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## Evaluating structure-property relationship in a new family of mechanically flexible co-crystals

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**A structure-property analysis of ten compositionally and chemically similar co-crystals of N-(pyridin-2-yl)alkylamides and carboxylic acids show that three co-crystals of targets bearing a methyl chain were brittle, while the remaining co-crystals of targets bearing ethyl or propyl chains were flexible. Five of these displayed elastic deformation while two displayed plastic deformation. Compounds with different mechanical behaviour (brittle, plastic, and elastic deformation) in response to external mechanical stimuli, could be organized into structurally similar groups based on the presence of specific intermolecular interactions and packing features in each crystal structure.**

The response of a crystalline material to external mechanical stress can range from brittleness, plastic (bending/shearing), and elastic bending. While all materials have a certain degree of elasticity,<sup>1</sup> a crystalline solid in which either elastic or plastic deformation is readily observed is termed 'flexible'.<sup>2</sup> Mechanical flexibility of crystalline materials is a relatively rare phenomenon as such solids typically have a brittle nature.<sup>3</sup> Practical applications of mechanically flexible crystals include new luminescent materials,<sup>4</sup> organic actuators,<sup>5</sup> electronics<sup>6</sup>/optoelectronics,<sup>7</sup> molecular machinery,<sup>8</sup> and pharmaceuticals with improved processing features.<sup>9,10</sup> Over the last two decades, there has been a shift in focus of crystal engineering to proceed from a targeted assembly (structure) of molecules, towards bottom-up supramolecular synthesis that yield desired functions and performance.<sup>11</sup>

The plastic bending of organic crystals was initially rationalized by the slip-plane model proposed by Reddy *et al* which attributes flexibility to the movement of slip planes.<sup>12</sup> The slip planes are formed where weak dispersive interactions are present (e.g. CH<sub>3</sub>...CH<sub>3</sub> in 2-(methylthio)nicotinic acid)<sup>12</sup>. Additionally, such plastic bending crystals were identified to

have corrugation, π-π stacking and anisotropic interactions.<sup>12,13,14,15</sup> Micro-focused X-ray diffraction experiments carried out on N-(4-ethynylphenyl)-3-fluoro-4-(trifluoromethyl)benzamide confirmed this mechanism of bending where a CF<sub>3</sub>...CF<sub>3</sub> slip plane was proposed.<sup>16</sup> Plastic deformation of crystals may also occur by shearing. Shearing has been noted to occur in the presence of a layered structure with strong in-plane and non-specific interlayer interactions.<sup>17</sup> Several hypotheses have been put forward to explain elastic flexibility in crystalline material.<sup>18</sup> In systems examined by Reddy *et al* the focus was on structural corrugation and interlocking, and the presence/absence of slip planes and isotropic intermolecular interactions.<sup>5,12,19,20</sup> The necessary contraction and expansion to facilitate elastic bending was thought to be provided by the crystal packing which resembles a set of hinges.<sup>18,21,22</sup> However, many crystals with structural features that deviate from those identified as pre-requisite for elastic flexibility have been noted. eg- CuACAC has slip planes<sup>23</sup>, mixed haloimidazole crystals have anisotropic packing<sup>24</sup> Additionally, dimethyl sulfone which has isotropic interactions shows plastic deformation.<sup>25</sup> The Fibril lamella morphology hypothesis, developed by Hayashi *et al* is based on the analysis of crystal packing arrangements in conjunction with fluorescence spectroscopy and describes an arrangement of slip stacked molecular wires.<sup>26,27</sup> However, neither hypothesis has provided an explanation that is widely applicable.<sup>18</sup> More recently, micro-focused x-ray diffraction on CuACAC<sup>24</sup> and 4-chloro-3-nitrobenzoic acid<sup>28</sup> has revealed that individual molecules within the crystal structure reversibly rotate when bent. Different elastic crystals may have slightly different modes of molecular movement.<sup>24,28</sup> While absence of slip planes/interlocking may prevent permanent slippage of molecules these studies refute interlocking being essential for elastic flexibility. Thus, the third hypothesis by Clegg *et al* describes the requirement for elasticity as "the molecules must be able to re-organize reversibly to allow compression of the crystal along the interior of the arc with subsequent expansion in orthogonal directions (and vice versa along the exterior of the arc)".

