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Computed Crystal Energy Landscapes for Understanding and Predicting Organic Crystal Structures and Polymorphism

Abstract:

The international blind tests have shown considerable progress in the ability of the computational community to predict simple organic crystal structures. In 2007, all four crystal structures were correctly predicted by two different approaches to evaluating the lattice energy.[1] However, the structure which is the global minimum in the lattice energy is only the structure which is the most thermodynamically stable independent of temperature, with the "correct answer" in the blind test being the first crystal structure that had been characterised by single crystal diffraction. There is a huge difference between the proportion of molecules with two or more well-characterised polymorphs in the CSD and those found to have multiple crystalline forms when an extensive effort is made to find polymorphs. The industrial importance of polymorphism and the need to characterise many forms from powder samples means that we need to consider the crystal energy landscape, i.e. all the structures which are within the energy range of potential polymorphs, rather than just the global minimum.

The crystal energy landscape can predict polymorphs that are found later, either by serendipity or by deliberate targeting using the predicted crystal structure. The range of hydrogen bond motifs in the low energy structures can help rationalise solvate as well as polymorph formation. There are cases where the interchangeably of motifs in the low energy crystal structures rationalises disorder in the observed crystal structure. There are usually many more structures on the crystal energy landscape than known polymorphs, and the hydrogen-bonded motifs in some of them often appear in multi-component forms. Hence computing the crystal energy landscape is a worthwhile complement to experimental sold form screening,[2] particularly when the dominant structural motifs are compared with those in the experimental forms. However, it is only a first step on the path to genuine control and prediction of the solid state of many organic materials.

1. Day GM, Cooper TG, Cruz Cabeza AJ, Hejczyk KE, Ammon HL, Boerrigter SXM, Tan J, Della Valle RG, Venuti E, Jose J, Gadre SR, Desiraju GR, Thakur TS, van Eijck BP, Facelli JC, Bazterra VE, Ferraro MB, Hofmann DWM, Neumann M, Leusen FJJ, Kendrick J, Price SL, Misquitta AJ, Karamertzanis PG, Welch GWA, Scheraga HA, Arnautova YA, Schmidt MU, van de Streek J, Wolf A, Schweizer B. Significant progress in predicting the crystal structures of small organic molecules - a report on the fourth blind test. Acta Crystallogr , Sect B 2009, In Press.

2. Price SL. Computed Crystal Energy Landscapes for Understanding and Predicting Organic Crystal Structures and Polymorphism. Accounts of Chemical Research 2009;42:117-126.