Theoretical Chemistry: Thermodynamics and Kinetics of Molecular Crystals

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Gaining quantitative insight into the thermodynamics and kinetics of molecular crystals is vital for drug development and for advancing solvent-free, sustainable synthesis methods that rely on solid-state reactions. However, this remains a difficult task as molecular crystals often exhibit multiple polymorphs that differ by only a few kJ/mol in their Gibbs free energies while other properties can be significantly different. Thus, a reliable description of these polymorphs requires very accurate calculations to correctly capture their relative stabilities [1].

To make such calculations computationally more affordable, we are developing multimer embedding approaches [2, 3], which approximate expensive periodic quantum-mechanical calculations by embedding multimers into lower-cost periodic calculations. For instance, embedding PBE0+MBD multimers into periodic PBE+MBD reproduces lattice energies within 1 kJ/mol, unit cell volumes within 1 %, and harmonic vibrational free energies within 1 kJ/mol of the canonical periodic PBE0+MBD results. This approach also performed very well in a recent crystal structure prediction blind test [4]. Moreover, we can also use this methodology to incorporate anharmonic vibrational effects.

Additionally, we investigate energy barriers and transition pathways of molecular crystal transformations via solid-state nudged elastic band (NEB) calculations, covering interconversions between polymorphs and single-crystal chemical reactions. A key enabler is a new interpolation method that automatically generates viable initial pathways without atomic collisions, facilitating NEB studies of crystals containing larger and quite flexible molecules [5]. Since density functional theory (DFT) calculations are often already prohibitively expensive for this kind of simulation, we employ machine-learning force fields (MLFFs) to massively speed up the calculations while still maintaining near-DFT accuracy. These MLFFs can further be used to perform explicit molecular dynamics simulations of complex molecular crystal transformations. Together, these advances move toward a comprehensive and computationally efficient description of stability, polymorph transformation pathways, and reaction mechanisms in molecular crystals.

References:

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