

CRYSTAL STRUCTURE PREDICTION OF SMALL ORGANIC MOLECULES; KINETICS VERSUS THERMODYNAMICS

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The prediction of the crystal structures of small organic molecules from first principles is a tremendous asset in crystal engineering. This area is fraught with difficulties, as demonstrated in the series of Blind Tests in Crystal Structure Prediction (CSP) organised by the Cambridge Crystallographic Data Centre, and progress has been slow until recently. The application of a dispersion corrected solid state Density Functional Theory (DFT-D) approach in the 2007 Blind Test resulted in a perfect four out of four score [1]. The same method has been successfully applied to re-evaluate previous Blind Test predictions [2]. Considering all five Blind Tests held to date, the DFT-D method has correctly predicted 18 out of 21 target structures according to the Blind Test rules.

Past failures in CSP have been attributed to the kinetic nature of the crystallisation process as well as the selection criterion of thermodynamic stability used in CSP to predict which few crystal structures out of a large number of candidates are most likely to exist in reality. An example is Molecule VI from the 2001 Blind Test, a sulfonimide now known to exist in three polymorphic forms. None of these polymorphs had been predicted; indeed they were believed to be “beyond prediction” [3]. However, a full CSP study using the DFT-D method has now predicted its known polymorphs as the three most stable crystal packing alternatives, in the correct stability order [4]. These results indicate that past failures to predict the polymorphs of Molecule VI were not due to the kinetic nature of the crystallisation process, but due to the inaccuracies of the energy calculation methods used. In other words, lattice energies suffice as a selection criterion in CSP of small molecules provided they are calculated accurately.

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