Supporting Information

Crystal to Crystal Polymorphic Phase Transition in a Cocrystal Accompanied by Expansion and Surface Wettability Change

Plabon Saikia,^a Poonam Gupta,^a Tridib R. Nath^b and Naba K. Nath^a*

^aDepartment of Chemical and Biological Sciences, National Institute of Technology Meghalaya, Shillong, India.

^bSophisticated Analytical Instrumentation Centre, Tezpur University, Tezpur 784001, Assam, India.

E-mail: nabakamal.nath@gmail.com, nabakamal.nath@nitm.ac.in

Content

	Page no
1. Supporting methods	S3-S4
Reagents	S3
Synthesis of PP	S3
Synthesis of BPA	S3
Synthesis of cocrystal	S3
Instrumentation	S4
2. Supporting figures	S5-S17
Figure S1. FT-IR spectra of BPA, PP and PP	S5
Figure S2. ¹ H NMR spectra of PP	S 6
Figure S3. ¹ H NMR spectra of BPA	S 7
Figure S4. ORTEP with 50% probability ellipsoid	S 7
Figure S5. TGA for the cocrystal.	S8
Figure S6. Simulated and experimental PXRDs of polymorph 1	S9
Figure S7. FT-IR comparison of the polymorphs.	S10
Figure S8. PXRD of polymorph 1 after grinding experiments.	S11
Figure S9. PXRD of polymorph 2 after grinding experiments.	S12
Figure S10. Pictures of crystals before and after the phase transition.	S13
Figure S11. BFDH morphology showing wider face.	S14
Figure S12. Contact angle for polymorph 1 and polymorph 2 using water as a	S14-S15
probe liquid	
Figure S13. Contact angle for both polymorphs using diiodomethane as a	S16-S17
probe liquid.	
3. Supporting Table	S18-S20
Table S1. Crystallography Table	S18
Table S2. Length and width of the crystals before and after phase transition.	S19
Table S3. Surface free energy (in mJ/m^2) calculation for Polymorph 1.	S20
Table S4. Surface free energy (in mJ/m^2) calculation for Polymorph 2.	S20
3. Supporting Video	S20

1. Supporting Methods

Reagents: *p*-Hydroxybenzoic Acid (SRL), *n*-propyl alcohol (Spectrochem), sulfuric acid (Finar), hydrazine monohydrate (Spectrochem), 4-pyridine carboxaldehyde (Sigma-Aldrich), ethanol (SRL) diiodomethane (TCI) were used as received.

Synthesis of PP: 1 equivalent (3.62 m mol, 0.5 g) of *p*-hydroxybenzoic acid was added to a one necked round bottom flask containing 10.16 equivalent (36.57 mmol, 2.73 ml) *n*-propanol. Catalytic amount of conc. H_2SO_4 (0.21 equivalent, 0.756 m mol, 0.04 ml) was added to the reaction mixture and the resulting solution was refluxed for 4 hours. Excess *n*-propanol was distilled off, and the residue obtained was purified by solvent extraction. The residue was mixed with dichloromethane and water and shaken vigorously in a separatory funnel. The lower organic layer containing the product was collected, and the upper layer (aqueous) was discarded. The organic layer was again introduced in the separatory funnel, mixed with a sodium hydrogen carbonate solution and shaken vigorously to eliminate any leftover free acid. The organic layer was collected in a beaker containing anhydrous sodium sulphate to remove traces of water, filtered, and the solution was distilled off to obtain the pure PP.



Scheme S1. Synthesis of PP.

Synthesis of BPA: 1 equivalent (4.67 m mol, 0.44 ml) of 4-pyridine carboxaldehyde was added to a beaker containing a solution of 0.5 equivalent of hydrazine hydrate (2.33 m mol, 0.11 ml) in ethanol. The resulting reaction mixture was stirred vigorously at room temperature for 4 hours. The obtained precipitate was filtered, dried, and recrystallized to purify the product.



Scheme S2: Synthesis of BPA

Synthesis of Cocrystal: The cocrystal BPA and PP was prepared by grinding both the compounds in a ball mill grinder, at a speed of 400 RPM for 3 hours. The BPA and PP were taken in a 1:2 stoichiometric ratio, and a block-type crystal of the co-crystal was obtained by slow evaporation from methanol solvent.

