

Structure–Stability Relationships in Cocrystal Hydrates: Does the Promiscuity of Water Make Crystalline Hydrates the Nemesis of Crystal Engineering?

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ABSTRACT: This contribution addresses the role of water molecules in crystal engineering by studying the crystal structures and thermal stabilities of 11 new cocrystal hydrates, all of which were characterized by single crystal X-ray crystallography, powder X-ray diffraction (PXRD), infrared spectroscopy (IR), thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC). The cocrystal hydrates can be grouped into four categories based upon thermal stability: (1) water is lost at $< 100\text{ }^{\circ}\text{C}$; (2) water is lost between 100 and $120\text{ }^{\circ}\text{C}$; (3) water is lost at $> 120\text{ }^{\circ}\text{C}$; (4) dehydration occurs concurrently with the melt of the cocrystal. In order to address if there is any correlation between structure and stability, the following factors were considered: type of hydrate (tunnel hydrate or isolated hydrate); number of hydrogen bond donors and acceptors; hydrogen bond distances; packing efficiency. Category 1 hydrates exhibit water molecules in tunnels. However, no structure/stability correlations exist in any of the other categories of hydrate. To complement the cocrystal hydrates reported herein, a Cambridge Structural Database (CSD) analysis was conducted in order to address the supramolecular heterosynthons that water molecules exhibit with two of the most relevant functional groups in the context of active pharmaceutical ingredients, carboxylic acids, and alcohols. The CSD analysis suggests that, unlike cocrystals, there is great diversity in the supramolecular heterosynthons exhibited by water molecules when they form hydrogen bonds with carboxylic acids or alcohols. It can therefore be concluded that the promiscuity of water molecules in terms of their supramolecular synthons and their unpredictable thermal stability makes them a special challenge in the context of crystal engineering.

Crystal engineering,^{1,2} the understanding of intermolecular interactions in crystalline solids and their exploitation for the rational design of new crystal forms with controlled properties, continues to be a vibrant and growing topic in solid state chemistry. The relevance of crystal engineering to pharmaceutical science is particularly high since crystal forms of active pharmaceutical ingredients (APIs) are preferred by industry and regulatory bodies for use in oral dosage formulations of drugs.³ However, crystal forms of APIs have an Achilles' heel: their rate of dissolution is directly related to the thermodynamic (equilibrium) solubility of the crystal form,⁴ a physicochemical property that cannot be readily optimized for a particular clinical need. Indeed, the rate of dissolution may also be affected by particle size and diffusion phenomena, but thermodynamic solubility is a fixed property of the crystal form. Whereas controlled release technologies are available to modulate the dissolution rate of a highly soluble, highly permeable API (BCS class I, Scheme 1) or a highly soluble, poorly permeable API (BCS class III), there is little that can be done to control a poorly soluble, highly permeable API (BCS class II) or a poorly soluble, poorly permeable API (BCS class IV). Hence, the rate of dissolution of an API (BCS II and BCS IV) critically impacts the pharmacokinetic profile of orally delivered APIs, and the majority of new chemical entities in drug development (ca. 80%) suffer from poor solubility.⁵ Therefore, there is heightened interest in and awareness of the need to diversify the range of crystal forms exhibited by

APIs, which were traditionally limited to the pure API, its salts, solvates, and hydrates and polymorphs thereof. Pharmaceutical cocrystals,⁶ that is, cocrystals formed via complexation between different molecules, an API and a pharmaceutically acceptable “cocrystal former”, have recently gained interest in this context as exemplified by bioavailability studies upon compounds such as fluoxetine hydrochloride (Prozac),⁷ a sodium channel blocker that was developed by Pfizer,⁸ and carbamazepine (Tegretol).⁹ Pharmaceutical cocrystals can be highly amenable to design because the very nature of APIs means that they contain exterior hydrogen bonding groups that will readily engage in supramolecular synthons¹⁰ with appropriate cocrystal formers. Furthermore, cocrystals that are highly soluble but form unstable complexes can produce a “spring-and-parachute” effect with APIs with low bioavailability that can modulate both T_{max} and C_{max} . In short, pharmaceutical cocrystals offer innovative approaches to controlling the bioavailability of APIs in ways that cannot be readily achieved through traditional approaches.¹¹

Hydrates represent another class of multiple-component crystal that is of relevance to both crystal engineering and pharmaceutical science. Water molecules readily incorporate into crystal lattices because of their small size and their versatile hydrogen bonding capabilities.¹² Indeed, water molecules can even stabilize crystal structures when there is an imbalance in the number of acceptors and donors¹³ by forming a diverse arrangement of supramolecular heterosynthons, and hydrates can be the preferred crystal form of an API¹⁴ if they are more stable to hydration than the corresponding anhydrate: the antiplatelet agent picotamide¹⁵ was found to be

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Scheme 1. Cocrystal Formers Used Herein, Abbreviated as Follows: CFA, FER, GAL, INM, NAM, ELA, QUE, HCT, TBR, CAF

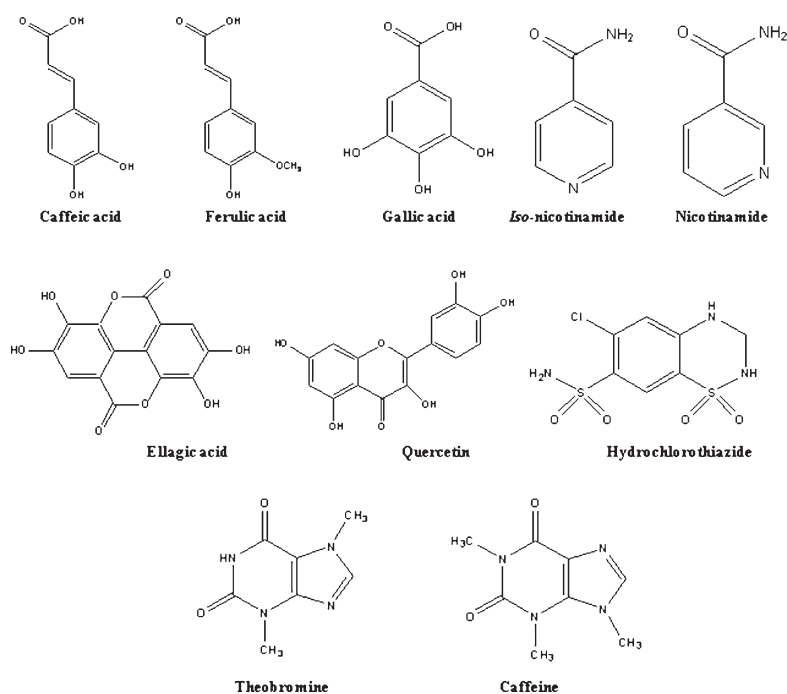


Table 1. Crystallographic Data and Structure Refinement Parameters for the 11 Cocrystal Hydrates Presented Herein

	FERINM·H ₂ O	FERNAM·H ₂ O	ELAINM·1.7H ₂ O	GALNAM·0.75H ₂ O	GALTBR·2H ₂ O	GALINM·H ₂ O
formula	C ₁₆ H ₁₈ N ₂ O ₆	C ₁₆ H ₁₈ N ₂ O ₆	C ₂₆ H _{21.4} N ₄ O _{11.7}	C ₁₃ H _{13.5} N ₂ O _{6.75}	C ₁₄ H ₁₆ N ₄ O ₉	C ₁₃ H ₁₄ N ₂ O ₇
MW	334.32	334.32	574.65	305.76	386.32	310.26
crystal system	monoclinic	monoclinic	triclinic	orthorhombic	monoclinic	monoclinic
space group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> $\bar{1}$	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>C</i> 2/ <i>c</i>	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> (Å)	6.908 (1)	6.9389(2)	3.6207(2)	3.7606(1)	27.737(9)	17.448(1)
<i>b</i> (Å)	34.600(6)	33.460(1)	12.4908(6)	15.2613(3)	6.664(3)	3.709(4)
<i>c</i> (Å)	7.197(1)	7.3179(3)	13.5227(6)	22.7185(4)	17.345(8)	20.134(2)
α (deg)	90	90	72.641(3)	90	90	90
β (deg)	116.928(9)	116.652(2)	89.258(3)	90	92.962(9)	96.567(5)
γ (deg)	90	90	83.979(3)	90	90	90
<i>V</i> /Å ³	1533.7(4)	1518.51(9)	580.39(5)	1303.85(5)	3202(2)	1294.6(2)
<i>D_c</i> /g cm ⁻³	1.448	1.462	1.644	1.558	1.603	1.592
<i>Z</i>	4	4	1	4	8	4
2 θ range	2.55–63.61	2.64–67.35	3.42–65.36	3.49–68.09	2.35–25.03	3.18–65.52
Nref/Npara	2145/232	2680/234	1916/210	2295/218	2815/272	2174/219
<i>T</i> /K	100(2)	100(2)	100(2)	100(2)	173(2)	100(2)
<i>R</i> ₁ [<i>I</i> > 2 σ (<i>I</i>)]	0.0700	0.0336	0.0439	0.0323	0.0563	0.0376
<i>wR</i> ₂	0.1527	0.0878	0.1093	0.0815	0.1383	0.0942
GOF	0.996	1.026	1.037	1.085	1.076	1.044
abs coef	0.944	0.954	1.136	1.097	0.136	1.128

	GALCAF·0.5H ₂ O	QUETBR·2H ₂ O	ELACAF·H ₂ O	CFANAM·H ₂ O	HCTINM·H ₂ O
formula	C ₁₅ H ₁₇ N ₄ O _{7.5}	C ₂₂ H ₂₄ N ₄ O ₁₁	C ₂₂ H ₁₈ N ₄ O ₁₁	C ₁₅ H ₁₆ N ₂ O ₆	C ₁₃ H ₁₆ ClN ₅ O ₆ S ₂
MW	373.33	518.44	514.40	320.30	437.88
crystal system	monoclinic	triclinic	triclinic	triclinic	triclinic
space group	<i>C</i> 2/ <i>c</i>	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$
<i>a</i> (Å)	19.966(4)	7.0113(3)	9.705(3)	6.2726(2)	7.3100(1)
<i>b</i> (Å)	15.800(3)	11.2981(4)	10.926(5)	7.2730(2)	9.3156(2)
<i>c</i> (Å)	13.111(3)	14.9611(6)	11.469(7)	16.4002(5)	13.5309(3)
α (deg)	90	106.545(2)	104.74(3)	98.430(2)	74.573(1)
β (deg)	130.780(3)	101.826(3)	95.68(3)	94.791(2)	87.442(1)
γ (deg)	90	94.794(3)	113.80(3)	95.896(2)	73.856(1)
<i>V</i> /Å ³	3131.8(11)	1099.15(8)	1047.9(9)	732.48(4)	852.76(3)
<i>D_c</i> /g cm ⁻³	1.584	1.566	1.630	1.452	1.705
<i>Z</i>	8	2	2	2	2
2 θ range	1.86–25.25	3.17–62.63	4.09–65.36	2.74–65.01	3.39–65.33
Nref/Npara	2825/291	3376/341	3301/349	2404/243	2805/268
<i>T</i> /K	100(2)	95(2)	100(2)	225(2)	100(2)
<i>R</i> ₁ [<i>I</i> > 2 σ (<i>I</i>)]	0.0383	0.0429	0.0549	0.0342	0.0349
<i>wR</i> ₂	0.1031	0.1163	0.1380	0.0934	0.0895
GOF	1.044	1.037	1.013	1.050	1.064
abs coef	0.129	1.097	1.150	0.964	4.702

