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On the predictability of supramolecular interactions in molecular cocrystals – the view from the bench†

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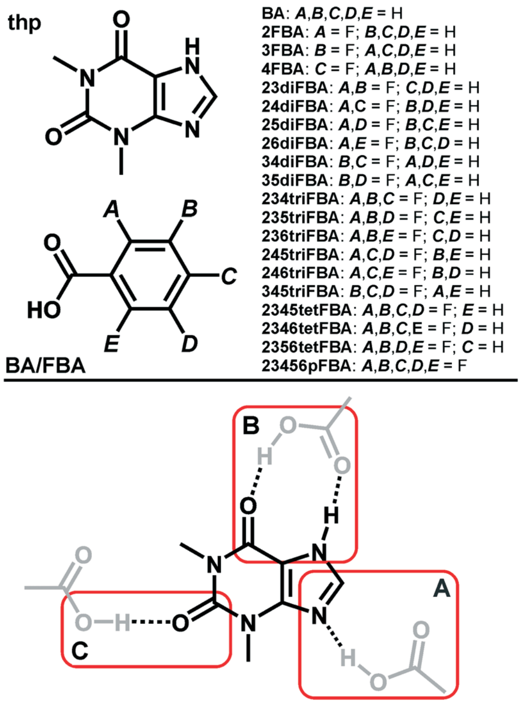
A series of theophylline cocrystals involving fluorobenzoic acids was prepared and structurally characterised. The cocrystals display compositions and hydrogen-bond patterns that could not be predicted based on extensive literature/database surveys and the use of other tools. The study demonstrates that – without the use of first-principles crystal structure prediction methods – it is still remarkably difficult to predict and understand the outcomes of cocrystallisation attempts involving small and rigid molecules.

Crystal engineering concerns the understanding, design, assembly and use of crystalline materials.[1] Although great strides have been made in all four spheres in the last few decades,[2,3] understanding and designing molecular crystals remains a substantial challenge for solid-state chemists.[4] The design of organic crystals relies on the concept of supramolecular synthons,[5] *i.e.* persistent structural motifs within molecular assemblies that are formed through robust and directional non-covalent interactions, such as hydrogen or halogen bonds. The use of this concept has enabled the straightforward design and assembly of targeted discrete, one-, two- and three-dimensional structures using a single molecular building block.[6] However, the assembly of more complex targeted structures, based on several molecules, is much more demanding[7] and associated with more modest success rates.[8–10]

Early successful instances of the synthon approach to molecular assembly were informed by crystallographic studies of molecular crystals.[11] It is widely believed that the design and construction of cocrystals involving complex molecules will be similarly enabled by further crystallographic studies focusing on synthon hierarchies in multicomponent crystals.[12–16] At present, cocrystal design is also aided by the use of statistical tools (*e.g.* knowledge-based hydrogen-bond propensity calculations or HBPC[17,18]) and computational methods (*e.g.* predictions of molecular complementarity,[19] ΔpK_a calculations[20] and calculations of molecular electrostatic potential surfaces[21–23] or MEPS). Despite the availability of such tools, and despite our evolving understanding of how molecules interact in the solid state, it still remains impossible to empirically and statistically predict (*i.e.* without first principles calculations) the arrangement of individual or multiple molecules in a crystal lattice.[9,24–26] Likewise, it is extremely



Scheme 1 Molecular structures of **thp** and **FBA** cocrystal formers.

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difficult to empirically predict the formation of supramolecular synthons in cocrystals composed of molecules containing a broad range of functional groups.[4,8,27]

In order to facilitate the design of cocrystals containing such complex entities, it will be necessary to considerably deepen our understanding of self-assembly processes in the solid state.

The current contribution suggests that such understanding can only be reached through well-planned crystallographic studies, and by embracing modern computational solid-state methods (such as crystal structure prediction[28,29] or CSP) as standard tools in crystal engineering. We present here a case study involving cocrystals of theophylline (**thp**) and fluorobenzoic acids (**FBAs**) (Scheme 1), *i.e.* cocrystals based on small and rigid molecules with multiple functional groups capable of hydrogen bonding. The study demonstrates the difficulty of empirically predicting compositions and synthon hierarchies in such cocrystals, and is complemented by information from crystallographic database surveys, as well as HBPC and MEPS calculations.

