

# Kinetic insights into polymorphism in pharmaceutical (solid state) chemistry

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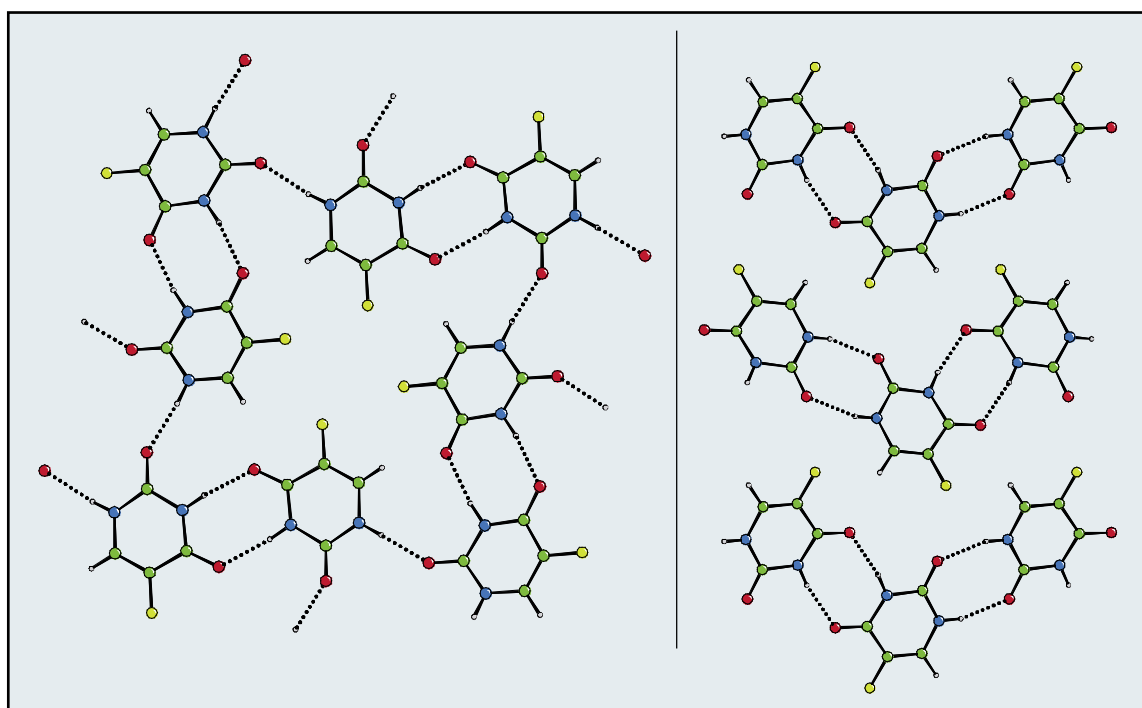


Figure 1. The sheets in the crystal structures of form I (left) and form II (right) of 5-fluorouracil ( $C_4H_3FN_2O_2$ ).

Why can a new solid form of an organic molecule only be found after many man-years of work on the compound?

The late discovery of new polymorphs, which are often more thermodynamically stable, can lead to problems in producing the original solid form in a controlled manner. This is a major problem for the pharmaceutical companies, who are only licensed to sell their products in a specified solid form, as although polymorphs are chemically identical, their physical properties, such as dissolution rates, differ. As recently as 1998, Abbott Laboratories had to reformulate their anti-HIV drug ritonavir, when the manufacturing process suddenly started to produce a more stable polymorph [1]. The discovery of a new polymorph by a rival pharmaceutical company, even if it is metastable but can be controllably produced, is a threat to the company's patent on their active molecule. Thus an ability to predict polymorphism computationally would be of considerable practical utility to the pharmaceutical and other organic materials industries, as well as aiding the design of new materials.