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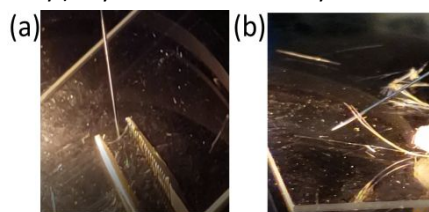
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† Electronic supplementary information (ESI) available: Crystal packing features, X-ray crystallography results, Synthesis of targets and co-crystals. CCDC deposit no.s 2092007(I-Me:BA), 2092009(I-Me:3,5M-BA), 2092010 (I-Me:4Cl-BA), 2092012(I-Et:BA), 2103264(Br-Et:BA), 2092013(I-Pr:BA), 2092014 (I-Et:4Cl-BA), 2092015(H-Et:4Cl-BA), 2092016(I-Et:3,5M-BA), 1092017 (Br-Et:3,5M-BA)( See DOI: 10.1039/x0xx00000x

Table 1 Composition, crystal description, and response to mechanical stress of co-crystals*			
Composition	Code	Color and morphology	Mechanical behaviour
N-(5-iodopyridin-2-yl)acetamide:benzoic acid	I-Me:BA	Colorless, Parallelepiped	Brittle
N-(5-iodopyridin-2-yl)acetamide:3,5-dimethyl benzoic acid	I-Me:3,5M-BA	Colorless, Parallelepiped	Brittle
N-(5-chloropyridin-2-yl)acetamide:benzoic acid	I-Me:4Cl-BA	Colorless, Parallelepiped	Brittle
N-(5-iodopyridin-2-yl)propionamide:benzoic acid	I-Et:BA	Colorless, Rectangular	Elastic
N-(5-bromopyridin-2-yl)propionamide:benzoic acid	Br-Et:BA	Colorless, needle	Elastic
N-(5-iodopyridin-2-yl)butyramide:benzoic acid	I-Pr:BA	Colorless, Rectangular	Elastic
N-(5-iodopyridin-2-yl)propionamide:4-chloro benzoic acid	I-Et:4Cl-BA	Colorless, Rectangular	Elastic
N-(5-pyridin-2-yl)propionamide:4-chloro benzoic acid	H-Et:4Cl-BA	Colorless, needle	Elastic
N-(5-iodopyridin-2-yl)propionamide: 3,5-dimethyl benzoic acid	I-Et:3,5M-BA	Colorless, plate	Plastic
N-(5-bromopyridin-2-yl)propionamide: 3,5-dimethyl benzoic acid	Br-Et:3,5M-BA	Colorless, needle	Plastic

\* See SI for some images

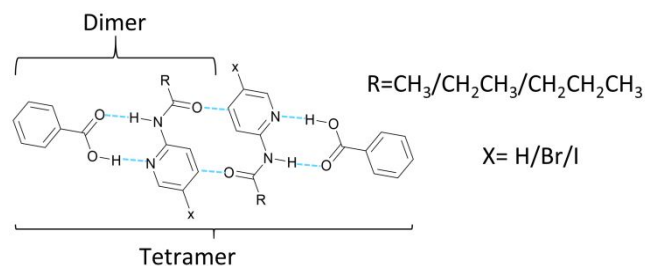
This may be viewed as a more unified approach to explain elastic bending as it also supports the requirements described previously. Brittle crystals have been associated with interdigitated<sup>29</sup> or layered arrangement of molecules.<sup>12</sup> The study of structurally similar compounds and polymorphic materials with different responses to mechanical stress reveal that in order for a crystal to exhibit mechanical flexibility, both topological and energetic requirements must be met.<sup>30,31,32,33,34</sup> During a study of co-crystals of N-(5-halopyridin-2-yl) amides, we serendipitously discovered that N-(5-iodopyridin-2-yl)propionamide:benzoic acid, displayed remarkable mechanical flexibility (Figure 1). Given the broad interest in improving our understanding of how flexibility of crystalline materials is related to structure (packing features), we decided to systematically explore possible structure-property relationships of similar co-crystals *i.e.* those formed by N-(pyridin-2-yl)alkylamides and carboxylic acids.



