

# Cocrystal architecture and properties: design and building of chiral and racemic structures by solid–solid reactions†‡

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The concept of the so-called “supramolecular synthon” has been employed to construct chiral and centrosymmetric cocrystals with predictable short-range order. The reactants included nicotinamide, mandelic acid and ibuprofen. In order to maximize the efficiency of cocrystal synthesis, the solids were constructed using the liquid-assisted grinding approach. The predictability of the cocrystal architecture was further employed to study in detail the effects of chirality upon physical properties of the synthesized materials, especially the melting point. The combined results of crystallographic and thermochemical studies enable, at least partially, the rationalisation of cocrystal thermal behaviour with respect to the corresponding cocrystal formers.

## Introduction

Interest in organic solid-state materials has steadily increased.<sup>1,2</sup> The past ten years, however, have witnessed a significant increase in research in the field, mainly as the result of the advances achieved using supramolecular and crystal engineering approaches.<sup>3</sup> An overview of recent papers<sup>4</sup> indicates that current state-of-the-art design of molecular solids is achieved through the construction of multi-component molecular solids, or cocrystals.<sup>5</sup> Indeed, cocrystals have proven particularly successful as functional materials with applications in pharmaceuticals,<sup>6</sup> molecular electronics,<sup>7</sup> optical applications,<sup>8</sup> and synthetic organic chemistry.<sup>9</sup> The principal reasons for the successful use of cocrystals are the discovery of reliable supramolecular synthons for cocrystal design, as well as modularity, an emergent property of multicomponent molecular solids.<sup>10</sup> Modularity provides an opportunity to fine-tune the structural and physical properties of a solid without significantly affecting chemical properties (*e.g.* when dissolved).<sup>11,12</sup>

Opportunities and challenges provided by cocrystals have inspired both the exploration of optimum supramolecular synthons, as well as the development of synthetic methodologies for producing cocrystals. Whereas the first topic, *i.e.* addressing the synthesis and identification of supramolecular synthons for cocrystal

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† The HTML version of this article has been enhanced with colour images.

‡ Electronic supplementary information (ESI) available: Fig. S1–S15: X-ray powder diffraction patterns, DSC thermograms and hot-stage microscopy images of cocrystals. See DOI: 10.1039/b616399h

synthesis, has been pursued with great intensity by the research groups of Aakeröy,<sup>13</sup> Zaworotko,<sup>4</sup> Desiraju<sup>14</sup> and Nangia,<sup>15</sup> our own research has focused on the second topic, *i.e.* methods for cocrystal synthesis. In that context we have been, along with others,<sup>16</sup> exploring mechanochemical approaches (*i.e.* grinding) as a means of constructing molecular cocrystals.<sup>17</sup> Specifically, we have been developing the technique of liquid-assisted grinding, a rapid and efficient method to conduct supramolecular synthesis in the solid state. In our laboratory, the potential of liquid-assisted grinding has established the approach as a general way to discover and construct cocrystals. For that reason, we find it appropriate to first provide a brief overview of the application of liquid-assisted grinding to construct cocrystals and identify specific advantages over conventional solution cocrystallisation methods.<sup>18</sup> In the light of the ongoing discussion on the definition of the term cocrystal, we have used the term herein to describe all multi-component crystalline molecular solids, including the ones that would otherwise be classified as solvates, clathrates or inclusion compounds.<sup>5</sup>

### Neat and liquid-assisted grinding

In its simplest approach, a cocrystal can be formed by the neat grinding of two (or more) components together. The addition of a small amount of a liquid phase can, however, significantly accelerate the formation of cocrystals, and grinding methods involving a catalytic amount of a liquid have been termed “kneading”,<sup>19</sup> as well “solvent-drop” grinding.<sup>20</sup> The mechanism by which an accelerating effect is produced is still not fully understood. In some cases it has been interpreted as a purely physical effect, *i.e.* the liquid acting as a lubricant for the process.<sup>21</sup> In other cases, however, effects related to the solubility of the materials and the chemical nature of the liquid phase have been suggested. Indeed, the importance of the chemical nature of the liquid is apparent in the solvent-dependent selective formation of different polymorphs of cocrystals of caffeine and glutaric acid.<sup>22</sup> In many cases, however, the actual role of the liquid phase during grinding has not been established with certainty, and it is possible that it may vary from case to case. For that reason we consider it appropriate to encompass all possible mechanisms for using a liquid phase to accelerate cocrystal formation under the common name liquid-assisted grinding.<sup>23</sup> Defined in that way, liquid-assisted grinding describes the use of a liquid to accelerate (or enable) a cocrystallisation reaction between two solids, regardless of whether the liquid acts largely through physical effects (*e.g.* lubrication, enhanced dissolution of the reactants), or if specific chemical properties of the liquid phase are more relevant (*e.g.* formation of an intermediate solvate of a reactant or molecules of the added liquid becoming constituents of the final cocrystal). From that perspective, solvent-drop grinding is a strategy of liquid-assisted grinding that exploits the solubility of solid reactants in the liquid phase.<sup>24</sup>

