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Adducts of N-Heterocyclic Drugs, Niacin, Allopurinol, and Amiloride, with 2,4-Pyridinedicarboxylic Acid Coformer

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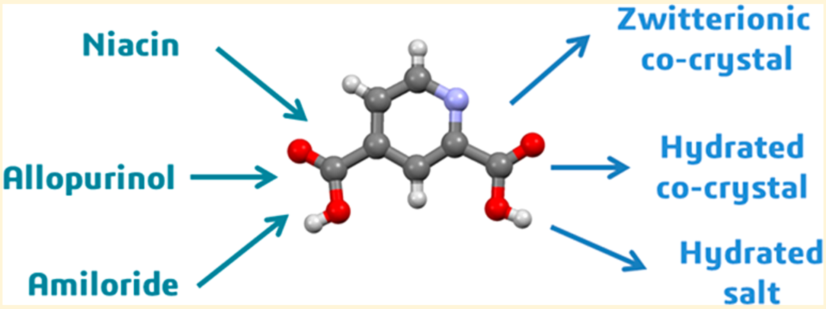
Supporting Information



ABSTRACT: A co-crystallization of three drug molecules, niacin (3-pyridine-carboxylic acid = NIA), allopurinol (pyrazolo(3,4-d)pyrimidin-4-one = ALP), and amiloride (3,5-diamino-6-chloro-pyrazine-2-carbonyl)-guanidine = AMI), with the same coformer, 2,4-pyridinedicarboxylic acid (PDA), resulted in three new crystalline products, (NIA)(PDA) (**1**), $(ALP)_2(PDA)\cdot 1.5H_2O$ (**2**), and $(AMI)_2(PDA)_2(H_2O)_2$ (**3**). The formation of new phases was confirmed by IR spectra and X-ray single-crystal and powder diffraction analysis. The proton transfer resulted in the zwitterionic co-crystal **1**. In co-crystal **2**, neutral ALP molecules existed in the oxo-tautomeric form. Compound **3** crystallizes as the salt with the guanidinium cationic part as in the started amiloride hydrochloride hydrate, and the PDA coformer as the zwitterionic pyridinium dicarboxylate anion. Thus, the diversity of the PDA coformer ionization states included the neutral, zwitterion, and zwitterion anionic forms. All compounds were layered structures where the heterocyclic molecules were linked in the H-bonded corrugated layers stabilized by the diverse conventional and charge-assisted hydrogen bonds with $\pi-\pi$ stacking interactions between the layers supported by the mediated water molecules in **2** and **3**.

INTRODUCTION

Ever since the seminal works by Kitaigorodsky,[1,2] the attention of the chemical scientific community to mixed crystals (or adducts) has increased. Nowadays, the deeper understanding of the impact of different forces such as conventional and charge-assisted hydrogen bonds[3−6] and specific interactions, including $\pi-\pi$ stacking[7] and halogen−halogen interactions,[8] that contribute to the crystal structures has been achieved, and the interest to these organic solids is focused on their potential application fields that cover, but are not limited by, their properties as semiconducting[9] and NLO materials[10] and as pharmaceutics with improved properties.[11−30]

In particular, the strategy of crystal engineering[12−14] demonstrates a significant potential to tune the physicochemical and pharmacokinetic profile of active pharmaceutical ingredients (APIs) by rational design of multicomponent pharmaceutical solids, thus influencing the solubility and dissolution rate, bioavailability, particle morphology and size, melting point, biochemical and hydration stability, and permeability.[11,16] Currently, co-crystals are considered as supplementary options to the pharmaceutical ionic solid forms, capable of improving the solubility and other pharmacological drug properties.[11−16] So far, in parallel with a discussion on terminology and suggested classifications for these multicomponent adducts,[17−20] both pools of studied drugs and useful coformers are growing tremendously.[16,21−30]

Five- and six-membered N-heterocycles, such as pyridine, pyrimidine, pyrazine, imidazole, and triazole moieties, are well-known pharmacophores,[31,32] which is why numerous studies in crystal engineering are accentuated at the supramolecular synthons formed between those moieties and functional groups of the coformer. The libraries of aliphatic and aromatic mono-

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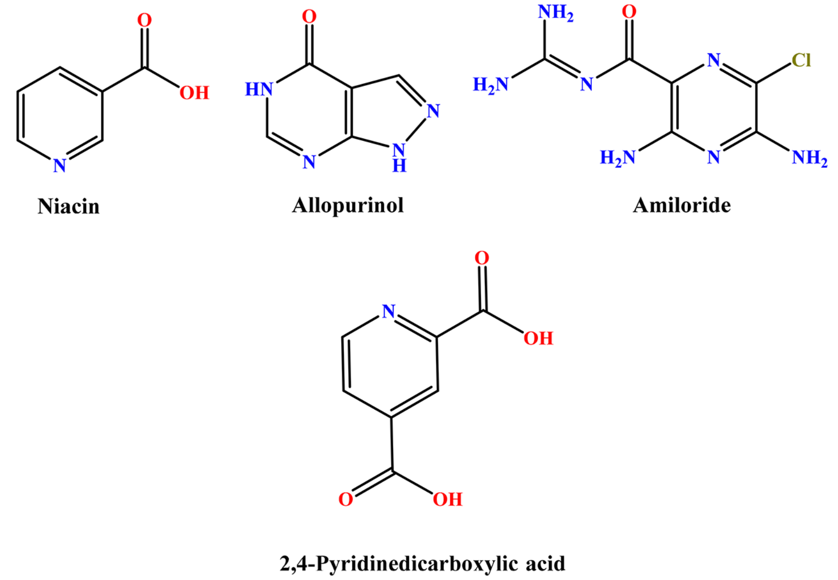
Scheme 1. Schematic Presentation of the Drug and Coformer Molecules Used in This Study



and poly(carboxylic acid)s as useful coformers are reported in numerous sources.[33−42] Along with coformers with single functionality (carboxylic, carbonyl, amide, hydroxyl-group, heterocyclic N atom), coformers with mixed functions (like acids equipped with additional amino, hydroxy, or halogen substituents) are particularly attractive. However, the more complicated the components are (API and coformer), the less predictable are the final products, both from the viewpoint of their composition (ratio of participants of this act), and the possible supramolecular synthons stabilizing the final crystal forms, since the interplay of intermolecular forces complicates the interaction scenario.[36−42]

