

# Pharmaceutical Cocrystallization: Engineering a Remedy for Caffeine Hydration

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**ABSTRACT:** A systematic crystal engineering study was performed on the model pharmaceutical compound caffeine to prepare a cocrystal that, unlike caffeine, is physically stable at all relative humidities (RH). Six cocrystal materials containing caffeine with one of several dicarboxylic acids are described herein. Methods of cocrystallization included solution growth, neat solid-state grinding, and grinding with solvent-drop addition. Crystal structures are reported for a total of five cocrystals containing caffeine (with oxalic acid, malonic acid, maleic acid, and glutaric acid), including two recently reported polymorphic caffeine cocrystals. In each of these structures, a predicted intermolecular hydrogen-bonding motif is observed. The stability with respect to RH is evaluated for the six cocrystal materials. The cocrystal with oxalic acid exhibits complete stability to humidity over a period of several weeks. Other cocrystals demonstrate lesser degrees of stability with respect to humidity.

## Introduction

The field of crystal engineering enables the design of crystalline molecular complexes, or cocrystals, using robust, reliable supramolecular synthons.<sup>1–4</sup> The extension of the field to pharmaceuticals has been previously demonstrated with several drug substances.<sup>5,6</sup> Cocrystallization of pharmaceutically active molecules represents a viable means of enhancing the physical properties of a drug substance, particularly when the options for forming ionic complexes are limited and the inherent instability of the amorphous material is undesired. In recent literature, pharmaceutical cocrystals have been demonstrated to alter the physical properties of melting point<sup>7,8</sup> and solubility.<sup>9</sup> In a related example, the solid-state chemistry of a pharmaceutical cocrystal containing two active pharmaceutical ingredients was investigated with regard to its anhydrous and hydrate crystal forms.<sup>10</sup>

The stability of a solid drug substance in the presence of atmospheric moisture is of concern to the pharmaceutical industry as it has practical implications for processing, formulation, packaging, and storage.<sup>11,12</sup> It is sometimes the case that an anhydrous crystal form is stable below a certain critical relative humidity (RH), but at higher RH it will convert to a crystalline hydrate.<sup>13</sup> In these cases, solid form selection is often employed to search for a polymorph or salt form that exhibits greater stability at high RH values.

Caffeine (1,3,7-trimethyl-2,6-purinedione) is a model pharmaceutical compound that is known to exhibit instability with respect to humidity, with the formation of a crystalline nonstoichiometric hydrate.<sup>14</sup> Caffeine is a central nervous system stimulant and a smooth muscle relaxant, and is commonly employed as a formulation additive to analgesic remedies. Its solid-state properties have been widely investigated; it is

known to exist as two anhydrous crystal forms ( $\alpha$ ,  $\beta$ ) and one crystalline nonstoichiometric hydrate.<sup>15</sup> The stable anhydrous  $\beta$ -caffeine crystal form converts to the metastable  $\alpha$ -caffeine at high temperature.<sup>16</sup> Neither anhydrous crystal structure has been fully determined according to the most recent version of the Cambridge Structural Database (CSD).<sup>17,18</sup>

The nonstoichiometric crystalline hydrate of caffeine has been reported to contain 0.8 moles of water per mole of caffeine.<sup>14</sup> This unusual ratio appears to result from a channel inclusion of water in the hydrate crystal structure, which has been previously determined (CSD reference code CAFINE01).<sup>19</sup> Crystalline powder of anhydrous  $\alpha$ - or  $\beta$ -caffeine converts to caffeine hydrate at high RH; conversely, caffeine hydrate loses its water of hydration at low RH and reverts to  $\beta$ -caffeine.<sup>20</sup> The dehydration of caffeine hydrate has been studied in detail,<sup>19,21,22</sup> with one study in particular finding that the critical humidity necessary for conversion, the dehydration boundary, occurs at 61% RH, although the dehydration rate varies with particle size.<sup>14</sup> Significantly less research has been done on the hydration process, i.e., crystalline hydrate formation, from anhydrous caffeine to caffeine hydrate.<sup>20</sup>

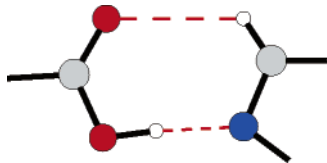
Given the hydration behavior of caffeine, the development of this model drug substance into a marketed form would potentially require the synthesis of a crystalline salt form to improve upon its physical properties. A search of the CSD reveals only one pharmaceutically acceptable salt form of caffeine, a hydrochloride dihydrate.<sup>23</sup> It appears, however, that a stable, anhydrous, pharmaceutically acceptable<sup>24</sup> form of caffeine is not yet known. The fact that the structure of only one pharmaceutically acceptable caffeine salt has been reported may result from the limited salt-forming capability of caffeine. The weakly basic imidazole nitrogen of caffeine results in a  $pK_a$  of 3.6.<sup>25</sup> As salt formation requires a significant acid–base  $pK_a$  difference (ca. 3.75 for a series of pyridine/benzoic acid complexes<sup>26</sup>), the potential salt-

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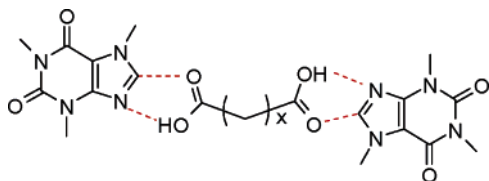
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**Scheme 1. Heteromeric Synthon Showing Strong O–H···N and Weaker C–H···O Hydrogen Bond Interactions**



**Scheme 2. Expected Intramolecular Interactions of 2:1 Caffeine/Dicarboxylic Acid Cocrystals**



forming acids for caffeine are limited to only strong acids.

By the same token, given its weak basicity, caffeine may be particularly suited for cocrystallization in its neutral form. A search of the CSD reveals 12 neutral organic cocrystals of caffeine. Several of these are pharmaceutically acceptable cocrystals, including 1:1 complexes of caffeine with the antibiotic sulfa drugs sulfacetamide<sup>27</sup> and sulfaproxyline<sup>28</sup> (CSD reference codes SACCAF and VIGVOW), and a cocrystal of caffeine with the sedative barbital<sup>29</sup> (CAFBAR20). Two other cocrystals, while not pharmaceutically acceptable, illustrate a hydrogen-bonded interaction between the imidazole nitrogen of caffeine with an un-ionized aromatic carboxylic acid (CAFSAL and DIJVUN). However, despite the existence of a number of caffeine cocrystals, a systematic crystal engineering study of pharmaceutical cocrystals of caffeine has not been described.