**Figure 1.** Evaluating mechanical responsiveness of the crystals (I-Et:BA) using a needle when secured by (a) forceps (b) cotton bud

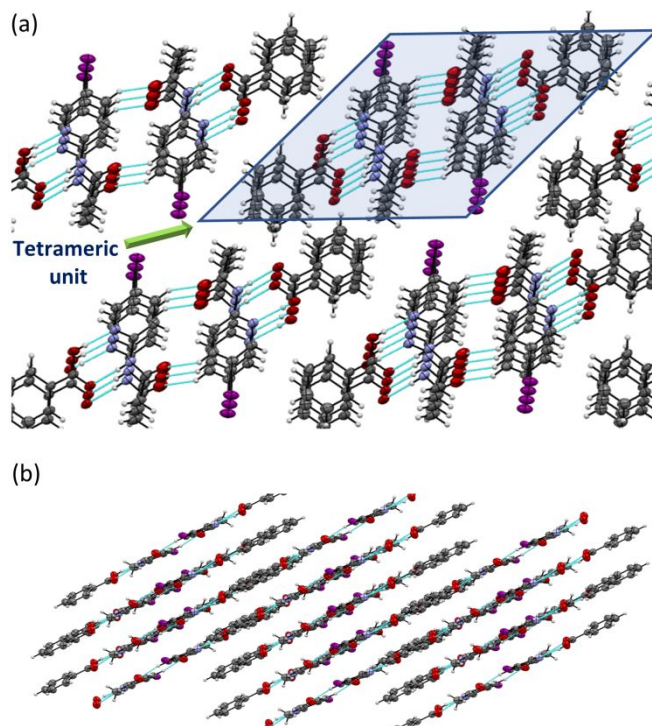
A simple qualitative mechanical testing was done by examining if the crystal would “fold” by pushing at it with a metal needle on one end, while having the other end secured with forceps or a cotton bud or by pushing a crystal held between forceps (Figure 1). Upon removing the needle, if the bent crystal regained its original position it was categorized as elastic. If it did not spring back after releasing pressure it was categorized as plastic. The descriptions of the ten co-crystals obtained are given in Table 1. In all ten co-crystals, the primary hydrogen bond motif remains the same. The NH-N “pocket” of the target interacts with a carboxylic acid through a  $-\text{COOH}\cdots\text{N}(\text{py})-\text{NH}$  synthon (Figure 2). In all ten co-crystals, the resulting dimers are subsequently connected into tetrameric units through C-H $\cdots$ O=C hydrogen bonds. (Figure 2, SI-1 and SI-2).

Despite the fact that the primary synthons, as described above, are identical in all 10 co-crystals, three distinct responses to mechanical stimuli were obtained. Thus, the extended packing



**Figure 2.** Primary hydrogen-bond motifs in all ten co-crystals producing tetrameric supramolecular building blocks.

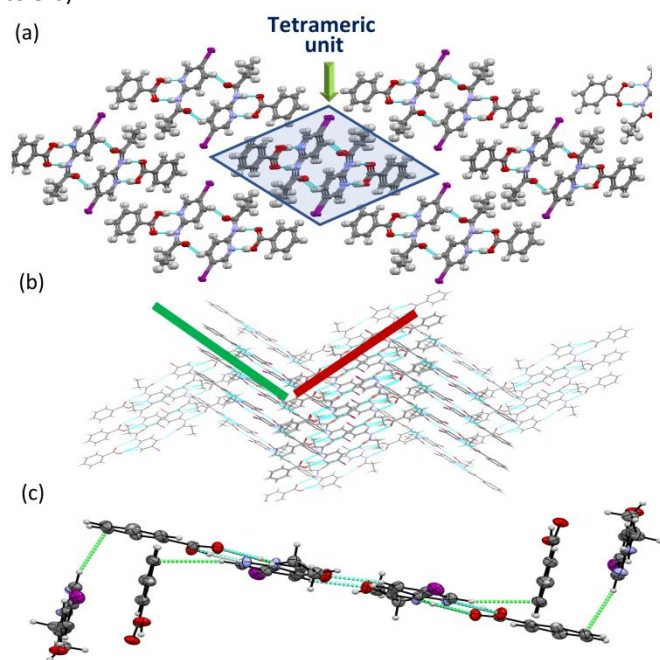
features were carefully analysed. The three brittle compounds **I-Me:BA**, **I-Me:3,5-MBA** and **I-Me:4Cl-BA** all displayed a layered arrangement. In **I-Me:BA** (Figure 3) and **I-Me:4Cl-BA** (SI-3.2)  $\pi$ - $\pi$  stacked columns of tetrameric units are present. The tetrameric units align, while in **I-Me:3,5-MBA** (SI-3.1) they are slightly displaced *i.e.* symmetry related molecules do not stack directly above each other. In each layer, apart from within the



