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Guiding Crystal Habit Modification

using Full Interaction Maps

Investigation of preferred interaction patterns in differing crystal growth directions enables strategies for control of crystal morphology.

The particle shape of chemical compounds can have a profound effect on how the solid state behaves. Tableting, flow, dispersion and filtering properties, and even shelf-life may be dependent to some extent on the habit or morphology of the crystalline solid state, and it is therefore an important parameter to understand in an industrial development process, for example in the production of a drug or medicine. In the first instance, the crystal habit depends on the arrangement of molecules within the crystal, and can therefore vary between different polymorphs or crystal forms, but it is possible to exercise some control over the morphology to obtain improved handling properties. Use of the Cambridge Crystallographic Data Centre (CCDC) Full Interaction Maps tool can help to guide strategies for crystal habit modification.

The Full Interaction Maps capability relies upon the CCDC's IsoStar[1] software. This is a library of preferred intermolecular interaction geometries, derived for a very broad range of combinations of specific organic functional groups by superposing close interactions from hundreds of thousands of entries in the Cambridge Structural Database (CSD)[2]. The Full Interaction Maps functionality takes all relevant interactions and maps the space around a single molecule, or collection of molecules (*e.g.* a crystal surface or simulated particle), to show the preferred positions of interactions with specific organic functional groups of different types, such as H-bond donors and acceptors, and hydrophobic groups. Factors such as steric hindrance and scaling are automatically taken into account.

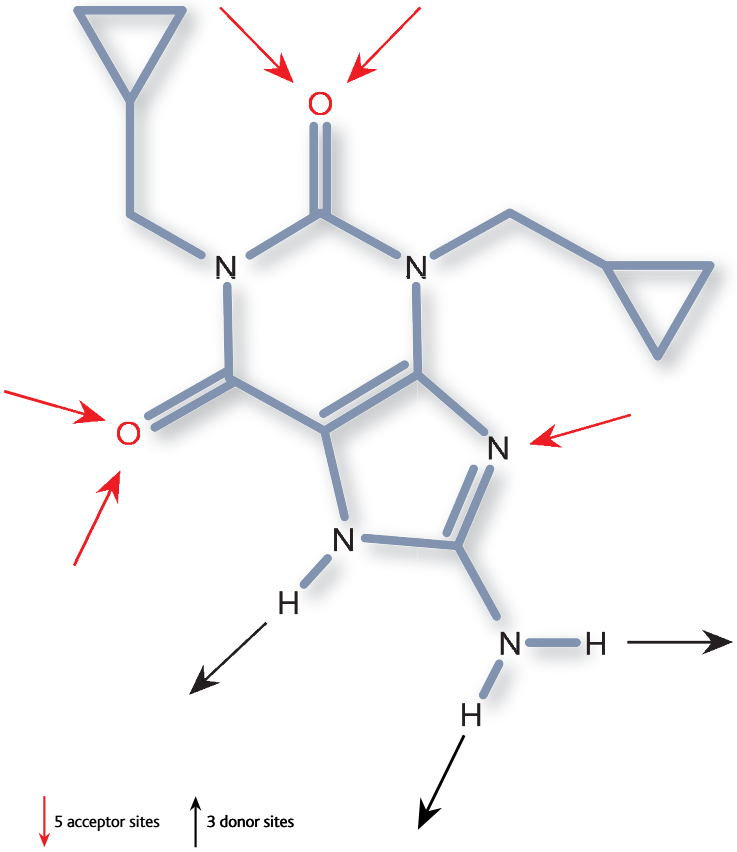

Fig. 1: The 2D chemical structure of cipamfylline, showing available acceptor and donor interactions

Cipamfylline (see **Fig. 1**) is an anti-inflammatory drug which is known to have at least three polymorphs. Two of these – forms A and C – exhibit needle-like habits, which can cause problems in pharmaceutical development as tableting, filtering and flow properties are not optimal. **Fig. 2** shows the predicted BFDH[3] morphology for form A of cipamfylline, created using the program Mercury[4] and packed with molecules in the corresponding lattice orientation. It is elongated along the crystallographic *c*-axis, corresponding well with experiment[5].

