Plastically Bendable Crystals of Flufenamic Acid Form III

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Abstract

Bendable organic crystal is a burgeoning research field due to interesting phenomenon and broad application prospects. Here we report a plastic bendable pharmaceutical crystal, flufenamic acid (FFA) form I crystal. The crystal exhibits plastic bending when the force is applied on (100) face. The column-like structure and the slip planes among them are the basic features responsible for the exceptional plasticity. The spatially resolved atomic-level studies via X-ray diffraction and micro-Raman reveal the structural perturbations in FFA crystal after bending, illustrating that the packing in each “column” is also critical for the plastic bending, which contributes to the exploration of plastic bending mechanism and inspires the design of flexible organic crystal materials.

Introduction

Organic crystals are generally considered brittle, since the observation of plastic and elastic organic crystals, this common perception has been challenged.\textsuperscript{1–5} From the perspective of applications, the plastic and elastic crystals are attractive since they have both mechanical flexibility and crystallinity.\textsuperscript{6, 7} Combined with other functions, these flexible organic single crystals have potential applications in various fields, such as pharmaceuticals,\textsuperscript{8–11} optical devices,\textsuperscript{12–17} artificial mechanosensors,\textsuperscript{18} bioinspired materials\textsuperscript{19, 20} and molecular machinery\textsuperscript{21}. Thus, the investigation of organic crystals with unique mechanical properties is gradually becoming a hot topic in crystal engineering.\textsuperscript{22–25}

Many efforts have been devoted to this novel field to establish rules for guiding the flexible crystal materials design.\textsuperscript{7} Desiraju and Reddy et al. have proposed the structural characteristics for plastic crystals, namely the anisotropic interactions and the existence of a slip plane in the crystal structure.\textsuperscript{1, 7, 26} Recently, Spackman et al. reported a plastic crystal with quasi-isotropic packing,\textsuperscript{27} challenging the prevailing view that anisotropy and slip planes are prerequisites for plastic bending. It appears that the current rules for the bendable crystal design are still not comprehensive and are a subject of ongoing debate.\textsuperscript{28} Moreover, several problems have not yet been solved completely. What happens or what changes at the atomic level when the crystal is bent?\textsuperscript{26} Is it still a single crystal when the deformation occurred?\textsuperscript{29} Which features in the crystal structure will lead to flexibility in macroscopic crystal?\textsuperscript{22} What role do different groups in crystals play in plastic bending?\textsuperscript{22} However, the cases of bendable crystals are still sporadic, which are insufficient to entirely solve these thorny questions and establish the rules of bendable crystals to guide the functional crystal design.

Herein we report a new plastic organic crystal of a well-known non-steroidal anti-inflammatory drug, flufenamic acid (FFA, Fig. 1a). The FFA has been widely investigated on the polymorphs,\textsuperscript{30–32} crystal structure,\textsuperscript{33–36} spectroscopy,\textsuperscript{37–39} nucleation behavior\textsuperscript{40} and tableting performance.\textsuperscript{41} However, no one reported its plastic bending performance and explored its bending mechanism. In this work, we tried to observe the performance when stress was applied in different crystal faces and conducted the bending as well as nanoindentation experiment to analyze the mechanical properties of FFA form I crystal. Micro-
Raman spectroscopy and single crystal X-ray diffractometer were further carried out to analyze the changes after deformation occurred. Based on the multiple characterizations, we explain the structural perturbations at the atomic level and the possible bending mechanism of FFA.

**Results And Discussion**

Single crystal of FFA form III prepared by evaporation in methanol is needled-shaped with a major face (100) and a minor face (001), as shown in Figs. 1b and S1. When stress is applied on the long narrow faces (001), the crystal break readily like other common organic molecular crystals. However, the crystal can be bent without fracturing when stress is applied on the wide face (100), exhibiting excellent plasticity (Fig. 1c, Supplementary movie 1 and 2).

