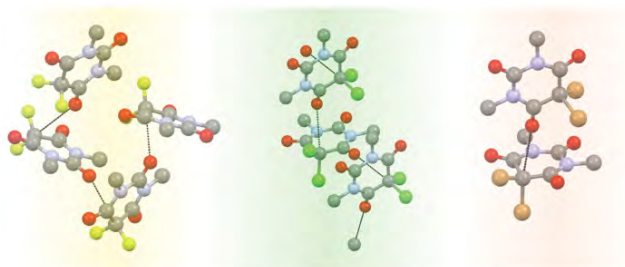


Fig. 1 Adducts present in crystals of 5,5-difluoro- (left), 5,5-dichloro- (mid), and 5,5-dibromo-N,N'-dimethylbarbituric acid (right); F–C⋯O=C tetrel bonds are dashed black lines.



References:

- [1] Murray, J. S. et al. (2017) *Faraday Discuss.* 203, 113–130.
 [2] Scilabra, P. et al. (2017) *J. Fluorine Chem.* 203, 62–74.
 [3] Cavallo, G. et al. (2014) *Cryst. Growth Des.* 14, 2697–2702.

Keywords: Tetrel bond, Pnictogen bond, Crystal engineering

MS32-O3

Is it usual to be unusual? - An investigation into Molecular Conformations in Organic Crystals

S. E. Wright¹, M. Bryant², R. J. Davey¹, A. J. Cruz-Cabeza¹

1. School of Chemical Engineering and Analytical Science, University of Manchester, Manchester, United Kingdom
 2. Cambridge Crystallographic Data Centre, Cambridge, United Kingdom

email: sarah.wright-6@postgrad.manchester.ac.uk

The molecular complexity and size of novel drug molecules is ever increasing, and so is their conformational flexibility. Complex flexible drug compounds may often be challenging to crystallise. Crystallisation is the final step in the manufacture of active pharmaceutical ingredients and with over 90% of pharmaceuticals being crystalline it is important to understand and control this process. The poor crystallisation behaviour of flexible molecules has been linked to the conformational diversity found in solution [1]. In solution, conformers are in equilibrium and their relative populations depend on their relative stabilities. If a crystal conformation is similar to that of a stable conformer in solution, no conformational change or adjustment would need to occur for the system to nucleate and grow [2]. However, if the crystal conformation corresponds to a highly distorted conformer or a higher-energy conformer, then significant conformational adjustment or change would need to occur during crystallisation [3]. Such conformational changes and adjustments may limit crystal growth and are the subject of the present research.

We have investigated the occurrence of unusual conformations in the Cambridge Structural Database (CSD) for various subsets of molecular crystals. Torsion angles in flexible molecules were classified as being “unusual” when they were observed in less populated areas of the CSD torsion distributions. We then investigate the conformational energy landscape of these molecules crystallising with unusual torsions. How usual is it to be unusual? Do these “unusual” torsions relate to high-energy conformations? How much conformational distortion is required for some molecule to crystallise? What causes these torsions to become unusual? Are certain torsions more prone to distortion and change? This contribution attempts to answer all of these questions by providing new insightful data on the effect of crystal structure on conformations.

References:

- [1] L. Derdour, S. K. Pack, D. Skliar, C. J. Lai and S. Kiang, *Chem. Eng. Sci.*, 2011, 66, 88–102.
 [2] A. J. Cruz-Cabeza and J. Bernstein, *Chem. Rev.*, 2014, 114, 2170–2191.
 [3] H. P. G. Thompson and G. M. Day, *Chem. Sci.*, 2014, 5, 3173–3182.

Keywords: Molecular Conformation, Energy, Crystallisation