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Co-Crystals of Caffeine and Hydroxy-2-naphthoic Acids: Unusual Formation of the Carboxylic Acid Dimer in the Presence of a Heterosynthon

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Abstract: A group of caffeine-containing co-crystals of hydroxy-2-naphthoic acids were synthesized and analyzed *via* single-crystal X-ray diffraction and IR analysis. The imidazole−carboxylic acid synthon was observed in co-crystals involving 1-hydroxy-2-naphthoic and 3-hydroxy-2-naphthoic acid. In the case of 6-hydroxy-2-naphthoic acid, the co-crystal exhibits a hydrogen-bonded carboxylic acid dimer in the presence of a hydroxyl−caffeine heterosynthon.

Keywords: Pharmaceutical co-crystals; co-crystal screening; hydrogen bond; caffeine; naphthoic acid; supramolecular synthon; crystal engineering; 1-hydroxy-2-naphthoic acid; 3-hydroxy-2-naphthoic acid; 6-hydroxy-2-naphthoic acid

Introduction

Although the term "crystal engineering" was introduced in 1955 by Pepinsky[1] as a new concept in crystallography, it was first applied much later in 1971 by Schmidt in the context of synthetic and mechanistic photochemistry.[2] Two decades later, in the early 1990s, crystal engineering began to evolve from a concept to a scientific discipline focused on the design of organic solids with desired structures and properties engineered at the molecular level and derived from molecular building blocks associated by intermolecular forces (i.e., supramolecular synthons).[3−5]

Crystal engineering can be considered as the design and synthesis of crystalline solids based on supramolecular synthons, which are utilized as robust structural units (*cf.* "reactants" in conventional organic chemistry) to control the structures of single- and multicomponent solids. Co-crystals, one of the synthetic targets in crystal engineering, are a long known class of compounds, but they were not extensively studied until the late 1990s when they became recognized as valuable materials.[6−9] Even now, more than one hundred

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years after the first co-crystals were reported,[10,11] the definition of the term co-crystal is a current theme and a topic for discussion.[12,13] The most recent definition of co-crystals has been given by Aakeröy and co-workers.[14] They defined co-crystals as (1) compounds constructed from neutral molecules; (2) made from reactants that are solids at ambient conditions; and (3) structurally homogeneous crystalline materials that contains at least two neutral building blocks with a well-defined stoichiometry.

In recent years, concepts of crystal engineering have been successfully applied in the template-directed solid-state synthesis of molecular targets,[15−17] development of organic semiconductors,[18] and development of other functional materials.[19−23] In the field of pharmaceutical sciences, however, crystal engineering has emerged only recently.[24−32] Despite such recent emergence, however, several attempts to design new pharmaceutical solids to improve properties of pharmaceutical agents (PAs) (e.g., solubility, dissolution rate, bioavailability, stability) have already been reported. Studies show that PA-containing co-crystals may have a significant impact on pharmaceutical formulations. These studies have focused primarily on the improvement of solubility/dissolution[33,34] and hygroscopicity[35] by co-crystallization of the PA with appropriate co-crystal formers.

In this contribution, we focus on the syntheses and structural characterizations of co-crystals of caffeine and three hydroxy-2-naphthoic acids; namely, 1-hydroxy-2-naphthoic acid (1HNA), 3-hydroxy-2-naphthoic acid (3HNA), and 6-hydroxy-2-naphthoic acid (6HNA) (Scheme 1). Recently, co-crystals of caffeine and various carboxylic acids

