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Preferred formation of the carboxylic acid–pyridine heterosynthon in 2-anilinonicotinic acids†

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The carboxylic acid–carboxylic acid homosynthon and carboxylic acid–pyridine heterosynthon are two competing supramolecular synthons in 2-anilinonicotinic acids that possess both carboxylic acid and pyridine functionalities. Previously we demonstrated that carboxylic acid–pyridine heterosynthons can be selectively formed in crystals by chemically introducing bulky functional groups to the aniline ring of the molecules. In this study we show that with the same philosophy, but a different strategy, *i.e.*, adding substituent groups to the nitrogen bridging the two aromatic rings, we can also achieve the preferential formation of the carboxylic acid–pyridine heterosynthon over the carboxylic acid–carboxylic acid homosynthon. This is a new case of how molecular conformation can affect intermolecular interactions and consequent crystal packing.

The modern definition of crystal engineering, in Desiraju's words, is "the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties".[1] Nevertheless, the origin of the term dates at least to 1955 as Pepinsky[2] coined it. It was subsequently used by Schmidt.[3] With the foundations laid by Schmidt and Kitaigorodskii,[4] the field enjoyed a rapid growth in the past two decades or so and is still blooming.[5–8] Thanks to generations of crystal engineers, our understanding of the roles of intermolecular interactions in the design and synthesis of new materials has advanced dramatically. Numerous structural motifs, widely known as supramolecular synthons, have been identified.[9,10] Particularly, these synthons are well represented in organic molecules because they generally possess multiple functional groups, by chance and/or by choice. Yet the presence of many functional groups provides both opportunities and challenges. On the one hand, it can afford the possibility to participate in various intermolecular interactions, and thus lead to diverse end products, *i.e.* polymorphs, solvates, salts or co-crystals. On the other hand, crystal engineers may lose control over the final product due to undesired interactions, thus control remains a challenge to crystal engineers.

The carboxylic acid–carboxylic acid homosynthon and carboxylic acid–pyridine heterosynthon are two competing synthons in compounds containing both a carboxylic acid and a pyridine moiety. The occurrence of carboxylic acid–pyridine heterosynthon is more common than one of the carboxylic acid homosynthons in those compounds even though many of them contain multiple functional groups according to two CSD surveys.[11,12] This is partially due to the fact that the carboxylic acid–pyridine heterosynthon is more energetically favorable than the carboxylic acid–carboxylic acid homosynthon.[12–15] And the robust carboxylic acid–pyridine heterosynthon is widely used in the design of co-crystals formed between compounds possessing carboxylic groups and molecules containing pyridine functionality, in materials science and pharmaceuticals.[16–24] Nonetheless, selective formation of either carboxylic acid–carboxylic acid homosynthon or carboxylic acid–pyridine heterosynthon in 2-anilinonicotinic acids, a group of compounds with both carboxylic acid and pyridine functionalities can be achieved, as shown in our previous studies.[25,26]

One of the 2-anilinonicotinic acids, 2-(phenylamino)nicotinic acid (2-PNA), was found to exist in four polymorphs (a fifth form has also been discovered recently), with two modifications

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‡ Peng Chen and Zhifei Zhang contributed to this work equally.