Table 2. Hydrogen Bond Distances and Parameters for Cocrystal Hydrates

	hydrogen bond	$d(\text{H}\cdots\text{A})/\text{\AA}$	$D(\text{D}\cdots\text{A})/\text{\AA}$	$\angle(\text{DHA})$
FERINM·H ₂ O	O—H···O	1.91	2.681(5)	152.0
	O—H···O	2.29	2.733(5)	113.1
	O—H···O	1.77	2.578(5)	161.8
	O—H···O	2.26(3)	3.037(5)	149(5)
	O—H···N	1.98(3)	2.835(6)	165(6)
	N—H···O	2.10(5)	2.997(5)	167(5)
FERNAM·H ₂ O	N—H···O	2.19(5)	2.991(5)	147(5)
	O—H···O	1.84	2.624(2)	155
	O—H···O	2.26	2.687(1)	111
	O—H···O	1.66(2)	2.587(1)	171(2)
	N—H···O	2.10(2)	2.992(2)	168(2)
	N—H···O	2.26(2)	3.010(2)	158(2)
ELAINM·1.7H ₂ O	O—H···N	1.91(2)	2.777(2)	175(2)
	O—H···O	2.17(2)	2.973(2)	158(2)
	O—H···O	1.91	2.749(2)	177.1
	O—H···N	1.86	2.611(2)	147.8
	O—H···O	2.32	2.754(2)	112.8
	N—H···O	2.03(3)	2.930(3)	174(3)
GALNAM·0.75H ₂ O	N—H···O	2.06(3)	2.988(3)	173(3)
	N—H···O	1.98(3)	2.896(2)	169(2)
	N—H···O	2.06(3)	2.897(2)	157(2)
	O—H···O	1.82(3)	2.541(3)	145(4)
	O—H···O	2.04	2.793(2)	149.4
	O—H···O	2.29	2.732(2)	112.9
GALTBR·2H ₂ O	O—H···N	1.87	2.710(2)	175.5
	O—H···O	1.82	2.647(2)	169.4
	O—H···O	2.07(2)	2.877(3)	160(4)
	O—H···O	1.86(2)	2.688(4)	163(4)
	N—H···O	1.91	2.790(3)	174.9
	O—H···O	1.88	2.688(3)	161.2
GALINM·H ₂ O	O—H···O	2.31	2.747(2)	113.0
	O—H···O	1.90	2.722(5)	166.1
	O—H···O	1.93	2.732(4)	158.1
	O—H···O	1.84	2.671(2)	170.5
	O—H···O	2.03	2.824(3)	158.6
	O—H···O	2.50(3)	2.862(3)	110(3)
GALCAF·0.5H ₂ O	O—H···O	1.90(4)	2.807(3)	174(3)
	O—H···O	2.07(3)	2.902(5)	158(5)
	O—H···N	2.13(2)	2.975(5)	162(3)
	O—H···O	2.01(3)	2.853(6)	156(5)
	O—H···N	2.13(2)	2.961(5)	151(3)
	N—H···O	2.17(3)	3.013(2)	162(2)
QUETBR·2H ₂ O	N—H···O	2.04(3)	2.891(2)	171(2)
	O—H···N	1.81	2.645(2)	172.8
	O—H···O	1.92	2.756(2)	174.9
	O—H···O	2.13	2.832(2)	141.3
	O—H···O	2.28	2.722(2)	113.4
	O—H···O	1.97	2.803(2)	169.2
ELACAF·H ₂ O	O—H···O	2.12(3)	2.888(2)	160(3)
	O—H···O	2.00(3)	2.853(2)	157(3)
	O—H···O	1.84(2)	2.703(2)	177(2)
	O—H···O	1.96(2)	2.750(2)	158(2)
	O—H···O	2.12(2)	2.857(1)	154(2)
	O—H···O	2.31(2)	2.712(2)	112(2)
QUETBR·2H ₂ O	O—H···N	1.76(2)	2.705(2)	171(2)
	O—H···O	1.90(2)	2.752(2)	163(2)
	N—H···O	1.96	2.834(3)	172.5
	O—H···O	1.90	2.722(3)	165.2
	O—H···O	1.86	2.615(2)	149.3
	O—H···O	2.26	2.709(2)	113.7
ELACAF·H ₂ O	O—H···O	1.89	2.705(2)	163.0
	O—H···O	1.92	2.753(2)	171.1
	O—H···O	1.83	2.582(2)	147.5
	O—H···N	1.89	2.822(3)	167.4
	O—H···O	1.97	2.909(3)	165.0
	O—H···O	1.92	2.860(3)	160.6
ELACAF·H ₂ O	O—H···O	2.15	3.115(3)	169.9
	O—H···N	1.93	2.702(4)	151.7
	O—H···O	2.30	2.742(3)	113.3
ELACAF·H ₂ O	O—H···O	1.90	2.708(3)	161.3

Table 2. Continued

	hydrogen bond	$d(\text{H}\cdots\text{A})/\text{\AA}$	$D(\text{D}\cdots\text{A})/\text{\AA}$	$\angle(\text{DHA})$
CFANAM·H ₂ O	O—H···O	1.78	2.608(3)	167.2
	O—H···O	1.93	2.701(3)	152.4
	O—H···O	2.27	2.706(3)	112.6
	O—H···O	2.08(2)	2.920(4)	164(4)
	O—H···O	1.99(2)	2.854(4)	162(4)
	O—H···O	1.68(3)	2.608(4)	177(2)
HCTINM·H ₂ O	O—H···O	1.75(3)	2.646(4)	161(2)
	O—H···O	2.07(2)	2.769(2)	135(2)
	O—H···O	2.19(2)	2.721(2)	118(2)
	O—H···O	1.61(2)	2.548(2)	166(2)
	N—H···O	2.16(2)	2.982(2)	157(2)
	N—H···O	2.04(2)	2.950(2)	171(2)
HCTINM·H ₂ O	O—H···N	1.90(1)	2.725(4)	160(2)
	O—H···O	1.89(2)	2.754(3)	166(5)
	O—H···O	2.05(3)	2.882(6)	159(5)
	N—H···O	2.48(3)	3.088(2)	130(2)
	N—H···O	2.17(3)	3.011(3)	161(2)
	N—H···O	2.12(2)	2.959(2)	164(3)
HCTINM·H ₂ O	N—H···O	2.08(2)	2.944(2)	168(3)
	N—H···O	2.45(2)	3.303(2)	168(3)
	N—H···O	2.178(2)	3.038(2)	174(3)
	O—H···N	1.94(2)	2.787(2)	163(3)
	O—H···O	2.23(2)	2.986(2)	148(3)

most stable as the monohydrate, and several drugs such as cephalexin,¹⁶ ampicillin,¹⁷ cromolyn sodium (disodium cromoglycate),¹⁸ and sildenafil citrate¹⁹ are being developed or are currently marketed as hydrates. It has been suggested that ca. 33% of organic compounds form hydrates, whereas solvates are less prevalent (10%).²⁰ However, a survey of the Cambridge Structural Database, v5.30 (CSD)²¹ reveals that only 8224 of the 159 565 molecular organic crystal structures that have had their 3D coordinates determined contain discrete water molecules. The corresponding numbers for organic, organometallic, and coordination compounds suggest that hydrates are more prevalent in general since 49 283 out of the 443 505 structures in the CSD are hydrates. Given their ubiquity, relevance, and that many hydrates occur from adventitious water, it should be unsurprising that a number of researchers have addressed the frequency,²² formation,²³ and the water environment of organic crystalline hydrates,²⁴ and crystalline hydrates have been classified according to their structure or energetics.²⁵ Morris and Rodriguez-Hornedo²⁶ proposed a classification system whereby hydrates are subdivided into three classes (1) channel hydrates in which water molecules interact with each other to form tunnels within the crystal lattice, (2) isolated site hydrates in which water molecules are not directly hydrogen bonded to each other, (3) metal ion associated hydrates in which water molecules form strong interactions with transition metals or alkali metals. Byrn et al. reported upon the macroscopic behavior of caffeine hydrate at room temperature and its dehydration, which was explained by the preferential escape of water molecules along a channel.²⁷ Other reports have discussed intermolecular interactions of water molecules in crystalline hydrates with other water molecules as well as interactions with APIs.²⁸ However, very little published research has addressed the thermal stability of hydrates in terms of why there is a variation in the temperature at which the water is lost from the crystal lattice, and cocrystal hydrates remain a largely unexplored class of compounds. In this contribution, we report 11 new cocrystal hydrates and analyze them to address

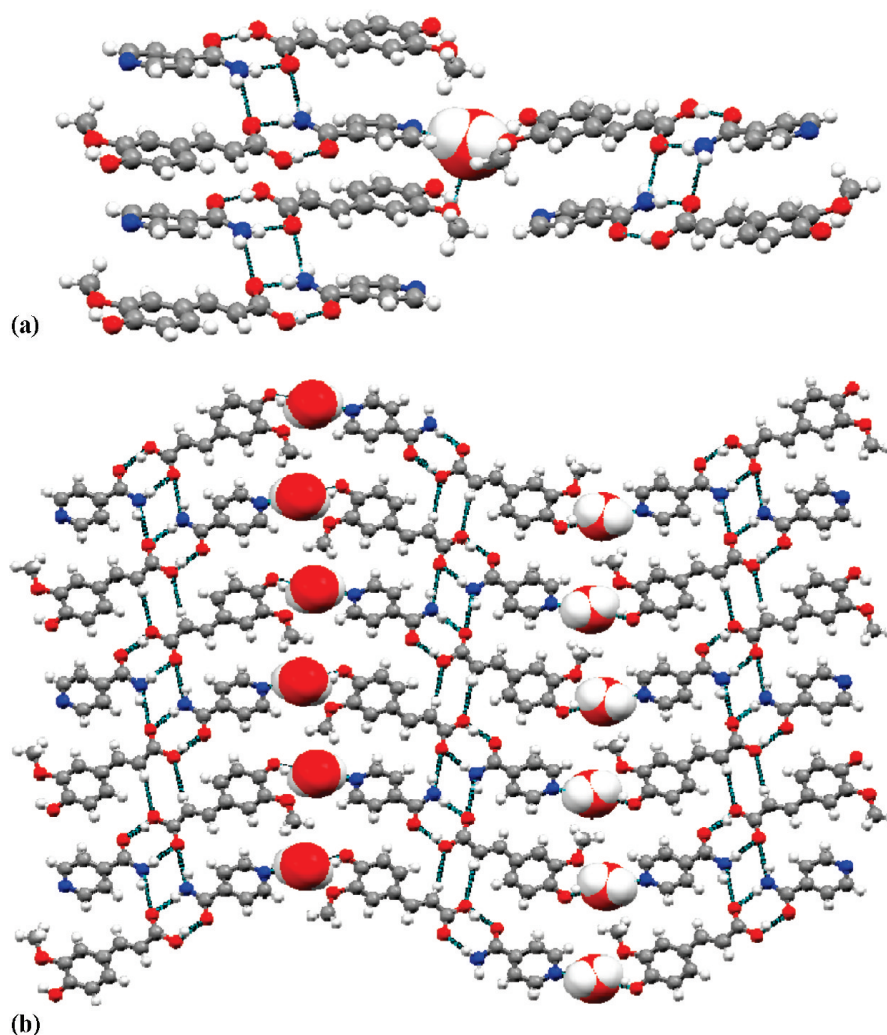


Figure 1. (a) Illustration of the water molecule in **FERINM · H₂O** that links three **FER₂INM₂** tetramers. (b) Crystal packing in **FERINM · H₂O** reveals 2 + 2 acid-amide hydrogen bonded tetramers that H-bond to water molecules so as to form H-bonded chains that pack as undulating sheets because of CH...O hydrogen bonds between adjacent chains.

whether or not there is any correlation between their structure and thermal stability.

