

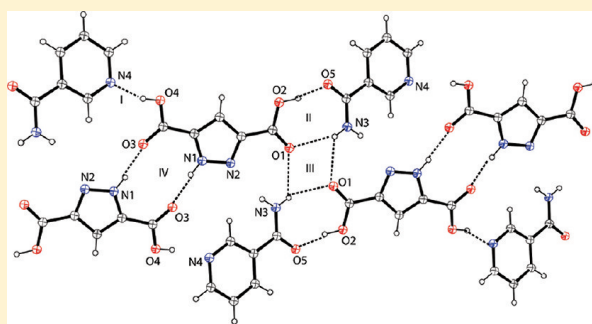
Supramolecular Synthons and Hydrates in Stabilization of Multicomponent Crystals of Nicotinamide and Isonicotinamide with N-Containing Aromatic Dicarboxylic Acids

Babulal Das and Jubaraj B. Baruah*

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, Assam, India

Supporting Information

ABSTRACT: Multicomponent crystals (either cocrystal or salt) of nicotinamide (nicotinic acid amide) and isonicotinamide with various nitrogen heterocycle-containing aromatic dicarboxylic acids, namely, 3,5-pyrazole dicarboxylic acid (pzdca), dipicolinic acid (dpa), and quinolinic acid (qna), have been synthesized and characterized by single-crystal diffraction and thermal studies. The nicotinamide (nic) and isonicotinamide (isonic) cocrystals with 3,5-pyrazole dicarboxylic acid (**1** and **2**, respectively) possess four different heteromeric supramolecular synthons in each cocrystal, which is rare. The nicotinamide dipicolinic acid cocrystal, **3**, showed formation of water-bridged assembly, whereas isonicotinamide-dipicolinic acid cocrystal, **4**, led to a six-component assembly through the isolated solvent water molecules occupying the interstitial positions. The salt formed from quinolinic acid with nicotinamide **5** has a hydrogen-bonded 1D water chain in its crystal lattice, whereas quinolinic acid with isonicotinamide resulted in formation of **6** with 2D sheets of multiple heterosynthons. Thermal studies show evaporation of various water molecules with a trend that has relevance to their hydrogen-bonding environment in the multicomponent crystal.



INTRODUCTION

Supramolecular synthons (either homo or hetero) based on hydrogen bonding are considered to be the prototypical tool for crystal engineering.¹ The ease of X-ray diffraction studies has given momentum to exploration of supramolecular synthons in multicomponent crystals of active pharmaceutical ingredients (API). Carboxylic acid–API cocrystals are emerging as useful means for targeted crystal-engineering strategies.² It has been reported that organic solids or pharmaceutical components with a number of carboxylic acid–aromatic N-heterosynthons can be exploited to generate binary crystalline phases and also provide robust structures.³ Crystallized water molecules or cocrystal hydrates are also considered as an integral part of many cocrystal structures. Since the hydrates can be involved in formation of diverse supramolecular heterosynthons in cocrystals of carboxylic acid or alcohols, they are also the essence of crystal engineering.⁴ On the other hand, each water molecule has two donors and two acceptor sites to form a tetrahedral network. Because of its small size and multiple H-bonding capabilities of water molecules,⁵ it has been reported that water molecules can incorporate in crystal structures (i) when there is an imbalance in the number of donor/acceptors⁶ and (ii) when the hydrated form is more stable.⁷ Cocrystal hydrates are also known to provide stability under conditions of high relative humidity to these materials.⁸ Among amides, benzamide is a good cocrystal former with different carboxylic acids to generate different synthons;⁹ thus, the cocrystals of nitrogen-containing aromatic amides with polycarboxylic acid have high prospect to unearth new

synthons. Nicotinamide and isonicotinamide are the two most frequently used model compounds in pharmaceutical cocrystal studies.¹⁰ We observed that despite a large amount of their structures as cocrystals of carboxylic acids, there is no study with nitrogen-containing carboxylic acids. We have chosen 3,5-pyrazole dicarboxylic acid (H-bond donor, O4; H-acceptor, O7), dipicolinic acid, or quinolinic acid (H-bond donor, O2; H-bond acceptor, O5, in each case) as cocrystal former because of their multiple hydrogen-bonding sites in a different chemical environment that makes them an interesting architecture to study supramolecular synthons via cocrystal formation. Thus, in this study, our aim is to examine (i) the structural changes caused by incorporating N-heterocyclic functional groups in the aromatic periphery of dicarboxylic acids to organize multiple API molecules that already contain both pyridine N and an amide group, (ii) formation of new heterosynthons, other than the commonly observed synthons (scheme 1), and (iii) changes in properties of nicotinamide/isonicotinamide molecules upon interacting with these acids.

EXPERIMENTAL SECTION

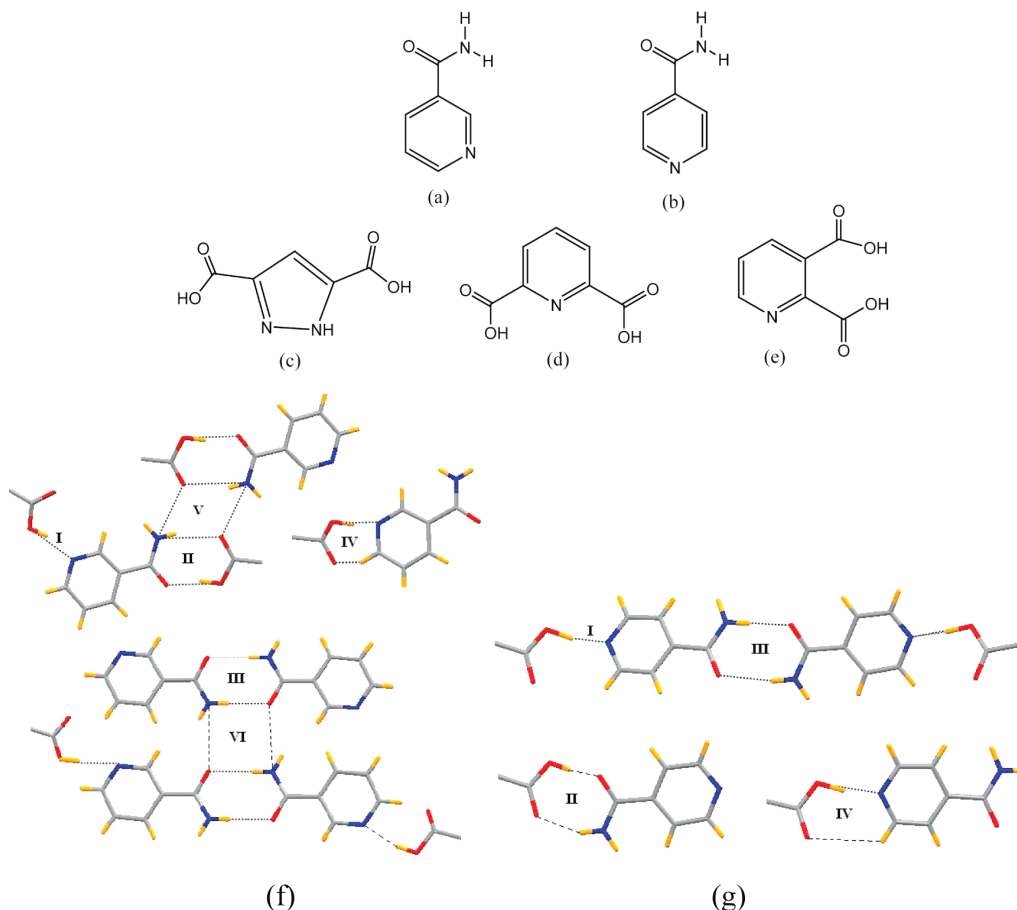
Materials. Nicotinamide, isonicotinamide, 3,5-pyrazole dicarboxylic acid monohydrate (97%), dipicolinic acid (99%), and quinolinic acid

Received: August 22, 2011

Revised: September 30, 2011

Published: October 08, 2011

Scheme 1. Structural Backbone of the Investigated Molecules (a) Nicotinamide, (b) Isonicotinamide, (c) 3,5-Pyrazole Dicarboxylic Acid, (d) Dipicolinic Acid (alternative name 2,6-pyridine dicarboxylic acid), (e) Quinolinic Acid (alternative name 2,3-pyridine dicarboxylic acid), and (f and g) Commonly Observed Heterosynthons in Nicotinamide and Isonicotinamide Carboxylic Acid Cocrystals



(97%) were purchased from commercial sources (Sigma-Aldrich) and used without further purifications. Methanol (Merck) and Millipore direct Q water was used both as solvent and for crystallization purposes.

