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From Competition to Commensuration by Two Major Hydrogen-Bonding Motifs

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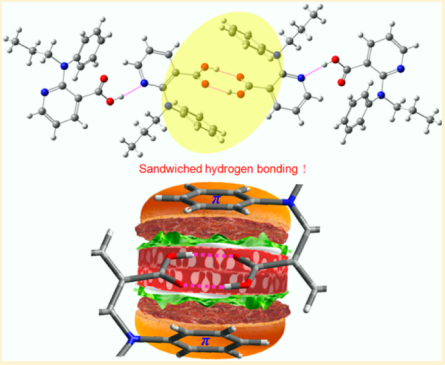
Supporting Information

ABSTRACT: Carboxylic acid−acid hydrogen-bonding dimer and acid−pyridine hydrogen-bonding motif are two competing supramolecular synthons that a molecule possessing both carboxylic acid and pyridine functional groups could form in the solid state. Their coexistence has been observed but for the molecules with the molar ratio of carboxylic acid and pyridine groups being greater than 1:1. In this crystal engineering study, 2-[phenyl(propyl)amino]nicotinic acid with a 1:1 molar ratio of these two functional groups was discovered to have two polymorphs, in which one consists of unique hydrogen-bonded tetramer units bearing both acid−acid and acid−pyridine hydrogen-bonding motifs, while the other is composed of acid−pyridine hydrogen-bonded chains. Quantum mechanical calculations were employed to unravel the essence of the coexistence of the two vying counterparts as well as the origins of the tetramer and chain structures.



Crystal formation of organic molecules is a balanced art of noncovalent interactions, including hydrogen bonding,[1−5] halogen bonding,[6,7] $\pi-\pi$ interactions,[8−10] and van der Waals forces,[11,12] in conjugation with the conformational change caused by the constituent functional groups. Appropriate molecular design makes these weak noncovalent interactions and the molecular flexibility tunable and enables the molecules to assemble into desired packing pattern. Such a process is of great importance because organic molecules may assemble into different crystal forms, the so-called polymorphs,[13,14] in which these forms exhibit different properties and performance. Therefore, design of particular molecular packing architectures in the solid state requires manipulation and a thorough understanding of intermolecular interactions as well as the molecular flexibility.

Among various intermolecular interactions, hydrogen bonding is the most important one which has been utilized extensively in structural design and crystallization control. Carboxyl−carboxyl hydrogen-bonded dimer (−COOH···−COOH) and carboxylic acid−pyridyl nitrogen hydrogen-bonded motif (−COOH···N═) are two of the most prevalent building blocks in crystal engineering. Our previous study showed that 2-(phenylamino)nicotinic acid (2-PNA) (Figure 1) is capable of forming both of the aforementioned hydrogen-bonding patterns.[15] Of its four known polymorphs, two consist of the acid−acid dimers while the other two are composed of the acid−pyridine hydrogen bond. Note that in the acid−pyridine motif of 2-PNA and its derivatives, the carbonyl typically does not form another hydrogen bond with any

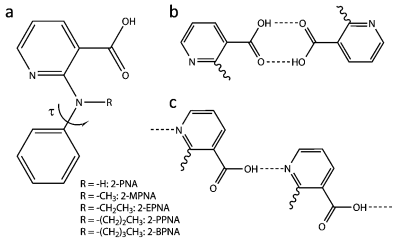


Figure 1. (a) 2-PNA and its derivatives. (b) Acid−acid hydrogen-bonding dimer. (c) Acid−pyridine hydrogen-bonding chain.

hydrogen from the pyridine ring. No crystal form bears two motifs simultaneously. It is further revealed that the acid−pyridine hydrogen bond is significantly stronger than that of the acid−acid hydrogen bond (by about 11 kJ/mol).[16] But the formation of the stronger acid−pyridine hydrogen bonding forces its constituent molecule to twist from a planar conformation, with a loss of conformational stability by several kilojoules per mol. As a result, the two hydrogen-bonding motifs of 2-PNA share similar, overall energetic states (considering dimers as distinct building units), indicating the strong interplay between the molecular conformation and intermolecular interaction. To further explore their cooperativity, a series of 2-PNA derivatives was synthesized by

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introducing alkyl groups to the phenyl ring, thereby forcing the molecules to adopt twisted conformations.[17] Such design led the modified molecules to form the acid−pyridine hydrogen-bonded chains in their respective crystal structures. Conversely, the derivatives obtained by conjugating electron-withdrawing groups to the phenyl ring have their planar conformations effectively enforced,[18] and the formation of the acid−acid dimer in their crystal structures is observed. The results illustrate that the carboxyl−pyridyl N hydrogen bonding is energetically preferred over the carboxyl−carboxyl one, but it requires molecules to rotate the phenyl ring so that the pyridyl N becomes accessible for electron donation. Obviously, a particular hydrogen-bonding synthon in the crystalline state can be generated by inducing steric effects via conformational change (planar or twisted) of a molecule.