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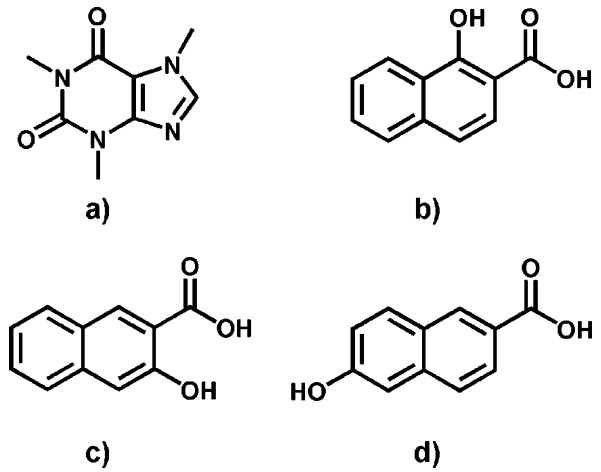
Scheme 1. The Chemical Structure of (a) Caffeine, (b) 1-Hydroxy-2-naphthoic Acid, (c) 3-Hydroxy-2-naphthoic Acid, and (d) 6-Hydroxy-2-naphthoic Acid



have emerged as materials to improve the physical properties of caffeine (e.g., physical stability against hydration), as well as model compounds for studying preparation methods (e.g., solvent-free grinding)[35] and structural effects associated with pharmaceutical co-crystals in general. In these solids, caffeine invariably forms molecular complexes in which the carboxylic acid group interacts with the N atom of the imidazole ring *via* an O−H···N hydrogen bond.[36] A literature search of the Cambridge Structural Database (CSD)[37] has revealed 21 complexes in which the caffeine and carboxylic acid components are held together by one of two heterosynthons: (1) an $R_2^2(7)$ heterosynthon and (2) an $R_3^3(11)$ network based on $R_2^2(7)$ and $R_2^2(6)$ heterosynthons (Figure 1).[35,38−40,44c] A general goal of this study is to begin to examine the structural effects of adding a hydrogen-bond-donating functional group (i.e., hydroxyl group) along the periphery of a carboxylic acid in a caffeine−carboxylic acid co-crystal. Indeed, studies to introduce additional synthons to co-crystals are emerging as useful means to refine crystal engineering strategies of organic solids. Upon further searching the CSD, we noticed that the carbonyl group of caffeine, in a molecular complex of caffeine with methyl 3,4,5-trihydroxybenzoate,[41] served as a hydrogen-bond acceptor group in an O−H···O hydrogen bond with the benzoate component. Moreover, this observation suggested to us that the incorporation of an additional heterosynthon to a caffeine−carboxylic acid co-crystal was possible. To our surprise, although we have found that the O−H···O=C heterosynthon can be introduced within the co-crystal of caffeine and 6HNA, we have discovered that the introduction of the heterosynthon disrupts the COOH···N interaction and, in addition to the new heterosynthon, yields the well-known hydrogen-bond carboxylic acid dimer. To our knowledge, the co-crystal of caffeine and 6HNA represents a rare case in which the carboxylic acid dimer coexists with a heterosynthon.

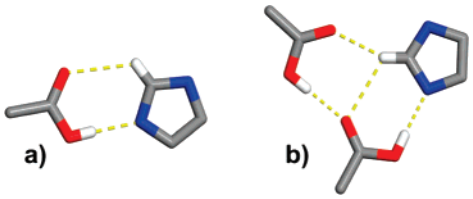


Figure 1. The most common acid−imidazole heterosynthons present in caffeine:carboxylic acid co-crystals.

Experimental Section

Materials. Caffeine (ReagentPlus), 1HNA (99%), 3HNA (98%), 6HNA (98%), and acetonitrile (anhydrous, 99.8%)

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Table 1. Crystallographic Data for **A**, **B** and **C**

