# Electronic Supporting Information (ESI)

# How Elastically Flexible can Molecular Crystals Be? - A New Record

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#### S1. Materials

The commercial celecoxib (CEL) was purchased from Aarti Drugs Ltd. (Mumbai, India), and used directly without further purification. The solid form of starting material for CEL was confirmed by powder X-ray diffraction as form III.

## Preparation of CEL form I crystal seeds

The crystal seeds of CEL form I were prepared using the following procedure: (1) Preparing amorphous CEL thin films by melt-quenching. Approximately 3~5 mg form III CEL powder was sandwiched between a glass slide and cover glass, keeping the overlapping area constant; (2) Placing the sandwiched sample on a hot stage (Linkam LTS 420, Linkam Scientific Instruments, Ltd., Waterfield, U.K.), heated to 180 °C and held for 5 min until the molten sample spread out and filled the overlapped area to create amorphous thin films. (3) Taking the sandwiched sample out of the hot stage and placed it in the room temperature for quenching. (4) Placing the thin film of amorphous CEL in an oven at 80 °C for overnight. Collected the sample to obtain the crystal seeds of CEL form I.<sup>1</sup>

## S2. Thermal analysis of CEL form I

A differential scanning calorimetry (DSC, Q1000, TA Instruments, New Castle, USA) was used to collect the thermograms of CEL form I. Approximately 3 mg sample was transferred into a crimped aluminum pan and heated from 40 °C to 180 °C at 10 °C/min under 50 mL/min nitrogen purge.



Figure S1. DSC thermogram of CEL form I.

# S3. Single crystal X-ray diffraction experiments of CEL form I CEL form I single crystal preparation.

Approximately 10 µg of form I containing CEL sample from above sample was placed on a glass slide without a cover glass, which was heated on a hot stage (Linkam LTS 420) to ~169.5 °C and held till only one single crystal seed is present in the melt. Then, the temperature was lowered in 2-degree steps and held for 20 min at each step. The last step was at 160 °C, at which the sample was held for at least one hour to obtain a sufficiently large single crystal. A drop of silicone oil was placed beside the unconsumed melt and the single crystal was pushed into the oil by a needle while the temperature was maintained at 160 °C. A single crystal free from a coat of fine crystal was isolated from the silicone oil after the sample is cooled to room temperature.



**Figure S2.** (a) A CEL form I single crystal prepared by melt crystallization and (b) the same crystal cut for single crystal X-ray diffraction analysis.

# Crystal structure analysis of CEL form I

A Bruker D8 Venture diffractometer (Bruker AXS Inc., Madison, WI, USA) coupled with a Bruker PHOTON-II CMOS detector was used to collect the single crystal X-ray diffraction data of CEL form I at 130.0 K, using a Mo  $K_{\alpha}$  radiation source. The SAINT and SADABS programs were used for data integration and scaling, and absorption correction, respectively. Hydrogen atoms were located geometrically and refined using SHELX programs.<sup>2</sup> All non-hydrogen atoms were refined by anisotropic processing. The cif of CEL form I was deposited in CCDC (2343182). These data can be obtained free of charge via www.ccdc.ac.uk/data request/cif, or by emailing data request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. Table S1. Key crystallographic parameters of CEL forms I and III.

	Form I	Form III <sup>[3]</sup>	
Formula	$C_{17}H_{14}F_3N_3O_2S$	$C_{17}H_{14}F_3N_3O_2S$	
Molecular weight	381.381	381.37	
Crystal system	Triclinic	Triclinic	
Space group	$P^{\overline{1}}$	PĪ	
Temperature (K)	130.00	100 (2)	
<i>a</i> (Å)	4.9533 (10)	5.0627(5)	
<i>b</i> (Å)	16.174 (3)	10.0139(11)	
<i>c</i> (Å)	32.778 (6)	16.3981(17)	
α (°)	101.872 (3)	89.874(4)	
β (°)	93.300 (4)	85.867(3)	
γ (°)	97.149 (4)	80.530(4)	
Volume (Å <sup>3</sup> )	2540.5 (9)	817.84(15)	
Z/Z'	6 / 3	2 / 1	
ρ (g/cm³)	1.496	1.549	
F (000)	1177.679	392	
R <sub>1</sub>	0.0442	0.0409	
wR <sub>2</sub>	0.1026	0.0911	
Goodness-of fit	1.041	1.100	
CCDC No.	2343182	1875184	

Table S2. Hydrogen bonds of CEL form I (Donor: D; Acceptor: A).