Recently, amphoteric coformers with mixed functions, such as nitrogen-containing carboxylic acids, have become more intensively investigated as the possible source of zwitterion generation *in situ* that assists to improve solubility.[43−49] A systematic search of the Cambridge Structural Database for co-crystals that involve zwitterionic coformers unveiled that charge-assisted hydrogen bonds play an essential role, being present in the majority of structures.[46] The piroxicam in the zwitterionic form was reported in a co-crystal with 4-hydroxybenzoic acid.[43] MacGillivray et al.[47] reported the co-crystal formation between acetaminophen and the 2,4-pyridinedicarboxylic acid (PDA) coformer which produced a bright orange co-crystal from colorless starting materials. Structural analysis revealed PDA to exist in a hitherto unreported zwitterionic form in the co-crystal. The red color was attributed to a decrease in the $\pi-\pi$ separation in the co-crystal relative to the two separate components, as suggested by DFT calculations of the solid forms. The competition of binding sites in drugs and a co-crystal former was evaluated as well. Das and Baruah[48] chose 3,5-pyrazole dicarboxylic acid, dipicolinic acid, or quinolinic acid as coformers because of their multiple hydrogen-bonding sites that make them attractive for studying supramolecular synthons via co-crystal formation.

In support of recent studies,[14,50−52] we have shown the reoccurrence of the pyridinium-carboxylate and 2-aminopyridinium-carboxylate robust heterosynthons in organic salts produced by co-crystallization of mono- and diaminopyridines with aliphatic dicarboxylic acids.[53,54] On the other hand, the reoccurrence of the stacking motifs in the presence of strong charge-assisted $NH^+\cdots O(COO^-)$ hydrogen bonds has been shown by some of us taken as the examples two systems, NSAID drug mefenamic acid-cyclic (acyclic) amine, and salicylic acid-cyclic amine (azacrown-ether).[55,56]

In this study, we present the crystal structures of adducts obtained by co-crystallization of three N-heterocyclic drug molecules, niacin (NIA = pyridine-3-carboxylic acid), allopurinol (ALP = pyrazolo(3,4-d)pyrimidin-4-one), and amiloride (AMI = 3,5-diamino-6-chloro-pyrazine-2-carbonyl)-guanidine), with the same coformer, amphoteric 2,4-pyridinedicarboxylic acid (PDA, Scheme 1). All drug molecules and coformer have several binding sites of different acidity/basicity capable of participating in hydrogen-bonding systems and proton transfer, while their planar skeletons are predisposed for potential stacking interactions in these systems. The results of this study contribute to the quite limited crystallographic data available in the CSD (CSD version 5.38 updates Feb 2017) for ALP[57−59] and AMI[60−62] drugs.

Niacin (NIA), also known as vitamin B_3, is primarily used to treat hypercholesterolemia and pellagra (niacin deficiency). Insufficient niacin in the diet can cause nausea, skin and mouth lesions, anemia, headaches, and tiredness. Contrary to ALP and AMI, niacin and its derivatives, nicotinamide and isonicotinamide, are popular agents for co-crystallization in pharmaceutical co-crystal studies. For NIA, the extended information in the CSD is available, and NIA is reported in four different ionization states, as a pyridinium cation (the mostly frequently met form), as a nicotinate anion in the drug−drug solids with blonanserin, clofazimine, pyrimethamine, tegaserod, and lamotrigine.[63−67] In the zwitterion form, due to the intramolecular proton transfer, NIA is reported in adducts with *rac*- and (+)-hesperetin, hydrochlorothiazide, pyrogallol,[44,68,69] and with several carboxylic acids.[44,52,70] Finally, only two examples report NIA in the neutral form in adducts with β-cyclodextrin (β-CD) and 4-aminobenzoic acid.[71,72]

Allopurinol (ALP) belongs to a class of purines whose molecules consist of a pyrimidine ring fused to an imidazole ring. Since its approval in 1966 by the FDA, ALP has been prescribed for the treatment of gout and tumor lysis syndrome,