The aim of this study, therefore, was to rationally design and prepare a series of pharmaceutically acceptable caffeine cocrystals and to evaluate the stability of the cocrystals with respect to atmospheric humidity. Dicarboxylic acids were selected as cocrystal formers. The desired supramolecular interaction was the  $R_2^2(7)$  acid–base heterodimer synthon (Scheme 1), so as to permit strong O–H···N and weaker C–H···O hydrogen bonding.<sup>30</sup> The CSD illustrates the precedence of this heteromeric synthon: a search of all organic compounds for heteromeric interactions involving the Scheme 1 synthon yields 131 crystal structures.<sup>31</sup> In the context of the current crystal engineering experiment, it was expected that the combination of caffeine with dicarboxylic acids would induce the formation of trimeric caffeine–acid–caffeine hydrogen-bonded units (Scheme 2). This arrangement would necessitate a resultant 2:1 caffeine/acid cocrystal stoichiometry.

The following caffeine cocrystals were prepared in this study: **A** caffeine/oxalic acid (2:1); **B** caffeine/malonic acid (2:1); **C** caffeine/maleic acid (2:1); **D** caffeine/maleic acid (1:1), **E** caffeine/glutaric acid (1:1) form I; and **F** caffeine/glutaric acid (1:1) form II. The chemical structures of the successful cocrystallizing agents are presented in Scheme 3. Crystal structures are reported here for the first time for **A**, **B**, and **D**. They are compared to the recently reported structures of **E** and **F**.<sup>32</sup> All of the crystal structures exhibit the expected Scheme 1 su-

pramolecular synthon. Stoichiometry of 2:1 caffeine/acid is observed for **A**, **B**, and **C**, and the crystal structures of **A** and **B** confirm the hydrogen-bonded trimers described in Scheme 2. A stoichiometry of 1:1 caffeine/acid was observed for **D**, **E**, and **F**. In these instances, one of the carboxyl groups participates in the Scheme 1 synthon with caffeine, while the other carboxyl group associates in an alternative hydrogen-bonding arrangement. The pharmaceutical acceptability of each of these cocrystallizing agents has been confirmed by their precedence as pharmaceutical salt formers,<sup>24</sup> with the exception of glutaric acid.

Cocrystal preparation was attempted by the methods of solution precipitation and solid-state grinding. While less common than solution methods, cocrystal preparation in the solid state is well established and offers several advantages, such as a more environmentally friendly synthesis and an experimental design free from solubility considerations.<sup>33–36</sup> It was recently reported that solvent-drop grinding, i.e., grinding with the addition of a small amount of appropriate solvent, allowed for polymorphic control of the cocrystallization of caffeine with glutaric acid.<sup>32</sup> In this work, solvent-drop grinding was employed to obtain bulk powder of **D**, which could not otherwise be prepared as essentially phase-pure.

## Experimental Procedures

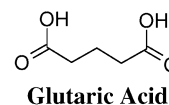
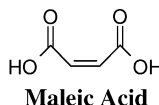
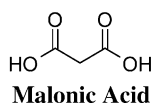
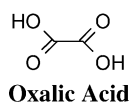
**Materials.** All chemicals were obtained from the Sigma-Aldrich Company, Ltd. (Gillingham, UK) and were used as received.

**(a) Caffeine.** Anhydrous  $\beta$ -caffeine was used as received from the Sigma-Aldrich Company. PXRD analysis of this material agreed with that of previously analyzed  $\beta$ -caffeine.<sup>19</sup>

**(b) Cocrystal A (2:1 Caffeine/Oxalic Acid).** This material was prepared by both solution precipitation and by solid-state grinding. From solution, caffeine (4.85 g; 25.0 mmol) and maleic acid (1.12 g; 0.5 eq) were dissolved in 7:2 (v:v) chloroform/methanol (90 mL) by heating to reflux. The solution was concentrated in vacuo until precipitation commenced. Crystals were isolated by filtration. Cocrystals were also prepared by grinding  $\beta$ -caffeine (0.38 g; 2.0 mmol) and oxalic acid (0.89 g; 0.5 eq) for 60 min. A single crystal for XRD analysis was obtained by slow evaporation of a chloroform/methanol solution of dissolved cocrystal material.

**(c) Cocrystal B (2:1 Caffeine/Malonic Acid).** This material was prepared by solution and grinding techniques. Caffeine (1.43 g; 7.4 mmol) and malonic acid (0.38 g; 0.5 eq) were dissolved in 30:1 (v:v) chloroform/methanol (30 mL) and heated to reflux. The solution was then seeded (with single crystals as obtained below) and stirred at ambient temperature while permitting evaporation until precipitation commenced. This cocrystal material was also obtained by grinding caffeine (0.30 g; 1.5 mmol) and malonic acid (0.81 g; 0.5 eq) for 30 min. Single crystals were obtained by dissolving this material in chloroform/methanol and evaporating slowly at ambient conditions.

**(d) Cocrystal C (2:1 Caffeine/Maleic Acid).** Cocrystal material with minor  $\beta$ -caffeine content could be prepared by dissolving caffeine (2.42 g; 12.5 mmol) and maleic acid (0.73 g; 0.5 eq) in 8:1 (v:v) chloroform/methanol (17 mL) with heating to reflux, followed by seeding, and then prompt addition of *n*-hexane to effect sudden crystallization. Initial seeds of essentially phase-pure **C** material were obtained in small quantities by the removal of a small (ca. 1 mL) aliquot from a solution of caffeine (2.70 g; 13.9 mmol) and maleic acid (0.82 g; 0.5 eq) in 15:1 chloroform/methanol (32 mL), and the addition of cyclohexane (ca. 1 mL) to the aliquot to effect crystallization, followed by filtration. As an alternative to the solution-based approach, cocrystal powder of **C** with substan-

**Scheme 3. Molecules That Successfully Formed Cocrystals with Caffeine**

tial  $\beta$ -caffeine content was obtained by grinding caffeine (0.41 g; 2.1 mmol) and maleic acid (0.12 g; 0.5 eq) for 60 min. The 2:1 caffeine/maleic acid stoichiometry was confirmed by  $^1\text{H}$  NMR analysis of crystals filtered from solution. While the crystal structure of **C** was not successfully determined, X-ray diffraction from a single crystal at 180(2) K provided unit cell dimensions of  $a, b, c = 13.1356(5), 6.8750(3), 26.1807(12)$ ;  $\alpha, \beta, \gamma = 90, 97.739(3), 90$ ; volume =  $2342.77(17) \text{ \AA}^3$ . This unit cell volume agrees with the existence of eight caffeine molecules and four maleic acid molecules per unit cell.<sup>37</sup> The experimental PXRD pattern was indexed to similar unit cell parameters.

