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Rationalizing Distinct Mechanical Properties of Three Polymorphs of a Drug Adduct by Nanoindentation and Energy Frameworks Analysis: Role of Slip Layer Topology and Weak Interactions

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ABSTRACT:

Three concomitant polymorphs of 3-((4-chlorophenyl)imino)indolin-2-one, Schiff's base are identified and sorted based on morphology and mechanical response of their crystals. Form I grows as blocks and shows brittle fracture. Form II as long needles and shows plastic bending and Form III also as long needles and shows elastic bending under similar qualitative mechanical deformation tests. Furthermore, the brittle Form I was found to exhibit thermosalient behavior (jumping) when heated on a hot plate. The distinct mechanical behavior of the three forms is rationalized by analyzing intermolecular interaction energies from energy frameworks analysis, slip layer topology, Hirshfeld surface analysis and nanoindentation. The quantitative nanoindentation studies unveiled that Form III has higher elastic modulus and stiffness than Forms I and II while the hardness was lowest for the plastic Form II. Despite high structural similarity in Forms II (plastic) and III (elastic), the E of elastic Form III was found to be three orders of magnitude higher than that of plastic Form II crystals, which is attributed to the subtle differences in interaction energies and slip layer topology in the two cases. Consideration of slip layer topology and interaction energies from structure are very useful for rationalizing mechanical properties, but may not be always sufficient and one may also need to know the topology of the potential energy surface of the slip layers for understanding the distinct mechanical behavior.

Keywords: Polymorphism, mechanical properties, weak interactions, slip layer topology, and energy frameworks.

INTRODUCTION:

Study of structure-mechanical property correlation in organic crystals has attracted much attention in recent times owing to the utility of such understanding for addressing solidstate issues in pharmaceutical processes,¹ design of smart materials such as mechanical actuators,^{2,3} mechanochromic luminescent materials,^{4,5} mechanical sensors, flexible optoelectronic materials etc. ⁶⁻¹⁰ Recent investigations involving qualitative deformation,¹¹⁻¹⁵ nanoindentation (quantitative),¹⁶ powder compaction,¹⁷ high-pressure¹⁸ and computational techniques¹⁹⁻²¹ have attempted to determine and/or predict the mechanical properties of molecular crystals. However, design of organic crystals with desired mechanical behavior remains a challenge due to the complexity of three dimensional crystal structures, inadequate understanding of the interplay of strong and weak intermolecular interactions in complex situations and the dynamics of weak and strong interactions during the mechanical deformations or actions of crystals.²²⁻²³ Some valuable insights in this direction have been obtained from recent studies, particularly from certain simple polymorphic and isostructural solid forms, where the complexity is reduced, for instance, due to the similarity of molecular structures in polymorphs and same crystal structure in isostructural forms.^{1, 24, 25}

Polymorphs are distinct crystalline phases with different spatial arrangement of the same chemical compound or composition.²⁶ Polymorphism, one of the most fascinating aspects in solid-state chemistry, can profoundly alter the physicochemical properties, including mechanical properties of molecular crystals.²⁷ The structural differences between the crystalline species can be generally classified into *packing polymorphs, conformational polymorphs* and *synthon polymorphs*.²⁸⁻³⁰ The former could arise due to molecules adopting different packing patterns, whereas the conformational polymorphism involves the conformationally flexible molecules crystallizing with varied conformations in different forms. The synthon polymorphism is due to adoption of different supramolecular synthons by the competing functional groups in polymorphs. The majority of molecules among the active pharmaceutical ingredients (API) contain rotatable bonds with moderate to high conformational flexibility as well as competing functional groups, hence polymorphism is not uncommon in them.³¹⁻³⁷ On the other hand, identification, separation^{38,39,40} and characterization of properties of polymorphs is indispensable for successful development of a

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benchmark product in the context of academic and industrial interest.³⁷ In recent times,^{38,39} a good progress has been made in predicting the mechanical properties and tabletability of polymorphs and other solid forms by efficient identification of (i) facile slip layers in crystals, (ii) topology of slip layers, and (iii) interaction energies among molecules in different directions. However, it still remains a challenge to accurately predict whether a crystal is going to deform in a brittle fashion or show plastic or elastic flexibility under an external mechanical stress. This is particularly true in borderline cases where there exist clear slip planes but with some degree of interdigitation. In such cases, comparison of interaction energies across the slip planes from energy frameworks analysis could help but this technique is relatively new and yet to be fully exploited. In continuation to our work on the structure-mechanical property relationship in pharmaceutical solid forms,^{1, 4-6} during a co-crystallization attempt we serendipitously obtained concomitant polymorphs of a Schiff's base, 3-((4-chlorophenyl))imino)indolin-2-one (hereafter, CPII) (Figure 1) formed between the isatin drug (indoline-2,3-dione) and 4-chloroaniline (4CA) upon mechanical grinding followed by solution crystallization.