D-H	<i>d</i> (D-H, Å)	d (HA, Å)	∠DHA (°)	d (DA, Å)	A
N3-H3A	0.809	2.159	170.57	2.961	O2 [ x+1, y, z ]
N3-H3B	0.936	2.096	171.96	3.025	N5 [ x+1, y, z ]
C14-H14	0.950	2.495	138.30	3.266	F8 [ x+1, y+1, z ]
N6-H6A	0.898	2.000	168.36	2.885	O3 [ x-1, y, z ]
N6-H6B	0.843	2.199	163.11	3.016	O5
C23-H23	0.950	2.450	129.79	3.144	O4 [ -x, -y, -z+1 ]
N9-H9A	0.848	2.887	148.26	3.635	S1
N9-H9A	0.848	2.183	177.49	3.031	O2
N9-H9B	0.868	2.024	160.83	2.858	O5 [ x+1, y, z ]
C40-H40	0.950	2.472	132.66	3.194	O1 [ x-1, y, z ]

## S4. Crystal structure analysis for three molecules in CEL form I

Figure S3 presents the packing diagram comparison of CEL forms I and III. The dihedral angles between the pyrazole ring and the other two aromatic rings in each molecule of CEL form I were calculated. The angles between pyrazole rings and 4-methylphenyl rings for the

three molecules are all greater than 25° (61.12°, 29.71°, 25.80°) (Figures S4a–c). This is different from CEL form III where the dihedral angle between those two planes is less than  $18.0^{\circ}$ .<sup>3</sup> The angles between the pyrazole and benzenesulfonamide rings in the three molecules are 33.83°, 60.80°, and 59.18°, which are significantly less than 90° (i.e., not perpendicular) (Figure S4a–c). Thus, the three molecules in CEL form I asymmetric unit adopt significantly different conformations from each other as well as the CEL in form III. Along the *a*-axis, three molecules stack together to form a chain, which is stabilized by weak  $\pi$ ... $\pi$  stacking interactions with parallel-displacement type (centroid-to-centroid distance between two aromatic planes is 4.953 Å) (Figure S4d). Figures S5 and S6 present the tetramers formed in CEL form I, while Figure S7 shows 1D chain and the 3D layered structures of form I.



Figure S3. Packing diagrams of CEL forms I (a, b) and III (c, d) viewed along the *a*-axis.



**Figure S4.** Dihedral angles between the pyrazole ring (light blue) and the other two aromatic rings (benzenesulfonamide: light green; 4-methylphenyl: light red) for the three molecules in the asymmetric unit of CEL form I. (a) Molecule 1; (b) Molecule 2; (c) Molecule 3; (d) The centroid-to-centroid distance between two aromatic rings.



**Figure S5.** The six types of hydrogen-bonded tetramers in CEL form I. Each tetramer is highlighted in light red.



Figure S6. Two categories of CEL hydrogen bonded tetramers.



**Figure S7.** (a) 1D chain along a-axis; (b) Layered structures of CEL molecules, two adjacent tetramers are connected to each other by  $\pi \cdots \pi$  interactions (*d*= 5.030 Å, light red color). Hydrogen atoms are deleted for clarity.

# S5. Face indexing of CEL form I

Face indexing of blade-shaped CEL form I single crystal was performed on a Bruker D8 Venture diffractometer (Bruker D8 Venture diffractometer, Bruker AXS Inc., Madison, WI, USA). Results show that the major faces are (001)/(00-1), the side faces are (010)/(0-10), and the end faces are (100)/(-100).



Figure S8. Face indexing of blade-shaped CEL form I.

## S6. Flexible bending and looping tests for CEL form I by surface tension

Numerous bending tests on the major (001) CEL form I crystal face were performed by a contact-free surface tension method under a polarized light microscope (Nikon Eclipse E200, Nikon, Tokyo, Japan). The thickness of the bending crystal face and radius of the bending loop were measured using ImageJ.<sup>4</sup> The elastic strain ( $\varepsilon$ ) is calculated based on the Euler-Bernoulli beam theory (equation S1),<sup>5</sup> where *t* is the measured thickness and *d* is the measured diameter of curvature:

$$\varepsilon = \frac{t}{d \times 100\%}$$
 Eq. S1

Two circles were drawn to encompass the inner and outer faces of a bent crystal, from which the crystal thickness was reliably calculated. The loop diameter is the average of those of inner and outer circles. The thickness ranged 0.989 - 18.0  $\mu$ m, the diameter ranged 82.8 - 1001.1  $\mu$ m, and the elastic strain ranged 0.54%~8.70% in this work.