However, to the best of our knowledge, for the molecules with 1:1 of the acid and pyridine functional groups, there is no observation of the coexistence of both the competing acid−acid and acid−pyridine hydrogen-bonding motifs in their crystals. Although two single-component crystals (FILDOU and HUYYEF) in a CSD survey of crystal structures with both carboxylic acid and aromatic base (669 hits) possess both acid−acid and acid−pyridine hydrogen-bonding counterparts, the molar ratios of carboxylic acid and pyridine N groups in the molecules are 3:1 and 2:1 for FILDOU and HUYYEF, respectively. Also, a few cocrystals show both synthons in the same crystal structure, but the hydrogen bonds are formed between two different molecular constituents.[19−21] Thus, our goal in this study is to achieve this particular feature through crystal engineering. From the structural design viewpoint, it requires that the strength of the carboxylic acid−acid hydrogen bonding (O−H···O) should be energetically brought up to be comparative or close to that of the acid−pyridine (O−H···N═) one. To tackle this challenge, our strategy is focused on forcing the phenyl ring sterically close to the vicinity of the carbonyl group of the same molecule, which may introduce $\pi-\pi$ electronic interactions between the phenyl ring and carboxyl and thus strengthen the carbonyl−hydroxyl hydrogen bonding. The rationale is inspired by the so-called resonance-assisted hydrogen bonds (RAHBs), in which π-electron delocalization is seen to enhance the hydrogen bonding.[22−25]

Accordingly, several alkyl groups including methyl, ethyl, propyl, and butyl were chemically linked to the amino group of 2-PNA, respectively (Figure 1). The methyl-substituted 2-PNA (2-MPNA) has four polymorphs identified but all consist of acid−pyridine chains.[26] The basic chain-packing features are very similar, so only one chain structure is illustrated in Figure 2a as an example. Two polymorphs for the ethyl substituted 2-PNA (2-EPNA) were obtained; both are composed of the acid−pyridine chains (Figure 2, panels b and c). Only one polymorph for the butyl-substituted 2-PNA (2-BPNA) was observed, and it is also a chain-like structure composed of the acid−pyridine hydrogen bonding (Figure 2d). Excitingly, for the propyl-substituted 2-PNA (2-PPNA), one polymorph (form I) has a structure where both acid−acid and acid−pyridine synthons coexist, while the other polymorph (form II) shows only the acid−pyridine hydrogen bond! The two structures are shown in Figure 2 (panels e and f). Crystallographic data for these compounds are listed in Tables S1, S2, and S3 of the Supporting Information. Clearly, form I of 2-PPNA achieved our goal by forming the two competing hydrogen-bonding motifs concurrently. Among the four alkyl-substituted derivatives, the size of the substituent appears to be