	A	B	C
molecular formula	$(C_8H_{10}N_4O_2)\cdot(C_{11}H_8O_3)$	$(C_8H_{10}N_4O_2)\cdot(C_{11}H_8O_3)$	$(C_8H_{10}N_4O_2)\cdot(C_{11}H_8O_3)$
M_r	382.37	382.37	382.37
crystal system	monoclinic	monoclinic	triclinic
space group	$P2_1/n$	$P2_1/c$	$P\bar{1}$
a, Å	7.606(2)	9.040(9)	8.029(3)
b, Å	14.042(3)	24.42(2)	8.592(3)
c, Å	16.327(4)	8.654(8)	13.996(5)
α, deg	90.000	90.000	106.475(5)
β, deg	94.030(4)	117.2(1)	98.162(5)
γ, deg	90.000	90.000	104.904(6)
V, Å^3	1739.6(7)	1702(3)	870.3(5)
Z	4	4	2
D_c/g cm^{-3}	1.460	1.492	1.459
F(000)	800	800	400
μ(Mo Kα)/cm^{-1}	0.108	0.111	0.108
crystal size/mm	0.5 × 0.25 × 0.10	0.3 × 0.2 × 0.1	0.4 × 0.2 × 0.15
range of indices	−10, 9; −18, 18; −21, 21	−11, 12; −32, 32; −11, 11	−10, 10; −11, 11; −18, 18
no. of reflections collected	20038	19094	10422
unique reflections	4246	4167	4196
R_{int}	0.1294	0.1024	0.0804
reflections with $I > 2\sigma(I)$	3374	4167	3270
no. of parameters	265	264	303
$R(F)$, $F > 2\sigma$(F)	0.0926	0.0631	0.0605
$wR(F^2)$, $F > 2\sigma$(F)	0.1198	0.1038	0.0757
$wR(F^2)$, all data	0.2166	0.1011	0.1187
Δ_r (max, min) e Å^{-3}	0.346, −0.319	0.270, −0.199	0.371, −0.198

Table 2. Carbon−Oxygen Bond Distances in the Caffeine−Hydroxy-2-naphthoic Acid Co-Crystals

co-crystal	d(C−O)/(Å)	d(C═O)/(Å)
A	1.318(4)	1.236(4)
B	1.320(3)	1.217(3)
C	1.312(2)	1.240(2)

were purchased from Sigma-Aldrich (St. Louis, MO) and were used as received.

Cambridge Crystallographic Database Search. The CSD database survey was accomplished on version 5.27 (including Update 3, August 2006) using ConQuest[42] (version 1.8). The CSD was searched with respect to fragments with a single filter in place: hits are organic compounds and with 3-D coordinates.

Co-Crystal Screening. A recently developed co-crystal screening method that utilizes the thermodynamically driven solution-mediated phase transformation[43] was used to screen the hydroxy-2-naphthoic acids for co-crystal formation[44] with caffeine. Caffeine (1 mmol) was mixed with 1 molar equiv of 1HNA, 3HNA, and 6HNA, respectively. Acetonitrile (2 mL) was added to the physical mixture. The suspension was briefly sonicated and equilibrated overnight at ambient conditions. The residual solid was filtered and examined by powder X-ray diffractometry. In all cases, a new solid phase was formed from the suspension, indicating a potential co-crystal formation. Single crystals were then grown and structures were determined as described below to confirm the co-crystal formation.

Single-Crystal Preparation. Single crystals of compounds **A** (caffeine:1HNA co-crystal), **B** (caffeine:3HNA co-crystal), and **C** (caffeine:6HNA co-crystal) were obtained by slow evaporation from solution. Caffeine (0.1 mmol) was individually mixed with 1HNA, 3HNA, and 6HNA, respectively (0.1 mmol). Acetonitrile (2 mL) was added to the solid mixtures. The suspension was heated until the caffeine: hydroxy-2-naphthoic acid mixture was completely dissolved. The resulting mixture was kept at 348 K for 10 min and filtered. The filtrate was left to evaporate slowly at 298 K. Single crystals of **A** suitable for X-ray diffraction study were obtained after 1 day, while those of **B** and **C** were obtained after 2 days.

Infrared (IR) Spectroscopy. Transmission infrared spectra of the solids were obtained using a Fourier-transform infrared spectrometer (Nicolet Magna 750 FT-IR spectrometer) equipped with a Nicolet NIC-PLAN microscope. The microscope has an MCT-A liquid nitrogen cooled detector. The samples were rolled on a 13 mm x 1 mm BaF_2 disk sample holder; 64 scans were collected at 4 cm^{-1} resolution.

