Pharmaceuticals in Boston, Massachusetts, argues that drug companies value not the synthetic prowess per se but the concomitant ability to solve problems fast — and to cope with the inevitable disappointments, because most drugs, like most organic reactions, do not work without a lot of tinkering.

George Whitesides at Harvard University in Cambridge, Massachusetts, raises a different concern. He worries that training US graduate students to do organic synthesis when most of it is now being done in China, risks equipping them for jobs that do not exist. In this view, molecule-building is just another kind of manufacturing technology: if it can be done more cheaply elsewhere, it is best not even to try to compete, just to outsource.

In any case, the utility of resulting skills and products is only part of the argument advanced for why chemical synthesis matters. Great synthetic chemists of the mid-to-late twentieth century, such as Robert Woodward and Elias Corey, are revered not so much for what they made but for how they made it: for the way they refined the art. Woodward argued[4] that an innate aesthetic appeal is involved: "The unique challenge which chemical synthesis provides for the creative imagination and the skilled hands ensures that it will endure as long as men write books, paint pictures, and fashion things which are beautiful, or practical, or both."

These notions are part of the lore of the field. Milestones of synthesis are recounted in heroic terms, their pathways examined step by step as exemplars of elegant strategy. The comparison is often made with games of chess: victory is seen as a triumph of personal style and flair. One team of expert total synthesizers has more recently justified the pursuit by saying[5] that it "demands the following virtues from, and cultivates the best in, those who practice it: ingenuity, artistic taste, experimental skill, persistence, and character … its dual nature as precise science and fine art provides excitement and rewards of rare heights". The baroque carbon frameworks that still grace the pages of chemistry journals are often presented with a virtuoso flourish.

"Like architecture, chemistry deals in elegance in both design and execution."

BUILD IT WELL

Nonetheless some chemists feel that total synthesis of large and complicated natural products has now become a scaling of peaks just because they are there — with, moreover, a meaningless race to the summit that is often won by brute force. Lowe calls this the "human-wave-attack style" of making gigantic natural products, which, he jokes, ends in papers reporting the total synthesis of a molecule that no one much cares about, "made in a way you'd figure would probably work, using reactions everyone already knows".

He contends that useful chemistry — a new method of making bonds, say — is rarely discovered along the way, partly because the field is so competitive. No one is going to dawdle to search for clever shortcuts if they can just follow tried and tested paths. When some enormous and intricate natural product becomes the next Everest, elegance is sacrificed for speed, and ingenuity for graduate-student hours, Lowe says.

Advocates of total synthesis retort that priority races and showboating — who can make the hardest molecule fastest — are less common now. The aim is no longer just to build the desired structure but to build it well. For example, chemists seek a route that is economical in atoms (producing few waste products and side reactions), environmentally friendly and sustainable. As Steven Ley of the University of Cambridge, UK, put it in 2007 after completing a 22-year effort to synthesize the complicated natural insecticide azadirachtin, "I don't have to be first; the elegance of the approach is what interests me" (see *Nature* **448,** 630–631; 2007).

Thanks to the efforts of the giants of synthesis past and present, almost any molecule can now be made in principle. The question is whether it can be made in a practical and fruitful way.

COLLECTIVE COMPLEXITY

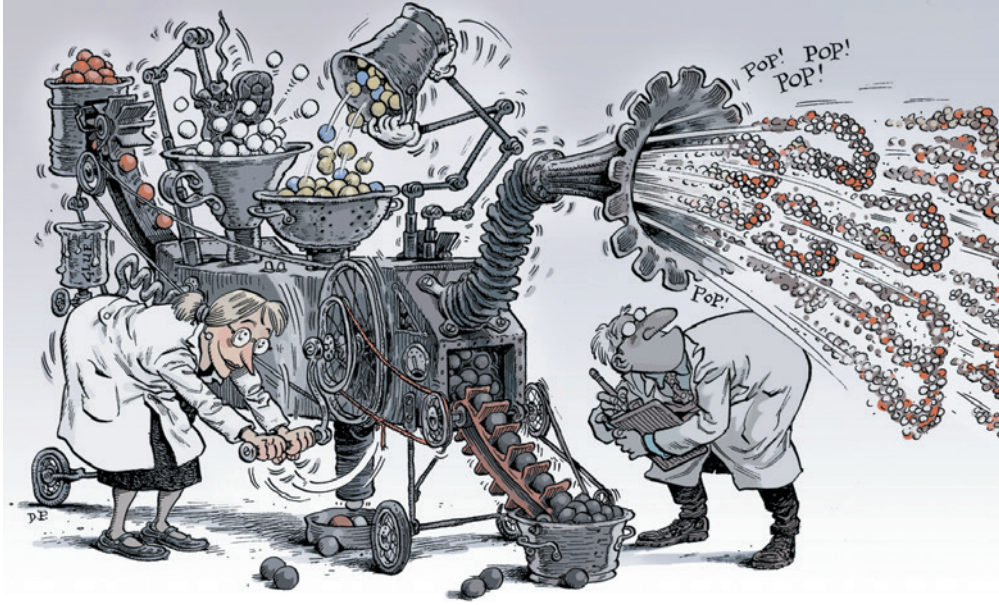
To some chemists then, making complex molecules for their own sake no longer seems the pinnacle of craft. That arguably reflects changes in the objectives of chemistry as a whole. Whitesides has suggested[6] that if chemistry is regarded as a science of atoms and individual molecules, then its low-hanging fruits are gone. The future of chemistry, according to him, lies with complex molecular systems that display collective properties and functions at a range of size scales. This may be the only means by which chemistry can fulfil its obligations in areas ranging from medicine to materials, energy and information.

