

Supporting Information

Ritonavir Form III: Lightning strikes twice at the same time, 137 miles apart

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EXPERIMENTAL METHODS

X-ray Powder Diffraction (XPRD)

The XPRD pattern was collected on the material crystallized from the macro crystallization with a PANalytical Empyrean diffractometer in Bragg-Brentano geometry using a Cu radiation source generated at 45 kV / 40 mA. A silicon standard was analyzed to check the instrument alignment. Prior to the analysis, a specimen of the sample was packed into a silicon zero background diffraction holder with a 10x0.2 mm well and analyzed in reflection geometry. The X-ray source was configured with Soller slits of 0.04 radians, a fixed anti-scatter slit of 1/4°, a mask of 4 mm, and a fixed divergence slit of 1/16°. The diffracted beam passed through a 7.5 mm anti-scatter slit and large Soller slit of 0.02 radians to the detector. Diffraction patterns were collected with Data Collector software v. 6.1b using a PIXcel3D-Medipix3 1x1 detector located 240 mm from the specimen. The data was acquired using 12 repetitions of a continuous scan from 2 to 40° 2 θ with the sample spinning at a revolution time of 2 seconds.

Indexing and Pawley Refinement

TOPAS 6 [7] was used for Indexing and Pawley refinements. Refinements were performed on all parameters simultaneously to a convergence of 0.001 in χ^2 . Refined unit cell parameters, space group and fit residual as well as a graphical representation of the Pawley refinement result were determined. Further refinement parameters included but may not be limited to the following: The background was modeled using a Chebychev polynomial function and a 1/x contribution to account for air scattering. A broad intensity feature centered at ~20° accounts for scattering and was modeled by a broad first principle peak contribution.

Bragg peaks were fitted to a first principles peak function with Gaussian crystallite size broadening (τ_G), and Lorentzian strain broadening (ϵ_L). Peak asymmetry due to axial divergence was modeled using the simple axial model (SAM) with a start value of 10 mm. Sample displacement (d_{samp})/Zero error (z_0) correction was used to account for Bragg peak shifts and listed in the parameter table if used.

Differential Scanning Calorimetry (DSC)

DSC was performed using a TA Instruments model Q10 differential scanning calorimeter. The instrument was calibrated using indium. The sample was placed into a standard aluminum DSC pan, covered with a lid, and the weight was accurately recorded. An aluminum pan configured as the sample pan was placed on the reference side of the cell. The pan lid was crimped prior to sample analysis. Samples were analyzed in a single run from 25 to 200 °C at a heating rate of 10 °C/min under nitrogen gas.

Hot Stage Polarized Light Microscopy (HSOM)

Analyses were completed using an Olympus BX51TRF polarized light microscope using crossed-polarizers, a 20X, 0.40 Numerical Aperture, LM PLAN FL N objective, and a first-order red compensator (530 nm). Heating was conducted with a Linkam LTS420 hot stage with a T95 LinkPad system controller. Images were acquired with a Lumenera Series Infinity 3-3URC (Teledyne Lumenera, Ottawa, Ontario, Canada) digital camera. Image capture and image processing using Image-Pro® version 10.0.12 Build 7452 (Date: 01-April-2020).

Determination of melting point was examined using 1f, the macro crystallization experiment. A small portion of sample was placed onto a scrupulously clean microscope slide. The sample was covered with a No. 1 ½ cover glass. The Linkam hot stage system controller was programmed with the following temperature ramp routine:

- 1) Heat at 5.00 °C/min to 113.7 °C
- 2) Heat at 2.00 °C/min to 119.0 °C

Thermal stability was assessed by exposing Form III (1f) sequentially to 50°C, 70°C, or 90°C for 15 minutes at each temperature point, followed by Raman analysis (of sample 1c, after storing for 5 weeks).

Thermogravimetric Analysis (TG)

TG analysis was performed on a TA Instruments Discovery TGA 55 using Platinum sample and reference pans. The temperature calibration was performed with nickel. The sample was placed into the pan, heated at 10°C/min. from ambient to a final temperature of 200 °C under a balance nitrogen purge of 40 mL/min.

Dynamic Vapor Sorption

DVS data were collected on a VTI SGA-100 Vapor Sorption Analyzer. The sample was not dried prior to analysis. Sorption and desorption data were collected over a range from 5% to 95% RH at 10% RH increments under a dry air purge. The equilibrium criterion used for analysis was less than 0.0100% weight change in five minutes with a maximum equilibration time of three hours and a 2-minute data logging interval. Data were not corrected for the initial moisture content of the sample.

Raman Microscopy

A HORIBA Scientific XploRA Series Confocal Raman Microscope (Piscataway, NJ) was used to collect Raman spectra using the following parameters: 785 nm laser at 100% power, 1200 g/mm grating, 300 micrometer confocal hole, 100 micrometer slit entrance to the spectrograph, 1 second spectral acquisition with 30 accumulations. The Raman signal is detected using a Sincerity Model 356399, thermoelectrically cooled-CCD detector. Spectra were acquired over the range -125 to 1800 cm^{-1} . An Olympus Series BX51TRF polarized light microscope (Olympus America Inc., Melville, NY) provided the base optical platform. An Olympus MPlan N Series 20X, 0.40 NA microscope objective was used to focus the laser light onto the sample and to collect the Raman signal. The microscope was equipped with a Marzhauser Wetzlar computer-controlled mapping stage to translate the sample for focus and data acquisition. Digital images were acquired using a Lumenera Series Infinity 3-1C (Teledyne Lumenera, Ottawa, Ontario, Canada) camera using Infinity software version 6.5.6 and Infinity Analyze software version 7.0.2.930 (Build date 1-May-2020). System calibration was performed prior to each analysis using a silicon disc to monitor peak position at 520.7 cm^{-1} . All calibrations passed specifications prior to data collection.

The sample was prepared by placing a small amount of material from the hot stage melt recrystallization experiment onto either a gold-coated microscope slide or a fused-silica microscope slide using a tungsten needle and dispersed to a thin layer. The small sample was illuminated with white light using 200X magnification for specific sample area analysis. Analyses were conducted on what appeared microscopically to be a single crystal whenever possible.

The same instrument parameters were used for all Raman micro spectroscopy data collection.