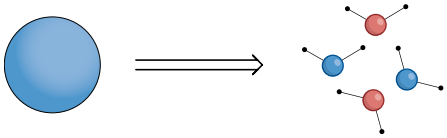
Materials go retro

Retrosynthesis is a common strategy for the design of synthetic routes to organic molecules. Implementing the concept in materials science is a further step towards guided approaches to materials synthesis.

Organic chemists often use retrosynthetic analysis to find synthetic routes to target molecules, including those with a diverse range of functional groups and of high complexity. Despite its prevalence in organic chemistry, the concept of retrosynthesis — making a series of disconnections to revert the target product to simple, precursor structures — has not expanded into other related disciplines. However, for syntheses of molecules and materials that have traditionally used a more trial-and-error approach, this guided method has considerable potential to accelerate the synthesis of useful products.

In a retrosynthetic approach, every step is planned in reverse with precision and with knowledge of previous similar reactions. This 'database' of reactions that was previously in the minds of the chemists determining the retrosynthetic route can also be learned by computers in machine learning routes incorporating retrosynthetic thinking (M. H. S. Segler et al., *Nature* **555**, 604–610; 2018). In a trial-and-error approach, there is minimal design in the synthesis of the molecules or materials, with the reagents and reaction conditions often varied until a useful or notable product is made. In spite of this, over past decades, the systematic variation of reagents and reaction conditions in such reactions has enabled the synthesis of many materials with target properties and in improved yields.

But what if it was possible to produce a desired material with more accuracy by considering the reverse of its formation?



And what information is needed to be able to follow the retrosynthesis of materials? In a Perspective in this issue, Loiudice and Buonsanti consider these questions and applying them to the synthesis of colloidal nanocrystals. In a similar way to the retrosynthesis of organic molecules, where the sequential steps and intermediate products are considered, they discuss how it is possible to implement retrosynthesis in materials syntheses by identifying the reaction intermediates in the synthesis of the nanocrystals. By building up a knowledge of the reaction intermediates, in the same way that finite steps are considered in organic chemistry, a retrosynthetic strategy may be possible.

Compared with even the most intricate of organic molecules, complexity seems notably greater for materials. For example, in the case of colloidal nanocrystals, as Loiudice and Buonsanti explain, the elemental composition of the core of the nanocrystal as well as the chemical composition of the peripheral ligands can be varied, leading to a huge number of possible nanomaterials. In addition, the size and shape of the nanomaterial can be varied, leading to even more possibilities. To tackle the concept of applying retrosynthesis, they discuss the need to isolate intermediates, determine mechanisms of formation and to characterize the intermediates in situ. These intermediates may be complexes, molecular clusters, coordination polymers or mesophases and must have some degree of stability. In the Outlook section of the Perspective, the need to collate data on reaction intermediates and formation pathways in databases to enable machine learning techniques in materials synthesis is emphasized.

Also in this issue, a Review by Sarpong, Levin and co-workers defines and discusses a concept related to high-precision synthesis of organic molecules — namely, molecular editing. With a focus on single-atom editing in heterocycles, ring expansion and contractions, as well as deletions and insertions of atoms outside of the ring structures are outlined. The value of such late-stage transformations in medicinal chemistry is potentially high with the possibility to synthesize analogues by switching atoms and hence widening the range of molecules for biological testing. The post-synthetic modifications that some materials, such as metal–organic frameworks, undergo may also benefit from routes to switch atoms in specific locations.

In both articles, there is a strong vision for the future of how these concepts could be used in the synthesis of molecules and materials. We hope you enjoy reading these visions and that these concepts create discussion on guided and precise approaches going forward. ❐

Published online: 12 May 2022
https://doi.org/10.1038/s44160-022-00087-4