Table 1. Hydrogen Bonds in Crystalline Products 1−3

D-H···A	d(H···A), Å	d(D···A), Å	∠(DHA), deg	symmetry transformation for acceptor
1				
O(4)-H(4)···O(6)	1.56	2.472(4)	178.1	$x - 2, y, z$
N(1)-H(1)···O(5)	1.97	2.774(7)	148.6	$2 - x, y - 1/2, 1 - z$
N(2)-H(2)···O(1)	2.56	3.164(7)	125.1	$x, y, z + 1$
N(2)-H(2)···O(2)	1.76	2.656(7)	175.8	$x, y, z + 1$
C(5)-H(5)···O(1)	2.48	3.318(9)	150.2	$-x, y - 1/2, 1 - z$
C(13)-H(13)···O(1)	2.57	3.185(8)	123.8	$x, y, z + 1$
C(13)-H(13)···O(3)	2.20	2.987(8)	142.5	$-x, y + 1/2, 2 - z$
2				
O(2)-H(2A)···N(3)	1.82	2.653(7)	178.4	x, y, z
O(4)-H(4A)···N(7)	1.86	2.685(7)	174.6	$x - 1, y - 1, z$
N(2)-H(2N)···O(1)	2.52	3.088(7)	124.1	$2 - x, 1 - y, -z$
N(2)-H(2N)···N(1)	2.09	2.935(7)	164.0	$2 - x, 1 - y, -z$
N(5)-H(5N)···O(6)	1.92	2.782(7)	172.9	$-x, 1 - y, 1 - z$
N(6)-H(6)···O(5)	1.93	2.747(6)	155.8	$x - 1, y, z$
N(9)-H(9)···O(1W)	1.79	2.660(11)	173.9	$1 - x, 1 - y, 1 - z$
N(9)-H(9)···O(1WA)	2.09	2.920(13)	158.2	$1 - x, 1 - y, 1 - z$
C(2)-H(2)···O(2W)	2.58	3.494(11)	165.8	x, y, z
C(5)-H(5)···O(5)	2.54	3.250(8)	132.1	$2 - x, 1 - y, -z$
C(11)-H(11)···O(1)	2.50	3.206(7)	131.6	x, y, z
C(11)-H(11)···O(1)	2.40	3.061(8)	126.7	$2 - x, 1 - y, -z$
C(12)-H(12)···O(6)	2.42	3.291(7)	153.3	$x + 1, y, z$
C(17)-H(17)···N(4)	2.58	3.465(9)	156.6	$-x, 1 - y, 1 - z$
3				
N(1)-H(1)···O(5)	1.90	2.684(3)	151.7	$-x, 1 - y, 1 - z$
N(2)-H(2)···O(1)	1.90	2.692(3)	151.7	$-x, 1 - y, 1 - z$
N(3)-H(3A)···O(4)	2.05(2)	2.892(3)	167(3)	$1 - x, 1 - y, -z$
N(3)-H(3B)···O(9)	2.07(2)	2.726(3)	131(3)	x, y, z
N(4)-H(4A)···O(3)	1.89(2)	2.757(3)	174(3)	$1 - x, 1 - y, -z$
N(4)-H(4B)···O(2W)	2.14(2)	2.907(4)	148(3)	x, y, z
N(5)-H(5N)···O(2W)	2.15	2.934(3)	151.7	x, y, z
N(8)-H(8A)···O(2)	2.06(2)	2.917(3)	175(3)	$1 - x, 1 - y, 1 - z$
N(8)-H(8B)···O(9)	2.10(2)	2.796(3)	137(3)	x, y, z
N(9)-H(9A)···N(14)	2.11(2)	2.952(3)	170(3)	$1 - x, 1 - y, 1 - z$
N(9)-H(9B)···O(6)	2.25(2)	2.944(3)	139(2)	$x, y - 1, z$
N(10)-H(10A)···O(7)	2.15(2)	2.987(3)	173(3)	$1 - x, 2 - y, -z$
N(10)-H(10B)···O(7)	2.39(2)	3.141(3)	147(2)	$x + 1, y, z$
N(10)-H(10B)···O(10)	2.24(2)	2.781(3)	121(2)	x, y, z
N(11)-H(11A)···O(8)	1.85(2)	2.725(3)	175(3)	$1 - x, 2 - y, -z$
N(11)-H(11B)···O(1W)	2.16(2)	2.924(3)	146(3)	$1 - x, 1 - y, 1 - z$
N(12)-H(12N)···N(13)	2.16	2.602(3)	111.4	x, y, z
N(12)-H(12N)···O(1W)	2.33	2.984(3)	133.0	$1 - x, 1 - y, 1 - z$
N(15)-H(15A)···N(7)	2.08(2)	2.970(3)	177(3)	$1 - x, 1 - y, 1 - z$
N(15)-H(15B)···O(2)	2.18(3)	2.901(3)	143(3)	x, y, z
N(16)-H(16A)···O(6)	2.01(2)	2.896(3)	172(3)	$1 - x, 2 - y, 1 - z$
N(16)-H(16B)···O(10)	2.14(2)	2.794(3)	131(2)	x, y, z
O(1W)-H(2W)···O(7	1.94(2)	2.802(3)	166(3)	$1 - x, 1 - y, 1 - z$
O(1W)-H(1W)···O(4)	1.90(2)	2.718(3)	163(3)	$x + 1, y, z + 1$
O(2W)-H(3W)···O(3)	2.02(2)	2.809(4)	164(3)	x, y, z
O(2W)-H(4W)···O(1W)	2.09(2)	2.931(4)	161(4)	$x, y, z - 1$
C(6)-H(6)···O(10)	2.51	3.293(3)	141.7	$x - 1, y - 1, z$
C(13)-H(13)···O(9)	2.49	3.267(3)	141.0	$x - 1, y, z$
C(3)-H(3)···Cl(2)	2.87	3.773(3)	165.4	x, y, z
C(10)-H(10)···Cl(1)	2.87	3.782(3)	166.8:	$x, y + 1, z$

and recently discovered to have multifaceted therapeutical potential, effective in the treatment of leukemia, lymphoma, heart damage caused by oxygen free radicals in patients undergoing cardiac bypass surgery and coronary angioplasty, and in the therapy of cerebral ischemia.[73] Melting and solvent evaporation methods were used to improve dissolution characteristics and water solubility of this drug. Solid dispersions of ALP were prepared with different polymers or carriers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), urea, mannitol, sodium salicylate, and β-CD