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EXPERIMENTAL SECTION:

Materials used.

Indoline-2,3-dione (IND) and 4-chloroaniline (4CA) were purchased from Sigma-Aldrich chemicals, Bangalore, India. Commercially available solvents were used as received without any further purification, for crystallization.

Synthesis and single crystal preparation.

The Schiff's base could be prepared in two ways. The first, by solid-state mechanical grinding of an equimolar ratio of IND and 4CA; and second, by dissolving the equimolar components in hot methanol at 60 °C in about 15 minutes. Form I crystals were obtained concomitantly along with Form III from methanol solvent by slow evaporation. However, mixture of methanol and ethanol (1:1) produced Form II and III concomitantly. It was possible to prepare pure Form I crystalline material by overnight reflux of equimolar ratio of IND and 4CA in methanol, followed by evaporation of solvent under rotary evaporator. Crystallization from toluene yielded needle type crystals of Form I. But we always obtained Form II and Form III concomitantly in 1:1 methanol and ethanol solution (Figure S1). We never obtained Forms I and II together in our limited screening attempts. Good quality single crystals suitable for X-ray diffraction were obtained in 5 to 6 days in all the cases.

Solid-state characterization.

Single crystal X-ray diffraction (SCXRD).

X-ray diffraction data of suitable single crystals were recorded on a SuperNova, Rigaku diffractometer using monochromatic Mo-K α radiation ($\lambda = 0.71073$ Å). The data collection was performed at low temperature (100 K) for Forms I and II, and room temperature (298 K) for Form III. Using Olex2, (1.2.9 version)⁴⁷ the structures were solved with the SHELXT⁴⁶ structure solution program using intrinsic phasing solution method and refined with the ShelXL⁴⁹ refinement package using Least Squares minimization. All the non-hydrogen atoms were refined anisotropically. All the crystal packing diagrams were prepared using Mercury (3.10.1 version) software (ORTEP diagrams, Figure S2).

Powder X-ray diffraction (PXRD).

The bulk samples of all the new solid forms were characterized by PXRD analysis on a Rigaku Smart Lab with a Cu K α radiation (1.54056 Å). The tube voltage and amperage were set at 20 kV and 35 mA respectively for all the experiments. Each sample was scanned between 5 and 50° 2 θ with a step degree of 0.02°.

The three polymorphs were distinguished from their unique powder XRD patterns (Figure S3). The experimental patterns of Forms I and III were matched with the corresponding simulated PXRD patterns generated from their single crystal XRD structures to confirm phase purity. The slight variations and the broadness of peaks in the experimental

PXRD patterns of plastic Form II could be because of the lattice strain or presence of grain boundaries, dislocations etc. in the crystals.

FT-Infrared spectroscopy (FT-IR).

Transmission infrared spectra of the solids were obtained using a Fouriertransformation infrared spectrometer (Bruker). KBr samples (2 mg in 20 mg of KBr) were prepared and 10 scans were collected at 4 cm⁻¹ resolution for each sample. The spectra were measured over the range of 4000-400 cm⁻¹ (Figure S5).

Differential scanning calorimetry (DSC).

The DSC for all the samples was performed on a Mettler-Toledo DSI1 STAR^e instrument. About 2–4 mg of samples were crimped in hermetic aluminum crucibles (40 μ L) and scanned from room tepmerature to 300 °C at a heating rate of 10 °C/min under a dry N₂ atmosphere (flow rate 80 mL/min). The data was dealt with STAR^e software (Figure 8).

Hirshfeld surface analysis.

The package CrystalExplorer 3.1⁵⁰ was used for the Hirshfeld surface analysis on each of the symmetry independent molecules of all the three forms. The analysis was carried out based on their respective crystal geometries. The corresponding 2D fingerprint plots were also generated using CrystalExplorer 3.1.

Energy frameworks analysis and interaction energy calculations.

