NANOTECHNOLOGY

A molecular assembler

The idea of nanometre-scale machines that can assemble molecules has long been thought of as the stuff of science fiction. Such a machine has now been built — and might herald a new model for organic synthesis. SEE LETTER P.374

T. ROSS KELLY & MARC L. SNAPPER

In 1986, the futurist K. Eric Drexler published *Engines of Creation: The Coming Era of Nanotechnology*[1], in which he laid out his vision for the field that became nanotechnology. *Engines* fired many imaginations, including that of one of the current authors[2] (T.R.K.), but the big picture of Drexler's vision also drew well-founded criticisms[3,4] because some of the details were incompatible with real-world constraints. One element of this vision attracted particularly strong censure[5]: the concept of "molecular assemblers" — nanomachines that "will serve as improved devices for assembling molecular structures". On page 374, Kassem *et al.*[6] report a non-biological example of what could be regarded as a molecular assembler.

The authors' machine is a molecule that can be reversibly switched between two assembly modes, designated as left-handed and right-handed, by the addition of a proton (a hydrogen ion, H^+) or its subsequent removal (Fig. 1). The multistep assembly process is initiated by the attachment of a substrate molecule to the assembler. The substrate is then 'primed' in a second step, readying it to take part in reactions.

Next, two chemical groups are attached to the substrate in separate steps, but the precise outcome of these reactions depends on whether the assembler has been switched to its left- or right-handed mode. Four different products can thus be made, depending on the sequence of reactions and switching steps. A useful analogy is the pattern of a necklace of coloured beads, which depends on the order in which the beads are strung. The products are stereoisomers — molecules that contain the same set of atoms connected identically in two dimensions, but arranged differently in three dimensions.

The product is released from the assembler at the end of the assembly process, typically as the seventh step. The individual steps sometimes lead to mixtures of products that only favour a particular stereoisomer, rather than producing it uniquely, but this is often the case in the development of new reactions. Future improvements should overcome this limitation.

The chief appeal of molecular assemblers is the long-term prospect of streamlining organic synthesis. Currently, most organic synthesis is carried out in stepwise processes. A chemist mixes a commercially available starting material with reagents and solvent in a flask, sometimes along with a promoter or a catalyst that can control the outcome of the reaction, such as which stereoisomer forms. When the reaction is complete, the chemist isolates the product and usually needs to purify it. That product is then put into a fresh flask to undergo the next reaction in the synthetic pathway. Syntheses requiring 10–30 reactions are commonplace.

The overall process is therefore time-consuming, inefficient and expensive. The extent of the problem is demonstrated by the fact that most pharmaceutical companies have stand-alone groups of chemists whose sole task is to develop efficient ways to synthesize drug candidates on a kilogram scale — a process that takes months or years for each candidate.

By contrast, the virtues of the authors' assembler are that each product is made in one flask, without the need for purification steps after each assembly step; and that each of the four products can be made efficiently using