### Discovery of new cocrystals

That cocrystallisation by grinding can provide a cocrystal of different composition than cocrystallisation from solution has been demonstrated in the case of cocrystals involving caffeine and acetic acid. Cocrystallisation from acetic acid resulted in a solid made up of finite assemblies comprising a molecule of caffeine and two molecules of acetic acid. Identical cocrystals were obtained by grinding caffeine with an excess of the acid. However, upon grinding equimolar amounts of caffeine and acetic acid, a solid containing the two components in a 1 : 1 molar ratio was obtained. Repeated attempts to produce the 1 : 1 material from solution failed, however, and structure solution from X-ray powder diffraction data became necessary, revealing two-component 1 : 1 molecular assemblies.<sup>25</sup>

Changing the reaction scale can also affect the nature of the cocrystal formed by grinding: small amounts of caffeine and trifluoroacetic acid yield an orthorhombic

form of the 1 : 1 cocrystal, whereas a triclinic polymorph is obtained upon increasing the reaction scale.<sup>25</sup>

### Construction of ternary solids and efficiency of liquid-assisted grinding

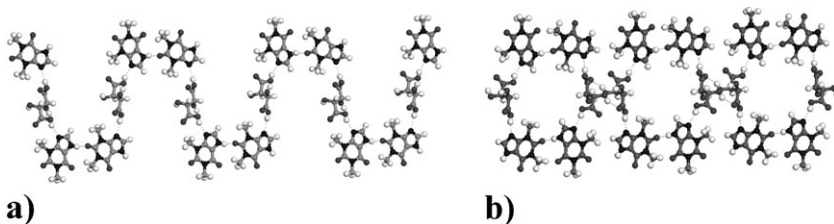
In addition to forming binary cocrystals, we have recently reported liquid-assisted grinding as a means to construct ternary solids. In particular, we have compared the efficiencies of neat grinding, liquid-assisted grinding and cocrystallisation from solution in screening inclusion compounds of a two-component lattice host.<sup>23</sup> The results demonstrated liquid-assisted grinding is more efficient than cocrystallisation from solution, providing a ternary solid with 20 out of 30 investigated guest molecules, compared to four obtained from solution. The effectiveness of ternary cocrystal formation was independent on the state of aggregation of the guest (*i.e.* whether the guest was a liquid or a solid).

### Exploring the effect of chirality: chiral vs. racemic cocrystal formers

Although cocrystals are readily amenable to synthesis by design, the relationship between cocrystal structure and physical properties remains unexplored. Indeed, most approaches to functional solids *via* cocrystals are based on screening, rather than an understanding of the cocrystal structure–property relationship.<sup>26,27</sup> In order to explore such relationships and develop strategies to tailor physical properties of cocrystals, we have begun to investigate the influence of chirality on the reactivity of potential cocrystal formers and on the thermal properties of resulting cocrystals.

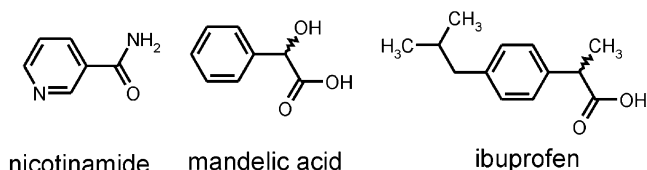
Our first experiments involved the cocrystallisation of model active pharmaceutical ingredients (APIs) caffeine and theophylline with either chiral or racemic forms of tartaric acid.<sup>28</sup> The results showed that theophylline and caffeine exhibited different reactivity towards different “forms” of tartaric acid. Theophylline readily provided cocrystals with both chiral and racemic tartaric acid by liquid-assisted grinding. Crystal structure analysis revealed that racemic cocrystals consist of hydrogen-bonded tapes based on ring-like assemblies of theophylline and tartaric acid, whilst in chiral cocrystals the tapes are based on hydrogen-bonded helices (Fig. 1).§