CrystalExplorer 17.5⁵¹ was used to evaluate and visualize the pair wise interaction energies of all three forms. The tube size (scale factor) used in all the energy frameworks was 25 for all forms and the lower energy threshold (cut-off) value was set to 5 for Forms I, II and III. The energy components calculated within this method are electrostatic, polarization, dispersion and exchange-repulsion and finally the total interaction energy (Tables S1-S3). These energy calculations are accomplished at the B3LYP/6-31G**⁵²⁻⁵⁴ level of theory and using crystal geometries (experimental structures) of the respective forms.

Nanoindentation (NI).

Face indices of the three polymorphs were identified and described based on SCXRD, which matched with predicted BFDH morphology (Mercury, version 3.10.1). The selected crystals of Forms I, II and III were mounted on a sample holder using a cyanoacrylate glue at

least 12 hours prior to nanoindentation. The experiments were performed on (0 1 0) face of Form I and (1 0 0) face of Form II using a nanoindenter (Hysitron Triboindenter, Ubi 700, Minneapolis, USA) with an *in situ* Scanning Probe Microscopy (SPM) facility. In case of Form III, (0 0 1) face was indented using a different nanoindenter (Hysitron Triboindenter, TI Premier, Minneapolis, USA) The machine constantly monitors and records the load, *P*, and displacement, *h*, of the indenter with force and displacement resolutions of 1 nN and 0.2 nm, respectively. A three-sided pyramidal Berkovich diamond indenter (tip end radius ~150 nm) was used to indent the crystals. In all cases, loading and unloading rates of 600 μ N.s⁻¹ was maintained keeping maximum load constant at 6000 μ N and hold time of 10 s. A minimum of 10 indentations were performed on each crystallographic face. The indentation impressions were captured immediately after unloading so as to avoid any time-dependent elastic recovery of the residual impression. The *P*–*h* curves obtained were analyzed using the standard Oliver–Pharr method⁵⁵ to extract the elastic modulus, *E*, and hardness, *H*, of the crystal in that orientation.

RESULTS & DISCUSSION:

Crystallization of CPII from methanol yielded thick blocks and needle shaped crystals concomitantly (Figure S1a), while 1:1 mixture of methanol and ethanol produced only long needle shaped crystals (Figure S1b). The block type crystals (which we call as Form I (Figure 1(a)) could be easily separable from the needles. Simple qualitative mechanical deformation tests by using a metal pin and forceps revealed that the block shaped crystals are brittle (Figure 1(d), also see Video 1, SI). The needle shaped crystals (Form III, Figure 1(c)) obtained from methanol deformed elastically (Figure 1(f), see Video 3, SI), but on the other hand those from 1:1 mixture of methanol and ethanol showed either elastic flexibility (Form III) or plastic flexibility (Form II, Figure 1(b) & (e), see Video 2, SI). The two types of needle shaped crystals had nearly the same aspect ratio and visually indistinguishable. To check if the needle shaped morphology alone was responsible for flexibility, we tried different crystallization methods to grow the Form I in needle morphology instead of thick blocks. We succeeded to grow them as needles from toluene solvent (Figure S1c, SI). Qualitative mechanical tests on these needles of Form I were brittle and showed no sign of either elastic or plastic flexibility (see videos 1a and 1b, SI), confirming that the morphology alone is not a sufficient condition for flexibility. Nevertheless, the qualitative mechanical tests allowed us to identify and separate the Forms I (brittle), II (plastic) and III (elastic) based on deformation

behavior. We carried out further characterization by various analytical techniques, such as SCXRD, PXRD, DSC and FT-IR.



Figure 1. Optical images depicting morphologies of Form I (a), Form II (b) and Form III (c) crystals of CPII. Mechanical deformation tests on the crystals of Form I, brittle (d), Form II, plastic (e) and Form III, elastic (f). Inset shows molecular structure of CPII.

