Solid Decolorization: Dismantling of an Orange-Red Zwitterionic Cocrystal by Multicomponent Milling

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An application of multi-component milling is described to achieve a decolorization by dismantling the orange-red zwitterionic cocrystal (PDA)•(APAP) (where PDA = 2,4-pyridinedicarboxylic acid, APAP = acetaminophen) using *n*,*n*′-BPE (BPE = *trans*-1,2-bis(*n*-pyridylethylene and for *n* = *n*′ = 3 or 4). Each of *n*,*n*′-BPE forms a colorless hydrogen-bonded cocrystal with PDA.

1. Introduction

Decolorization is a process that removes color from chemical substances.[1] The process is typically performed in the liquid phase through the dissolution of a solid product. Processes that involve decolorization include the removal of synthetic dyes in textiles, foods, drinks, paper, inks, cosmetics, and pharmaceuticals.[2] Decolorization has found applicability, for example, in the treatment of wastewater with high azo dye contents emanating from textile industries.[1] Colors are removed before discharging the water into rivers and lakes to avoid pollution and other environmental damages and health risks owing to toxicity, carcinogenicity, and resistance to biodegradation.[3] Decolorization can be achieved using methods that include activated carbon treatment,[4] physical and chemical treatment such as adsorption, photolysis, oxidation, reduction, and chemical, and electrochemical precipitation.[5–7] Biological treatments such as degradation also result in decolorization, with the turning of leaves in autumn being a familiar related decolorization of solid substances.[8]

The bulk properties of organic molecular solids such as solubility, optical properties, thermal stability, and mechanical strength can be improved by co-crystallization.[9,10] Through crystal engineering and the use of supramolecular synthons, non-covalent interactions such as conventional hydrogen bonds, as well as halogen bonds,[11,12] $\pi-\pi$ stacking, and charge-assisted hydrogen bonds have been exploited to design multi-component solids with modifiable and enhanced properties.[13]

Mechanochemistry is a rapidly emerging synthetic approach to form cocrystals that relies on a chemical change and/or reaction induced by mechanical energy.[14] Mechanochemical methods used to synthesize cocrystals include mortar-and-pestle grinding, as well as ball and planetary milling, all of which often result in fast and quantitative yields of products with little or no solvent.[15] The methods and approaches of mechanochemistry adhere to many principles of green chemistry.[16] An emerging approach in the mechanochemical synthesis of cocrystals is multicomponent milling.[17] Multicomponent milling is rooted in displacement and metathesis reactions associated with the field of inorganic solid-state chemistry.[18,19] The results of multicomponent milling experiments can be challenging to predict because of the shallow crystal energy landscapes of organic materials in the crystalline state.[20,21] Despite challenges, however, research on multicomponent milling can be expected to afford opportunities to design and discover new crystalline solids and aid understanding of material thermodynamic stabilities.[22]

Herein, we describe an application of multicomponent milling that results in a decolorization. Specifically, multicomponent milling when applied to the orange-red zwitterionic cocrystal **(PDA)·(APAP)** (where: **PDA** = 2,4-pyridinedicarboxylic acid, **APAP** = acetaminophen) using the bipyridines **n,n′-BPE** (where: **BPE** = *trans*-1,2-bis(*n*-pyridyl)ethylene and *n* = n′ = 3 or 4) results in dismantling[23] of the orange-red binary solid and corresponding loss of color. Our application of multicomponent milling arises from work on developing cocrystals of **PDA.** To the best of our knowledge, we report the first use of cocrystals in a solid decolorization process and the application of multicomponent milling to affect bulk physical properties of molecular solids. Dismantling has only been thus far reported in the context of the preparation of multicomponent pharmaceuticals.[23] The dismantling here occurs in a minimalist sense, involving the binary cocrystal and a single-component solid (**Scheme 1**).

