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Zwitterion Formation and Subsequent Carboxylate-Pyridinium NH Synthon Generation through Isomerization of 2-Anilinonicotinic Acid

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Abstract:

Through structural modification of 2-anilinonicotinic acid by isomerization, the ΔpKa between the carboxylic acid and pyridinium NH increased dramatically over the threshold to form zwitterion in the newly designed 4-anilinonicotinic acids. This in trun led to the formation of a hydrogen bond between carboxylate and pyridinium NH, and the absence of two commonly observed synthons, i.e., the acid-acid homosynthon and acid-pyridine heterosynthon. The new synthon has a stronger hydrogen bond than that of the acid-acid homosynthon and the acid-pyridine heterosynthon, as suggested by theoretical calculations. This, together with the much larger ΔpKa, explains its formation.

Keywords: structural modification, 4-anilinonicotinic acids, ΔpKa, carboxylate-pyridinium NH synthon, hydrogen bond strength, calculation

Material properties are directly correlated to structure. In materials science and medicinal chemistry, subtle structural modifications can produce dramatic variations in physical properties. In compounds of pharmacological importance, these can affect efficacy by altering bioactivities and bioavailability, etc[1-4]. In crystal engineering, molecular structure variations are utilized to create new supramolecular synthons in the solid state, and thus new properties/applications for the entity [5-8].

2-Anilinonicotinic acids (2-ANAs) are multifunctional compounds with potential as nonsteroidal anti-inflammatory drugs (NSAIDs). Clonixin and flunixin are two representative NSAIDs[9-11]. The presence of both carboxylic acid and pyridine N gives 2-ANAs the ability to form different synthons, including an acid-acid homosynthon and an acid-pyridine heterosynthon with the latter being energetically and statistically favored[6,12-16]. However, structural modification, such as the introduction of electronegative or sterically bulky functional groups on 2-ANAs can change the result of tug-of-war between the two synthons, as demonstrated by a series of studies performed by our group[5, 17, 18]. Recently, structural isomerization was found to exert great influence on the synthon formation of 6-anilinonicotinic acids, which are structural isomers of 2-ANA, leading to a new synthon, i.e., an acid-aminopyridine synthon in the solid state (Figure 1) [19].

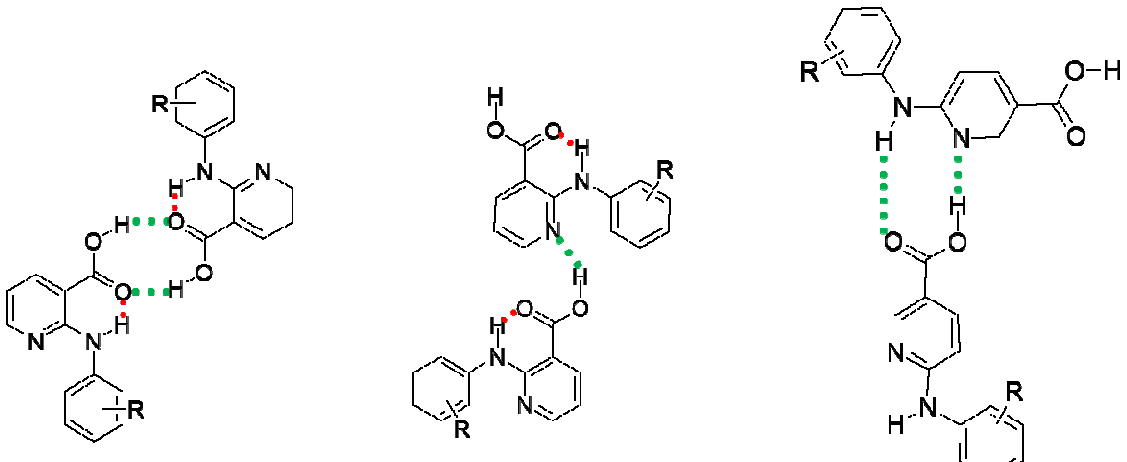


Figure 1 Acid-acid and acid-pyridine synthons observed in 2-ANAs and acid-aminopyridine in 6-ANAs

In this study, we further probe the impact of structural isomerization on synthon formation of a new series of compounds, 4-anilinonicotinic acids (4-ANAs). 4-ANAs are also structural isomers of 2-ANAs, with the anilines at the 4-position of the nicotinic acid ring. Some 4-ANAs have been found to show anti-inflammatory properties[20]. With the aniline group at the ortho position relative to the carboxylic acid, an intramolecular hydrogen bond between NH and the C=O of the COOH is expected, which eliminates the possibility of the acid-aminopyridine hydrogen bond observed in 6-ANAs. This paper addresses the question of what synthon will be observed: the acid-acid homosynthon, the acid-pyridine heterosynthon, or some new species due to possible intramolecular proton transfer?

