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## Moving Mechanochemistry Forward: Mechanochemistry and the non-covalent bond

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The ability to manipulate, destroy or create covalent bonds by mechanical force has a long history. For decades, covalent mechanochemistry has been used to manipulate, degrade or recycle polymers.<sup>1</sup> More recently, mechanochemistry has emerged as a route to synthesise molecules,<sup>2</sup> including polymers, by methods such as ball milling, resonant acoustic mixing,<sup>3</sup> or screw extrusion.<sup>4</sup> Manipulating covalent structures by mechanical force continues to be important for polymer remediation,<sup>5</sup> developing mechanophore-based sensors,<sup>6</sup> and for the ability to modify photo-chemical (or other) reactions through mechanical strain. With decades, if not centuries, of research under its belt, the mechanochemistry of covalent bonds is relatively mature.

In contrast, the manipulation of the much weaker non-covalent bonds – exemplified by hydrogen or halogen bonds,  $\pi$ – $\pi$  stacking, or van der Waals' interactions – is much less well understood in the realm of mechanochemical reactivity. This is remarkable, given the importance of such interactions for understanding and controlling the mechanochemistry of materials and synthesis. Guidance can be taken from the high-pressure community, who for decades have been studying how non-covalent bonds are affected by

extremes of mechanical force. These studies have established deep insights into the relative strengths of non-covalent bonds,<sup>7</sup> how they underpin mechanically induced transformations, and have helped to understand how solid-state reaction kinetics are influenced by mechanical strain.<sup>8,9</sup> Pressure is now being used to explore the mechanochemistry of non-covalent bonds in great detail, with exciting opportunities for inducing chemical reactions by compressing<sup>10</sup> (or shearing<sup>11,12</sup>) non-covalently bound assemblies, without needing additional energy sources. Such reactions may even provide direct insights into the mechanisms of ball milling transformations, where cocrystallisation can lead to favourable solid-state alignment of reactant molecules prior to covalent bond formation.<sup>13–15</sup> Indeed, real-time monitoring has revealed an important role of self-assembly processes in mechanochemical covalent bond formation, as evidenced by the increasingly common observation of cocrystal intermediates in reactions ranging from transition metal-catalysis<sup>16</sup> and topochemical photodimerisation<sup>17</sup> to making covalent–organic<sup>18</sup> and metal–organic frameworks (COFs, MOFs).<sup>19</sup>

Arguably the first step in the mechanochemical transformation of molecular solids by milling, shear, or related types of mechanical agitation is the introduction of defects and the rearrangement of (supra)molecular architectures.<sup>20</sup> This

occurs *via* the disruption of non-covalent bonds. Such processes might be similar to the way in which inorganic materials undergo surface amorphisation and reconstruction upon mechanical treatment, which can sometimes be captured through high-resolution electron microscopy.<sup>21</sup> Unfortunately, analogous deformations cannot be readily imaged in molecular crystals due to the high mobility of molecules and the fragility of the non-covalent bonds holding them together. Taken together, these features lead to significant and fast molecular rearrangements in molecular crystals after mechanical deformation of their surfaces,<sup>22</sup> making the patterns of non-covalent bonds that underpin molecular crystal reactivity difficult to detect and, consequently, they are typically overlooked. Nevertheless, supramolecular mechanochemistry, the mechanochemistry of non-covalent bonds, provides a fertile ground for research, for the development of new materials and reactions, and for understanding mechanochemical reaction mechanisms.

The practical importance of supramolecular mechanochemistry is evident from the transformations of polymorphs and cocrystals, which have been the major drivers behind explorations of milling-induced transformations of organic molecules over the past two decades. Mechanochemical methods have emerged as highly efficient tools to

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discover and scale-up cocrystal forms relevant to the pharmaceutical<sup>23</sup> and energetic materials industries,<sup>24</sup> and to screen for molecular recognition properties of molecules.<sup>25</sup> The ability to synthesise organic molecules *via* solid-state transformations has led to further efforts to control the resulting solid form, be it a polymorph, solvate, cocrystal, or a salt. Controlling polymorphism requires a delicate balance of non-covalent bonds, and this balance can be manipulated – and polymorph outcomes controlled – through subtle changes in mechanochemical processing strategies. This includes introducing small quantities of an additive (liquid, polymer, solid), or by changing the type<sup>26,27</sup> or magnitude<sup>28,29</sup> of mechanical force that is applied to the crystal. This degree of control results from a subtle manipulation of the non-covalent bonding, either by templating specific molecular assemblies,<sup>30</sup> or by playing with the different mechanical stability of polymorphic forms,<sup>31</sup> thereby determining which polymorph is stable, or even whether a non-covalently bound structure can be synthesised at all.<sup>32</sup> Moreover, mechanochemistry offers opportunities to manipulate the relative stability of polymorphs through particle size effects,<sup>33</sup> which can help to reproducibly synthesise challenging solid forms.<sup>34</sup> A very productive area of supramolecular mechanochemistry is the transformation of metal–ligand coordination bonds, relevant in the synthesis of small-molecule complexes, coordination polymers,<sup>35</sup> and MOFs, where mechanochemistry can enable selective syntheses and interconversions of topologically-distinct frameworks.<sup>36</sup>

Beyond their role in understanding reaction mechanisms and enhancing product stability, the low-energy, easily deformable nature of non-covalent bonds allows solid-state chemical reactivity to be manipulated in new ways. For example, the mechanochemical disruption of non-covalent bonds in ammonium perchlorate<sup>37</sup> or silver oxalate<sup>38</sup> creates defect channels in these materials, which completely changes both the kinetics and pathways of subsequent thermal decomposition. Recent work is considering how mechanical force can combine with

other stimuli like heat<sup>39</sup> or light<sup>40</sup> to add new dimensions to solid-state reactivity, all thanks to our ability to mechanically manipulate weak, non-covalent bonds in crystals.

The ubiquity of non-covalent interactions, beyond crystalline solids, means that supramolecular mechanochemistry encompasses a wide variety of processes, including the motion, deformation, or reaction of synthetic and biological polymers, including peptides, enzymes, and nucleic acids. Investigations into “soft” mechanochemistry<sup>41</sup> serve to showcase the breadth and diversity of the field, including phenomena that appear to be very distinct from transformations that occur by ball milling or under high-pressure conditions. This includes the binding of biomolecules on mechanically-activated receptor sites or the scission of chemical bonds due to slow swelling of gels and polymers.<sup>42</sup>

The implications of non-covalent mechanochemistry are vast, underpinning myriad phenomena, but there remains much still to be understood.<sup>43</sup> The community has only begun to scratch the surface of the mechanochemistry of non-covalent bonds, and, as our understanding deepens, there is no telling what exciting new opportunities await. It remains for the mechanochemistry community to continue investigating how non-covalent bonds contribute to the ever-growing examples of mechanochemical reactions, pushing the boundaries of using mechanical force to control and manipulate these weak, deformable bonds to unlock new opportunities to design, create, and modify matter.

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