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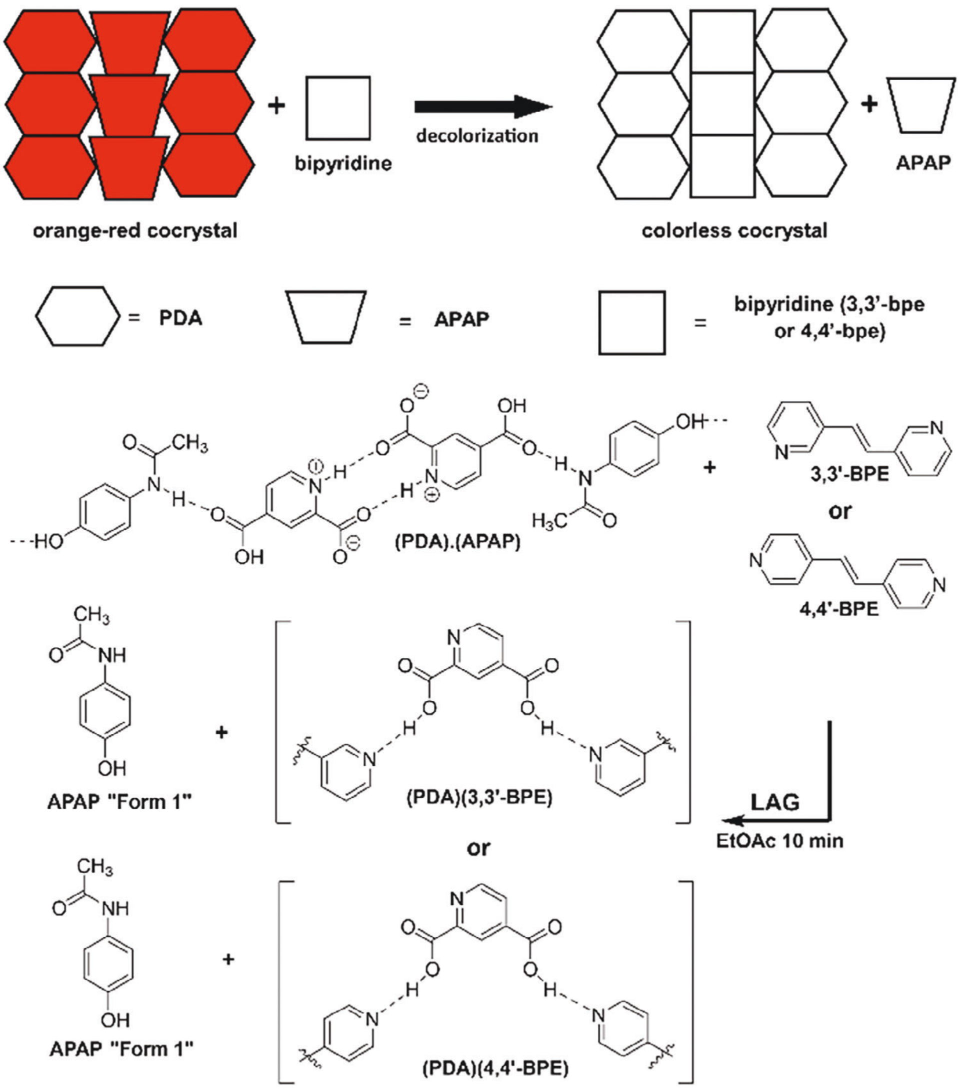


Scheme 1. Decolorization of orange-red zwitterionic **(PDA)· (APAP)** through multi-component milling.

2. Results and Discussion

PDA is an amphoteric bioactive molecule that acts as a potential inhibitor of human 2-oxoglutarate (2OG-oxygenases), which is implicated in wide-ranging human diseases that include cancer.[24,25] **PDA** can function as a zwitterionic conformer in cocrystals owing to the acid-base properties of the carboxylic acid and pyridine groups. Zwitterions have been implicated in improving properties of cocrystals such as solubility.[26,27] Specifically, we have reported the pharmaceutical cocrystal **(PDA)·(APAP)** wherein **PDA** exists in a zwitterionic form. The resulting cocrystal is bright orange-red in color, which contrasts the starting solids that are colorless.[28] The origin of the color is ascribed to charge transfer.