The feasibility of intramolecular proton transfer depends on the pKa difference (ΔpKa) between pyridinium NH and COOH. In 2-ANAs, most of the time, the intramolecular proton transfer was not observed with only a few exceptions [21, 22], and in the six 6-ANAs studied, no intramolecular proton transfer was found [23, 24]. The general rule-of-thumb for intramolecular proton transfer is that the ΔpKa must be greater than 4[25, 26]. The calculated ΔpKa for two 2-ANAs, clonixin (CLX) and 2-(p-tolylamino) nicotinic acid (TNA), is 3.63 [27, 28]. For 6-ANAs △pKa is expected to be smaller due to the steric hindrance between pyridinium NH and either ^{sp2}C-H or the bridging NH, which makes protonation of pyridine N less likely (Figure 2). With the anilino group at the 4-position, the above steric interaction is no longer a concern, which should make the pKa of pyridinium NH increase significantly compared with that of both 2-ANAs and 6-ANAs, thus leading to a higher ΔpKa for 4-ANAs, which should enable ready proton transfer. With the proton now on the pyridine N, the acid-acid homosynthon is prohibited, leaving the formation of a carboxylate and pyridinium NH hydrogen bond only possibility (Figure 3).

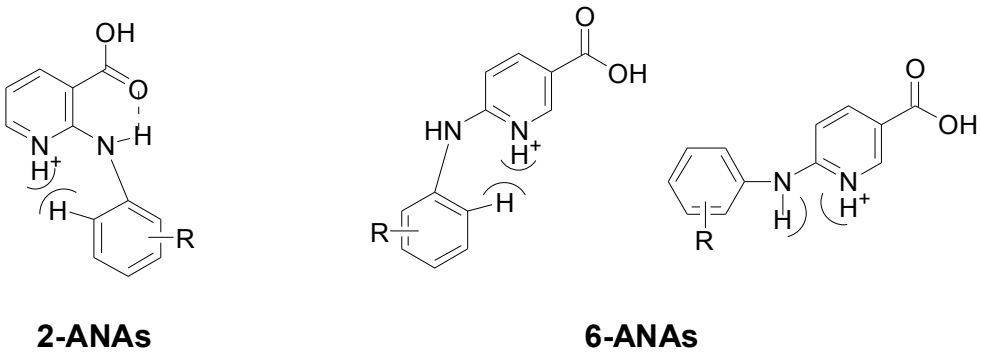


Figure 2 Steric hindrance in both 2-ANAs and 6-ANAs

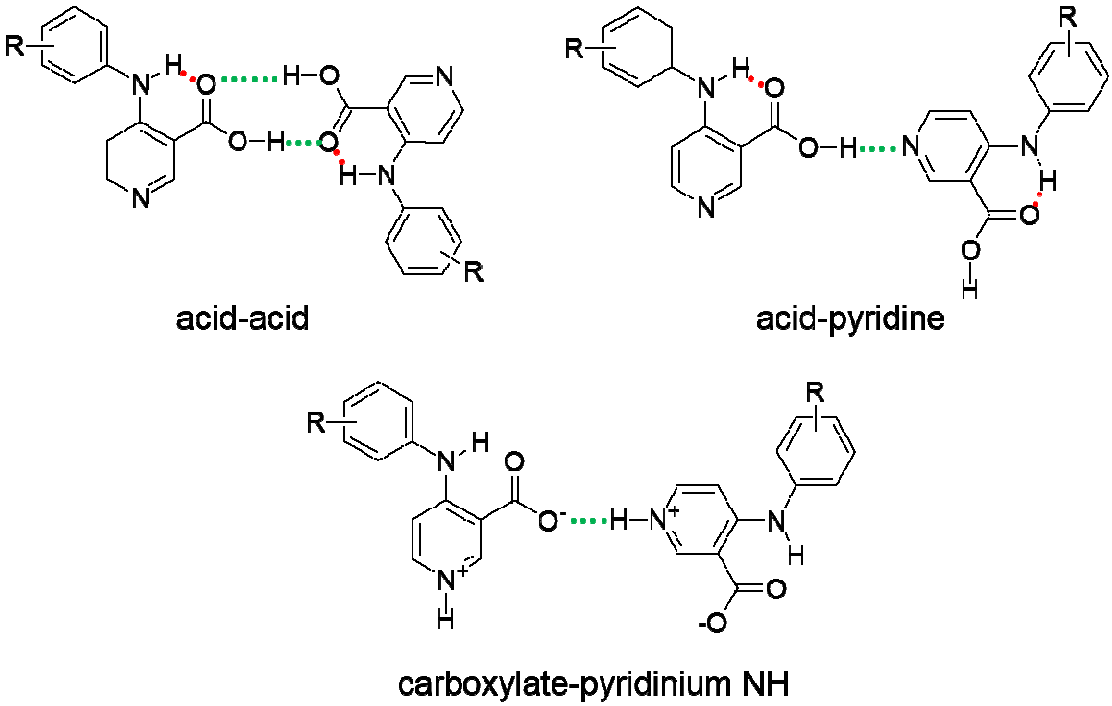
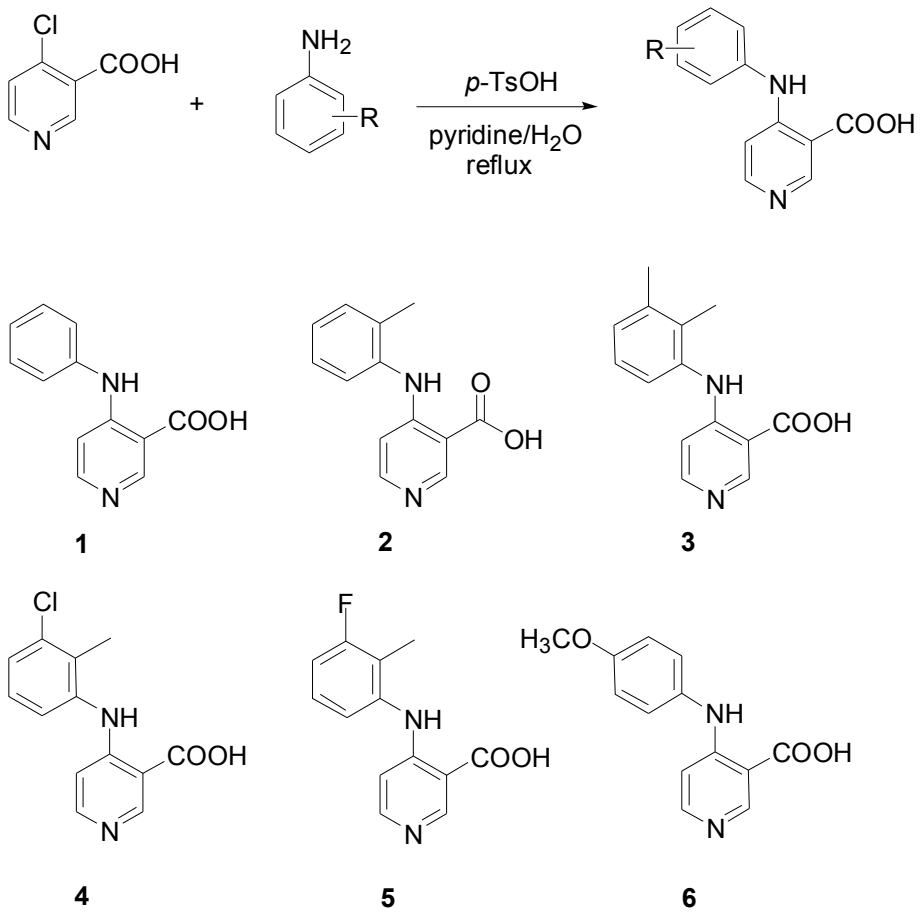


