Electronic Supplementary Material (ESI) for Chemical Communications.

Electronic Supporting Information (ESI)

Probing stress induced phase transformation in aspirin polymorphs using Raman spectroscopy enabled nanoindentation

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S1. Crystals preparation and single crystal X-ray diffraction experiment (SCXRD)

Single crystals of the aspirin (purchased from Sigma-Aldrich) polymorphs form I and form II were grown under the same crystallization conditions reported by Varughese et. al.[1] Form I crystals were obtained by slow evaporation of a methanol solution of aspirin. Form II crystals were prepared by following steps: 5 g of aspirin was dissolved in 10 mL of acetic anhydride and the solution was continuously stirred under reflux at 80 °C for 5 hours. Later, acetic anhydride was evaporated at room temperature and the final solid product was recrystallized from acetone/EtOH to produced single crystals of form II. For from II crystals, we confirmed by single-crystal X-ray diffraction without any measurable form I Bragg peaks or diffuse scattering.

The crystals of aspirin polymorphs confirmed by checking the cell parameters and comparison with the reported structure (Refcode: **ACSALA14** (form I) and **ACSALA19** (form II). X-ray diffraction was carried out on a Rigaku Mercury 375R/M CCD (XtaLAB mini) diffractometer using graphite monochromatic Mo-Kα radiation. Face indexing of good quality single crystals was performed with the Rigaku CrystalClear 2.0 software[2] and confirmed with the reported face indexing to perform the nanoindentation device (Bruker Nano Surfaces, USA) enabled with micro-Raman spectroscopy.

S2. Nanoindentation and Raman experiments:

To probe pressure induced structural changes on aspirin a custom indentation and Raman technique was developed. Illustration of the integrated Raman spectroscopy-indentation setup is shown in figure S2. Hysitron TI 980 Triboindenter (Bruker Nano Surfaces, USA) is integrated with confocal Raman probe (Horiba Scientific, USA). Both transducer and Raman probe mounted onto a shared stage. A motorized XY stage translates the sample from indentation position to Raman probe. A 532 nm laser was used as an excitation source. A Mitutoyo long working distance, 50 x objective lens (N.A 0.52), was used to collect the Raman scattered light from the sample. The Raman probe and spectrometer were coupled using a fiber optic cable (diameter 100 μm). With 1800 lines/mm grating, ~1 cm^{-1} spectral resolution was achieved.

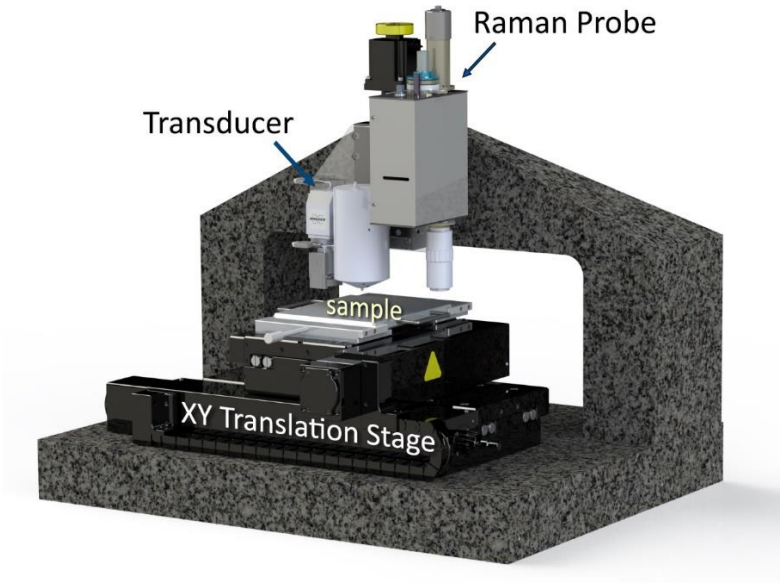


Figure S1. Illustration of Raman integrated indentation setup. XY translation stage moves sample between transducer and Raman optics with nanometer precision, thereby enabling synchronized Raman and indentation measurements on a single platform.

The mechanical characterization of form I and form II crystals were carried on structurally similar faces {100} and {10$\bar{2}$}. Representative load Vs displacement curved recorded from form I {100} and form II {10$\bar{2}$} are shown in figure S2.