For caffeine, liquid-assisted grinding provided cocrystals with *R*- or *S*-tartaric acid, but not with *RS*-tartaric acid. Different behaviour of chiral and racemic tartaric acids towards caffeine motivated us to further explore the effect of chirality on cocrystal formation and physical properties. To facilitate our study, we focused on cocrystal components that were likely to interact through a set of robust supramolecular synthons, providing racemic and chiral solids having similar architectures. In order to make use of model APIs for these studies, we selected



**Fig. 1** A ball-and-stick representation of a fragment of the theophylline cocrystal with: (a) *R*- or *S*-tartaric acid and (b) *RS*-tartaric acid.

§ We use the description “chiral” and “racemic” to indicate that the solid is either enantiomerically pure or contains both enantiomers.

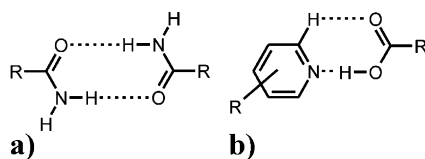


**Scheme 1** Schematic representation of nicotinamide, mandelic acid and ibuprofen.

nicotinamide (vitamin D) and pairs of chiral and racemic monocarboxylic acids: *R/S*- and *RS*-mandelic acid, as well as *S*- and *RS*-ibuprofen (Scheme 1), as suitable cocrystal components.¶

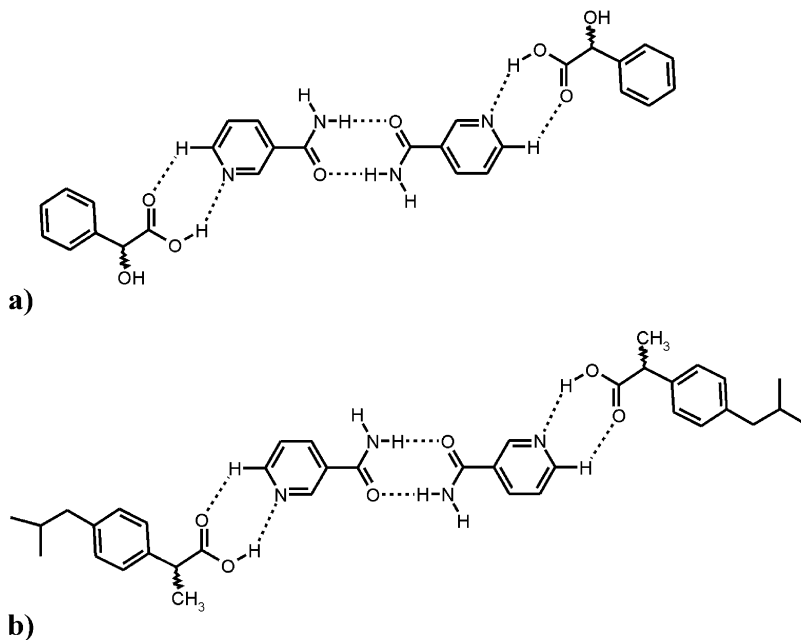
An overview of the Crystal Structure Database revealed that cocrystals involving nicotinamide and a monocarboxylic acid generally comprise four-membered assemblies involving two nicotinamide and two acid molecules. The central part of each assembly is a nicotinamide dimer, held together by an amide–amide supramolecular synthon of two N–H···O hydrogen bonds (Scheme 2a). The carboxylic acids are held at the peripheral part of the assembly through the carboxylic acid–pyridine supramolecular synthon consisting of an O–H···N and a C–H···O hydrogen bond between carboxylic acid and pyridine groups that are coplanar (Scheme 2b). This arrangement is anticipated from the hydrogen bonding hierarchy formulated by Etter.<sup>29</sup> A similar design was exploited with great success by Aakeröy and coworkers to construct cocrystals of isonicotinamide with benzoic acids.<sup>30</sup> Thus, we anticipated nicotinamide would assemble with mandelic acids in a 1 : 1 stoichiometric ratio to form chiral and racemic cocrystals **1a** and **1b**, respectively, and with *S*- and *RS*-ibuprofen to form chiral and racemic cocrystals **2a** and **2b**, respectively. All cocrystals were expected to contain four-membered assemblies with nicotinamide in the center and acid molecules on the periphery (Scheme 3).