Experimental Section

General. All reagents (Scheme 1) were purchased from commercial vendors and used as received. Solvents were obtained from commercial sources and distilled before use. Single crystals were obtained via slow evaporation of stoichiometric amounts of starting materials in an appropriate solvent. Cocrystals were characterized by infrared spectroscopy (IR), X-ray powder diffraction (PXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and single crystal X-ray analysis.

Ferulic Acid · Isonicotinamide Monohydrate, FERINM · H₂O. Ferulic acid (19.9 mg, 0.1 mmol) and isonicotinamide (61.3 mg, 0.5 mmol) were dissolved in 3 mL of ethanol. The solution was left to slowly evaporate at room temperature and needles of **FERINM · H₂O** were harvested after 7 days. m.p.: 153 °C.

Ferulic Acid · Nicotinamide Monohydrate, FERNAM · H₂O. Ferulic acid (19.9 mg, 0.1 mmol) and nicotinamide (61.3 mg, 0.5 mmol) were dissolved in 3 mL of ethanol. The solution was left to slowly evaporate at room temperature. Colorless needles of **FERNAM · H₂O** were harvested after 7 days. m.p.: 127 °C.

Ellagic Acid · Isonicotinamide Hydrate, ELAINM · 1.7H₂O. Ellagic acid dihydrate (20.0 mg, 0.06 mmol) was dissolved in 2 mL of *N,N*-dimethylacetamide, and isonicotinamide (290 mg, 2.37 mmol) was dissolved in 1 mL of deionized water. The resulting solutions were mixed and left for slow evaporation. Yellow plates were harvested after one month. m.p.: 300 °C.

Gallic Acid · Nicotinamide Monohydrate, GALNAM · 0.75H₂O. Gallic acid (59.5 mg, 0.348 mmol) and nicotinamide (49.9 mg, 0.405 mmol) were dissolved in 5 mL of ethanol and allowed to slowly evaporate at room temperature. Colorless needles were harvested after 3 days. m.p.: 210 °C.

Gallic Acid · Theobromine Dihydrate, GALTBR · 2H₂O. Gallic acid (50.5 mg, 0.297 mmol) and theobromine (53.3 mg, 0.296 mmol) were dissolved in 6 mL of water/ethanol (1:1 volume ratio) by heating and allowed to slowly evaporate at room temperature. Colorless prisms were harvested after 6 days. m.p.: 270 °C.

Gallic Acid · Isonicotinamide Monohydrate, GALINM · H₂O. Gallic acid (59.5 mg, 0.348 mmol) and isonicotinamide (49.9 mg, 0.405 mmol) were dissolved in 5 mL of ethanol until a clear solution was obtained. The solvent was allowed to slowly evaporate at room temperature. Colorless needles were harvested after 3 days. m.p.: 203 °C.

Gallic Acid · Caffeine Hemihydrate, GALCAF · 0.5H₂O. Gallic acid (50.3 mg, 0.296 mmol) and caffeine anhydrous (57.4 mg,

0.296 mmol) were dissolved in 5 mL of methanol and allowed to slowly evaporate at room temperature. Colorless prisms were harvested after 14 days. m.p.: 242 °C.

Quercetin·Theobromine Dihydrate, QUETBR·2H₂O. Quercetin dihydrate (33.8 mg, 0.0999 mmol) and theobromine (18.0 mg,

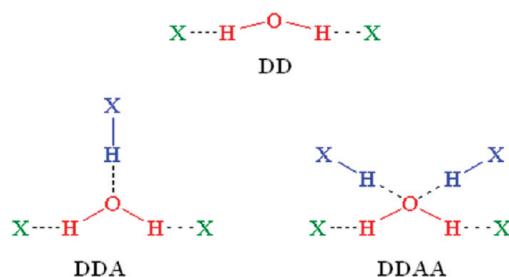
0.0999 mmol) were dissolved in 5 mL of ethanol and 10 mL of 1:1 mixture of water and ethanol respectively by heating. Resulting solutions were filtered together and placed in the refrigerator for slow evaporation. Colorless needles were harvested after 4 days. m.p.: 293 °C.

Ellagic Acid·Caffeine Monohydrate, ELACAF·H₂O. Ellagic acid dihydrate (10.0 mg, 0.0296 mmol) and caffeine (29.0 mg, 0.148 mmol) were dissolved in 5 mL of 1,2-propanediol/ethanol (6:4 volume ratio) by heating, filtered, and allowed to slowly evaporate at room temperature. Yellow plates were harvested after a week. m.p.: 299 °C.

Caffeic Acid·Nicotinamide Monohydrate, CFANAM·H₂O. Caffeic acid (9 mg, 0.04995 mmol) and nicotinamide (30 mg, 0.1000 mmol) were dissolved in 3 mL of ethanol/water (1:1 volume ratio) by heating and allowed to slowly evaporate at room temperature. Colorless needles were harvested after two days. m.p.: 108 °C.

Hydrochlorothiazide·Isonicotinamide Monohydrate, HCTINM·H₂O. Hydrochlorothiazide (15 mg, 0.05 mmol) and isonicotinamide (6.1 mg, 0.049 mmol) were dissolved in 4 mL of ethyl acetate by heating, filtered, and allowed to slowly evaporate at room temperature. Colorless plates were harvested after two days. m.p.: 127 °C.

Scheme 2. The Water H-Bond Environments That Have Been Observed in Cocrystal Hydrates (D: donor; A: acceptor)^a



^a Only strong H-bonds were included (i.e., no C—H···O H-bonds).

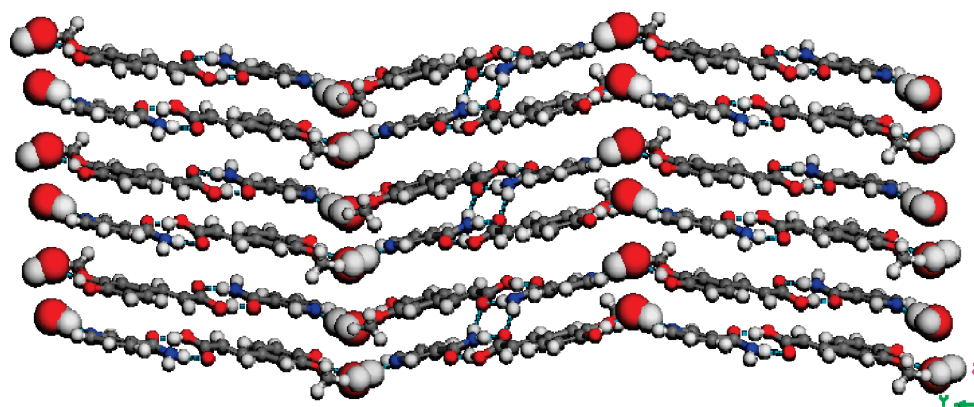


Figure 2. Crystal packing in **FERNAM·H₂O** exhibits 2 + 2 acid-amide tetramers that are cross-linked by H-bonded water molecules.

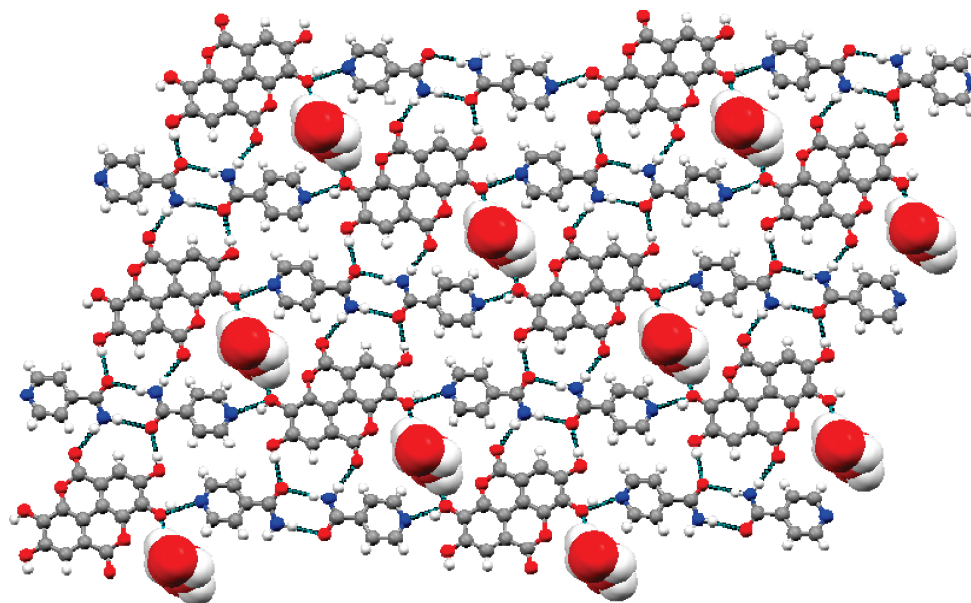


Figure 3. Crystal packing of **ELAINM·1.7H₂O** reveals molecular tapes of INM dimers with lateral H-bonding to phenol and carbonyl moieties of ELA. Water molecules form channels perpendicular to the aromatic rings and donate H-bonds to the phenol moieties of ELA.