Table 1 Dihedral angle *vs.* synthon

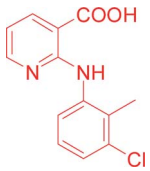
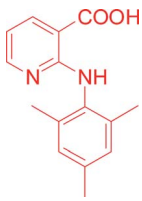
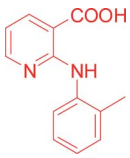
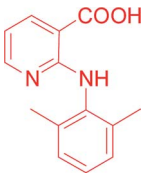
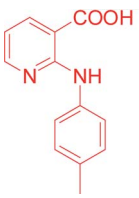
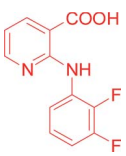
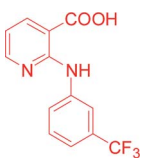
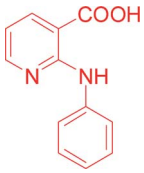
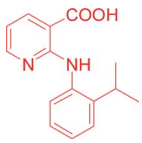
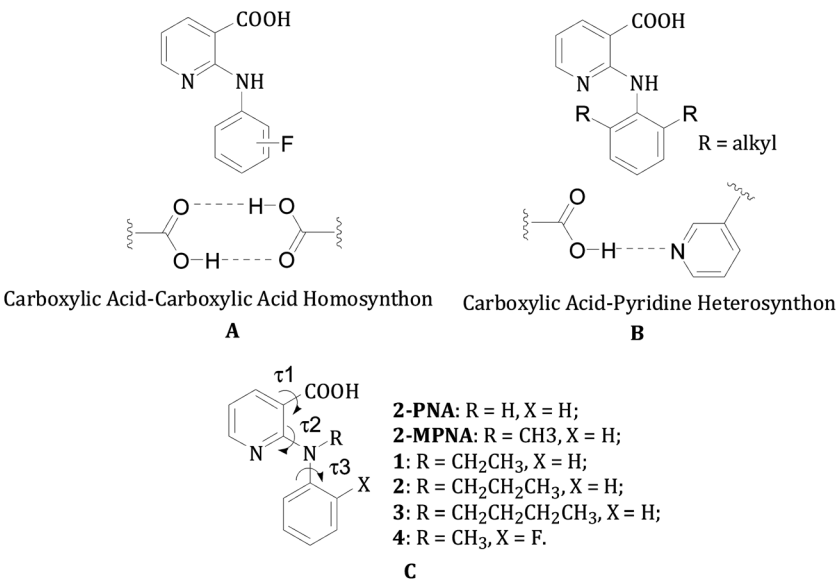
Structures	CSD Refcode	Dihedral angle	Synthon
	BIXGIY	70.675	Carboxylic acid–pyridine
	BIXGIY01	40.003(57)	Carboxylic acid–pyridine
	BIXGIY02	21.226	Carboxylic acid–carboxylic acid
	BIXGIY03	0.457	Carboxylic acid–carboxylic acid
	CUNKAY	84.707(78), 83.576(75)	Carboxylic acid–pyridine
	CUNKAY01	78.516(112)	Carboxylic acid–pyridine
	CUNKAY02	68.398(48)	Carboxylic acid–pyridine
	CUNKOM	2.512(33)	Carboxylic acid–carboxylic acid
	CUNKUS	70.436(65), 70.436(63)	Carboxylic acid–pyridine
	CUNKUS01	82.684(76), 88.239(80), 77.467(87), 78.559(83), 80.690(99), 79.468(98)	Carboxylic acid–pyridine
	DAMPEO	69.354(101)	Carboxylic acid–pyridine
	DAMPEO01	56.343(45)	Carboxylic acid–pyridine
	DAMPEO03	70.976(118)	Carboxylic acid–pyridine
	MUYRAA	26.018(49)	Carboxylic acid–carboxylic acid
	MUYREE	27.401(358)	Carboxylic acid–carboxylic acid
	MUYROO	23.333(91)	Carboxylic acid–carboxylic acid
	MUYROO01	3.610(125)	Carboxylic acid–carboxylic acid
	MUYROO02	20.371(86)	Carboxylic acid–carboxylic acid
	MUYSOP	60.338(46)	Carboxylic acid–pyridine
	MUYSOP01	66.289(91), 73.634(99), 65.973(83), 83.353(93), 56.091(98)	Carboxylic acid–pyridine
	NIFLUM10	5.025(2)	Carboxylic acid–carboxylic acid

Table 1 (*Contd.*)

Structures	CSD Refcode	Dihedral angle	Synthon
	TOKSAO	2.338(27)	Carboxylic acid–carboxylic acid
	TOKSAO01	22.128(41), 27.030(46)	Carboxylic acid–carboxylic acid
	TOKSAO02	57.433(55), 41.455(52), 42.509(53), 60.614(55)	Carboxylic acid–pyridine
	TOKSAO03	76.889(95), 54.613(105)	Carboxylic acid–pyridine
	XENHII	88.094(52), 61.753(56)	Carboxylic acid–pyridine