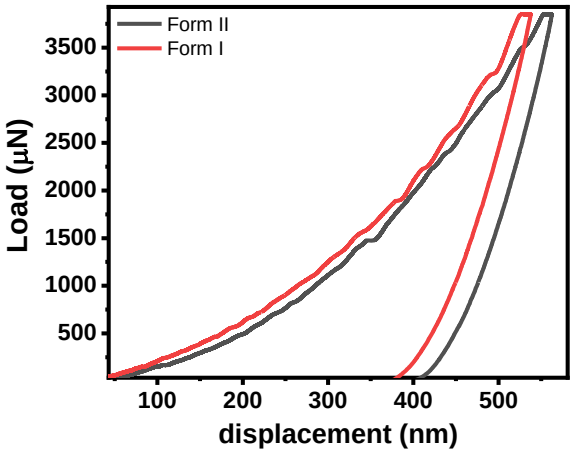


Figure S2. Representative load vs. displacement recorded from form I and form II aspirin crystals.

The hardness and modulus values are estimated by fitting unloading portion of the load vs displacement curve.[3] The equation used to estimate hardness and modulus are:

$$\text{Hardness,} \quad H = \frac{P_{\max}}{A(h_c)} \qquad (1)$$

$$\text{reduced modulus,} \quad E_r = \frac{\sqrt{\pi}}{2\sqrt{A(h_c)}} \cdot S \qquad (2)$$

h_c is contact depth, P_{max} is maximum indentation load applied, $A(h_c)$ is the contact area and S is stiffness. Reduced Modulus E_r is defined as:

$$\frac{1}{E_r} = \frac{(1-\nu_i^2)}{E_i} + \frac{(1-\nu_s^2)}{E_s} \qquad (3)$$

E_i , E_s and ν_i, ν_s, are Young's modulus and Poisson's ratio of indenter and sample respectively.

For hardness measurements, diamond Berkovich probe was used. Indentation load was varied from 30 µN-6 mN. The average hardness of form I and form II are 0.26 ± 0.07 GPa and 0.17 ± 0.05 GPa, respectively. Average modulus recorded from form I and form II are 5.7 ± 0.3 GPa and 4.9 ± 0.4 GPa, respectively.

Raman measurements were done on indents generated at different loads (30 µN-6 mN). Post indentation, the sample was translated to Raman optics and spectral maps were generated over a 10 x 10 µm region. Further, the hardness maps were generated using accelerated property measurement (XPM) technique, in built in Hysitron TI 980. To avoid overlapping of plastic zones, 10 x 10 indentation grids were generated using 100 µN normal load and a spacing of 2 µm was given between the indents.

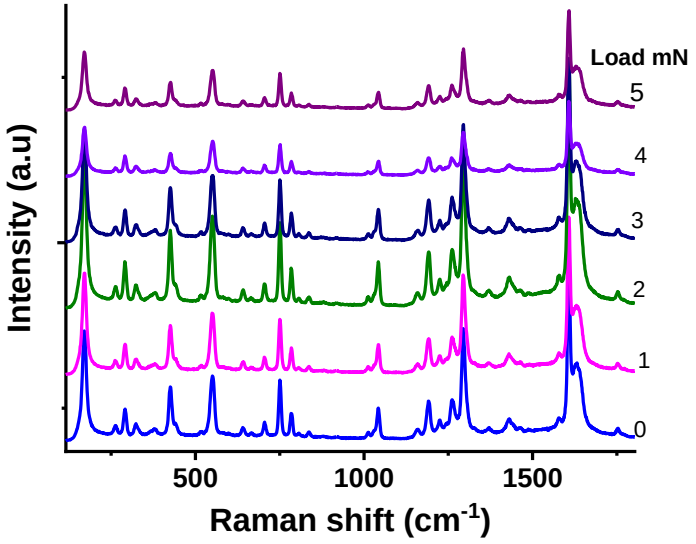


Figure S3. Raman spectra (100-1800 cm^{-1} range) recorded from the indentation zone at different indentation loads on form II crystal.