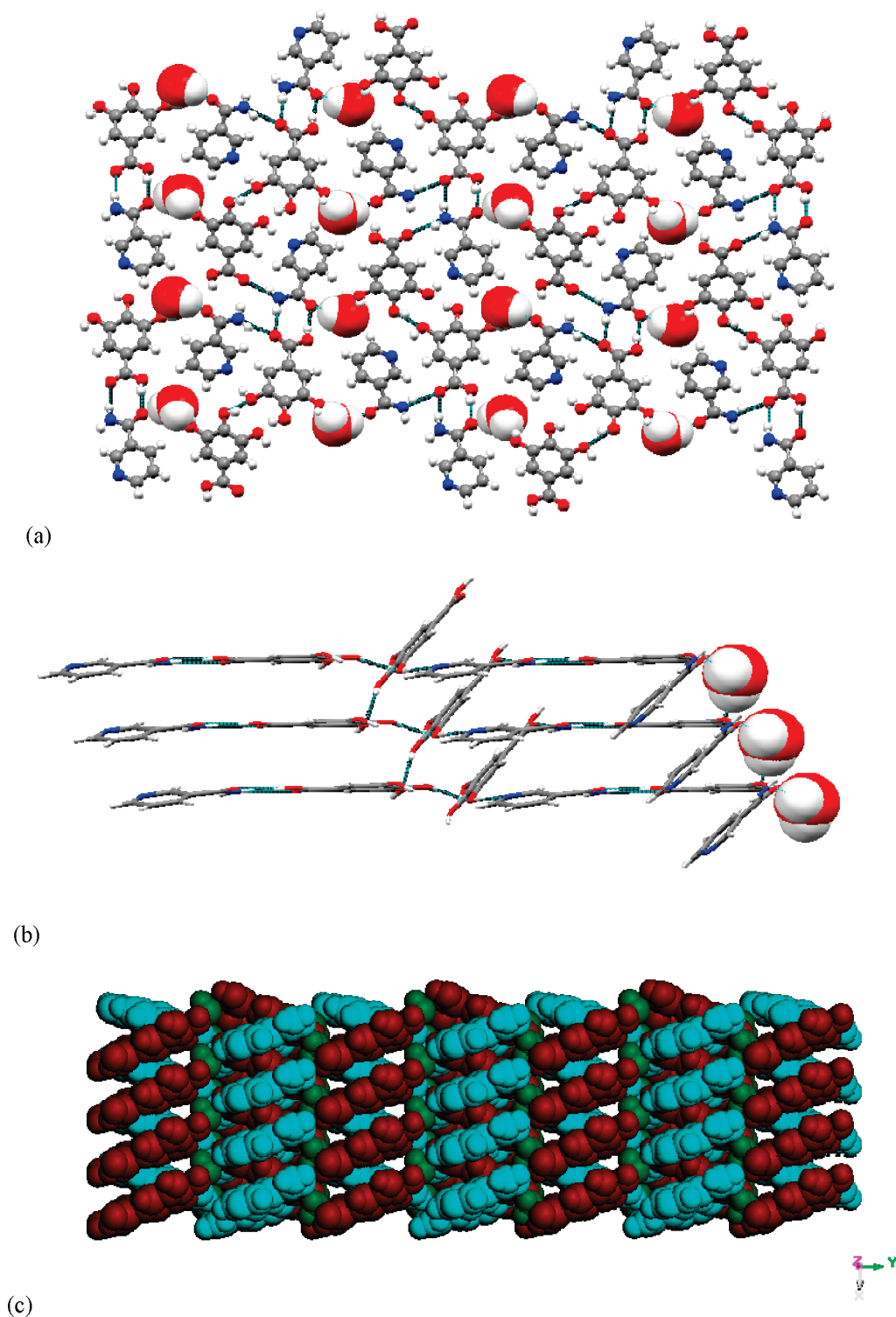


Figure 4. (a) Crystal packing in $\text{GALNAM} \cdot 0.75\text{H}_2\text{O}$ reveals molecular tapes of heterodimers of **GAL** and **NAM** with disordered water molecules cross-linking each dimer. (b) Lateral view of heterodimers. (c) Crystal packing shows heterodimers forming an interwoven 3D network.

Differential Scanning Calorimetry (DSC). Thermal analysis was carried out employing a TA Instruments DSC 2920 differential scanning calorimeter. Aluminum pans were used for all samples and temperature calibrations were made using indium as a standard. An empty pan, sealed in the same way as the sample, was used as a

reference. The thermograms were run at a scanning rate of $2\text{--}10\text{ }^\circ\text{C}/\text{min}$ from $30\text{ }^\circ\text{C}$ on $3\text{--}5\text{ mg}$ crystalline samples.

Thermogravimetric Analysis (TGA). TGA was performed with a Perkin-Elmer STA 6000 simultaneous thermal analyzer. Open alumina crucibles were used for analysis in the temperature range

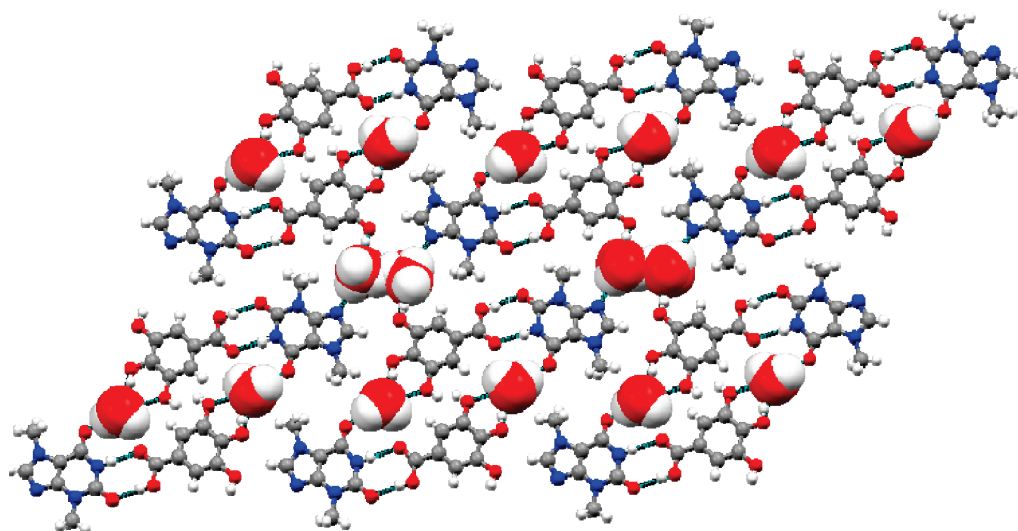


Figure 5. Crystal packing of $\text{GALTBR} \cdot 2\text{H}_2\text{O}$ reveals that GALTBR dimers are connected by water molecules so as to form H-bonded sheets.

30 °C to the appropriate temperature at 2–10 °C/min scanning rate under nitrogen stream.

Infrared Spectroscopy (FT-IR). All crystalline samples were characterized by infrared spectroscopy using a Nicolet Avatar 320 FT-IR instrument. 2–3 mg of material was used for all samples. Spectra were measured over the range of 4000–400 cm^{-1} and data were analyzed using EZ Omnic software.

Powder X-ray Diffraction (PXRD). Bulk samples were analyzed by X-ray powder diffraction with a Bruker AXS D8 powder diffractometer. Experimental conditions: Cu $K\alpha$ radiation ($\lambda = 1.54056 \text{ \AA}$); 40 kV; 30 mA; scanning interval 3–40° 2 θ ; time per step 0.5 s. The experimental PXRD patterns and calculated PXRD patterns from single crystal structures were compared to confirm the composition of materials.

Single-Crystal X-ray Data Collection and Structure Determinations. Crystalline products were examined under a microscope, and suitable crystals were selected for single crystal X-ray crystallography. Data were collected on single crystals of $\text{GALCAF} \cdot 0.5\text{H}_2\text{O}$ and $\text{GALTBR} \cdot 2\text{H}_2\text{O}$ on a Bruker-AXS SMART APEX CCD diffractometer with monochromatized Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), whereas data for single crystals of the hydrates of $\text{FERINM} \cdot \text{H}_2\text{O}$, $\text{FERNAM} \cdot \text{H}_2\text{O}$, $\text{ELAINM} \cdot 1.7\text{H}_2\text{O}$, $\text{GALNAM} \cdot 0.75\text{H}_2\text{O}$, $\text{GALINM} \cdot \text{H}_2\text{O}$, $\text{QUETBR} \cdot 2\text{H}_2\text{O}$, $\text{ELACAF} \cdot \text{H}_2\text{O}$, $\text{CFANAM} \cdot \text{H}_2\text{O}$, and $\text{HCTINM} \cdot 2\text{H}_2\text{O}$ were collected on a Bruker-AXS SMART APEX 2 CCD diffractometer with monochromatized Cu $K\alpha$ radiation ($\lambda = 1.54178 \text{ \AA}$). Both diffractometers were connected to a KRYO-FLEX low temperature device. Indexing was performed using SMART v5.625²⁹ or using APEX 2008v1-0.³⁰ Frames were integrated with SaintPlus 7.51³¹ software package. Absorption corrections were performed by a multiscan method implemented in SADABS.³² The structures were solved using SHELXS-97 and refined using SHELXL-97 contained in SHELXTL v6.10³³ and WinGX v1.70.01³⁴ program packages. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrically calculated positions or found in the Fourier difference map and included in the refinement process using riding model or without constraints. Occupancy factors were refined for disordered water molecules of $\text{ELAINM} \cdot 1.7\text{H}_2\text{O}$ and $\text{GALNAM} \cdot 0.75\text{H}_2\text{O}$. For $\text{ELAINM} \cdot 1.7\text{H}_2\text{O}$, it was not possible to locate all hydrogen atoms attached to disordered water molecules.

Crystallographic data are presented in Table 1. Hydrogen bond parameters are given in Table 2.

Results

FERINM·H₂O. $\text{FERINM} \cdot \text{H}_2\text{O}$ crystallizes in the monoclinic space group $P2_1/n$, and the asymmetric unit contains

one molecule of each component. The crystal structure is sustained by a 2-point supramolecular heterosynthon between the carboxylic acid moiety of FER and the amide moiety of INM ($\text{O} \cdots \text{O}$: 2.578(5) Å, $\text{N} \cdots \text{O}$: 2.997(6) Å). The acid-amide supramolecular heterosynthon³⁵ further dimerizes to form an $R^2_4(8)$ tetramer sustained by $\text{N}-\text{H} \cdots \text{O}$ hydrogen bonding ($\text{N} \cdots \text{O}$: 2.991(5) Å, Figure 1a,b). The water molecules exhibit DDA H-bonding (Scheme 2): they link tetramers by donating bifurcated hydrogen bonds to the methoxy moieties ($\text{O} \cdots \text{O}$: 3.037(5) Å) and the pyridyl moieties ($\text{OH} \cdots \text{N}$: 2.835(6) Å) and accepting $\text{OH} \cdots \text{O}$ hydrogen bonds from phenolic moieties ($\text{O} \cdots \text{O}$: 2.681(5) Å, Figure 1a). $\text{CH} \cdots \text{O}$ hydrogen bonds ($\text{C} \cdots \text{O}$: 3.608 Å) cross-link the resulting zigzag chains to form an undulating sheet. Adjacent water molecules lie in tunnels parallel to the c axis, but they are not hydrogen bonded to each other.

FERNAM·H₂O. $\text{FERNAM} \cdot \text{H}_2\text{O}$ crystallizes in the monoclinic space group $P2_1/n$, and it exhibits a crystal packing similar to that of $\text{FERINM} \cdot \text{H}_2\text{O}$. Indeed, the versatility of the water molecule compensates for the different orientations of the pyridyl moieties in NAM and INM, and $\text{FERNAM} \cdot \text{H}_2\text{O}$ is isostructural with $\text{FERINM} \cdot \text{H}_2\text{O}$. Water molecules form tunnels along the c axis and are hydrogen bonded in the DDA environment (Figure 2).