(α and β) exhibiting the carboxylic acid–carboxylic acid homosynthon and the other two (γ and δ) having the carboxylic acid–pyridine heterosynthon.[27] The preference for the formation of the carboxylic acid–carboxylic acid homosynthon or the carboxylic acid–pyridine heterosynthon is related to the overall conformations of the molecule in each crystal form. When the molecule adopted a near planar conformation, as in forms α and β, the carboxylic acid–carboxylic acid homosynthon was observed, whereas when the molecule had a twisted conformation, as in forms γ and δ, the carboxylic acid–pyridine heterosynthon was preferred. When the molecule takes a near flat conformation, the pyridine N forms an intramolecular $^{sp^2}$CH⋯N hydrogen bond with the *ortho* C–H from the benzene ring, thus preventing it from forming a H-bond with the carboxylic acid. In the non-coplanar conformation, however, the pyridine N is available, which leads to formation of the stronger carboxylic acid–pyridine heterosynthon. The loss of conformational energy due to breaking the conjugation between the two aromatic rings caused by steering away from the planar conformation was compensated by the energy gain from the more favorable carboxylic acid–pyridine heterosynthon. By introducing bulky substituent groups to the *ortho* position(s) of the aniline ring, a nonplanar conformation can be forced. This preferentially leads to the carboxylic acid–pyridine heterosynthon in the solid state. In contrast, inclusion of strong electron withdrawing groups (fluorines) on the benzene ring, ought to stabilize the near planar conformation, and might lead to carboxylic acid–carboxylic acid homosynthon in the crystals. This hypothesis was verified by designing two series of compounds, one with bulky groups such as methyl at the *ortho* positions,[25] the other with Fs on the benzene ring.[26] The first series of compounds produced crystals that included the carboxylic acid–pyridine heterosynthon because the influence of steric hindrance led to a nonplanar conformation. As expected, compounds with fluorine on the aniline ring indeed gave crystals based on the carboxylic acid–carboxylic acid



Scheme 1 Two synthons and the compounds.

Table 2 Crystallographic data of compounds **1–4**

	1-I	**1-II**	**1-III**	**2-I**	**2-II**	**3-I**	**3-S**	**4**
Formula	$C_{14}H_{14}N_2O_2$	$C_{14}H_{14}N_2O_2$	$C_{14}H_{14}N_2O_2$	$C_{15}H_{16}N_2O_2$	$C_{15}H_{16}N_2O_2$	$C_{16}H_{18}N_2O_2$	$C_{16}H_{18}N_2O_2{\cdot}C_7H_8$	$C_{13}H_{11}FN_2O_2$
Formula weight	242.27	242.27	242.27	256.30	256.30	270.32	362.46	246.24
Crystal size	0.50 × 0.20 × 0.20	0.30 × 0.30 × 0.10	0.40 × 0.30 × 0.20	0.30 × 0.30 × 0.10	0.60 × 0.20 × 0.10	0.40 × 0.20 × 0.10	0.40 × 0.30 × 0.30	0.30 × 0.20 × 0.10
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Triclinic	Triclinic	Triclinic	Monoclinic	Monoclinic
Space group	*Pbca*	$P2_1/c$	$C2/c$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	*Pn*
a/Å	9.283(1)	10.3769(2)	34.4290(3)	9.6119(2)	10.9920(1)	11.1175(2)	11.2030(2)	5.3295(1)
B/Å	14.248(2)	8.8497(2)	7.45830(10)	11.0473(2)	11.1848(2)	11.5416(2)	14.0780(2)	8.7988(2)
c/Å	37.628(4)	13.5431(3)	24.2139(3)	14.6432(3)	13.2362(2)	12.2025(2)	13.0633(2)	12.3776(3)
α/°	90	90	90	74.6603(8)	107.4105(6)	105.7668(7)	90	90
β/°	90	96.8897(8)	126.0307(5)	72.0162(8)	94.4240(6)	102.7156(7)	105.6710(7)	99.7900(11)
γ/°	90	90	90	64.8393(9)	115.7150(7)	98.4533(8)	90	90
Z, *Z*′	16, 2	4, 1	16, 2	4, 2	4, 2	4, 1	4, 1	2, 1
V/Å^{-3}	4976.8(10)	1234.72(5)	5028.25(10)	1322.47(5)	1357.82(3)	1433.77(4)	1983.71(5)	571.97(2)
D_{cal}/g cm^{-3}	1.293	1.303	1.280	1.287	1.254	1.252	1.214	1.430
T/K	90(2)	90(2)	90(2)	90(2)	90(2)	90(2)	90(2)	90(2)
Abs coeff (mm^{-1})	0.088	0.089	0.087	0.087	0.084	0.084	0.078	0.109
F(000)	2048.0	512.0	2048	544.0	544.0	576.0	776.0	256
θ range (deg)	1.08–27.48	1.98–27.47	1.46–27.47	1.48–27.46	1.66–27.50	1.80–27.50	1.89–27.49	2.85–27.43
Limiting indices	$-12 \le h \le 12$	$-13 \le h \le 13$	$-43 \le h \le 44$	$-12 \le h \le 12$	$-14 \le h \le 14$	$-14 \le h \le 14$	$-14 \le h \le 14$	$-6 \le h \le 6$
	$-18 \le k \le 18$	$-11 \le k \le 11$	$-9 \le k \le 9$	$-14 \le k \le 14$	$-14 \le k \le 14$	$-14 \le k \le 14$	$-18 \le k \le 18$	$-11 \le k \le 11$
	$-48 \le l \le 48$	$-17 \le l \le 17$	$-31 \le l \le 31$	$-18 \le l \le 18$	$-17 \le l \le 17$	$-15 \le l \le 15$	$-16 \le l \le 16$	$-16 \le l \le 15$
Completeness to 2*θ*	99.9%	99.8%	99.8%	99.8%	99.9%	99.9%	99.9%	99.9%
Unique reflections	3795	2358	4394	4911	4294	5049	3309	1279
$R_1[I > 2\sigma(I)]$	0.0423	0.0399	0.0426	0.0402	0.0464	0.0421	0.0462	0.0252
wR_2 (all data)	0.1262	0.1019	0.1289	0.1080	0.1304	0.1108	0.1408	0.0612