As our first entry into investigating the physical properties of chiral and racemic cocrystals, we decided to focus on thermal behavior. In that context, studies by Bond and Nangia indicated that the melting points of a series of cocrystals can reflect the thermal behaviour of parent cocrystal formers.<sup>31</sup> Our interest was to investigate a possible relationship between thermal properties of cocrystals built on a similar architecture but involving either enantiomerically pure or racemic cocrystal formers. We have found mandelic acid and ibuprofen to be especially interesting cocrystal formers for that purpose, since they exhibit different relationships between thermal properties of chiral and racemic forms. The melting point and density are higher for racemic ibuprofen than for the pure enantiomer, in accordance with the empirical Wallach's rule.<sup>32</sup> The two forms of mandelic acid contradict the rule, with the melting point and density being higher in the case of the enantiomerically pure form.



**Scheme 2** Schematic representation of: (a) an amide–amide synthon and (b) pyridine–carboxylic acid synthon. Hydrogen bonds are shown as dotted lines.

¶ Results of cocrystallisation experiments involving nicotinamide and *D/S*- or *RS*-tartaric acid from solution and *via* liquid-assisted grinding will be published at a later date. Attempts to cocrystallise caffeine or theophylline with either mandelic acids or ibuprofen have, so far, failed.



**Scheme 3** Structure of molecular assemblies expected to form in the cocrystal of nicotinamide with: (a) mandelic acid and (b) ibuprofen.

## Materials and methods

### Synthesis of cocrystals

Nicotinamide, *R*-, *S*- and *RS*-mandelic acids, *S*- and *RS*-ibuprofen and nitromethane were commercially available from Sigma-Aldrich and were used without further purification. All liquid grinding experiments were performed using a Retsch MM200 grinder mill operating at a frequency of 30 Hz. For the synthesis of cocrystals, 0.20 g of an equimolar mixture of nicotinamide and the cocrystal former were placed in a 25 mL volume stainless steel grinding jar, along with 5 drops of nitromethane. The samples were then ground over a period of 30 min using two stainless steel grinding balls of 7 mm diameter. The samples prepared were then dried in air.

All cocrystals were also obtained by cocrystallisation of equimolar amounts of the appropriate two components from solutions in either nitromethane, acetonitrile or ethyl methyl ketone.

### X-Ray diffraction experiments

X-Ray powder diffraction patterns were obtained using a Philips X'Pert Pro diffractometer equipped with an X'celerator RTMS detector, using Ni-filtered Cu-K $\alpha$  radiation. Single crystal X-ray diffraction data for **1a** were collected on a Nonius Kappa CCD diffractometer equipped with a graphite monochromator and an Oxford Cryosystems cryostream, using Mo-K $\alpha$  radiation.

### Differential scanning calorimetry (DSC) and hot-stage microscopy

Thermal calorimetric measurements were performed on samples with a weight in the range of 5–12 mg using a Mettler DSC30 instrument. The samples were placed in 40  $\mu$ L aluminium crucibles and measurements were taken in the temperature range

30–150 °C, using a heating rate of 5 K min<sup>-1</sup> in a dynamic atmosphere of nitrogen gas. Hot-stage microscopy experiments were performed on a Mettler FP84HT TA microscopy cell connected to the Mettler FP90 central processor unit. The samples were placed in open glass crucibles and their thermal behaviour was monitored in the temperature range 30–150 °C at a heating rate of 10 K min<sup>-1</sup>.

X-Ray powder diffraction patterns of all reactants and products are provided as ESI,† along with selected hot-stage microscopy images and DSC thermograms.

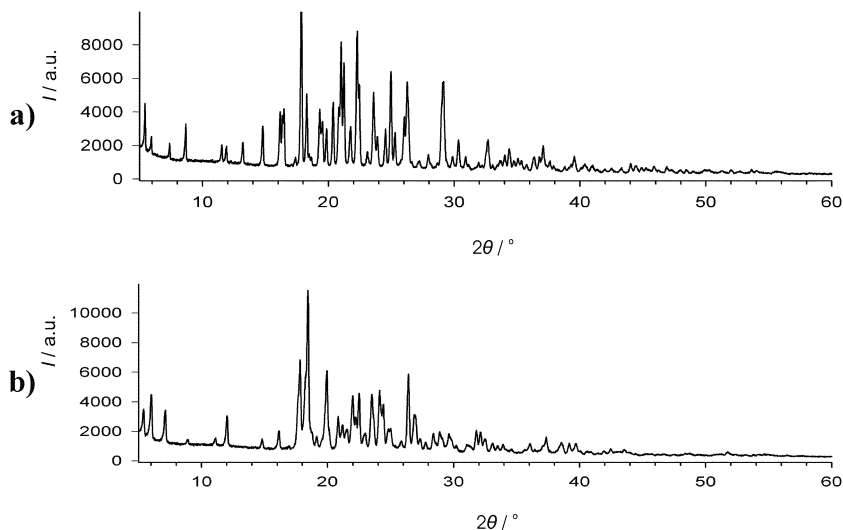
CCDC reference number 626647 for **1a**.