**Quantitative measurement of mechanical property**

Quantitative nanoindentation experiments were performed on the (100) face of the straight crystal to explore the accurate mechanical properties of the bending face.\textsuperscript{42–44} The representative load (P) versus depth (h) curve is shown in Fig. 1d. The plot exhibits a large residual depth which indicates a significant plastic deformation of the crystal during indentation. Under the peak load of 4 mN, the maximum depths of penetration (h\textsubscript{max}) were 2121.42 ± 12.98 nm, which is a high value compared with that of other organic crystals.\textsuperscript{1, 43–45} The high value of h\textsubscript{max} and the large residual depths are associated with excellent plastic behavior. The elastic modulus (E) and nanohardness (H) was then estimated from the P-h response using the standard Oliver-Pharr method,\textsuperscript{46} and the average E and H values for (100) face are 7.9049 GPa and 0.1087 GPa, respectively. Since the H reflects the resistance to plastic deformation, the very small H value indicates FFA form III is a super soft crystal\textsuperscript{45} and correlates well with the plastic properties of (100) face. From the P-h curves (Figs. 1d and S2), several pop-ins were observed, which can be attributed to the macroscopic elastic compression of the layer.\textsuperscript{42, 47} Since the indentation direction is perpendicular to the slip layers, the pop-ins observed in (100) face is probably due to the sudden slip of layers upon reaching a critical load to instant release of the stress.

**Structural basis for plastic bending**

FFA form III crystallizes in space group C2/c with Z = 8 (CSD refcode: FPAMCA). The main interactions in FFA structure and the crystal packing viewed into (001), (100) and (0−10) faces were presented in Figs. 2a and 2b. It can be seen that FFA molecules form dimers through strong O-H…O interactions. The dimers further expand along the b-axis through C-H…π interactions and aromatic stacking. The strong hydrogen bonds and the aromatic interactions lead to a stable column-like structure. These columns are parallel to the (100) face, with spherical -CF\textsubscript{3} groups exposed on both sides. Thus, the columns are weakly interconnected through the exterior -CF\textsubscript{3} groups, resulting in some smooth “slip planes” between columns, as shown in the shaded area in Fig. 2a. According to Reddy et al.,\textsuperscript{1, 7} such “slip plane” features
facilitate plastic bending of crystal. When pressure is applied on (100) face, the internal columns will slide along the c-axis and the bulk crystals exhibit excellent plasticity.

Furthermore, energy framework was applied to visualize intermolecular interactions quantitatively and rationalize the observed mechanical behavior (Figures S3 and S4).\textsuperscript{48,49} The calculated energies between molecular pairs are represented as cylinders with proportionate thickness (Figs. 2c and S3). As visualized from the 3D topologies of energy framework, the FFA molecules were strongly connected through hydrogen bonds to form stable dimers (-65.5 kJ mol\textsuperscript{-1}), and these dimers interacted with each other through aromatic interactions as previously analyzed (-34 kJ mol\textsuperscript{-1}). These two strong interactions make FFA molecules form several stable columns that are difficult to destroy. Conversely, the interactions between columns are rather weak (-10.6 kJ mol\textsuperscript{-1}). Therefore, the slip plane formed by the -CF\textsubscript{3} group is very facile, allowing for the columns' sliding as a response to external pressure.

**Short-range structure changes in the bent crystal**

Although the existence of the mature "slip plane" bending model, it is still a question what happened and changed in "columns" of the FFA crystal after bending. The crystal structure of the bent crystal was thus resolved using single crystal X-ray diffraction (SCXRD) to investigate the atomic-level structural changes. The data for the straight crystal and the bent region of the bent crystal were both collected for comparison (Figure S5). The crystallographic data were shown in Table S1. We first compare the changes in crystal volume and the unit cell parameters. While, the volumes of the straight crystal and bent crystal is almost the same and the unit cell parameters remain almost unchanged after bending (Since the quality of the crystal is not as good as original, the slight change is within the margin of error).

Surprisingly, slight expansion along a axis was detected after bending. The a axis is just parallel to the applied bending force, which was envisaged to be affected more after bending. The direction of O-H...O hydrogen bonds and the intercolumn interactions is along the a-axis. The slight expansion of the a-axis is mainly due to the changes of these interactions intensity.