We have recently found [2] a new polymorph of 5-fluorouracil, an anti-cancer agent that has been known since 1957. The original crystal structure (now form I) is unusual, with 4 molecules in the asymmetric unit cell and close contacts between the fluorine

atoms (Figure 1). A computational search for minima in the lattice energy, calculated using a realistic model for the electrostatic intermolecular interactions, found that there were many hypothetical structures with lattice energies up to 6 kJ/mol more stable than the known form, and more typical hydrogen bonding motifs. A large series of crystallisation experiments finally yielded a crystal of a new polymorph, form II, which was shown by X-ray diffraction to have the structure predicted as the global minimum in the lattice energy within a few percent error in the cell lengths.

It proved remarkably difficult to obtain further samples of form II, until it was realised that the solvent from which it was crystallised, nitromethane, had to be dry. The hygroscopicity of nitromethane and the low solubility of 5-fluorouracil imply that there would be between 4 and 40 water molecules to each 5-fluorouracil in a solution that had been exposed to normal air. The specificity of the solvent required for the production of form II suggested that the kinetics of molecular association within different solvents might explain the polymorphism of 5-fluorouracil.

HPCx was used to investigate [3] this hypothesis, by performing a series of Molecular Dynamics simulations, using DL\_POLY [4], of 5-fluorouracil in water and nitromethane. It was observed that water molecules hydrogen-bonded strongly to the carbonyl

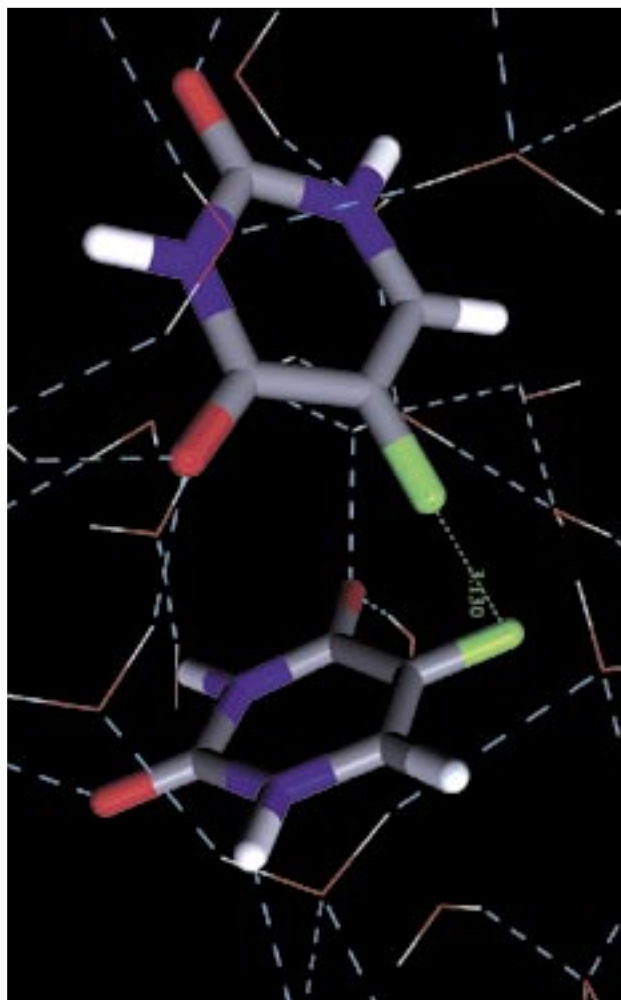
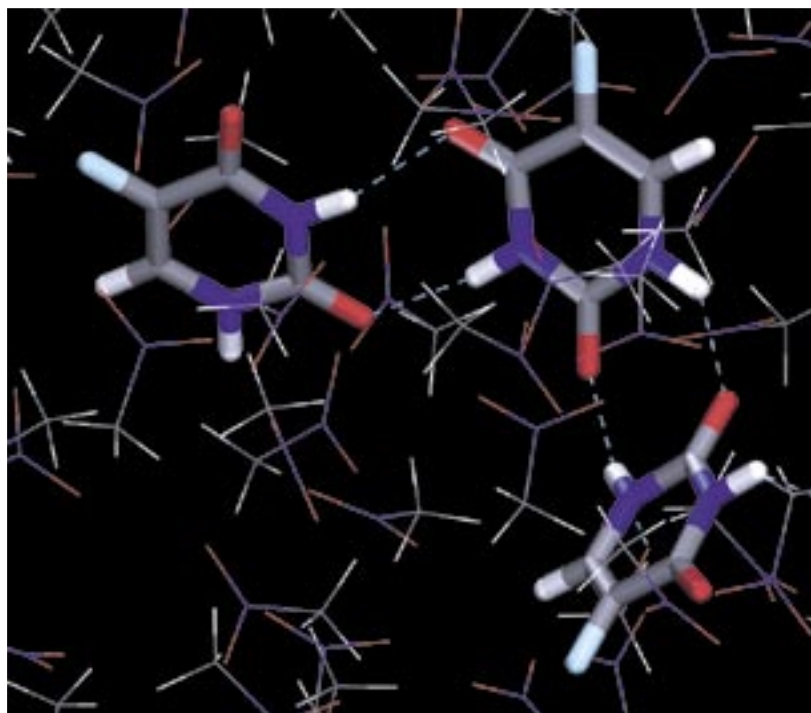


