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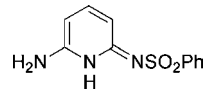
Editorial

Polymorphism - Still Unpredictable?

I have been fascinated by polymorphism ever since a routine preparation of a 2−4-nitrophenylhydrazone, during my undergraduate work in 1966−67, produced two different coloured crystals, with different melting points, depending on the crystallisation solvent used. More than 40 years on, this subject retains its fascination, partly because of the lack of predictability of polymorphism. A statement in a recent paper "Serendipity often plays a key role in the discovery of new forms, because no general methodology exists for producing new forms of a given compound"[1], will ring true to many process chemists, who may have seen a new crystalline form appear late in the development of a new drug substance. There are many examples of this in *Org. Process Res. Dev.* (OPRD) papers, one of the most interesting being the paper from Bristol Myers Squibb, where two new forms appeared after many batches had been made.[2]

Prediction of crystal structure from a given chemical substance, and hence its polymorphism, is a desired goal which has not been routinely achieved, despite one or two successes with specific molecules. Periodically, blind tests are organised where scientists are challenged to predict crystal structures of specific molecules, and the results are compared to the actual experimental results. Such a blind test in 2001 for the molecule shown below ended in failure, with none of the participants being able to predict the structure correctly. A later study found a second polymorph of the molecule, that was claimed to be the more thermodynamically stable form.



Now a reinvestigation of the polymorphism of this molecule,[2] which clearly has lots of H-bonding options, has revealed a new form III, and the relative stability of the three forms has been elucidated by slurry experiments. These have shown that form I, the structure originally reported as the blind-test solution, is in fact more stable than form II by 0.44 kcal/mol and more stable than form III by 0.23 kcal/mol. The results of all teams in the 2001 blind prediction trial were re-examined, and it was still shown that the two more stable forms (I and III) were absent from all predictions.

Therefore, structure prediction, which would be most valuable for process chemistry, has still a way to go, which is both good news and bad news. The good news is stated in the conclusion in the cited paper.[2] "After two decades, although improvements have been made, there is still considerable job security for the experimental chemist and crystallographer"— a much needed view in the current economic climate.

Trevor Laird
Editor

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(1) Roy, S.; Matzger, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8505–8508.
(2) Desikan, S.; Parsons, R. L., Jr.; Davis, W. P.; Ward, J. E.; Marshall, W. J.; Toma, P. H. *Org. Process Res. Dev.* **2005**, *9*, 933–942.

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