ELAINM·1.7H₂O. The crystal structure reveals that $\text{ELAINM} \cdot 1.7\text{H}_2\text{O}$ contains one ELA molecule, two INM molecules, and disordered water molecules in the unit cell. $\text{ELAINM} \cdot 1.7\text{H}_2\text{O}$ exhibits hydrogen bonding between the pyridyl group of INM and the phenolic hydrogen atoms of ELA ($\text{O} \cdots \text{N}$: 2.611(2) Å). The neutral nature of INM is supported by the C–N–C angle of 118.07° in the pyridyl moiety. Two INM molecules further interact through amide–amide supramolecular homosynthons ($\text{N} \cdots \text{O}$: 2.988(3) Å). The phenol–pyridine supramolecular heterosynthon³⁶ and the amide dimer supramolecular homosynthon³⁷ generate a tape (Figure 3). The amide dimer also acts as both a hydrogen bond donor and acceptor toward the carbonyl moiety ($\text{NH} \cdots \text{O}$: 2.930(3) Å) and phenolic hydrogen atom of ELA ($\text{OH} \cdots \text{O}$: 2.749(2) Å) to form an $R^3_3(10)$ trimer that links the INM–ELA chains. Disordered water molecules form channels

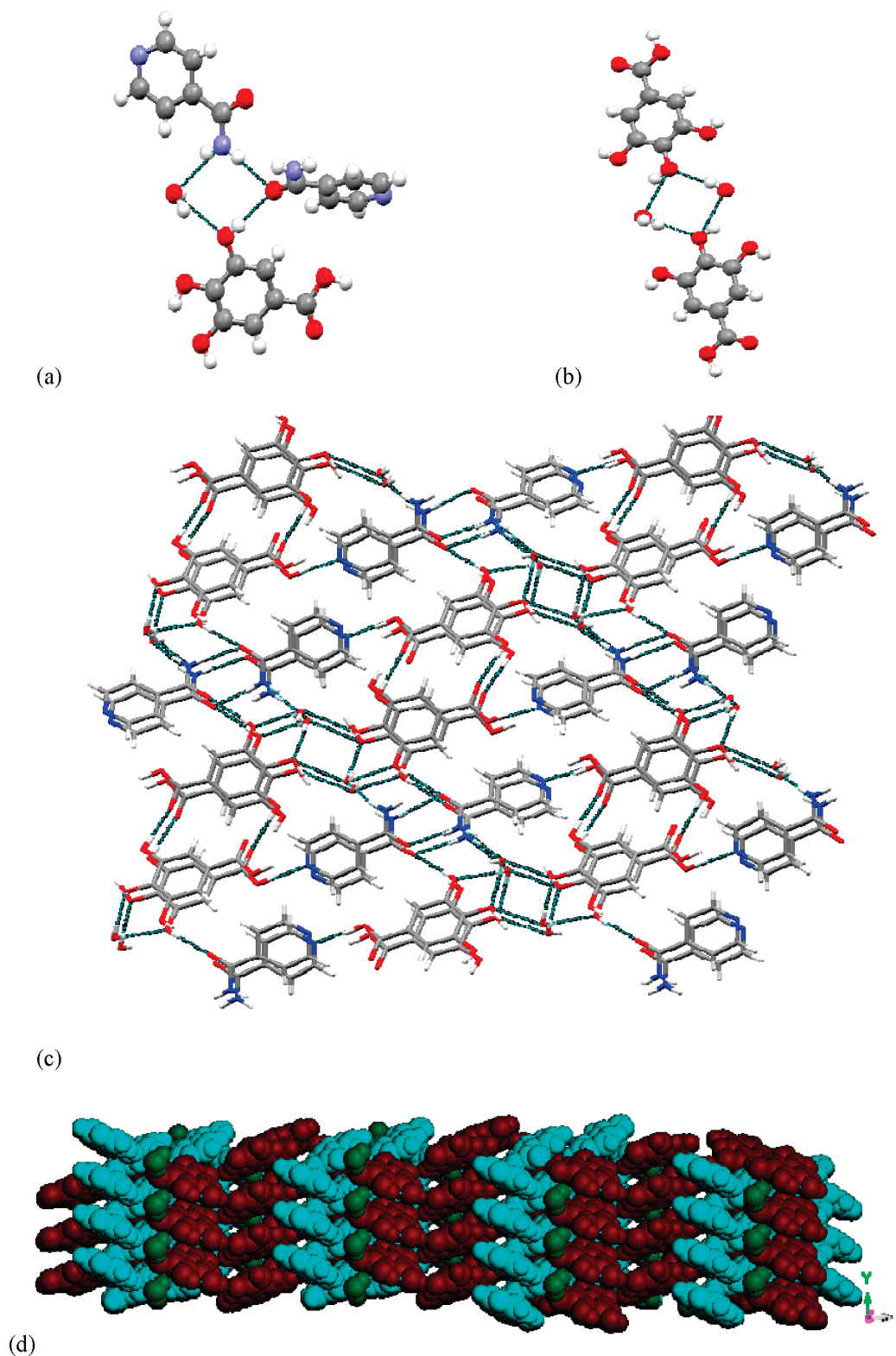


Figure 6. (a) $R^3_4(8)$ tetrameric motif involving two INM molecules, a GAL molecule, and a water molecule; (b) $R^4_4(8)$ tetrameric motif involving phenolic moieties of two GAL molecules and two water molecules. (c) The crystal packing of GALINM · H₂O reveals sheets sustained by COOH ··· N supramolecular heterosynths. (d) Crystal packing is that of a 3D network with water molecules (green) parallel to the *b* axis.

parallel to the crystallographic *a* axis and exist in DDA environments.

GALNAM · 0.75H₂O. GAL and NAM crystallize with a disordered water molecule in the orthorhombic space group

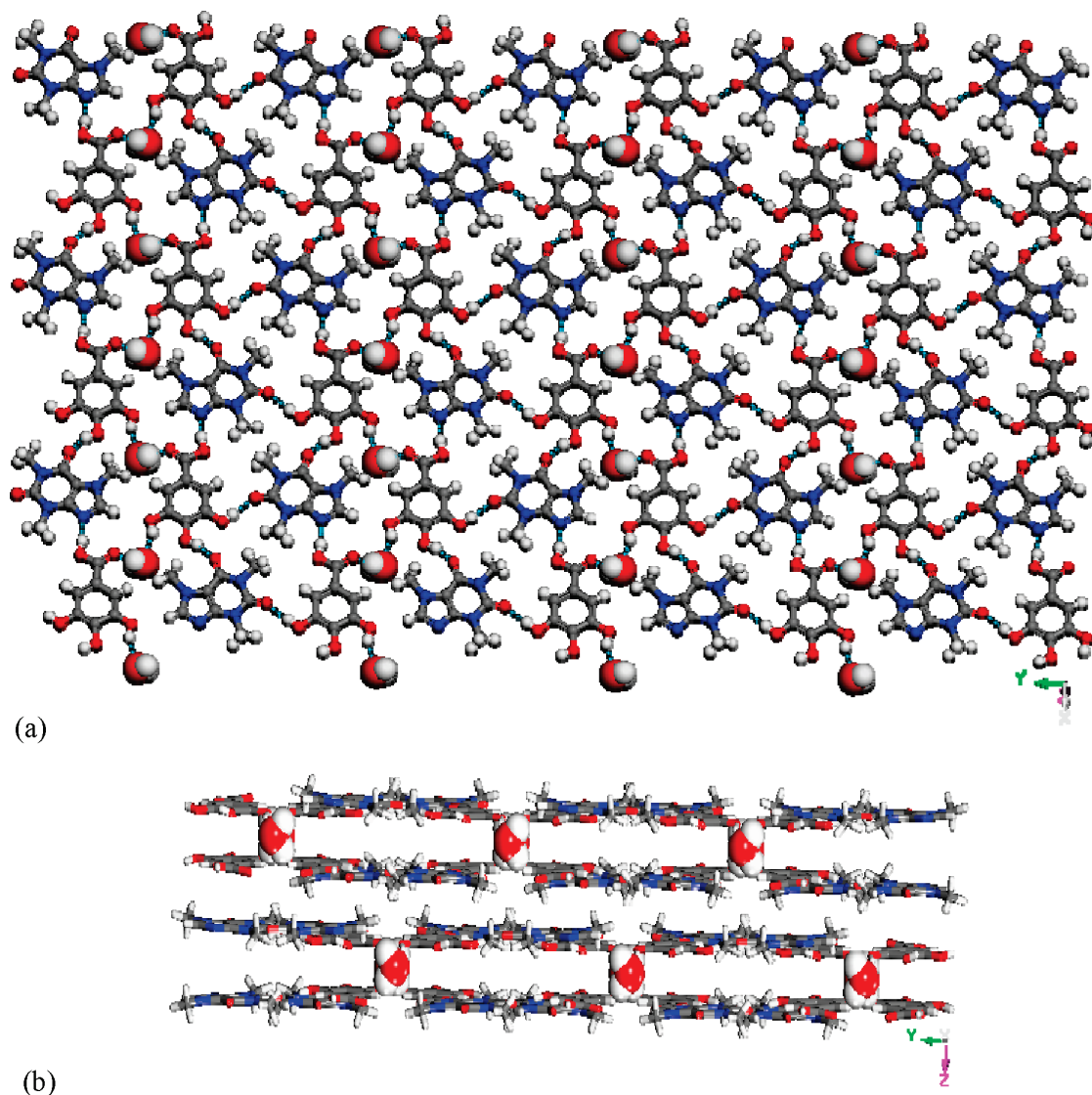


Figure 7. (a) Crystal packing of GALCAF·0.5H₂O tapes cross-linked by water molecules. (b) The water molecules sustain bilayers that pack ABAB.

*P*2₁2₁2₁. **GAL** and **NAM** form a 1:1 complex sustained by acid-amide supramolecular heterosynthons³⁵ (N···O: 2.896(2) Å, O···O: 2.647(2) Å, Figure 4a). The heterodimers link to one another via OH···N_{arom} H-bonds (2.710(2) Å) to adjacent heterodimers that are at dihedral angles of 46.3 °C. In addition, the carbonyl moiety of GAL accepts a hydrogen bond from the NH₂ moiety of an adjacent heterodimer at a dihedral angle of 46.83 °C (N···O: 2.897(2) Å). The disordered water molecule is in a DDA environment and connects three heterodimers as follows: accepting a bifurcated H-bond from the phenolic moieties of contiguous heterodimers; donating an H-bond to the carbonyl moiety of an adjacent heterodimer in an offset manner (Figure 4b); H-bonding with phenolic moieties so as to forms tunnels parallel to the *a*-axis. The crystal packing is that of an interwoven 3D H-bonded network (Figure 4c).

GALTBR·2H₂O. The crystal structure of **GALTBR·2H₂O** reveals a 1:1 cocrystal dihydrate which crystallizes in the monoclinic space group *C*2/*c*. The crystal structure

consists of **GAL** and **TBR** molecules that form acid-imide supramolecular heterosynthons (N···O: 2.790(3) Å, O···O: 2.671(2) Å) interconnected by ordered water molecules to form 6-component assemblies that are further connected by disordered water molecules into sheets (Figure 5). The GAL:TBR dimers are also connected through water molecules to **GAL:TBR** dimers that lie above and below the sheets (O···O: 2.902(5) Å) and by π - π stacking so that the overall crystal packing can be described as a 3D network. The disordered water molecules exist in a DDAA environment, whereas the ordered water molecules H-bond in a DDA environment.

