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Moving mechanochemistry forward: accelerating and tuning organic synthesis by mechanochemistry

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The ability of organic chemistry to solve humanities most serious problems is a story as old as chemistry itself. Major advancements in the field have been built on the foundation of optimization, creativity, and by seizing bold opportunities for growth. More recently, organic chemists have sought to merge other technologies with organic reactions to push the boundaries of synthesis strategies. Thus, photochemistry,[1] flow chemistry,[2] electrochemistry,[3] biochemistry,[4,5] as well as others have found their way into the sphere of organic syntheses and have proven robust tools for the chemist. Mechanochemistry has proven extremely useful to the organic chemist with the appropriate experimental optimizations and tool selection.[6,7] The core areas in which mechanochemistry can accelerate the development of new organic chemical approaches are through (a) the adoption of advanced molecule preparation and total synthesis, (b) the development of combinatorial methods, and (c) the creation of mechanochemical tools for industrial applications. While mechanochemistry can add to the organic chemist's toolbox, the field of mechanochemistry can benefit from organic chemists developing tools for making mechanochemistry more predictable and desirable.

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Areas in which mechanochemistry needs help from organic chemists

Traditionally, organic chemistry is divided into two complementary branches: synthetic and physical organic chemistry that work in tandem to expand the boundaries of our understanding and capabilities in chemistry. On one hand, synthetic organic chemists focus on making molecules to play a crucial role in human advancement, particularly in areas such as pharmaceuticals, agrichemicals, devices, polymers, and fine chemical production. On the other, physical organic chemists delve into the underlying principles to seek a deeper understanding of reaction mechanisms and processes. This allows chemists to more effectively predict and control reactions, making syntheses more efficient and reliable.

The Wöhler synthesis of urea in 1828 was the first recognized organic reaction and showed that organic compounds could be created from inorganic substances but the term "Physical Organic Chemistry" was coined over a century later by Louis P. Hammett.[8] Since then, physical organic chemists have significantly enhanced the understanding of chemical reactions, as exemplified by Woodward and Hoffmann, whose rules revolutionized organic chemistry.[9]

Mechanochemistry is at a similar early stage; its synthetic capabilities have outpaced the understanding of its underlying mechanisms. It involves the use of mechanical force to induce chemical reactions, offering a solvent-free and often more environmentally friendly approach to synthesis. However, for the field to advance, stronger collaborations with physical organic chemists are essential because synthetic chemists are often cautious about adopting new methodologies without a solid understanding of the reaction pathways.

One of the main challenges facing mechanochemistry is the lack of *in situ*, structure-sensitive instruments. Physical organic chemists often rely on techniques such as real-time, *in situ* NMR to provide insights into the dynamic processes occurring during a reaction.[10] In contrast, mechanochemists typically carry out post-reaction analyses. There are some exceptions, and *in situ* techniques have significantly contributed to our understating of metal–organic frameworks (MOFs), cocrystals, and various inorganic syntheses.[11–27]

Mechanochemistry in total synthesis and advanced molecule preparation

Some of the seminal accomplishments are in synthesizing large, complex molecules such as natural products, active pharmaceutical ingredients, macrocyclic peptides, complex dyes, to demonstrate the versatility of mechanochemistry. Syntheses of molecules such as morphine,[28] taxol,[29] saxitoxin,[30] strychnine,[31] and countless others are examples of robust chemical syntheses across challenging chemical landscapes. While technologies such as biocatalysis,[32–34] photocatalysis,[35,36] and electrocatalysis[37] have been applied to total synthesis in numerous ways, mechanochemistry has yet to find its footing.

Despite the potential benefits of mechanochemistry, such as solvent reduction, the use of unique reagents by removing solubility hurdles, or by accelerating reactions due to more efficient mixing, mechanochemistry has not yet been broadly adopted for advanced molecule preparation. However, the continually expanding library of mechanically susceptible reactions provides an important opportunity for organic chemists to integrate mechanochemistry into total synthetic strategies. Examples include reactions such as Friščić and Colacino's synthesis of tolbutamide, an active anti-diabetic pharmaceutical ingredient.[38] Work by Lamaty and coworkers has developed sustainable mechanochemical methods for peptide synthesis such as aspartame, a commercially used artificial sweetener, on a multi-gram scale.[39] Other groups have explored multi-peptide synthesis and have transformed complex molecules such as the work by Yu and Su *et al.*,[40] but it is still necessary to employ mechanochemistry for more complex syntheses and advanced molecules. A solvent-free or solvent-minimal total synthesis of a natural product would be a significant feat and propel mechanochemistry into the same relevance as photochemistry or electrochemistry. Thus, mechanochemistry has the potential to facilitate organic syntheses by not requiring a solution phase.[40] Mechanocatalysis has become more common due to the use of the reaction vessel as an active reagent.[41,42] The use of auxiliaries in grinding to tune reactivity has also added versatility[43,44] so that the mechanochemical toolbox is rapidly expanding and is poised for use in total synthesis in a robust way.