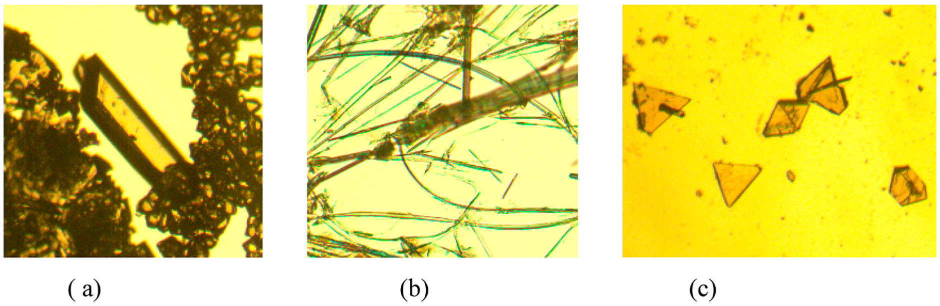


Figure 1. Pictures of the crystals **1** (a), **2** (b), and **3** (c).

aimed to decrease the crystallinity of ALP and complexing abilities and to investigate their role in enhancement of drug release through the membrane barrier. Due to the formation of hydrogen bonds between ALP and urea and mannitol, the transition from the crystalline to the better soluble amorphous state was achieved.[74,75] Its limited solubility in both polar and nonpolar media accompanied by the presence of nine different canonical tautomeric forms, resulting from the prototropic (pyrazole moiety) and lactam−lactim (pyrimidine moiety) tautomerism, clearly indicates the significance of proton transfer, which is an important factor in biochemical and pharmacological research.[76] ALP is often used as an efficient model for quantum-chemical simulations for clarifying the details of crystalline packing and predicting an unknown crystal structure of xanthine.[76−79] According to the X-ray data,[57] the layered structure of ALP is built of hydrogen-bonded molecules with a stacking distance between molecules equal to 3.301 Å. The oxo-form fixed in the crystal of ALP agrees well with the predicted higher stability among the possible tautomers.[77−80] In addition to ALP's pure crystalline form, only two crystal structures of its hydrochloride and sulfate salts where the pyrimidine moiety is protonated are known.[58,59]

Amiloride hydrochloride ((3,5-diamino-6-chloro-pyrazine-2-carbonyl)-guanidine = AMI, Brand name: Midamor), a pyrazinecarboxamide derivative of guanidine, was first synthesized in the Merck, Sharp, and Dohme Research Laboratories as a potassium-sparing diuretic. This API is used in combination with other APIs to treat high blood pressure or congestive heart failure. In the 1960s, the first patents were registered on the dihydrate, the form in which AMI is used in drug formulations.[80,81] It has been reported that AMI exists in two polymorphic dihydrate forms, either of which can be dehydrated to an anhydrous crystalline form.[82] Polymorph A was found to be more physically stable than polymorph B using X-ray powder diffraction to follow solid-state transformations upon milling or compressing both forms. It is sparingly soluble in water. Protonation of AMI occurs on the guanidine group and not on the pyrazine ring or amino groups (which are, in fact, acidic). Thus, in the physiological pH range, AMI exists primarily as a monovalent cation, with the positive charge located at the guanidinium fragment.[83] The coformer, 2,4-pyridinedicarboxylic acid (PDA), possesses biological activity and was identified as a potential inhibitor with possible selectivity over human 2OG oxygenases.[84,85]

This study impacts a broad area of study of adducts of APIs which underpins the need for understanding of supramolecular compatibility and stoichiometry of adducts which will be used toward the development of optimal and synergistic combinations for drug formulations.

EXPERIMENTAL SECTION

Materials and Physical Measurements. All chemicals were purchased from Aldrich and used without further purification. Melting points were determined on a Stanford research system (SRS) melting point apparatus and are uncorrected. IR spectra were registered using a Nicolet Magna-IR 550 spectrometer having Omnic software version 7.3 equipped with Spectra-Tech foundation series ZnSe ATR accessory. The powder diffraction data were collected with a GBC Miniflex X-ray powder diffractometer equipped with a Cu−Kα radiation (λ = 1.54056 Å) source. The diffractometer was operated at 30 kV and 35 mA. The data were collected over an angle range of 5−60° 2θ at a scanning speed of 0.5° 2θ per minute.

Co-crystallization Experiments. The slow evaporation method was used to co-crystallize the drug molecules with a PDA coformer. All molecular adducts were prepared similarly by dissolving separately equimolar amounts of drug and coformer listed in Scheme 1 in distilled water, mixing these solutions, and then by slow evaporation of the obtained solutions. Single crystals were obtained in 2 weeks for crystalline product **1**, and in a month for products **2** and **3**. In a typical example, niacin (12.3 mg/0.1 mmol) and the hydrate of PDA (16.7 mg/0.1 mmol) were dissolved in water while heating and sonicating until both compounds completely dissolved to a clear solution. The solution was allowed to slowly evaporate to obtain the crystals in 2 or more weeks.