For crystallographic data in CIF or other electronic format see DOI: 10.1039/b616399h

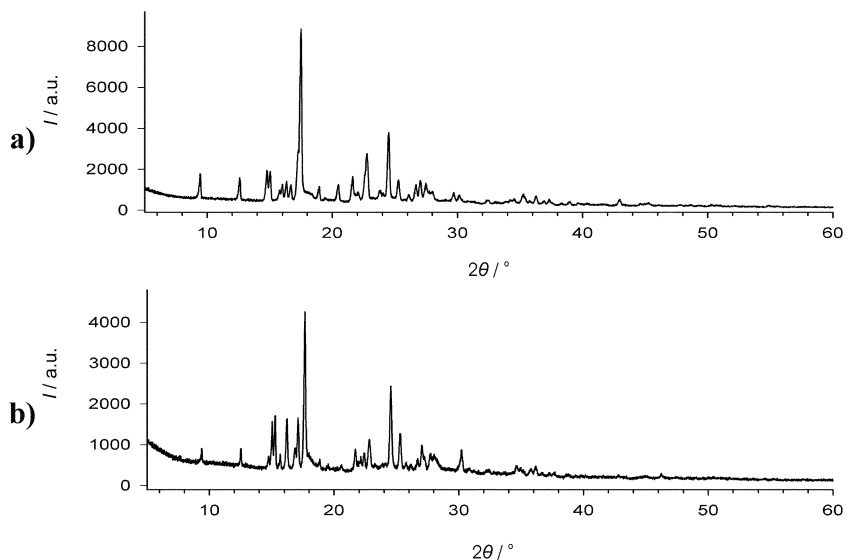
## Experimental results

Liquid-assisted grinding of equimolar quantities of nicotinamide with either *R*- or *S*-mandelic acid and nitromethane produced a solid with a X-ray powder diffraction (XRPD) pattern different from that of the solid reactants. The product powder pattern was identical for both *R*- and *S*-mandelic acid as the reactant, suggesting (as expected) that the two product crystals were enantiomeric. The XRPD pattern of the product of liquid-assisted grinding of nicotinamide with *RS*-mandelic acid and nitromethane also contained no evidence for unreacted material. It was also different than the pattern obtained using the chiral mandelic acid (Fig. 2). Cocrystals with *R*- or *S*-mandelic acid could be readily obtained from acetonitrile solution and were identical to those obtained by liquid-assisted grinding. Cocrystals of nicotinamide and the racemic acid could be obtained from acetonitrile solution only after prolonged standing or rapidly upon addition of a few seeds of the solid obtained by liquid-assisted grinding. In both cases the resulting cocrystals exhibited the same XRPD pattern as the material obtained *via* grinding. As established by <sup>1</sup>H NMR spectroscopy, each cocrystal contained equimolar amounts of nicotinamide and mandelic acid. The results are consistent with the products of liquid-assisted grinding being the anticipated cocrystals **1a** and **1b**.

In a similar way it was established that liquid-assisted grinding of nicotinamide with either *S*- or *RS*-ibuprofen produces new crystalline solids (Fig. 3). As evidenced by XRPD, the products obtained by grinding were identical to those obtained from solution. Moreover, <sup>1</sup>H NMR spectroscopy indicated the cocrystals were composed



**Fig. 2** X-Ray powder diffraction patterns of cocrystals: (a) **1a** and (b) **1b**, obtained by liquid-assisted grinding.



**Fig. 3** X-Ray powder diffraction patterns of cocrystals: (a) **2a** and (b) **2b**, obtained by liquid-assisted grinding.

of nicotinamide and ibuprofen in a 1 : 1 stoichiometric ratio. Again, the results are consistent with the formation of anticipated cocrystals **2a** and **2b** both by grinding as well as solution cocrystallisation.