Figure 3 Possible synthons in 4-ANAs

To investigate the synthon formation in 4-ANAs, we synthesized six 4-ANA derivatives and examined their solid-state properties following the same general scheme as for 2-ANAs[29]. The pure compounds were subjected to crystal growth from a variety of solvents.



Scheme 1 Synthesis of 4-ANAs

A preliminary polymorph screening was carried out for each compound. These compounds are not particularly soluble in most common solvents used for crystal growth. Good quality single crystals were only obtained for two of the compounds (compounds **1** and **4**). For compound **1**, three crystal forms including two polymorphs (forms **1-I** and **1-II**) and one solvate (**1-S**) were harvested. For the other four compounds, they were either not soluble in the solvents used or the crystals were too thin for structure determination with single-crystal X-ray diffraction. All the crystals formed were colorless, and showed various morphologies. The two polymorphs of **1** were monoclinic, space group $P2_1/c$, while the solvate gave orthorhombic crystals with space group Pbca. The crystals of **4** were monoclinic, space group C2/c. Crystallographic data are given in Table 1. For complete CIF files, see the Supporting Information. All the crystals have only one molecule per asymmetric unit (Z'=1) except for that of **1-II**, which has two independent molecules (Z'=2). All molecules adopt the E configuration. The molecules are nonplanar

with varying dihedral angles (**1-I**: 42.24(5)°; **1-IIA:** 50.71(4)°, **1-IIB:** 55.42(4)°; **1-S**: 31.24(5)°; **4**: 81.06(4)º).

Table 1. Crystallographic data of polymorphs and solvate of **1** (**1-I, 1-II**, and **1-S**) and **4**.