**Figure 3.** Key packing features in **I-Me:BA** (a) Stacked columns of tetrameric units (b) layered arrangement of molecules

hydrogen-bonded tetramers, there are no additional noteworthy intralayer interactions. The building blocks in each layer are thus, structurally 'isolated'. These packing features may be indicative of the brittleness of these three crystals.

In the structures of **I-Et:BA**, **Br-Et:BA**, **I-Pr:BA**, **I-Et:4Cl-BA** and **H-Et:4Cl-BA**, the tetramers are assembled into  $\pi$ - $\pi$  stacked columns. The columns are tilted, which leads to corrugation and there are no slip planes. In addition, the alkyl chains of the tetramers (which are skewed in opposite directions), align and likely function as 'strain buffers' along with other weak dispersive interactions such  $\text{CH}\cdots\pi$  (in **I-Et:BA**, **Br-Et:BA**, and **I-Pr:BA**),  $\text{C-I}\cdots\text{Cl}$ ,  $\text{CH}\cdots\text{Cl}$  (in **I-Et:4Cl-BA**) and  $\text{Cl}\cdots\text{Cl}$  (in **H-Et:4Cl-BA**). The elastic bending observed in the crystals can likely be attributed to these structural characteristics (Figure 4 and SI-3.3 to 3.6).

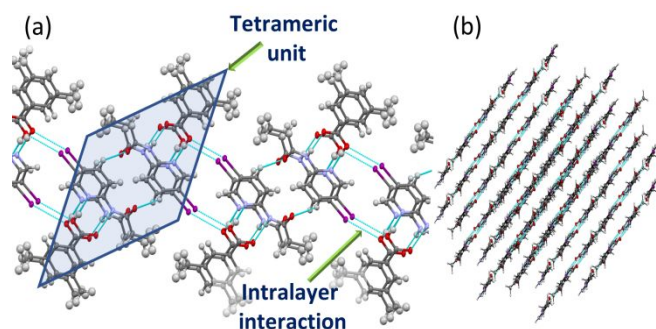


**Figure 4.** Packing features in **I-Et:BA** (a) Stacked columns of tetramers (b) corrugated arrangement of molecules (c)  $\text{CH}\cdots\pi$  interactions between columns

In the crystal structures of **I-Et:3,5-MBA** (Figure 5) and **Br-Et:3,5-MBA** (SI-3.7) the central tetramers experience both  $\pi$ - $\pi$  stacking and they have a layered arrangement. In both solids  $\text{Br/I}\cdots\text{O(OH)}$  intralayer halogen bonds interconnect the tetrameric building blocks, thus facilitating the plastic (sheer) deformation observed in the bulk materials.