homosynthon. In this case, the near planar conformation was preferred because of the extension of conjugation between the two aromatic rings, and is supported by quantum chemistry calculations showing partial double bond character between the bridging N and both the pyridine and benzene rings. Thus the message is clear: near planar 2-PNA analogs tend to show carboxylic acid–carboxylic acid homosynthon, while twisted conformations favor the carboxylic acid–pyridine heterosynthon. This observation is also made in other related compounds. As shown in Table 1, when the dihedral angle between the pyridine ring and the benzene ring is above 30°, the molecules would form carboxylic acid–pyridine chain in the crystal, and when the dihedral angle is less than 30°, the molecules would prefer the carboxylic acid–carboxylic acid dimer motif.[25,26,28–32] Based on the insight gained in those studies, we may utilize the philosophy of forcing the molecule into twisted conformations to select the carboxylic acid–pyridine heterosynthon in the solid state. A new strategy for inducing non-planar conformations was devised to design further 2-PNA analogs, *i.e.* introducing substituent groups on the N bridging the two aromatic rings.

The introduction of substituent groups on the amino N leading to the formation of carboxylic acid–pyridine heterosynthon was first observed in 2-[methyl(phenyl)amino]nicotinic acid (2-MPNA).[31] In the four polymorphs as well as the hydrate, only the carboxylic acid–pyridine heterosynthon was observed. The molecules (multiple conformers) formed one-dimensional chains sustained on the heterosynthon, with chain direction dependent upon the individual polymorph. The presence of a methyl group on the amino N effectively precludes a planar conformation, as indicated by the dihedral angles (~65°) of the conformers. Thus the pyridine N is available as an acceptor for hydrogen bonding with the carboxylic acid donor. Since the carboxylic acid–pyridine heterosynthon is energetically favored, the carboxylic acid–carboxylic acid heterosynthon is excluded. To validate the effect of substituent groups on the amino N upon the preferred formation of the carboxylic acid–pyridine heterosynthon, we synthesized a series of 2-MPNA analogs and investigated their crystal structures. We also introduced a fluorine atom to the *ortho* position of the benzene ring of 2-MPNA to see if we could induce the carboxylic acid–carboxylic acid synthon in the compound since the electron withdrawing atom was found to cause the planar conformation in fluorinated 2-PNAs. Meanwhile, a CSD (2016) survey was performed to search for structurally related compounds and it didn't result in any new hits similar to 2-MPNA.