Powder X-ray Diffractometry (PXRD). PXRD data were collected using a G3000 diffractometer (Inel Corp., Artenay, France) equipped with a curved position sensitive detector and parallel beam optics. The diffractometer was operated with a copper anode tube (1.5 kW fine focus) at 40 kV and 30 mA. An incident beam germanium monochromator provided monochromatic $K\alpha_1$ radiation. The diffractometer was calibrated using the attenuated direct beam at 1° intervals. Calibration was checked using a silicon powder

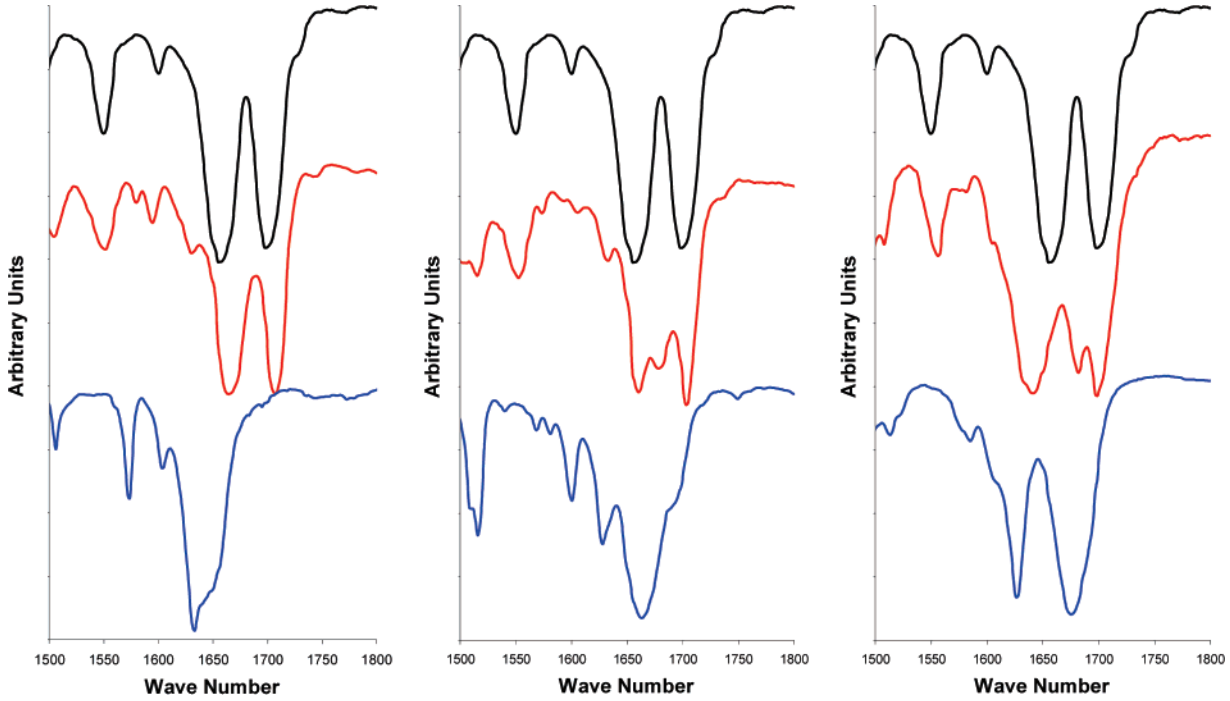

Figure 2. Infrared spectra of the carbonyl stretching region for caffeine (top, black), co-crystal (middle, red), and co-crystal former (bottom, blue). Left: caffeine−1HNA. Middle: caffeine−3HNA. Right: caffeine−6HNA.

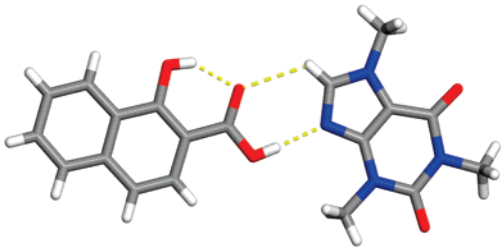

Figure 3. A perspective view of the two-component complex of caffeine and 1-hydroxy-2-naphthoic acid with an $R_2^2(7)$ hydrogen-bond pattern.