Preparation of Multicomponent Crystals. A 1:1 stoichiometric amount of nicotinamide (61 mg, 0.5 mmol) and isonicotinamide (61 mg, 0.5 mmol) was dissolved independently with 3,5-pyrazole dicarboxylic acid monohydrate (87 mg, 0.5 mmol), dipicolinic acid (84 mg, 0.5 mmol), and quinolinic acid (84 mg, 0.5 mmol) in 20 mL of methanol/water mixture. The resulting solution was left stirring at 70–80 °C for 1 h. The colorless solution obtained in each case after filtration was left to evaporate slowly at room temperature. Colorless needle and block types of single crystals suitable for X-ray diffraction studies were obtained after 3/4 days. Solvent–drop grinding experiments using a water and methanol mixture also produced the expected multicomponent crystals with the same stoichiometric ratio.

Physical Measurements. Infrared spectra (KBr pellets) of the solids were recorded with a Perkin-Elmer Spectrum One FT-IR spectrophotometer in the spectral region 4000–400 cm^{-1} . TGA and DSC analyses were performed on a TA Instruments SDT Q600 thermogravimetric analyzer and Q20 differential scanning calorimeter, respectively, under an atmosphere of dry nitrogen from 40 to 400 °C with a heating rate of 7 °C.

X-ray Crystallographic Studies. Diffraction data for compounds 1–6 were collected at 296 K with Mo K α radiation ($\lambda = 0.71073$ Å) using a Bruker Nonius SMART APEX CCD diffractometer equipped

with a graphite monochromator and Apex CD camera. The SMART software was used for data collection and also for indexing the reflections and determining the unit cell parameters. Data reduction and cell refinement were performed using SAINT software, and the space groups of these crystals were determined from systematic absences by XPREP and further justified by the refinement results. The structures were solved by direct methods and refined by full-matrix least-squares calculations using SHELXTL software. All non-H atoms were refined in the anisotropic approximation against F^2 of all reflections. The H atoms attached to heteroatoms in these crystals were located in the difference Fourier synthesis maps and refined with isotropic displacement coefficients. The locations of acidic protons were justified by a difference Fourier synthesis map, and in the refinement these were allowed for as riding atoms. Due to the high U_{eq} of disordered oxygen, the H atoms in the solvent water molecule in crystals 1 and 5 could not be located. Negligible absorption was found in each crystal. The crystal structure and details of the final refinement parameters are summarized in Table 1.

RESULTS AND DISCUSSION

Nicotinamide and 3,5-pyrazole dicarboxylic acid form a 1:1 cocrystal 1 ($\text{nic} \cdot \text{pzdca} \cdot \text{H}_2\text{O}$) in hydrated form. It crystallizes in the triclinic space group $P\bar{1}$ with a disordered solvent water

Table 1. Crystal Structure and Refinement Parameters of 1–6

cocrystal	1 (nic·pzda·H ₂ O)	2 (2isonic·pzda)	3 (nic·dpa·H ₂ O)	4 (isonic·dpa·H ₂ O)	5 (nic·qna·H ₂ O)	6 (isonic·qna)
molecular formula	(C ₇ H ₄ N ₂ O ₄)·(C ₆ H ₆ N ₂ O)·H ₂ O	(C ₇ H ₄ N ₂ O ₄) ₂ (C ₆ H ₆ N ₂ O)	(C ₇ H ₃ NO ₄)·(C ₆ H ₆ N ₂ O)·H ₂ O	(C ₇ H ₃ NO ₄)·(C ₆ H ₆ N ₂ O)·H ₂ O	(C ₇ H ₄ NO ₄)·(C ₆ H ₇ N ₂ O)·H ₂ O	(C ₇ H ₄ NO ₄)·(C ₆ H ₇ N ₂ O)
<i>M_r</i>	296.25	400.36	307.26	307.26	307.26	289.25
cryst size (mm ³)	0.30 × 0.16 × 0.08	0.35 × 0.20 × 0.12	0.15 × 0.08 × 0.04	0.40 × 0.17 × 0.08	0.42 × 0.18 × 0.10	0.28 × 0.17 × 0.10
cryst syst	triclinic	monoclinic	monoclinic	monoclinic	monoclinic	triclinic
space group	<i>P</i> -1	<i>P</i> ₂ / <i>n</i>	<i>P</i> ₂ / <i>c</i>	<i>P</i> ₂ / <i>c</i>	<i>P</i> ₂ / <i>c</i>	<i>P</i> -1
<i>a</i> (Å)	3.6888(5)	13.8752(5)	13.111(3)	13.5546(7)	3.7184(3)	8.0151(3)
<i>b</i> (Å)	11.9356(13)	7.1838(3)	3.7622(8)	5.0299(2)	13.3383(9)	8.2236(3)
<i>c</i> (Å)	14.3954(15)	17.8301(8)	27.767(6)	20.1150(9)	25.3647(18)	10.1892(4)
<i>α</i> (deg)	77.356(7)	90.00	90.00	90.00	90.00	97.859(2)
<i>β</i> (deg)	87.328(7)	99.906(3)	92.905(15)	101.635(3)	93.400(5)	111.100(3)
<i>γ</i> (deg)	87.862(8)	90.00	90.00	90.00	90.00	90.847(3)
<i>V</i> (Å ³)	617.52(13)	1750.75(12)	1367.9(5)	1343.23(11)	1255.80(16)	619.20(4)
<i>Z</i>	2	4	4	4	4	2
<i>ρ</i> _{calcd} (g·cm ^{−3})	1.593	1.519	1.492	1.519	1.625	1.551
<i>μ</i> (Mo Kα)(mm ^{−1})	0.132	0.118	0.120	0.123	0.131	0.122
<i>F</i> (000)	308	832	640	640	640	300
<i>T</i> (K)	296	296	296	296	296	296
range of indices	−4, 4; −14, 13; −17, 17	−16, 16; −8, 8; −21, 20	−15, 14; −4, 4; −33, 27	−16, 15; −5, 5; −23, 23	−4, 4; −17, 17; −31, 33	−9, 9; −9, 9; −12, 12
no. of reffs collected	8379	22 517	11 115	15 392	19 266	8235
no. of unique reffs	2155	3063	2409	2341	3124	2148
<i>θ</i> range (deg)	1.45–25.00	1.72–25.00	1.47–25.00	1.53–25.00	1.61–28.47	2.17–25.00
<i>R</i> _{int}	0.1102	0.0432	0.1100	0.0634	0.0414	0.0284
goodness-of-fit	1.021	1.011	0.941	0.925	1.081	1.144
<i>R</i> ₁ [<i>I</i> ≥ 2σ(<i>I</i>)]	0.0661	0.0436	0.0790	0.0458	0.0630	0.0388
w <i>R</i> ₂ [<i>I</i> ≥ 2σ(<i>I</i>)]	0.1728	0.1264	0.1899	0.1261	0.2191	0.1009
<i>R</i> ₁ (all data)	0.0770	0.0600	0.1460	0.0766	0.0956	0.0556
w <i>R</i> ₂ (all data)	0.1852	0.1388	0.2526	0.1494	0.2350	0.1113
<i>Δ</i> _c (max, min), e [−] ·Å ^{−3}	0.383, −0.328	0.161, −0.220	0.293, −0.232	0.225, −0.241	0.222, −0.744	0.157, −0.204

