Locating Hydrogen Atoms with Sensitivity Enhanced NMR Spectroscopy

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Abstract: This contribution will describe how fast magic angle spinning (MAS) or DNP-enhanced solid-state NMR experiments can be used to locate hydrogen atoms. In a dynamic nuclear polarization (DNP)-enhanced NMR experiment the large spin polarization of unpaired electrons is transferred to nuclear spins, resulting in sensitivity gains of one to two orders of magnitude. DNP can now be routinely applied to microcrystalline solids, such as active pharmaceutical ingredients (APIs).[1] DNP can significantly accelerate natural isotopic abundance ^{15}N solid-state NMR experiments, enabling the measurement of ^{1}H-^{15}N dipolar coupling constants.[2] Dipolar coupling constants provide a direct measure of N-H bond lengths in multicomponent APIs, allowing them to be assigned as salts or cocrystals.[2]

Fast magic angle spinning ($\nu_{rot} \geq 50$ kHz) greatly improves the resolution of ^{1}H solid-state NMR spectra, enabling efficient ^{1}H detection schemes that can provide improved resolution and sensitivity. For example, we have recently shown how dipole-based INEPT and HMQC pulse sequences can be used to obtain 2D heteronuclear correlation (HETCOR) NMR spectra between ^{1}H and half-integer quadrupolar nuclei such as ^{17}O and ^{35}Cl that are commonly found in APIs.[3] Recently, we have demonstrated that fast MAS ^{1}H detected ^{17}O solid-state NMR spectroscopy can be used to resolve overlapping ^{17}O NMR signals on the basis of proximity to ^{1}H spins and measure ^{1}H-^{17}O dipolar and scalar coupling constants.[4] ^{1}H-^{17}O dipolar coupling constants provide a direct measure of O-H bond lengths, while scalar couplings provide insight into the covalent character of O-H bonds.[4]

Fast MAS and ^{1}H detection with HMQC schemes has enabled ^{14}N solid-state NMR experiments in a variety of chemical systems.[5] Here we will demonstrate improved ^{1}H{^{14}N} HMQC and RESPDOR pulse sequences that provide 2-fold improvements in sensitivity and ca. 4-fold reduction in experiment times. We will then demonstrate the measurement of N-H bond lengths with these techniques in multi-component APIs and inorganic materials.

Finally, we note that all of our NMR-based N-H and O-H bond length measurements are validated by plane-wave DFT optimization of H atom positions.

References

(1) Zhao, L.; Pinon, A. C.; Emsley, L.; Rossini, A. J. DNP-Enhanced Solid-State NMR Spectroscopy of Active Pharmaceutical Ingredients. *Magn. Reson. Chem.* **2018**, *56*, 583-609.
(2) Zhao, L.; Hanrahan, M. P.; Chakravarty, P.; DiPasquale, A. G.; Sirois, L. E.; Nagapudi, K.; Lubach, J. W.; Rossini, A. J. Characterization of Pharmaceutical Cocrystals and Salts by Dynamic Nuclear Polarization-Enhanced Solid-State NMR Spectroscopy. *Crystal Growth & Design* **2018**, *18*, 2588-2601.
(3) Venkatesh, A.; Hanrahan, M. P.; Rossini, A. J. Proton Detection of Mas Solid-State NMR Spectra of Half-Integer Quadrupolar Nuclei *Solid State Nucl. Magn. Reson.* **2017**, *84*, 171-181.
(4) Carnahan, S. L.; Lampkin, B. J.; Naik, P.; Hanrahan, M. P.; Slowing, I. I.; VanVeller, B.; Wu, G.; Rossini, A. J. Probing O–H Bonding through Proton Detected 1H–17O Double Resonance Solid-State NMR Spectroscopy. *J. Am. Chem. Soc.* **2019**, *141*, 441-450.
(5) Cavadini, S.; Antonijevic, S.; Lupulescu, A.; Bodenhausen, G. Indirect Detection of Nitrogen-14 in Solid-State NMR Spectroscopy. *ChemPhysChem* **2007**, *8*, 1363-1374.