Take the much bewailed drying-up of the drugs pipeline. Although the reasons are complicated, one factor could be that the old model of developing and refining a single drug molecule by a long process of screening and clinical trials is no longer the best option. The future of molecular medicine might instead include suites of molecules performing operations in concert, as biomolecules do in the cell. This, after all, is how the transformative gene-editing technique of CRISPR–Cas9 works.

Moreover, the complexity and versatility of life's molecules come not from a huge array of synthetic substrates and reactions, but from combinations of a rather small set of parts, assembled through a limited arsenal of bond-forming processes and guided by natural selection. Certainly, natural products of extreme intricacy can result. But theoretical and experimental surveys of 'chemical space' — the astronomical array of possible molecules — give no reason to think that ornate solutions are essential or unique.

Complicated natural products with synthetically challenging frameworks do not tend to feature in nature's methods of making or transforming energy, replicating, information processing, locomotion

or much else. Work like that of David Liu and collaborators at Harvard[7] shows that nature's synthetic principles of information-guided templating coupled to variation and selection might be a productive way to make useful synthetic molecules. In fact, that approach has also yielded new ways of assembling them[8]: new bond-forming chemistry, which was found by explicitly looking for it and not by hoping that it would emerge in the course of scaling a molecular Eiger. Such work suggests that, even though molecule-building is sure to remain a crucial part of the chemical enterprise, conventional organic synthesis need not be the only, or even the best, way to do it.



AUTOMATING THE ART

One of the common criticisms of total synthesis is that it rarely offers a route that the chemical or pharmaceutical industries can use: it takes too long, there are too many steps, the yields are too low and the costs too high. If you want to make a complicated molecule, do you really need an army of dedicated graduate students working through the night? Or could it be done by machine?

Automated synthesis is already possible for peptides and nucleic acids, which can be obtained by mail order with essentially any sequence. Oligosaccharides are also yielding to this approach. As a result we have lucrative peptide and oligonucleotide drugs, and glycoprotein drugs are on the way. Work[9] by Martin Burke at the University of Illinois at Urbana–Champaign suggests that a great variety of small and medium-sized organic molecules could be made this way too.

Burke uses a single, general-purpose reaction to assemble carbon-framework building blocks. He deploys the Suzuki coupling, in which a boronic acid substituent on one carbon reacts with a halogen substituent on the other in the presence of a palladium catalyst. The crucial trick is first to control this process for stepwise assembly[10], and then to automate the procedure by trapping the products of each step on silica beads to extract and release them for the next step. It is not by any means possible to build everything this way. But the method gives access to an impressive array of molecules rapidly and cheaply at the push of a button. Burke and his colleagues have used it to make less toxic derivatives of the antifungal natural product amphotericin B.

Automation is nothing new. Microfluidic flow processes for conducting multistep syntheses without the need for purification at each step have been used for at least a decade. And with a small repertoire of standard, reliable bond-forming reactions, even the synthetic strategy itself could conceivably now be planned by machine.

The idea that synthesis could become the workaday cranking-out of any structure is disturbing to anyone brought up to regard it as an art. It seems akin to the notion that artificial intelligence will one day compose our music and write our novels. But the 'art' of chess has been overtaken by brute-force number-crunching. There is no fundamental reason why chemical synthesis should be any different — nor, in fact, why machine-learning should not one day find superior, smoother and more efficient synthetic strategies than we can intuit (see *Nature* **512,** 20–22; 2014).

If that happens, some magic would be lost. But there could be practical gains. Today we need to make many molecules fast, to outpace the rise of antibiotic resistance, for example. This is acknowledged by the Dial-a-Molecule project, funded since 2010 by the UK Engineering and Physical Sciences Research Council, which aims to extend the assembly-line principle of oligonucleotide synthesis to any small organic molecule.

The project's vision is that "In 20–40 years, scientists will be able to deliver any desired molecule within a timeframe useful to the end-user, using safe, economically viable and sustainable processes" (see www.dial-a-molecule.org). It aims to use computer algorithms to devise the best route for making a target molecule with a suite of 'click' reactions, which are efficient, predictable and dependable. The goal is to make any given molecule in a matter of days.

Easier synthesis could free chemists to think creatively about molecular design: to focus on the question of what is worth making. That is currently the other big obstacle to effective drug discovery. As Burke explains, we do not yet know the rules that nature uses to 'design' complex natural products, in large part "because the process of trial and error in this complex chemical space is very slow due to barriers to synthesis".

HUMAN ENDEAVOUR

Chemistry, then, shares a great deal with conventional manufacturing: it changes through innovations in design and fabrication. We don't make cars or televisions the way we used to, so why should molecules be any different? We need to avoid romanticizing an imagined bygone age, as the designer William Morris harkened back to the folk crafts of a fictitious Middle Ages.

Better than making molecules more complicated or larger is making them more useful, and making them in more useful ways. Like architecture, chemistry deals in elegance in both design and execution. There has not been enough discussion of these aspects of the science: how they are manifested, how they motivate, how much they are worth conserving.

In contemplating automated synthesis, for example, a comparison from mathematics comes to mind. There is debate over whether a mathematical proof should be celebrated for its own sake, regardless of method, or for its elegance and form — how it was done. Does 'proof by machine' count? Such questions go to the heart of science as a human endeavour. We tell ourselves that the goals are knowledge and capability. But there are other things we value in it too. ■

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For a list of further reading on this topic, see go.nature.com/xrsdms.