Figure 2 (left). Snapshot from the MD simulation of 5-fluorouracil in water, showing the hydrogen bonds within the solvent and to 5-fluorouracil, and the short F...F contact in the solute association.

Figure 3 (below). Snapshot from the MD simulation of 5-fluorouracil in nitromethane, showing the hydrogen bonding that is also seen in form II.



groups, forming a partial hydration sphere around the polar part of the molecule, but not approaching the fluorine closely. Thus there was a tendency for the 5-fluorouracil molecules in water to associate through close F...F contacts as shown in Figure 2. Some single hydrogen bonds were also formed in aqueous solution, but the hydrating waters seemed to prevent the formation of a second hydrogen bond between the solute molecules. In contrast, nitromethane molecules were more evenly and loosely associated with the 5-fluorouracil molecules in the simulated nitromethane solution. In this case, the contacts between a pair of 5-fluorouracil molecules generally formed two hydrogen bonds quickly and this dimer motif was very persistent. Indeed, some instances of trimer formation were also observed, such as that shown in Figure 3, which forms the building block for form II. Thus the MD simulations seem to account for the different crystal forms in terms of the differences in the molecular association in the different solvents, in a way that has also been recently inferred from FTIR solution spectroscopy to account for the polymorphism in tetrolic acid [5].

These simulations were only designed to study the very first step in crystallisation, the initial association of the solute molecules. Following this success, we hope to use the HPCx capability to give molecular level insights further into the nucleation process for other organic systems, but this will require even larger system sizes and simulation times.

This Molecular Dynamics investigation was carried out by Said Hamad under the direction of Richard Catlow at the Royal

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*If you are interested in the project's progress, please see the website <http://www.cposs.org.uk> which includes an invitation to an open day on 13th September.*

#### Reference List

- [1]. Chemburkar, S. R.; Bauer, J.; Deming, K.; Spiwek, H.; Patel, K.; Morris, J.; Henry, R.; Spanton, S.; Dziki, W.; Porter, W.; Quick, J.; Bauer, P.; Donaubauer, J.; Narayanan, B. A.; Soldani, M.; Riley, D.; McFarland, K. *Organic Process Res. Dev.* 2000, 4, 413-417.
- [2]. Hulme, A. T.; Price, S. L.; Tocher, D. A. *J. Am. Chem. Soc.* 2005, 127, 1116-1117.
- [3]. Hamad, S.; Moon, C.; Catlow, C. R. A.; Hulme, A. T.; Price, S. L. *in preparation.*
- [4]. Smith, W.; Forester, T. R. *J. Mol. Graphics* 1996, 14, 136-141.
- [5]. Parveen, S.; Davey, R. J.; Dent, G.; Pritchard, R. G. *Chem. Commun.* 2005, 1531-1533.