To obtain more information about structure perturbations after bending, we compared the intermolecular interactions in straight and bent crystal. What we focused on are three parts that affect the crystal packing of FFA: (i) hydrogen bonds to form dimers, (ii) aromatic interactions, (iii) intercolumn interactions (the close packing of the -CF\textsubscript{3} group). As shown in Fig. 3b and table S2, the most affected part is the intermolecular hydrogen bonds. The bond length (d) changes from 1.750 Å to 1.812 Å and the bond angle changes from 175.54° to 173.76°, indicating the weakening of the hydrogen bonds. Moreover, the distance of C-H...π and the closest F...F exhibits almost the same after bending.

Furthermore, we compared the original diffraction images to obtain information about the structural order and the integrity of the crystal, as shown in Fig. 3b. The images for (h0l) and (0kl) planes remained almost unchanged after bending, which exhibit discrete diffraction spots and have the same spot position as those of the straight crystal. The results indicate that the molecular packing in bent crystal viewed into (010) and (100) face remains the same as the original crystal. As for the (hk0) plane, the
spots show significant elongations, which indicates the decrease of crystallinity and the local movements of molecules away from their original lattice points. Based on these results, we can conclude that the molecular packing in (001) face has been intensively affected. The (001) face is just the side plane of the bending crystal, which is perpendicular to the “slip planes”. The tailing in the reflections from (hk0) plane is most likely due to the slip-sliding. Although the sliding process preserves the crystal integrity to some extent, defects and dislocations are inevitably generated between columns, which could be thus reflected in crystal packing viewed down (001) face as well as the tailing in the reflections from (hk0) plane.

Micro-Raman spectra were also carried out to analyze the effect of bending at a molecular level (Fig. 4). On the one hand, the absence of any obvious increase in Raman spectra's background for the bent region rules out the possibility of significant amorphization of the structure. On the other hand, the Raman spectra of the bent crystal show no apparent differences from the concave region to the convex region but are slightly different from the straight one. The 1143 cm$^{-1}$ band for the aromatic C-H deformation of α benzene ring blue shifts to 1154 cm$^{-1}$. Besides, the band representing the deformation of α benzene ring also exhibits a blue shift (from 1583 cm$^{-1}$ to 1593 cm$^{-1}$). Both suggest the aromatic interactions were weakened owing to the bending. The band for C-OH deformation shows a blue shift from 1163 cm$^{-1}$ to 1170 cm$^{-1}$, supporting the weakening of the intermolecular hydrogen bonds, which is consistent with the previous single crystal results. The weakening of hydrogen bonds and aromatic interactions is probably due to the splaying of molecules in the columns as a response to the external strain.

**Bending mechanism for FFA**

Based on the above analysis, the plastic bending mechanism of FFA form III crystal can be rationalized with the model presented in Fig. 5. The crystal is composed of several columns, which were stabilized through strong hydrogen bonds and aromatic interactions. These columns are parallel to each other and are flanked by spherical groups(-CF$_3$). There is basically no strong interaction between these spherical groups, thus forming slip planes, and playing a lubricating role between columns. Therefore, the columns are easy to slide when the pressure is applied on the (100) face. As a result, the bulk crystal shows plastic bending rather than brittle behavior.

Nevertheless, the column sliding alone is not enough for plastic bending. The interactions in each column also need to be adjusted to maintain the softness of each column. From the results, we can see that the interactions and molecular packing in each column exhibit tiny but significant changes as a response to the external stress. During the bending process, the molecules in each column gradually splay. The overall packing in the bent region is thus low density with several defects and reduced structural order. The length of hydrogen bond and the effective distance among benzene rings become longer with the splay of molecules. As a result, the intermolecular hydrogen bonds and the aromatic interactions are both weakened (Fig. 5). All the changes and short-range movements can be seen as a self-adjustment process to maintain the crystallinity and crystal integrity as much as possible under external pressure. Thus, the bulk crystal exhibits plastic bending when stress is applied on (100) face. However, when the stress is
applied on (001) face, staggered structure and steric hindrance will prevent molecular movement and internal adjustment. The crystal breaks readily as the strain accumulates, rather than bend or shear.

