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Preparation and Reactivity of Nanocrystalline Cocrystals Formed via Sonocrystallization

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A recent study by Nakanishi has described a method to achieve single-crystal-to-single-crystal (SCSC) chemical reactivity in organic solids by reducing crystal size.[1] Specifically, pure diolefin crystals of nano- and micrometer dimensions synthesized via a reprecipitation method exhibited SCSC photoreactivity to give a polycyclobutane polymer. This contrasted diolefin crystals of macroscopic dimensions that cracked during the photoreaction. Nano- and micrometer-sized crystals often exhibit different physical properties (e.g., magnetic) relative to macrocrystalline solids. Solids that exhibit SCSC behavior are rare and promising for sensor and high-density data storage applications. In the case of the diolefin,[1] that the solid exhibited SCSC reactivity was attributed to a large deformability of the nanocrystals, which enabled the solid to maintain single crystallinity under the stressful UV conditions of the photoreaction.

Despite possessing prerequisite reactive centers, olefins are typically not reactive in the solid state. This is attributed to unpredictable effects of molecular close packing, which contrast stringent geometric parameters for a reaction in a solid. To help alleviate this problem, we have described a method to control reactivity in the solid state based on molecular cocrystals.[2] Cocrystallization of ditopic template molecules (e.g., resorcinol) with functionalized olefins [e.g., *trans*-1,2-bis(4-pyridyl)ethylene) (4,4′-bpe)] has produced hydrogen-bonded aggregates [e.g., 2(resorcinol)·2(4,4′-bpe)] with olefins that reliably undergo [2 + 2] photodimerizations. The utility of the method has been realized through the supramolecular construction of cyclophane and ladderane molecules.[3]

The observation of Nakanishi described above[1] suggests that an important step toward generalizing cocrystals as media for controlling chemical reactivity would be to achieve reaction in cocrystals of nano- and micrometer-sized dimensions. Cocrystals, in contrast to single-component solids, however, present a fundamentally different challenge with respect to those reprecipitation methods used to form organic nanocrystals[1,4] since the molecular components of a cocrystal will, de facto, exhibit different solubilities. Moreover, critical matching of solubilities for controlled precipitation and growth is important and expected to be difficult. This is particularly true in the context of supramolecular cocrystals where the complementary nature of the noncovalent bonds, or heterosynthons,[5] that hold the components together will tend to be associated with molecules that exhibit considerably different solubilities.

With this in mind, we wish to introduce here a convenient sonochemical method[6,7] to prepare organic cocrystals of nano- and micrometer-sized dimensions. In particular, we demonstrate that the application of low-intensity ultrasonic radiation to cocrystals of composition 2(resorcinol)·2(4,4′-bpe) **1** through sonocrystallization produces nano- and micrometer-sized cocrystals that are shown to exhibit SCSC reactivity. We demonstrate that the sonochemical treatment succeeds where sole reprecipitation fails. Whereas sonochemistry is typically used to prepare nanostructured inorganic solids,[8] induce rapid crystallization,[9] and effect properties of pharmaceutical materials,[10] such application of sonochemistry to prepare a nanostructured organic solid has, to the best of our knowledge, not been reported.

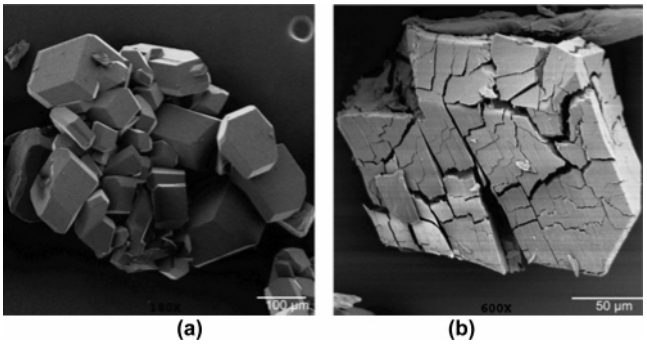

Figure 1. SEM micrographs of macro-sized cocrystals of **1** showing the effects of the UV light: (a) before and (b) after photoreaction.

Our first experiment involved growing macro-sized single crystals of **1**. Macrodimensional crystals of **1** were prepared by slow evaporation of a solution of resorcinol and 4,4′-bpe in ethanol at room temperature (Figure 1a). A SEM micrograph of the solid revealed the presence of well-defined millimeter-sized prisms. The majority of the prisms varied from 1 to 4 mm. An X-ray powder pattern of the cocrystals confirmed that the structure of the solid corresponded to the photoactive hydrogen-bonded aggregate 2(resorcinol)·2(4,4′-bpe).

To determine the photochemical properties of the macrocrystals, the cocrystals were irradiated with UV irradiation (medium pressure Hg lamp) for 1 day. A ^{1}H NMR spectrum indicated that the olefins reacted to give *rctt*-tetrakis(4-pyridyl)cyclobutane (4,4′-tpcb) in 100% yield. A SEM micrograph demonstrated that the prisms lost structural integrity upon reaction (Figure 1b). In particular, the crystals cracked into smaller particles to eventually give a powder. The cracking can be attributed to the release of accumulated strain, the result of molecular movement induced by the UV light.

