Oral Contributions

[MS23-03] The road not taken: the crystal energy landscape as an interpretive tool

Matthew Habgood

(Imperial College London)
email: m.habgood@imperial.ac.uk

Contemporary crystal structure prediction methods often aim not just to predict a single crystal structure, but to generate a 'crystal energy landscape', a set of hypothetical crystal structures which are thermodynamically stable. The most stable of these, the global minimum of the landscape, is expected to correspond to the most stable polymorph of the molecule. All too often, the rest of the structures in the landscape are simply treated as (vague) suggestions as to possible metastable polymorphs. This need not be the case, since the landscape as a whole contains a wealth of information on the range of feasible solid state behaviours of the molecule. If we wish to modify the solid state behaviour of (for example) an active pharmaceutical ingredient, the predicted crystal structures that are not found experimentally may be unexpectedly valuable, alerting us to alternative interaction modes that could be exploited, for example by chemical modification, or by introduction of a second component in a salt or cocrystal. Crystal energy landscapes have already been interpreted to rationalize the formation of disordered crystals and multiple solvates. [1-3] In this talk I will discuss the use of predicted but (as yet) unobserved crystal structures to identify the critical molecular features and intermolecular interactions in two case studies. The first of these is salicylsalicylic acid (salsalate) which notably forms an amorphous phase that is long-term stable both below and above its glass temperature. [4] Generation of the crystal energy landscapes for different conformers reveals a pair of hydrogen bonding motifs that appear to promote amorphous behaviour, being associated with less-stable, badly packed crystal structures that nonetheless dominate the landscape in terms of frequency. The stability of the amorphous phase is also rationalized by the conformer associated with these motifs, which would require considerable rearrangement (and hence a considerable kinetic barrier) to reproduce the crystalline form. The second case study is the contrasting chiral cocrystallisation behaviour of the molecule pairs levetiracetam : mandelic acid, levetiracetam : tartaric acid, and tartaric acid : malic acid. The former two systems are enantioselective, [5] with levetiracetam (S-2-(2¬oxopyrrolidin-1-yl)butyramide) reported to cocrystallise only with S-mandelic acid and (2S, 3S)-tartaric acid, whereas the latter system forms a diastereomeric cocrystal pair. [6] Crystal energy landscapes allow us to study the hypothetical levetiracetam : R-enantiomer cocrystals, and hence to identify the structural mechanisms of chiral selection. In each of these systems the key is shown to be the $R_2^2(8)$ dimer's response to the change in enantiomer and the presence or absence of competitive strong hydrogen bonding motifs. I will also report on recent improvements to the crystal structure prediction methodology used at Imperial College, and in particular the use of quadratic Local Approximate Models (LAMs) to model intramolecular energy at the structure generation stage.

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