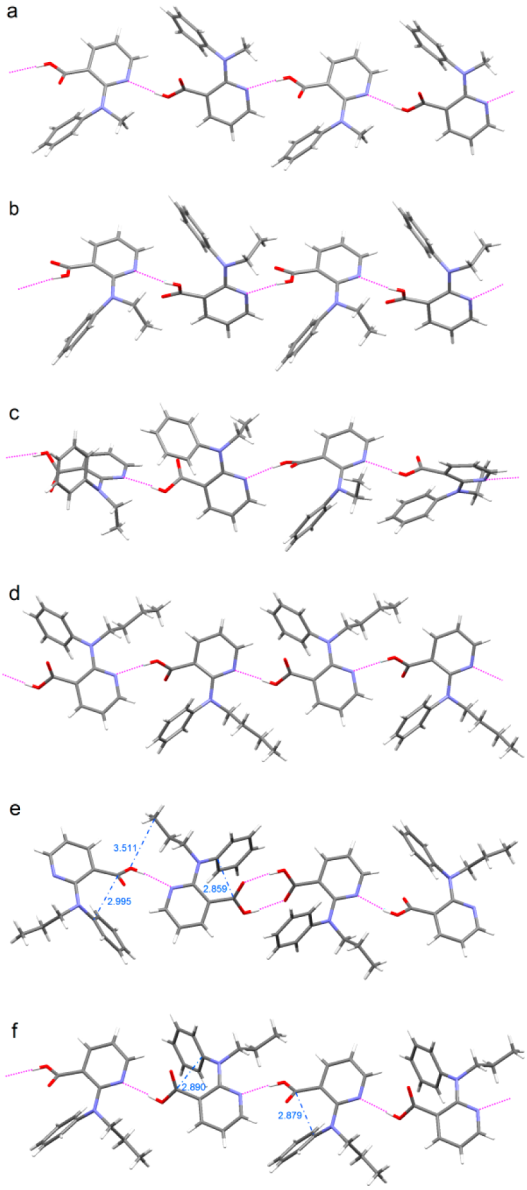

Figure 2. (a) Crystal packing of representative chain structure of 2-MPNA polymorphs, forms (b) I and (c) II of 2-EPNA, (d) 2-BPNA, and forms (e) I and (f) II of 2-PPNA.

the key factor for success. The propyl group has the steric size similar to that of the phenyl ring,[27,28] and in our case, it forces the phenyl to rotate toward the carboxyl, yielding three almost equivalent bond angles (θ_1 = 121°, θ_2 = 117°, and θ_3 = 118°; Figure 3a). No such feature was observed for other substituted alkyl groups, most probably due to either smaller or larger steric sizes of the groups.[27,28] Still, only one of the two resulting crystal structures of 2-PPNA exhibits the desired supramolecular motif, suggesting that the crystal engineering strategy can be further complicated by polymorphism.

Form I of 2-PPNA consists of unique hydrogen-bonded tetramer units stacking as multilayers in the crystal. The centrosymmetric tetramer structure (Figure 2e) is formed by four molecules with two in the middle sharing one conformation and another two at the ends having a different conformation (Table S4 of the Supporting Information). The central molecules form the acid−acid dimer synthon, which are sandwiched by two phenyl rings from the respective molecules.

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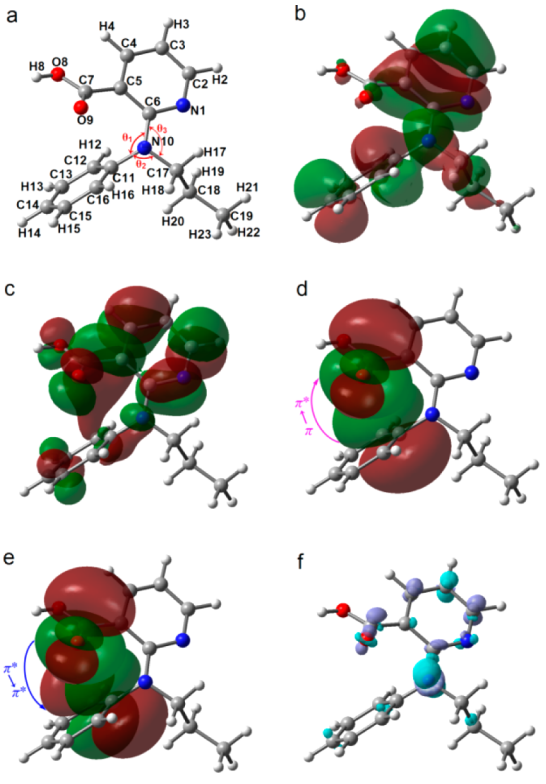

Figure 3. (a) Optimized molecular structure of 2-PPNA with atoms numbered; (b) HOMO and (c) LUMO of 2-PPNA; schematic representations of (d) $\pi \rightarrow \pi^*$ and (e) $\pi^* \rightarrow \pi^*$ between C11═C12 and C7═O9 bonds; and (f) dual descriptor. Isovalues of HOMO and LUMO are 0.02 and that of the dual descriptor is 0.08 au. Positive dual descriptors are shown in violet, while negative ones are in cyan.

