

A new NMR crystallographic protocol based on quadrupolar nuclei

Austin A. Peach,^{1,2} Kirill Levin,³ Carl Fleischer,^{1,2} Sean T. Holmes,^{1,2} and Robert W. Schurko^{1,2,*}

¹*Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL, 32306*

²*National High Magnetic Field Laboratory, Tallahassee, FL 32310*

³*Department of Chemistry and Biochemistry, University of Windsor, Windsor, ON, Canada N9B3P4*

NMR crystallography uses a combination of solid-state NMR (SSNMR), X-ray diffraction (XRD), and quantum chemical calculations for the determination and/or refinement of crystal structures.^{1,2} Currently, the majority of NMR crystallographic studies rely upon the measurement and calculation of isotropic chemical shifts (CS) or CS tensors and their computation by density functional theory (DFT) methods; by contrast, electric field gradient (EFG) tensors of quadrupolar nuclei are used much less extensively.^{3–6} EFG tensors at the origins of quadrupolar nuclei are sensitive to their surrounding electronic environments, including longer-range interactions that do not greatly influence chemical shifts, yielding unique sets of quadrupolar parameters for each magnetically distinct environment. Furthermore, EFG tensors are less computationally demanding to compute than CS tensors. Since EFG tensors are sensitive probes of local atomic environments, we believe that it is crucial to explore and develop quadrupolar NMR-based crystal structure prediction (CSP) methods within the context of modern plane-wave DFT computational packages. In particular, such methods would be very useful for the study and characterization of organic solids, including pharmaceutical drug products, nutraceuticals, and a wide variety of multi-component crystals.⁵

Herein, we demonstrate the use of experimentally-measured and computationally-derived ³⁵Cl EFG tensor parameters in a new NMR crystallographic protocol for the refinement of crystal structures, which are developed and optimized on a training set of four organic HCl salts with known crystal structures. The stages of this protocol include: (i) selection/assignments of molecular fragments, charges, motion groups, and potential unit cells; (ii) simulated annealing using the Polymorph software package to generate tens of thousands of candidate structures, (iii) coarse geometry optimizations using DFT-D2* methods (which include dispersion effects),^{7–9} and (iv) subsequent fine geometry optimizations. Between each of these stages, filters involving the unit cell dimensions, EFG tensor parameters, and static lattice energies have been optimized to select for the best candidate structures. The robustness of this new protocol is demonstrated via comparison of EFG tensors, PXRD patterns, and overlays of the known and refined crystal structures. Finally, this new protocol is demonstrated in several blind tests for the structural determination and refinement of organic HCl salts with unknown structures.

- (1) Taulelle, F. *Encycl. Magn. Reson.* 2009, 1–14.
- (2) *NMR Crystallography*; Harris, R., Wasylishen, R., Duer, M., Eds.; John Wiley & Sons Ltd.: Chichester, U.K., 2009.
- (3) Ashbrook, S. E.; McKay, D. *Chem. Commun.* 2016, 52, 7186–7204.
- (4) Bryce, D. L. *IUCrJ* 2017, 4, 350–359.
- (5) Hodgkinson, P. *Prog. Nucl. Magn. Reson. Spectrosc.* 2020, 118–119, 10–53.
- (6) Widdifield, C. M.; Farrell, J. D.; Cole, J. C.; Howard, J. A. K.; Hodgkinson, P. *Chem. Sci.* 2020, 11, 2987–2992.
- (7) Grimme, S. J. *Comput. Chem.* 2006, 27, 1787–1799.
- (8) Holmes, S. T.; Vojvodin, C. S.; Schurko, R. W. *J. Phys. Chem. A* 2020, 124, 10312–10323.
- (9) Holmes, S. T.; Schurko, R. W. *J. Phys. Chem. C* 2018, 122, 1809–1820.

Keywords: NMR crystallography, crystal structure prediction, solid-state NMR, quantum chemical computation, DFT