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1 Coformer Replacement as an Indicator for
2 Thermodynamic Instability of Cocrystals:
3 Competitive Transformation of
4 Caffeine:Dicarboxylic Acid

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11
12 **ABSTRACT:** The thermodynamic stability of caffeine (CA) cocrystals with dicarboxylic acids
13 (DAs) as coformers was investigated in the presence of a range of structurally related
14 dicarboxylic acids (SRDs). Two experimental conditions (slurry and dry-grinding) were studied
15 for mixing the cocrystal and the SRD additive. The additives oxalic, malonic and glutaric acid
16 led to the replacement of the acid coformer for certain cocrystals. Interestingly, a change in
17 stoichiometry was observed for the CA: maleic acid system. A stability order among the

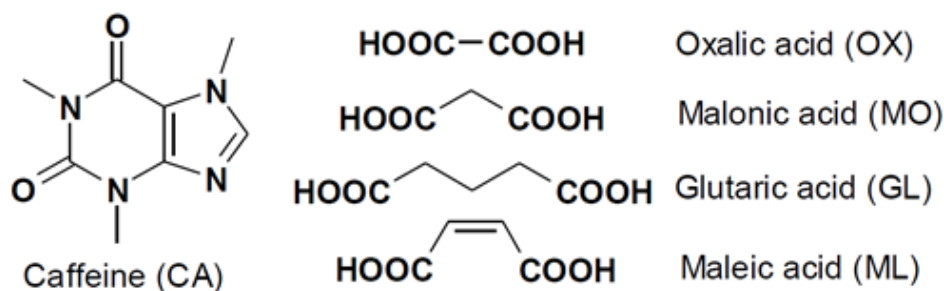
18 cocrystals was established depending on their tendency to replace the coformer. To understand
19 the factors controlling the relative stabilities, lattice energies were calculated using dispersion
20 corrected Density Functional Theory (DFT). Gibbs free energy changes were calculated from
21 experimental solubilities. The observed stability order corroborated well with lattice energy and
22 Gibbs free energy computations.

23 Cocrystal systems are increasingly being considered for many industrial applications including
24 explosives,¹ semiconductors,² pigments,³ and pharmaceuticals.⁴ Recently, the FDA approved the
25 valsartan:sacubitril cocrystal Entresto™ as a dosage form in the treatment of heart failure.⁴ In the
26 last decade there have been reports about the development of innovative technologies for the
27 manufacture and formulation of cocrystals.^{5,6} To obtain a successful pharmaceutical cocrystal
28 product, it is crucial to understand cocrystal behavior during manufacturing, storage, and
29 administration as cocrystals can undergo different types of structural changes. Recent reports
30 suggested that solvent mediated transformations such as dissociation,⁷ polymorphism,⁸ and
31 solvation⁹ are mainly due to a large solubility^{7,10} or a small pKa^{11,12} difference between the
32 molecules involved in cocrystallization. Notably, solvent-free thermal or shear force
33 mediated^{13,14} transformations that include stoichiometric conversion¹⁵ have been reported which
34 were ascribed to the energy differences between the cocrystal and the individual components.^{15,16}
35 The stability issue in formulations is further complicated due to the presence of additives. Caira
36 et al. have reported selective formation of sulfonamide cocrystals with some aromatic carboxylic
37 acids and demonstrated the role of hydrogen bonding in such preferential cocrystal formation.¹⁷
38 Fischer et al. studied a set of cocrystal competitive grinding reactions and inferred the role of
39 kinetic factors.¹⁸ Similarly, the affinity of aminobenzonitrile isomers with a 1,1,6,6-
40 tetraphenylhexa-2,4-diyne-1,6-diol host molecule was also assessed experimentally and

41 mathematically by calculating lattice energies for the isomers using an atom-atom potential
42 method.¹⁹

43 Here we report the effect of structurally related dicarboxylic acid (SRD) additives on the
44 stability of cocrystals. The stabilities of caffeine (CA) and dicarboxylic acid (DA) cocrystals are
45 determined in the presence of SRDs, which are hypothesized to compete with the DA cofomers
46 and could potentially impact the integrity of the cocrystals. The outcomes of this study provide
47 important input to formulators as the presence of structurally related components is routinely
48 seen in complex and multi-component formulations. To understand such competitive
49 transformations further, we utilized and compared two methods for predicting whether a system
50 is stable or not. The first method calculates lattice energies after optimizing known crystal
51 structures determined from single crystal X-ray diffraction, using Density Functional Theory.^{20,21}
52 The second method calculates cocrystal stability from the Gibbs free energy change determined
53 from experimental solubilities.^{22,23}