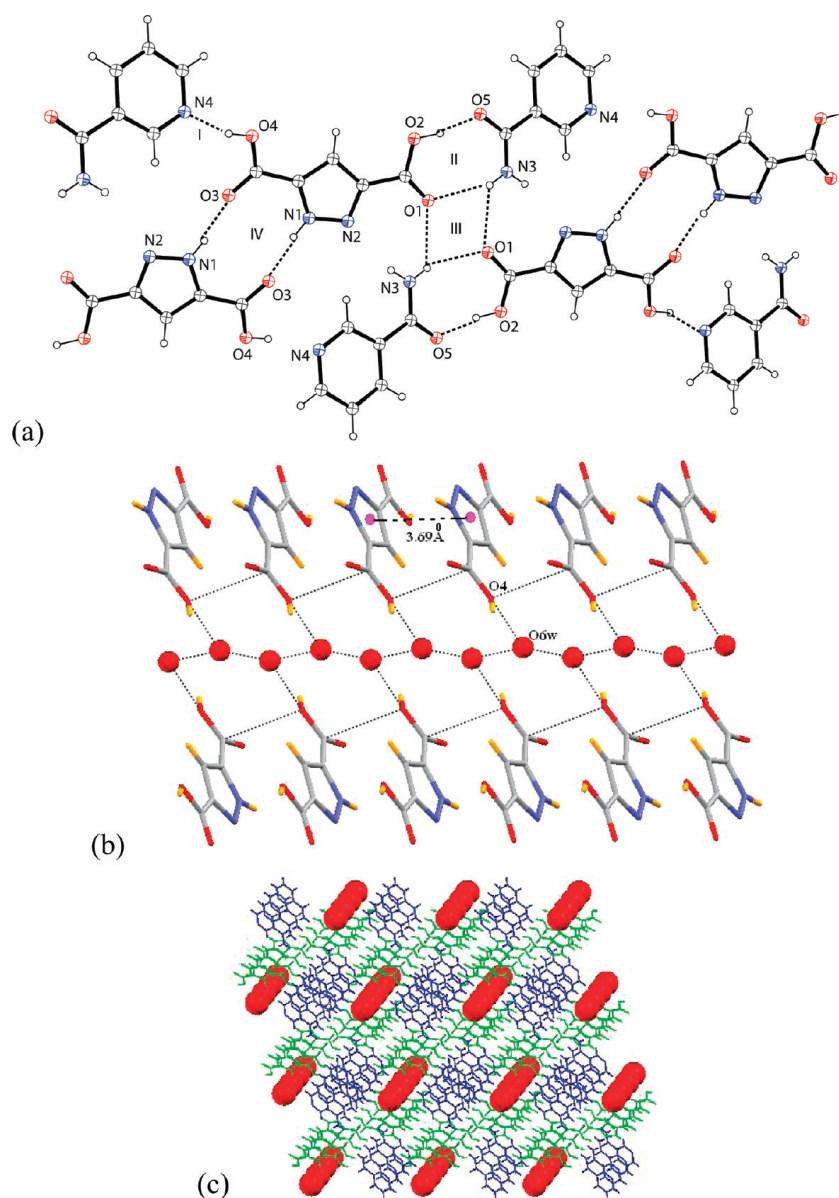


Figure 1. (a) Four different synthons in crystal 1, (b) view of water chains and π - π stacking between adjacent pzdca molecules, and (c) water chains (red) in space-filling mode along the crystallographic *a* axis.

molecule. The cocrystal is sustained by acid–pyridine and acid–amide supramolecular heterosynthons, but the commonly observed amide–amide supramolecular homosynthon is absent. It features formation of a rare four hydrogen-bonded heterosynthon (Figure 1a). The hydrogen bond of the carboxylic acid groups of pzdca with the N atom of the pyridine of nicotinamide leads to discrete synthon I. The other acid group of pzdca forms a heterodimer $R^2_2(8)$ classified as synthon II with the amide group of nicotinamide ($O2-H \cdots O5$ and $N3-H \cdots O1$). The heteromeric dimers are further associated to another similar unit to form a $R^2_4(8)$ heteromeric tetramer, synthon III. Synthon IV is the homomeric $R^2_2(10)$ dimer of pzdca through pyrazole N1 proton and acid group. It may be mentioned that the

amide-containing systems rarely show four heterosynthons. For example, formation of four different supramolecular synthon with the citric acid molecule was observed recently.¹¹ In this report, nicotinamide is shown to interact with citric acid, through acid–pyridine, acid–amide, dimer of amide followed by acid–pyridine which is further enhanced by $C-H \cdots O$ interactions, $R^2_2(7)$ synthon. The heteromeric synthons accompanied by homomeric synthons lead to an infinite helical sheet in a 3D hydrogen-bonded network. It is to be mentioned that pzdca also forms carboxylic acid dimer based on well-known $R^2_2(8)$ homosynthon in theophylline cocrystal.¹² The other noncovalent forces stabilizing the cocrystal 1 are the face-to-face π - π stacking interactions between the two

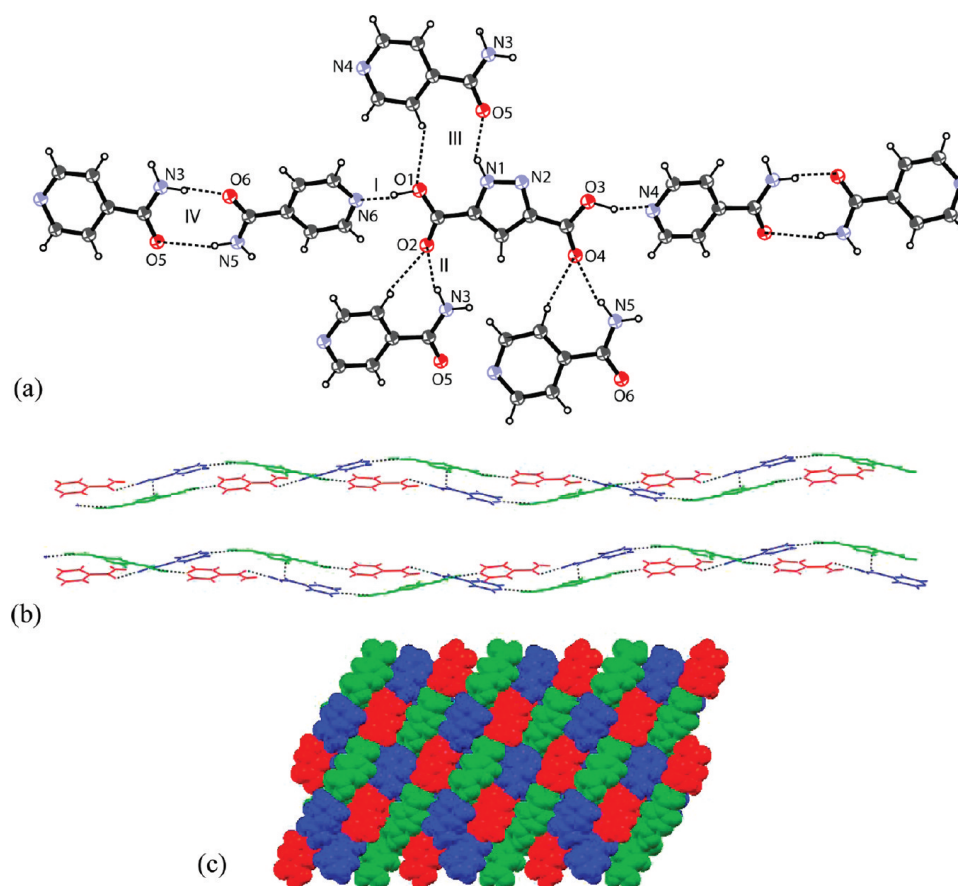


Figure 2. (a) Four different heterosynths in cocrystal 2, (b) H-bonded infinite helical chains of 2 viewed along the *a* axis, and (c) packing diagram along the crystallographic *b* axis in the ABBA manner.

planar pyrazole heterocycles of pzdca (centroid to centroid distance = 3.69 Å).