Our next experiment involved attempts to grow nano- and micro-sized single crystals of **1** via the reprecipitation method. Thus, 200 μL of a ethanol solution of resorcinol and 4,4′-bpe (5 mmol/L) was injected using a microsyringe into pure water (100 mL) that was vigorously stirred. The addition of the ethanolic solution produced a cloudy suspension. A SEM micrograph of the resulting solid revealed crystals of predominantly micrometer dimensions (i.e., >5 μm) (Figure 2a). In contrast to the millimeter-sized prisms, a majority of the crystals were nonuniform in shape, exhibiting jagged edges and flake-like morphologies. An X-ray powder pattern confirmed that the structure of the solid corresponded to the photoactive hydrogen-bonded aggregate 2(resorcinol)·2(4,4′-bpe). Similar to the prisms, UV irradiation of the solid largely resulted in cracking and destruction of the cocrystals (Figure 2b).

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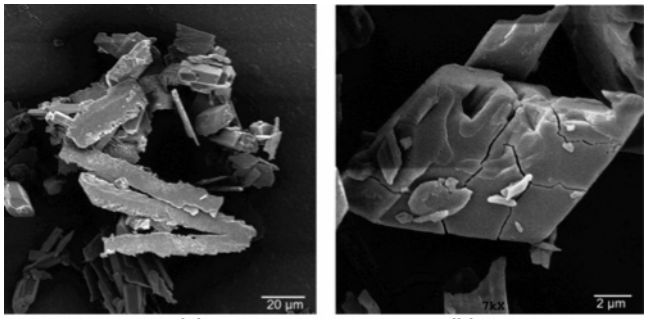

Figure 2. SEM micrographs of cocrystals of **1** grown via the reprecipitation method: (a) before and (b) after photoreaction.

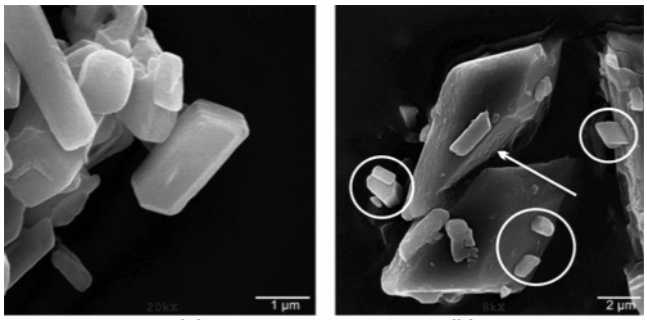

Figure 3. SEM micrographs of cocrystals of **1** grown via sonocrystallization: (a) before and (b) after photoreaction. Circles show intact crystals, while the arrow shows crack in a large crystal.

To synthesize nano- and micro-sized cocrystals of **1**, we next turned to sonochemistry. For this experiment, low-intensity ultrasonic radiation using an ultrasonic cleaning bath[11] was applied to **1** grown using the reprecipitation method. Thus, ultrasonic radiation was immediately applied to a cloudy low-temperature suspension (5 °C) of resorcinol, 4,4′-bpe, ethanol, and water prepared using a microsyringe for a period of 3 h. In contrast to the solid obtained using reprecipitation alone, a SEM micrograph revealed the formation of well-defined crystals of nano- and micro-sized dimensions. The crystals obtained via the sonocrystallization were uniform in shape, exhibiting prism morphologies. The size distribution ranged from 500 nm to 8 μm. An X-ray powder pattern demonstrated that the structure of the solid corresponded to the photoactive aggregate 2(resorcinol)·2(4,4′-bpe). Importantly, in contrast to the cocrystals prepared using the reprecipitation method alone, UV irradiation of the solid resulted in a SCSC reaction of **1**. The SCSC transformation generally occurred in crystals smaller than 2 μm. This is clearly evident in a SEM micrograph taken following the photodimerization in which the larger micro-sized crystals exhibited cracks while the submicron and nano-sized crystals remained intact (Figure 3b).

That the sonochemical treatment yielded well-defined nano- and micro-sized cocrystals of **1** may be attributed to effects of cavitation. In this process, the formation, growth, and collapse of bubbles of micrometer-sized dimensions associated with intense, shortly lived heating and pressure occurs.[6] Although shear forces and crystal fragmentation from cavitation enhance nucleation and crystallization rates, respectively, it has been suggested that the process may also reduce or eliminate supersaturation in the immediate vicinity of the bubbles and, thus, remove a driving force to nucleation.[7] In other words, cavitation can also provide a mechanism to solubilize component molecules. Indeed, we believe that our observations are consistent with this model. In effect, the ultrasonic radiation can be considered to have provided an environment that favors rapid solubilization of the components of the cocrystal **1** (i.e., irrespective of the inherent solubility of each component) while also providing a mechanism for rapid precipitation and formation of the small (i.e., nano- and submicron) crystals. These observations are important since they suggest that sonocrystallization may be more generally applied to additional cocrystalline solids.

In this report, we have introduced sonochemistry as a method to prepare nanostructured organic cocrystals. The method takes into account inherent differences in solubilities encountered in cocrystals and has been shown to succeed where reprecipitation alone fails. The system described here has been developed to exhibit SCSC reactivity. We are currently working to apply this method to additional reactive cocrystals and anticipate that the approach can be applied to other cocrystal systems[12] (e.g., pharmaceutics) to affect additional properties (e.g., solubility).

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Supporting Information Available: ^{1}H NMR spectra and X-ray powder patterns of macro- and nano-sized cocrystals of **1** before and after UV irradiation. This material is available free of charge via the Internet at http://pubs.acs.org.

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