These compounds differ from 2-MPNA in the chain length of the substitution groups on the amino N. Similar to the methyl group in 2-MPNA, these longer chains are expected to limit the conformational flexibility of these molecules by forcing them to take a nonplanar conformation and thereby form the carboxylic acid–pyridine heterosynthon. Shown in Scheme 1 are the molecules that were synthesized and tested in this study, including 2-[ethyl(phenyl)amino]nicotinic acid (**1**), 2-[propyl(phenyl)amino] nicotinic acid (**2**), 2-[butyl(phenyl)amino]nicotinic acid (**3**), and 2-[(2-fluoro-phenyl)-methyl-amino]-nicotinic acid (**4**). Attempts to prepare 2-[isopropyl(phenyl)amino]nicotinic failed, likely due to insurmountable steric hindrance. A preliminary polymorph screening was conducted for all the compounds and the crystal structures were solved by single-crystal X-ray diffraction and the phase purity was examined by powder X-ray diffraction (for details, see ESI†). Crystallographic data of all the crystals are listed in Table 2. For compound **1**, three conformational polymorphs were discovered with two (**1-I** and **1-III**) also exhibiting conformational isomorphism.[33] Crystals of **1-I** have space group *Pbca* (Z' = 2), **1-II** $P2_1/c$, and **1-III** $C2/c$ (Z' = 2); for compound **2**, two conformational polymorphs (**2-I** and **2-II**) were obtained with both also displaying conformational isomorphism. Both forms of **2** are triclinic, **P-1** (Z' = 2). Compound **3** gave one form with **P-1** space group (Z' = 2) and one solvate (toluene as the solvent) that had space group $P2_1/c$. For compound **4**, only one form was identified. The conformational variation among the crystallographically independent molecules in the unit cells of each polymorphic system is shown by the superposition of these molecules (Fig. 1).

Not surprisingly, for all four compounds, the carboxylic acid–pyridine heterosynthon was found to exist in the crystals and the molecules form one-dimensional hydrogen-bonded chains except for one structure, *i.e.* **2-I**. In **2-I**, both the carboxylic acid–carboxylic acid homosynthon and the carboxylic acid–pyridine heterosynthon co-exist in the same crystal. No proton transfer from the COOH to the pyridine N is observed in any of the structures. According to the ΔpK_a rule, if the difference in ΔpK_a between the conjugated acid of the base and the carboxylic acid is less than 3, proton transfer would happen between the acid and the base. For these compounds, the calculated pK_a of the carboxylic acid is around 2 (1.70 ± 0.36, 1.71 ± 0.36, 1.71 ±

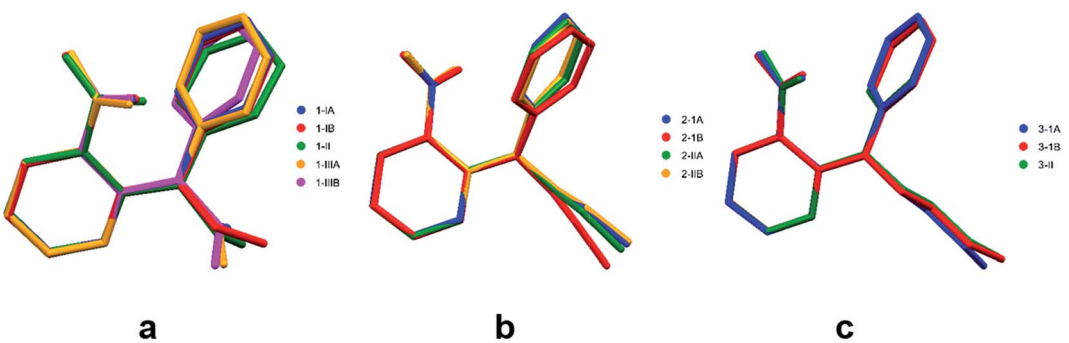


Fig. 1 Superposition of molecules in the asymmetric units of the polymorphs of compounds **1**, **2**, **3**.

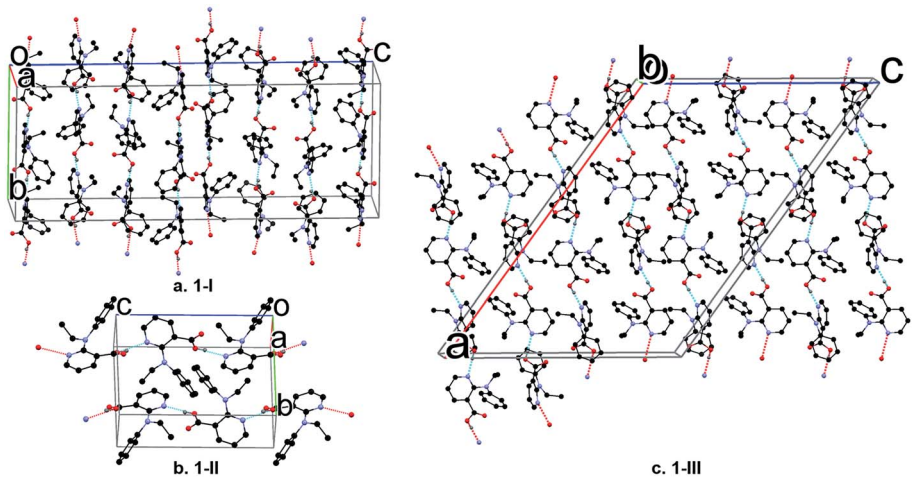


Fig. 2 Crystal packing of **1-I** (a), **1-II** (b), **1-III** (c). For clarity, only intermolecular hydrogen bonds are shown.