Although the hydrogen atoms of the solvent water molecule could not be located in this particular case, simple geometric arguments coupled with chemical intuition allows us to place them in reasonable positions. It exhibits hydrogen contact with the acid group of the adjacent pzdca molecule as a donor and also with the adjacent water molecule leading to a one-dimensional infinite water chain in the crystal lattice (Figure 1b and 1c). The minimum pore diameter of the water chain along the *a* axis observed is ~5.2 Å. The distance between the chain oxygen atoms ($O \cdots O$, 1.93 Å) is relatively smaller compared to the water chain/water wire observed in hydrophobic crystal channels or aqua pores of various organic solids.¹³

Crystal structure analysis of 2 (2isonic.pzdca) reveals a 2:1 cocrystal that crystallizes in monoclinic space group $P2_1/n$ with two molecules of isonicotinamide and one molecule of pzdca in the asymmetric unit. In the cocrystal, pzdca forms four different heterosynths with the two crystallographically independent isonicotinamide molecules (Figure 2a). It is to be noted that formation of three different heteromeric interactions is considered as an ideal precondition for cocrystal formation.¹¹ The carboxylic acid group of pzdca and pyridine N of isonicotinamide form synthon I. Donation of hydrogen bonds from the $-NH_2$ moiety of isonicotinamide to the carbonyl moiety of the pzdca

molecule form synthon II. The pyrazole N1 proton of pzdca interacting with the carbonyl moiety of isonicotinamide led to synthon III, which is further enhanced by a $C-H \cdots O$ interaction between the two crystal partners. Synthon IV is the homomeric $R_2^2(8)$ amide dimer of isonicotinamide. Although four different heteromeric synths are featured in both the crystals of nicotinamide and isonicotinamide with pzdca, except the acid–pyridine, the other synths observed in cocrystals 1 and 2 are quite different. Crystal 1 shows formation of homomeric pzdca dimer, whereas crystal 2 exhibits isonicotinamide dimer (Table 2). Furthermore, the pyridine ring of isonicotinamide exhibits face-to-face $\pi-\pi$ stacking interactions with the pyrazole heterocycles of pzdca. The centroid to centroid distance between two such heterocycles is 3.57 Å. In crystal packing, these supramolecular heterosynths generate an infinite 3D hydrogen-bonded helical network that further sustained via $\pi-\pi$ stacking and various $C-H \cdots O$ interactions in the ABBA manner (Figure 2b and 2c).

Nicotinamide–dipicolinic acid cocrystal 3 ($nic \cdot dpa \cdot H_2O$) crystallizes in $P2_1/c$ space group in the hydrated form with a 1:1 stoichiometric ratio. The interaction of nicotinamide with dipicolinic acid takes place through well-established acid–pyridine ($N \cdots H-O$) as well as through acid–amide ($O-H \cdots C=O$) heterosynths. Thus, the two carboxylic acid groups of dipicolinic acid act both as a hydrogen-bond donor with the N atom of

Table 2. Geometrical Parameters for Hydrogen Bonds in 1–6^a

cocrystal/salt	bond (symmetry)	d_{D-H} (Å)	$d_{H...A}$ (Å)	$d_{D...A}$ (Å)	$\angle D-H...A$ (deg)
1	N(1)–H(1N)···O(3) ⁱ	0.84(3)	2.01(3)	2.821(3)	160(2)
	O(2)–H(2O)···O(5) ⁱⁱ	0.96(4)	1.65(4)	2.600(3)	168(4)
	N(3)–H(3A)···O(1) ⁱⁱⁱ	0.86	2.57	2.925(3)	106
	N(3)–H(3A)···O(1) ⁱⁱ	0.86	2.21	3.003(3)	153
	N(3)–H(3B)···N(2) ⁱⁱⁱ	0.86	2.33	3.152(3)	161
	O(4)–H(4)···N(4) ^{iv}	0.82	1.76	2.552(3)	161
2	N(3)–H(3NA)···O(6) ^v	0.98(3)	1.87(3)	2.839(2)	177(3)
	N(1)–H(1N)···O(5) ^{vi}	0.92(2)	2.02(2)	2.835(2)	147(2)
	O(1)–H(1O)···N(6) ⁱⁱⁱ	1.04(2)	1.52(2)	2.551(2)	175(3)
	N(5)–H(5NA)···O(5) ^{vi}	0.90(3)	2.26(3)	3.146(2)	167(2)
	N(3)–H(3NB)···O(2) ^{vii}	0.96(2)	1.96(2)	2.916(2)	170.3(19)
	O(3)–H(3O)···N(4)	1.06(3)	1.57(3)	2.605(2)	165(2)
	N(5)–H(5NB)···O(4) ^{viii}	0.92(2)	2.12(2)	3.008(2)	163.7(19)
3	O(2)–H(2)···N(2) ^{ix}	0.82	1.73	2.545(7)	172
	N(3)–H(3A)···O(5) ^x	0.86	2.04	2.902(7)	178
	N(3)–H(3B)···O(3) ^{xi}	0.86	2.17	3.002(7)	164
	O(4)–H(4)···O(6)	0.82	1.94	2.679(7)	149
	O(4)–H(4)···N(1) [Intra]	0.82	2.20	2.679(6)	118
4	N(3)–H(3NA)···O(2) ^{xii}	0.88(3)	2.08(3)	2.953(3)	173(2)
	O(1)–H(1O)···N(2) ^{xiii}	1.00(3)	1.59(3)	2.583(3)	178(4)
	N(3)–H(3NB)···O(3) ^{xii}	0.97(3)	1.95(3)	2.919(3)	176(2)
	O(6W)–H(6WA)···O(5) ^{xiv}	0.92(5)	1.83(5)	2.744(3)	173(5)
	O(6W)–H(6WB)···O(3) ^{xv}	0.84(4)	2.28(4)	2.957(3)	138(4)
	O(4)–H(4O)···O(6W) ^{xvi}	0.91(3)	1.67(3)	2.570(3)	170(3)
5	N(2)–H(2N)···O(1) ⁱⁱⁱ	1.01(4)	2.21(4)	2.830(3)	118(3)
	N(2)–H(2N)···N(1) ⁱⁱⁱ	1.01(4)	1.80(4)	2.778(3)	162(3)
	O(2)–H(2O)···O(3) [intra]	0.93(5)	1.47(5)	2.382(3)	168(5)
	N(3)–H(3A)···O(5) ^{xi}	0.86	2.04	2.896(3)	177
	N(3)–H(3B)···O(4) ^v	0.86	2.10	2.896(3)	153
6	O(1)–H(1O)···O(3) [intra]	1.01(3)	1.40(3)	2.407(2)	171(2)
	N(2)–H(2N)···O(4) ^{xvii}	0.98(2)	1.87(2)	2.741(2)	147(2)
	N(2)–H(2N)···N(1) ^{xvii}	0.98(2)	2.16(2)	2.903(2)	131.9(19)
	N(3)–H(3A)···O(5) ^{ix}	0.86	2.09	2.9449(19)	172
	N(3)–H(3B)···O(4) ^{xviii}	0.86	2.12	2.931(2)	157