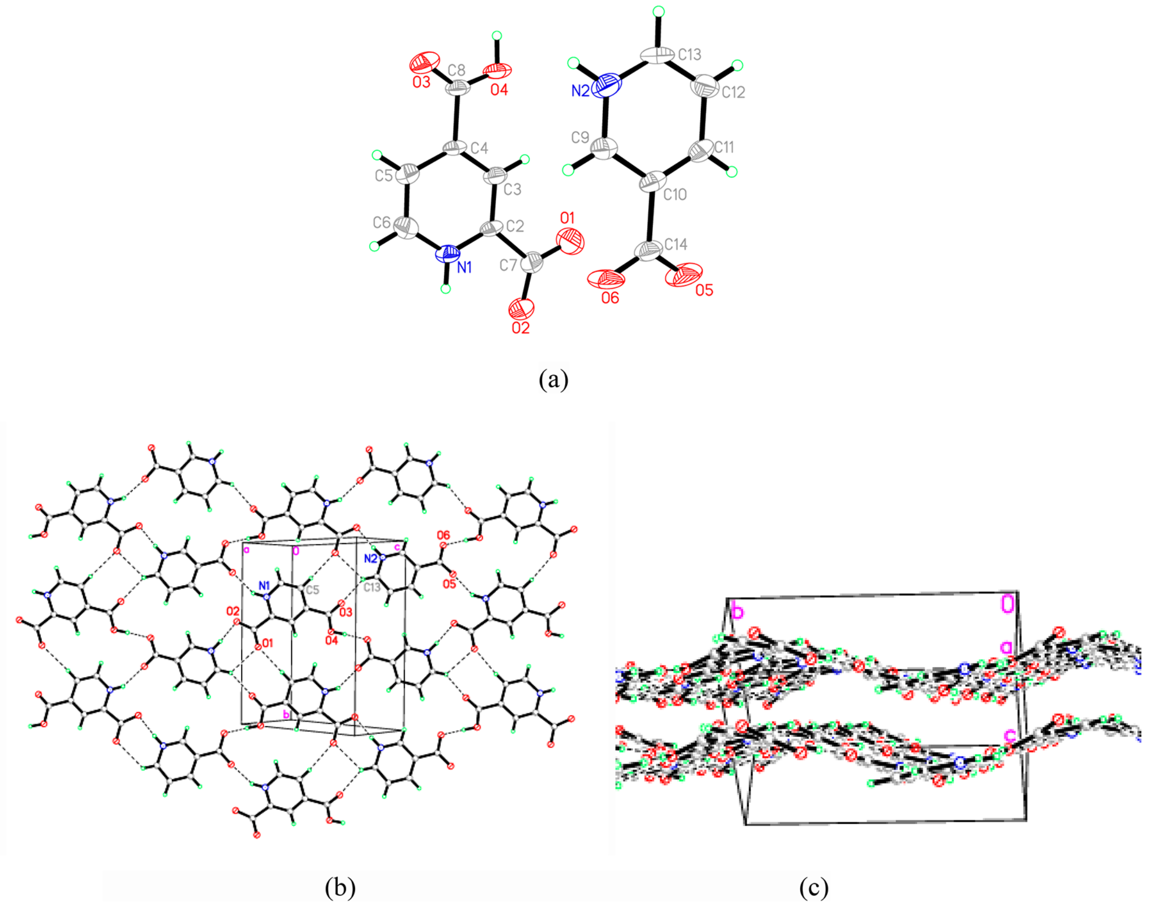
(NIA)(PDA) (**1**) IR (cm^{-1}): 3094, 2981, 2889, 1722, 1661, 1592, 1505, 1380, 1303, 1215, 1148, 1088, 954, 861, 770, 751, 713. MP 226.2 °C.

$(ALP)_2(PDA)\cdot1.5H_2O$ (**2**) IR (cm^{-1}): 3091, 2832, 2459, 1884, 1714, 1683, 1610, 1554, 1511, 1460, 1331, 1300, 1244, 1205(sh), 1177, 1003, 977, 947, 927, 881, 862, 821, 778, 760, 721. MP 230.3 °C.

$(AMI)_2(PDA)_2(H_2O)_2$ (**3**) IR (cm^{-1}): 3379, 3105, 1705, 1667, 1647, 1614, 1587, 1545, 1503, 1386, 1356, 1297, 1266, 1238, 1156, 1075, 1053, 1007, 961, 941, 889, 861, 816, 769, 735, 712. MP 225.5 °C.

Graphical presentation of IR spectroscopic data is given in Figures S1−S4.

X-ray Crystallography. Single-crystal X-ray diffraction experiments were performed on a Bruker AXS SMART APEX II CCD[86] diffractometer equipped with a cryostat system [graphite monochromatic Mo Kα radiation, λ = 0.71073 Å]. Data integration and final unit cell parameters were obtained using SAINT+.[87] Absorption corrections were applied by a semiempirical approach using SADABS,[88] and the crystal structures were solved by direct methods and refined using SHELXS and SHELXL program packages.[89] The non-H atom positions were located using difference Fourier methods and refined in anisotropic approximation. The hydrogen atoms bonded to C atoms were positioned geometrically and refined using a riding model with U_{iso} (H) = $1.2U_{eq}$ (C). The locations of acidic protons were justified by a difference Fourier synthesis map, and in the refinement, these were allowed for as riding atoms. Compound **2** was grown as very thin crystals, which explains the missing reflections in the data set. In **2**, the water molecule O(1w) was disordered over two positions which were refined with equal occupancies, while the O(2w) water molecule was refined with the partial half occupancy; that is why the hydrogen atoms in two of these molecules were not localized. The



(a)

(b) (c)

Figure 2. Structure of compound **1**. (a) View of the asymmetric unit with atom labeling scheme. (b) Fragment of H-bonded layer in **1** with indication of hydrogen bonds. (c) Packing of the H-bonded layers in **1**.

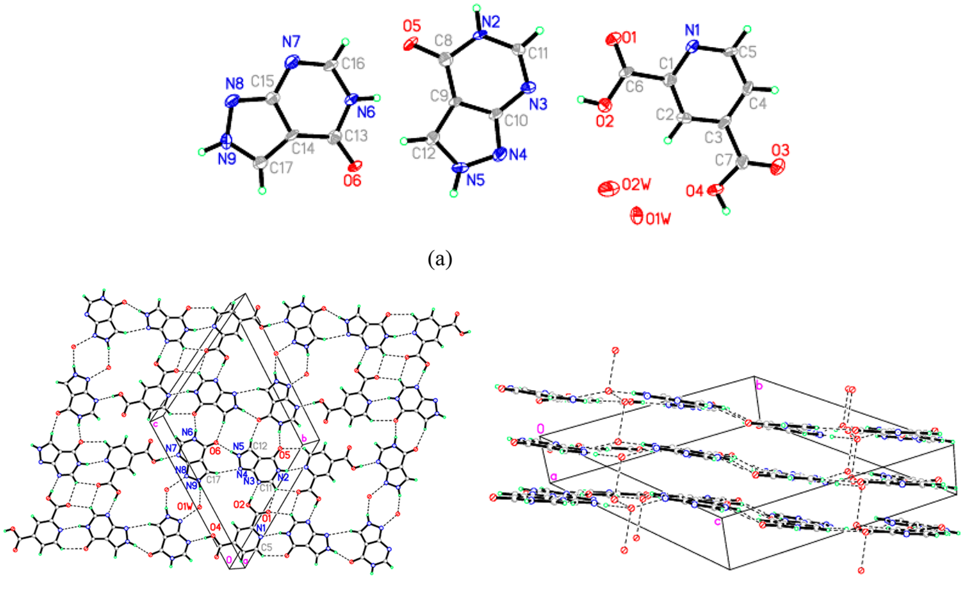
crystallographic data and the final refinement parameters are summarized in Table S1, the selected bond distances and angles are given in Table S2, and the H bonds are given in Table 1. Structural data were deposited in the Cambridge Structural Database; the deposition numbers are CCDC 1542759−1542761.