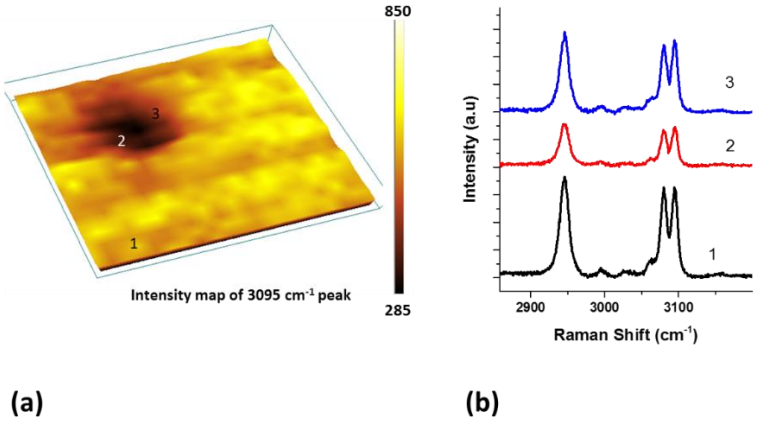


Figure S4. (a) Raman intensity map (3096 cm^{-1}) recorded from the indentation zone on form I aspirin crystal (5 mN load) (b) spot spectra recorded at three different regions. In form I crystal, no polymorphic transformation was observed.

S3. Indentation stress strain analysis

The yielding behavior of aspirin forms I and II crystals were studied using spherical probe indentation (Probe radius 16.6 µm). Conversion of indentation load displacement curve into indentation stress–strain requires dynamic mechanical analysis (DMA) mode indentation. The

analysis model is based on Hertz theory and previously Pathak *et al.* adopted this methodology to generate indentation stress strain curves from ion-irradiated metals, bone samples.[4,5] Equations used to calculate stress (σ) and strains (ε) are as follows:

$$\sigma = P/\pi a^2 \qquad (4)$$

$$\varepsilon = \frac{4}{3\pi}\frac{ht}{a} \qquad (5)$$

$$a = S/2Er \qquad (6)$$

Where a, is contact radius, P normal load applied, h_t, total indention depth, Er, reduced modulus and S stiffness measured during loading segment of indentation. For stiffness measurement, DMA testing mode was applied to the loading segment of the load function.

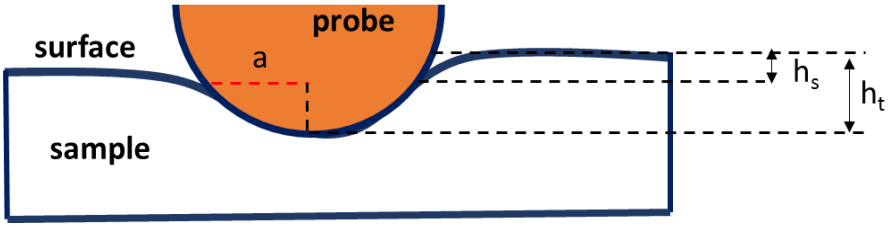


Figure S5. Schematic showing spherical indentation and parameters

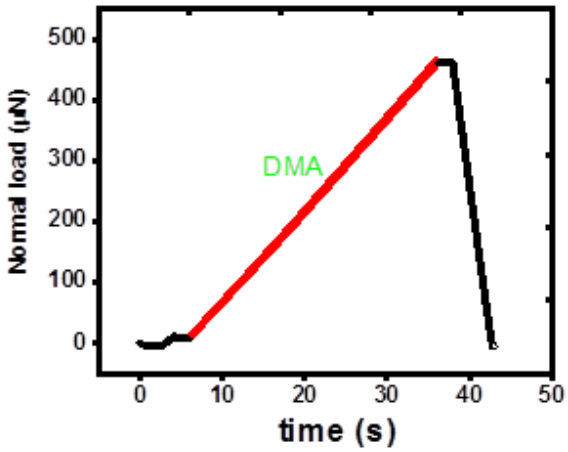
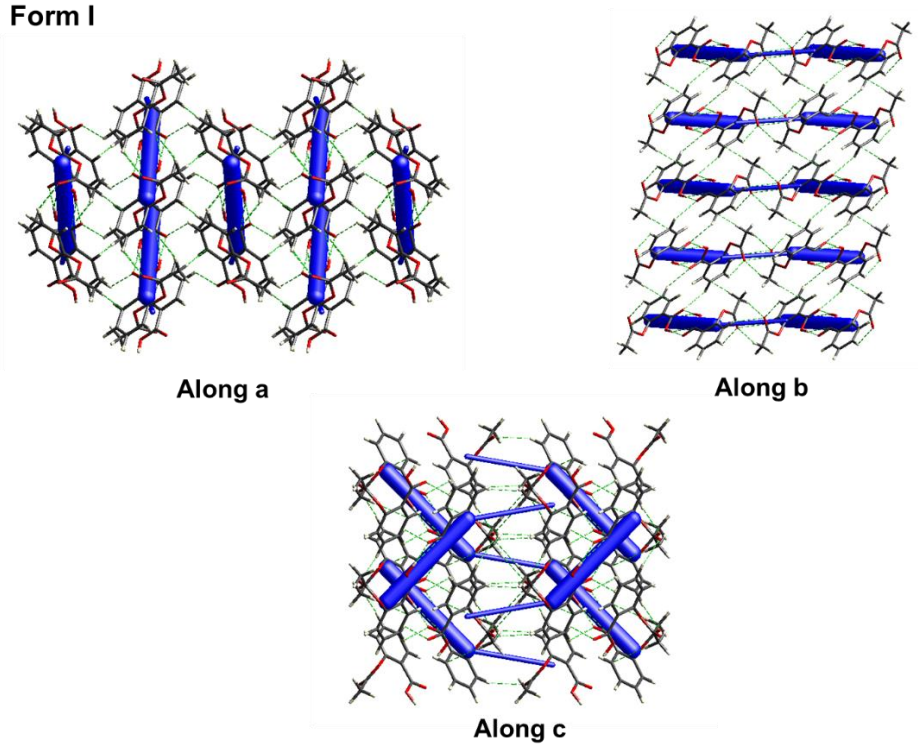