### Thermal analysis

For all cocrystals, DSC thermograms were characterised by a sharp endothermic signal that was interpreted as the melting point of the solid. The interpretation was confirmed using hot-stage microscopy. The melting points of the cocrystals, along with the melting points of precursor materials are given in Table 1.

### Crystal structure analysis

In order to verify the formation of the anticipated four-membered molecular assemblies, we undertook a single crystal X-ray diffraction study of **1a**. Needle-shaped single crystals of **1a** of sufficient quality for the X-ray diffraction experiment were obtained by slow cooling and evaporation of a solution of an equimolar mixture (0.100 g) of nicotinamide and *R*-mandelic acid in acetonitrile (2 mL). The most relevant crystallographic data for **1a** are summarised in Table 2. Crystal structure determination revealed that the asymmetric unit of the cocrystal consists of the expected molecular assembly comprising two nicotinamide and two mandelic acid molecules, see Fig. 4.

**Table 1** Melting points of reactants and prepared cocrystals

Reactant	$T_{\text{melting}}/^{\circ}\text{C}$	Cocrystal	$T_{\text{melting}}/^{\circ}\text{C}$
<i>R/S</i> -mandelic acid	130	<b>1a</b>	89
<i>R/S</i> -mandelic acid	117	<b>1b</b>	76
<i>S</i> -ibuprofen	50	<b>2a</b>	82
<i>RS</i> -ibuprofen	76	<b>2b</b>	91
Nicotinamide	150		

**Table 2** General and crystallographic data for **1a**

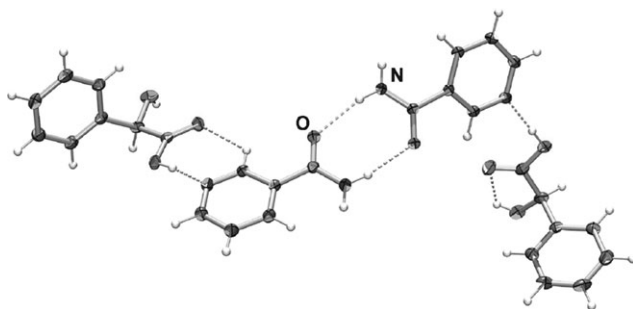
Empirical formula	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub>	Z	8
Formula weight	274.3	$\rho_{\text{calc}}/\text{g cm}^{-3}$	1.384
Temperature/K	150(2)	$\mu/\text{mm}^{-1}$	0.103
Wavelength/Å	0.71073	<i>F</i> (000)	1152
Crystal system	Monoclinic	Crystal size/mm <sup>3</sup>	0.46 × 0.07 × 0.07
Space group	C2	$\theta$ range/°	3.77 to 27.43
Unit cell dimensions/Å, °	<i>a</i> = 32.6557(9) <i>b</i> = 5.475(1) <i>c</i> = 14.9264(5) $\beta$ = 99.400(1)	Data/restraints/parameters	5773/1/361
<i>V</i> /Å <sup>3</sup>	2632.9(5)	<i>S</i>	1.12
		<i>R</i> <sub>1</sub> , <i>wR</i> <sub>2</sub> for <i>I</i> > 2 $\sigma$ ( <i>I</i> )	0.055, 0.128
		<i>R</i> <sub>1</sub> , <i>wR</i> <sub>2</sub> for all data	0.070, 0.138
		$\Delta/e \text{ \AA}^{-3}$ , min, max	−0.295, 0.293

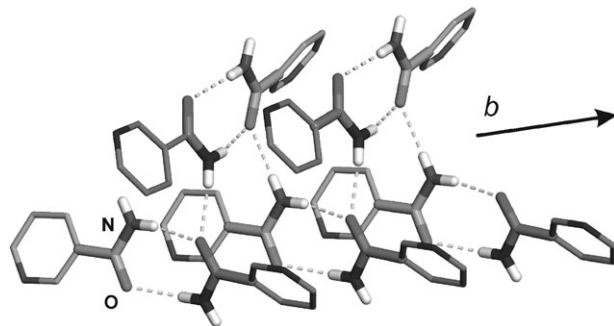
The assemblies in the crystal link by way of intermolecular N–H···O hydrogen bonds, forming chains that propagate parallel to the crystallographic *b*-direction (Fig. 5).