RESULTS AND DISCUSSION

Synthesis and X-ray Studies. Compounds **1**−**3** were prepared similarly by mixing the equimolar aqueous solutions of the components. For the co-crystallization experiments, the series of dicarboxylic acids that include glutaric, adipic, malonic, succinic, azealic, L-glutamic, L-aspartic, and 2,4-pyridinedicarboxylic (PDA) acids were tested, with the obtainment of only the crystalline products **1**−**3** reported herein. Compounds **1** and **2** were colorless, while compound **3** was light yellow (Figure 1). The formation of new phases was confirmed by the IR spectra and X-ray powder diffraction (XRPD) patterns for all products (Figures S1−S4 and Figures S5−S7 in the Supporting Information). IR spectra clearly demonstrated that a new phase was obtained of PDA with NIA, ALP, and AMI and did not give positive results for other combinations of coformers. Therefore, only compounds **1**−**3** were further studied with the diffraction method.

NIA and PDA co-crystallize as a binary compound **1** with the 1:1 molar ratio in the noncentrosymmetric monoclinic $P2_1$ space group (Figure 2a). Functional H atoms were localized at the pyridine nitrogen atoms in both NIA and PDA molecules, and in one carboxylic group in the PDA molecule. Their positions were also justified by the consistent hydrogen-bonding system. The neutral character of only one of three carboxylic groups in **1** is also supported by the difference in the C−O bond distances in this compound (Table S2). Such a location of hydrogen atoms means that both components exist in the zwitterion forms previously reported for both.[44,47,68−71]

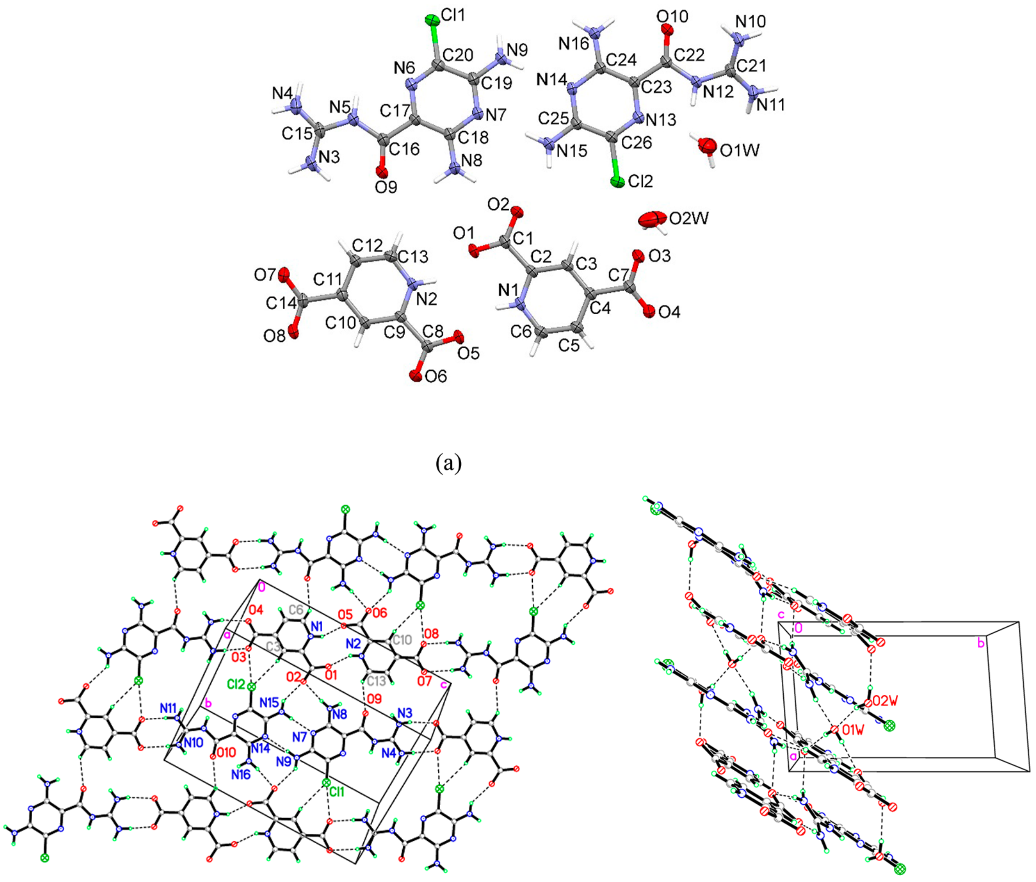
In crystalline product **1**, two molecules are characterized by the almost planar molecular skeletons. In the NIA molecule, the twisted angle between the pyridine ring and the carboxylic group is equal to 13(1)°. In the PDA molecule, the deprotonated carboxylic group lies in the plane of the pyridine ring, while the neutral carboxylic group is twisted relative to the same plane at the dihedral angle of 14(1)°. This dissimilarity is explained by the different modes of their involvement in the hydrogen-bonding systems (Figure 2b). The association of the molecules in the infinite corrugated sheets that are extended parallel to the (102) crystallographic plane occurs via cooperativity of seven unique hydrogen bonds that include one OH···O (O···O = 2.472(4) Å), three NH···O (N···O = 2.656(7)−3.164(7) Å), and three CH···O (C···O = 2.987(8)−3.318(9) Å) hydrogen bonds (Table 1, Figure 2b). These bonds act between the successive rows of the NIA and PDA molecules in the forms of the robust pyridinium-carboxylate $R_2^2(8)$ heterosynthon,[3,4] which is supported by one COOH···O(COO−), one NH^+···$O(COO^-)$ charge-assisted hydrogen bond,[5] and two CH···O hydrogen bonds.[6] Thus, all directed interactions are realized within the sheets. Both types of pyridinium-carboxylate heterosynthons, cyclic and linear ones, are statistically among the most frequently reported.[14,90,91] The drug and coformer molecules are situated in nearly the same