54 The selected cocrystals consist of CA with the DAs, oxalic acid (OX), malonic acid (MO),
55 glutaric acid (GL), and maleic acid (ML) (Scheme 1). Cocrystals; CA:OX 2:1 (A), CA:MO 2:1
56 (B), CA:GL 1:1 FII (C), CA:GL 1:1 FI (D), CA:ML 1:1 (E), and CA:ML 2:1 (F) were prepared
57 by solution crystallization (see also Supporting information, SI).



59 **Scheme 1. Molecular structures of caffeine and cofomers**

60 The intermolecular hydrogen bonding motif between CA and DAs is the same in all
61 cocrystals.¹¹ CA:DA – SRD binary mixtures were prepared with sufficient SRD to form a
62 cocrystal. Mixtures were split into two lots, the first was transferred to slurries (for aqueous
63 processing) and the second was used for dry grinding (mechanical processing).

64 The aim was to mimic typical formulation processes such as wet granulation, drying, milling,
65 or storage. CA:DAs without SRDs were subjected to aqueous processing and mechanical
66 processing to analyze the effect of processing alone. Structural analysis was performed by
67 powder X-ray diffraction (PXRD). Thermogravimetric analysis (TGA) was used to determine the
68 solvent content of all binary mixtures before subjecting them to mechanical processing (see SI).

69 The results are summarized in Table 1. Slurry processing revealed that most of the cocrystals
70 undergo coformer replacement in the presence of SRDs. In addition, the presence of ML with **F**
71 caused a change in stoichiometry and the formation of **E**. For cocrystals processed without SRD
72 (NA samples), no change in cocrystal composition was observed except for **F** and **D** where
73 dissociation and polymorph transformation into **C** occurred, respectively. The stability order,
74 based on the ability of the cocrystal to withstand replacement of its original coformer or any
75 other transformation, was; **A > B > C > E > F ≈ D**. The stability order obtained by dry grinding
76 was **A > B > C ≈ E > F > D**, which is similar to the order obtained with slurry processing.
77 Figures 1 and 2 show the PXRD patterns of **C** and **F** after aqueous processing in the presence of
78 SRD. The PXRD patterns of the other cocrystals after aqueous processing and mechanical
79 processing are provided in the SI.

80

81

82

Table 1. Results of mixing SRD with CA:DA cocrystals using slurry and dry grinding (DG)

| SRD | CA:DA | Slurry | DG | CA:DA | Slurry | DG | CA:DA | Slurry | DG |
|-------------------|----------|----------|----------|----------|----------|----------|----------|---------------------------|----------|
| OX | | A | A | | A | A | | A | A |
| MO | | A | A | | B | B | | B | B |
| GL | A | A | A | B | B | B | C | C | C |
| ML | | A | A | | B | B | | C | C |
| NA ^[a] | | A | A | | B | B | | C | C |
| OX | | A | A | | A | A | | A | A |
| MO | | B | B | | B | B | | B | B |
| GL | D | C | C | E | C | E | F | C | C |
| ML | | C | C | | E | E | | E | E |
| NA ^[a] | | C | C | | E | E | | CA ML ^[b] + | F |

[a] Cocrystals processed without SRD. [b] Cocrystal dissociated into its native components. For ready reference, cocrystals, **A** = CA:OX 2:1, **B** = CA:MO 2:1, **C** = CA:GL 1:1 FII, **D** = CA:GL 1:1 FI, **E** = CA:ML 1:1 and **F** = CA:ML 2:1.