**(e) Cocrystal D (1:1 Caffeine/Maleic Acid).** **C** material, obtained by grinding, was dissolved in dichloromethane, and the solution was permitted to evaporate slowly to yield a single crystal of 1:1 stoichiometry, **D**. This is the only instance of solution precipitation of the **D** material. This cocrystal material could be prepared in bulk powder form by grinding caffeine (0.40 g; 2.1 mmol) and maleic acid (0.24 g; 1 eq) with the addition of methanol (5 drops from a pipet; ca. 0.06 mL) for 90 min.

**(f) Cocrystals E and F (1:1 Caffeine/Glutaric Acid Forms I and II, respectively).** Essentially pure form I was prepared by grinding caffeine (0.53 g; 2.7 mmol) and glutaric acid (0.63 g; 1 eq) with cyclohexane (5 drops from a pipet; ca. 0.06 mL) for 90 min. Essentially pure form II was prepared by grinding caffeine (0.51 g; 2.6 mmol) and glutaric acid (0.35 g; 1 eq) with chloroform (5 drops from a pipet; ca. 0.04 mL) for 90 min. Single crystals of form I (rods) and form II (blocks) were obtained concomitantly by slow evaporation of a chloroform solution of the starting components, in which there was a slight excess of caffeine.<sup>32</sup>

**General Methods.** RH conditions were achieved at ambient temperature (ca. 20 °C) within sealed glass desiccator jars containing  $\text{P}_2\text{O}_5$  for the 0% RH condition and the appropriate saturated aqueous salt solutions for other RH values ( $\text{K}_2\text{CO}_3$  for 43%; NaCl for 75%; and  $\text{K}_2\text{SO}_4$  for 98%).<sup>38</sup> RH conditions were monitored with humidity-indicator cards (Sigma-Aldrich Company).

To compare the stability of anhydrous caffeine to the various cocrystals produced, cocrystals **A** through **F** were evaluated along with anhydrous caffeine for physical stability at the conditions of 0, 43, 75, and 98% RH for time periods of 1 day, 3 days, 1 week, and 7 weeks. Cocrystal materials formed from solution (**A**, **B** and **C**) were ground gently with a mortar and pestle to homogenize the particle size to ca. 10–50  $\mu\text{m}$ , as observed by optical microscopy, before the experiment commenced. The cocrystal materials necessarily formed by solid-state grinding (**D**, **E** and **F**) were obtained as microcrystalline powders and were used as isolated. Open glass vials containing 40–60 mg of powdered cocrystal material were stored in the RH chambers at ambient temperature. A vial was removed for each cocrystal material at each time point. Upon removal from the chamber, the samples were promptly evaluated for any form change by PXRD.

Powder X-ray diffraction (PXRD) data was collected on a Philips X'Pert Pro diffractometer, using Ni-filtered  $\text{CuK}\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ ) at 40 kV and 40 mA with a X'Celerator RTMS detector. Each sample was analyzed between 4 and 40  $^\circ 2\theta$  with a step size of ca. 0.02  $^\circ 2\theta$  and a total scan time of 3 min 5 s. Experimental PXRD patterns were compared to PXRD patterns simulated from available crystal structures to confirm the composition of those materials.<sup>39</sup>

Fourier transform infrared (FT-IR) spectra were collected in the mid-IR region on crystalline powders with a Thermo Nicolet Nexus spectrometer equipped with a Smart Golden Gate Attenuated Total Reflection accessory.

Solid-state grinding was performed with a Retsch MM200 Mixer mill, equipped with stainless steel 10-mL grinding jars and two 7-mm stainless steel grinding balls per jar. All grinding was performed at a rate of 30 Hz. The temperature of the grinding jars following grinding experiments did not exceed ca. 30 °C.

Single-crystal X-ray diffraction data was collected at 180(2) K with a Nonius Kappa CCD diffractometer using  $\text{MoK}\alpha$  radiation ( $\lambda = 0.71073$ ) and equipped with an Oxford Cryosystems cryostream. Data reduction and cell refinement were performed with the programs *DENZO* (University of Texas, Southwestern Medical Center at Dallas, HKL Denzo and Scalepack, USA, 1997) and *COLLECT* (Nonius, B. V. Delft, The Netherlands, 1998). Multiscan absorption corrections were applied with the program *SORTAV*.<sup>40</sup> Structures were solved by direct methods using *SHELXS-97* (University of Göttingen, Germany, 1997) and refined on  $F^2$  against all data using *SHELXL-97* (University of Göttingen, Germany, 1997). All non-hydrogen atoms were refined with anisotropic displacement parameters. The OH hydrogen atoms were located in difference Fourier maps and refined isotropically. All other hydrogen atoms were placed geometrically and were allowed to ride during subsequent refinement. Experimental details of the structure determinations of **A–F** are given in Table 1.

**Results and Discussion**

**Cocrystal Structure Analysis.** In examining the caffeine/acid materials, the matter of locating the acidic proton was of significance, as it differentiated between salts (ionic complexes) and cocrystals (neutral complexes). For each of the crystal structures obtained, acidic protons were located on the acid in the X-ray difference maps, which confirmed in each case that salt formation (ionization) had not occurred. Typical O–H bond distances were observed in all instances.<sup>41</sup> It is also noted that ambient temperature FT-IR spectra of each powder sample exhibited a broad peak ranging from ca. 2200 to 2800  $\text{cm}^{-1}$ , interpreted as the O–H stretching modes of un-ionized, strongly hydrogen-bonded carboxylic acids.<sup>26</sup> The lack of a band associated with a symmetric carboxylate stretch, which typically would be observed from ca. 1300 to 1420  $\text{cm}^{-1}$ , is further indication of the nonionic character of these complexes.