	1-I	**1-II**	**1-S**	**4**
formula	C_{12} H_{10} N_2 O_2	C_{12} H_{10} N_2 O_2	C_{12} H_{10} N_2 O_2, C O	C_{13} H_{13} N_2 O_2 Cl
formula weight	214.22	214.22	246.26	262.5
crystal size (mm)	0.36 ×0.12 ×0.10	0.40 ×0.20 ×0.05	0.20 ×0.20 ×0.05	0.40 ×0.20 ×0.10
crystal system	monoclinic	monoclinic	orthorhombic	monoclinic
space group	*P* $2_1/c$	*P* $2_1/c$	*P b c a*	*C2/c*
a/Å	10.8415(2)	13.8180(2)	11.5260(2)	12.2170(2)
b/Å	13.7771(4)	11.3050(2)	7.2220(2)	10.6890(2)
c/Å	6.9369(2)	13.5600(3)	26.9490(7)	18.2180(5)
α/º	90.00	90.00	90.00	90.00
β/º	102.685(1)	107.6860(9)	90.00	90.039(1)
γ/º	90.00	90.00	90.00	90.00 0
Z, *Z'*	1	2	8	16
V/$Å^3$	1010.84(5)	2018.12(6)	2243.26(9)	2379.04(9)
D_{cal}/g×cm^{-3}	1.408	1.410	1.458	1.394
T/K	90.0(2)	90.0(2)	90.0(2)	90.0(2)
abs coeff (mm^{-1})	0.098	0.098	0.105	0.311
F(000)	448	896	1040	992
q range(deg)	1.00 —27.48	1.55—27.49	3.024—27.499	2.24—27.49
limiting indices	-14≤h≤14 -17≤k≤17 -9≤l≤9	-17≤h≤17 -14≤k≤14 -17≤l≤17	-13≤h≤14 -9≤k≤9 -34≤l≤35	-15≤h≤15 -13≤k≤7 -23≤l≤23
completeness to 2θ	100%	100%	99.7%	99.8%
Unique reflections	1596	3503	1811	2335
$R_1[I>2\sigma(I)]$	0.0477	0.0416	0.0384	0.0359
wR_2 (all data)	0.1417	0.1191	0.1173	0.0934
CCDC accession code	1856977	1856978	1856979	1856980

Conformational variability in the forms of compound **1** is readily apparent in a superposition of all four experimental conformations (Figure 4).

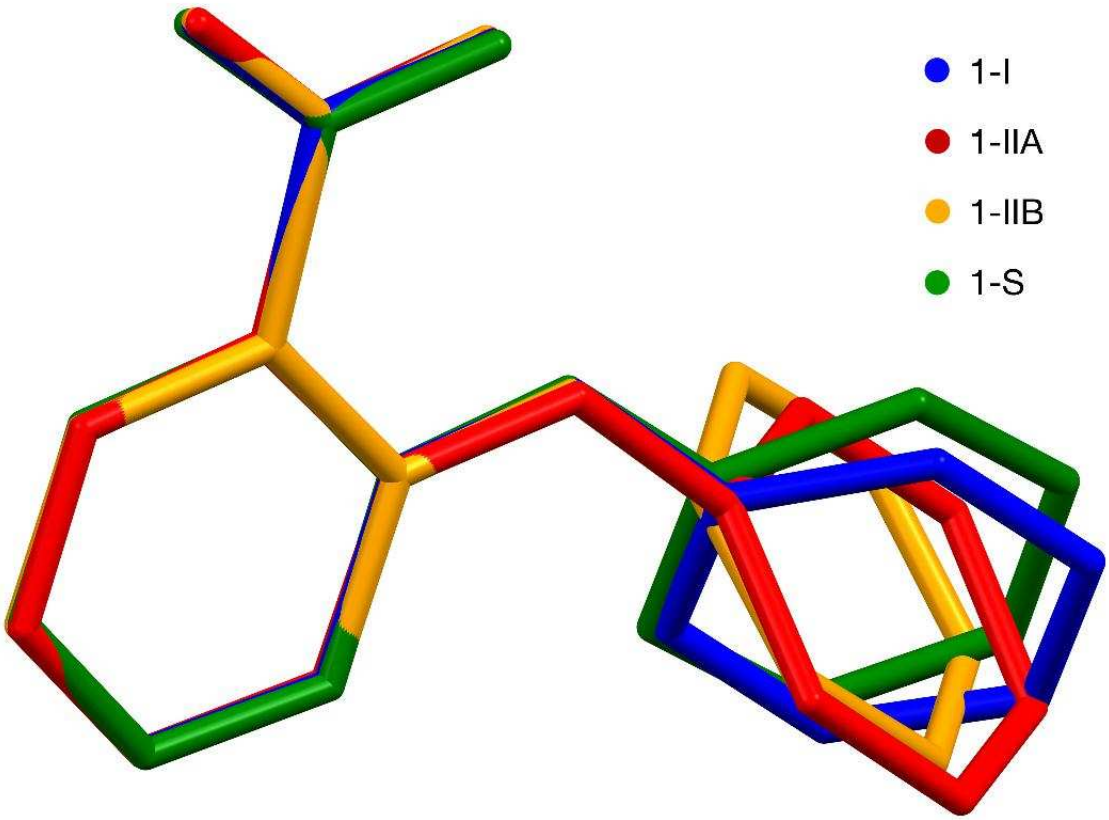


Figure 4. Superposition of all four molecular conformations in the asymmetric units of the three forms of **1**.

Neither the conventional acid-acid homosynthon, the acid-pyridine heterosynthon, nor the newly discovered acid-aminopyridine heterosynthon was observed in the crystal structures. Instead, an intermolecular hydrogen bond between the carboxylate of one molecule and the pyridinium NH of another, was formed due to intramolecular proton transfer from the carboxylic acid to the pyridine N.