Given that **(PDA)·(APAP)** is bright orange-red in color, and a paucity of cocrystals of **PDA**, we focused on the ability of **PDA** to form cocrystals with ***n,n′*-BPE**. When **PDA** was cocrystallized with each ***n,n′*-BPE**, novel solid phases were obtained. The compositions of the solids were confirmed by single-crystal and powder X-ray diffraction, as well as ^{1}H NMR spectroscopy.

Specifically, cocrystallization of **PDA** (20.1 mg, 0.12 mmol) and **3,3′-BPE** (21.9 mg, 0.12 mmol) in EtOH/DMSO (1:1) (5 mL) afforded colorless prism-like crystals of the binary solid **(PDA)·(3,3′-BPE)** following slow solvent evaporation after a period of 3 days.

SCXRD analysis revealed the components to form **(PDA)·(3,3′-BPE)**, with the molecules crystallizing in the monoclinic space group *C2/c* (**Figure 1**). The asymmetric unit consists of one full molecule each of **PDA** and **3,3′-BPE** (Figure 1a) that self-assemble to form a 1D wave-like hydrogen-bonded polymer (repeat distance: 35.5 Å) sustained by O-H···N hydrogen bonds (O1···N2 2.584(3) Å; ∠ O–H···N 175°, and O3···N3 2.569(3) Å; ∠ O–H···N 175°) (Figure 1b). The geometry of each carboxyl group of **PDA** is consistent with **PDA** in a non-zwitterionic form (C = O1 1.308(3), C-O2 1.219(3), C = O3 1.310(3), C-O4 1.215(3) Å). The 1D polymers exhibit a tongue-and-groove fit held together by bifurcated C-H···N (3.654(4) Å) and C-H···O (3.131(4) Å)