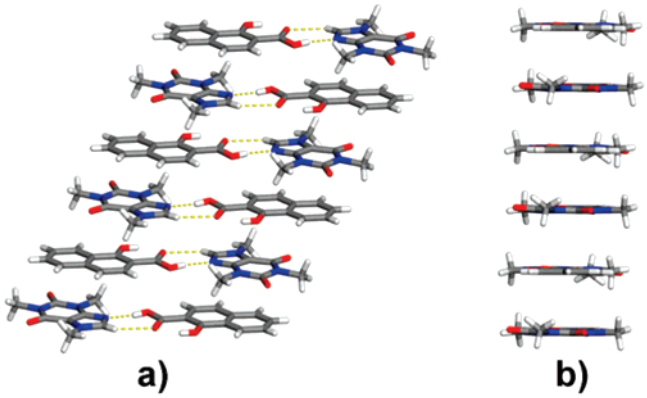

Figure 4. Perspective views of caffeine:1-hydroxy-2-naphthoic acid assemblies in the solid state, stacked in a "head-to-tail" manner.

line position reference standard (NIST 640c). The instrument was computer controlled using the Symphonix software,[45] and the data was analyzed using the Jade 6.5 software.[46] The sample was loaded onto an aluminum sample holder and leveled with a glass slide.

Crystallography. Single crystals of **A**, **B**, and **C** were individually mounted on glass fibers. Intensity data were collected on a Bruker SMART system equipped with an APEX CD camera. Data were collected at 173 K with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Data were collected in four sets using $\omega-\phi$ scans with ω steps of 0.3° and ϕ steps of 90°. A total of 2350 frames were collected with 20 s frame exposures. Data were processed using Saint*Plus*.[47] Corrections for Lorentz−polarization effects were applied. Absorption was negligible. All structures were solved using direct methods that yielded the non-hydrogen atoms. All presented hydrogen atoms were located in Fourier-difference electron density maps. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms associated with carbon atoms were refined in geometrically constrained riding positions. Hydrogen atoms associated with oxygen atoms were included in the located positions. Refinement was achieved with the use of SHELX-97.[48]

Results

The crystal structure analyses reveal a 1:1 stoichiometry of caffeine:acid in each solid. The asymmetric units of **A**, **B**, and **C** contain one molecule of caffeine and one molecule of hydroxy-2-naphthoic acid. To classify the new caffeine

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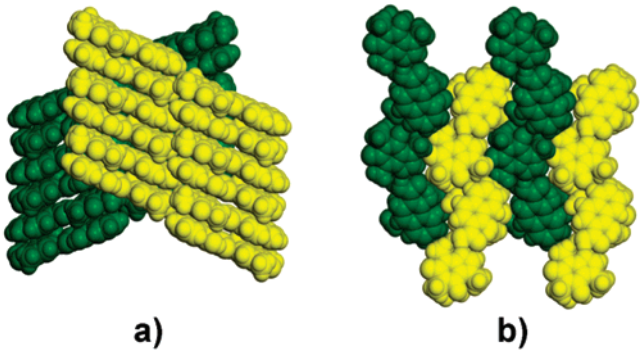

Figure 5. A space-filling model of the crystal packing of stacked caffeine:1-hydroxy-2-naphthoic acid assemblies viewed along the crystallographic planes: (a) (1 1 0) and (0 1 0); (b) (1 1 0) and (0 0 1).