In form **1-I**, the asymmetric unit contains one zwitterionic molecule (Z' = 1)[30, 31]. It has a twisted conformation, with a dihedral angle between the two aromatic rings of 42.24(5)º. The molecules form one-dimensional chains sustained on hydrogen bond between carboxylate O and pyridinium NH (C(6) by graph set annotation)[32-34]. The intermolecular

hydrogen bond has a bond distance and bond angle of 2.607(2) Å and 175.5(2)° for N1-H1…O9. In addition to the intermolecular hydrogen bond, an intramolecular hydrogen bond links the carboxylic acid carbonyl O and the NH bridging the two aromatic rings (S(6) [32-34]), with a bond distance of 2.612(2) Å and bond angle 138.0(1)° Thus O9 forms bifurcated hydrogen bonds with two hydrogen bond donors, one being the bridging NH, and the other the pyridinium NH [35, 36] (Figure 5).

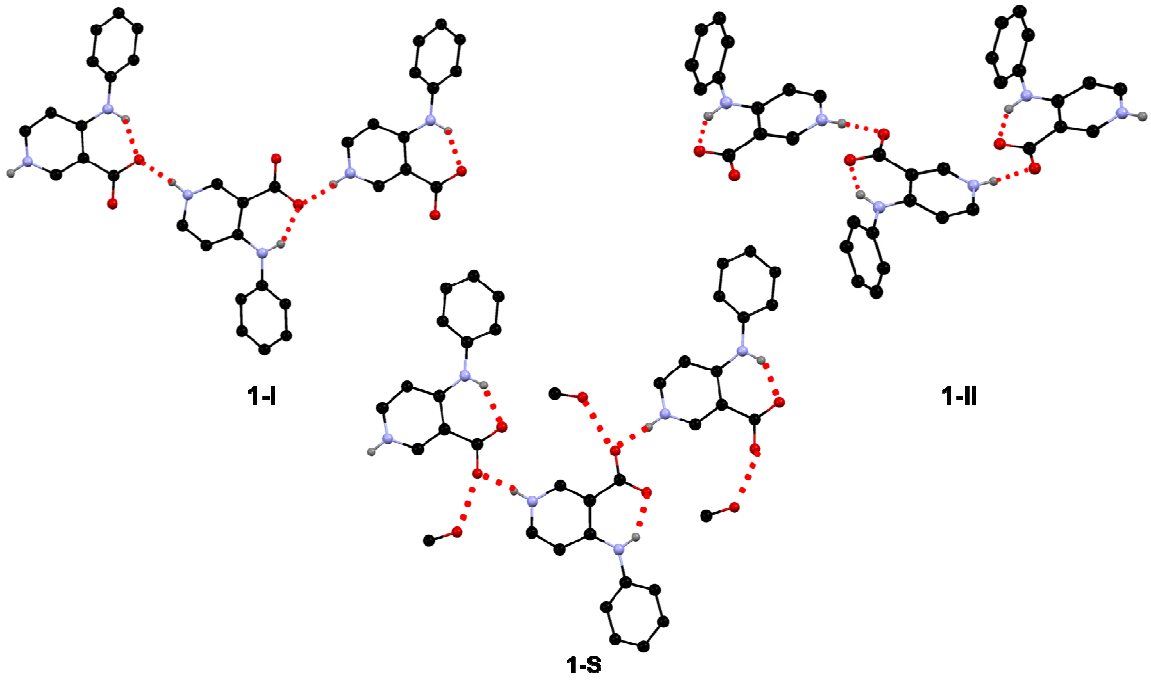


Figure 5. Crystal packing of **1-I**, **1-II**, and **1-S**. For clarity, only hydrogens participating in hydrogen bonds are shown.

Form **1-II** consists of two zwitterionic molecules (A and B) in the asymmetric unit (Z' = 2), both of which have twisted conformations, as shown by the dihedral angles between the aromatic rings (50.71(4)° and 55.42(4)° for the A and B molecules). The molecules self-associate into one-dimensional chains by means of a hydrogen bond between carboxylate O (O8) and pyridinium HN (C(6)), yet in a different way from that of form **1-I,** since the hydrogen bond acceptor is O8 in **1-II** rather than O9, and thus no bifurcated hydrogen bonds are observed. The intermolecular hydrogen bond distances and angles are: 2.645(1) Å and 173.4(2)° for N1AH1A-O8A, and 2.673(1) Å and164.5(2)° for N1BH1B-O8B. An intramolecular hydrogen bond is formed between the carbonyl O (O9) of the carboxylate and the anilino NH, with a bond distance of 2.614(1) Å and bond

angle of 137.9(1)° for N10AH10A-O9A, and 2.614(1) Å and 136.9(1) ° for N10BH10B-O9B.

In the solvate **1-S**, the solvent molecule was not strongly hydrogen-bonded with the host molecule thus it was not well modeled. Still, molecules of **1** are connected with each other through the carboxylate O and pyridinium NH hydrogen bond (bond parameters: 2.598(2) Å, 176.0(3)°) in a way similar to that of form **1-II**, forming one-dimensional chains (C(6)). Meanwhile, the solvent molecule is associated with the host molecule through a OH…O hydrogen bond (d_{D-A}: 2.835 Å). An intramolecular S(6) hydrogen bond between NH and carbonyl O (parameters of 2.648(2) Å and 140.1(1)°) is also observed.