GALINM·H₂O. The crystal structure of **GALINM·H₂O** reveals a 1:1 cocrystal monohydrate that crystallizes in space group *P*2₁/*n* with one molecule of each component in the asymmetric unit. The crystal structure is sustained by the COOH···N_{arom} supramolecular heterosynthons,³⁸ but the amide–amide supramolecular homosynthon is absent. Instead, the carbonyl moiety of **INM** H-bonds to the amide moiety of an adjacent molecule of **INM** (N···O: 2.891(2) Å),

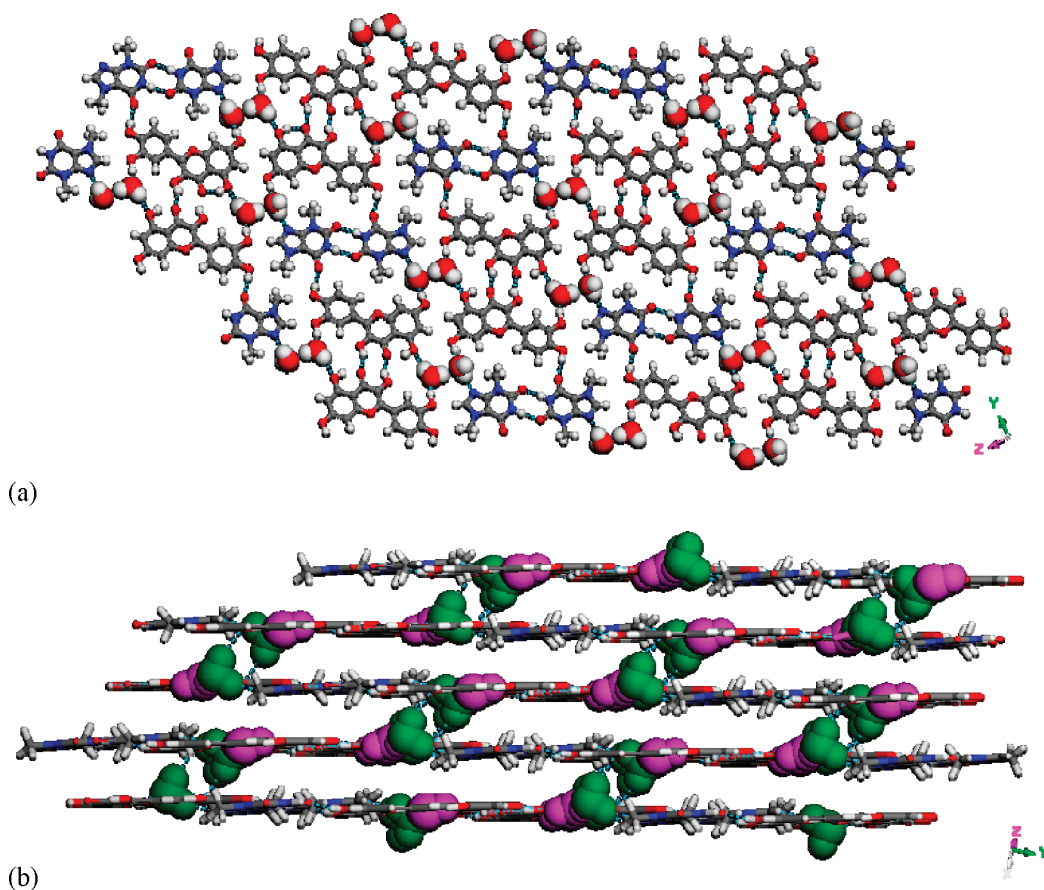


Figure 8. (a) Crystal packing in **QUETBR·2H₂O** is sustained by dimers of **QUE** and **TBR** molecules linked by pairs of water molecules. (b) Lateral view of the sheets that are sustained by $R_6(12)$ motifs.

a water molecule and a **GAL** molecule to generate a tetrameric ring motif (Figure 6a). A centrosymmetric $R_4^4(8)$ tetrameric ring motif occurs between phenolic moieties of two different **GAL** molecules and two water molecules, ($O\cdots O = 2.853(2)$ and $2.833(2)$ Å, Figure 6b). Overall, the crystal packing can be described as a 3D H-bonded network with water molecules in DDAA environments that form tunnels parallel to the *b* axis.

GALCAF·0.5H₂O. The crystal structure of **GALCAF·0.5H₂O** reveals a 1:1:0.5 ratio of gallic acid, caffeine, and water molecules. **GAL** and **CAF** molecules form H-bonded tapes that are sustained by $COOH\cdots N^{38}$ supramolecular heterosynthons ($O\cdots N: 2.705(2)$ Å) and $OH\cdots O$ supramolecular heterosynthons formed between adjacent phenolic moieties of **GAL** molecules and carbonyl moieties of adjacent **CAF** molecules ($O\cdots O: 2.703(2), 2.750(2)$ Å). These tapes lie parallel to the *a* axis and are cross-linked by water molecules that H-bond with the third phenolic moiety of each **GAL** molecule ($O\cdots O: 2.857(1)$ Å, Figure 7a). The neutral nature of the molecules is supported by the C–O bond distances, 1.320 and 1.224 Å and the C–N–C bond angle, 103.49°. The water molecules exist in DDAA environments and generate bilayers that stack in an ABAB manner sustained by π – π interactions.

QUETBR·2H₂O. The crystal structure of **QUETBR·2H₂O** reveals supramolecular homosynthons of **QUE** dimers ($O\cdots O: 2.615(2)$ Å) and **TBR** dimers ($N\cdots O: 2.834(3)$ Å). These dimers interact via donation of H-bonds from the phenolic moiety of **QUE** molecules to the carbonyl moiety of

TBR molecules ($O\cdots O: 2.753(2)$ Å). The **QUE** and **TBR** homodimers alternate to form molecular tapes (Figure 8a). The two crystallographically independent water molecules (DDA and DDAA environments) cross-link the homodimers through an $R_6^6(12)$ ring motif involving four water molecules and the phenolic moieties of two **QUE** molecules (Figure 8b).

ELACAF·H₂O. Analysis of the crystal structure reveals that **ELACAF·H₂O** contains two **ELA** molecules, two **CAF** molecules, and two water molecules in the unit cell. The phenolic hydrogen atoms of **ELA** act as H-bond donors to basic nitrogen and carbonyl moieties of **CAF** molecules at 2.702(4) and 2.708(3) Å so as to form straight chains of alternating **ELA** and **CAF** molecules. Adjacent chains are linked via $OH(ELA)\cdots O = C(CAF)$ H-bonds (2.708(3) Å) and water molecules at (2.609(3) and 2.854(4) Å) that H-bond to two **ELA** molecules, thereby forming a sheet (Figure 9a). Adjacent sheets are cross-linked by H-bonds between water molecules and carbonyl oxygen atoms of **ELA** (2.920(4) Å). Water molecules are isolated and sit in DDA environments (Figure 9b).

CFANAM·H₂O. The crystal structure of **CFANAM·H₂O** reveals that **CFA** and **NAM** molecules form carboxylic acid–amide supramolecular heterosynthons ($O\cdots O: 2.548(2)$ Å; $N\cdots O: 2.950(2)$ Å) that self-assemble to form tapes rather than 2 + 2 tetramers. These tapes are cross-linked by phenolic dimer supramolecular homosynthons ($O\cdots O: 2.769(2)$ Å, Figure 10). Disordered water molecules

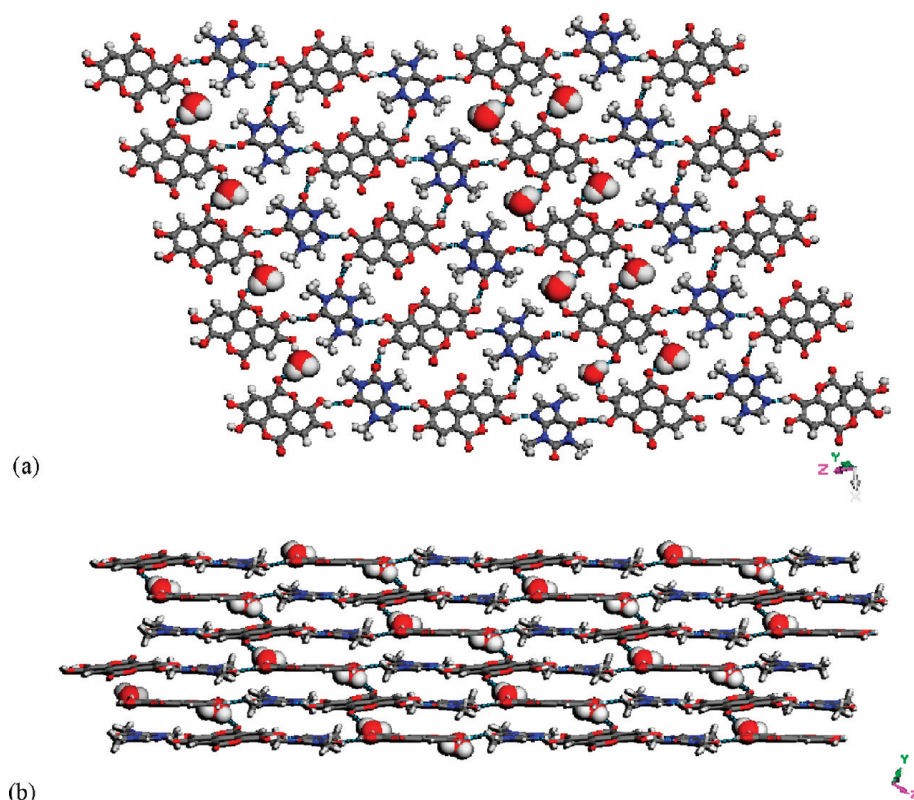


Figure 9. (a) Crystal packing in **ELACAF·H₂O** reveals H-bonding between **ELA** and **CAF** molecules via **OH...N** supramolecular heterosynthons. (b) View along the *c* axis illustrates isolated water molecules.

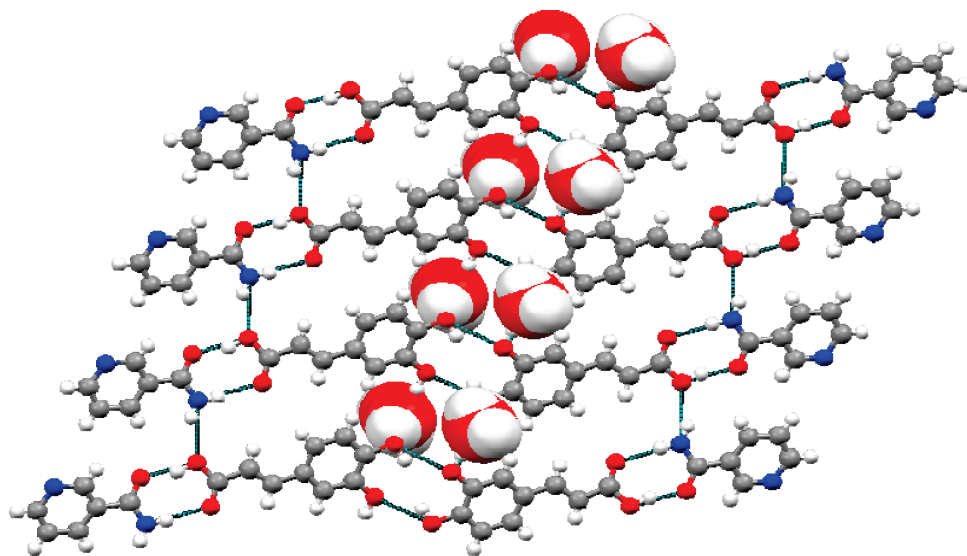


Figure 10. Molecular tapes of **CFANAM·H₂O** cross-linked by phenol–phenol interactions.

exist in **DDAA** environments as they H-bond with the phenolic dimers via $R^6_6(12)$ motifs and form tunnels parallel to the *b* axis.

HCTINM·H₂O. The crystal structure of **HCTINM·H₂O** reveals that it is a monohydrate of the 1:1 cocrystal of **HCT** and **INM**. **INM** molecules form amide–amide supramolecular homosynthons ($N\cdots O$: 3.038(2) Å) that are linked to **HCT** molecules by water molecules that donate H-bonds

to the pyridyl moieties of **INM** molecules and the sulfonamide groups of **HCT** molecules ($O\cdots N$: 2.787(2) Å, $O\cdots O$: 2.986(2) Å, Figure 11). Water molecules are in **DDAA** environments since they accept H-bonds from two different **HCT** molecules and they form tunnels in which they are not H-bonded to each other. The overall crystal packing consists of H-bonded sheets that pack via π – π stacking.