**Figure S9.** Representative elastic strain calculation of CEL form I ( $R_1$  equals to radius of outer edge,  $R_2$  equals to radius of inner edge of the bent region, *Thickness (t)* =  $R_1$ - $R_2$ )

	Thickness (µm)	Diameter (µm)	Strain (%)		
1	0.9892	182.1	0.54		
2	4.782	523.9	0.91		
3	9.217	1001.1	0.92		
4	2.670	282.2	0.95		
5	3.725	383.8	0.97		
6	3.530	317.7	1.11		
7	7.655	686.0	1.12		
8	7.849	687.9	1.14		
9	3.825	217.8	1.76		
10	9.792	539.0	1.82		
11	6.612	330.4	2.00		
12	4.772	221.9	2.15		
13	5.617	234.7	2.39		
14	7.740	315.4	2.45		
15	6.65	261.6	2.54		
16	18.75	730.6	2.57		
17	5.896	206.5	2.86		
18	9.051	296.7	3.05		
19	10.08	252.0	4.00		
20	8.618	192.6	4.47		
21	14.91	283.8	5.25		
22	4.529	82.77	5.47		
23	18.022	323.7	5.57		
24	16.59	286.5	5.70		
25	6.554	99.29	6.60		
26	10.44	136.1	7.67		
27	12.97	149.1	8.70		

**Table S3.** Distribution of strain values of CEL form I.



**Figure S10.** (a) A neat celecoxib form I single crystal under a scanning electron microscope and (b) the same crystal immersed in celecoxib melt under a polarized light microscope.

There is the possibility that crystal thickness measured in this study may have been inadvertently affected by a melt. To verify accuracy of the measured crystal thickness by optical microscopy, we measured the thickness of a form I crystal using SEM (Figure 1a). The same crystal was introduced to a celecoxib melt, simulating the crystal growing from a melt, and then its thickness was measured using the optical microscope (Figure 1b). Results show thickness measured by optical microscopy is ~3% less than that by SEM. Hence, we consider the potential impact of optical phenomena, such as light scattering, on measured crystal thicknesses to be negligible. If the 3% difference is real, it means the actual elastic strain is ~3% more than what is reported in this work, which strengthens our finding.

## S7. Nanoindentation and scanning electron microscopy of CEL form I

Nanoindentation experiments were performed using a Triboindenter (TI 980, Hysitron Inc., Minneapolis, MN, USA), equipped with a standard Berkovich diamond indenter tip. Accuracy of the area function of the tip was verified by indenting a fused silica standard before the experiment. The fused silica standard was also indented to ensure tip was free from contamination by the sample. All indents on the bending face (001) were performed in a load-controlled manner with a maximum force of 5 mN. The loading, hold, and unloading times were 1 s, 10 s, and 1 s, respectively. The reduced elastic modulus (*E*) and hardness (*H*) were calculated based on the Oliver-Pharr method.<sup>6</sup>



**Figure S11**. The nanoindentation load - displacement profiles for (001) face of CEL form I. Each curve represents an indent made on a separate location on the crystal face.

The single crystal morphology was investigated by a focused ion beam (FIB)scanning electron microscope (SEM) (Helios 5 DualBeam, Thermo Fisher-FEI, Waltham, MA, USA) operated at 2 kV high voltage using an ETD detector. Prior to conducting SEM experiments, the sample was sputter-coated with gold to a thickness of 50 Å using an Ion Beam Sputter (IBS/TM200S, VCR Group Inc., CA, USA).