For compound **4**, the two aromatic rings of the compound are almost perpendicular to each other (dihedral angle: 81.06(4)°) (Figure 6), likely due to the steric hindrance caused by the methyl group at the ortho position of the aniline. Proton transfer again leads to a zwitterion. The hydrogen bond is similar to that in form **1-II** (parameters of 2.698(2) Å and 168.1(2)°), leading to one-dimensional chains. The intramolecular hydrogen bond has parameters of 2.617(2) Å and 140.6(2)° (Table 2).

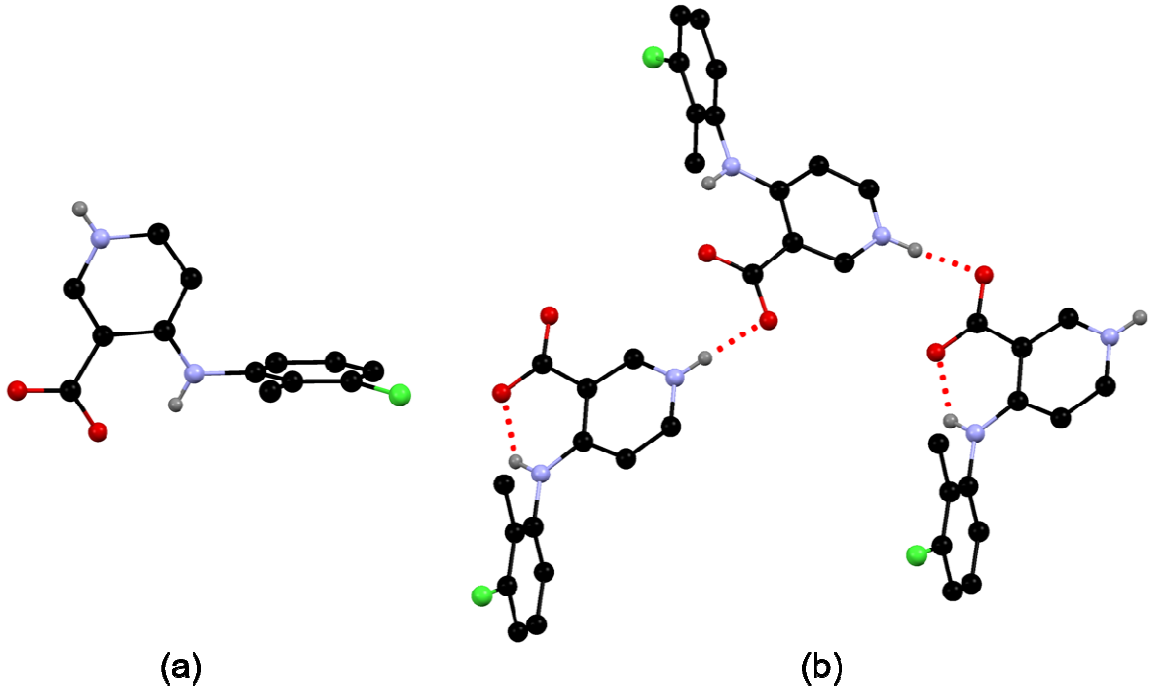


Figure 6 Single molecule of compound **4** with near orthogonal aromatic rings (a), and one-dimensional hydrogen bond chain sustained on the carboxylate O and pyridinium NH.

Table 2. Hydrogen bond parameters of NH…O (intermolecular) and NH…O (intramolecular) in four 4-ANA crystals

	1-I	**1-II**	**1-S**	**4**
NH…O bond length (Å) (intermolecular)	2.607(2)	2.645(1) 2.673(1)	2.598(2)	2.698(2)
NH…O bond angle (º) (intermolecular)	175.5(2)	173.4(2) 164.5(2)	176.0	168.1(2)
NH…O bond length (Å) (intramolecular)	2.612(2)	2.614(1)2.614(1)	2.648(2)	2.617(2)
NH…O bond angle (º) (intramolecular)	138.0(1)	137.9(1)136.9(1)	140.1(1)	140.6(2)

Intuitively, the aforementioned steric hindrance in 2- and 6-ANAs is eliminated in 4-ANAs due to the isomerization, which results in 4-ANAs having a larger ΔpKa between pyridinium NH and COOH. Still, we are keen to know to what degree the isomerization impacts the ΔpKa. Also as known, the proton transfer prohibits the formation of acid-acid homodimer, but it is intriguing to know if the formation of the carboxylate-pyridinium NH hydrogen bond could provide additional stability to the system, i.e., what is the strength of the carboxylate-NH interaction, compared with the conventional acid-acid and acid-pyridine dimers. To answer these questions, we performed a series of calculations.