^a Symmetry codes: (i) $2-x, 1-y, -z$; (ii) $1-x, 1-y, 1-z$; (iii) $-1+x, y, z$; (iv) $-x, 1-y, -z$; (v) $1/2+x, 1/2-y, -1/2+z$; (vi) $-1/2+x, 1/2-y, 1/2+z$; (vii) $1+x, y, z$; (viii) $1/2-x, 1/2+y, 1/2-z$; (ix) $1-x, 1/2+y, 1/2-z$; (x) $2-x, 1-y, -z$; (xi) $1-x, 1-y, -z$; (xii) $x, 1/2-y, 1/2+z$; (xiii) $1-x, -1/2+y, 1/2-z$; (xiv) $x, 1+y, z$; (xv) $x, 3/2-y, 1/2+z$; (xvi) $-x, 2-y, -z$; (xvii) $2-x, 1-y, 1-z$; (xviii) $2-x, -y, 1-z$.

pyridine ring and as acceptor with the amide group of nicotinamide. The notable feature of cocrystal **3** is the existence of a quite ordered interstitial discrete solvent water molecule which is involved in simultaneous hydrogen bonding with the two acid groups of dipicolinic acid and two neighboring solvent water molecules (Figure 3a). The presence of an interstitial water molecule in this cocrystal may be due to an imbalance in the donor/acceptor functionality arising from two acid groups in the 2 and 6 positions of dipicolinic acid. It should be mentioned that Fourier analysis could not locate the hydrogen atoms of the water molecule due to poor-quality single-crystal diffraction data. The extensive hydrogen bonding of intervening solvent water molecule with the dpa acid lead to infinite bilayer zigzag chains, simultaneously resulting in π – π stacking interactions between the dipicolinic acid and the nicotinamide molecules independently (Figure 3b). Interestingly, the centroid to centroid distances between the two pyridine rings of both dpa and nicotinamide

are equal, which is measured as 3.76 Å. Further, nicotinamide itself forms the $R^2_2(8)$ homodimer through its $N-H\cdots O$ homosynthon, which is observed frequently in nicotinamide–carboxylic acid cocrystal (Figure 3a). In packing, the acid–base assemblies interact in a parallel and an offset manner via weak van der Waals forces to form stacks along the crystallographic c axis (Figure 3c). These stacks are further sustained by various complementary $C-H\cdots O$ hydrogen bonds.

Isonicotinamide–dipicolinic acid (1:1) cocrystal (isonic·dpa·H₂O), **4**, crystallizes in the monoclinic space group, $P2_1/c$, with a solvent water molecule in the asymmetric unit. The crystal structure is sustained by energetically more favorable $COOH\cdots N_{arom}$ and $COOH\cdots N_{amine}$ supramolecular heterosynthons, but the amide–amide homomeric synthon of isonicotinamide is absent. Isonicotinamide in the cocrystal is positioned in such a way that the amide group can simultaneously form the $R^2_2(10)$ motif with the two planar carboxylic groups of dpa and also

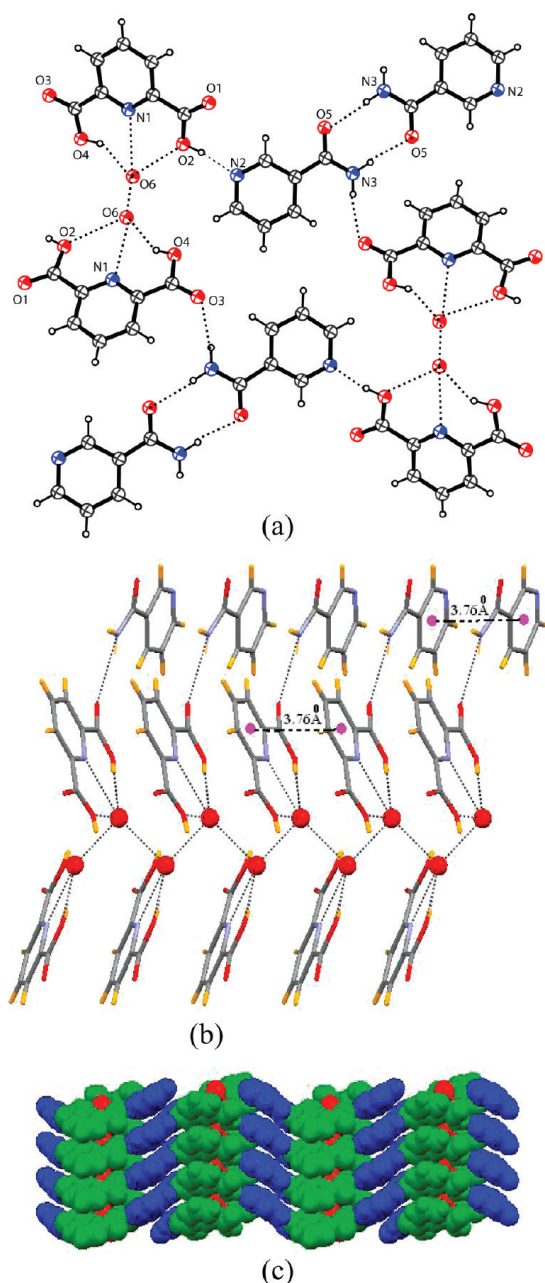


Figure 3. (a) H-bonded interaction between the organic base, acid, and crystal hydrates, (b) interaction of crystal hydrates with acid in zigzag motion and π - π stacking interactions, and (c) packing diagram along the crystallographic c axis.

with the solvent water molecule and the carboxylic group resulting in the $R^2_3(8)$ motif (Figure 4a). The $-\text{NH}_2$ moiety of amide group and the water molecule both act as a donor, whereas the carbonyl oxygen of $-\text{COOH}$ as a hydrogen-bond acceptor in these motifs. The solvent water molecule involved in three different hydrogen-bonding interactions in the cocrystal. It forms a hydrogen bond with the hydroxyl moiety of the $-\text{COOH}$ group as an acceptor and also establishes a second and third hydrogen bond with the two carbonyl

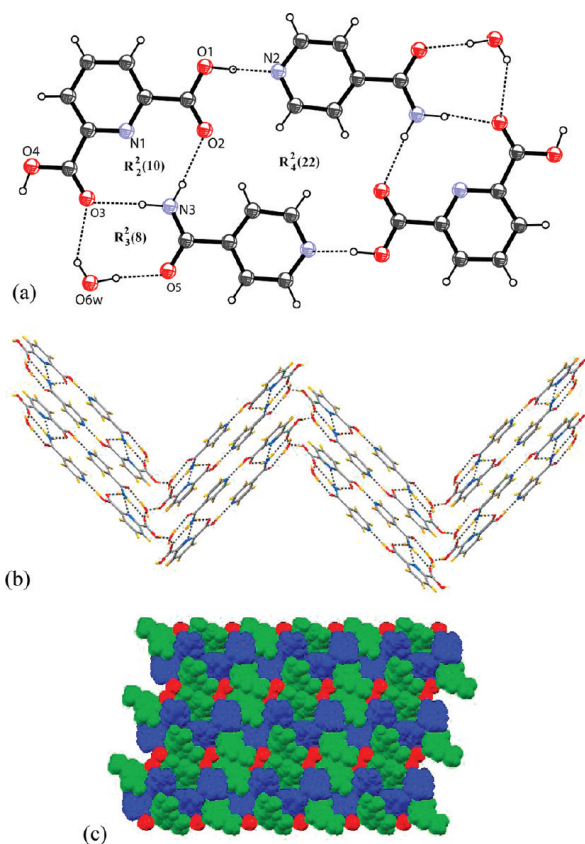


Figure 4. (a) Different H-bonded synthons in 6-components assembly of 4, (b) perpendicular sheets of 6-components assembly, and (c) packing diagram along the b axis (green = dpa, blue = isonic, and red = solvent water).

groups of the amide and acid groups, respectively. The three-component assembly process thus produced is further linked to another similar unit to form a supramolecular ring motif $R^2_4(22)$, which may be identified as six-component hydrogen-bonded supramolecular sheets in the cocrystal (Figure 4a). The discrete 6-component assembly is again associated through intermolecular $\text{O}-\text{H}$ (carboxyl) $\cdots \text{O}$ (water) hydrogen bonds to another similar unit at a dihedral angle of 81.85° , resulting in an infinite 'V'-shaped molecular sheet as shown in Figure 4b. The assemblies stack in a parallel manner, being further held together via weak van der Waals forces and various $\text{C}-\text{H} \cdots \text{O}$ interactions (Figure 4c). It is to be mentioned that the $-\text{NH}_2$ moiety of the amide group interacts with the acid group of dpa in a similar manner; the solvent water molecule interacts in cocrystal 3, also preventing formation of homomeric synthon.