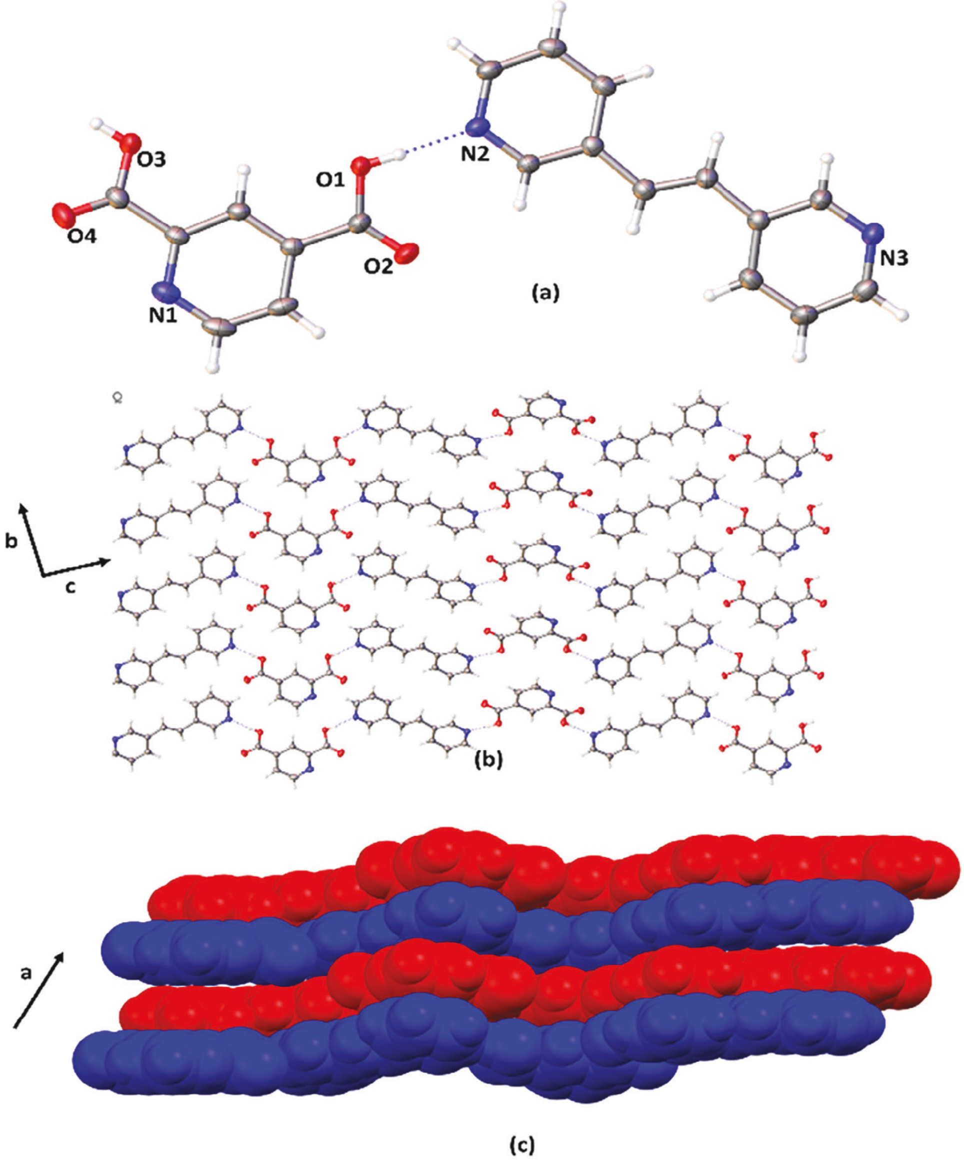


Figure 1. X-ray structure **(PDA)·(3,3′-BPE)**: a) asymmetric unit, b) wave-like polymer, and c) packing of layers (space-filling).

interactions to form a layered structure within the *bc*-plane that stacks along the *a*-axis face-to-face (3.63 Å) (Figure 1c).

When **PDA** (23.0 mg, 0.14 mmol) and **4,4′-BPE** (25.0 mg 0.14 mmol) were dissolved in DMSO (5 mL), colorless prism-like crystals of (**PDA**)·(**4,4′-BPE**) formed by slow-solvent evaporation after 7 days.

A SCXRD analysis showed the components to form (**PDA**)·(**4,4′-BPE**), which crystallizes in the triclinic space group $P\bar{1}$ (**Figure 2**). The asymmetric unit consists of one full molecule of each of **PDA** and **4,4′-BPE** (Figure 2a). The ring of **PDA** lies disordered over two positions. Similar to (**PDA**)·(**3,3′-BPE**), the molecules form a 1D wave-like polymer sustained by O-H···N (O1···N3 2.525(15) Å; ∠ O–H···N 175° and O3···N2 2.551(18) Å; ∠ O–H···N 174°) hydrogen bonds (repeat distance 35.2(3) Å) (Figure 2b) and with **PDA** in the neutral form (C = O1 1.327(2), C-O2 1.216(1), C = O3 1.316(2), C-O4 1.222(1) Å). The polymers self-assemble to form layers within the *ab*-plane that stack face-to-face along the *c*-axes (3.53 Å) (Figure 2c). A lack of bifurcated C-H···N and C-H···O forces may be attributed to a lack of fit of the polymers in each layer, which may also lead to the disorder of **PDA**.

Having established **PDA** forms hydrogen-bonded binary cocrystals with each of ***n*,*n*′-BPE**, we turned to co-grind orange-red **(PDA)·(APAP)** with each bipyridine (Table S3, Supporting Information). We hypothesized that multicomponent milling involving **(PDA)·(APAP)** and each of ***n*,*n*′-BPE** could result in the dismantling of **(PDA)·(APAP)** to generate the novel cocrystals **(PDA)·(*n*,*n*′-BPE)**. With both **(PDA)·(*n*,*n*′-BPE)** being colorless, a result of the multi-component milling would be the loss of the orange-red color and, thereby, effective decolorization of the solid sample in a highly selective milling process. From a supramolecular chemistry standpoint, dismantling **(PDA)·(APAP)** to form

