How many Ritonavir cases are still out there?

Marcus A. Neumann, Jacco van de Streek, Hanno Dietrich, Kiran Sasikumar, Asbjörn Burow, Avant-garde Materials Simulation Deutschland GmbH, Germany, marcus.neumann@avmatsim.eu

On rare occasions, a crystal structure that has been prepared for years is unexpectedly "superseded" by a thermodynamically more stable polymorph, rendering the initial crystal structure almost impossible to obtain—a so-called "disappearing polymorph" [1]. Famous cases included the drug compounds Ritonavir and Rotigotine: the thermodynamically more stable polymorph is substantially less soluble and required a costly reformulation before a product with comparable specifications could be manufactured again.

On a case-by-case basis, the probability of a kinetically hindered but thermodynamically stable polymorph having been missed in an experimental polymorph screen can be assessed by a computational crystal structure prediction study: the calculations do not suffer from kinetics and will in principle enumerate all possible crystal structures for a given compound; comparison against the experimental structures identifies any missed polymorphs. In a recent paper, we presented the results of 41 such computational crystal structure prediction studies to draw up statistics regarding the number of hidden Ritonavir cases [2]. The main finding of the paper was that between 15 and 45% of all experimental crystal structures are in fact thermodynamically unstable.

The large spread in our estimate was due to the computational error in the calculation of the relative free energies of the predicted polymorphs. Even though the computational error is estimated to be as small as 0.5 kcal/mol, about half the size of the gold standard referred to as "chemical accuracy", the experimental energy differences between polymorphs are also around the 0.5 kcal/mol mark, and to reduce the large spread in our estimate an even more accurate energy model was needed.

The shortcomings of our old energy model—neglect of temperature, relatively poor accuracy of the exchange part of the functional used in the DFT calculations, and the assumption that Van der Waals interactions are pairwise additive—are well documented, and in this contribution we will present the results of an energy model in which these shortcomings have been addressed [3]. With the availability of more accurate relative lattice energies, we are able to narrow down our estimate of how many pharmaceutical compounds are out there for which the most stable crystal polymorph has not yet been observed.

References

[1] D.-K. Bučar, R. W. Lancaster & J. Bernstein (2015), "Disappearing Polymorphs Revisited" *Angew. Chem., Int. Ed*. **54**, 6972-6993.

[2] M. A. Neumann & J. van de Streek (2018), "How Many Ritonavir Cases Are There Still out There?" *Faraday Discuss*. **211**, 441-458.

[3] J. Hoja, Hsin-Yu Ko, M. A. Neumann, R. Car, R. A. DiStasio Jr. & A. Tkatchenko (2019), "Reliable and Practical Computational Description of Molecular Crystal Polymorphs" *Sci. Adv*. **5**, eaau3338.