What can solid-state NMR spectroscopy tell us about mechanochemistry?

Austin A. Peach,[1] Christopher A. O'Keefe,[1] Sean T. Holmes,[1] Jacqueline E. Gemus,[1] Cameron S. Vojvodin,[1] Cristina Mottillo,[2] Tomislav Friščić,[2] and Robert W. Schurko[1]

1. Department of Chemistry & Biochemistry, University of Windsor, Windsor, Ontario, Canada, N9B 3P4
2. Department of Chemistry, McGill University, Montreal, Québec, Canada, H3A 0B8

Mechanochemical synthesis has emerged as an attractive alternative to conventional solvothermal synthesis,[1,2] as it adheres to many of the *Twelve Principles of Green Chemistry*,[3] affording high atom economy (high yields, low wastes), involving low energy input, using little solvent, and reducing reaction times. Mechanochemistry may be key in minimizing negative environmental impacts associated with innumerable chemical reactions, especially those on the industrial scale. Mechanochemistry uses mechanical forces (*i.e.*, grinding, shearing, and stretching) to initiate and propagate chemical reactions and physical transformations.[4] While extensive research is being conducted towards accessing synthetic pathways that are not available via conventional solvothermal procedures, there is comparatively little research directed at monitoring and understanding the reaction pathways underlying these processes, which could be beneficial in developing new, more efficient synthetic procedures.

Solid-state NMR (SSNMR) is an ideal technique for both characterizing molecular-level structures of solid phases and potentially monitoring reactions to elucidate pathways and mechanisms; there are very few reports of its use for the latter.[5-7] In this presentation, I will describe two areas of research in this vein. The first is the use of ^{111}Cd SSNMR (along with other multinuclear SSNMR methods and pXRD experiments) for the structural characterization of porous Cd-containing zeolitic imidazolate framework (ZIFs) materials and the monitoring of the mechanochemical reactions involved in their formation. ^{111}Cd SSNMR spectra are shown to be useful for rapidly identifying a variety of products and by-products and offering information that is crucial for structural prediction and the elucidation of reaction pathways. The second is the application of ^{35}Cl and ^{13}C SSNMR for the study of HCl salts of active pharmaceutical ingredients (APIs) that have been prepared as cocrystals with an assortment of pharmaceutically-acceptable coformers using mechanochemical syntheses.[8] ^{35}Cl SSNMR provides an exquisite probe of the intricate hydrogen-bonding network about each Cl^- anion, yielding a unique spectral fingerprint for each compound, as well as for associated polymorphs and hydrates. It is also demonstrated that ^{35}Cl SSNMR is also extremely useful for monitoring competitive ball milling (API + multiple coformers) and stability ball milling (HCl API cocrystal + a different coformer) reactions. Finally, a brief discussion of the use of NMR crystallography for structural prediction will be presented,[9] highlighting a powerful method developed in our group for refining crystal structures that uses dispersion-corrected plane-wave DFT, which relies upon the computation of electric field gradient (EFG) tensors.[10]

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