0.36, and 1.63 ± 0.36 for I, II, III, and IV, respectively), and the predicted pK_a of the conjugated acid of pyridine is 4.8. Thus there is no significant drive force for proton shift.[32]

Compound **1-I** has two molecules (**1-IA** and **1-IB**) in the asymmetric unit ($Z' = 2$) and these two molecules have a similar conformation except for the slight difference in the orientation of the ethyl group (Fig. 1a); interestingly, each conformer forms its own hydrogen-bonded chain, denoted as C(6) by graph set notation, between carboxyl OH and pyridinyl nitrogen. The chains extend parallel to the *b* axis with four chains pointing in one direction and the other four pointing in the opposite direction – the direction of a hydrogen bond is taken as that from the donor to acceptor (Fig. 2a).[31] The two hydrogen bonds have similar lengths (2.673 Å for **1-IA** and 2.683 Å for **1-IB**) and angles (169.74° for **1-IA** and 165.30° for **1-IB**). **1-II** has one molecule in the asymmetric unit and the molecule forms alternating one-dimensional chains sustained by the carboxylic acid–pyridine heterosynthon (Fig. 2b). The hydrogen bond has a length of 2.721 Å and angle of 167.19°. **1-III** also possesses two crystallographically independent molecules (**1-IIIA** and **1-IIIB**) in the asymmetric unit ($Z' = 2$) and they are conformationally distinct from each other and different from the other three conformers (Fig. 1a). In contrast to **1-I**, these two molecules form one-dimensional chains based on the carboxylic acid–pyridine heterosynthon in a repeating AB pattern, and the direction of the hydrogen-bonding chains alternates (Fig. 2c). The hydrogen bond lengths and angles differ depending on which molecule acts as the hydrogen bond donor: when the carboxylic acid in molecule A is the hydrogen bond donor and the pyridine in molecule B is the acceptor, the hydrogen bond length and angle are 2.717 Å and 176.09°, respectively; the hydrogen bond length and angle are 2.643 Å and 167.55° when it is the other way around.

Both forms of compound **2** are triclinic, space group $P\bar{1}$. The asymmetric unit of both forms contains two molecules ($Z' = 2$), **2-IA** and **2-IB** for form **2-I**, and **2-IIA** and **2-IIB** for form **2-II**. All four molecules have similar conformations as indicated by the superposition of the four molecules (Fig. 1b).

The two molecules/conformers (**2-IA** and **2-IB**) in the asymmetric unit of form **2-I** are virtually enantiomerically related.[27] The crystal structure is based on hydrogen-bonded four-molecule assemblies. Each unit consists of two copies of both conformers. Two **2-IA** conformers form a hydrogen-bonded dimer based on the carboxylic acid–carboxylic acid homosynthon, or $R_2^2(8)$ hydrogen bonding motif according to the graph set concept.[34–36] The carboxylic acid–carboxylic acid dimer is flanked by the two **2-**

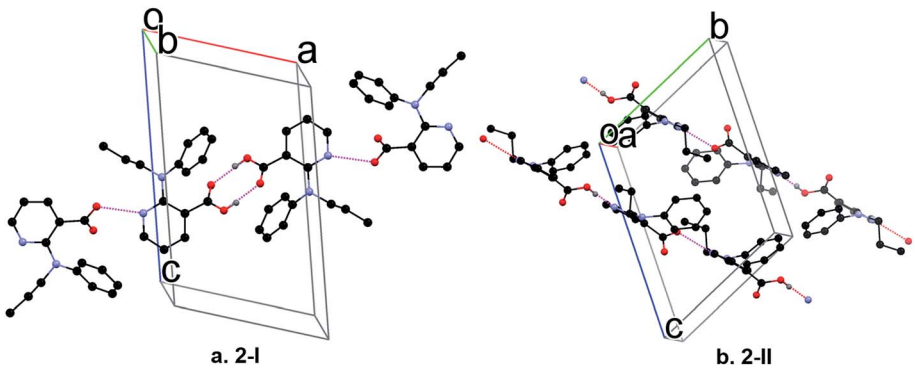


Fig. 3 Crystal packing of **2-I** (a) and **2-II** (b). For clarity, only intermolecular hydrogen bonds are shown.

