Extensive polymorph screening of the nucleobase adenine

D. Šišak Jung[a*], I. Halasz[b], D. McDonagh[c,] G.M. Day[c]
[a] *DECTRIS, Switzerland*
[b]*Division of Physical Chemistry, Ruđer Bošković Institute, Croatia*
[c]*School of Chemistry, University of Southampton, UK*
** dubravka.sisak@dectris.com*

Crystal structure prediction algorithms often result in densely populated energy landscapes, featuring a (very) high number of polymorphs. However, the experience tell us that a successful polymorph screening of small molecule is not likely to yield more than three polymorphs and a (couple of) amorphous phase(s). Success of the polymorph screening depends the optimization of three factors (i) the use of many different synthetic procedures to create new polymorphs, (ii) resolution and sensitivity of the X-ray diffractometer to detect the new polymorphs (iii) good understanding of the energy landscape and a possibility to rank the predicted structures.

This work presents how a combination of experimental techniques and theoretical methods can result in a surprising number of polymorphs, even if the molecule in question is very simple. The target molecule of this research is adenine, one of the smallest molecules of life. However, *ab initio* structure prediction conducted only in the common space groups resulted in more than 1500 low-energy structures. In order to explore the energy landscape, several synthetic paths were used: crystallization from a solution, sublimation, slurrying and thermally-induced phase transition. This resulted in four adenine polymorphs, of which only one was obtained as a single crystal. Further two were detected as a component in a powder mixture. This was possible only due to the fact that highly resolving diffractometers were used for the measurement, including a diffractometer optimized for *in situ* x-ray diffraction. As last, structure determination of these polymorphs was based on four different techniques: single crystal diffraction, powder diffraction, total scattering and *ab initio* structure prediction.

This focus of this work are the procedures used to obtain and characterize polymorphs, particularly on polymorphs detected in *in situ* powder diffraction studies. One new polymorph is characterized as a liquid crystal. The other polymorph cannot be isolated from the mixture, so a*b initio* structure prediction was used for its characterization. The novel laboratory diffractometer will also be presented.

[1] Mahapatra, S.; Nayak, S. K.; Prathapa, S. J.; Guru Row, T. N. *Cryst. Growth Des*. 2008, 8, 1223.

[2] Stolar T. et al. *Cryst. Growth Des*. 2016, 16, 3262.

[3] Proffen, T.; Neder, R.B. J. Appl. Cryst. 1997, 30, 171-175.

[4] Case, D. H. et al. J. Chem. Theory Comput. 2016, 12, 910-924.

[5] Price, S. L. et al. *Phys. Chem. Chem. Phys.* 2010**,** 12, 8478-8490.

Keywords: crystal structure prediction, in situ, polymorph screening