The distance between the carboxyl C and phenyl *ipso*-C is 2.859 Å (Figure 2e; labeling of the atoms shown in Figure 3a). The two phenyl groups and the acid−acid synthons are positioned in parallel, facilitating the formations of intramolecular $\pi-\pi$ interactions. Each side of the acid−acid dimer is flanked by one molecule via the acid−pyridine hydrogen bonding, which is also sandwiched by a phenyl ring and a propyl from the interacting molecules. The distances between the sandwiching groups are very close for the intermolecular contacts, 2.995 Å between the carboxyl C and phenyl *ipso*-C and 3.511 Å between the carboxyl O and propyl's end C (Figure 2e). In addition, although the pyridine N of the molecule at each end of the tetramer can act as a hydrogen-bonding acceptor and extend the tetramer structure infinitely, the steric hindrance arising from neighboring layers blocks other molecules' access to the pyridine N (illustrated in Figure S1a of the Supporting Information). In contrast, form II consists of acid−pyridine hydrogen-bonding chains (Figure 2f). Because the phenyl ring is in the syn orientation with regard to the carboxyl, the chains are extended infinitely without any steric hindrance (Figure S1b of the Supporting Information). Two different, yet similar, conformers alternate throughout each chain. Moreover, every hydrogen bonding is sandwiched by a phenyl ring and a propyl; the distances between the phenyl and carbonyl are similar to those in form I. Additional evidence from IR measurement shows that form I has two characteristic peaks at 1303.9 and 925.8 cm^{-1} (Figure S2 of the Supporting Information), corresponding to the stretching vibration of C−O bond and the out-of-plane bending vibration of the O−H bond, respectively. It indicates the presence of the carboxylic acid dimer. No such peaks are observed in form II.

Intermolecular strengths of the two hydrogen-bonding motifs of 2-PPNA were evaluated by quantum mechanical calculations (Table S5 of the Supporting Information). The intermolecular interaction of the acid−acid synthon in form I is −91.23 kJ/mol (the negativity signifies attraction), while the scale of interaction decreases to −73.69 kJ/mol by removing the two phenyl rings from the dimer model. Thereby, roughly, an O−H···O hydrogen bonding in the acid−acid dimer is about −36.85 kJ/mol and the energy contribution of each sandwiching phenyl to the hydrogen bonding is around −8.77 kJ/mol. Similarly calculated, the acid−pyridine synthon in the tetramer is −61.29 kJ/mol, and it reduces to −42.94, −54.30, or −49.53 kJ/mol when both the phenyl and propyl, propyl, or phenyl group is removed. For the acid−pyridine synthon, therefore, an O−H···N hydrogen bonding is about −42.94 kJ/mol and the contributions from the phenyl and propyl groups are about −11.36 and −6.59 kJ/mol, respectively. Evidently, the steric effects coming from the phenyl and propyl stabilize both the two competing synthons. This should be an important reason leading to their coexistence as a supramolecular tetramer structure. On the other hand, in form II, because of two different conformations, two acid−pyridine dimers exist, having the interaction strengths of −56.91 and −60.29 kJ/mol, respectively. The strengths reduce to −44.04/−46.58, −50.60/−54.30, or −50.44/−52.95 kJ/mol when both the phenyl and propyl, propyl, or phenyl group is removed. It is thus argued that, despite the acid−pyridine hydrogen bonding still being stronger than the acid−acid pairing (per bond), the significant increase in the absolute values of the hydrogen-bonding strengths permits the formation of the unique tetramer structure in form I. In addition, the two structures have similar lattice energy values, −87.59 and −85.68 kJ/mol, for forms I and II, respectively. It suggests form I is slightly more stable than form II (Table S6 of the Supporting Information). The calculated density values based on the crystal structures, 1.287 and 1.254 g/cm^3 of forms I and II, respectively (Table S1 of the Supporting Information), echo the rank. This relative stability was further confirmed by wet grinding experiments in which form II converted into form I when ground in wet slurry together with form I; form I also had a higher melting point (Figures S3 and S5 of the Supporting Information). Altogether, the strategy to enforce hydrogen bonding is achieved by sterically placing an electron-donating propyl group in the vicinity of the interacting region.