Crystal structure analysis:

Single crystal X-ray diffraction studies on Form I reveal that in the packing (monoclinic, $P2_1/c$ (Table 1) the molecules constitute a centrosymmetric dimer synthon via N-H···O $(D/\text{\AA}, d/\text{\AA}, \theta)^\circ$: 2.862 Å, 2.014 Å, 168.74°) hydrogen bonds (Figure 2a). These dimer molecules are further connected by C-H···N (3.456 Å, 2.642 Å, 146.51°) hydrogen bonds to form 1D tapes along the $[0 \ 0 \ 1]$ direction (Figure S6a). The adjacent tapes are connected with weak C-H...Cl (3.696 Å, 2.880 Å, 147.12°) interactions to further form corrugated sheets (Figure S6b). These sheets are stacked along the $\begin{bmatrix} 1 & 0 \end{bmatrix}$ direction to optimize the weak intermolecular interactions (C-H··· π and C-Cl··· π). It is also to be noted that the 1D tapes are mechanically interlocked in (0 1 0) by zipper type arrangement *via* chlorinated aromatic groups from the adjacent tapes. The Cl-groups from opposite layers crossover each other (by -2.328 Å), past the Miller plane (0 1 0) and result in the interdigitation (Figure 2a). Visual inspection suggests that the mechanical interlocking or zipper type packing of sheets is unlikely to make it a facile slip plane. There are no other crystallographic planes that are supported entirely by van der Waals interactions. Hence, the overall packing can be described as a three dimensionally (3D) interlocked system. Hence the Form I crystals showed brittle mechanical behavior on application of a mechanical stress.¹²

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The Form II crystallizes in monoclinic space group *Cc* (Table 1). The molecules form 1D tapes along the crystallographic *c*-axis *via* intermolecular N–H…N (3.019 Å, 2.202 Å, 153.84°; 3.269 Å, 2.470 Å, 156.61°) and C–H…O (3.127 Å, 2.351 Å, 138.53°) hydrogen bonds. The tapes run parallel to each other (Figure 2b). The adjacent tapes are connected through very weak C–H…Cl (3.676 Å, 2.958 Å, 133.36°) interactions across (1 0 0) plane. Inspection of topology of this plane suggests that layers are separated by 0.868 Å and have low ruggedness. Hence, this plane is likely to be a facile slip plane (Figure S8a). The 1D tapes are stacked along the [0 1 0] to stabilize *via* weak C–H…O hydrogen bonds. The (1 0 0) slip plane exists orthogonal to the stacking interactions. Thus, the plastic bending observed on (1 0 0) in these crystals is perceivable. The crystals break upon application of a similar stress on the other pair of faces, (0 0 1)/(0 0 -1), confirming anisotropic plasticity in these crystals.



(b)

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Figure 2. Crystal packing diagrams of Form I (a), Form II (b) and Form III (c). Note that the tapes in Form II are parallel (follow pink arrows) while they are antiparallel in Form III, leading to the difference in the topology of slip layers. Red arrows indicate the indentation direction on (0 1 0) face of Form I, (1 0 0) face of Form II and (0 0 1) face of Form III.

In the crystal structure of Form III (orthorhombic, P n a 2₁,) (Table 1), the molecules form very similar 1D tapes *via* N–H···N (3.063 Å, 2.275 Å, 152.31°; 3.357Å, 2.546 Å, 157.52°) and C–H···O (3.167 Å, 2.394 Å, 140.50°) hydrogen bonds along the crystallographic *a*-axis. However, the adjacent tapes in this case are arranged antiparallel to each other (Figure 2c). A careful visual inspection of the arrangement of antiparallel tapes in the slip layer reveal that the chlorinated phenyl groups in this case point in opposite direction to each other. The layer separation in this case is 0.836 Å, which is slightly lower than that of (1 0 0) slip plane of Form II (0.868 Å). Otherwise, there are hardly any other significant visual differences in the topology of the slip layers in Form III compared to Form II packing (Figure S8b). Hence, intrigued by the contrasting mechanical properties of Forms II (plastic) and III (elastic), we further carried out nanoindentation experiments and, energy frameworks and Hirshfeld surface analyses.

Cell parameters	Form I (brittle)	Form II (plastic)	Form III (elastic)	
Formula	C ₁₄ H ₉ ClN ₂ O	C ₁₄ H ₉ ClN ₂ O	C ₁₄ H ₉ ClN ₂ O	
Formula mass	256.68	256.04	256.04	
Crystal System	Monoclinic	Monoclinic	Orthorhombic	
Space group	$P 2_1/c$	Сс	<i>P n a</i> 2 ₁	
a [Å]	5.4359(3)	25.7936(6)	20.7181(8)	
b [Å]	25.8282(8)	4.2902(6)	4.4806(3)	
c [Å]	8.4934(5)	20.6791(7)	25.5553(8)	
α[⁰]	90	90	90	
β[⁰]	98.902(5)	92.170(3)	90	
γ [⁰]	90	90	90	
V [Å ³]	1178.10(11)	2286.69(12)	2372.30(19)	
Ζ	4	8	8	