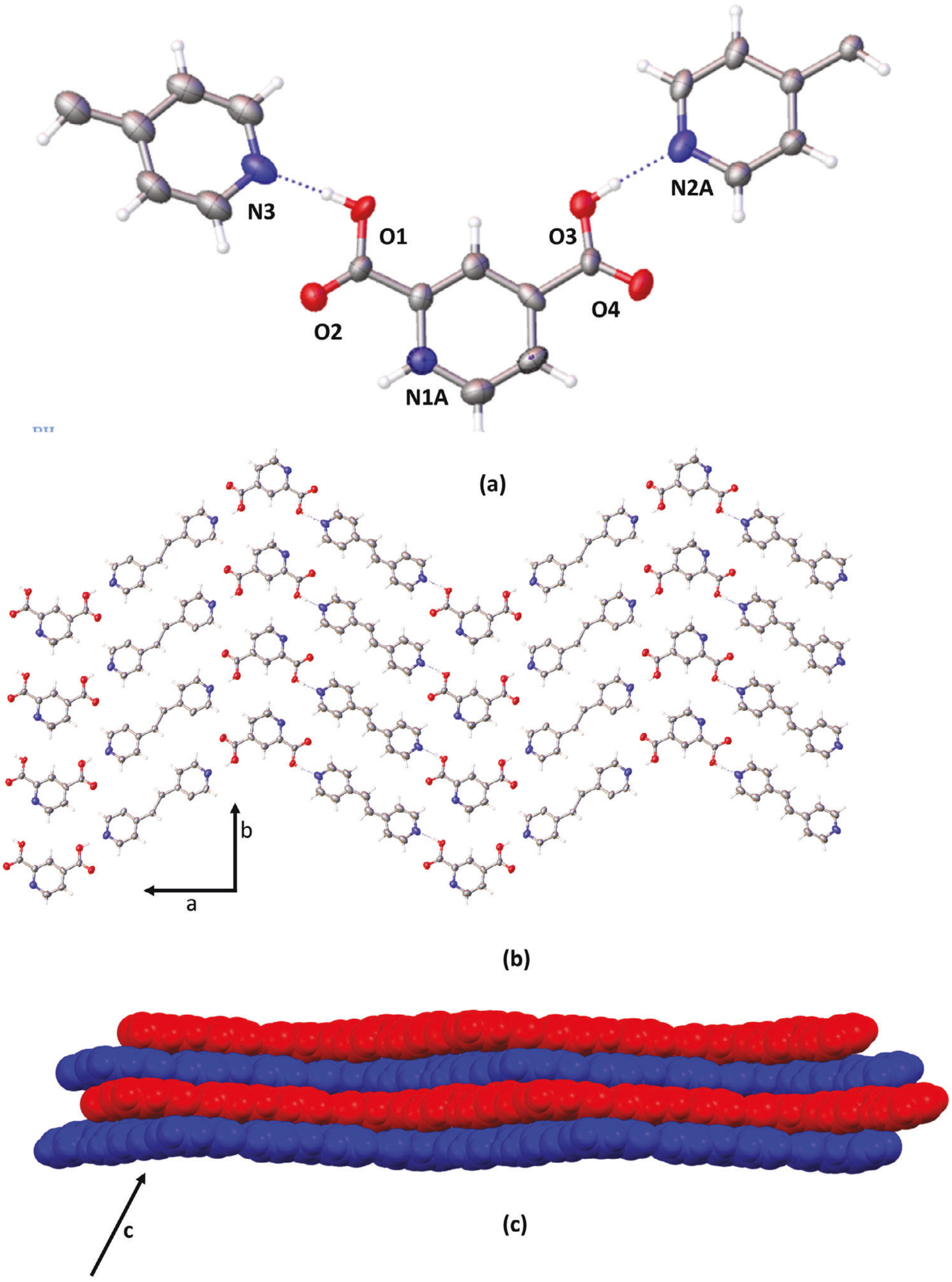


Figure 2. X-ray structure **(PDA)·(4,4′-BPE)**: a) asymmetric unit, b) zig-zag polymer, and c) packing of layers (space-filling).

