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# Probing the crystal structure landscape by doping: 4-bromo, 4-chloro and 4-methylcinnamic acids

Shaunak Chakraborty, Sumy Joseph and Gautam R. Desiraju\*

Abstract: Accessing the data points in the crystal structure landscape of a molecule is a challenging task, either experimentally or computationally. We have charted the crystal structure landscape 4-bromocinnamic acid (4BCA) experimentally of and computationally: experimental doping is achieved with 4methylcinnamic acid (4MCA) to obtain new crystal structures; computational doping is performed with 4-chlorocinnamic acid (4CCA) as a model system, because of the difficulties associated in parameterizing the Br-atom. The landscape of 4CCA is explored experimentally in turn, also by doping it with 4MCA, and is found to bear a close resemblance to the landscape of 4BCA, justifying the ready miscibility of these two halogenated cinnamic acids to form solid solutions without any change in crystal structure. In effect, 4MCA, 4CCA and 4BCA form a commutable group of crystal structures, which may be realized experimentally or computationally, and constitute the landscape. Unlike the results obtained by Kitaigorodskii, all but two of the multiple solid solutions obtained in the methyl-doping experiments take structures that are different from the hitherto observed crystal forms of the parent compounds. Even granted that the latter might be inherently polymorphic, this unusual observation provokes the suggestion that solid solution formation may be used to probe the crystal structure landscape. The influence of  $\pi \cdots \pi$  interactions, weak hydrogen bonds and halogen bonds in directing the formation of these new structures is also seen.

The crystal structure landscape<sup>[1]</sup> is a mapping of the various dynamic events occurring during the final stages of the crystallization process.<sup>[2]</sup> It encompasses diverse crystallization possibilities available to a molecule, such as polymorphs, pseudopolymorphs and high *Z* variations.<sup>[3]</sup> Attempts at charting the landscape computationally have met with some degree of success; crystal structure prediction (CSP) samples possible crystallization pathways,<sup>[4]</sup> but can fail to predict the final experimental crystal form because it ignores kinetic factors associated with the process.<sup>[5]</sup> Most putative structures in the landscape are difficult to isolate under laboratory conditions, but knowledge of the various packing possibilities is certainly useful, especially when a particular solid form can be associated with a particular property.<sup>[6]</sup>

The initial stages of the crystallization process can be probed with spectroscopy,<sup>[2]</sup> whereas crystallography can chart out the final steps.<sup>[3d, 8]</sup> Small chemical perturbations at certain innocuous positions of the molecule can be used to probe regions of the landscape that are otherwise inaccessible. The Fatom, although sterically like the H-atom, has an electronic

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nature rather different from it. This makes it a handy tool in the exploration of the crystal structure landscape.<sup>[9]</sup> This is so because of the packing diversity that is caused by the very weak C–H···F hydrogen bonds that might manifest themselves after the stronger interactions are paired off and insulated.<sup>[10]</sup> Multicomponent solids have also proven effective on occasion by capturing molecular conformations and packing modes that cannot be accessed under laboratory conditions.<sup>[3c, 9b]</sup>