Table 3. Selected Hydrogen-Bond Parameters of Co-Crystals **A**, **B**, and **C**

co-crystal	D−H···A	*d*(H···A)/Å	*d*(D···A)/Å	*θ*(D−H···A)/deg
A	O5−H2o···O4	1.71(4)	2.545(3)	156(4)
	O3−H1o···N3	1.78(5)	2.669(3)	173(4)
B	O5−H2o···O4	1.81(3)	2.576(3)	150(3)
	O3−H1o···N3	1.75(3)	2.692(3)	170(2)
C	O5−H2o···O2	1.84(2)	2.742(2)	170(2)
	O3−H1o···O4	1.66(2)	2.642(2)	177(2)

phases **A**, **B**, and **C** as either a neutral (i.e., co-crystal) or ionic (i.e., salt) complex, it was necessary to analyze the geometry of the carboxyl group and locate the acidic proton. The carbon−oxygen bond distances were consistent with the formation of a co-crystal in each case (Table 2). Moreover, an analysis of the Fourier difference map revealed that the acidic proton was located 0.887−0.983 Å from the O atom of the carboxylic acid. Thus, compounds **A**, **B**, and **C** were classified as co-crystals. Additionally, analyses of the carbonyl stretching bands in the infrared spectra, which are all above 1600 cm^{-1} (Figure 2), confirmed un-ionized carboxylic acids and thus co-crystal formation for these new phases. A typical ionized carboxylic acid salt band would be expected to occur below 1600 cm^{-1}.

1. Co-Crystal A. Co-crystal **A** crystallizes in the monoclinic $P2_1/n$ space group. Caffeine and 1HNA form a two-component assembly based on an $R_2^2(7)$ hydrogen-bond pattern that involves the carbonyl and imidazole moieties. The hydroxy group of 1HNA is involved in an intramolecular O−H···O hydrogen bond[49] with the carboxylic group to form an $S_1^1(6)$ ring (Figure 3). The two-component assemblies stack in a "head-to-tail" manner (Figure 4), being held together by weak van der Waals interactions. The stacks are sustained by C−H···O hydrogen bonds (Figure 5). Selected hydrogen-bond parameters are listed in Table 3.

2. Co-Crystal B. Co-crystal **B** crystallizes in the monoclinic $P2_1/c$ space group. Similar to **A**, the caffeine and acid components form a two-component assembly involving both an intramolecular O−H···O and an intermolecular O−H···N hydrogen bond (Figure 6). The acid−base pairs interact in a parallel and offset manner *via* weak van der Waals forces to form stacks. The stacks are sustained by C−H···O hydrogen bonds (Figures 7 and 8). The pairs within the stacks are offset by one caffeine molecule. Selected hydrogen bond parameters are shown in Table 3.

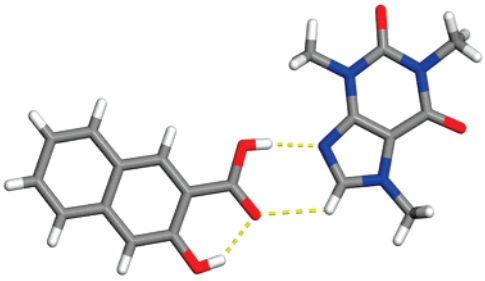

Figure 6. A perspective view of the neutral 1:1 caffeine:3-hydroxy-2-naphthoic acid assembly.

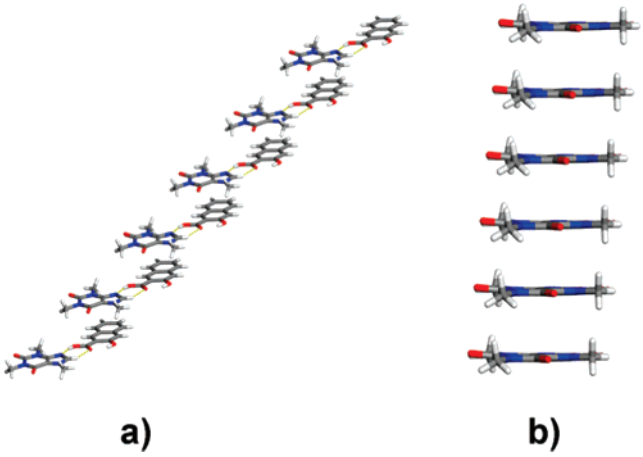

Figure 7. Perspective views of caffeine:3-hydroxy-2-naphthoic acid assemblies in the solid state, stacked in a "head-to-head" manner.