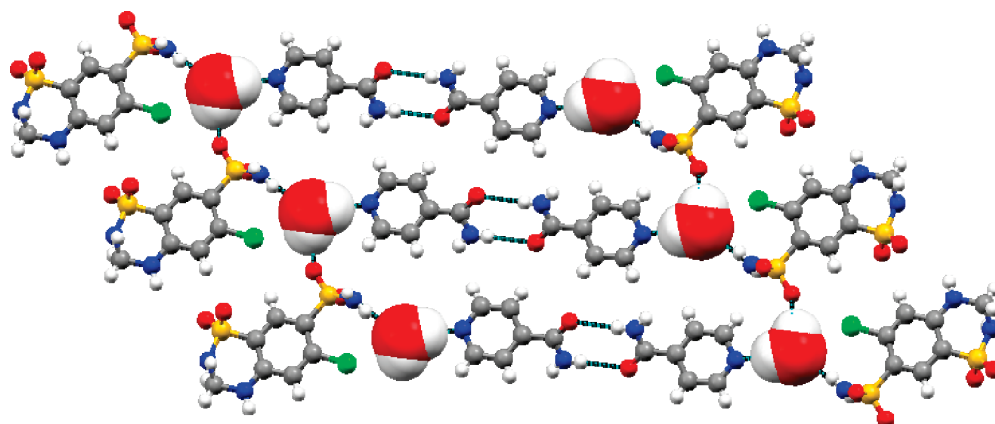


Figure 11. The crystal packing of **HCTINM·H₂O** is sustained by amide–amide supramolecular homosynths between **INM** molecules that are in turn H-bonded to **HCT** molecules via water molecules.

Discussion

Table 3 tabulates selected structural features of the 11 cocrystal hydrates reported herein and 8 cocrystal hydrates involving zwitterions that have been reported elsewhere.³⁹ The following structural features were addressed: local water environment in terms of strong H-bond donors and acceptors, whether water molecules are isolated or in tunnels, and packing efficiency index. Table 3 also provides parameters related to thermal stability: temperature at which water loss occurs, melting point, and result of dehydration. In terms of thermal stability, the cocrystal hydrates in Table 3 can be grouped as follows: (1) water is lost at < 100 °C for loosely held water or channel hydrates; (2) water is lost between 100 and 120 °C for water molecules exhibiting the hydrogen bonding patterns of bulk water; (3) water is lost at > 120 °C for tightly bound crystalline water molecules; (4) dehydration occurs concurrently with the melt of the cocrystal. This is grouped according to the classification of hydrates proposed by Morris and Rodríguez-Hornedo²⁶ where the dehydration temperature is related to the degree of how tightly the water molecule is bound, that is, whether the water molecule is an integral part of the crystal structure or loosely held. Each group is discussed individually and then collectively.

Group 1. Inspection of group 1 reveals that all the cocrystal hydrates in this group exhibit water molecules that lie in tunnels and they are not hydrogen bonded with each other except for **ELAINM·1.7H₂O**, in which water molecules form H-bonded chains parallel to the *a* axis. The dehydration of Group 1 cocrystal hydrates occurs at temperatures ranging from 58 to 98 °C. Group 1 cocrystal hydrates exist in the DDA environment except for **CITINA·2H₂O**, which contains water molecules that lie in both DDA and DDAA environments. Interestingly, in **CITINA·2H₂O** the dehydration of the water molecules occurs in two steps, at temperatures of 93 and 136 °C. These water molecules exhibit a D2 water motif,⁴⁰ which indicates that there are two water molecules connected by hydrogen bonding in a discrete chain. The packing indices calculated using Platon⁴¹ were in the range 71.7–74.0. The dehydration of these cocrystal hydrates revealed new crystal forms for **FERINM·H₂O**, **FERNAM·H₂O**, and **CITINA·2H₂O**, whereas an isostructural anhydrate occurred following dehydration of **ELAINM·1.7H₂O**.

Group 2. The Group 2 hydrates exhibit dehydration temperatures from 109 to 118 °C. Tunnels of water molecules not H-bonded to each other are exhibited in **GALNAM·0.75H₂O**, **GALINA·H₂O**, **GALNAC·H₂O**, and **GALTBR·2H₂O**, whereas in **PCAINA·H₂O** and **GALNAC·1.5H₂O** isolated water molecules are observed. The water molecules are H-bonded in DDA environments in all Group 2 cocrystal hydrates. However, in **GALTBR·2H₂O** and **GALNAC·1.5H₂O**, DDAA environments are also exhibited by a second crystallographically independent water molecule. Packing indices range from 68.5 to 75.9. Dehydration of Group 2 hydrates afforded crystal forms with new crystal packing according to PXRD patterns.

Group 3. With the exceptions of **CITINA·2H₂O**, **QUEINA·H₂O**, and **GALINM·H₂O**, crystal structures in Group 3 contain waters of crystallization that lie in isolated sites. **GALINM·H₂O**, **QUEINA·H₂O**, and **CITINA·2H₂O** exhibit water loss at 124, 175, and 136 °C, respectively. These crystal structures displayed tunnels of water molecules not hydrogen bonded to each other. The crystal structures of Group 3 hydrates reveal DDA water environments except **GALCAF·0.5H₂O**, **CITINA·2H₂O**, and **QUETBR·2H₂O**, which display DDAA environments, and **BTNRES·H₂O**, which display a DD environment. The packing indices range from 70.4 to 75.6. PXRD of the dehydrated crystal forms reveals new crystal packing for **BTNRES·H₂O**, **GALINM·H₂O**, **CITINA·2H₂O**, **ELACAF·H₂O**, and **QUEINA·H₂O**. However, dehydration of **GALCAF·0.5H₂O** and **QUETBR·2H₂O** resulted in isostructural anhydrides.

Group 4. In Group 4, water loss occurs concurrently with melt of the cocrystal. The water molecules in **CFANAM·H₂O** and **HCTINM·H₂O** sit in DDAA environments, whereas in **FERBAC·0.5H₂O** it sits in a DDA environment. Tunnels of water molecules not hydrogen bonded to each other are observed in **CFANAM·H₂O**, **FERBAC·0.5H₂O**, and **HCTINM·H₂O** and packing indices range from 68.8 to 73.3.

In summary, there appears to be little or no correlation between structure and thermal stability in the 11 new cocrystal hydrates reported herein other than for tunnel hydrates, which exhibit a tendency to lose water at or around the boiling point of water. Isolated water molecules that form at least three H-bonds were observed to exhibit greater thermal stability, and it might be anticipated that the presence of strong hydrogen bonding (short hydrogen bond

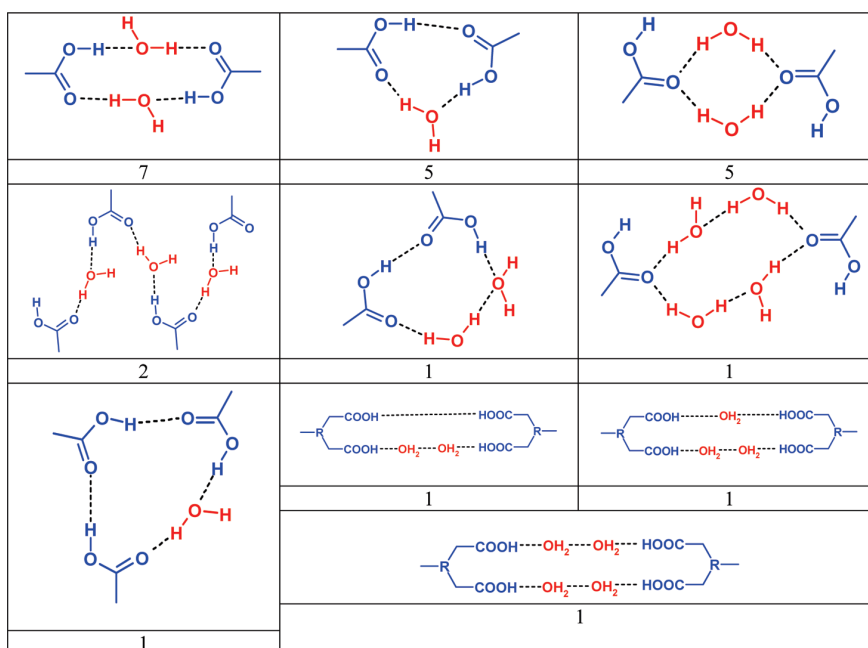
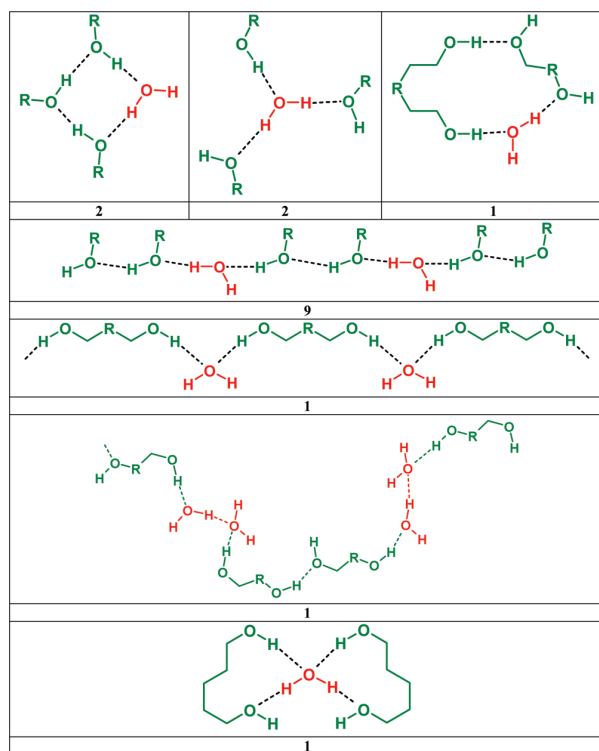
Table 3. Structural and Thermal Stability Properties of Selected Cocrystal Hydrates^a