Conclusions

In conclusion, we reported a plastically bendable pharmaceutical crystal, FFA form III crystal. The atomic-level structure perturbations in the bending process were further validated through single crystal X-ray diffraction and micro-Raman. The results show that the crystal could retain the crystal integrity and short-range structural order in the bending process, although the mosaicity was inevitably increased. Besides column sliding, the interactions in each column were slightly adjusted accordingly to maintain the softness of each column. Our work with FFA as a case highlights that both the classical slip plane and the packing in each “column” were critical for the plastic bending, which contributes to the bending mechanism research and provides more guidance for the future smart materials design.

Materials And Methods

Materials

Flufenamic acid (> 99%) was obtained from Dalian Meilun Biotechnology Co., Ltd. All solvents were purchased from Aladdin Industrial Co., Ltd and of analytical grade. All chemicals were used without further purification.

Single crystal preparation

Single crystal of FFA was obtained through slow evaporation in either methanol or toluene at ambient conditions.

Single crystal structure determination

The straight crystal was glued on the glass fiber using epoxy and the SCXRD data were collected. After then, the same single crystal was bent using mechanical force and was also glued on the glass fiber for data collection. All the crystallographic data were collected at106K.

SCXRD measurement was performed on a Rigaku XtaLAB FRX Diffractometer equipped with a Hypix6000HE detector, using Cu Kα radiation (λ = 1.54184 Å). Data reduction was accomplished using the program crysAlispro (version 1.171.35.45 g). The structures were solved by intrinsic phasing method using SHELXT, and was refined by the full-matrix least-squares technique using SHELXL-2015 embedded into OLEX2 1.3. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in calculated positions and refined using a riding model with an isotropic displacement parameter.

Micro-Raman spectroscopy
Raman spectra for straight and bent crystal were recorded in the range 50-3500 cm\(^{-1}\) with a micro-Raman spectrometer (DXR Microscope, Thermo Fisher Scientific). Laser spot on the samples was focused to \(\sim 1.1 \, \mu\text{m}\) using a 100x zoom lens. All measurements were performed employing a wavelength of 532 nm (He–Ne laser) at 10 s exposure time.

**Nanindentation**

Select a crystal with no defects on the surface for the nanoindentation test and the experiment were performed on (100) face using the instrumentation set up from Hysitron Triboindentor, TI Premier, Minneapolis, the USA equipped with a Berkovich diamond tip. The tests were conducted in the load-controlled mood with a load of 4mN. A minimum of 6 indentations was collected. The elastic modulus, \(E\), and hardness, \(H\), were obtained from the P-h curves using the standard Oliver–Pharr method.\(^{46}\)

**Energy framework analysis**

*CrystalExplorer*\(^{17,48,49}\) was used to evaluate and visualize the pairwise interaction energies of FFA crystal. The calculations are based on the B3LYP/6-31G (d,p) molecular wavefunctions. The energy components calculated within this method are electrostatic, polarization, dispersion, and exchange-repulsion and finally the total interaction energy, where \(E_{\text{total}} = 1.057E_{\text{ele}} + 0.740E_{\text{pol}} + 0.871E_{\text{disp}} + 0.618 \, E_{\text{rep}}\). Pairwise interaction energies between molecules were calculated considering radius of 3.8 Å from centroid of a molecule to an atom (of another molecule) belonging to its nearest neighbor. The tube size used in all the energy frameworks was 150, and the lower energy threshold (cutoff) value was set to 0.

**Declarations**

**Data availability**

The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers 2034097 and 2034319. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

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**Author contributions**

Y. L. and K. Z. planned the experiments. Y. L., K.Z. and S. W. wrote the paper. J.X. measured crystal structure of the bent and straight crystal. L. performed all other experiments and analyses. S. W. and J. G. managed the project. All authors commented to this manuscript.
Competing interests

The authors declare no competing interests.

Additional information

Supporting information is available free of charge. Face indexing results; Nanoindentation data; Energy framework results; The images of the bent crystal used for the SCXRD experiment; Crystallographic data for FFA crystals. (PDF).

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