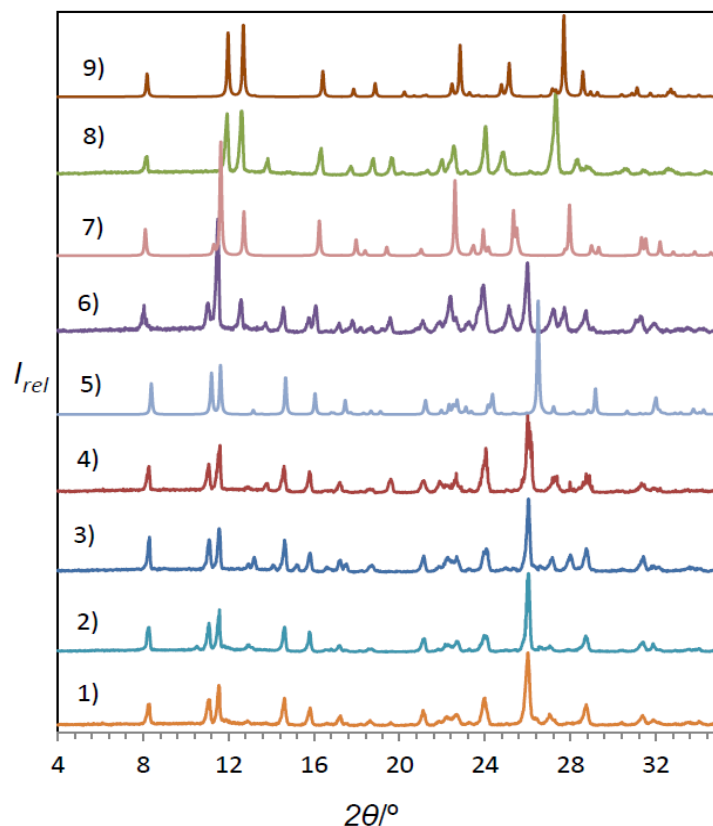
83 The results (Table 1) suggest that for certain mixtures the presence of an SRD led to the
 84 replacement of the original coformer of the cocrystal by the SRD, which we refer to as coformer
 85 replacement.

86 To better understand the process of coformer replacement, consider the following equilibrium;

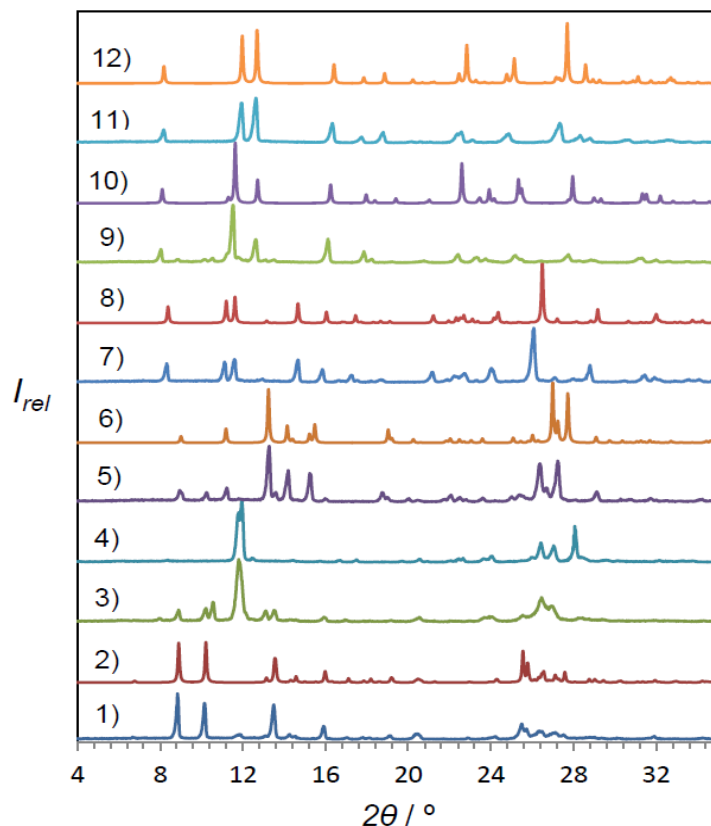


88 Where X_aY_b is the starting cocrystal, Z is the additive, X_aZ_c is the cocrystal after coformer
 89 replacement, Y is the coformer replaced by the additive and a , b and c are numbers of molecules.

90 A negative value of ΔG for the equilibrium indicates that the cocrystal containing the new
91 coformer is thermodynamically more stable than the original cocrystal, i.e., the reaction favors
92 coformer replacement. The current study has explored two methods to calculate energy changes
93 for replacement reactions. The first involves DFT calculations and the second uses experimental
94 equilibrium solubility data.