Multicomponent crystal 5 crystallizes in the monoclinic $P2_1/c$ space group with one molecule each of nicotinamide and quinolinic acid in the asymmetric unit. Fourier analysis shows there is a proton transfer from one of the carboxyl groups of the quinolinic acid to the nicotinamide moiety, suggesting salt formation in this case. The $\text{C}-\text{O}$ bond distances, $D_{\text{C}-\text{O}}$, of the carboxyl group also confirmed the presence of an ionized carboxylic group. However, the ΔpK_a value between nicotinamide ($\text{pK}_a = 3.35$) and that of quinolinic acid ($\text{pK}_{a1} = 2.78$ and $\text{pK}_{a2} = 5.02$) suggests the possibility of formation of both cocrystal and salt.¹⁴ It is to be

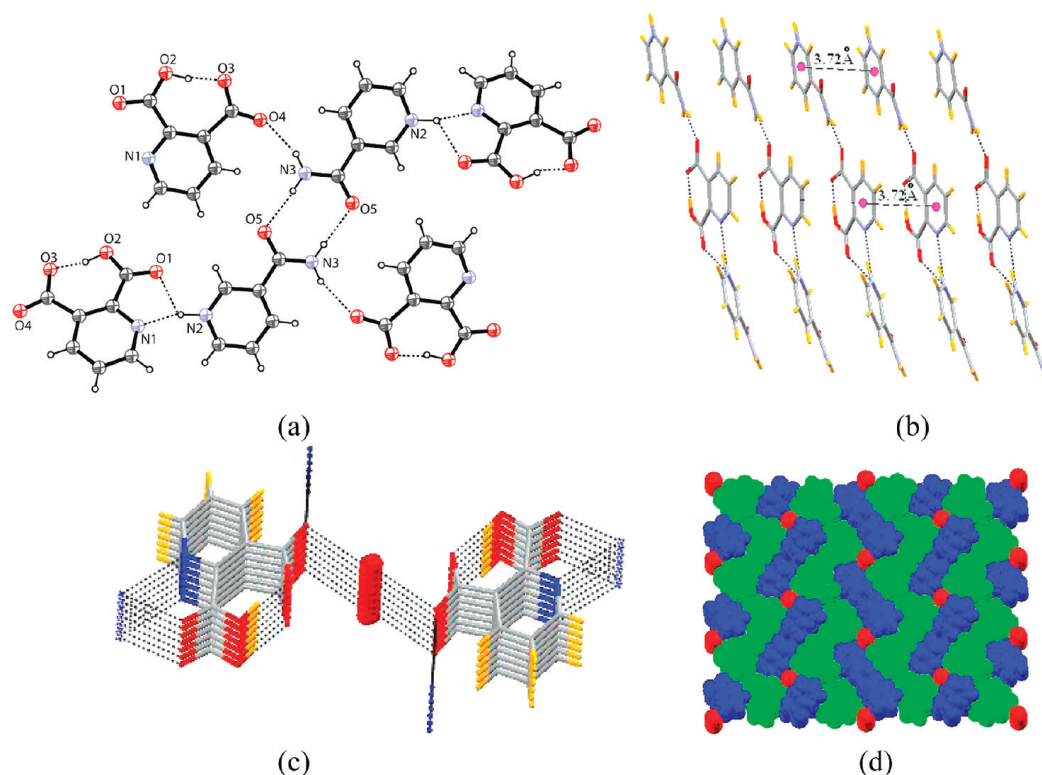


Figure 5. (a) Various H-bond interactions between nicotinamide and quinolinic acid, (b) π – π stacking interactions, (c) water chain of disordered crystal hydrates, and (d) packing diagram along the a axis in crystal 5.

noted that salt formation is very rare, although a large number of nicotinamide carboxylic acid supramolecular complexes have been studied.^{10a} In addition to charge-assisted interactions, $N^+ - H \cdots O^-$, nicotinamide interacts with the quinolinic acid via acid–amide heterosynthon. It also forms a hydrogen bond between the two protonated and nonprotonated pyridine moieties of salt formers (Figure 5a). The acidic proton of quinolinic acid is involved in an intramolecular hydrogen bond with the adjacent carboxylate group. The protonated nicotinamide is further involved in formation of homomeric $R_2^2(8)$ amide dimer in the crystal. The pyridine rings of either moiety exhibit face-to-face π – π stacking interactions (centroid to centroid distance = 3.72 Å in both cases) with the adjacent units (Figure 5b). In packing, these well-directed hydrogen bonds lead to formation of a layered molecular assembly supported by complementary $C-H \cdots O$ interactions (Figure 5d).

The crystal also contains one disordered solvent water molecule with 50% split occupancy. Since the hydrogen of the disordered water molecules could not be located (high U_{eq} of water oxygen atom), the exact hydrogen-bonding environment of the hydrate could not be presented. Aggregation of water molecules leading to the 1D water chain accommodated between the quinolinic acid units has similarity to the arrangements of water molecules in the crystal lattice of **1** (Figure 5c).

Crystal **6** has a 1:1 ratio of isonicotinamide and quinolinic acid in the asymmetric unit. One of the carboxylic acid groups of quinolinic acid is deprotonated and forms strong charge-assisted $N^+ - H \cdots O^-$ bonds with protonated isonicotinamide. Isonicotinamide also interacts with the acid through acid–amide and the

pyridine N atom. The two protonated isonicotinamide molecules form a noncentrosymmetric $R_2^2(8)$ homodimer in the asymmetric unit (Figure 6a). The different hydrogen bonds observed in these ionic species all lie in a plane leading to a two-dimensional sheet in the crystal lattice (Figure 6b).

The packing of the crystals studied irrespective of salt or cocrystal varies significantly with the differences in synthon formation. Crystal **1** shows the acid–base pairs interacting in a “head-to-head” manner via acid–amide synthon assembled in an offset fashion, crystal **3** exhibits a parallel-layered structure of acid–base pairs with hydrate-assisted assembly and a dimer of nicotinamide, while crystal **5** also preferred amide–amide homodimer in its lattice. We observed a characteristic deviation of crystal hydrates related to hydrogen-bonding interaction with the acid/base entities. In this study, the crystal hydrates, surprisingly, do not show any interaction with the base, but the crystal hydrates reported recently in nicotinamide crystals with caffeic acid, ferulic acid, and gallic acid show a hydrogen-bonded interaction with the host–guest moiety.⁴

Isonicotinamide crystal **2** shows that the acid–base interacts via a “head-to-tail” manner in a 3D helical network with strong face-to-face π – π stacking interactions between the acid–base and the base–base pairs; crystal **4** is a well-organized “V”-shaped sheet structure, the only structure where the hydrate interacts with both the acid and the base, while salt **6** exhibits a similar packing structure with crystal **5** with isonicotinamide homodimer. Thus, it seems that a homosynthon is preferred in the nicotinamide/isonicotinamide salts also observed by Guru Row et al. in the oxalic acid–nicotinamide crystal.^{10a} The hydrates in isonicotinamide crystals with ferulic acid, gallic acid, or ellagic