(a)

(b) (c)

Figure 3. Structure of compound **2**. (a) View of the asymmetric unit with atom labeling scheme. (b) Fragment of H-bonded layer in **2** with indication of the hydrogen bonds. (c) Packing of the H-bonded layers in **2**.



(a)

(b) (c)

Figure 4. Structure of compound **3**. (a) View of the asymmetric unit with atom labeling scheme. (b) Fragment of H-bonded layer in **3** with indication of the hydrogen bonds. (c) Stacking of the H-bonded layers in **3** interlinked by the water molecules.

plane as the dihedral angle between their pyridine rings equal to 2.1(4)° indicates. Such an arrangement predisposes that the other noncovalent forces stabilizing compound **1** are the face-to-face $\pi-\pi$ stacking interactions,[92] since the shortest interplanar separation of 3.4 Å was found between the neighboring parallel-displaced NIA molecules stacked with the partial overlap along the shortest crystallographic *a* axis (Table S1, Figure 2c).

Compound **2** with the composition $(ALP)_2(PDA)\cdot1.5H_2O$ crystallizes as a hydrate in the triclinic centrosymmetric space group $P\bar{1}$. The content of the asymmetric unit is shown in Figure 3a. The hydrogen atoms in the two disordered water molecules were not localized. The distribution of N- and O-bound hydrogen atoms in the ALP drug and PDA coformer molecules and the bond distances values (Table S2) unambiguously indicate that no proton transfer occurs, and all components exist in the neutral forms. Thus, compound **2** can be interpreted as a co-crystal hydrate.[17,20] Two crystallographically unique ALP molecules exist in the oxo-tautomeric form that is agreed with the ALP crystalline pure form and its chloride and sulfate salts.[57−59] Both ALP and PDA heterocyclic molecules have almost planar molecular skeletons. Similar to **1**, one of the carboxylic groups in PDA displays in the plane of the pyridine ring, while another one is twisted relative to the same plane as the corresponding dihedral angles of 1.4(8)° and 8.1(8)° indicate. The drug and coformer molecules are located almost in the same plane as shown by values of the dihedral angles between the mean planes of the drug skeletons ALP1/ALP2 of 4.8(2)°, and between each of them and the pyridine ring of the PDA coformer, ALP1/PDA and ALP2/PDA, being of 2.3(2)° and 7.0(2)°, respectively. Similar to **1**, this predisposes the association of the molecules in the sheets running parallel to the (−1 2 −1) crystallographic plane and supported by the extended H-bonding system that includes OH···N (O···N = 2.653(7), 2.685(7) Å), NH···N (N···N = 2.935(7) Å), NH···O (N···O = 2.66(1)−3.088(7) Å), CH···O (C···O = 3.061(8)−3.49(1) Å), and CH···N (C···N = 3.465(9) Å) contacts (Table 1). Within the layer, four ALP molecules are linked in the centrosymmetric tetramer $(ALP1)_2(ALP2)_2$ through the two types of alternating noncentrosymmetric supramolecular synthons, $R_2^2(9)$ and $R_2^2(8)$, based on the H bonds N(6)-H···O(5), C(12)-H···O(6), and N(5)-H···O(6), C(17)-H···N(4) (Figure 3b). Each homomeric tetramer in the layer is surrounded by six PDA coformers, four of which are involved in the two centrosymmetric heteromeric tetramers $(ALP)_2(PDA)_2$ through the hydrogen-bonded cross-linked zippers, $R_2^2(7)R_2^2(8)R_2^2(4)R_2^2(8)R_2^2(7)$, interconnected with an $R_2^2(7)R_2^2(4)R_2^2(7)$ sequence (Figure 3b). Two other PDA molecules are involved into the carboxylic acid···pyridine heterosynthon each, (COOH)O(4)-H···N(7) (Table 1). Thus, the homomeric and heteromeric tetramers alternate due to the PDA mediating function, while O(1w) water molecules link ALP tetramers. The majority of strong hydrogen bonds and weaker ones, that include CH···O and CH···N interactions, are realized within the layer. The layers, stacked along the shortest crystallographic *a* axis, are connected through the intermediate water molecules and through the face-to-face $\pi-\pi$ stacking interactions acting between the uniform stacks of ALP and PDA molecules with the interplanar separation of 3.3 Å in each type of stacks (Figure 3c).