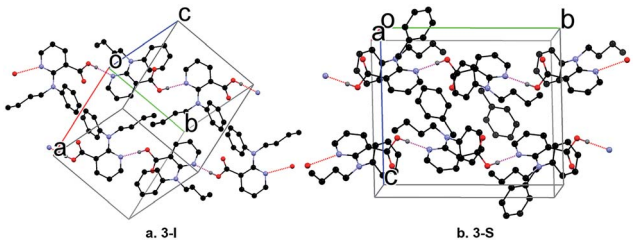


Fig. 4 Crystal packing of **3-I** (a) and **3-S** (b). For clarity, only intermolecular hydrogen bonds are shown.

IB conformers which interact with the **2-IA** conformers through the carboxylic acid–pyridine heterosynthon (Fig. 3a). The hydrogen bond in the carboxylic acid–carboxylic acid heterosynthon is shorter in distance and more linear in geometry than that of the carboxylic acid–pyridine heterosynthon: 2.59 Å *vs.* 2.73 Å, and 172.1° *vs.* 169.7°. The occurrence of this unique structure with both carboxylic acid–carboxylic acid homosynthon and carboxylic acid–pyridine heterosynthon was attributed to the similar energy of these two synthons due to the sandwich-like arrangement of the two benzene rings and was investigated in a separate study.[37]

The two crystallographically independent molecules (**2-IIA** and **2-IIB**) in the asymmetric unit of form **2-II** are similar in conformation and similar to molecules in the other polymorph. Hydrogen-bonded chains sustained on the carboxylic acid–pyridine heterosynthon (or C(6) hydrogen bonding motif in graph set) between the two conformers are observed in the crystal structure. These chains alternate in direction and propagate parallel to the (0 −1 1) plane (Fig. 3b). The two types of carboxylic acid–pyridine heterosynthon (**2-IIB** to **2-IIA** and **2-IIA** to **2-IIB**) are alike in geometry: 2.68 Å *vs.* 2.70 Å in distance, and 172.3° *vs.* 176.1° in angle.

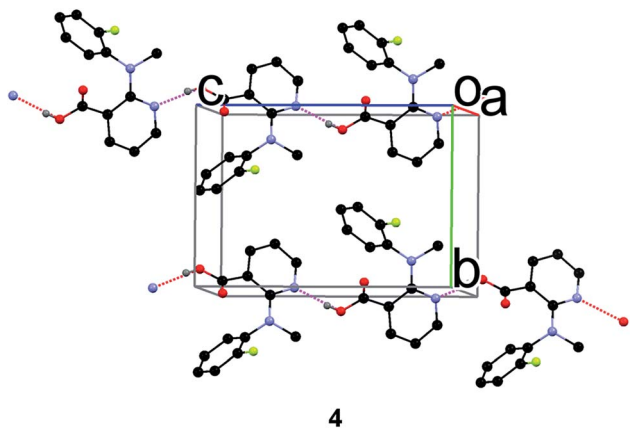


Fig. 5 Crystal packing of **4**. For clarity, only intermolecular hydrogen bonds are shown.

The chain motif is also found in the two crystals of compound **3**, which show three similar conformers (Fig. 1c). In the solvent-free form, the hydrogen-bonded chains extend along the *c* axis, formed between alternate conformers; the chain directions alternate due to the centrosymmetry (Fig. 4a). The two hydrogen bonds have similar lengths (2.66 and 2.67 Å) and angles (169.1 and 172.6°). In the solvate, the chains propagate parallel to the *b* axis (Fig. 4b). The hydrogen bond has bond length and angle of 2.703 Å and 173.23°, respectively. The toluene molecule is likely held in place by van der Waals interactions.

Molecules in compound **4** form uni-directional one-dimensional chains based on the carboxylic acid–pyridine hydrogen bond with a bond length of 2.711 Å and bond angle of 164.87° (Fig. 5). Although the introduction of F on the benzene ring is known to help 2-PNA analogs take a planar conformation, in compound **4**, the conformational energy of a theoretical flat conformer is insurmountable (~1000 kJ mol^{-1}),[27] thus the molecule can only exist in the twisted conformation. As a result, only the carboxylic acid–pyridine heterosynthon is observed in the solid state.