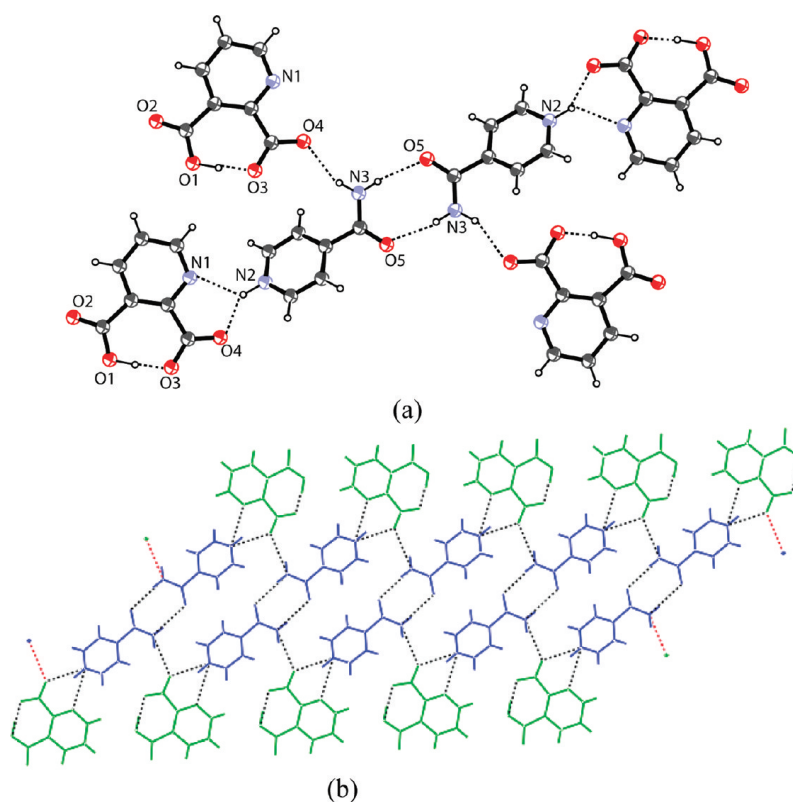


Figure 6. (a) Interaction of the two salt formers, and (b) 2D hydrogen-bonded sheet in the crystal lattice of 6.

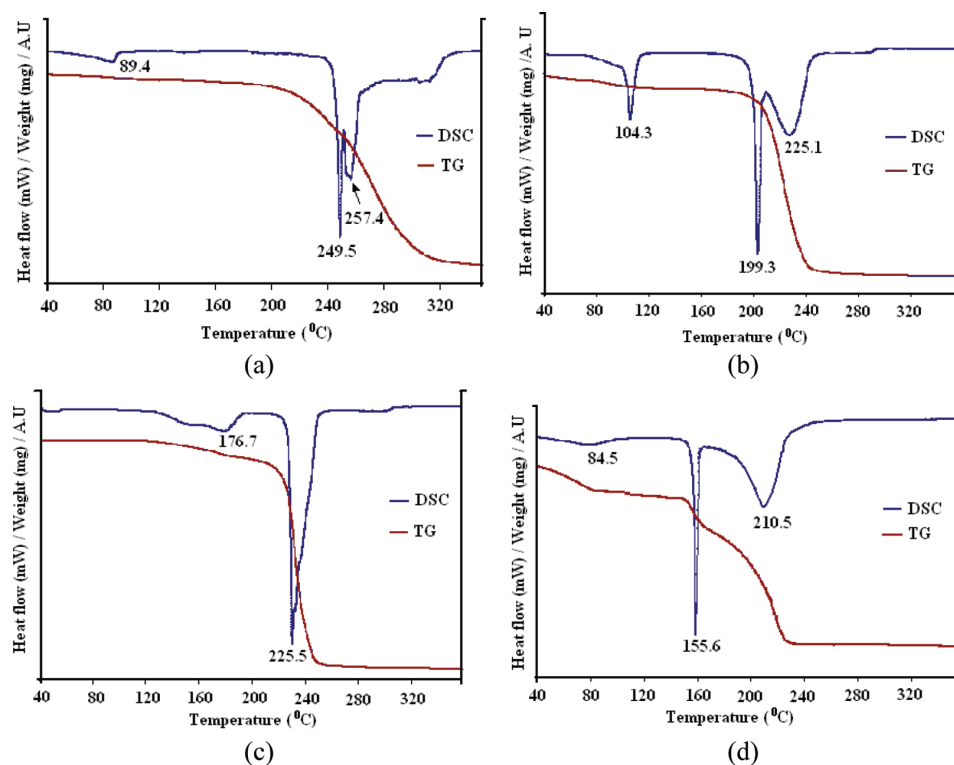


Figure 7. DSC and TG plot of multicomponent crystals 1, 3, 4 and 5 (a, b, c, and d, respectively) showing thermal loss of cocystal hydrates.

Table 3. Thermal Behavior of Water of Crystallization in the Multicomponent Crystals

cocrystal/salt	stoichiometric ratio	disordered/ ordered hydrate	thermal loss of water (°C)	melting point of crystal (°C)	water environment	type of hydrate
nic·pzdca·H ₂ O	1:1:1	yes	89.4	249.5; 257.4		1D chain
2isonic·pzdca	2:1:0	no		254.5; 266.6		
nic·dpa·H ₂ O	1:1:1	yes	104.3	199.3; 225.1	DDA	isolated
isonic·dpa·H ₂ O	1:1:1	yes	176.7	225.5	DDA	isolated
nic·qna·H ₂ O	1:1:1	yes	84.5	155.6; 210.5		1D chain
isonic·qna	1:1:0	no		170.0; 226.3		

acid show interactions with both acid/base pairs, being an exception with hydrochlorothiazole, where it does not interact with isonicotinamide.⁴ It can therefore be concluded that different types of crystal hydrates irrespective of environment in the lattice by combination with other available synthons stabilize the organic solids significantly. It has been suggested that the electronic properties associated with the substituents on the aromatic ring of a carboxylic acid play a major role in formation of cocrystals with benzamide.⁹ However, in the present study the nitrogen atom on the aromatic ring as well as on the heterocycle attached to dicarboxylic acids along with the hydrated water molecules contribute to the stabilization of cocrystals and salts.

The presence of water in these multicomponent crystals as isolated hydrate or in the water chains was confirmed by TG and DSC analysis of the freshly grown air-dried crystals. The endotherms for water evolution from the multicomponent crystals **1** and **5** occur at 89.4 and 84.5 °C, respectively, in DSC. Thus, it appears that loosely held water in 1D chains evaporates at or around the boiling point of water (Figure 7). Dehydration of isolated water of crystals **3** and **4** occurs at temperatures of 104.3 and 176.7 °C, respectively. Since the water molecule forms three H bonds in the cocrystal **3** are expected to exhibit greater thermal stability, whereas in **4** the loss of water which is in a DDA environment occurs concurrently just before the melt of the cocrystal. It appears that the presence of strong hydrogen bonding makes the water molecule an integral part of the crystal structure.⁴ The TG plots revealed weight loss equivalent to a single water molecule per crystal in each case. Most of these crystals exhibit a lower melting point than the pure acids. The thermal stability of the multicomponent crystals is summarized in Table 3.

CONCLUSIONS

All multicomponent crystals possess persistent carboxylic acid–aromatic N-heterosynthons together with other well-established supramolecular heterosynthons. Introduction of pyridine rings of both crystal formers resulted in at least three different heteromeric interactions for the hydrogen-bonded ring motifs. However, overall such interactions do not form new heterosynthons other than the reported one. The presence of two additional hydrogen-bond donor/acceptor functional groups in the pyrazole ring of 3,5-pyrazole dicarboxylic acid showed formation of four synthons in its cocrystals. The cocrystal which forms hydrates possesses extensive hydrogen bonds with various acids which prevent formation of new heterosynthons and also reduce the API-to-acid ratio. The different hydrates irrespective of discrete or the water chain shows little or no correlation between the structure and the thermal stability. The exception is the observation of loss of chain water molecules at a relatively lower temperature than the discrete hydrates.

