Organic synthesis

Atom-swap chemistry could aid drug discovery

Filippo Ficarra & Mattia Silvi

An unconventional route for modifying pharmaceutically relevant molecules swaps an atom of carbon for one of nitrogen. The resulting derivatives might open up avenues of research in medicinal-chemistry campaigns. See p.77

The molecules of the active ingredients in pharmaceuticals and agrochemicals consist largely of 'skeletons' made of carbon atoms, but these carbon frameworks also contain other atoms such as nitrogen, oxygen and sulfur. Modifying the skeletons by replacing one of their atoms with another of a different element would be a valuable tool for chemists, because it would provide a simple way to generate analogues of biologically active compounds. However, this conceptually straightforward and potentially versatile transformation is missing from much of the extensive repertoire of reactions used for organic synthesis. On page 77, Woo *et al.*[1] present a practical strategy for replacing a carbon atom with a nitrogen atom in molecules known as quinolines, which are often found in pharmaceuticals — providing an inspiring example of a single-atom substitution.

Controlling the atomic make-up of organic molecules is essential for tuning their physical and chemical properties, and is a key strategy in the rational design of pharmaceuticals and agrochemicals. Ideally, the construction of organic molecules would involve a sequence of single-atom operations such as the insertion, deletion or substitution of individual atoms — similar to how 'ball-and-stick' molecular models are assembled or modified. However, in practice, the synthesis of organic molecules requires the manipulation of groups of atoms through sequences of chemical reactions. Developing these sequences is the daily challenge of the synthetic organic chemist, and involves negotiating an intricate web of rules that govern the chemical reactivity of molecules — thereby providing an intellectual playground that has stimulated great feats of imagination and creativity[2].

"Future adventures in single-atom substitutions will lead to methods that are truly general."

But the limitations of conventional synthetic methods have restricted the chemist's ability to assemble molecules. A striking consequence of the complexity of the field is that, to make two otherwise alike molecules that differ only in the identity of one atom in the central part of the skeleton, two distinct chemical syntheses might need to be designed. There are no such things as 'microscopic tweezers' that would allow the atom concerned to be swapped with an atom of a different element, directly converting one molecule into the other.

Woo *et al.* now report a cleverly designed sequence of chemical steps that enables the selective substitution of a carbon with a nitrogen atom in the central skeleton of quinoline molecules (Fig. 1a). Crucially, the sequence is carried out as a 'one-pot' method (in the same reaction vessel, with no intermediates needing to be isolated), effectively constituting a single, practical chemical process. This single-atom substitution is a striking example of a molecular skeletal editing technique, allowing the quinoline skeleton to be modified without perturbing anything else in the original molecular structure. The strategy differs from other such techniques, which generally involve the removal or insertion of an atom[3,4], rather than substitution. Exciting strategies for skeletal single-atom substitutions have previously been described[5–10], but they mostly require intermediate compounds to be isolated during the process, result in structural modifications elsewhere in the original structure, or work only for specific molecules.

Woo and colleagues' chemistry tolerates structural variations in the starting molecule, and even works with some examples of naphthyridines — analogues of quinolines that have two nitrogen atoms in their skeletons, rather than one. Perhaps most importantly, the authors show that the substitution process can be used to modify skeletons found in the inner regions of relatively complex, medicinally relevant molecules, to synthesize derivatives. As an example, they prepared a new derivative of talnetant (Fig. 1b), a compound that has been investigated as a treatment for several conditions, including schizophrenia[11]. Nitrogen atoms participate in various interactions that have key roles in biology, such as acid–base equilibria and electrostatic interactions with proteins. Strategies for substituting carbon atoms with nitrogen atoms are therefore highly sought after in medicinal chemistry[12], which means that the new process can be expected to find applications in this field.

What next for this research? As for every chemical process, the individual steps of Woo and colleagues' substitutions must obey the strict rules of organic chemistry, inevitably leading to some limitations. For instance, the method is mostly restricted to quinolines. Inspired by the authors' findings, we predict that future adventures in single-atom

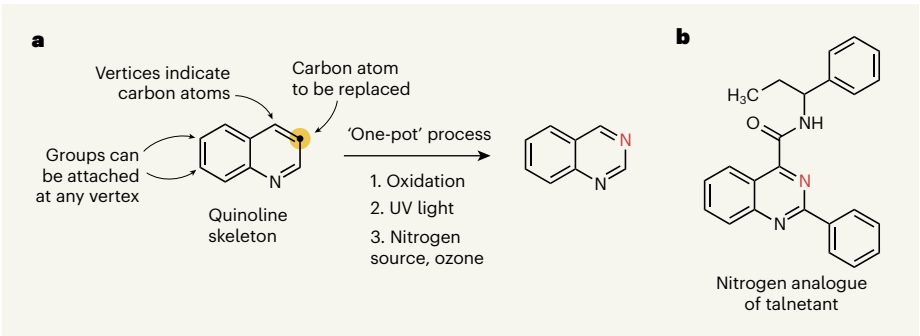

Figure 1 | A carbon-to-nitrogen substitution. Woo *et al.*[1] report a chemical process in which a carbon atom in the 'skeleton' of quinoline molecules is replaced by a nitrogen atom. **a**, The process involves three chemical steps: oxidation; irradiation with ultraviolet (UV) light; and an ozone-mediated oxidation (ozonolysis) in the presence of a nitrogen source. These steps are carried out sequentially in the same reaction vessel, making the overall process simple to implement, and the chemistry tolerates structural variations such as the presence of chemical groups attached to any of the carbon atoms in the quinoline skeleton. **b**, In drug-discovery programmes, the reactions will be especially useful for generating analogues of compounds, such as the molecule shown, a nitrogen-enriched derivative of talnetant. Talnetant has been investigated as a drug for the treatment of various conditions, including schizophrenia. The nitrogen shown in red replaced a carbon atom.

substitutions will lead to methods that are truly general.