In contrast to our expectations, only one carboxylic acid moiety in each assembly is coplanar with a nearby pyridine group, while the second one is significantly twisted out of the plane of the pyridine ring (respective angles between planes defined by six non-hydrogen atoms of the pyridine ring and the three non-hydrogen atoms of the carboxylic acid functionality: 11.3(4)° and 34.2(3)°). Consequently, only one carboxylic acid group forms the expected pyridine–carboxylic acid supramolecular synthon through a pair of O–H···N and C–H···O bonds (O···N and C···O separations: 2.60 and 3.31 Å, respectively). The second carboxylic acid group is held to a neighbouring pyridine moiety through only a single O–H···N hydrogen bond (O···N separation 2.60 Å).

The failure of one mandelic acid molecule in the assembly to form the carboxylic acid–pyridine synthon can be related to the behaviour of the alcohol moiety in the acid. Notably, the hydroxyl group forms an intramolecular O–H···O hydrogen bond with an oxygen atom of the carboxylic acid group (O···O separation: 2.67 Å).

The ability of the carboxylic acid oxygen atom to act as a hydrogen bond acceptor is thus diminished, hindering the formation of a C–H···O bond. In the case of the mandelic acid unit that forms the C–H···O bond, the hydroxyl group is involved in an intermolecular O–H···O hydrogen bond (O···O separation: 2.68 Å). Such O–H···O bonds act together with intermolecular N–H···O bonds (N···O distances 2.97 and 3.00 Å), to link neighbouring molecular chains into layers. The layers are parallel to the {100} set of crystallographic planes. The core of each layer is populated mostly by polar groups, whereas hydrophobic aromatic residues decorate the layer surface (Fig. 6).

**Fig. 4** ORTEP representation of the asymmetric unit of the **1a** cocrystal. Non-hydrogen atoms are shown as ellipsoids at 30% probability level.

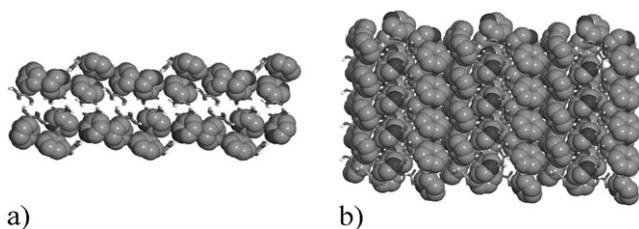


**Fig. 5** A wire frame representation of molecular chains in the cocrystal **1a**. For clarity, hydrogen atoms bonded to carbon atoms, and mandelic acid molecules are omitted.

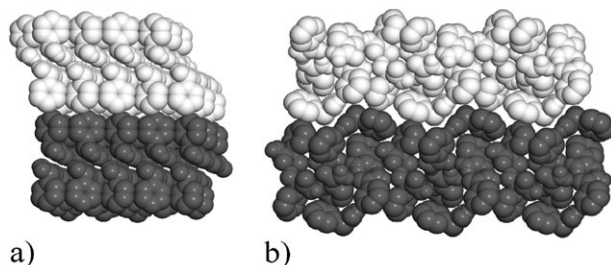
## Discussion

Liquid-assisted grinding has provided cocrystals of nicotinamide with all the examined cocrystal formers. Consequently, in the cases studied, nicotinamide does not appear to discriminate between chiral and racemic cocrystal formers. The products obtained *via* liquid-assisted grinding were identical to products obtained by cocrystallisation from solution. In contrast to cocrystallisation from solution, however, the products obtained by grinding did not require any purification procedures (*i.e.* filtering) and, according to the X-ray powder diffraction patterns, the reaction yield was quantitative. Crystal structure analysis of **1a** demonstrated that short-range ordering of molecules in a cocrystal of nicotinamide and a carboxylic acid can be tentatively predicted by considering possible supramolecular synthons. Such an ability to design the architecture of a cocrystal simplified the study of the effects of chirality on the physical properties of the cocrystals. Whilst only compound **1a** could at present be investigated by single crystal X-ray analysis (attempts to determine the crystal structures of **2a** and **2b** *via* single crystal X-ray diffraction have so far failed, owing to the pronounced needle-like habit of the cocrystals), we note that the similarity of XRPD patterns between **1a** and **1b**, and between **2a** and **2b**, suggests some structural similarity within the members of each pair.