How the hydrogen bonding becomes enforced was also elaborated to deepen the understanding. The frontier orbitals of the fully optimized 2-PPNA molecule show that the phenyl and propyl groups are dominated by the highest-occupied molecular orbital (HOMO) and are thereby electron-rich, whereas the carboxyl group is mainly covered by the lowest-unoccupied molecular orbital (LUMO) and is electron-depleted (Figure 3, panels b and c). It can be expected that the electron-transfer interaction would occur between the phenyl and the carboxyl in the molecule. And such interaction surely would influence the acid−acid hydrogen bonding of the dimer. Natural bond orbital (NBO) analyses[29,30] further confirm that donor−acceptor or hyperconjugation interactions contribute to the strength of the hydrogen bonds (Table S7 of the Supporting Information). The $\pi \rightarrow \pi^*$ hyperconjugation interaction (Figure 3d) between the phenyl ring (C11═C12) and the carbonyl group (C7═O9) in the acid−acid dimer

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becomes much stronger when compared with the single molecule (by 2.85 kJ/mol), augmenting the O−H···O hydrogen-bonding strength. Similarly, the $\pi \rightarrow \pi^*$ interaction also increases for the two molecules in the acid−pyridine pair (by 0.55 and 0.30 kJ/mol, respectively), impacting the O−H···N hydrogen-bonding strength to a smaller extent. Meanwhile, the $\pi^* \rightarrow \pi^*$ interaction between C11═C12 and C7═O9 bonds (Figure 3e) of the acid−acid dimer increases considerably (4.01 kJ/mol), while the increase for the acid−pyridine pair is 1.34 kJ/mol. The difference in the donor−acceptor interaction is related to not only the molecular conformation but also the environment of the interaction (i.e., sandwiched by two phenyl rings or by one phenyl ring and one propyl). The results show that the $\pi \rightarrow \pi^*$ and $\pi^* \rightarrow \pi^*$ interactions in both synthons play a major role in strengthening the hydrogen bonding due to the steric arrangement of the phenyl and/or propyl toward the carbonyl group.

Moreover, to illustrate the origins of the tetramer and chain structures, dual descriptors were calculated for the molecular systems (Figure 3f; Table S8 of the Supporting Information). In accordance with the conceptual density functional theory (CDFT),[31,32] a dual descriptor is generally utilized to characterize the electrophilicity and nucleophilicity of an atom.[33] The condensed dual descriptor of pyridine N (−0.0168) of the 2-PPNA single molecule suggests its electron-donating ability, while the positive value of the carbonyl O atom (0.0659) indicates its electrophilic nature. Compared with the pyridine N, carbonyl O is thus a poor hydrogen-bonding acceptor.[16] The electron-donating ability of pyridine N increases significantly (−0.0211) when the acid−acid dimer forms, most likely due to the two phenyl rings that sandwich the O−H···O hydrogen-bonding moiety. The formation of the O−H···N hydrogen bonding on each side of the acid−acid dimer can thus be expected, forming the tetramer containing the acid−acid dimer in the center flanked by the acid−pyridine pairs on the ends. But the dual descriptors for pyridine N (−0.0163) and carbonyl O atom (0.0654) change slightly when the O−H···N hydrogen-bonding moiety is sandwiched by a phenyl ring and a propyl, indicating that the acid−pyridine chain motif would form continuously as an infinite structure.

In conclusion, alkyl derivatives of 2-PNA (2-MPNA, 2-EPNA, 2-PPNA, and 2-BPNA) were synthesized and their crystal structures were examined. All but one (form I of 2-PPNA) have acid−pyridine synthons stabilized by the alkyl and phenyl groups sterically positioned near the hydrogen bonding as building block. For 2-PPNA, one of its polymorphs (form I) possesses a unique steric effect of the intimate contact between the phenyl ring and the carbonyl group as well as the resulting stereoelectronic effect of π-electron delocalization (i.e., $\pi \rightarrow \pi^*$ and $\pi^* \rightarrow \pi^*$ interactions) between them. Aided by such intramolecular interaction, an acid−acid dimer forms, leading to an eight-membered ring of centrosymmetric O−H···O hydrogen bonds sandwiched between two phenyl rings. Its hydrogen-bonding interactions are considerably enhanced by the π electron delocalization from the phenyl ring. It coexists with another sandwichlike acid−pyridine motif due to their similar intermolecular interaction strengths. To our knowledge, this is the first case of the coexistence of both hydrogen-bonding synthons in the same crystal when the molecule has equimolar carboxyl and pyridine functional groups. Note that enhancement of hydrogen bonding due to steric delocalization of π electrons has already been utilized in designing solid-state reactions.[34−36] The results reported here should shed light on molecule design to achieve novel crystal structures.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures along with crystallographic data and CIF files for 2-EPNA, 2-PPNA, and 2-BPNA and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

‡S.L. and P.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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