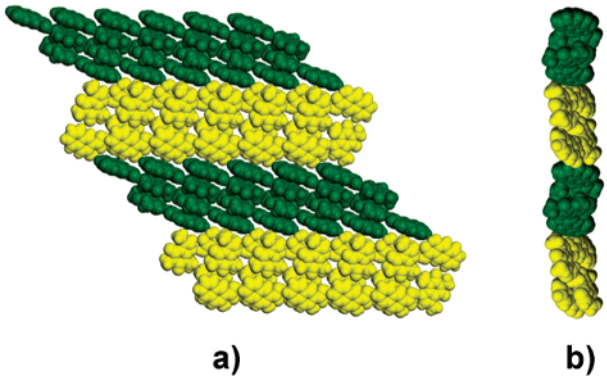

Figure 8. A space-filling model of the crystal packing of stacked caffeine:3-hydroxy-2-naphthoic acid assemblies viewed along the crystallographic planes: (a) (1 0 1) and (0 1 0); (b) (1 0 −1) and (0 1 0).

3. Co-Crystal C. Co-crystal **C** crystallizes in the triclinic $P\bar{1}$ space group. Similar to **A** and **B**, an intermolecular hydrogen bond has formed between the caffeine and hy-

(49) Cochran, W. The Crystal and Molecular Structure of Salicylic Acid. *Acta Crystallogr.* **1953**, *6*, 260−268.

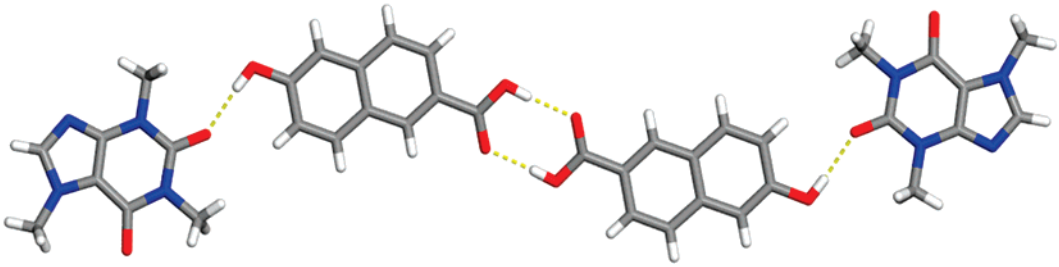

Figure 9. A perspective view of the 1:1 caffeine:6-hydroxy-2-naphthoic acid (the second position of the disordered caffeine is omitted for clarity).

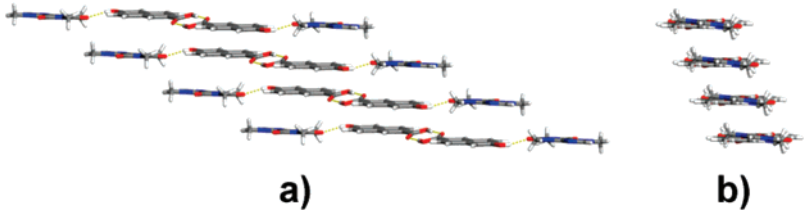

Figure 10. Perspective views of caffeine:6-hydroxy-2-naphthoic acid assemblies in the solid state, stacked in a "head-to-head" manner.