A stable crystal structure is primarily guided by the principle of close-packing, according to which the protrusions of one molecule fit into the voids of another. In cases where the intermolecular interactions are weak, the structure is driven almost entirely by packing considerations, i.e., by isotropic electrostatic dispersion and exchange repulsion terms. A direct consequence of this is the fact that it is possible for a non-polar substituent to be replaced by one sterically similar to it, without such a replacement bringing about any changes in the crystal structure.<sup>[11]</sup> This is in accordance with the observations of Kitaigorodskii,<sup>[12]</sup> who saw that when two compounds A and B with very similar molecular structures are cocrystallized, two outcomes may ensue: (1) when A and B have the same crystal structure, the result is a solid solution (SS)  $A_x B_{1-x}$  with this same crystal structure. Kitaigorodskii selected tolane-diphenylmercury as a case in point; (2) when A and B have different crystal structures, solid solutions  $A_x B_{t-x}$  are still formed and they take either or both parent structures. He selected the anthraceneacridine system as representative of this situation. When there are no distinctly directional interactions that may significantly affect the packing, there is no enthalpic gain to be achieved in forming a stoichiometric compound (cocrystal) of A and B, but there could be some entropic advantage in forming a solid solution  $A_x B_{1-x}$ . When there is significant anisotropy in the form of strong and directional A····B interactions in the system, however, the result is mostly a stoichiometric cocrystal  $A_x B_y$ . Now what if A were to be doped with B such that the A···B interactions are neither completely isotropic, nor highly anisotropic? The expected result in such a scenario could be still a SS  $A_x B_{1-x_1}$ , but in a crystal structure that is neither that of A nor B; rather this would adopt a different packing, effectively allowing experimental access to points in the landscape that were hitherto unavailable. An SS of two compounds crystallizing in a new structure type, which is not taken by either pure compound, is almost novel, and we have seen only a few examples  $^{[13]}$  This communication explores this possibility in detail.

The isosteric, but electronically different characters of the F and the H atoms have been exploited in landscape exploration exercises.<sup>[9]</sup> We have shown in a recent report that partial fluoro-substitution, achieved in SS of fluorocinnamic acids, can serve as a finer probe in the landscape of unsubstituted cinnamic acid than the coarser full fluoro-substitution.<sup>[13a]</sup> The question that naturally arises at this point is whether this principle is applicable to other atom pairs as well. The bromine (Br) atom and the methyl (Me) group, with their closeness of volume (24.4 and 24 Å<sup>3</sup> respectively), have the potential to be exchanged in crystal structures without bringing about any deep-seated changes, if only geometrical effects are important.<sup>[14]</sup> However, their very different electronic nature could change this outcome and this is what makes them an attractive test pair in the present context. Profiling the

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landscape of a brominated molecule presents an additional challenge because of the anisotropy and polarizability of the Br atom and the resultant computational difficulties associated with it. We therefore chose to explore the landscape of 4-bromocinnamic acid (4BCA) by doping it with 4-methylcinnamic acid (4MCA).

4BCA [ZZZOJI03; P2<sub>1</sub>/n; a = 6.8823(2) Å, b = 3.90430(10) Å, c = 31.4618(12) Å,  $\beta$ = 90.077(3)°] is a structure that may be described as a linear ribbon (Figure 1a),<sup>[15]</sup> of the (7-4-31) type.<sup>[16]</sup> This 4Å structure consists of stacks of planar sheets containing laterally C-H···O hydrogen bonded 4BCA molecules. <sup>[15]</sup> Horizontally related stacks are offset with respect to each other according to the geometric demands of Br...Br quasi type I/II contacts (ESI). 4BCA molecules in vertically related stacks can be produced by simple translation operations; it is a  $\beta$ structure.<sup>[17]</sup> 4MCA [ZZEFW01;  $P\bar{I}$ ; a = 7.968(2) Å, b = 9.144(2)Å, c = 7.733(2) Å,  $\alpha$  = 106.87(2) °,  $\beta$  = 125.46(2) °,  $\gamma$  = 86.87(2) °], on the other hand, is a planar sheet structure (Figure 1b). We call it a (8-9-8) structure. The 4MCA molecules in vertically related stacks can be produced by inversion operations, i.e., it is an  $\alpha$  structure. From the trends observed by Kitaigorodskii, the SS of 4BCA and 4MCA would also be expected to take either of the parent structures. However, one must not rule out the possibility of Br...Br and C-H...Br interactions in these SS.



**Figure 1.** (a) Schematic representation of the linear ribbon structure of 4BCA. Both the blue and green sheets consist of laterally C–H···O hydrogen bonded 4BCA molecules. Throughout this paper, use of the same color in a stack indicates symmetry equivalence, i.e. the molecules are related by a simple translation operation. (b) shows a schematic representation of the planar sheet structure of 4MCA. 4MCA molecules in vertically related sheets are related by inversion operations as indicated by different shades of green.