Table 1: Crystal data of three	olymorphs of S	Schiff's base,	CPII.
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λ[Å]	0.71073	0.71073	0.71073	
$\rho_{calcd} [gcm^{-3}]$	1.447	1.497	1.437	
<i>F[000]</i>	528.0	1064.0	1056.0	
μ [mm ⁻¹]	0.311	0.321	0.309	
θ [⁰]	5.1 to 52.74	3.16 to 52.74	3.94 to 50.06	
index ranges	$-6 \le h \le 6, -31 \le k$ $\le 32, -9 \le 1 \le 10$	$-32 \le h \le 12, -4 \le k \le 5, -25 \le l \le 25$	$-18 \le h \le 24, -3 \le k \le 5, -30 \le l \le 29$	
T [K]	293	100	298	
R1	0.0423	0.0322	0.0433	
wR2	0.0958	0.0682	0.1098	
Parameters	163	325	325	
CCDC No.	1822620	1822621	1822622	

We now discuss the structural relationship of the three polymorphs briefly. The structure of Form I is significantly different from the crystal structure of Forms II and III (Figure 3a). <u>Although</u> the Form II and Form III of CPII belong to different space groups, they both have similar unit cell parameters and synthons within the 1D tape (Figure 3b and 3c). Form I with completely different synthons can be described as a synthon polymorph with respect to the Forms II and III, while the latter two may be called as packing polymorphs, as they both have similar 1D tapes and synthons but their further packing is different.



Figure 3. Hydrogen bonding and different synthons in the CPII polymorphs. (a) Dimer formed by N–H···O hydrogen bonded synthon in 1D tape along *c*-axis in Form I, (b) N–H···N and C–H···X (X = O, N) hydrogen bonding in the sheet along the *c*-axis in Form I, and (c) N–H···N and C–H···X (X = O, N) hydrogen bonding in

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the sheet along the *a*-axis in Form II. (d) Overlay diagram of molecules in asymmetric unit from Form I (brittle; red), Form II (plastic; orange and yellow) and Form III (elastic; magenta and violet).

The conformationally flexible aromatic ring in C=N–Ar group leads to the conformational polymorphism in the Schiff's base, CPII. Based on the analysis of the crystal structure of the three polymorphs, it is noted that torsional rotation angles of C=N–C–C(Ar) are different for different molecular conformations. The torsion angle for form I is - 126.75°(3), and for two independent molecules in Form II and Form III are 125.7°(3), 120.2°(3) and, 119.1°(4), 122.7°(4), respectively as shown in overlay diagram in Figure 3d. Other torsion angles are depicted in Table S4.

Energy frameworks analysis:

In order to visualize intermolecular interactions in the three polymorphs of CPII in a more quantitative way, we calculated the pair wise interaction energies for the three forms using *'energy frameworks'*,⁵¹ which allowed us to display rigid 3D topologies for all the forms. The separate energy frameworks corresponding to (a) the total, (b) dispersion term and (c) electrostatic term interaction energies are depicted in the Figure 4.

In case of Form I (brittle), the aggregate of total interaction energies of molecules forming 1D tape was found to be -130.4 KJ mol⁻¹, which includes the N–H···O (0D centrosymmetric dimer) and C–H···N hydrogen bonds (between dimers) etc. (Figure S11). The aggregate of total interaction energies corresponding to the zipper-type inter-tape interactions (C–Cl··· π and C–H···Cl) along [0 1 0] is -57.2 KJ mol⁻¹, while it was -30.3 KJ mol⁻¹ for stacking direction [1 0 0]. This suggests that the stacking interactions have lowest interaction energy, but since the layers in this direction are highly corrugated (Figure S7, SI), the slip is not expected.

In Form II, the aggregate of total interaction energies for 1D tape is -137.8 KJ mol⁻¹, while it is -38.5 KJ mol⁻¹ for stacking direction [0 1 0]. The slip layer (1 0 0) with C–H···Cl weak intermolecular interactions has an aggregate total interaction energies of -30.6 KJ mol⁻¹. This clearly suggests that the intra-tape interactions are the largest and inter-tape interactions in slip plane are the lowest while for the stacking direction of tapes is moderate. Hence, in this case the weakest plane (1 0 0) may act as the active slip plane, as also suggested by our visual identification.