Figure S6. Representative load function used for stress strain analysis.

S4. Energy framework analysis

The intermolecular interaction energy or energy framework calculation was done based on B3LYP-D2/6-31G(d,p) molecular wavefunctions calculated at the crystal geometry (CrystalExplorer V.17) with an energy cut off of 20 kJ mol^{-1}.[6] Hydrogen positions of the aspirin form I and form II were normalized to standard neutron diffraction values during the calculation. The interaction energies of a selected molecule with all molecules having any atom within 3.8 Å were calculated.



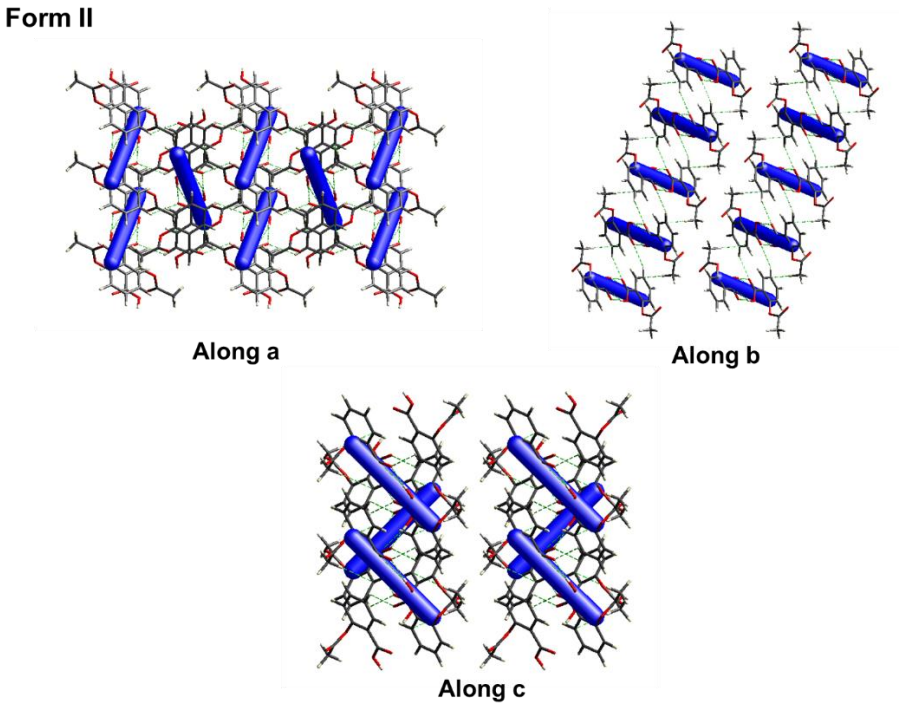


Figure S7. Total energy framework of form I and from II seen along *a*, *b* and *c* axes.

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