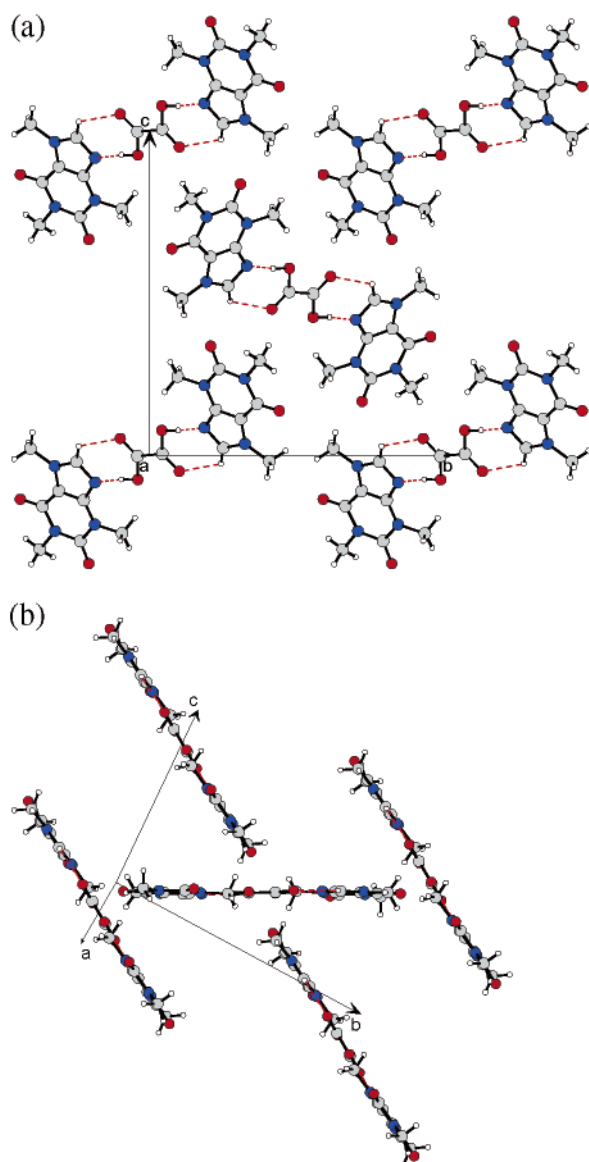
A stoichiometry of 2:1 caffeine/acid is observed for **A** and **B** from the solved crystal structures, and for **C** from  $^1\text{H}$  NMR. The expected heteromeric synthon (Scheme 1) is observed in the crystal structures of **A** and **B**. Further, the trimeric caffeine–acid–caffeine motif (Scheme 2) is also demonstrated in both structures. However, the varied geometries of oxalic and malonic acids necessitate differences in crystal packing.

Cocrystal **A**, which crystallizes in the  $P2_1/c$  space group, has the highest calculated density (1.542  $\text{g cm}^{-3}$ ) of all the solved cocrystal structures. The planarity of the oxalic acid molecule allows a flat trimeric motif to stack along the  $a$  axis (Figure 1a). If the trimeric units are considered to be “dumbbell-shaped,” whereby the acid is the “handle” and the bulky caffeine are the “weights,” then it can be noted that these units best fill space on  $(h, 0, 0)$  by placing the end of one weight

**Table 1.** Crystallographic Data for Caffeine Cocrystals

|  | A 2:1 caffeine/<br>oxalic acid  | B 2:1 caffeine/<br>malonic acid   | D 1:1 caffeine/<br>maleic acid   | E <sup>32</sup> 1:1 caffeine/<br>glutaric acid form I  | F <sup>32</sup> 1:1 caffeine/<br>glutaric acid form II   |
|--|---|---|--|--|--|
| experimental formula                       | 2(C <sub>8</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> )·<br>C <sub>2</sub> H <sub>2</sub> O <sub>4</sub> | 2(C <sub>8</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> )·<br>C <sub>3</sub> H <sub>4</sub> O <sub>4</sub> | C <sub>8</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> ·<br>C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> | C <sub>8</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> ·<br>C <sub>5</sub> H <sub>8</sub> O <sub>4</sub> | C <sub>8</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> ·<br>C <sub>5</sub> H <sub>8</sub> O <sub>4</sub> |
| formula weight                             | 478.44  | 492.46  | 310.27   | 326.31   | 326.31   |
| crystal system                             | monoclinic  | orthorhombic  | monoclinic   | monoclinic   | triclinic  |
| space group                                | <i>P</i> 2 <sub>1</sub> / <i>c</i>  | <i>F</i> dd2  | <i>P</i> 2 <sub>1</sub> / <i>n</i>   | <i>P</i> 2 <sub>1</sub> / <i>c</i>   | <i>P</i> $\bar{1}$   |
| <i>a</i> (Å)                               | 4.41430(10)   | 30.3992(12)   | 6.8565(2)  | 13.0129(5)   | 8.3212(8)  |
| <i>b</i> (Å)                               | 14.7701(5)  | 31.2845(16)   | 12.5051(4)   | 6.6017(2)  | 8.6667(8)  |
| <i>c</i> (Å)                               | 15.9119(6)  | 4.6739(2)   | 15.8362(5)   | 17.1427(8)   | 11.3636(12)  |
| $\alpha$ (deg)                             | 90  | 90  | 90   | 90   | 68.955(4)  |
| $\beta$ (deg)                              | 96.4850(10)   | 90  | 93.6100(10)  | 97.8360(10)  | 78.559(4)  |
| $\gamma$ (deg)                             | 90  | 90  | 90   | 90   | 74.236(4)  |
| <i>V</i> (Å <sup>3</sup> )                 | 1030.81(6)  | 4445.0(3)   | 1355.12(7)   | 1458.93(10)  | 731.43(12)   |
| <i>Z</i>                                   | 2   | 8   | 4  | 4  | 2  |
| $\theta$ range (deg)                       | 3.78–27.46  | 3.74–27.45  | 3.56–27.48   | 1.58–27.5  | 3.69–27.47   |
| data/restraints/parameters                 | 2354/0/161  | 1413/1/168  | 3093/2/208   | 3343/2/217   | 3094/0/217   |
| $\rho_{\text{calc}}$ (g cm <sup>-3</sup> ) | 1.541   | 1.472   | 1.521  | 1.486  | 1.482  |
| <i>T</i> (K)                               | 180(2)  | 180(2)  | 180(2)   | 180(2)   | 180(2)   |
| R1   | 0.0462  | 0.0425  | 0.0437   | 0.0645   | 0.0581   |
| wR2  | 0.1162  | 0.0855  | 0.0962   | 0.1870   | 0.1592   |

