Theoretical Calculations to Assist Experimental Crystal Form Screening

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Abstract

Crystal structure prediction can be used to identify possible stable crystal forms that may not be easily obtainable through experimenters due to kinetics. The success of a crystal structure prediction study crucially depends on the quality of the method used for evaluating the lattice energies. Dispersion-corrected Density Functional Theory (DFT-D) calculations have proven to provide the accuracy required for crystal structure prediction of molecular compounds. The strengths and weaknesses of *in silico* polymorph screens with such high-quality quantum-mechanical calculations are discussed using results on the antiretroviral agent Efavirenz as an example.

Introduction

APIs can crystallise in multiple distinct forms, each with their own physical properties such as dissolution rate, crystal habit or melting point. This phenomenon, known as polymorphism, has long been recognised by pharmaceutical industry and regulatory bodies alike as playing a crucial role in the formulation of drugs marketed in crystalline form. Experimental screens for polymorphs, salt forms or co-crystals are an important instrument in determining the most suitable solid form. Especially the thermodynamic stability landscape needs to be explored thoroughly, as identification of the thermodynamically most stable form is paramount. Discovery of a more stable polymorph after a plant has been commissioned has implications for patents and for the manufacturing process—especially if the more stable polymorph is discovered by a competitor. The Achilles' heel of experimental polymorph screens is kinetics: the route to the thermodynamically most stable form may not be accessible during the experiments, causing the most stable form to be missed completely. Theoretical polymorph screens (generally referred to as crystal structure prediction) do not suffer from kinetics and are therefore the instrument of choice to complement experimental polymorph screens in order to check if possible stable polymorphs have been overlooked. In the early days, such *in silico* polymorph screens were highly unreliable due to the quick and dirty nature of the methods used in evaluating the relative thermodynamic stabilities of the predicted polymorphs. The availability of relatively cheap computing power, however, has changed this completely, as demonstrated in the 2007 Crystal Structure Prediction Blind Test when the application of high-quality quantum-mechanical calculations correctly predicted the crystal structures and relative stabilities of all four target compounds. In this presentation, the strengths and weaknesses of *in silico* polymorph screens with such high-quality quantum-mechanical calculations will be demonstrated using results on the antiretroviral agent Efavirenz as an example.

Material and Methods

In the 2007 crystal-structure prediction Blind Test for molecular compounds, the only method to correctly predict all target crystal structures was a method employing dispersion-corrected density functional theory (DFT-D) calculations; it is this method that is used in this work. The

VASP software (Kresse & Furthmüller, 1996, Kresse & Hafner, 1993, Kresse & Joubert, 1999) was used for single-point pure DFT calculations, which were augmented with a dispersion correction (see *e.g*. Grimme *et al*., 2010). The details of the crystal-structure prediction procedure can be found in the 2007 Crystal Structure Prediction Blind Test paper (Day *et al*., 2009). The main point that needs to be mentioned is that the DFT-D method is several orders of magnitude too slow to be used for the structure generation step. This problem is solved by creating an intermediate dedicated force field for the compound at hand. The details of such a parameterisation are described in a paper by Neumann (2008), but briefly, the procedure consists of generating a balanced, unbiased set of reference structures, covering all intra- and intermolecular parameters, that are energy-minimised with the DFT-D method and against which the tailor-made force field is fitted. This crystal-structure prediction procedure has been applied successfully to many model compounds (see *e.g*. Chan *et al*, 2011 or Van de Streek & Neumann, 2011) and to several confidential pharmaceutical case studies. Here we will present the results for Efavirenz (Figure 1), a non-nucleoside reverse transcriptase inhibitor that is used for the treatment of HIV-1. Efavirenz is chiral, and the crystal-structure predictions were carried out in all space groups that are allowed for an enantiomerically pure compound, with one and with two independent molecules. The molecules were fully flexible during the crystal structure generation step and during all following energy-minimisation steps.

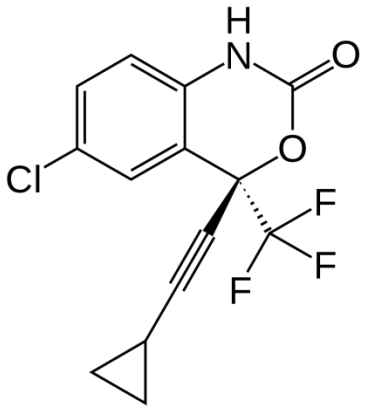

Figure 1. Structural formula of Efavirenz. The molecule has a chiral centre.

When the theoretical calculations were started, five patents on the polymorphism of Efavirenz had been published, claiming a total of 24 forms. For none of these forms had a crystal structure been published. Careful review of the five patents combined with an experimental polymorph screen showed that the 24 claimed forms corresponded to eight distinct forms, which we will designate A, B, C, D, E, F, H1 & N.

Results and Discussion

The results of the crystal structure prediction study are summarised in Figure 2. The simulated powder diffraction patterns of the predicted crystal structures were matched with the experimental powder diffraction patterns from the experimental polymorph screen and the patent literature. According to the predictions, the two crystal structures corresponding to experimentally observed forms C and F are the two most stable forms; this agrees with the information from the patent literature. The crystal structure of form F was later confirmed by a published single crystal study (Ravikumar & Sridhar, 2009).