Molecules of compounds **1–4** all exhibit twisted conformations due to the steric repulsion effected by the introduction of alkyl groups on the N atom bridging the two aromatic rings. Dihedral angles between the pyridine ring and the benzene ring of the identified crystal structures, τ, are listed in Table 3. The two aromatic rings of the molecules in the crystals of compounds **1–4** are perturbed from the planar conjugation of π electrons by twisting of the rings toward each other. Due to the lack of extended conjugation, all the crystals are colorless. This can also be inferred from the UV-Vis study. As shown in Fig. 6, only one peak was observed for all the compounds except for 2-PNA, which shows two absorption bands with the one at the longer wavelength indicating the extended conjugation between the two aromatic rings. Thus, the substitution groups on the N can introduce sufficient steric repulsion that the molecules have to give up the otherwise favorable conjugation and adopt twisted conformations. This conclusion is also supported by the potential energy scan of 2-MPNA with respect to τ_2 and τ_3.[27] Neither τ_2 nor τ_3 can be 0° or 180°. For τ_2, the lowest energy is located at around −142.5°; and for τ_3, the lowest energy lies at 45°. For a planar conformation, the energy reaches a maximum as high as 1000 kJ mol^{-1}. Nonetheless, polymorphs are possible since conformational adjustment as well as conformational change can take place.

In summary, a new strategy, *i.e.*, adding substituents to the N bridging the two aromatic rings of 2-PNA in order to force

Table 3 Values of the dihedral angle, τ, of the molecules in crystal structures of compounds **1–4**. Unit: degree

1-I	1-II	1-III	2-I	2-II	3-I	3-S	4
60.842(46), 62.145(46)	65.013(41)	55.422(47), 70.941(46)	56.548(43), 61.462(39)	60.068(49), 65.331(55)	62.217(43), 58.569(42)	61.746(43)	65.649(49)

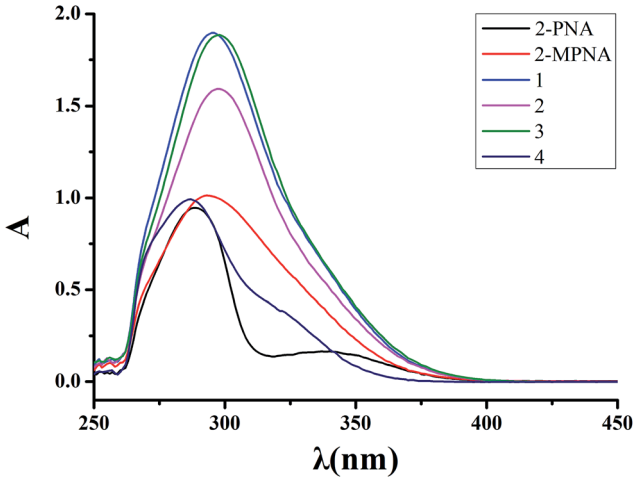


Fig. 6 UV-Vis spectra of the compounds.

the molecules into nonplanar conformations was applied to produce 2-anilinonicotinic acid crystals with exclusive carboxylic acid–pyridine heterosynthons. A series of compounds were synthesized and their crystal structures were investigated. As expected, the conformations of all the molecules in the solid state are nonplanar (with the dihedral angles between the two aromatic rings all above 30°) and the carboxylic acid–pyridine heterosynthon was observed in all the crystals except for one polymorph of **2** which had the unique co-existence of both synthons. The twisted conformations are caused by the steric repulsion of the alkyl groups attached to the bridging N, and can render the pyridine N available for hydrogen bonding with the carboxylic acid OH, similar to 2-PNA analogs with bulky groups at the *ortho* position(s) of aniline. Theoretically, even smaller groups on N should be able to induce non-planar conformations, yet experimentally, methyl is the smallest substituent group available. Although compared with unhindered 2-anilinonicotinic acid, these new compounds have less conformational flexibility, there are still the two N–C sigma bonds that can rotate within a restricted range, and this is reflected in the conformational polymorphism and isomorphism demonstrated by the compounds. From the aspect of molecular shape–intermolecular interactions relationship, this study provides a new example of the mutual influence of molecular conformation and crystal packing.

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