Chirality affects the melting point of the ibuprofen cocrystals in a way different to those of mandelic acid as a cocrystal former. Specifically, the melting point of the racemic cocrystal **2b** is higher than the melting point of the corresponding enantiomerically pure cocrystal **2a**. In the case of mandelic acid cocrystals the situation is reversed, *i.e.* the melting point of the chiral cocrystal **1a** is higher than the melting point of the racemic cocrystal **1b**. As evident from Table 1, differences in the melting points of chiral and racemic cocrystals agree well with the behaviour of the pure cocrystal formers. Such a result is reminiscent of the reports by Bond, and Nangia,<sup>31</sup>



**Fig. 6** Two views of molecular layers in **1a**: (a) cross-section and (b) a view perpendicular to the layer surface, exhibiting the predominance of polar groups within and aromatic moieties on the surface of each layer. Aromatic residues are displayed using a space-filling model.



**Fig. 7** Two adjacent layers in the crystal structure of: (a) *R*-mandelic acid and (b) cocrystal **1a**. For clarity, hydrogen atoms not bonded to oxygen are omitted.

that the alternation in melting points of a homologous series of alkanecarboxylic acids is also exhibited in the series of corresponding cocrystals. Although the few results presented herein do not allow a broad generalisation, they nevertheless suggest that a simple relationship may exist between the thermal properties of cocrystals and the parent cocrystal formers.

It is also interesting to consider the melting points of the cocrystals with respect to those of the pure cocrystal formers. Here again the cocrystals of ibuprofen follow a different trend to those of the cocrystals of mandelic acid. The melting points of **1a** and **1b** are lower than the melting point of either *R*- or *RS*-mandelic acid. The opposite is true for the melting points of **2a**, **2b** and ibuprofen. We believe that such behaviour can be rationalised through a comparison of the solid-state structures of the cocrystal and the corresponding cocrystal former. Our rationalisation is based on the assumption that all the cocrystals studied are based on molecular assemblies similar to the ones that constitute **1a**. Following that assumption, cocrystals of ibuprofen would be expected to have a higher melting point than the cocrystal former, since the isolated carboxylic acid dimers in crystalline ibuprofen would be replaced by a network of N–H···O hydrogen bonds in the cocrystal. In the case of chiral mandelic acid, molecules in the free acid, as well as in the corresponding cocrystal **1a**, are connected into hydrogen-bonded layers. In *R*-mandelic acid the layers are held together *via* O–H···O and C–H···O hydrogen bonds, and in **1a** the molecules in each layer are connected by O–H···O, O–H···N and N–H···O hydrogen bonds. Consequently, lowering of the melting point of the cocrystal with respect to the cocrystal former is probably not a result of changes to the hydrogen-bonding framework. We find that the analysis of the packing of layers in *R*-mandelic acid and **1a** provides a plausible explanation of the thermal behaviour. In layers of the crystalline acid, phenyl moieties of each molecule are approximately perpendicular to the plane of the layer. Consequently, the adjacent layers are partially interdigitated, reminiscent of a molecular version of a Velcro™ fastener. Such interdigitation is expected to make the parallel sliding of layers difficult. In contrast, the surface of each layer **1a** is covered by flat aromatic moieties (Fig. 7). As a result, adjacent layers in **1a** are expected to slide more readily than in *R*-mandelic acid, thereby possibly facilitating melting. Based on structural similarity evident from the similarity of the XRPD patterns, a similar explanation is expected to be valid for the cocrystal **1b**.

## Conclusion

We have applied a synthon-based approach to construct cocrystals that would have similar architectures, but different symmetry properties. The difference in symmetry is introduced by utilising an enantiomerically pure or a racemic cocrystal former. We demonstrate that the thermal properties of cocrystals change with the symmetry of the cocrystal former. The melting points of pairs of chiral and racemic cocrystals,

based on a similar supramolecular architecture, appear to follow the same trend as the melting points of the pure cocrystal. Notably, we have recognised a pair of racemic and chiral cocrystals that contradicts the Wallach's rule as far as melting points are concerned. We consider the observation is promising in the context of engineering cocrystals with desired thermal stability, a possibility that is particularly attractive for pharmaceutical materials. Indeed, the results presented in this contribution also demonstrate that cocrystallisation can increase the melting of a low-melting point drug ibuprofen. However, the change in thermal stability upon cocrystallisation is difficult to predict and we show that both changes in hydrogen bonding pattern, as well as changes to molecular close packing are relevant. To achieve a better understanding of how the thermal behaviour of a cocrystal emerges from thermal properties of cocrystal components, we are now pursuing structural characterisation of nicotinamide cocrystals with *RS*-mandelic acid, *S*- and *RS*-ibuprofen, as well as other cocrystal formers that exist in chiral and racemic forms.

## Acknowledgements

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