

From Model Compounds to Complex Reality: Structural Accuracy as a Foundation for Property Prediction

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Polymorphism plays a key role in determining the physicochemical properties of crystalline materials, yet accurately capturing the structural subtleties that distinguish one form from another remains challenging. This complexity becomes especially important when predicting thermodynamic stability, which requires accounting not only for lattice energy but also for molecular vibrations. These vibrational contributions to enthalpy and entropy—captured through normal mode analysis—are important for estimating free energy and phase transitions. However, for complex molecular crystals, such calculations remain computationally demanding, particularly due to the difficulty in accurately describing low-frequency modes.

To address this, we developed NoMoRe [1], a refinement method refines vibrational frequencies from periodic DFT calculations against single-crystal X-ray data rather than conventional ADPs, offering improved insight into thermal motion within the Independent Atom Model (IAM). We further extended this approach to AAM_NoMoRe [2], combining it with advanced aspherical atom models (Hirshfeld Atom Refinement (HAR) [3] or Transferable Aspherical Atom Model (TAAM) [4]), to provide a more realistic description of both hydrogen positions and thermodynamic properties.

We applied AAM_NoMoRe to classical polymorphic systems such as alanine, glycine, and glutamic acid, achieving improved structural fits and accurate prediction of temperature-dependent properties like heat capacity [2]. For glutamic acid, the calculated Gibbs free energy curves successfully reproduced the known phase transition between the α and β forms.

Encouraged by these results, we investigated a more complex system—oxytetracycline hydrochloride (OxyCl)—where large solubility differences were reported between two forms initially thought to be classical polymorphs [5]. Single-crystal XRD analysis revealed, however, that the forms were not true polymorphs, but rather an anhydrous salt and its hydrate. Additional solvated and hydrated forms were also characterized, underscoring the role of hydration, not polymorphism, in driving solubility.

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Financial support from Polish National Science Centre (SONATA17 grant 2021/43/D/ST4/03136) is kindly acknowledged.