Thp is commonly used as a model compound in studies of pharmaceutical cocrystals,[8,30–33] and as such has been primarily cocrystallised with carboxylic acids.[34] It is well known that **thp** engages in cocrystallisation with carboxylic acids through the formation of either an O–H(carboxyl)···N(imidazole) hydrogen bond (marked as synthon **A** in Scheme 1) or a cyclic array of N–H(imidazole)···O=C(carboxyl) and O–H(carboxyl)···O=C(amide) hydrogen bonds (marked as synthon **B** in Scheme 1). Our interest in (**thp**)·(**FBA**) cocrystals was sparked by our recent investigation of the (**thp**)·(**BA**) cocrystal (where **BA** = benzoic acid, Scheme 1). The latter is a solid reported in numerous prior studies,[35,36] but one for which no crystal structure had been reported in the literature at the time we commenced our studies. Initial Cambridge Structural Database[37] (CSD) surveys and HBPC suggested that interactions of type **A** and **B** are almost equally likely to occur in (**thp**)·(**BA**) (see ESI), while a subsequent single crystal X-ray diffraction study revealed that **thp** and **BA** interact through a type **B** synthon (Fig. 1a).[38]

Another study of **FBA** cocrystals performed in our laboratories[39] then inspired us to investigate whether minimal structural changes in **BA** could potentially reorganise the self-assembly process to yield **thp** cocrystals based on type **A** synthons. The choice of **FBAs** as cocrystal formers appeared appropriate, as all mono, di-, tri-, tetra- and penta-substituted **FBA**s are similar in size and shape to **BA** due to the relatively small size difference between hydrogen and fluorine atoms (van der Waals radii: 120 pm *vs.* 147 pm, respectively).[40] Moreover, organic fluorine is not likely to act as a hydrogen-bond acceptor,[41,42] while short intermolecular C–H···F contacts in molecular crystals only make a minor contribution to the cohesive energy of a molecular crystal.[43] It was therefore postulated that the presence of fluorine atoms in the (**thp**)·(**FBA**) cocrystals would only minimally interfere with the formation of O–H···N, N–H···O and O–H···O hydrogen bonds between the cocrystal components. This hypothesis was also in agreement with results of a recently published cocrystal study involving **FBAs**.[44]

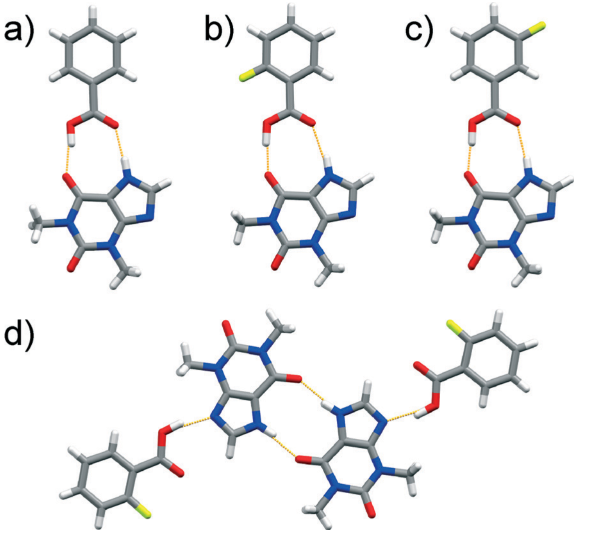

Fig. 1 Perspective views of **thp** : **BA** and **thp** : **FBA** assemblies in the crystal structures of: a) (**thp**)·(**BA**), b) (**thp**)·(**2FBA**), c) (**thp**)·(**3FBA**) and d) (**thp**)·(**2FBA**)·(CH_3NO_2).

The cocrystallisation of **thp** with all nineteen **FBAs** was attempted by liquid-assisted grinding[45] (LAG) using equimolar amounts of **thp** and the relevant **FBA** (see ESI†). The formation of the cocrystals was recognised *via* powder X-ray diffraction (PXRD) in fifteen out of nineteen cases – only cocrystal screens involving **4FBA**, **23diFBA**, **24diFBA** and **26diFBA** did not result in cocrystal formation under the investigated crystallisation conditions.[46] The crystal structures of all produced solids were determined either directly from the LAG samples using laboratory PXRD data (by simulated annealing,[47] Rietveld refinement[48] and CASTEP[49] DFT geometry optimisation), or by single crystal X-ray diffraction (SCXRD) using crystals that were obtained through solution-mediated phase transformation[50] (SMPT) or by slow solvent evaporation (see ESI†).