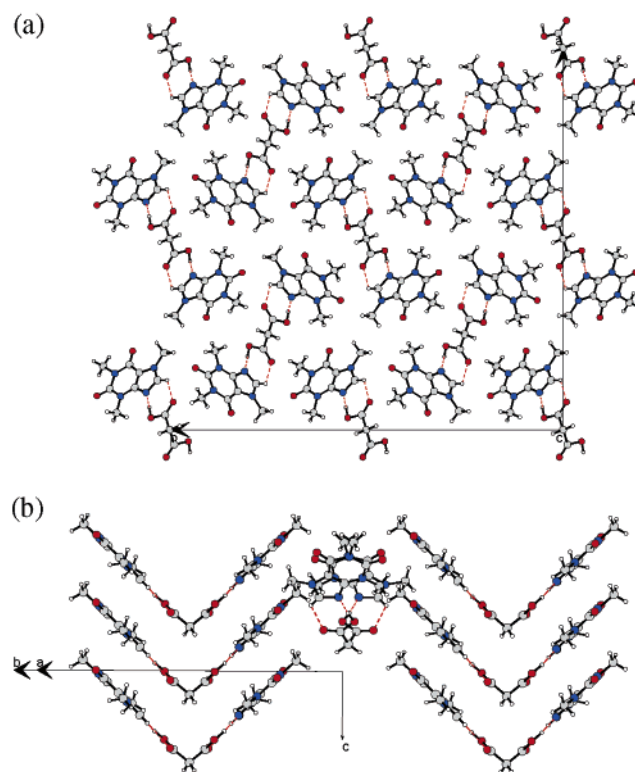
adjacent to a neighboring handle. An angling of the stacks with respect to one another appears necessary to achieve a close-packed arrangement (Figure 1b).



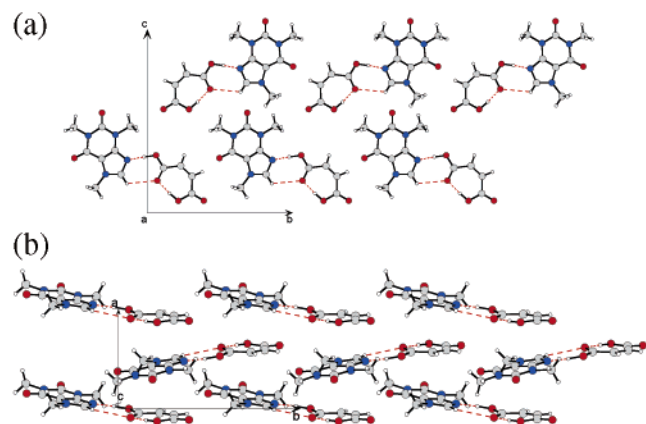
**Figure 1.** Crystal packing of **A**, showing (a) stacks of planar trimeric units along the *a* axis, and (b) an angling of the trimeric units with respect to one another.

Cocrystal **B** crystallizes in the orthorhombic *F*dd2 space group, with a calculated crystal density of 1.472 g cm<sup>-3</sup>. Like **A**, this cocrystal also possesses stacks of trimeric intermolecular hydrogen-bonded units, whereby the weights and handles interdigitate as before (Figure 2a). However, the central *sp*<sup>3</sup> carbon of malonic acid imposes a V-shaped geometry to the trimeric unit, so that the motif may be better described as a kinked dumbbell. As a result, packing is significantly different from **A** (Figure 2b). The stacks of V-shaped trimeric units fill space by a 90° rotation of each successive stack to allow interdigitation.

The 1:1 caffeine/acid stoichiometry was observed for **D**, **E**, and **F**. In each of these cocrystals, the Scheme 1 heteromeric synthon was observed with only one of the



**Figure 2.** 2:1 Caffeine/malonic acid crystal packing, showing (a) stacks of trimeric units as viewed down the *c* axis, and (b) V-shaped geometry of the interdigitated trimeric units.



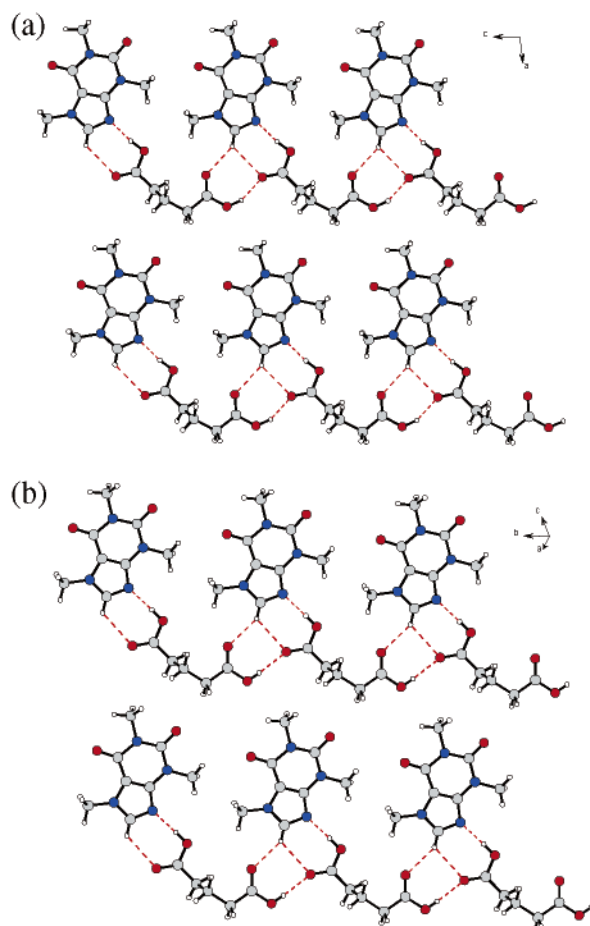
**Figure 3.** Cocystal **D** showing (a) sheets of dimeric hydrogen-bonded units and (b) angled vertical stacks of dimeric units.

two carboxyl groups of each dicarboxylic acid. The other carboxyl group formed a hydrogen bond to another carboxyl group. This implies that in these cocrystals the hydrogen bond acceptor ability of the caffeine imidazole nitrogen did not successfully compete with that of a carboxyl group in dictating the hydrogen-bonding preference of the second carboxyl of each acid.