Instrumentation

Thermal microscopy: Thermal microscopy was carried out with a Leica DM 2700P microscope attached to a Linkam thermal stage and equipped with a Leica MC170HD camera. The heat-induced mechanical effects were studied with a Leica M80 microscope equipped with an MC170HD camera. Analysis of the videos was carried out with LAS Ver. 4.9.0 software. The crystals were heated with IKAC-MAG HS 7 hot plate to induce the mechanical motion of the crystals.

FT-IR: The FT-IR spectra were recorded with a Perkin Elmer FTIR spectrometer in UATR mode.

¹**HNMR:** ¹HNMR spectra of the two starting materials PP and BPA were recorded by using Bruker Avance 400 MHz spectrometer (Bruker-Biospin, Karlsruhe, Germany) in a CD₃OD solvent.

Scanning Electron Microscope: The scanning electron microscopy (SEM) of the two polymorphs was carried out with JSM 6390LV scanning electron microscope.

Differential Scanning Calorimetry: DSC was performed on a Mettler Toledo DSC instrument at a heating rate of 10 $^{\circ}$ C min⁻¹ aluminium pan under an ultra-high pure nitrogen environment purged at 40 mL min⁻¹.

Powder X-ray Diffraction: Powder X-ray Diffraction was carried out using Cu K α (λ = 1.54 Å) radiation in the range of 5°-50° using Rigaku powder X-ray diffractometer (Model: SmartLab SE).

Contact Angle: The contact angle measurements were carried out using a DMs-401 contact angle meter.

Single Crystal X-ray Diffraction: The X-ray diffraction data was collected on a Bruker AXS SMART APEX-I diffractometer. The APEX II program was used to determine the unit cell parameters and data collection. SADABS (Bruker, 2016/2) was used for absorption correction. SAINT (V8.38A, Bruker, 2018) is used for unit cell refinement and data reduction, and Olex 2 (Bourhis et al., 2015) is used for structural refinement. All hydrogen atoms except O—H hydrogens are placed at calculated positions, whereas O—H hydrogens are located from the electron density map.

2. Supporting Figures



Figure S1. FT-IR spectra of (a) BPA, (b) cocrystal, and (c) PP.



Figure S2. ¹H NMR spectra of PP.







Figure S4. ORTEP with 50% probability ellipsoid.



Figure S5. TGA for the cocrystal of BPA and PP.



Figure S6. Comparison of (a) simulated and (b) experimental PXRDs of polymorph 1 of the cocrystal. The difference in intensity on the experimental PXRD pattern may be due to the preferred orientation. Black dotted lines are drawn to show the matching of major peak positions.



Figure S7. FT-IR comparison of the polymorph 1 and 2.



Figure S8. Experimental PXRD of (a) polymorph 1 crystals at room temperature, (b) after solid-state grinding of polymorph 1 crystal for 1 hour, (c) solvent-mediated grinding of polymorph 1 crystals for 1 hour, d) simulated PXRD of polymorph 1.



Figure S9. Experimental PXRD of (a) polymorph 2 crystals, (b) after solid-state grinding of polymorph 2 crystals or 1 hour, (c) after solvent-mediated grinding of polymorph 2 for 1 hour, (d) simulated PXRD of Polymorph 1.



Figure S10. Crystals of BPA-PP cocrystal are undergoing expansion and cracking after the phase transition.



Figure S11. BFDH morphology showing wider face.





Figure12. Contact angle for polymorph 1 and polymorph 2 using water as a probe liquid.





Figure 13. The contact angle for both polymorphs using diiodomethane as a probe liquid.

3. Supporting Tables

 Table S1. Crystallography Table

	Cocrystal (BPA + PP)
Crystal habit	Plate
Temperature/K	296.15
Radiation source	Мо
Formula weight	285.325
Crystal system	Triclinic
Space group	P-1
<i>a</i> / Å	7.048 (8)
<i>b</i> / Å	7.351 (8)
<i>c</i> / Å	15.499 (16)
α / °	78.09 (3)
β/°	84.05 (3)
γ/°	69.20 (3)
Volume / Å ³	734.1 (14)
Z	2
Density / (g cm ⁻³)	1.291
μ / mm^{-1}	0.090
F_{000}	302.206
h_{min}, h_{max}	-9, 9
k _{min} , k _{max}	-9, 9
l _{min} , l _{max}	-20, 20
No. of measured Reflections	23890
No. of unique reflections	3717
No. of reflections used	2170
$R_{ m all}, R_{ m obs}$	0.1099, 0.0581
$wR_{2,all}, wR_{2,obs}$	0.1688, 0.1356
$\Delta ho_{ m min,max}$ / (e Å ⁻³)	-0.2977, 0.3308
GooF	1.0435
CCDC number	2345382

