**MS31-O5 Ab initio \(^{35}\)Cl solid state NMR-based crystallography of active pharmaceutical ingredients.**

Angeles Pulido\(^1\), David A. Hirsh\(^2\), Robert W. Schurko\(^2\), Graeme M. Day\(^1\)

1. School of Chemistry, University of Southampton, Southampton, United Kingdom
2. Department of Chemistry and Biochemistry, University of Windsor, Windsor, Canada N9B 3P4

email: mjlp1m12@soton.ac.uk

Active pharmaceutical ingredients (APIs) are commonly commercialised in the form of HCl salts; but, as crystalline solids, they frequently exhibit polymorphism. The polymorphic forms may have different physico-chemical properties and the use of the undesired polymorph in a drug could produce catastrophic consequences, not to mention the economic cost. Therefore, knowledge about API polymorphism and accurate structural determination are of great importance in drug development. Structural resolution of polymorphic structures by X-ray diffraction (XRD) can be challenging, especially if single-crystal samples are not available (e.g., for drugs with an API in an amorphous phase).

In this contribution, we show that experimental \(^{35}\)Cl solid state NMR spectroscopy– and computational –crystal structure prediction and first principles NMR calculations– techniques can be successfully combined to study HCl API polymorphism. We establish a protocol for ab initio chlorine-35 solid state NMR crystallography of HCl APIs, see Figure 1. Crystal structure prediction techniques were used to produce a set of computationally generated trial crystal structures for a test set of HCl APIs and to inform about HCl APIs polymorphism trends. First principles \(^{35}\)Cl solid state NMR shielding and quadrupolar tensors were calculated, within the periodic DFT-D/GIPAW framework, on a subset of low energy calculated \(^{35}\)Cl NMR tensor parameters from the experimentally determined values allows the selection of a few predicted crystal structures as potential matches to experimentally determined values. The packing mode of three of the four anhydrates, A\(^\circ\) – C, only differ in the location of the oxygen and hydrogen atoms and are homeoenergetic. Forms A\(^\circ\) and B are ordered phases, whereas C shows disorder (X-ray diffuse scattering). The computationally generated structures provide models for stacking faults, so that intergrowth is likely. Anhydride A\(^\circ\) was identified as the thermodynamically most stable form at ambient conditions. The forms B and C are metastable but show high kinetic stability. The hydrate of thymine is stable only at water activities > 0.95 at temperatures ≤ 25 °C. It was found to be a stoichiometric stable hydrate, which dissociates above 135 °C and loses one small part of the water when stored over desiccants (25 °C) for more than one year. Depending on the dehydration conditions, either anhydrite C or D is obtained. The hydrate is the only known precursor to the experimental search for solid forms, which was guided by crystal structure prediction studies. The packing mode of three of the four anhydrates, A\(^\circ\) – C, only differ in the location of the oxygen and hydrogen atoms and are homeoenergetic. Forms A\(^\circ\) and B are ordered phases, whereas C shows disorder (X-ray diffuse scattering). The computationally generated structures provide models for stacking faults, so that intergrowth is likely. Anhydride A\(^\circ\) was identified as the thermodynamically most stable form at ambient conditions. The forms B and C are metastable but show high kinetic stability. The hydrate of thymine is stable only at water activities > 0.95 at temperatures ≤ 25 °C. It was found to be a stoichiometric stable hydrate, which dissociates above 135 °C and loses one small part of the water when stored over desiccants (25 °C) for more than one year. Depending on the dehydration conditions, either anhydrite C or D is obtained. The hydrate is the only known precursor to form D.

The monohydrate of orotic acid (OTA) is a highly stable hydrate, which dissociates above 135 °C and loses only a small part of the water when stored over desiccants (25 °C) for more than one year. Depending on the desolvation conditions of the hydrate or DMSO solvate variability in the crystallinity/ordering of anhydrous OTA is observed, which is also suggested by the computed low energy crystal structures. The variability in anhydride crystals is of practical concern as it affects the moisture dependence stability of the hydrate with respect to hydration. These studies highlight the value of

---

**Figure 1.** Schematic representation of the protocol for ab initio \(^{35}\)Cl solid state NMR crystallography of HCl salts of active pharmaceutical ingredients.

**Keywords:** Crystal structure prediction, NMR crystallography, \(^{35}\)Cl NMR, DFT calculated \(^{35}\)Cl NMR, Active Pharmaceutical Ingredients.