Possible 'dream processes' would include the selective substitution of a carbon atom by a nitrogen atom in fully carbon-containing rings, regardless of the groups attached to the ring – thereby providing direct access to nitrogen-containing rings known as pyridines and piperidines, often found in biologically active molecules. Although some exciting examples of such substitution reactions have been reported[6,8], they work only for rings that have been chemically activated by the attachment of groups at particular positions. A general approach for the reverse nitrogen-to-carbon substitution would also be desirable, because available methods are currently limited in scope[7]. Finally, universal substitution methods involving atoms such as oxygen or sulfur would provide access to other classes of medicinally relevant compounds.

The development of such methods would keep pushing the boundaries of organic chemistry, unveiling chemical steps that could form the basis of future substitution processes. With contributions from across the community of synthetic research chemists, the swapping of atoms, at will, in the core skeletons of pharmaceutically relevant molecules might become a reality.

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Biomedical engineering

Gel implant heals muscles with electrical stimulation

Milica Radisic

An electrically conductive hydrogel injected into an injured muscle can help the muscle to regenerate and reconnect with the nervous system. This effective soft prosthesis has enabled rats to walk soon after muscular injury. **See p.58**

When a muscle is injured, its electrical communication with the nervous system is disrupted, preventing it from functioning properly. Rigid prostheses can be used to help injured people move, but these devices don't actually restore the connections that enable conscious muscle contraction. An effective prosthesis needs to conduct electrical signals in two directions – towards the muscle to stimulate it, and away from the muscle to provide feedback about how the rehabilitation is progressing[1,2]. On page 58, Jin *et al.*[3] report a soft prosthesis made from an electrically conductive material that can be injected directly into the injured muscle to help it restore this electrical circuit.

There are specific design criteria for prostheses that are injected into the body. These devices must be constructed from biocompatible materials to prevent cell death and tissue damage. They should be soft to avoid tissue injury, yet mechanically durable. And, ideally, they should be biodegradable, so that they don't need to be removed surgically after the injured tissue has regenerated.

Prostheses for electrically active tissues have even more specific requirements. They need to conduct electrical signals over long periods with high sensitivity, and their ability to activate the immune system should be limited, because this can lead to tissue engulfing the implanted prosthesis and blocking electrical signals. The tissue-interfacing prostheses developed so far do not satisfy all of these criteria – in fact, most can't be injected easily into tight spaces[2,4,5].

Jin *et al.* came up with a clever design for a soft prosthesis made from a hydrogel, a swollen polymer network containing a large amount of water. Hydrogels can flow, which makes them easy to inject and enables them to mould to a space and fill it completely. Yet hydrogels have low electrical conductivity. They are also relatively weak, which can be a problem when they are used for long periods.

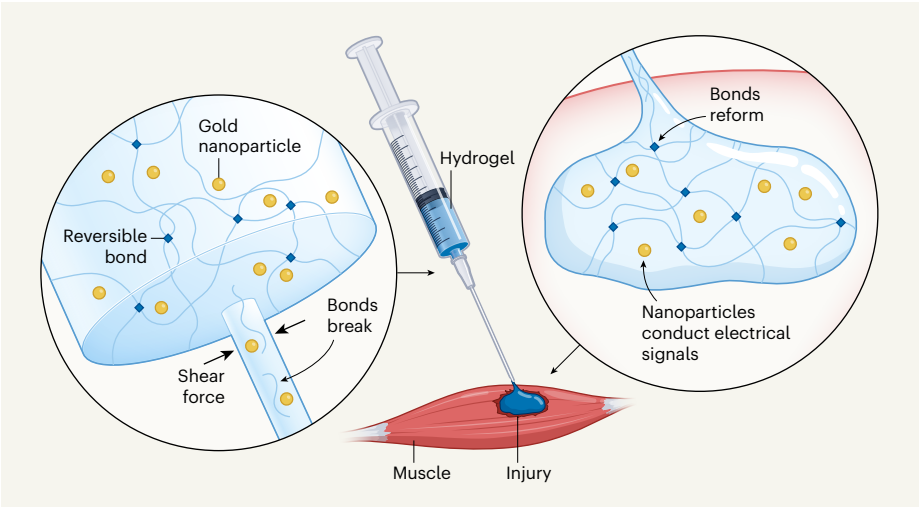

Figure 1 | An electrically conductive hydrogel prosthesis. Jin *et al.*[3] designed a soft hydrogel prosthesis to fill a defect in an injured muscle and repair its electrical connection to the nervous system. A hydrogel is a water-absorbing polymer network that can flow, but has low electrical conductivity and is relatively weak. The authors introduced gold nanoparticles to increase the hydrogel's conductivity and reversible bonds to improve its strength. The reversible bonds break under shear force, which makes the gel injectable, but they reform after the hydrogel sets in the wound.