95
96 **Figure 1.** PXR D patterns for C after aqueous processing in the presence of SRDs 1) exp^[a] C, 2)
97 C slurry, 3) C + ML slurry, 4) C + GL slurry, 5) sim^[b] C + ML slurry, 6) C + MO slurry, 7) sim
98 B, 8) C + OX slurry, and 9) sim A. [a]: experimental, [b]: simulated.



99

100 **Figure 2.** PXRD patterns for F after aqueous processing in the presence of SRDs 1) exp[a] F, 2)
 101 sim[b] F, 3) F slurry, 4) CA+ML 2:1 physical mixture, 5) F + ML slurry, 6) sim E, 7) F + GL
 102 slurry, 8) sim C, 9) F + MO slurry, 10) sim B, 11) F + OX slurry, and 12) sim A. [a]:
 103 experimental, [b]: simulated.

104

105 The lattice energies of the cocrystals computed by a dispersion corrected DFT method (DFT-
 106 D, see SI) were used to estimate the relative stabilities of the cocrystals in the presence of SRDs
 107 using equation (2), where E(X) refers to the lattice energy of X:

$$108 \quad \Delta E = E(X_a Z_c) + b E(Y) - [E(X_a Y_b) + c E(Z)] \quad (2)$$

109 The second method for calculating the free energy change in the equilibrium (reaction 1) uses
 110 equation (3) which follows previous work.^{22,23} For details of derivations see the SI.

$$\Delta G_{\text{Re}}^{\circ} = -RT \ln \frac{K_{\text{sp}}^{\text{XY}} S_Z^c}{K_{\text{sp}}^{\text{XZ}} S_Y^b} \quad (3)$$

111 Where K_{sp} is the solubility product for the cocrystal and S is the equilibrium solubility of the
112 pure components. Four general replacement reactions are proposed;

113 Type 1: $XY + Z \rightleftharpoons XZ + Y$

114 Type 2: $X_2Y + Z \rightleftharpoons X_2Z + Y$

115 Type 3: $2XY + Z \rightleftharpoons X_2Z + 2Y$

116 Type 4: $X_2Y + Z \rightleftharpoons XZ + Y + X$

117 K_{sp} and S in water for CA cocrystals and their pure components were determined (Tables 2 and
118 3). The shaking flask method followed by HPLC analysis was used for measurements (see SI).
119 Results for A and E are presented in Table 4. The data for the rest of the cocrystals are listed in
120 the SI.

121 There is no correlation between pK_a or solubility difference and cocrystal tendency to
122 destabilize by coformer replacement (Table 5). Both were investigated by Trask and Jones¹¹ as
123 the CA:GL system exhibits two polymorphs having profoundly different durabilities at high
124 %RH levels.

125

Table 2. Aqueous solubilities, pH and pK_a values at 25 °C of saturated solutions of pure CA and DAs

| Material | S (mg/mL) | S (M) | pH | pK_a ¹¹ |
|----------|-----------|-------|-----|----------------------|
| CA | 20.32 | 0.10 | 2.6 | 3.6 |
| OX | 116.7 | 1.30 | 1.2 | 1.3 |
| MO | 741.5 | 7.13 | 0.5 | 2.8 |
| GL | 531.4 | 4.02 | 1.3 | 4.3 |
| ML | 389.1 | 3.35 | 1.1 | 1.8 |

Table 3. CA:DA solubilities, K_{sp} , and pH values of saturated solutions in water

| Cocrystal | Code | CA S ^[a] | DA S ^[a] | K_{sp} ^[b] | pH |
|-----------|----------|---------------------|---------------------|-------------------------|-----|
| CA:OX | A | 0.06 | 0.02 | 8.3E-05 | 1.8 |
| CA:MO | B | 0.16 | 0.38 | 9.2E-3 | 1.5 |
| CA:GL FII | C | 0.31 | 0.78 | 0.24 | 2.3 |
| CA:GL FI | D | 0.47 | 1.07- | – | – |
| CA:ML 1:1 | E | 0.30 | 0.38 | 0.15 | 1.5 |
| CA:ML 2:1 | F | 0.25 | 0.49 | – | – |

[a] Unit is M. [b] Unit is M^2 for 1:1 cocrystals and M^3 for 2:1 cocrystals. “–” Results could not be obtained due to experimental difficulties.