Form B is found multiple times, with slightly different orientations of the cyclopropane ring. The experimental crystal structure confirms that this form is disordered (Cuffini *et al.*, 2009).

Form A turned out to be a crystal structure with a highly unusual number of independent molecules in the asymmetric unit (Mahapatra *et al.*, 2010); less than 0.5% of all published molecular crystal structures crystallise with three crystallographically independent molecules in the unit cell (Bond, 2008). Form D was confirmed by TGA to be a solvate. Neither of these two cases was considered during the crystal-structure generation, and these forms could therefore not be reproduced in the theoretical predictions.

The calculations took about two months on a cluster consisting of 64 1-GHz 64-bit quad-core Opteron processors.

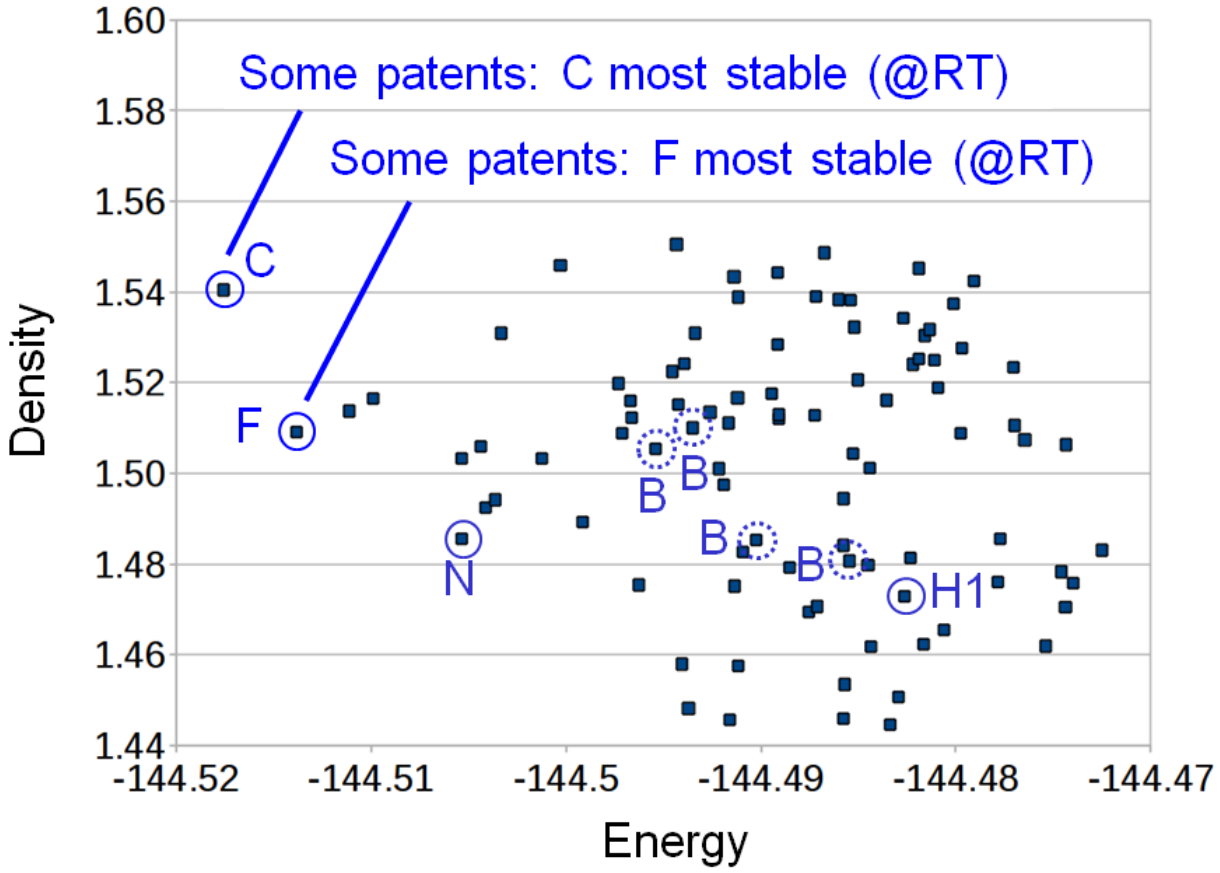

Figure 2. Summary of the results of the theoretical crystal structure prediction. *x*-axis: energy in kcal/mol/atom; *y*-axis: density in g/cm^3. Each point in the energy-*versus*-density plot represents a predicted crystal structure. Experimentally observed polymorphs are indicated by circles. Form B is disordered.

Conclusions

The results of the *in silico* polymorph screen on Efavirenz confirm the results of the experimental polymorph screens regarding the two most stable polymorphs; this is a strong indication that the most stable polymorph has been identified and that no more stable form will be found in the future. Polymorph prediction studies are not hampered by kinetics, but theoretical

predictions can only find polymorphs in the search space that was used for the prediction; solvates can only be predicted if the solvent molecule is included explicitly in the calculations. We conclude that *in silico* crystal form screening and experimental crystal form screening complement each other; when combined, the most stable modification of a compound can be identified with enhanced confidence.

The crystal-structure prediction study allowed the determination of several crystal structures from low-quality powder diffraction patterns of forms claimed in the patent literature.

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