Cocrystallisation of **thp** with **2FBA** and **3FBA** yielded 1 : 1 cocrystals, (**thp**)·(**2FBA**) and (**thp**)·(**3FBA**). Both cocrystals are isostructural with the (**thp**)·(**BA**) cocrystal and feature discrete **thp** : **FBA** assemblies being held together by type **B** synthons (Fig. 1b and c). Intriguingly, the mechanochemical synthesis of the (**thp**)·(**2FBA**) cocrystal could initially only be achieved in the Cambridge laboratory. Mechanochemical cocrystal screens performed under identical conditions in the London laboratory persistently yielded a cocrystal nitromethane solvate, namely (**thp**)·(**2FBA**)·(CH_3NO_2). The **thp** and **2FBA** components in this solvate were unexpectedly sustained by type **A** synthon (Fig. 1d). The non-solvated (**thp**)·(**2FBA**) cocrystal was finally also obtained in London under SMPT conditions (using acetonitrile as a solvent).

A cocrystal of an unexpected composition was formed in a LAG experiment involving equimolar amounts of **thp** and **25diFBA** where PXRD and SCXRD revealed the formation of a 1 : 2 cocrystal, (**thp**)·(**25diFBA**)$_2$. The structural study also showed that **thp** and **25diFBA** formed discrete three-component assemblies, which were sustained by synthons of both type **A** and **B** (Fig. 2a). Several attempts to produce a 1 : 1 **thp** : **25diFBA** cocrystal either mechanochemically or through solution-based crystallisation methods have, so far, failed.

Our investigations also led to the discovery of a 1 : 1 cocrystal comprised of **thp** and **35diFBA**, **(thp)**·**(35diFBA)**. This material surprisingly exhibits discrete four-component assemblies featuring a O–H(carboxyl)···O═C(urea) synthon (marked as type **C** in Scheme 1 and shown in Fig. 2b) that are statistically less likely to occur than synthons **A** and **B**, as determined by HBPC (see ESI†). More predictable synthons were, however, found in the 1 : 1 **(thp)**·**(34diFBA)** cocrystal wherein **thp** and the **FBA** interact *via* type **A** synthon (Fig. 2c).

Attempts to produce cocrystals using LAG and equivalent amounts of **thp** and tri-, tetra- and penta-**FBAs** yielded 1 : 1 cocrystals, namely **(thp)**·**(234triFBA)**, **(thp)**·**(235triFBA)**, **(thp)**·**(236triFBA)**, **(thp)**·**(245triFBA)**, **(thp)**·**(246triFBA)**, **(thp)**·**(345triFBA)**, **(thp)**·**(2345tetFBA)**, **(thp)**·**(2346tetFBA)**, **(thp)**·**(2356tetFBA)** and **(thp)**·**(23456pFBA)**. Their crystal structures (except the one involving **thp** and **245triFBA**) featured discrete four-component assemblies composed of two **thp** and two **FBA** molecules. In these assemblies, the **thp** molecules interact with each other *via* cyclic arrays of N–H(imidazole)···O═C(amide) hydrogen bonds, while the **FBAs** bind to the **thp** dimer through synthons of type **A** (some examples are featured in Fig. 3, others are illustrated in the ESI† file). Surprisingly, the crystal structure of **(thp)**·**(245triFBA)** exhibited assemblies that were held together by synthons of type **B** (Fig. 4a).

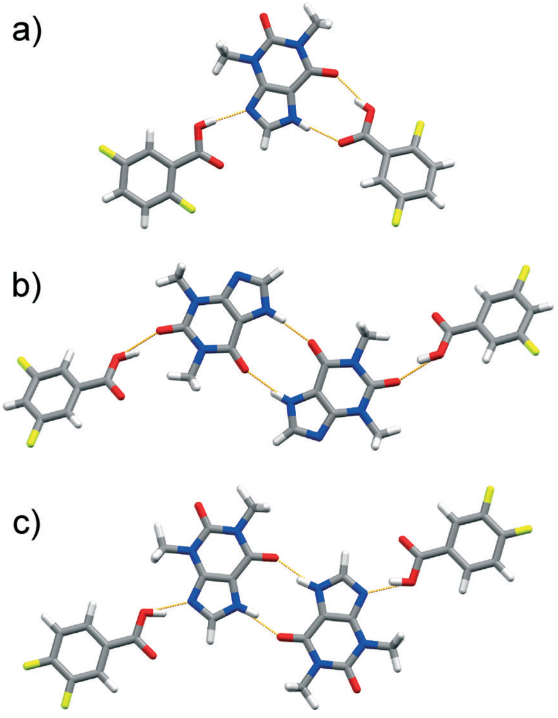

Fig. 2 Perspective views of **thp** : **FBA** assemblies in the crystal structures of: a) **(thp)**·**(25diFBA)**$_2$, b) **(thp)**·**(35diFBA)** and c) **(thp)**·**(34diFBA)** featuring distinct supramolecular synthons.