We obtained SS over a broad range of concentrations, *but in multiple structure types that are neither the native structure of 4BCA nor that of 4MCA* (Fig. 1). This is a highly unusual observation. The SS obtained when the concentration of 4BCA is higher than that of 4MCA is a planar sheet, but it is a  $\beta$  structure [*P*]; *a* = 3.907(9) Å, *b* = 7.580(19) Å, *c* = 15.05(4) Å, *a*= 101.77(6) °,  $\beta$ = 92.87(13) °,  $\gamma$ = 100.63(9) °] where the nearest molecules are related by translation operations. It, unlike 4BCA or 4MCA, is classified as a (4-7-15) structure. The Br···Br contact geometry in this structure is type I, as opposed to quasi type I/II in (7-4-31) (ESI). Another  $\beta$  structure [*C*2/*c*; *a* = 14.868(8) Å, *b* = 3.9586(15) Å, *c* = 30.040(12) Å,  $\beta$  = 103.964(16) °], classified as (15-4-30), is obtained at roughly

equal concentrations of 4BCA and 4MCA. It is a linear ribbon with type I inter-sheet Br...Br contacts, and the non-zero dihedral angle between adjacent sheets is the point of difference from (4-7-15) (Figure 2). A  $\gamma$  structure is obtained at high concentrations of 4MCA [P21/n; a = 6.014(2) Å, b = 4.970(2) Å, c = 28.312(12) Å, β= 90.74(2) °] which we label (6-5-28). It grows along the 2<sub>1</sub> axis via type II ( $\theta_1 = 91.24^\circ$ ,  $\theta_2 = 172.18^\circ$ ) Br...Br (interspersed with Me groups) contacts (Figure 2). This contact geometry is conducive to an effective C-H...Br interaction between the Me group of a 4MCA molecule on one planar sheet, and the Br atom on a 4BCA molecule on the one adjacent to it. This orthogonal geometry may also have some additional stabilization due to a C-H... $\pi$  interaction between the aromatic ring and the Me protons (ESI). We have thus obtained three different types of SS of 4BCA and 4MCA that take none of the native parent structures. We could also isolate two SS in the (7-4-31) structure, at 4BCA:4MCA ratios of 57:43 and 79:21 (Table 1). These are the only two cases among all our experiments where we isolated SS in the native structures of one of the parent compounds. We also see from Table 1 that SS 3 and 5. which have very close 4BCA-4MCA ratios, adopt (4-7-15) and (7-4-31) cells respectively. This indicates that these two structures are part of the same crystal structure landscape.



**Figure 2.** Schematic representations of the packing patterns and the interactions seen in the three types of SS obtained. Please note that use of the same colour in a stack means that the sheets are all related by simple translation. (a) shows the packing in the (4-7-15) structures, and (b) and (c) show the type I interactions seen in the 4BCA-4MCA and 4CCA-4MCA systems respectively. (d) shows the packing in the (6-5-28) structures, (e) and (f) show the type II interactions seen in the 4BCA-4MCA and 4CCA-4MCA systems respectively. (g) shows the packing pattern of the (15-4-30) structures, and (h) shows the interactions in this structure in the 4BCA-4MCA system. The (15-4-30) structure was not found experimentally in the 4CCA-4MCA system.