126 In the same way, we found that CA:ML has two stoichiometries with distinct stabilities.
127 Therefore, pK_a or solubility differences cannot explain the differences among polymorphs or
128 stoichiometries. Instead, thermodynamic parameters such as Gibbs free energies and lattice
129 energies show a robust relationship with experimental findings (Table 5).

130 The stability order obtained by the DFT-D calculations is **A** > **B** > **C** > **E** > **D** > **F**, which
131 follows the same trend as the stability order obtained by experimental methods. The stability
132 order obtained by ΔG_{Re}° calculations is **A** > **B** > **E** > **C** > **F** > **D**.

133 The differences between the slurry and dry grinding results indicate that mechanical processing
134 delivers lower energy than aqueous processing. Therefore, dry grinding may not reach the kinetic
135 barrier for some samples. This might explain why the replacement did not occur for **E** in the
136 presence of GL during mechanical processing whereas the coformer replacement did take place
137 during aqueous processing. Coformer replacement was easiest in **D** and **F**. However, the stability
138 order between the two systems is unclear as **D** converts to the more stable polymorph **C** if
139 slurried in the presence of ML instead of undergoing coformer replacement.

Table 4. Energy changes (kcal/mol) for coformer replacement reactions and cocrystal integrity observations whether replacement is taking place (√) or not (X) under slurry processing

| Starting Cocrystal | SRD | Result Cocrystal | ΔE | ΔG_{Ex}° | Replacement |
|-------------------------|-----|------------------|------------|-------------------------|-------------|
| B ^[b] | | | -5.79 | -7.50 | √ |
| C ^[c] | | | -6.62 | -10.06 | √ |
| D ^[c] | OX | A | -8.44 | – | √ |
| E ^[c] | | | -6.91 | -8.53 | √ |
| F ^[b] | | | -9.18 | – | √ |
| A ^[d] | | | 8.11 | 10.68 | X |
| B ^[d] | | | 2.32 | 3.18 | X |
| C ^[a] | ML | E | 0.15 | -0.76 | X |
| D ^[a] | | | -0.76 | – | X |
| F ^[d] | | | -1.07 | – | √ |

[a]: Reaction type 1, [b]: Type 2, [c]: Type 3, [d]: Type 4. “–” Results could not be obtained.

Table 5. CA:DAs stability orders for slurry, DFT method (ΔE_{Re}), solubility data method (ΔG_{Re}°), and stability relative to original components (ΔE_{Fo}) compared with S and pK_a difference, ΔS and ΔpK_a , respectively.

| CA:DA | Slurry | ΔE_{Re} | ΔG_{Re}° | ΔE_{Fo} | ΔS (M) | ΔpK_a |
|----------|--------|-----------------|-------------------------|-----------------|----------------|---------------|
| A | 1 | 1 | 1 | -9.3 | 1.20 | 2.3 |
| B | 2 | 2 | 2 | -3.5 | 7.03 | 0.8 |
| C | 3 | 3 | 4 | -1.3 | 3.92 | 0.7 |

| | | | | | | |
|----------|---|---|---|------|------|-----|
| D | 5 | 5 | – | -0.4 | 3.92 | 0.7 |
| E | 4 | 4 | 3 | -1.2 | 3.25 | 1.8 |
| F | 5 | 6 | – | -0.1 | 3.92 | 0.7 |

“–” Results could not be obtained.

140 This is supported by the lattice energy calculation results. The lattice energy change of **D**
 141 relative to its components (-0.4 kcal/mol, Table 2) is larger than for **F** (-0.1 kcal/mol). However,
 142 **C** is more stable (-1.3 kcal/mol). Moreover, the ΔE value of polymorph conversion from **D** to **C**
 143 (-0.91 kcal/mol, Table S6), is larger than the stability of **D**.

144 ΔG° values calculated using S data resulted in a stability order that is similar to both the
 145 experimental and the computational order, except that **E** and **F** are slightly more stable than **C**
 146 and **D**, respectively. This might be due to the fact that computational stability values (Table 5) of
 147 these systems are very similar; -1.3 and -1.2 kcal/mol for **C** and **E**, respectively, and -0.4 and -
 148 0.1 kcal/mol for **D** and **F**, respectively. Moreover, S values for **D** and **F** could not be reliably
 149 measured, therefore S and ΔG_{Re}° data is not mentioned (Tables 3 and 4).