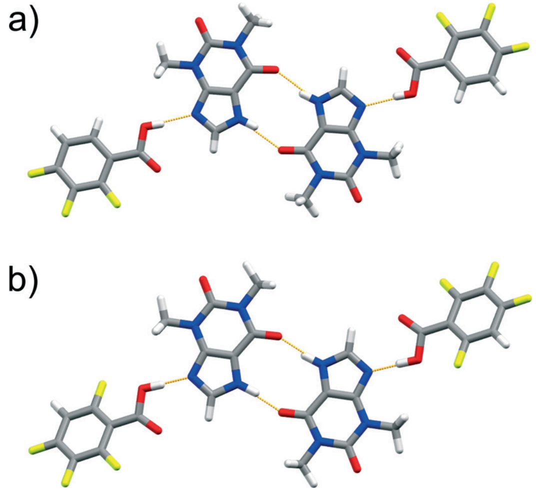

Fig. 3 Perspective views of **thp** : **FBA** assemblies in the crystal structures of: a) **(thp)**·**(234triFBA)** and b) **(thp)**·**(2346triFBA)**.

The **(thp)**·**(FBA)** cocrystals described above clearly demonstrate the unpredictability of synthon hierarchies in two-component cocrystals with several hydrogen-bonding functional groups. The observed supramolecular interactions could neither be predicted empirically nor with the use of HBPC and MEPS calculations. In particular, HBPC has been performed on all structurally characterised solids using Mercury 3.7 and the CSD 5.37 (see ESI†). Although the calculations encouragingly predicted the formation of the observed hydrogen bonds between **thp** and the **FBA** in each case, the synthon hierarchies could not be foreseen (see ESI†). In addition, DFT calculations of MEPS were also performed to predict optimal hydrogen-bond donor–acceptor pairs (see ESI†). The values of the electrostatic potentials on the hydrogen-bond donors and acceptors could, unfortunately, not be correlated to the formation of the observed synthons in the cocrystal series (see ESI†). We observed, however, that under the initially studied LAG conditions, almost all tri-, tetra- and penta-**FBAs** form cocrystals based on type **A** synthons, while the mono- and di-**FBAs** participated in hydrogen bonding through type **A**, **B** and **C** interactions (see ESI†).

The difficulty of predicting supramolecular synthons in cocrystals composed of **thp** and **FBA** is further highlighted by the discovery of polymorphs of four **(thp)**·**(FBA)** cocrystals, namely **(thp)**·**(34diFBA)**, **(thp)**·**(245triFBA)**, **(thp)**·**(246triFBA)** and **(thp)**·**(23456pFBA)**. These polymorphs were observed during attempts to grow single crystals of the mechanochemically obtained crystal forms by crystallisation through slow solvent evaporation (see ESI†). Structural analyses revealed that the four solids exhibited both packing and synthon polymorphism.[51] Packing polymorphism was observed in the case of **(thp)**·**(34diFBA)**, whereas **(thp)**·**(245triFBA)**, **(thp)**·**(246triFBA)** and **(thp)**·**(23456pFBA)** displayed synthon polymorphism. In particular, the synthon polymorphism of **(thp)**·**(245triFBA)** was realised through the formation of the type **A** synthon (Fig. 4a). On the other hand, synthon polymorphism in the cases of **(thp)**·**(246triFBA)** and