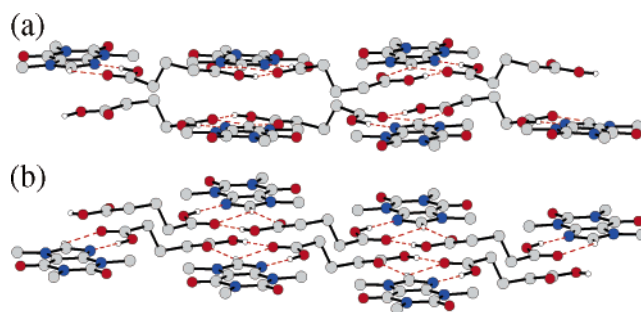
It is important to note that the caffeine/maleic acid cocrystal exists in both 2:1 and 1:1 stoichiometries (**C** and **D**); however, the crystal structure of **C** was not determined. It is perhaps not surprising to find a 1:1 stoichiometry involving maleic acid. A *cis* orientation of the carboxyl groups about the double bond predisposes maleic acid to form intramolecular  $S_1^1(7)$  hydrogen-bonded rings, as evidenced in its reported crystal structure (CSD Refcode MALIAC11)<sup>42</sup> and in a recently determined polymorph.<sup>43</sup> The crystal structure of **D** indeed validates this intramolecular hydrogen-bond preference. The structure packs in the space group  $P2_1/n$  with a relatively high calculated density of  $1.521 \text{ g cm}^{-3}$ . Dimeric caffeine–acid units are formed by the expected Scheme 1 hydrogen-bonded interaction. These units form two-dimensional sheets in the *bc* plane by translation and  $2_1$ -screw axis symmetry (Figure 3a). The units are propagated in the *a* axis direction via the *n* glide plane (Figure 3b)

The two caffeine/glutaric acid polymorphs **E** and **F** exhibit a similar hydrogen-bonded interaction to that of **D**, in that the Scheme 1 interaction occurs with one of the two carboxyl groups (Figure 4). The 1:1 stoichiometry may have resulted from the very weak acidity of the second carboxyl group of glutaric acid: the potential acid–base interaction between caffeine and glutaric acid was sufficiently weak that a hydrogen bond to another carboxylic oxygen was more favorable than a bond to the caffeine imidazole nitrogen. The two different structures of caffeine/glutaric acid are in fact conformational polymorphs,<sup>44</sup> differing in the torsion of the glutaric acid aliphatic chain (Figure 5).

**Cocystal Preparation by Grinding.** It was generally possible to prepare most cocrystals by the dual methods of solution growth and solid-state grinding, but the exceptions are of interest. Polymorphs **E** and **F** precipitated concomitantly from solution in our experiments. As described previously,<sup>32</sup> solvent-drop grinding enabled the preparation of essentially pure samples of both of these polymorphs. For this study, the solvent-



**Figure 4.** Sheets of caffeine:glutaric acid ribbons showing identical packing in projection of the two conformational polymorphs: (a) **E** (b) **F**.

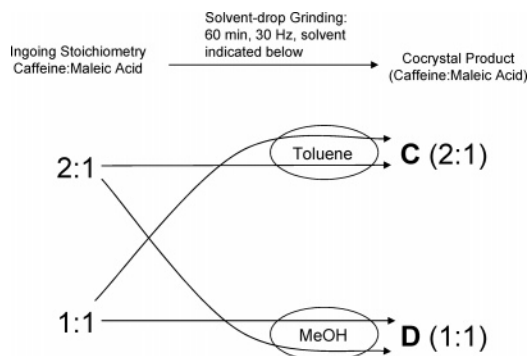


**Figure 5.** Stacked ribbons of caffeine:glutaric acid cocrystal polymorphs illustrating conformational differences in glutaric acid torsions: (a) **E** (b) **F**.

drop grinding approach was performed with cyclohexane and chloroform to prepare **E** and **F**, respectively.

The stoichiometric competition between the two caffeine:maleic acid cocrystals **C** and **D** also resulted in interesting crystallization behavior. Aside from the one instance in which a single crystal was obtained of **D**, solution growth never yielded the 1:1 stoichiometry in this system. Neat grinding of caffeine and maleic acid in a 2:1 ratio produced mostly **C** with residual unreacted material apparent by PXRD. Neat grinding of a 1:1 ratio of caffeine and maleic acid produced a mixture of **C** and **D** cocrystals. Thus, a bulk quantity of essentially pure **D** could not be prepared by traditional solution or dry grinding methods.

#### Scheme 4. Summary of Caffeine/Maleic Acid Stoichiometry Control via Solvent-Drop Grinding

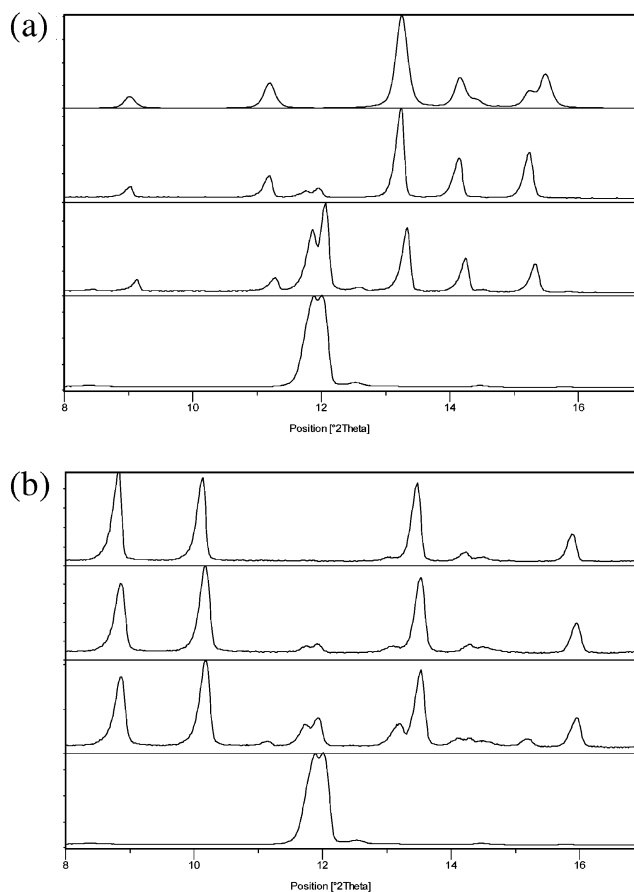


The solvent-drop grinding method was investigated as a potential means of obtaining pure **D**. Upon addition of several drops of methanol to the 1:1 ingoing mixture, the resulting product from grinding was predominantly **D**, with a slight component of unreacted starting materials and no **C** material observable by PXRD. It is noted that methanol addition provides a significant preference for **D** formation: grinding of an ingoing 2:1 caffeine/maleic acid ratio with methanol addition produces **D** with excess caffeine without any evidence of **C**, the 2:1 product, by PXRD.