Having obtained three different types of SS of 4BCA and 4MCA, we were curious as to whether these three structures would be found in the CSP of 4BCA. However, given the technical difficulties related to the anisotropy and polarizability of the Br atom, we decided to search for a system that would effectively model 4BCA, but would also be easier to handle computationally. The CI atom, being geometrically and electronically like Br, in addition to being considerably lighter, seemed to be a likely candidate. We therefore chose to explore 4-chlorocinnamic acid (4CCA), which in its pure form is isostructural with pure 4BCA, as a model. Naturally, this led to an experimental exploration of the landscape of 4CCA itself by methyl doping. Interestingly, the SS of 4CCA and 4MCA follow the same composition-structure correlation as the 4BCA-4MCA system (ESI). We see the (4-7-

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15) structure at relatively high concentrations of 4CCA, while relatively low concentrations of it produce the (6-5-28) structure. We could not isolate any SS in the (15-4-30) structure for the 4CCA-4MCA system, but interestingly, *in 4CCA too we see the unique phenomenon of the solid solutions taking crystal structures different from either of the native parent structure types.* 

To find out if the (6-5-28) structure would be seen when the molecule has a high propensity for the formation of orthogonal type-II interactions, we carried out cocrystallization experiments with 4-iodocinnamic acid (4ICA) and 4MCA. We isolated a structure containing 91% 4MCA and 9% 4ICA [*P*2<sub>1</sub>/*n*; *a* = 6.0085(5) Å, *b* = 4.908(3) Å, *c* = 28.126(18) Å, *β* = 90.82(4) °], which is a (6-5-28) structure, and is different from the structure of 4ICA itself [WAMZOZ, *P*2<sub>1</sub>/*n*; *a* = 4.118(2) Å, *b* = 6.274(4) Å, *c* = 34.672(2) Å, *β*= 90.32(2) °]. Both 4ICA and the 9% 4ICA-doped 4MCA exhibit type II I···I interactions, and it is obvious that these interactions and possibly C–H···I hydrogen bonds in case of SS 26, drive the molecules to pack thus (ESI).

Table 1. Solid solutions of 4	4BCA and 4CCA with 4MCA
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SS of 4BCA and 4MCA			SS of 4CCA and 4MCA		
SS	4BCA:4MCA	Structure	SS	4CCA:4MCA	Structure
1	60:40	(4-7-15)	11	74:26	(4-7-15)
2	56:44	(4-7-15)	12	62:38	(4-7-15)
3	76:24	(4-7-15)	13	54:46	(4-7-15)
4	57:43	(7-4-31)	14	49:51	(4-7-15)
5	79:21	(7-4-31)	15	65:35	(4-7-15)
6	6:94	(6-5-28)	16	66:34	(4-7-15)
7	6:94	(6-5-28)	17	20:80	(6-5-28)
8	43:57	(15-4-30)	18	9:91	(6-5-28)
9	46:54	(15-4-30)	19	11:89	(6-5-28)
10	51:49	(15-4-30)		A.	

To ascertain if these structures are indeed part of the landscape of 4CCA, we performed a computational CSP experiment with the 4CCA molecule as an input (ESI).<sup>[18]</sup> The (4-7-15), (15-4-30) and (7-4-31) structures turned up in the energy-density plot (Figure 3). We even obtained a structure like that of 4MCA, but the (6-5-28) structure was not found (ESI).



Figure 3. Energy-density plot of the structures obtained from the CSP of 4CCA. Structures close to the experimental structures occur in the highlighted region.

On examining the crystal structures 4ICA and 9% 4ICA doped 4MCA, the latter crystallizing with a (6-5-28) structure (ESI), it occurred to us that the CSP protocol, which takes only close-packing into consideration, had likely overlooked the interaction component, and this was why the (6-5-28) structure with the type II halogen bond geometry could not be found in the CSP results. A CSD search for structures with these cell parameters returned a polymorph of 4-formylcinnamic acid [COWRIP;  $P_{21}/n$ ; a = 6.261(2) Å, b = 4.825(1) Å, c = 27.614(9) Å,  $\beta$ =91.54(2) °] as a hit (ESI). This is essentially isostructural with these SS and is held together by orthogonal interactions between the carbonyl groups of adjacent molecules (Figure 4).