Figure 4. Energy frameworks showing (a, d, g) total interaction energy (blue), (b, e, h) dispersion (green) and (c, f, i) electrostatic components (red) for Forms I (brittle), II (plastic) and III (elastic), respectively. Note that the adjacent layers in Form II are parallel and in Form III antiparallel, respectively, giving rise to different layer topologies. The energy scale factor is 25 and the energy threshold is 5 KJ mol⁻¹.

In case of elastic Form III, the 1D tape has an aggregate total interaction energy of -139.6 KJ mol⁻¹ and for the stacking interactions -36.5 KJ mol⁻¹. However, total interaction energy corresponding to the antiparallel inter-tape interactions is -34.7 KJ mol⁻¹, which is slightly higher than the corresponding weak interaction plane in plastic Form II (-30.6 KJ mol⁻¹).

Determination of mechanical properties by nanoindentation:

Structural and mechanical property correlation is further evaluated quantitatively by nanoindentation⁵⁶ experiments. The major faces, $(0\ 1\ 0)$ for Form I, $(1\ 0\ 0)$ for Form II and $(0\ 0)$

0 1) for Form III (Figure S12) were identified based on the SCXRD, which are in good agreement with the BFDH morphology obtained from Mercury software (Figure S13). They were indented in load-controlled mode with a Berkovich tip. Representative load, P, versus depth, h, curves and the corresponding nanoindentation impressions of Form I, Form II and Form III crystals are shown in Figure 5.



Figure 5. Typical *P*–*h* curves of Forms I, II and III obtained from nanoindentation experiments (a). SPM images showing the nanoindentation impressions of (b) Form I (brittle), (c) Form II (plastic) and (d) Form III (elastic) crystals.

Table 2: Elastic modulus (E) and nanohardness (H) values obtained from the indentation tests on major faces of the crystals and aggregate values of total intermolecular interaction energies for the tape, stacking direction and halogenated slip layer calculated using energy frameworks for Forms I, II and III of CPII.

Sample	Crystal face/ Slip plane	Elastic modulus, <i>E</i> (GPa)	Hardness, <i>H</i> (GPa)	Melting point (°C)	Layer separation /crossover in Å	Total interaction energies (in KJ mol ⁻¹)		
						Tape	Stacking	Slip plane
Form I (brittle)	(010)	8.09±0.2	0.33±0.09	266.5	-2.328	-130.4	-30.3	-57.2
Form II (plastic)	(100)	3.54±0.05	0.13±0.015	267.1	0.868	-137.8	-38.5	-30.6
Form III (elastic)	(001)	11.5±1.2	0.38±0.05	260.7	0.836	-139.6	-36.5	-34.7

The P-h curves accomplished on these three polymorphs are different and show significant residual depths upon unloading, which indicates that the crystals undergo

significant elasto-plastic deformation upon nanoindentation. In case of Forms I and III, the maximum depths of penetration (h_{max}) were smaller but nearly same (~ 860 nm and ~790 nm) while that for Form II, it was much higher (~ 1367 nm) (Figure 6a). The high value of h_{max} for Form II crystal correlates well with its observed high plastic behavior.

There is a distinct presence of pop-ins (represented with arrows) in the *P-h* curves of Form I crystal (Figure 5a) which were otherwise absent in Form II and Form III crystals. The occurrence of pop-ins is possibly due to the heterogeneous or irregular flow nature of plastic behavior which can be attributed to the elastic compression of the interlocked layers of Form I crystal followed by a sudden slip upon reaching to a critical load.⁵⁷



Figure 6. (a) Depth of penetration (h_{max}), (b) nanohardness (H), (c) elastic modulus (E) and (d) stiffness (S) of Form I, Form II and Form III crystals.