(PDA)·(*n*,*n*′-BPE) would require breakage of a combination of charge-assisted N$^+$-H···$^-$O (1 total) and O-H···$^-$O (1 total) hydrogen bonds, as well as neutral O-H···O (1 total) and O-H···N hydrogen bonds (1 total) (**Table** 1). The formation of each of **(PDA)·(*n*,*n*′-BPE)** would generate neutral O-H···N hydrogen bonds (2 total) of the self-assembled 1D polymers. That ***n*,*n*′-BPE** as pure solids are sustained by weaker van der Waals forces owing to a lack of conventional hydrogen-bond donors would mean that successful co-grinding would not require breakage of such hydrogen bonds. Moreover, the dismantling would be expected to displace **APAP**, which as a pure form is sustained by O-H···O (1 total) and O-H···N hydrogen bonds (1 total) (Table 1). The components of all new solid phases would, thus and in contrast to the reactants, be sustained by appreciably strong hydrogen bonds.

When **(PDA)·(APAP)** and **3,3′-BPE** were subjected to multicomponent milling using a ball mill for a period of 10 minutes, the resulting sample lost the orange-red color (**Figure** 3). The diffraction pattern (**Figure** 4) showed losses of the most prominent peaks for **(PDA)·(APAP)** (i.e., $2\theta = 12.5°$, 17.8°and 28.8°). The losses were accompanied by appearances of peaks for **(PDA)·(3,3′-BPE)** (i.e., $2\theta = 16.3°$, 19.3°, 27.1° and 28.2°), as well as Form I of **APAP** (i.e., $2\theta = 12.1°$, 18.5°, 20.3°, and 26.5°) (Figure 4a). The color change and changes in the diffraction

Table 1. Hydrogen bonds broken and formed in multi-component milling of orange-red **(PDA)·(APAP)**.

Hydrogen bonds broken (PDA)·(APAP)	Hydrogen bonds formed	
	(PDA)·(*n*,*n*′-BPE)	APAP "Form 1"
N$^+$-H···O (1)	O-H···N (2)	O-H···O (1)
O-H···O$^-$ (1)		N-H···O (1)
O-H···O (1)		
O-H···N (1)		

pattern were consistent with the multicomponent milling to dismantle the orange-red zwitterionic cocrystal **(PDA)·(APAP)** and generate **(PDA)·(3,3′-BPE)**. When the milling time was increased to 2 h, the decolorization was more apparent, but there was no overall change in the PXRD peaks as compared to the 10 min milling period (Figure S5, Supporting Information). Decolorization was also realized by milling of **(PDA)·(APAP)** and **4,4′-BPE**. Specifically, when the two crystalline phases were subjected to co-grinding for a similar period, peaks consistent with the binary cocrystal **(PDA)·(4,4′-BPE)** appeared (i.e., $2\theta = 15.4°$, 18.3°, 21.1°, and 27.1°) along with Form I of **APAP** (Figure 4b).

We are unaware of decolorization occurring using multicomponent milling. In early work, Friščić described a cocrystal exchange whereby the cogrinding of two binary cocrystals did not generate a new cocrystal but dismantled the cocrystals to starting materials. Structural effects related to chirality were evoked as determinants for the reactions.[23] Emmerling[20] and later Schruko[21] described competitive milling to assess thermodynamic stabilities and affinities of cocrystals with different coformers. Supramolecular catalysis of photoreactivity has also been achieved by cogrinding photoreactive cocrystals with pure alkenes.[29]

The decolorizations described here can be explained on the basis of stability and, more specifically, as reflected by melting point. DSC analyses of orange-red zwitterionic **(PDA)·(APAP)** shows the solid to melt at 179–182 °C while **(PDA)·(3,3′-BPE)** and **(PDA)·(4,4′-BPE)** melt at higher temperatures in ranges of 205–208 °C and 245–250 °C, respectively. Higher melting points are generally indicative of tigher packings,[30] which suggests that the cocrystals **(PDA)·(3,3′-BPE)** and **(PDA)·(4,4′-BPE)** represent thermodynamic minima upon applications of the multicomponent millings. We note that the melting point of **APAP** Form I is 168–175 °C, which is comparable to the starting material orange-red **(PDA)·(APAP)**. The melting points of **3,3′-BPE** and **4,4′-BPE** are appreciably less than the other solid phases being in the 100–105 °C and 140–150 °C ranges, respectively (Figure S4, Supporting Information). The higher melting points of the bipyridine-containing cocrystals can likely be attrbuted to the components forming polymers, through packing arrangements which justifies why they dismantled **APAP** in the orange-red cocrystal. Moreover, the higher melting points are associated with the solids with components that self-assemble by the hydrogen bonds.