Figure 4. (a) shows where the (6-5-28) structure occurs in the CSP of COWRIP with DREIDING. (b) Packing diagram and (c) orthogonal interactions in COWRIP.

We hypothesized that since the positive charge on the C atom of the formyl group on the 4-position is accounted for, there is a good chance that a structure close to (6-5-28) may turn up in CSP of COWRIP; such a structure indeed arises at rank 2 with DREIDING. Thus, with the possible interactions accounted for, all the experimental structures may be obtained by the CSP protocol. The (4-7-15), (7-4-31), (15-4-30) and (6-5-28) structures are all parts of the landscape of 4CCA, and by token of the identical behaviour of 4BCA under the same cocrystallization protocols, of the landscape of 4BCA as well. Indeed there is just the one landscape and all the 4MCA, 4CCA and 4BCA structures identified experimentally and/or computationally constitute a commutable set of crystal structures within this landscape.

The mutual dissolution behaviour of 4BCA and 4CCA, and their ternary SS behavior with 4MCA place this on an even firmer footing. 4BCA and 4CCA exhibit continuous solubility with each other (SS 20-25) without any structural changes over the whole range of composition, meaning their energy hypersurfaces are similar not only in their general features, but also in the positions of their minima. The 4BCA-4CMA and 4CCA-4MCA systems also have similar phase diagrams as shown in Figure 5. Further details are given in the ESI.

The ternary SS (27 and 28) of 4CCA, 4BCA and 4MCA are both different. They are distinct from either 4BCA (which is the same as 4CCA) or 4MCA. This makes a total of four structure types in

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this set of compounds. Yet, all four structures are found in the same landscape, showing clearly that the latter is a pool from which equivalent structures may effectively be drawn.

We have explored the structural landscapes of 4BCA and 4CCA using bromo-methyl and chloro-methyl exchange phenomena as tools. One may draw several conclusions: (1) 4CCA, because of the geometric and electronic similarities of the Cl and the Br atoms, is a good model for charting the landscape of the more computationally challenging 4BCA. (2) 4BCA and 4CCA have virtually identical structural landscapes and so they are completely miscible. (3) Isolation of solid solutions with crystal structures that are different from either of the parent structures hints that interaction directionality plays a role in the packing of molecules. To the best of our knowledge, this is the first such report in the context of chloro-methyl and bromo-methyl exchange experiments.



Figure 5. Melting point vs. composition plots of (a) the 4BCA-4CCA, (b) the 4BCA-4MCA, and (c) the 4CCA-4MCA systems.

It is likely that we would obtain non-stoichiometric mixed crystals in a different structure type when the interactions involved are neither isotropic enough to allow the formation of a solid solution in one of the native parent structure types, nor strong/directional enough to give rise to a stoichiometric compound. We have also noted in a prior study that at least two of these structure types, namely (4-7-15) and (7-4-31), are part of the crystal structure landscape of unsubstituted CA. Another structure type (4-7-31) which is seen in the CSP of 4CCA, is also a part of the landscape of unsubstituted CA. One may also draw in the unsubstituted compound into the landscape. These structures constitute a closed set, recurring irrespective of the substituent (H, F, Cl, Br or Me) used in the exercise; this proves the generality of the concept of the crystal structure landscape.

#### **Experimental Section**

Experimental details are provided in the supplementary material.

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**Keywords:** Solid solution • Crystal structure landscape • Crystal engineering • Crystal structure prediction • Doping

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- [16] The numbers are the closest integer approximations to the cell dimensions, as per the convention described in reference 9a.
- [18] The CSP exercises were carried out using only the pure components as input. If solid solutions are to be used as input, the presence of two different atoms at the same crystallographic site must be accounted for, because such a procedure is liable to cause problems with the geometry optimization and the force fields.

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Experimental and computational crystal structures of 4-chloro, 4-bromo and 4-methylcinnamic acids, and their binary and ternary solid solutions define a single landscape.



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