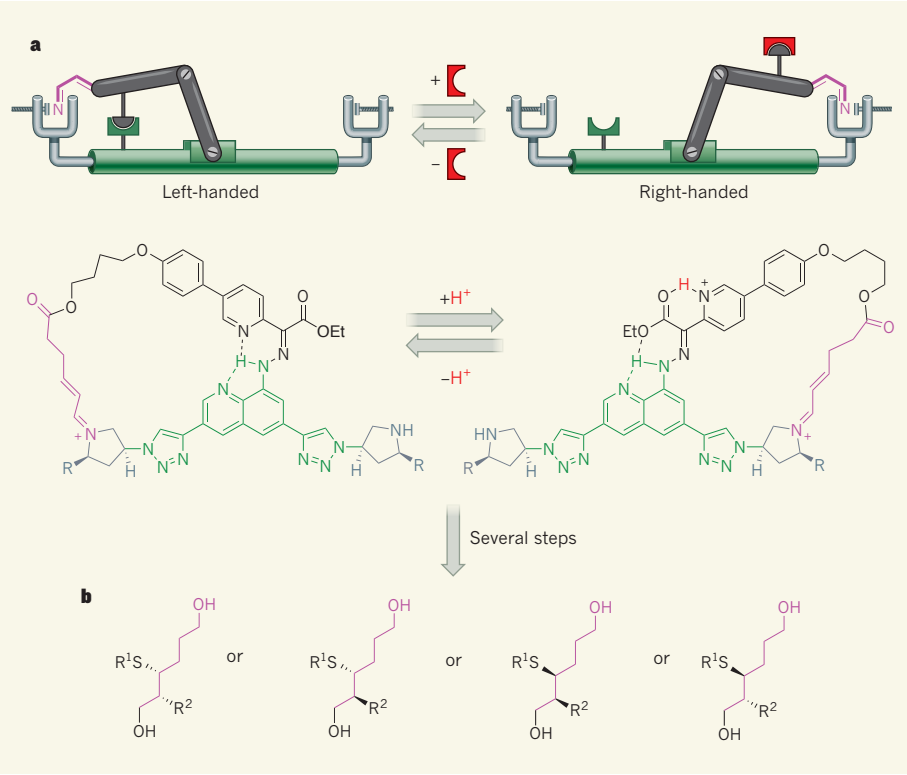

Figure 1 | A machine for assembling molecules. **a**, Kassem *et al.*[6] report a molecular machine that controls the assembly of other compounds. It can be switched between a left-handed mode and a right-handed one by the addition or subsequent removal of a hydrogen ion (H^+, represented by a red unit in the cartoon). Bonds shown as solid wedges project above the plane of the page; broken wedges project below. Thin dashed bonds represent non-covalent interactions. Et, ethyl group; R represents a bulky chemical group. **b**, Once a substrate molecule has been loaded onto the assembler and 'primed' to undergo reactions, the machine can assemble four stereoisomers of a compound in a multistep process; stereoisomers are molecules that contain the same set of atoms connected identically in two dimensions, but that are arranged differently in three dimensions. Which stereoisomer forms depends on the order in which the assembler is switched between its left- or right-handed modes during the assembly process. R^1 and R^2 represent different chemical groups.

the same assembler, rather than in separate synthetic routes that each need individual optimization to produce good yields. Moreover, the different types of promoter that are usually required to provide different stereoisomers are all contained in one molecular machine, and can be accessed selectively simply by changing the assembler's protonation state (that is, by changing the pH of the reaction conditions).

Kassem and colleagues' molecular assembly method has parallels with a technique called solid-phase synthesis, the development of which led to the award of the 1984 Nobel Prize in Chemistry[7]. In this approach, starting materials are attached to a macroscopic solid support and undergo a sequence of reactions before the final product is detached and isolated. Solid-phase synthesis eliminates the need to isolate and purify the compounds produced at each step of a synthetic route, and the consequences of this have been revolutionary for two areas in particular: peptide synthesis and DNA synthesis. For example, DNA chains containing 50–100 nucleotides are now prepared routinely using commercially available machines, and the only mechanical operations needed are filtrations and the opening and closing of valves.

The solid-phase synthesis of DNA and peptides is relatively simple, because there are just 4 different nucleotides from which DNA can be made, and only 20 types of amino acid are needed to construct most naturally occurring peptides. But developing a general solid-phase method for synthesizing other types of organic molecule is a daunting, complex challenge, because the number of known organic molecules that could be used as building blocks is upwards of 100 million[8] and increasing daily. Nonetheless, efforts to automate organic synthesis using solid-phase methods have begun[9]. In theory, molecular assemblers offer an alternative strategy, but it is too early to tell whether they will offer advantages over solid-phase synthesis.