Crystal number	polymorph	Length	Width	Percentage	Percentage
		(mm)	(mm)	increase in	increase in
				length	width
Crystal 1	1	6.88	3.32	1.30	0.90
	2	6.97	3.35		
Crystal 2	1	5.35	1.39	2.24	5.75
	2	5.47	1.47		
Crystal 3	1	1.96	0.95	6.63	1.05
	2	2.09	0.96		
Crystal 4	1	2.45	1.39	3.67	8.63
	2	2.54	1.51		
Crystal 5	1	0.88	0.46	1.13	8.69
	2	0.89	0.50		
Crystal 6	1	6.20	2.34	4.83	2.56
	2	6.50	2.40		
Crystal 7	1	6.43	2.51	0.93	13.54
	2	6.49	2.85		
Crystal 8	1	4.43	2.03	3.38	4.43
	2	4.58	2.12		
Crystal 9	1	3.41	3.20	1.46	3.125
	2	3.46	3.30		
Crystal 10	1	1.75	1.34	4.57	3.73
		1.83	1.39		
Crystal 11	1	2.30	1.61	2.60	6.83
	2	2.36	1.72		
Crystal 12	1	2.32	0.35	3.01	5.71
	2	2.39	0.37		
Crystal 13	1	2.51	0.59	1.99	3.38
	2	2.56	0.61		
Crystal 14	1	1.48	1.21	2.70	1.65
<u> </u>	2	1.52	1.23		
Crystal 15	1	3.44	1.55	0.87	3.87
	2	3.47	1.61		

 Table S2. Length and width of the crystals before and after phase transition.

Contact	Contact angle	Owens-Wendt		Kaelble-Uy			
angle for	for	d	h	Total	d	р	Total
water	diiodomethane						
73.8	22.7	43.3	4.9	48.2	42.5	5.1	47.6
78.9	29.9	41.4	3.5	44.9	40.9	3.6	44.5
87.1	45.4	34.8	2.2	37	34.6	2.3	36.9
70.8	21.5	43.1	6.1	49.2	42.1	6.4	48.5
86.2	41.4	37	2.1	39.1	36.8	2.2	39
80.3	30.7	41.4	3.1	44.5	40.9	3.1	44
84	40.7	37	2.7	39.7	36.6	2.8	39.4
75.3	29.4	40.9	4.9	45.8	40.1	5.1	45.2
83.4	36.4	39.2	2.5	41.7	38.8	2.6	41.4
83	32.4	41.1	2.3	43.4	40.9	2.4	43.3

Table S3. Surface free energy (in mJ/m^2) calculation for the wider face of the single crystals of Polymorph 1.

Table S4. Surface free energy (in mJ/m^2) calculation for the wider face of the single crystals of Polymorph 2.

Contact	Contact angle	Owens-Wendt		Kaelble-Uy			
angle for	for	d	h	Total	d	р	Total
water	diiodomethane						
67.1	3.1	46.1	7	53.1	44.9	7.3	52.2
79.4	22.5	44.6	2.8	47.4	44.2	2.8	47
68.5	6.1	46.1	6.4	52.5	45.1	6.6	51.7
86.6	27.5	44.1	4.4	45.2	44.3	1.1	45.4
73.5	11.4	46.4	6.8	50.8	45.7	4.5	50.2
67.6	4.3	46.1	4.9	52.9	45	7	52
72	8.8	46.5	4.2	51.4	45.7	5.1	50.8
74.7	18.1	45	4.2	49.2	44.3	4.4	48.7
54.1	0.9	43.7	14.2	57.9	41.6	15	56.6
72.3	11.3	46.1	4.9	51	45.4	5	50.4

3. Legends to the supporting movie

Video S1. Video of crystal showing expansion on heating. The video is fast forwarded to 3X speed.