The elastic modulus, *E*, and nanohardness, *H*, values obtained from the nanoindentation technique were evaluated using the standard Oliver–Pharr (O–P) method (Table 2).⁵⁵ The nanohardness (*H*) of Form I (~ 0.33 GPa) and Form III (~ 0.38 GPa) crystals was comparable but significantly higher compared to that of Form II (~ 0.13 GPa) crystal (Figure 6b). The elastic moduli (*E*) of Form I (~ 8 GPa) and Form III (~ 11.5 GPa) crystals are significantly higher than that of Form II (~ 3.5 GPa) crystals (Figure 6c). The 14

Crystal Growth & Design

corresponding stiffness (*S*) of the respective crystals, estimated using Equation S1, revealed that Form III crystals (~ 58 μ N.nm⁻¹) are relatively stiffer than both Form I (~ 36 μ N.nm⁻¹), and Form II (~ 26 μ N.nm⁻¹) crystals (Figure 6d). Therefore, the higher values of both the elastic modulus and stiffness of Form III crystals quantitatively confirm its superior elastic nature compared to that of both the Forms I and II. The lower values of nanohardness and stiffness of Form II is due to its intrinsic plastic behavior. The nanohardness values obtained for Form II compare well with that of other reported plastic crystals (~ 0.092 to 0.3 GPa).^{4,5}

The indentation direction on major face of all three polymorphs is perpendicular to the slip layers with halogenated groups (Figure 2; S14 (a)-(c)). In case of Form I, this (0 1 0) has highly interdigitated layer topology (-2.328 Å, see green lines in Figure 2a) while in Forms II and III the layers are relatively smooth and separated from each other by 0.868 Å and 0.836 Å, respectively (Table 2). The interdigitation of (0 1 0) in Form I as well as its higher total interaction energy (57.2 KJ mol⁻¹) from energy frameworks suggest that this plane is unlikely to be a facile slip plane. There are no other smooth slip layers in this form. Therefore, higher magnitudes of H, E and S were obtained for Form I. The lowest total interaction energy of Form II is in support of its lowest H(0.13 GPa) compared to Forms I (0.33 GPa), and III (0.38 GPa). The significantly higher H, E and S values of Form III are consistent with its highly elastic nature. In case of Forms II and III, the orientation of the overall packing and interaction energies (30.6 and 34.7 KJ mol⁻¹, respectively) are surprisingly close with only a difference in topologies of the slip layers (see Figure 2). Hence, any difference in their mechanical properties should be primarily attributed to the topological differences in their slip layers. Although very useful, the interaction energies obtained from energy frameworks alone fail to predict the marked differences in quantitative mechanical properties as well as the qualitative plastic and elastic flexibilities of Forms II and III, respectively.

Hirshfeld surface analysis:

The intermolecular interactions in three polymorphs are quantitatively discriminated with Hirshfeld surface (Figure 7; S18) and fingerprint plot analysis using Crystal Explorer 3.1^{50} (Figure S19). The contribution from strong hydrogen bonding interactions, N…H & O…H together in Form I (20%), Form II (21%) and Form III (19%) is nearly the same. Since weak interactions are much more crucial for analyzing the mechanical behavior of crystals, we carefully considered the weak Cl…C (includes C–Cl… π), Cl…H (includes C–H…Cl), C…H

(includes C–H··· π) and C···C (includes dispersive stacking) interactions across the relevant planes in the three forms, i.e. (0 1 0) in Form I (where molecules are mechanically interlocked), (1 0 0) in Form II (weakest interaction plane) and (0 0 1) in Form III (weakest interaction plane). The contributions from Cl···C, C···H interactions are higher and Cl···H interactions are lower in Form I (5%, 23% and 15% respectively) compared to Forms II (1%, 17% and 17%) and III (2%, 18% and 21%). The C···C interactions are in the following order: Form I (brittle; 2.3%) < Form III (elastic; 7.1 %) < Form II (plastic; 8.7%) (Figure 7).



Figure 7. Relative contributions of different intermolecular interactions in Forms I, II and III.

The higher contributions from relatively more specific Cl···C and C···H (among mechanically interlocked molecules) and lower contribution of dispersive C···C and Cl···H interactions correlates with the brittle nature of Form I. The plastic Form II has the lowest contribution from Cl···C, Cl···H and C···H and highest from dispersive C···C interactions. In case Form III, the Cl···C, Cl···H and C···H contributions are slightly higher and C···C are slightly lower compared to the same in Form II. As also was realized from the energy frameworks analysis, Hirshfeld surface analysis suggests that the Form III has slightly stronger intermolecular interactions in the slip plane compared to Form II.