150

151 In conclusion, the presence of a structurally similar additive during cocrystal destabilization,
 152 whether it is solvent or solvent free mediated, may have a profound effect on stability. Therefore,
 153 it is advisable to perform stability testing for the mixtures of cocrystal and additives to be
 154 formulated in a product. Lattice energy or Gibbs free energy calculations employing
 155 computational or solubility methods can predict the propensity of a cocrystal to destabilize,
 156 including cofomer replacement. Cofomer replacement of a given cocrystal can be deliberately
 157 stimulated to test the coherence of the cocrystal even for cofomers similar in binding strength.
 158 Both aqueous processing and mechanical processing involve components reaching a higher

159 energy level. Therefore, kinetic experiments, such as quantitative phase analysis, can be
160 performed to obtain a deeper knowledge about the mechanism.

161

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165 Dr. C. Malla Reddy for useful discussion about cocrystal stability.

166 ASSOCIATED CONTENT

167 **Supporting Information.** Cocrystal preparation, characterisation, experimental section,
168 Density Functional Theory method and further details, solubility determination and Gibbs free
169 energy calculations. This material is available free of charge via the Internet at
170 <http://pubs.acs.org>.

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180 **Author Contributions**

181 Alsirawan, Vangala and Paradkar have contributed with the idea, design and performing the
182 experimental work that includes slurry and grinding processes, Gibbs free energy calculations,
183 and write up of a manuscript. Kendrick and Leusen have performed DFT computations and
184 contributed in a manuscript preparation.

185 **ABBREVIATIONS**

186 HPLC, High performance liquid chromatography; DFT, Density functional theory; S, solubility;
187 SC, solution crystallization.

188

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For Table of Contents Use Only and Synopsis

229

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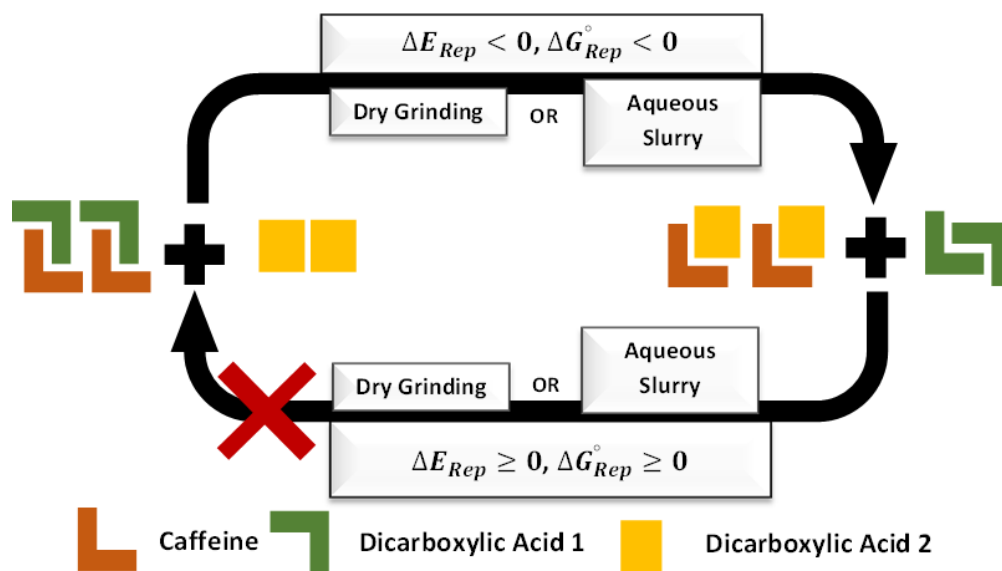
Transformation of Caffeine:Dicarboxylic Acid

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The thermodynamic stability of caffeine cocrystals is investigated by slurry handling and dry-

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grinding with structurally related dicarboxylic acids (SRDs). Mixing with SRDs led to coformer

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replacement or stoichiometry changes for some cocrystals. Lattice energy and Gibbs free energy

238

computations agreed well with the observed relative stabilities of the cocrystals.