Group 1: Thermal Loss of Water of Crystallization $T < 100$ °C									
cocrystal	stoichiometric ratio (T:CF:H ₂ O)	disordered water molecule	thermal loss of water	melting point of cocrystal	water environment	type of hydrate	packing index	energy of dehydration per mole of water (J/g, kJ/mol)	result after dehydration
CITINA·2H₂O	1:2:2	no	93	187	DDA, DDAA	tunnels D2 motif	72.7		new crystal form
FERINM·H₂O	1:1:1	no	58	153	DDA	tunnels of water molecules not H-bonded	74.0		new crystal form
FERNAM·H₂O	1:1:1	no	98	127	DDA	tunnels of water molecules not H-bonded	71.7		new crystal form
ELAINM·H₂O	1:1:2	yes	< 100	300	DDA	channel			new crystal form
Group 2: Thermal Loss of Water of Crystallization $100 > T > 120$ °C									
cocrystal	stoichiometric ratio (T:CF:H ₂ O)	disordered water molecule	thermal loss of water	melting point of cocrystal	water environment	type of hydrate	packing index	energy of dehydration per mole of water (J/g, kJ/mol)	result after dehydration
GALNAM·0.75H₂O	1:1:1	no	109	210	DDA	tunnels of water molecules not H-bonded	74.4	92.58, 37.74	new crystal form
GALINA·H₂O	1:1:1	no	115	234	DDA	tunnels of water molecules not H-bonded	73.3	87.25, 27.15	new crystal form
GALTBR·2H₂O	1:1:2	yes	115	270	DDA, DDAA	tunnels of water molecules not H-bonded		283.8, 54.81	new crystal form
PCANAC·H₂O	1:1:1	no	115	224	DDA	isolated	68.5	106.2, 31.35	new crystal form
GALNAC·1.5H₂O	2:2:3	no	118	211	DDAA, DDA	isolated, tunnels of water molecules not H-bonded D2-motif	75.9	236.2, 50.42	new crystal form
Group 3: Thermal Loss of Water of Crystallization $T > 120$ °C									
cocrystal	stoichiometric ratio (T:CF:H ₂ O)	disordered water molecule	thermal loss of water	melting point of cocrystal	water environment	type of hydrate	packing index	energy of dehydration per mole of water (J/g, kJ/mol)	result after dehydration
BTNRES·H₂O	2:1:1	no	~120	188	DD	isolated	70.4		new crystal form
GALINM·H₂O	1:1:1	yes	124	203	DDA	tunnels of water molecules not H-bonded	73.3		new crystal form
GALCAF·0.5H₂O	1:1:0.5	no	135	242	DDAA	isolated	74.7	69.7, 52.04	isostructural
CITINA·2H₂O	1:2:2	no	136	187	DDA, DDAA	tunnel D2-Motif	72.7		new crystal form
QUETBR·2H₂O	1:1:2	no	142	293	DDA, DDAA	isolated D2 motif	73.1	176.0, 45.62	isostructural
ELACAF·H₂O	2:1:1	no	175	299	DDA	isolated	75.6	124.8, 64.20	new crystal form
QUEINA·H₂O	1:1:1	no	196	282	DDA	tunnels of water molecules not H-bonded	74.2		new crystal form
Group 4: Thermal Loss of Water of Crystallization Occurs at Melt of the Cocrystal									
cocrystal	stoichiometric ratio (T:CF:H ₂ O)	disordered water molecule	thermal loss of water	melting point of cocrystal	water environment	type of hydrate	packing index		
CFANAM·H₂O	1:1:1	yes	occurs at melt	108	DDAA	tunnels of water molecules not H-bonded	71.7		
FERBAC·0.5H₂O	1:1:0.5	no	occurs at melt	156	DDA	tunnels of water molecules not H-bonded	68.8		
HCTINM·H₂O	1:1:1	no	occurs at melt	127	DDAA	tunnels of water molecules not H-bonded	73.3		

^a Energies of dehydration are only reported for compounds with a well-resolved endotherm in the DSC thermogram.

distances) would afford the high degree of thermal stability. However, this does not seem to be the case since the same environment from a structural perspective can exhibit a dramatically different thermal stability. Indeed, even the number of hydrogen bonds between the host molecules and the water molecules is not necessarily a good predictor of thermal stability. Likewise, packing indices show no correlations with thermal stability. In addition, the enthalpy of dehydration was calculated for the eight cocrystal hydrates that exhibited a well-defined DSC endotherm associated with dehydration. The range of values is wide,

27.15–64.20 kJ/mol, and in general the enthalpy of dehydration increases with thermal stability of the hydrate. However, there is a great deal of variability from compound to compound. That we are in a sense “comparing apples with oranges”, that is, the cocrystal hydrates reported herein exhibit variable hydrate stoichiometry, multiple hydrate packing environments, and several possible outcomes of dehydration (i.e., melting, isostructural anhydrate, anhydrate is a new crystal form), makes it hard to correlate thermal stability of the cocrystal hydrate and its enthalpy of dehydration.

Chart 1. Supramolecular Heterosynths Observed in Hydrates of Carboxylic Acids That Contain No Additional H-Bonding Groups^a^a The number given under each scheme indicates the times of occurrence.**Chart 2. Supramolecular Heterosynths Observed in Hydrates of Phenols That Contain No Additional H-Bonding Groups^a**^a The number given under each schematic indicates the times of occurrence in the CSD.

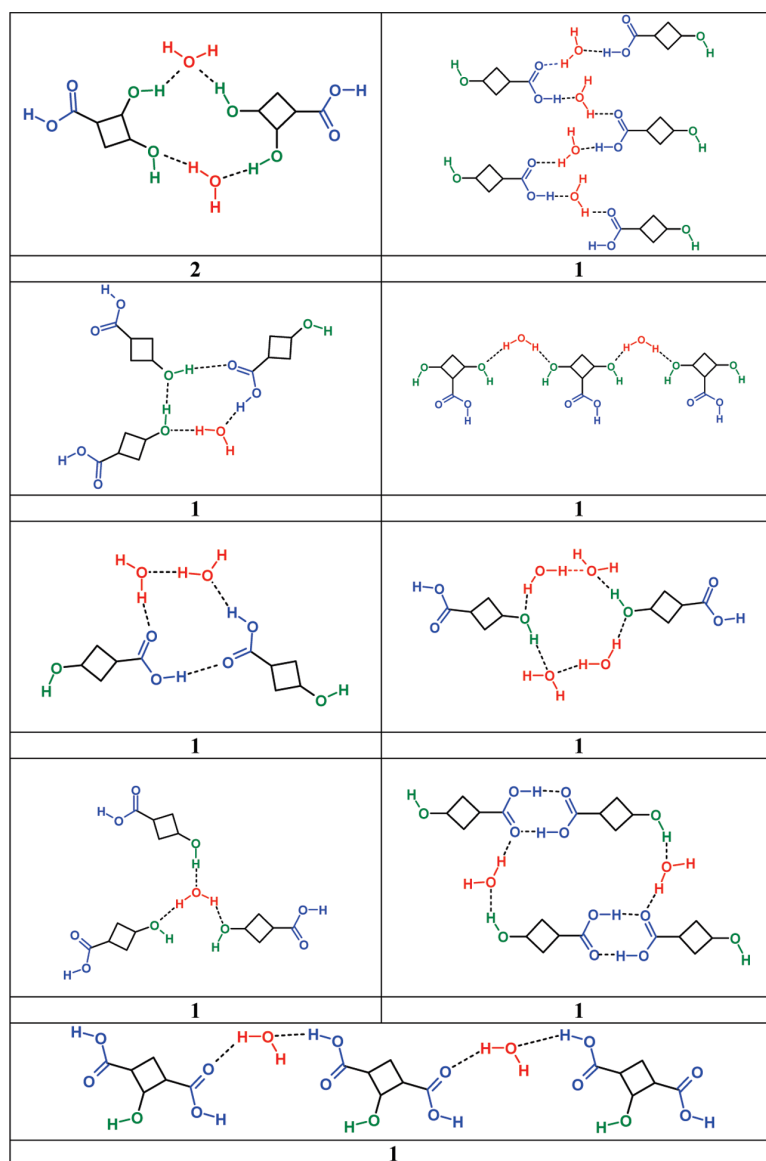
CSD Analysis. The persistence of supramolecular heterosynths is a feature of cocrystals that makes them particularly

Table 4. CSD Statistics of Polymorphs of Single and Multicomponent (Cocrystals and Hydrates) Organic Structures^a

	no. of entries	% of organic structures
organic crystal structures	196575 ^b	100 ^e
single component molecular	141350	71.9 ^e
organic structures		
single component polymorphic structures	2319 ^c	1.6 ^f
hydrates	15938	8.1 ^e
molecular organic hydrates ⁱ	6351	3.2 ^e
polymorphic molecular organic hydrates ⁱ	65	1.0 ^h
cocrystals ^j	2415 ^d	1.2 ^e
polymorphic cocrystals ⁱ	48	1.9 ^g

^a CSD May 09 update, 483 021 entries. ^b Structures containing Na, Li, K, As were excluded. ^c Only one refcode was counted for each polymorphic compound. ^d Cocrystals sustained by strong hydrogen bonds. ^e Percentages with respect to organic crystal structures only. ^f Percentages with respect to 141 350 subtotals. ^g Percentages with respect to 2415 subtotals. ^h Percentages with respect to 6351 entries only. ⁱ Conquest 1.11, only organics, 3D coordinates known, $R \leq 7.5$, no ions.

amenable to crystal engineering studies. For example, carboxylic acids and phenols both form persistent supramolecular synthons with pyridines³⁷ even in the presence of competing H-bond acceptors. However, as revealed by Charts 1–3, water molecules are rather promiscuous in terms of their H-bond interactions with carboxylic acids and phenols. These charts summarize a CSD analysis of the supramolecular heterosynths that exist when at least one water molecule is present in a crystal that contains a carboxylic acid or a phenol in the absence of competing functional groups. There are just 23 hydrates of simple carboxylic acids and remarkably 10 supramolecular heterosynths exist between the carboxylic acid moieties and the water molecules (Chart 1). Supramolecular heterosynths between water molecules and phenols are also diverse with 7 different supramolecular heterosynths out of

Chart 3. Supramolecular Heterosynthons Observed in Hydrates of Carboxylic Acids and Phenols^a

^a The numbers given under each schematic indicate the times of occurrence in the CSD.

just 17 crystal structures (Chart 2). There are only 10 crystal structures in which a carboxylic acid moiety, a phenol moiety and a water molecule are involved in the absence of competing H-bonding groups, and remarkably nine different supramolecular heterosynthons occur in this subset (Chart 3). These structural observations beg the question of whether or not the promiscuity in supramolecular synthons and polymorphs exhibited is general for multicomponent crystals or an artifact of the water molecules of hydration and their promiscuity. A CSD analysis (Table 4) reveals that structurally characterized polymorphs remain rare in single-component molecular crystals (2319/141350, 2.0%) and in multicomponent crystals such as hydrates (65/6351, 1.0%) and cocrystals (48/2415, 2.0%). However, there are enough compounds for which 3D coordinates are known on both polymorphic cocrystals (38 compounds) and polymorphic hydrates (44 compounds) to address polymorphism in multicomponent crystals. Analysis

of the 38 polymorphic cocrystals reveals that in 35 polymorphic pairs polymorphism is the result of conformational flexibility and/or structural changes in the overall packing; that is, the hydrogen bonded supramolecular synthons are persistent as had been previously suggested.³⁸ The remaining three cocrystals exhibit different supramolecular heterosynthons: carbamazepine and saccharin, ref codes: UNEZAO and UNEZAO01; bis(4-hydroxybenzoic acid) and 2,3,5,6-tetramethylpyrazine, ref codes: ODOBIT and ODOBIT01; urea and barbituric acid, ref codes: EFOZAB, EFOZAB 01 and EFOZAB02. However, this is not the case with polymorphic hydrates: 28 out of 44 polymorphic hydrates for which the 3D coordinates are known exhibit different supramolecular synthons with respect to the water molecules.

In conclusion, there are numerous structural features that might influence the thermal stability of organic crystalline hydrates, and the promiscuity of water molecules in

terms of supramolecular synthons mean that their composition, structure, and thermal stability remain largely unpredictable with the exception that channel hydrates tend to exhibit low thermal stability. It would therefore be appropriate to assert that water is indeed in many ways the nemesis of crystal engineering.

Supporting Information Available: X-ray crystallographic information in CIF format, IR, DSC, TGA, PXRD are available free of charge via the Internet at <http://pubs.acs.org>.

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