Figure S12. A typical SEM diagram of CEL form I single crystal

## S8. Powder true density determination of CEL form I

The true density of CEL form I was determined by helium pycnometry at room temperature using a pycnometer (Quantachrome Instruments, Ultrapycnometer

1000e, Boynton Beach, FL, USA). Approximately two thirds of the volume of the sample cell was filled with the form I powder. The weight of the powder was accurately weighed using an analytical balance (Mettler Toledo XS105, Columbus, OH, USA). A maximum of 50 runs were allowed to measure the density, but the experiment was terminated when the variation of the last five consecutive measurements was less than 0.005%. The mean value of the last five measurements was taken as the true density.<sup>7</sup> The true density of CEL form III, which was measured using the same method and instrument, was obtained from the literature.<sup>8</sup>

## S9. In-die mean yield pressure $(P_{y,i})$ from the Heckel analysis

Approximately 200 mg of bulk powders of CEL forms I and III were compressed on a compaction simulator (Styl'One Evolution, MedelPharm, Beynost, France) up to a maximum pressure of ~350 MPa. A flat-faced round tooling (8 mm diameter) with a dwell time of 206 ms were used for all compactions (simulating a Korsch KL100 at 10 rpm). In-die porosity,  $\varepsilon$ , was calculated from tablet thickness and weight (measured after ejection). Based on equation S2, all the  $P_{y,i}$  values were obtained from the linear section of the Heckel curves (-ln $\varepsilon$  vs pressure).<sup>9, 10</sup> The  $P_{y,i}$  value has been shown to be a reliable parameter to quantify material plasticity, with a lower  $P_{y,i}$  value corresponding to higher plasticity.<sup>4</sup> All measurements were triplicated.

$$-ln(\varepsilon) = \frac{1}{Py,i} P + A \qquad Eq. S2$$

**Table S4.** Fitted parameters of CEL forms I and III from the Heckel analysis ( $P_{y,i}$  values, n = 3)

•					
	Form I			Form III	
<b>P</b> <sub>y,i</sub> Mean (SD) 44.67 (0.17) 38.67 (0.13) 41.85 (0.13)	<b>R</b> <sup>2</sup> 1.00 1.00 1.00	<b>A</b> 1.47 1.52 1.47	<b>P</b> <sub>y,i</sub> Mean (SD) 70.68 (0.12) 75.53 (0.16) 77.63 (0.11)	<b>R</b> <sup>2</sup> 1.00 1.00 1.00	<b>A</b> 1.38 1.398 1.39
$\begin{bmatrix} 8 \\ - \\ 6 \\ - \\ - \\ 0 \\ 0 \\ - \\ 25 \end{bmatrix}$	50 75 100 Compaction Pressur	125 150 175 e (MPa)	0.08 0.06 0.04 0.02 0.02 Compaction F	100 125 150 ressure (MPa)	175

**Figure S13.** The plots of -ln ( $\epsilon$ ) and its first derivative versus compaction pressure of CEL form I.



Figure S14. The plots of -ln ( $\epsilon$ ) and its first derivative versus compaction pressure of CEL form III.

## S10. Energy frameworks for CEL forms I and III

CrystalExplorer (version 21.3) was used to calculate energy frameworks based on the B3LYP/6-31G (d,p) model.<sup>11, 12</sup> A 3.8 Å cluster of molecules surrounding a selected CEL molecule was used to calculate the energies. The default tube size was 50, and no cut-off value was applied, i.e., 0 kJ/mol cutoff.



**Figure S15.** Energy frameworks for the crystal structure of CEL form I viewed along different unit cell axes.



**Figure S16.** Energy frameworks for the crystal structure of CEL form III viewed along different unit cell axes.

# S11. Full interaction map and calculated slip plane of CEL forms I and III

Mercury 2023.1.0 program with the default setting was used to calculate the full interaction map and slip plane.



**Figure S17.** Full interaction map and calculated slip plane of CEL forms I (Top) and III (Bottom) viewed along the *a*-axis.

#### S12. Attachment energy and lattice energy of CEL forms I and III

Mercury (version 2023.1.0) was used to calculate attachment energy and lattice energy for CEL forms I and III using Dreiding II force field. The limiting radius with 30 Å was selected, and Evjen electrostatic correction was employed during the calculation. The total energy was a sum of electrostatic, van der Waals, and hydrogen bond contributions.

Table S5. Attachment energies of the (001) plane and lattice energies of CEL forms I and III.

	Attachment energy (001)	Lattice energy	
	(kJ/mol)	(kJ/mol)	
Form I	-3.165	-193.870	
Form III	-28.077	-195.006	

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