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Understanding Polymorph Stability

using Full Interaction Maps

An understanding of the relative stabilities of observed crystal forms may be gained by examining how satisfied the preferred intermolecular interactions are in the lattice.

An understanding of the relative stability of a compound's crystal form can be crucial if it is a candidate for a drug product. There have been occurrences in which a later emergence of a more stable polymorphic form has caused withdrawal of a drug product from the market, costing the manufacturers hundreds of millions of dollars; ritonavir is the classic example of this[1]. Use of the Cambridge Crystallographic Data Centre (CCDC) Full Interaction Maps tool can help bolster this understanding and mitigate this risk.

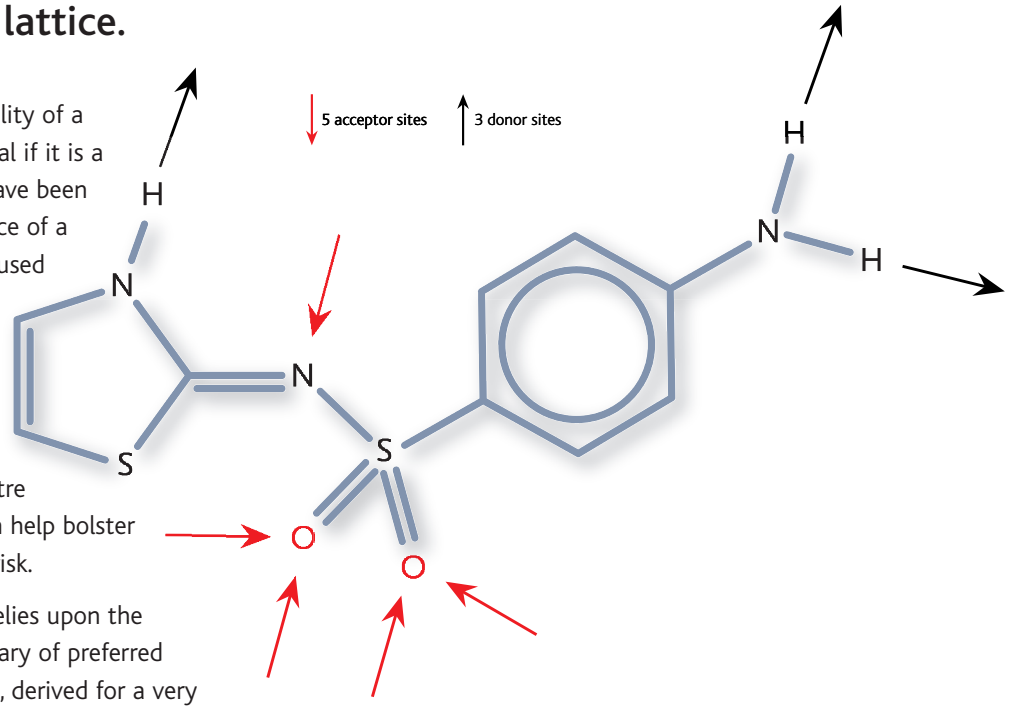

Fig. 1: The 2D chemical structure of sulfathiazole, showing available acceptor and donor interactions

The Full Interaction Maps capability relies upon the CCDC's IsoStar[2] 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)[3].

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.

The drug molecule sulfathiazole (**Fig 1**), which was used as an oral and topical anti-microbial agent until safer alternatives became available, currently has five observed pure crystal forms (not including salts, solvates, hydrates or co-crystals). If we examine the Full Interaction Maps for these forms, we can discern whether the packing of the molecules in each lattice satisfies the nature and geometry of preferred interactions for each sulfathiazole molecule.

Fig. 2 shows the H-bond donor (blue) and acceptor (red) maps at different contour levels for the sulfathiazole molecule as observed in form V (polymorph numbering as in Gelbrich et al.[4]). The illustration in (a) shows levels of 2, 4 and 6 times random probability (*i.e.* interactions appear in these positions multiple times what would be expected from a random distribution in space) with increasing opacity. At a level of probability contouring of 6 times random as in (b), there are five clear "hotspots" around the molecule, showing where donor and acceptor functional groups should sit for the molecule's interaction preferences to be satisfied.

If we look at the interaction maps in the context of the form V crystal structure packing (CSD entry SUTHAZ19; **Fig. 3a**), we can see clearly that all five of these hotspots around the molecule are satisfied by appropriate acceptors and donors, with near to ideal geometries. This implies that this polymorph is likely to be very stable, as all of its hydrogen bonding capability has been used in the lattice with good geometries, and indeed form V is the most stable known polymorph of this compound.

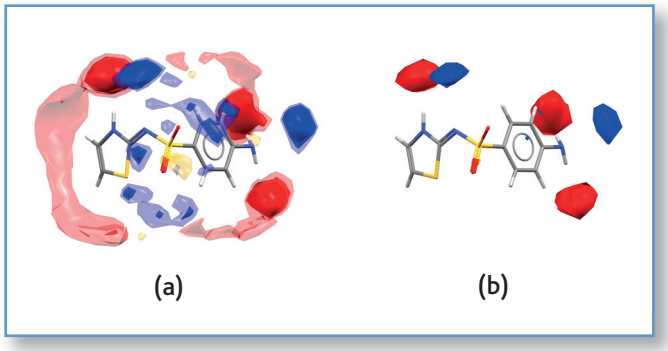

Fig. 2: Full Interaction Maps for a molecule in sulfathiazole form V, showing "hotspots"

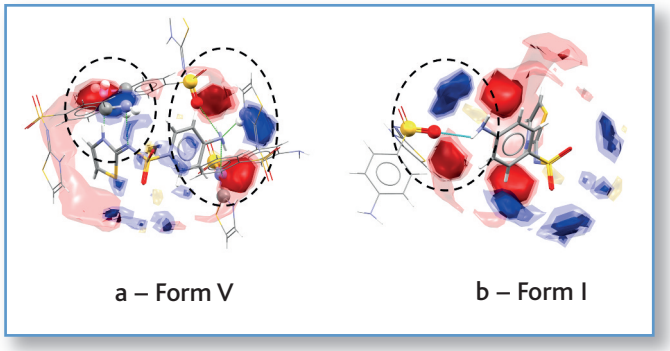

Fig. 3: Satisfaction of hotspots in Full Interaction Maps for molecules in sulfathiazole forms V and I

The form I crystal structure (CSD entry SUTHAZ16) is the least stable known polymorph. **Fig. 3b** shows the Full Interaction Maps hotspots and some of the crystal structure packing. In this structure no donor is interacting with the primary amine nitrogen acceptor, and a hydrogen bond is observed with non-ideal geometry in which the same nitrogen is the donor.

Should form I have been discovered first, an analysis using the Full Interaction Maps tool would have flagged that this may not be the most stable form, strongly suggesting that polymorph screens should be carried out before progressing to registration of the solid form and its use in drug products, thereby avoiding a potentially disastrous and costly late emergence of a more stable polymorph and subsequent withdrawal of the product from the market.

For further information about Full Interaction Maps, see Wood et al.[5]

References

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