

# Application and development of NMR crystallography on pharmaceutical solids at natural isotopic abundance: Utilization of $^1\text{H}$ - $^1\text{H}$ and $^1\text{H}$ - $^{13}\text{C}$ ( $^{15}\text{N}$ ) dipolar couplings for structure refinement

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Problems involving polymorphism of pharmaceutical compounds are widespread and cause great concern to industry. Unexpected transformations sometimes occurring during processing and storage can produce problems for patent establishment and protections that can result in complicated patent litigations. That is why any tool for precise solid-state characterization and recognizing polymorphs and solvates are a vital requirement.

NMR crystallography is an emerging discipline that is complementary to the traditional X-ray crystallography. Consequently in some attempts the diffraction techniques were extended and the information given by solid-state NMR was directly incorporated into the existing protocols for trial structure elucidation (Rietveld refinement). Basically this approach is based on calculation of shielding parameters using the fully periodic Gauge Including Projector Augmented Wave method and the current testing of CASTEP code is very promising. Unfortunately it has been shown that for the systems having two or more molecules in the asymmetric units and consisting of more than ca. 20 carbon atoms per molecule the CASTEP computation cannot be carried out on the complete crystal structure. That is why additional extension of the range of application of NMR crystallography toward larger systems would be valuable.

Obviously the additional information that may help in the crystal structure refinement is provided by dipolar couplings, the measurements of which yield direct information on internuclear distances. The requirement of labeled materials, however, renders application of standard  $^{13}\text{C}$ - $^{13}\text{C}$  ( $^{15}\text{N}$ ) techniques impractical for solution of some academic and industrial problems where synthetic effort necessary to selectively or uniformly label the molecules can be nearly daunting. That is why we focused our attention on the detection of dipolar coupling contacts involving  $^1\text{H}$  atoms ( $^1\text{H}$ - $^1\text{H}$  ( $^{13}\text{C}$ ,  $^{15}\text{N}$ )). Recent advances in NMR spectrometers and probeheads design improved sensitivity and resolution  $^1\text{H}$  frequency dimension in such way that a basic experimental concept of heteronuclear and homonuclear correlation involving new homodecoupling sequences (FSLG, PMLG, DUMBO, e—DUMBO etc.) can be successfully applied to acquire 2D  $^1\text{H}$ - $^{13}\text{C}$  correlation spectra with resolution sufficient to separate correlation signals.

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