Just as methanol favors **D** upon grinding, toluene appears to favor **C**. Solvent-drop grinding of ingoing 1:1 material with toluene provides **C** with excess maleic acid and some unreacted residual caffeine as a minor component. Additionally, solvent-drop grinding of ingoing 2:1 material with toluene provides **C** with some unreacted material, mimicking the results of neat (solvent-free) grinding. These results are summarized diagrammatically in Scheme 4, and PXRD data are presented in Figure 6. While the mechanism underlying this phenomenon has not yet been fully explained, it was employed to generate nearly phase-pure **D** material for use in the RH stability study.

It should be noted that not all the dicarboxylic acids that were attempted successfully formed cocrystals with caffeine. When screened for cocrystallization by the grinding method, the following three pharmaceutically acceptable dicarboxylic acids were determined to be unsuccessful cocrystallizing agents with caffeine: fumaric acid, L-tartaric acid, and adipic acid. Further, a cocrystal involving caffeine and succinic acid was isolated from solution, but due to significant physical instability resulting from weakly bound solvent of crystallization, it was not included in this study.

**Relative Humidity Challenges.** The RH stability results of caffeine and of each cocrystal are described in turn below and are summarized diagrammatically in Table 2. Analysis of powders by PXRD provided an effective means of analyzing the different cocrystals (Figure 7). Generally, it is noted that cocrystal hydrates were not formed from any of these cocrystals. Rather, the materials that possessed instability with respect to RH demonstrated dissociation of the cocrystal into its crystalline starting components, as observed by PXRD. The exception to this was one case of polymorph conversion seen from **E** to **F**. Dissociation at high RH (75 and 98%) was apparent from the emergence of crystalline caffeine hydrate peaks by PXRD; dissociation



**Figure 6.** PXRD patterns of results from caffeine:maleic acid solvent-drop grinding: (a) from top to bottom: simulated pattern of **D**; result from grinding an ingoing 1:1 mixture with methanol; result from grinding an ingoing 2:1 mixture with methanol; anhydrous  $\beta$ -caffeine; and (b) from top to bottom: pattern of **C** from solution precipitation; result from grinding an ingoing 1:1 mixture with toluene; result from grinding an ingoing 2:1 mixture with toluene; anhydrous  $\beta$ -caffeine. Patterns plotted in units of relative intensity.

at low RH (0 and 43%) was observed by the growth of crystalline anhydrous caffeine peaks. Acid peaks were less evident in the dissociated product.

**(a) Anhydrous  $\beta$ -Caffeine.** Crystalline anhydrous caffeine was stored in humidity chambers alongside the cocrystal materials. At 98% RH, caffeine showed partial conversion to the hydrate after 1 day and full conversion after 3 days and beyond. Interestingly, no hydration was apparent at 75% RH or below at seven weeks. The difference between this observed hydration behavior of anhydrous caffeine and the reported dehydration boundary of caffeine hydrate (61% RH)<sup>14</sup> may reflect the physical differences between the solid-state processes of hydration and dehydration. It is also possible that a hydration/dehydration hysteresis, as has been observed elsewhere,<sup>45,46</sup> may have had a kinetic influence on the transition.

**(b) Cocrystal A.** This material was found to be stable at all relative humidities across all time points. This cocrystal clearly demonstrates enhanced stability over anhydrous caffeine. Its stability was additionally demonstrated by slurrying the cocrystal material in water for 2 days at ambient temperature without any observed physical form change.

**Table 2. Stability of Cocrystals with Respect to RH**

| Material | Condition (% RH) | Observed Relative Humidity Stability* |        |        |         |
|----------|------------------|---------------------------------------|--------|--------|---------|
|          |                  | 1 day                                 | 3 days | 1 week | 7 weeks |
| Caffeine | 0                | ✓                                     | ✓      | ✓      | ✓       |
|          | 43               | ✓                                     | ✓      | ✓      | ✓       |
|          | 75               | ✓                                     | ✓      | ✓      | ✓       |
|          | 98               | ✗                                     | ✗      | ✗      | ✗       |
| A        | 0                | ✓                                     | ✓      | ✓      | ✓       |
|          | 43               | ✓                                     | ✓      | ✓      | ✓       |
|          | 75               | ✓                                     | ✓      | ✓      | ✓       |
|          | 98               | ✓                                     | ✓      | ✓      | ✓       |
| B        | 0                | ✓                                     | ✓      | ✓      | ✓       |
|          | 43               | ✓                                     | ✓      | ✓      | ✓       |
|          | 75               | ✓                                     | ✓      | ✓      | ✓       |
|          | 98               | ✓                                     | ✓      | ✓      | ✗       |
| C        | 0                | ✓                                     | ✓      | ✓      | ✓       |
|          | 43               | ✓                                     | ✓      | ✓      | ✓       |
|          | 75               | ✓                                     | ✓      | ✓      | ✓       |
|          | 98               | ✗                                     | ✗      | ✗      | ✗       |
| D        | 0                | ✓                                     | ✓      | ✓      | ✓       |
|          | 43               | ✓                                     | ✓      | ✓      | ✓       |
|          | 75               | ✓                                     | ✓      | ✓      | ✓       |
|          | 98               | ✗                                     | ✗      | ✗      | ✗       |
| E        | 0                | ✓                                     | ✓      | ✓      | ✓       |
|          | 43               | ✓                                     | ✗      | ✗      | ✗       |
|          | 75               | ✗                                     | ✗      | ✗      | ✗       |
|          | 98               | ✗                                     | ✗      | ✗      | ✗       |
| F        | 0                | ✓                                     | ✓      | ✓      | ✓       |
|          | 43               | ✓                                     | ✓      | ✓      | ✓       |
|          | 75               | ✓                                     | ✓      | ✓      | ✓       |
|          | 98               | ✓                                     | ✓      | ✗      | ✗       |

\*Note: The symbol ✓ indicates that the crystalline material was stable at that condition and time point. The symbol ✗ indicates that the crystalline material exhibited physical instability at that time point: caffeine converted to caffeine hydrate; cocrystals B, C, D and F dissociated into molecular components; and cocrystal E was observed in some instances to convert to polymorph F before dissociating. See text for details.

