MS33-O3

Accurate and efficient representation of intramolecular energy in ab initio generation of crystal structures. Part II: Smoothed Intramolecular potentials

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The CrystalPredictor[1] and CrystalOptimizer[2] codes have been used to explore the space of crystal structures successfully in several crystal structure prediction (CSP) investigations in recent years, including in the series of blind tests organised by the Cambridge Crystallographic Data Centre and in the prediction of the crystal structures of pharmaceutically-relevant molecules. One of the key research challenges in developing CSP capabilities is to enable the investigation of increasingly flexible compounds within tractable computational times, competitive with experimental polymorph screens.

We present recent advances in CrystalPredictor that are focussed on addressing this challenge. Specifically, we discuss the smoothing of the intramolecular potential,[3] an innovation in CrystalPredictor II that allows the most efficient use of computational effort to cover a flexible molecule's conformational space. This improvement achieves greater accuracy in the initial ranking of potential crystal structures, while managing computational cost, so that a thorough exploration of the search space is possible. We present CSP results for the highly polymorphic NSAID drug Flufenamic acid to demonstrate this capability, with a ≈ 30% increase in the efficiency of the global search stage, alongside increased confidence in the final polymorphic landscape.

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Phase diagram prediction by data mining via temperature-dependent force fields

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Modern force fields are accurate enough to describe thermal effects in molecular crystals. We applied the recently developed temperature-dependent force field (1) to predict the transition temperature for polymorphs. An estimation of the transition temperature of paracetamol demonstrated the possibility for prediction using the temperature-dependent force-fields.

The earlier approach of force fields for finite temperatures (2) is extended to a force field with a continuous function for the temperature. In this model the intermolecular potentials are described by effective atom pair potentials. Each atom pair potential is developed as Taylor series of $1/r^3$. The Pauli repulsion is extended by a temperature dependency: $1/r^{12} \rightarrow (1+alpha)/r^{12}$. For the parametrisation of the force field we used Data Mining on experimental structures (3) with the temperature as an additional descriptor. The temperature-dependent force field can be used as for the energy minimization at a finite temperature and for molecular dynamics, which requires zero-K potentials.

The parameters of the model have been obtained by training on 21,095 experimental crystal structures for hydrogen bonds in oxygen and nitrogen compounds. The force field is validated for the prediction of crystal density, temperature density gradients and transition temperature. The crystal density prediction was validated by minimization of all non-ambient crystal structures available in The Cambridge Structure Database. The mean error is halved by taking the temperature into account. We estimated the thermal density gradients of several organic crystals with experimental data of one substance at various temperatures. The error of the predictions varied from 0 to 29 %. Finally, a prediction of the transition temperature of paracetamol demonstrated the possibility for prediction phase diagrams.

In the abstract image the two polymorphs of paracetamol under investigation are shown. The orthorhombic modification (form II) transforms at 385 K to the monoclinic polymorph (form I) with the half cell volume.