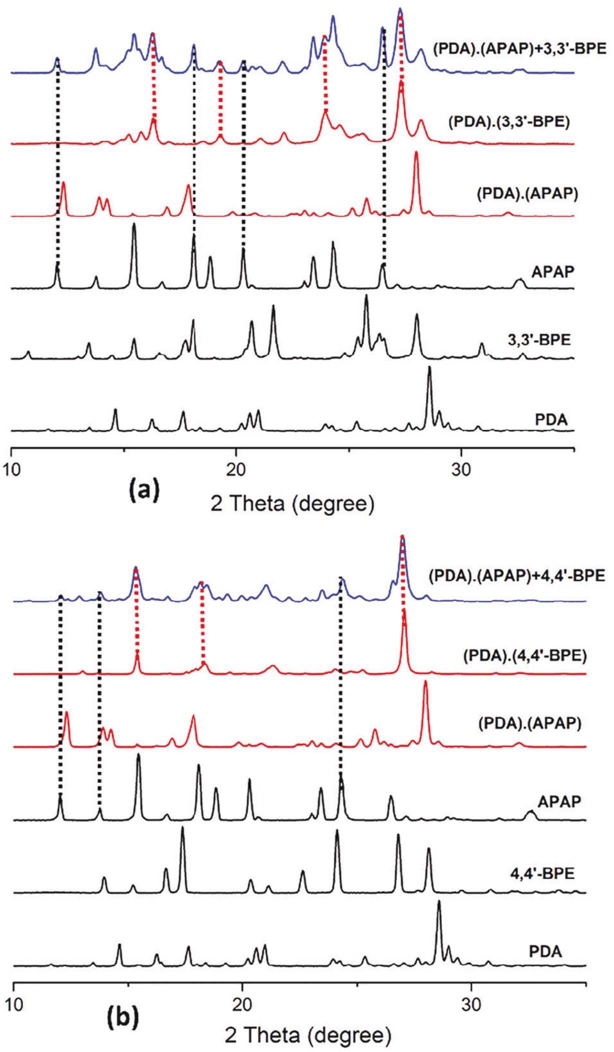
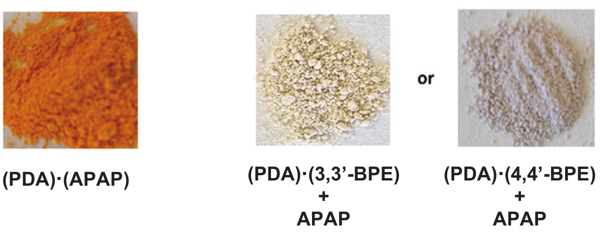


Figure 4. PXRD diffractograms from multicomponent millings (time = 10 min): a) **(PDA)·(APAP)** with **3,3′-BPE** and b) with **4,4′-BPE**. Red lines show peaks that correspond to binary cocrystals, and black lines show peaks corresponding to **APAP Form 1**.



(PDA)·(APAP)

(PDA)·(3,3'-BPE) + APAP

(PDA)·(4,4'-BPE) + APAP

Figure 3. Change in color from multicomponent milling of **(PDA)·(APAP)** with either **3,3′-BPE** or **4,4′-BPE**.

3. Conclusion

In summary, we have described decolorizations of a solid cocrystal sample that involves the dismantling of a zwitterionic binary cocrystal by application of multicomponent milling. Binary cocrystals of **PDA** with ***n*,*n*′-BPE** were achieved, and the solids used as reagents for the multicomponent millings. We expect the approach here can be expanded to other binary cocrystals, as well as higher-order solids (e.g., ternary cocrystals). The loss of color may also provide insight into how these phases are dismantled and formed, as well as interact. Changes to additional properties can also be explored using multicomponent milling approach.[31]

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Cambridge Structural Database at https://www.ccdc.cam.ac.uk, reference number 2326860.

Keywords

crystal engineering, hydrogen bonds, mechanochemistry, cocrystals, organic solid state

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