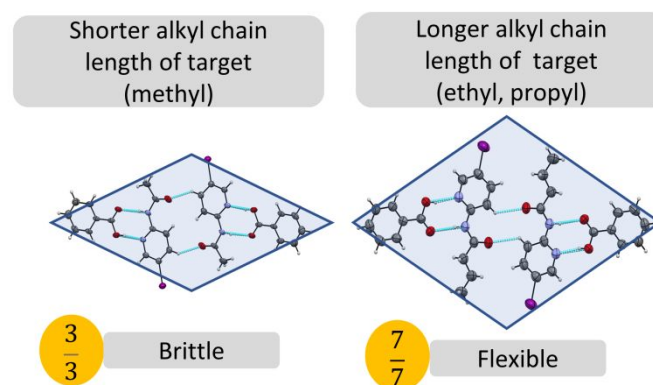
All three brittle crystals contained a target molecule decorated with a methyl chain. In the other seven cases, the target carried a slightly longer alkyl chain. Thus, in this "class" of co-crystals, a longer alkyl chain promotes flexible mechanical behaviour (Figure 6).

In the two co-crystals that showed plastic deformation, **I-Et:3,5M-BA** and **Br-Et:3,5M-BA**, the  $\text{X}\cdots\text{O(OH)}$  halogen bonds are likely essential for promoting plastic flexibility, as sheering would not be possible given the presence of layered topologies

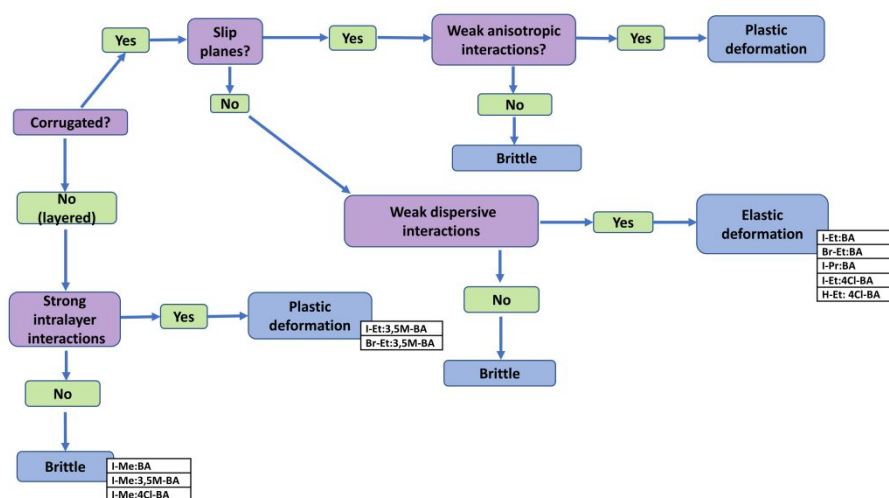


**Figure 5.** Packing features of **I-Et:3,5M-BA** (a) Stacked columns of tetrameric units (b) layered arrangement of molecules

in these crystals. None of the other co-crystals with halogenated targets (all bearing either bromine or iodine atoms) displayed any halogen-bond interactions; the halogen atoms are not in close proximity to the  $\text{O(OH)}$  group. The methyl groups (from the carboxylic acid) in the plastically deformable materials seem to exert a steric influence which promotes a short contact between the halogen atom and the  $\text{O(OH)}$  groups. This, in turn, facilitates the formation of a halogen bond which is instrumental in creating a structural feature of critical importance to the observed plastic deformation. In all ten co-crystals, the crystals with common extended structural features also bear the same macroscopic response to mechanical stimuli resulting in a road map for rationalizing, and even predicting, the mechanical behaviour in this class of compounds (Figure 7). It is important to note that currently, there are no universally accepted models or theories for how mechanical behaviour in the organic solid-state as well as in crystalline coordination polymers can be explained. The precise reversible movement of molecules promoting the elastic flexibility in the crystals discussed here is not yet explored. However, it is clear that systematic structure-property studies, such as presented here can offer considerable insight and a degree of predictability for assessing, in advance, whether a certain crystalline material is likely to be brittle, plastic, or elastic. This type of insight and understanding is an essential prerequisite for any reliable 'bottom-up' synthesis of materials with desirable macroscopic properties



**Figure 6.** Correlation between alkyl chain length of **N-(5-halopyridin-2-yl)amides** and observed physical properties.



**Figure 7.** Road map to assess responsiveness of crystalline solid to mechanical stress and corresponding co-crystals obtained

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