All structures discussed here were optimized from various initial conformations at the M06-2X/6-311G+(d,p)[37-39] level of theory to identify the most stable conformations using Gaussian16[40]. The solvent effect of water was taken into account by applying a SCRF (self-consistent reaction field) through the SMD model[41]. Frequency analysis of each compound was performed at the same level to achieve the optimized minimal/zero

imaginary frequency, so that zero point energies (ZPE) and Gibbs free energies (at 298.15 K and 1 atm) could be obtained. Intermolecular interactions were calculated with the basis set superposition error (BSSE) considered by the counterpoise method[42]. Dispersion energies were evaluated using Grimme's DFT-D3 corrections[43]. The principle of pKa calculations can be found in the reference of Shields and Zuilhof [44, 45]. In our calculations, benzoic acid (pKa = 4.20) was selected as the reference for the acids, and pyridine (pKa = 5.23) was selected as the reference for the bases because of its well-described pKa value. Niacin was also selected as a reference (pKa1=2.00 for the acid, pKa2=4.82 for the protonated base) due to its similar structure to these ANAs. Micro model was selected while the pKa was predicted by protonation plugin of Marvin [46].

Table 3. Calculated pKa(s)

	Quantum Calculated*			Marvin Calculated**		
	pKa of acid	pKa of protonated base	ΔpKa	pKa of acid	pKa of protonated base	ΔpKa
2-ANA	2.97(2.22)	3.41(2.60)	0.44(0.38)	3.64	3.66	0.02
4-ANA	2.85(2.10)	6.43(5.62)	3.57(3.52)	3.77	6.35	2.58
6-ANA	4.60(3.85)	2.75(1.94)	-1.86(-1.94)	3.81	3.77	-0.04

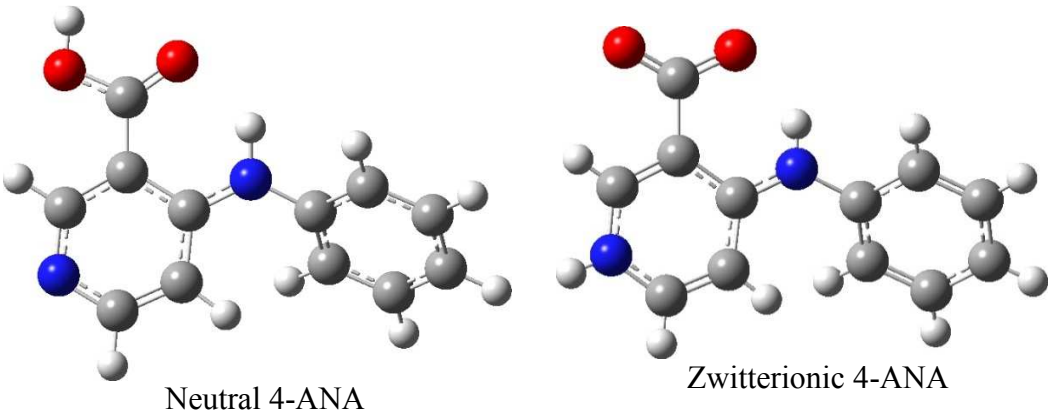
* Benzoic acid was selected as the reference for the acids, and pyridine for the bases. Values in the parentheses are based on the reference of niacin.
**Micro mode was selected

Two methods were used to calculate the ΔpKa (s) of 2/4/6-ANA. The quantum method gave ΔpKa values of 0.44, 3.57 and -1.86 for 2/4/6-ANA, respectively. In contrast, the Marvin approach generated ΔpKa values of 0.02, 2.58, -0.04, respectively. Although the exact values given by the two methods are different, the trend is obvious and consistent, i.e., 4-ANA has a significantly higher ΔpKa than that of either 2-ANA or 6-ANA. Also 2-ANA has a higher ΔpKa than 6-ANA. As mentioned before, the ΔpKa values of 2-ANAs are at the borderline of the higher end of ΔpKa rule, a drastically higher ΔpKa of 4-ANAs make proton transfer from COOH to pyridine N readily happen. This is in agreement with the observation made in the study. In addition, it also echoes the fact that no proton transfer was observed in 6-ANAs.

The relative free Gibbs energies of zwitterionic 4-ANA and five possible dimeric associations (acid-acid dimer, acid-pyridine dimer 1, acid-pyridine dimer 2, carboxylate-pyridinium NH dimer 1, and acid-pyridinium NH dimer 2) (Figures 6 and 7) in reference to neutral single 4-ANA molecule were calculated in water to be -3.49, 1.77, 0.12, 0.86, -5.39, -5.31 kcal/mol (Table 4). It is inferred that the zwitterion is significantly more stable than the neutral species, and both carboxylate-pyridinium NH dimers are much lower in energy than the conventional acid-acid dimer and acid-pyridine dimers. This echoes the observation of both carboxylate-pyridinium NH in the crystal structures. It is likely that both the higher ΔpKa of 4-ANAs and stronger intermolecular interactions contribute to the proton transfer in the crystal formation.

