

NMR Crystallography using Quadrupolar Nuclei: Applications to Active Pharmaceutical Ingredients and Multi-Component Crystals formed by Mechanochemical Syntheses

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Abstract

Recently, there has been increasing interest in the mechanochemical synthesis (MS) of different forms of active pharmaceutical ingredients (APIs), including crystalline polymorphs, solvates, amorphous solids, and multi-component crystals (MCCs). MS may enable the rational design of new forms with tuneable properties (*e.g.*, solubility, stability, and bioavailability), and adheres the tenets of green chemistry, including the use of little or no solvent, low energy inputs, reduced waste products, and facile scalability.

Paramount to the successful design and synthesis of new solid forms of APIs and MCCs is their structural characterization. An emerging discipline for the molecular-level characterization of structure in crystalline powders, amorphous solids, and heterogeneous materials is NMR crystallography, which combines solid-state NMR (SSNMR) spectroscopy, X-ray diffraction (XRD) methods, and computational approaches for the purposes of refining and determining molecular-level structures. To date, the majority of NMR crystallographic studies rely upon the measurement and calculation of ¹³C chemical shift parameters (and to a lesser degree ¹H and ¹⁵N chemical shifts). We are currently investigating the use of quadrupolar nuclei (*i.e.*, nuclear spins > ½) for structural prediction and refinement in the context of NMR crystallographic methods. The reason for this is twofold: (i) electric field gradient (EFG) tensors at quadrupolar nuclei give rise to unique powder patterns for even the most subtle structural differences, allowing for unambiguous structure-property correlations, and (ii) EFG tensors are facile to compute in comparison to magnetic shielding tensors.

In this lecture, I will discuss: (1) MS of solid forms of APIs, including (i) novel cocrystals of fluoxetine HCl prepared by ball milling (including competitive milling and stability milling), and (ii) various forms of xylazine HCl, including hydrated and dehydrated species; (2) the MS of MCl:yUrea:xH₂O MCCs (M = Li, Na, Cs, NR₄ [R = H, Et, Pr]; y = 1, 2, 3; x = 0, 1, 2), and the use of NMR crystallographic and Rietveld methods for their structural refinement; and (3) new dispersion-corrected DFT-D2* methods that utilize electric field gradient (EFG) tensors obtained from multinuclear SSNMR experiments for purposes of structural prediction and refinement.