The observation of only a small difference in the total energies of the weak interactions across the slip planes in the Forms II and III crystals is very intriguing considering their marked differences in the mechanical behavior (from plastic to elastic). We feel that the compared energies, calculated from the static positions of the molecules in

respective crystal structures, reveal only a part of the information and accurate predictions may require the full energy profiles (or potential energy surface of the plane) corresponding to the dynamic structural changes along the path of projected molecular movements during the mechanical deformation. In other words, topology of the potential energy surfaces of slip layers would reveal the barrier for moving molecules away from thermodynamic positions in a particular direction and this would be much more useful than just the interaction energies across the plane from a static thermodynamic structure. The energy frameworks calculations are very useful in most cases, but do not reveal the topologies of the potential energy wells of interactions, hence barriers for dynamic molecular movements that take place during mechanical actions are not known. Nevertheless, the subtle differences in the weak intermolecular interactions observed in the mechanically distinct Forms II and III here are interesting and clearly emphasize the role of weak intermolecular interactions and topology of slip layers in determining flexibility⁵⁸ of molecular crystals, which is important in the context of crystal engineering.^{9,18}

Thermosalient effect:

DSC experiments on the Form I single crystals at a heat flow of 10 °C per min revealed a small endothermic peak from 178 °C to 184 °C in the heating curve. A saw tooth like profile was observed around at 178 °C in DSC curve of Form I at the lower heating rate of 2 °C per min (Figure S20). In general, the saw tooth feature in the DSC curve indicates the martensitic phase transition that has been regularly used to explain the thermosalient effect in crystals.² To our surprise, Form I crystals underwent actuation (jumping) around at 178 °C to 200 °C by converting to high melting Form IV (see the PXRD pattern in Figure S4), when they were heated on a hot plate (SI; Video 4). The heating-cooling cycles clearly indicate that the sample underwent an irreversible phase transition (Figure S21), as also confirmed by the PXRD pattern. Despite our best efforts, structure determination of Form IV by SCXRD was not possible due to severe defects in the crystal after the phase transition.



Figure 8. DSC of three forms measured at a heating rate of 10 °C/min. The thermograms (marked with "on set" temperature values) reveal that only a single endotherm peak is observed for Forms II (267.1 °C) and III (260.7 °C) corresponding to their melting points with no evidence of phase transition. However, in case of Form I, two endotherms were observed; a minor peak at 177.5 °C, corresponding to solid-solid phase transition (responsible for thermosalient effect) to Form IV and a major peak at 266.5 °C, corresponding to its fusion.

CONCLUSION:

In conclusion, we presented three concomitant polymorphic forms of 3-((4chlorophenyl)imino)indolin-2-one Schiff's base. Form I crystals could be separated easily due to its block type morphology and brittle mechanical deformation behaviour. Whereas both Forms II and III crystals are needles and could only be sorted out based on their mechanical deformation behavior, *i.e.* plastic and elastic bending, upon application of a mechanical stress, respectively. Surprisingly, even though the mechanical behaviour of Forms II and III was very distinct, their crystal packing was found to be very similar. The interaction energies, particularly at the interface of the weakest plane in the two forms, were very much comparable as revealed by energy frameworks and Hirshfeld surface analyses. Hence the differences in the topologies of slip layers in two forms gain importance. Although

the energy frameworks analysis is proved to be a very useful tool for rationalizing mechanical behavior in molecular crystals, it has limitations as it only provides interaction energies from static crystal structure of a form and does not provide information on energy barriers (or topologies of potential energy wells) for causing local molecular movements that are involved in dynamic solid-state mechanical deformation processes. Hence, improving the existing computational methods to capture energies involved in dynamic aspects is the key for understanding mechanical flexibility of molecular crystals in a better way. We also studied the thermosalient effect in Form I, which is characterized by presence of saw tooth profile in the DSC.

ASSOCIATED CONTENT

Supporting Information

The figures related to PXRD, IR and DSC patterns of compounds along with different structural figures, tables and energy calculations related to the crystal structures reported in the supporting information. Jumping and mechanical deformation test videos are also available in SI. <u>CCDC 1822620-1822622</u> contains the supplementary crystallographic data for this paper in CIF format.

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Notes

The authors declare no competing financial interest.

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Rationalizing Distinct Mechanical Properties of Three Polymorphs of a Drug Adduct by Nanoindentation and Energy Frameworks Analysis: Role of Slip Layer Topology and Weak Interactions

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Trimorphs of a Schiff's base show distinct mechanical behavior. The subtle differences in weak interactions and layer topology along the slip plane play a crucial role in determining the flexibility in these polymorphs.

