

MS33-O3**Accurate and efficient representation of intramolecular energy in ab initio generation of crystal structures. Part II: Smoothed Intramolecular potentials**Isaac Sugden¹, Claire Adjiman¹, Costas Pantelides¹

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The CrystalPredictor¹ and CrystalOptimizer² 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 $\approx 30\%$ increase in the efficiency of the global search stage, alongside increased confidence in the final polymorphic landscape.

References:

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Keywords: Crystal Structure Prediction, polymorphism, computational chemistry

MS33-O4**Phase diagram prediction by data mining via temperature-dependent force fields**Detlef Hofmann¹, Liudmila Kuleshova²

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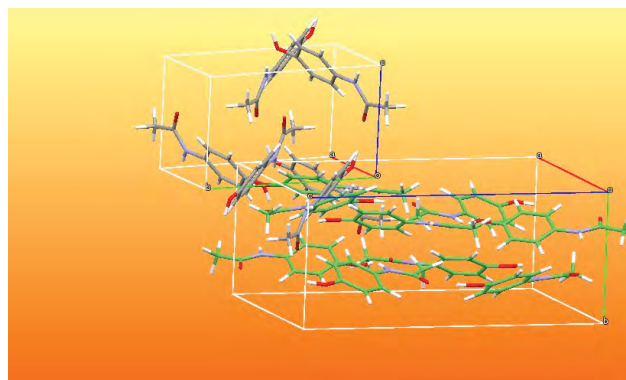
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Modern force fields are accurate enough to describe thermal effects in molecular crystals. We applied the recently developed temperature-dependent force field (1) to predict the transition temperature for polymorphs. An estimation of the transition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



References:

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Keywords: Crystal Structure Prediction, Data Mining, Force Fields

MS33-O5

X-ray diffraction data as a source of information of vibrational contribution to enthalpy and entropy of polymorphic systems

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The stability of crystals at a given temperature is determined not by the lattice energy, but by Gibbs free energy. Thus, to compare stabilities of polymorphs at given temperature beside lattice energy, one should take into account contributions from vibrational enthalpy, entropy and zero point energy. Those contributions can be calculated by means of DFT methods, but, as they require supercell calculations, they have high computational costs.

An idea of estimating entropy from X-ray diffraction data is not new - in 1956 Cruickshank [1] estimated entropy of crystalline naphthalene by means of TLS analysis from ADPs from single crystal X-ray diffraction data. In 1989 Jack Dunitz and co-workers used a similar approach to estimate the entropy of conformational polymorphs of dimethyl-3,6-dichloro-2,5-dihydroxyterephthalate [2]. Dunitz et al was able to explain the mechanism of phase-transformation based on an analysis of the Debye-Waller factors, but their results contradicted the well-established thermodynamic order of stability of the systems. They write:

“Why has our intuition led us astray in expecting that the crystal with the larger atomic ADP's should have the greater entropy?”

We decided to reinvestigate this particular polymorphic system with normal mode refinement, which enables the refinement of frequencies of normal modes obtained from *ab-initio* periodic computations at Γ point, against single crystal diffraction data. Frequencies obtained from *NoMoRe* can be used to estimate thermodynamic properties – heat capacity and vibrational contributions to entropy and enthalpy [3].

In order to conduct *NoMoRe* refinements we collected new high-quality single crystal X-ray diffraction data for polymorphs and we conducted DFT theoretical calculations of frequencies at Γ point and a reference supercell calculations. Estimates of the frequencies of acoustic modes, obtained after *NoMoRe* are in very good agreement with those from supercell calculations. Based on the *NoMoRe* analysis, we can predict, that white form is stable at high temperature range, and yellow at low temperature range, which is in agreement with experimental results. By discussing contributions from low and from high frequency modes to vibrational entropy and enthalpy we are able to explain the important question which was raised by Dunitz et al.