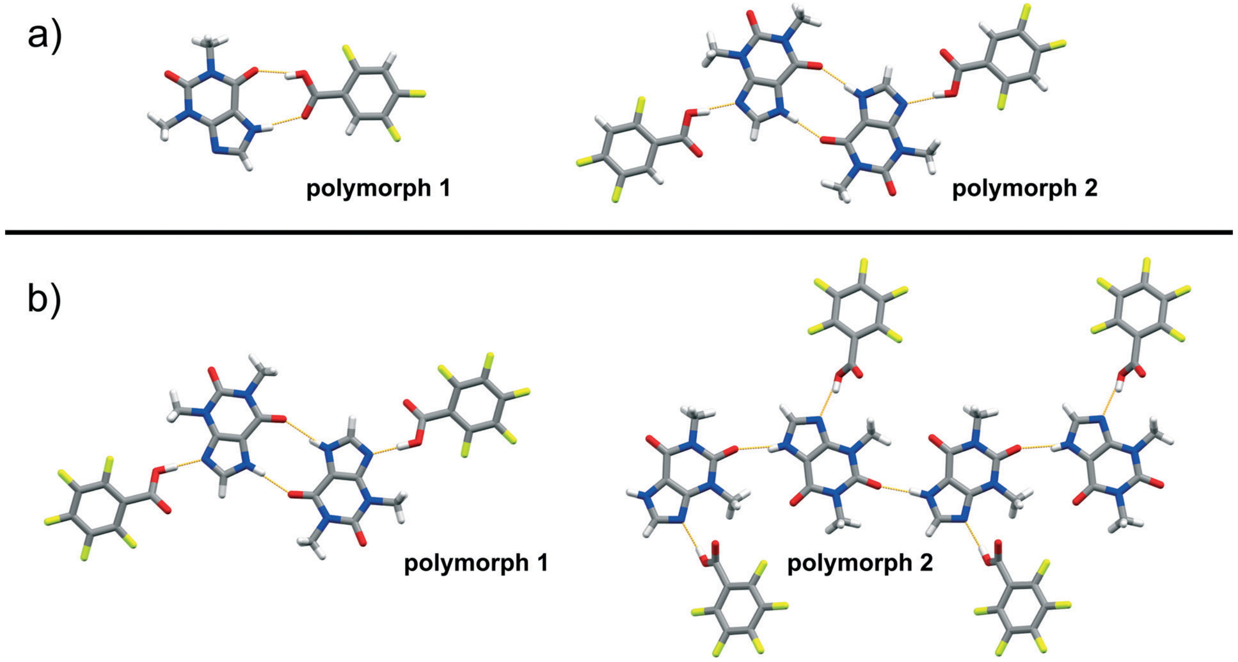

Fig. 4 Perspective views of **thp** : **FBA** assemblies in the crystal structures of cocrystal polymorphs: a) (**thp**)·(**245triFBA**) and b) (**thp**)·(**23456pFBA**).

(**thp**)·(**23456pFBA**) was realised through the occurrence of N–H(imidazole)···O═C(urea) hydrogen bonds between two **thp** molecules, rather than the generally observed cyclic arrays of N–H(imidazole)···O═C(amide) hydrogen bonds (Fig. 4b). The serendipitous discovery of the four polymorphs is not particularly surprising, considering the rapidly increasing number of studies reporting cocrystal polymorphs,[51] while a recent study recognised that cocrystals exhibit polymorphism as readily as single-component organic crystals.[52] In light of these findings, it appears that a better understanding of synthon hierarchies in cocrystals could be achieved by surveys of their structural landscapes[29,53] through polymorph screens, which are not regularly performed at the present time.[54]

So, what is the significance of the intriguing synthon diversity in the presented (**thp**)·(**FBA**) cocrystal series? The unpredictability of supramolecular interactions in the (**thp**)·(**FBA**) cocrystals, and lack of knowledge about the structural and electronic effects (on synthon hierarchies and cocrystal compositions) of fluorine substitutions in the cocrystal former, suggest that cocrystals are not as readily designed and predictably constructed as is so often portrayed in the literature. Supramolecular synthons are an incredibly useful synthetic tool that has greatly contributed to the development of advanced functional materials,[55] and to the preparation of strikingly complex solid-state structures.[56] The current state of the art in cocrystal design, however, does not support high-yielding supramolecular syntheses[57] of cocrystals for cases entailing molecules with more than two functional groups. To improve our ability to better design and more accurately construct cocrystals comprised of complex multifunctional molecules (such as pharmaceuticals), more targeted and systematic crystallographic studies need to be pursued and published.[11] But to fully understand cocrystals – their structural landscapes, synthon hierarchies and thermodynamic properties – computational methods (such as CSP[29,58] or lattice energy calculations[59] alone) need to be regularly used in crystal engineering. Comprehensive computational solid-state studies are very intensive (requiring a great deal of CPU time and time to process the generated data) and it can be argued that their use is, nowadays, only justified when dealing with specialty chemicals of particular interest (*e.g.* drug candidates in development for marketing).[60] Recent reports, however, have shown that even less exhaustive predictions can contribute substantially to experimental cocrystal research.[61] The maturity of contemporary first principles computational solid-state methods[62–65] and their relevance to crystal engineering is now widely recognised,[66,67] and it is time that they are equally widely embraced by the experimental community.

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