Advances and opportunities for combinatorial chemistry

Chemists have utilized different energy sources for conducting chemical reactions. The most common method involves thermal energy. In the 18th century, chemists discovered how to use electricity to conduct chemical reactions,[45] and by the late 18th and early 19th centuries, light emerged as a new energy source for facilitating new reactions not accessible under thermal or electrochemical conditions.[1] Over the past decades, biological materials, specifically enzymes, have been utilized to influence chemical reactions.[46] While each of these energy sources are powerful on their own, it is difficult to apply them together.[47]

Mechanochemistry, on the other hand, can be combined with other energy sources. Combining mechanical and thermal energy has unlocked pathways for synthesizing organic reactions that were not possible by simply just milling or heating;[48–55] for example, the combination of milling and thermal energy has been shown to provide direct control over the product distribution.[56]

Mechanochemistry and photochemistry have been combined to carry out solvent-free photomechanochemical reactions that are faster and typically have higher yield than their solution counterparts.[57–61] They can form different products from solid-state crystal photolysis or solution reactions. For instance, it was demonstrated that photomechanochemical [2 + 2] dimerization of acenaphthylene, yields *syn* stereoselectivity, while photochemistry in the solid state without mechanochemistry yields anti stereoselectivity, while solution photolysis is not selective.[62] More recently these processes were carried out on 300 mmol scale, roughly equivalent to 65 grams. By comparison to solution reactions, photomechanochemical reactions required anywhere from 20–90 minutes *versus* 48 hours in solution.[58]

One more effective combination is enzymatic chemistry under mechanochemical conditions, a field known as mechanoenzymology.[63–69] Enzymes have been shown to perform excellently in a variety of milling methods from ball mills to extruders. Similar to thermal- and photo-chemistry, they occur faster and with higher yields than their solvothermal counterparts.

As our understanding of mechanochemistry grows, its versatility and ability to develop tandem processes are becoming increasingly viable. Although there is great potential, the rate-limiting step is often the development of new mechanochemical tools so that these combinatorial fields will continue to expand as more tools are developed.

Development of industrial scale mechanochemistry tools

The tools utilized in mechanochemistry are not foreign to industrial-scale processes. Extrusion is commonly used in pharmaceutical formulation processes,[70] and ball milling has also been used at an industrial scale. Mixers of various types have been use for materials, fuels, paints and coatings manufacturing.[71,72] It is common for mechanochemistry to co-opt methodologies and tools from other fields, but for mechanochemistry to fully be adopted by industrial chemists, there must be more studies on scaling mechanochemistry, *in situ* monitoring, and developing continuous methods.

An excellent example of industrial mechanochemistry is the work by Hastings and coworker's on continuous extrusion for Sonogashira coupling.[73] The method was implemented using a process-scale extruder, which facilitated scale up of the reaction. Browne and coworkers recently performed a continuous extrusion for amide formation at the 500 g scale.[74] These examples, amongst many more, showcase the ability for mechanochemistry to be applied by industry.

In order for mechanochemistry to truly be applied industrially at the 1 kg scale or greater, it requires a closer connection between academics and emerging industrial technology groups, to create novel solutions. Additionally, industrial chemists should be encouraged by management to explore ways to have mechanochemical methods follow good manufacturing and regulatory standards, which would enable mechanochemical implementation at critical junctures not previously accessible. Additionally, improving the ability to understand and predict mechanochemistry will help give industrial chemists and engineers more reason to buy in to the use of mechanochemical methods in their workflow.

Mechanochemistry has the ability to serve as a powerful scouting tool for R&D scientists while also giving the opportunity for manufacturing and process chemists to minimize waste output and potentially lower risk. Browne and coworkers highlight the safety considerations of mechanochemistry, and their insights showcase the limitations of ball milling from a safety angle, which invoke thought-provoking conversations about the safety of other forms of chemistry.[75] Through the use of mechanochemistry, as well as other chemical technologies, we can help promote better chemical practice, more thoughtful chemical hygiene, and thus clear our conscience when doing chemistry at larger scales.

As mechanochemistry continues to evolve and expand, organic chemists will slowly add it to their toolbox. However, we as mechanochemists have to invite organic chemists into the conversation. The development of new tools, reactions, and platforms will encourage more cross collaborative efforts. As photochemistry, electrochemistry, and microwave chemistry all started with an idea and a few testbeds, mechanochemistry is continuing along a similar pathway towards broader adoption. Mechanochemistry can move organic chemistry forward by creating new and unique reaction platforms and testbeds but, in the same vein, organic chemistry can propel mechanochemistry upwards through providing targets of interest as well as the tools for better understanding at the mechanistic level.

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