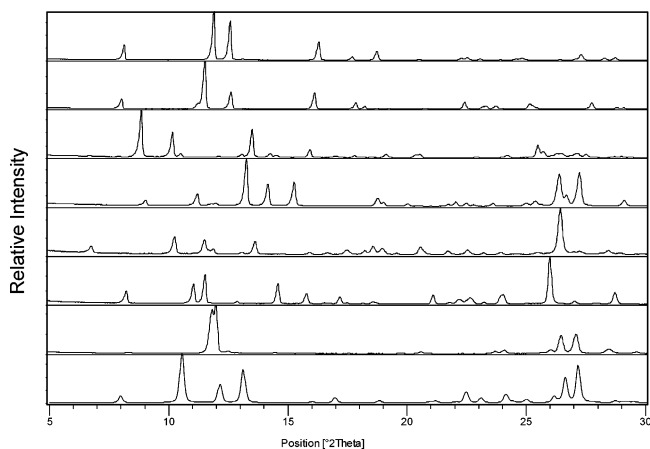
(c) **Cocrystal B.** This material was stable at 75% RH and below for the duration of the study. At 98% RH, however, **B** showed evidence of partial dissociation at 1 week, as seen by growth of peaks associated with crystalline caffeine hydrate. At 7 weeks, this material had deliquesced to a liquid.

(d) **Cocrystal C.** This material was stable at 75% RH and below for the duration of the study. Similar to the malonic acid cocrystal material, this cocrystal also demonstrated instability at 98% RH. At just 1 day at this RH condition, crystalline caffeine hydrate was observed by PXRD.

(e) **Cocrystal D.** The 1:1 cocrystal stoichiometry of **D** exhibited identical RH stability to the 2:1 material of **C**. It was stable at 75% RH and below for 7 weeks, and exhibited complete dissociation at 1 day at 98% RH.

(f) **Cocrystal E.** This cocrystal material demonstrated a tendency for conversion to **F**, the form II polymorph of the caffeine/glutaric acid system. The only storage condition at which **E** showed stability across all time points was 0% RH. Cocrystal **E** showed partial conversion to **F** at 1 day at 43% RH and full conversion to **F** at 43% RH, 3 days. At 75% RH **E** converted to **F** after 1 day. Cocrystal **E** at 98% RH converted by 1 day to **F** with some evidence of minor dissociation to caffeine hydrate. At one week, the 98% RH sample was predominantly caffeine hydrate by PXRD, and by 7 weeks the material had deliquesced. The stability of this material following polymorph conversion to **F** agreed with the RH stability observations of **F**, below.

(g) **Cocrystal F.** Of the two 1:1 caffeine/glutaric acid polymorphs that were analyzed, **F** was found to be more



**Figure 7.** PXRD patterns of caffeine cocrystals, from top to bottom: simulated pattern of **A**; simulated pattern of **B**; experimental pattern of **C**; simulated pattern of **D**; simulated pattern of **E**; simulated pattern of **F**; experimental pattern of anhydrous caffeine; simulated pattern of caffeine hydrate.

stable with regard to humidity. Cocrystal **F** remained unchanged at 75% RH and below for 7 weeks. At 98% RH, it showed a minor caffeine hydrate component at 1 day. This conversion was nearly complete by 1 week, and the material had deliquesced by 7 weeks.

In considering the RH stability of the caffeine cocrystals, it is clear that **A** was most stable, while **E** was least stable. Intermediate in stability were **C** and **D**, which had dissociated at 98% RH by 1 day, and **B** and **F**, which persisted at 98% RH for 7 and 3 days, respectively. An ordering of the stability of these intermediate cocrystals was not performed because the kinetic differences in stability at 98% RH may have been influenced by minor phase impurity or by variation in sample particle size, neither of which was rigorously controlled in this study. The overall cocrystal RH stability trend may thus be summarized as  $A > B \approx C \approx D \approx F > E$ . It is noted that the strongest acid employed, oxalic acid, produced the most stable caffeine cocrystal (**A**), while the weakest acid of the group, glutaric acid, produced the least stable cocrystal (**E**). However, from the fact that cocrystal **F**, a polymorph of **E**, demonstrated intermediate stability, it is clear that acid  $pK_a$  is not the only factor dictating cocrystal stability.

In the current study, it has been possible to design a series of caffeine cocrystals, which could then be evaluated for their RH stability. A remarkable variation in RH stability was observed across the series. It was found in this study that no cocrystal hydrates were produced by exposure of the caffeine cocrystals to high humidity. This lack of cocrystal hydrate formation could potentially be characteristic of cocrystals in general. One driving force for the formation of cocrystals is presumably the introduction of additional stabilization by hydrogen bonding, which may mean that fewer unsatisfied hydrogen bond donors or acceptors exist in cocrystals. As such, cocrystals may exhibit a reduced tendency for hydration. In the case of caffeine, the introduction of a carboxylic acid as a hydrogen bond donor for the basic imidazole nitrogen seems to prevent the incorporation of lattice water into the cocrystal.

## Conclusion

A series of cocrystals of the model pharmaceutical compound caffeine with dicarboxylic acids has been described. Cocrystals were formed in 2:1 and 1:1 caffeine/acid stoichiometries by the methods of solution precipitation and solid-state grinding. In some cases, solid-state grinding with the addition of a minor quantity of solvent afforded bulk cocrystal material that could not be produced by precipitation from solution.

The RH stability profile of these cocrystals differed from pure crystalline caffeine, in that no cocrystal hydrates have been found; rather, the cocrystals that were unstable with respect to RH generally exhibited dissociation into crystalline starting components. One humidity-induced cocrystal polymorphic transition was also observed. One cocrystal was stable at all relative humidities and for all time points, and thereby clearly demonstrated superior stability to anhydrous caffeine. Several other cocrystals demonstrated approximate stability to that of caffeine, whereby they were unstable at high RH but stable at lower RH.

The goal of pharmaceutical cocrystallization is to engineer pharmaceutical cocrystals with specific improved properties. While strategies for the design of pharmaceutical cocrystals appear to be growing increasingly rational and successful, the subject of property control has been largely latent. At least in the context of pharmaceuticals, crystal structure engineering is evidenced, while crystal property engineering has yet to fully emerge. It was the aim of this study to design a series of pharmaceutical cocrystals and measure the resultant change of a targeted physical property. Present work is focused on understanding the observed trend of RH stability of this series, with an aim toward predicting such properties in the future.

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**Supporting Information Available:** X-ray crystallographic information files (CIF) are available for cocrystals **A**, **B**, **C**, **E** and **F**. The list of refcodes resulting from the CSD search for the Scheme 1 synthon is available in Excel file format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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