As is the case for many people, the left and right hands of the machine described by Kassem *et al.* carry out their programmed tasks with different efficiencies. Moreover, the pseudo-symmetrical left- and right-handed chemical groups on the two ends of the machine probably operate quite differently from each other, in ways that are not always easy to predict. As the authors point out, it is therefore partly good fortune that their machine selectively prepares each of the four possible products (even if only as the major component of product mixtures) in the different reaction sequences. Chemists' limited understanding of — and control over — such issues of selectivity is often a challenge in the development of new reactions.

It is commonplace to dismiss seemingly impossible ideas, such as Drexler's molecular assemblers, out of hand, and the use of such devices in chemical synthesis might indeed never find favour. One could further argue that Kassem and colleagues' "programmable molecular machine" is more contrived than ingenious. But given that the most recent chemistry Nobel prize was awarded for the design and synthesis of molecular machines, those who dismiss the concept of molecular assemblers should heed the lesson of Lord Kelvin's infamous 1895 pronouncement[10] that "heavier-than-air flying machines are impossible". We look forward to seeing what other impossibilities take flight in the future. ■

T. Ross Kelly *and* **Marc L. Snapper** *are at the Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, USA.*
e-mails: ross.kelly@bc.edu; marc.snapper@bc.edu

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CELL SIGNALLING

Red alert about lipid's role in skin cancer

Some versions of the MC1R protein are associated with red hair and an increased risk of developing a skin cancer called melanoma. It emerges that a lipid that binds MC1R might provide a target to reduce this risk. SEE LETTER P.399

IAN J. JACKSON & E. ELIZABETH PATTON

Red hair has long been a subject of fascination in many cultures, and it is increasingly capturing the attention of scientists. On page 399, Chen *et al.*[1] report work in mouse models and human cells showing that the risk of skin cancer associated with certain versions of a protein connected to red hair can be reduced by increasing the degree to which this protein is modified by a lipid.

Melanocyte cells in the skin and hair follicles make a pigment called melanin, and can give rise to the deadly skin cancer melanoma. Melanin protects the skin against ultraviolet radiation from sunlight, which can cause DNA damage and possibly result in harmful mutations. The type of this pigment made by melanocytes is governed by the action of the MC1R protein. MC1R stimulation results in production of a dark form of melanin called eumelanin, but if MC1R signalling is low or absent, the primary type of melanin that is produced is a red or orange form called phaeomelanin (Fig. 1). Almost all red-haired individuals have a version of MC1R with reduced or absent signalling capacity, and most have fair skin that doesn't easily tan[2].

The *MC1R* gene was first identified in mice in which a loss-of-function mutation of the gene causes yellow fur[3]. Many other species also have pigment alterations associated with specific versions of *MC1R*, as is the case, for example, in dogs with red or yellow coats[4]. Humans who have ancient European ancestry often have variant forms of *MC1R*, and these differ in the strength of their association with red hair[5]: some variants almost always cause this coloration, whereas others have a weaker connection. MC1R variation is necessary, but not always sufficient, to produce red hair, suggesting that most variants retain some signalling activity that may be masked or enhanced depending on other genetic or cellular factors[5].

Chen *et al.* conducted a screen using human melanocytes grown *in vitro* to try to identify molecules that enhanced signalling downstream of MC1R in some versions of the protein that are associated with red hair. They found that the fatty-acid molecule palmitate met this criterion. This finding is notable because if palmitate is attached to a protein in a process known as palmitoylation, it adds a hydrophobic component that enhances the protein's interaction with the cell membrane. It is probable that such a change would increase MC1R targeting to, or time spent at, the cell surface, and thereby could be a mechanism to regulate the receptor's activity.

MC1R is a member of a large family of cell-surface proteins called G-protein-coupled receptors, which share common cell-signalling mechanisms. Many of these receptors are known to be palmitoylated. Although MC1R had not previously been shown to be modified in this way, it has an amino-acid group near its carboxy terminus that is characteristic of a palmitoylation site. Moreover, red and yellow dogs that lack MC1R signalling have a mutation that removes this site from the protein[4],