Table 4. Relative Free Gibbs Energies

	Δ G (kcal/mol)
4-ANA (Monomer)	0
AA (acid-acid dimer)	1.77
AP1 (acid-pyridine dimer)	0.12
AP2 (acid-pyridine dimer)	0.86
ZT (zwitterion)	-3.49
CP1 (carboxylate-pyridinium dimer)	-5.39
CP2 (carboxylate-pyridinium dimer)	-5.31



Neutral 4-ANA Zwitterionic 4-ANA

Figure 7. The optimized conformation of 4-ANA and its zwitterion

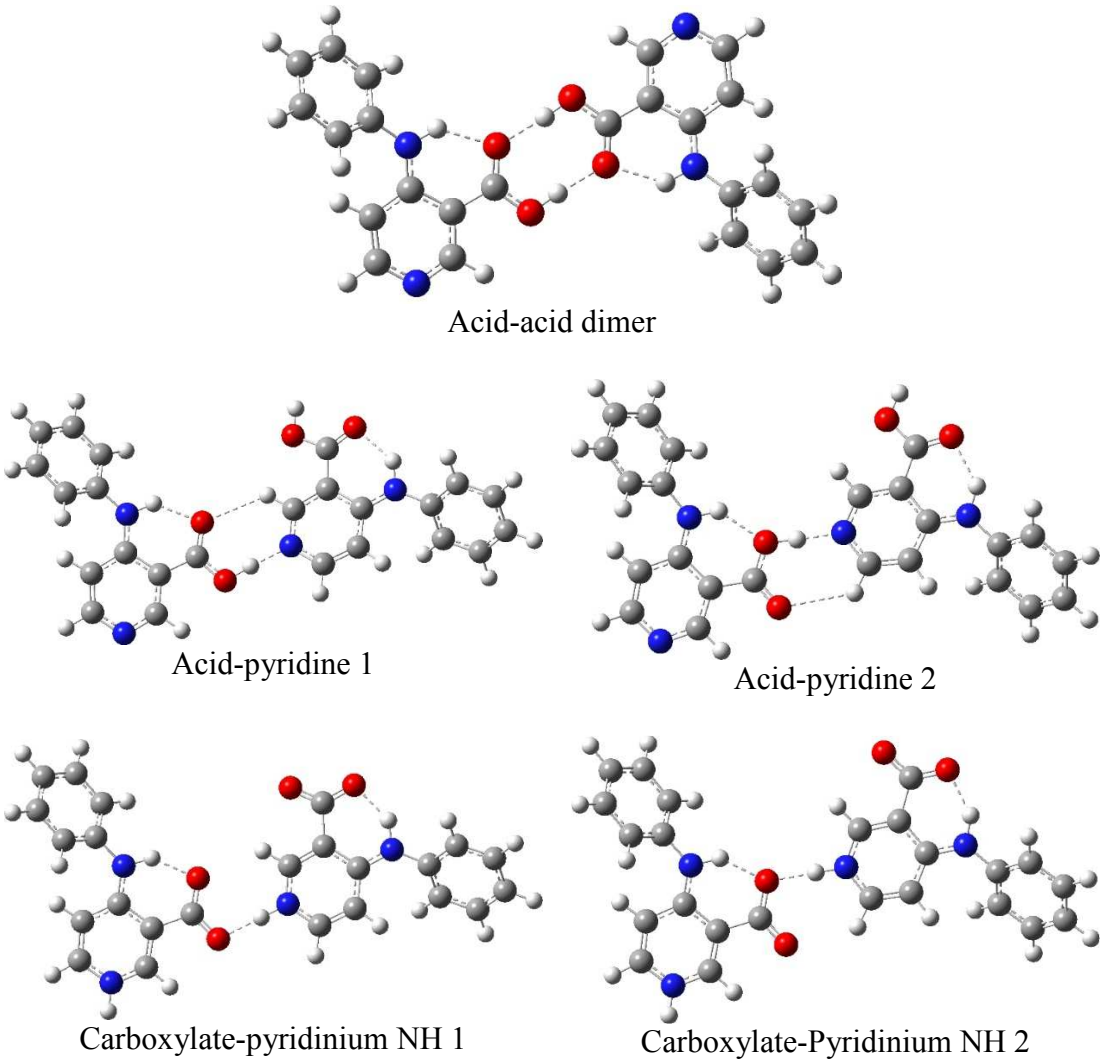


Figure 8 Five possible dimeric associations of 4-ANA molecules

2-/4-/6-Anilinonicotinic acids are potential NSAIDs with both acidic and basic groups (i.e., ampholytes). They may be able to exist in the zwitterionic state which could possess both excellent stability and solubility, thus rendering them desirable in pharmaceutical industry[31]. In this study, we achieved the exclusive formation of zwitterions and subsequent carboxylate-pyridinium NH interaction for 4-ANAs through structural isomerization based on the ΔpKa rule. This study attests to the general principle that properties can be designed through a rational, herein a crystal engineering approach.

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Supporting Information Available: Four crystal structures of two compounds in the form of crystallographic information file (CIF) were deposited in the Cambridge Crystallographic Data Centre (CCDC) with accession codes 1856977-1856980. This material is available free of charge *via* the Internet at https://www.ccdc.cam.ac.uk/.

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