ASSOCIATED CONTENT

S Supporting Information. TG and DSC of **2** and **6**; compared infrared spectra of **1–6** are available. This material is available free of charge via the Internet at <http://pubs.acs.org>. CIF files of all compounds reported here are deposited with the CCDC, CCDC Nos. 837853–837858.

AUTHOR INFORMATION

Corresponding Author

*E-mail: juba@iitgernet.in.

ACKNOWLEDGMENT

The authors thank the Department of Science and Technology (New-Delhi) India for the single-crystal X-ray facility.

REFERENCES

- (a) Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647. (b) Etter, M. C. *J. Am. Chem. Soc.* **1982**, *104*, 1095. (c) Desiraju, G. R. *Crystal engineering: The design of organic solids*; Elsevier: New York, 1989. (d) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120. (e) Desiraju, G. R. *Angew. Chem., Int. Ed.* **1995**, *34*, 2311. (f) Desiraju, G. R. Steiner, T. *The weak hydrogen bond in structural chemistry and biology*; Oxford University Press: New York, 1999.
- (a) Reddy, D. S.; Craig, D. C.; Desiraju, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 4090. (b) Bučar, D.-K.; Henry, R. F.; Lou, X.; Duerst, R. W.; Borchardt, T. B.; MacGillivray, L. R.; Zhang, G. G. Z. *Mol. Pharmaceutics* **2007**, *4*, 339. (c) Moorthy, J. N.; Natarajan, R.; Venugopalan, P. J. *Mol. Struct.* **2005**, *741*, 104.
- (a) Aakeröy, C. B.; Beatty, A. M.; Helfrich, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 14425. (b) Walsh, R. D. B.; Bradner, M. W.; Fleischman, S.; Morales, L. A.; Moulton, B.; Rodríguez-Hornedo, N.; Zaworotko, M. J. *Chem. Commun.* **2003**, 186. (c) Aakeröy, C. B.; Desper, J.; Leonard, B.; Urbina, J. F. *Cryst. Growth Des.* **2005**, *5*, 865. (d) Rodríguez-Hornedo, N. *Mol. Pharmaceutics* **2007**, *4*, 299.
- (a) Clarke, H. D.; Arora, K. K.; Bass, H.; Kavuru, P.; Ong, T. T.; Pujari, T.; Wojtas, L.; Zaworotko, M. J. *Cryst. Growth Des.* **2010**, *10*, 2152.
- (a) Gillon, A. L.; Feeder, N.; Davey, R. J.; Storey, R. *Cryst. Growth Des.* **2003**, *3*, 663.
- Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1991**, 426.
- Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.
- Karki, S.; Friščić, T.; Jones, W.; Motherwell, W. D. S. *Mol. Pharmaceutics* **2007**, *4*, 347.
- Seaton, C. C.; Parkin, A. *Cryst. Growth Des.* **2011**, *11*, 1502.
- (a) Hathwar, V. R.; Pal, R.; Guru Row, T. N. *Cryst. Growth Des.* **2010**, *10*, 3306. (b) Fleischmann, S. G.; Kuduva, S. S.; McMahon, J. A.; Moulton, B.; Walsh, R. D. B.; Rodríguez-Hornedo, N.; Zaworotko, M. J. *Cryst. Growth Des.* **2003**, *3*, 909. (c) Rodríguez-Hornedo, N.; Nehm, S. J.; Seefeldt, K. F.; Pagan-Torres, Y.; Falkiewicz, C. *Mol. Pharmaceutics* **2006**, *3*, 362. (d) Seefeldt, K.; Miller, J.; Alvarez-Nunez, F.; Rodríguez-Hornedo, N. *J. Pharm. Sci.* **2007**, *96*, 1147. (e) Porter, W. W., III; Elie, S. C.; Matzger, J.

- A. J. *Cryst. Growth Des.* **2008**, *8*, 14. (f) Chieng, N.; Hubert, M.; Saville, D.; Rades, T.; Aaltonen, J. *Cryst. Growth Des.* **2009**, *9*, 2377. (g) Gagniere, E.; Mangin, D.; Puel, F.; Bebon, C.; Klein, J.-P.; Monnier, O.; Garcia, E. *Cryst. Growth Des.* **2009**, *9*, 3376. (h) Maheshwari, C.; Jayasankar, A.; Khan, N. A.; Amidon, G. E.; Rodríguez-Hornedo, N. *CrystEngComm.* **2009**, *11*, 493. (i) Sheikh, A. Y.; Rahim, S. A.; Hammond, R. B.; Roberts, K. J. *CrystEngComm.* **2009**, *11*, 501. (j) Nicoli, S.; Bilzi, S.; Santi, P.; Caira, M. R.; Li, J.; Bettini, R. J. *Pharm. Sci.* **2008**, *97*, 4830. (k) Orola, L.; Veidis, M. V. *CrystEngComm.* **2009**, *11*, 415. (l) Remenar, J. F.; Peterson, M. L.; Stephens, P. W.; Zhang, Z.; Zimenkov, Y.; Hickey, M. B. *Mol. Pharmaceutics* **2007**, *4*, 386. (m) Berry, D. J.; Seaton, C. C.; Clegg, W.; Harrington, R. W.; Coles, S. J.; Horton, P. N.; Hursthouse, M. B.; Storey, R.; Jones, W.; Friscic, T.; Blagden, N. *Cryst. Growth Des.* **2008**, *8*, 1697. (n) Bathori, N. B.; Lemmerer, A.; Venter, G. A.; Bourne, S. A.; Caira, M. R. *Cryst. Growth Des.* **2011**, *11*, 75. (o) Buanz, A. B. M.; Parkinson, G. N.; Gaisford, S. *Cryst. Growth Des.* **2011**, *11*, 1177. (p) Vishweshwar, P.; Nangia, A.; Lynch, V. M. *Cryst. Growth Des.* **2003**, *3*, 783. (q) Fbin, L.; Hamill, N.; Eccles, K. S.; Moynihan, H. A.; Maguire, A. R.; McCausland, L.; Lawrence, S. E. *Cryst. Growth Des.* **2011**, *11*, 3522. (r) Seaton, C. C.; Parkin, A.; Wilson, C. C.; Blagden, N. *Cryst. Growth Des.* **2009**, *9*, 47. (s) Seliger, J.; Zagar, V. J. *Phys. Chem. A* **2010**, *114*, 12083. (t) Lu, J.; Rohani, S. *Org. Process Res. Dev.* **2009**, *13*, 1269. (u) Remenar, J. F.; Peterson, M. L.; Stephens, P. W.; Zhang, Z.; Zimenkov, Y.; Hickey, M. B. *Mol. Pharmaceutics* **2007**, *4*, 386.
- (11) Lemmerer, A.; Bernstein, J. *CrystEngComm.* **2010**, *12*, 2029.
- (12) Das, B.; Baruah, J. B. *Cryst. Growth Des.* **2011**, *11*, 278.
- (13) (a) Natarajan, R.; Charmant, J. P. H.; Orpen, A. G.; Davis, A. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 5125. (b) Saha, B. K.; Nangia, A. *Chem. Commun.* **2005**, 3024. (c) Yu, Z.-B.; Sun, J.; Huang, Z.-T.; Zheng, Q.-Y. *CrystEngComm* **2011**, *13*, 1287. (d) Cheruzel, L. E.; Pometun, M. S.; Cecil, M. R.; Mashuta, M. S.; Wittebort, R. J.; Buchanan, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5452.
- (14) Childs, S. L.; Stahly, G. P.; Park, A. *Mol. Pharmaceutics* **2007**, *4*, 323.