The crystals $(AMI)_2(PDA)_2(H_2O)_2$ (**3**) are triclinic, space group $P\bar{1}$ (Table S1). The asymmetric unit consists of two AMI cations, two PDA zwitterionic anions, and two water molecules (Figure 4a). The guanidine groups in both AMI molecules are protonated. The mode of the AMI protonation and the geometry of cations are consistent with the reported AMI hydrochloride and picrate salt forms.[60−62] The guanidinium planar fragments whose conformations were stabilized by the intramolecular NH···O short contacts between amino and neighboring carbonyl groups (N···O = 2.726(3)−2.797(3) Å) are characterized by the diversification of the C−N distances and the C−N−C bond angles increased up to 127.8(2)° (Table S2). Both cations are slightly nonplanar as the interplanar angles between the pyrazine ring and the guanidinium group are equal to 9.1(3)° in the AMI1 (bearing Cl1 atom) molecule, and 25.6(2)° in the AMI2 (bearing Cl2 atom) molecule indicate. The value of this angle in the AMI hydrochloride was of 11.63 (7)°.[61]

Upon the retrieval of CSD, the zwitterion anionic form of the PDA coformer found in this crystal structure is the thus far unreported ionization form. The proton transfer is confirmed by the increased cyclic C−N−C bond angles at the pyridinium nitrogen atoms, while the deprotonated character of the carboxylic groups is evidenced from the almost equalized values of the C−O bond distances (Table S2). In both molecules of the PDA coformer, one of the carboxylic groups reveals better conjugation with the pyridinium ring, as the corresponding dihedral angles of 2.2(3)° and 3.4(3)° indicate, while the second carboxylic group deviates stronger from planarity, as the COO/Py dihedral angles of 11.7(3)° and 14.6(3)° show. All the heterocyclic entities are situated roughly in the same plane as indicated by the narrow range of dihedral angles between their heterocyclic cores scattering from 0.9(1)° (PDA1/PDA2) to 3.7(1)° (AMI1/PDA1). Similar to two previous structures, the heterocyclic molecules form the slightly corrugated H-bonded layer sustained by the extended H-bonding system[84] based on the NH···N (N···N = 2.952(3), 2.602(3), 2.970(3) Å), NH···O (N···O = 2.684(3)−3.141(3) Å), and CH···O (C···O = 3.267(3), 3.293(3) Å) short contacts (Table 1). The H-bonded network is built of the alternating homomeric pseudo-centrosymmetric dimers $(AMI)_2$ and $(PDA)_2$ (Figure 4b). Two AMI cations are linked via a pair of $NH(NH_2)\cdots N$ hydrogen bonds acting in the form of an $R_2^2(8)$ supramolecular synthon, N(15)-H···N(7) and N(9)-H···N(14), while two PDA anions are linked via a pair of NH···O hydrogen bonds, N(1)-H···O(5) and N(2)-H···O(1), in the form of an $R_2^2(10)$ supramolecular synthon. These homodimers are interlinked into chains along the [0 1 −2] direction via two very similar heteromeric AMI-PDA urea-carboxylate heterosynthons, $R_2^2(8)$ N(3)-H···O(4) and N(4)-H···O(3), and N(10)-H···O(7) and N(11)-H···O(8). In approximately the perpendicular direction, these chains are interwoven via the interplay of CH···Cl, NH···O, and CH···O contacts. Two water molecules are situated outside the hydrogen-bonded plane both acting as double donors and double acceptors linking the neighboring layers (Figure 4c). Similar to **1** and **2**, in **3**, the separations between the components from neighboring layers, being in the narrow range of 3.33−3.39 Å, correspond to the $\pi-\pi$ stacking interactions acting between alternating stacks of AMI and PDA molecules.

In conclusion, a co-crystallization of three N-heterocyclic drug molecules, niacin (3-pyridine-carboxylic acid = NIA), allopurinol (pyrazolo(3,4-d)pyrimidin-4-one = ALP), and amiloride (3,5-diamino-6-chloro-pyrazine-2-carbonyl)-guanidine = AMI), with the same coformer, 2,4-pyridinedicarboxylic acid (PDA), gave rise to three new crystalline products, (NIA)(PDA) (**1**), $(ALP)_2(PDA)\cdot1.5H_2O$ (**2**), and $(AMI)_2(PDA)_2(H_2O)_2$ (**3**), that revealed 1:1, 2:1, and 2:2 drug:coformer molar ratios and existed either in anhydrous form (**1**) or as hydrates (**2**, **3**). The proton transfer resulted in the zwitterionic co-crystal **1**. In the co-crystal **2**, two crystallographically unique ALP molecules exist in the oxo-tautomeric form. Compound **3** crystallized as the salt with the guanidinium cationic part as in the started AMI hydrochloride hydrate, and the PDA coformer as the zwitterionic anion. Thus, the diversity of the PDA coformer ionization states included the neutral, zwitterion, and zwitterion anionic forms. The selectivity of PDA in co-crystallization experiments with the reported drug molecules in comparison with the other used dicarboxylic acids indicates in favor of the pyridine moiety as an additional important binding site that contributes significantly to the strengthening of the generated hydrogen-bonding system. The majority of the directional interactions including the interplay of conventional and charge-assisted hydrogen bonds that act in the form of virtually planar homo- and heteromeric supramolecular synthons assisted in the formation of H-bonded layers in all structures. The cooperative $\pi-\pi$ stacking interactions between the layers were supported by the mediated water molecules in **2** and **3**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.7b00542.

> Figures S1–S4 show IR spectra for 2,4-pyridinedicarboxylic acid, niacin, allopurinol, and amiloride, as well as adducts of 2,4-pyridinedicarboxylic acid with three APIs (compounds **1**–**3**). Figures S5–S7 show comparison of experimental and simulated X-ray powder diffraction data for compounds **1**–**3**. Tables S1 and S2 present a summary of crystallographic data and selected bond lengths for crystalline products **1**–**3** (PDF)

Accession Codes

CCDC 1542759–1542761 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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