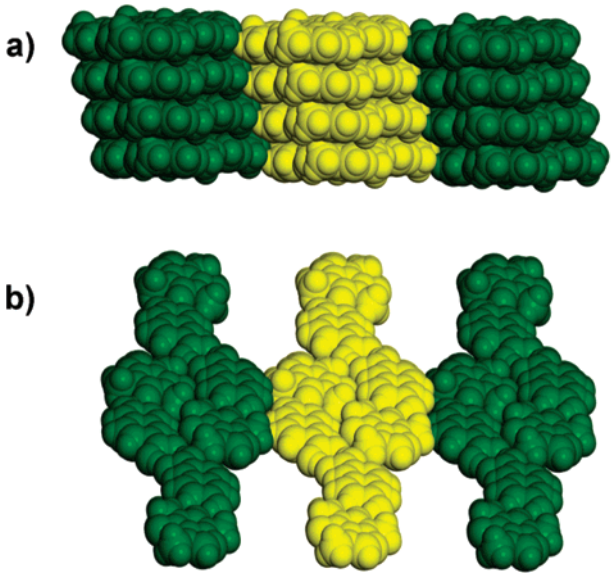

Figure 11. A space-filling model of the crystal packing of stacked assemblies of caffeine:6-hydroxy-2-naphthoic acid viewed along the crystallographic planes: (a) (1 2 0) and (0 0 1); (b) (0 1 0) and (0 0 1).

droxy-2-naphthoic acid molecule. In contrast to **A** and **B**, however, yet can be as expected, the intermolecular hydrogen bond involves the free hydroxy group of 6HNA. The free hydroxyl group participates in an O−H···O interaction with the carbonyl group of caffeine. Surprisingly, the carboxylic acid groups of the two acids interact with each other, forming a dimer that is based on the well-known $R_2^2(8)$ homosynthon. Consequently, the N atom of the imidazole ring, which lies disordered over two positions (site occupancies: 0.662: 0.338), does not participate in a hydrogen bond. The assembly process has, thus, produced a discrete four-component array that is held together by two intermolecular O−H(carboxyl)···O(carboxyl) and two intermolecular O−H(hydroxyl)···O(carbonyl) hydrogen bonds (Figure 9). The assemblies stack in a parallel and offset manner (Figure 10), being held together *via* weak van der Waals interactions. The stacks are sustained by C−H···O hydrogen bonds (Figure 11). Selected hydrogen bond parameters are listed in Table 3.

Discussion

Co-crystals **A** and **B** form two-component assemblies based on the well-established caffeine(imidazole)−carboxylic acid synthon. As in the case of 1HNA and 3HNA, ortho hydroxy groups of carboxylic acids are known to form intramolecular O−H···O hydrogen-bonds.[49] It was, therefore, expected that an intermolecular O−H(hydroxyl)···O(caffeine) heterosynthon would not likely form in those co-crystals involving 1HNA and 3HNA.

The introduction of a free (i.e., incapable of intramolecular hydrogen bonding) hydroxyl group of 6HNA resulted in the formation of an O−H···O hydrogen bond between the hydroxy group of 6HNA and the caffeine carbonyl group in **C**. To the best of our knowledge, this is the first reported case in which the imidazole(caffeine)−carboxylic acid synthon is absent in a caffeine−carboxylic acid co-crystal. Moreover, the coexistence of a carboxylic acid dimer in the presence of such a supramolecular heterosynthon[50,51] is rare.

(50) Aakeröy, C. B.; Desper, J.; Helfrich, B. A. Heteromeric Intermolecular Interactions as Synthetic Tools for the Formation of Binary Co-crystals. *CrystEngComm* **2004**, *6*, 19−24.

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Indeed, to date, there are only few reported cases of a carboxylic acid dimer homosynthon in the presence of a heterosynthon.[52−58] We are currently working to increase the number of co-crystals in this family of solids to determine those factors responsible for the coexistence of the O−H···O heterosynthon and carboxylic acid dimer.

Conclusion

In this contribution, three co-crystals of caffeine with hydroxy-2-naphthoic acids were structurally characterized. In addition to the known imidazole−acid synthon, structural analyses of these solids have revealed an unusual case in which a carboxylic acid dimer forms in the presence of a rationally introduced heterosynthon. Efforts are underway to further increase the structural diversity of co-crystals that can be achieved through the deliberate addition of functional groups into self-assembly processes involving organic co-crystals.

Supporting Information Available: Crystallographic information (.cif) for **A**, **B**, and **C**. This material is available free of charge via the Internet at http://pubs.acs.org.

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