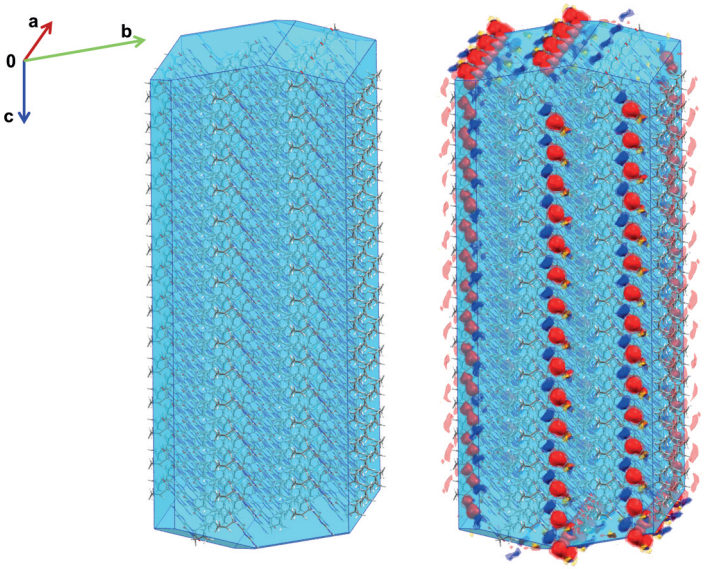

Fig. 2: BFDH predicted morphology for cipamfylline form A (CSD refcode MOVYEC), showing molecular arrangement (left) and calculated Full Interaction Maps (right)

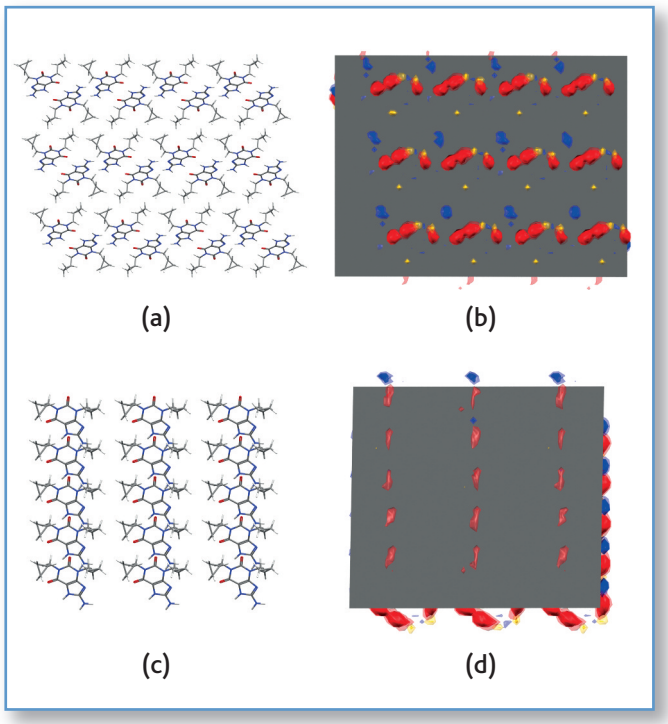

Fig. 3: Perpendicular views onto two surface planes of the cipamfylline crystal lattice, showing the arrangements of molecules and the corresponding Full Interaction Maps. The (001) surface is shown in (a) and (b), the (010) surface in (c) and (d)

The longest axis in a crystal's morphology indicates the fastest growing direction. **Fig. 3** shows the arrangements of molecules and the corresponding Full Interaction Maps for the (001) surface ((a) and (b)) and the (010) surface ((c) and (d)). The (001) surface is perpendicular to the fastest growing direction of the crystal – the long axis of the needle. Preferred inhibition of growth along this direction will tend to make the needle-like habit more isotropic, improving the handling properties during processing.

Investigation of the (001) surface – the fastest growing plane – shows a strong pattern of H-bond acceptor and donor interactions, as well as a component of hydrophobic stacking, whereas the interactions on the (001) surface – one of the slower growing sides of the needle – are weaker and ill-defined. This presents an opportunity for the design or discovery of a crystal growth inhibitor, which even at low concentrations would fit selectively onto the fast-growing (001) surface, slowing growth in that direction and thereby modifying the habit to improve particle handling behaviour.

For further information about Full Interaction Maps, see Wood et al.[6]

References

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