π-π Stacking in the Polymorphism of 2-(Naphthalenylamino)-nicotinic Acids and A Comparison with Their Analogues

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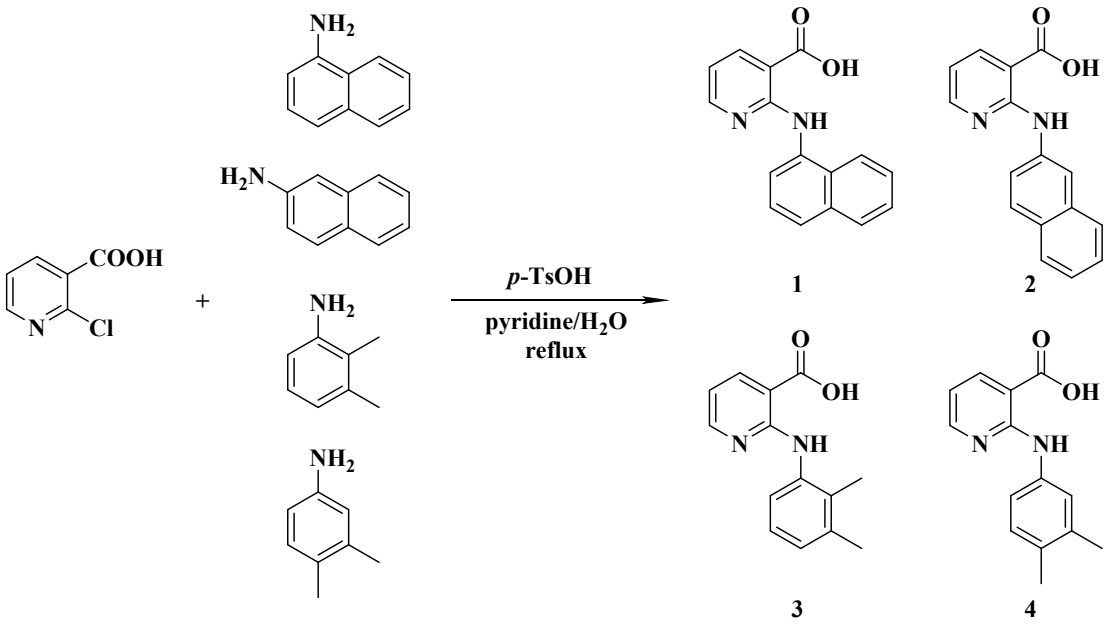
General

NMR spectra were recorded on an Agilent 400/54 Premium Shielded spectrometer (Agilent, USA) in DMSO-d_6. Molecular weight was measured using a Thermo LTQ XL, liquid chromatography-mass spectrometer (LC-MS). IR spectra were recorded on a PerkinElmer FI-IR spectrometer (PerkinElmer, USA) with samples dispersed in KBr pellets. DSC experiments were performed on TA instruments DSCQ20-1250. For measurement, Tzero® pans equipped with aluminum hermetic lids were used for a few milligrams of each sample at a heating rate of 10°C/min. TGA experiment was performed on TA Instruments SDT-Q600. The samples were placed in aluminum pans covered with a lid, and heated from 25 °C to 300 °C at a heating rate of 5 °C/min. Nitrogen was used as a purge gas at 20 mL/min in both DSC and TGA experiments.

Synthesis



1.1 Synthesis of 2-(naphthalen-1-ylamino)-nicotinic acid (1)

2-Chloronicotinic acid (5.0 g, 31.7 mmol), 1-naphthylamine (4.5 g, 31.7 mmol), pyridine (2.5 g, 31.7 mmol), and *p*-toluenesulfonic acid monohydrate (1.2 g, 6.3 mmol) were added to a round-bottom flask with 100 mL water. The resulting mixture was refluxed overnight. After completion of the reaction, the reaction mixture was cooled to room temperature and solid precipitated to yield a crude product. Pure product was obtained by recrystallization (3.0 g, yield%: 36).

^{1}H NMR (400 MHz, DMSO-d_6) *δppm* 13.72（br，1H）, 10.96（s，1H）, 8.37 (s, 2H), 8.31 (d, *J* = 6.2 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.59 (s, 1H), 7.58–7.53 (m, 2H), 7.51 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) *δppm* 169.3, 161.1, 151.1, 142.0, 139.5, 134.3, 128.6, 127.6, 126.0, 125.0, 124.7, 121.0, 119.0, 113.3, 111.9, 109.3; IR (KBr, cm^{-1}) 3507 (s), 3253 (s), 2479 (s), 1654 (m), 1604 (m), 1594 (m), 1301 (m), 754 (s); ESI-MS m/z (M+1) 265.95; mp: 199.2℃.

1.2 Synthesis of 2-(naphthalen-2-ylamino)-nicotinic acid (2)

2-Chloronicotinic acid (2.0 g, 12.7 mmol), 2-naphthylamine (1.8 g, 12.7 mmol), pyridine (1.0 g, 12.7 mmol), and *p*-toluenesulfonic acid monohydrate (0.5 g, 2.6 mmol) were added to a round-bottom flask with 40 mL water. The resulting mixture was refluxed overnight. After completion of the reaction, the reaction mixture was cooled to room temperature and solid precipitated to yield a crude product. Pure product was obtained by recrystallization (2.3 g, yield%: 69).

^{1}HNMR (400 MHz, DMSO-d_6) *δppm* 13.65（br，1H）, 10.66 (s, 1H), 8.45 (dd, *J* = 6.5, 4.8 Hz, 2H)，8.27 (d, *J* = 7.7 Hz, 1H), 7.91–7.73 (m, 3H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 6.90 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) *δppm* 170.0, 161.1, 151.9, 142.6, 139.5, 133.5, 127.8, 126.6, 126.4, 125.0, 124.5, 121.1, 117.0, 113.0, 111.9, 107.4; IR (KBr, cm^{-1}) 3254 (s), 3050 (s), 1631 (w), 1578 (m), 1301 (m), 757 (s); MS (EI) 263.20; mp: 198.5℃.

1.3 Synthesis of 2-(2,3-dimethyl-phenylamino)-nicotinic acid (3)

2-Chloronicotinic acid (1.0 g, 6.4 mmol) and 2,3-dimethylaniline (0.8 g, 6.4 mmol) were suspended in pyridine (0.5 g, 6.4 mmol), *p*-toluenesulfonic acid monohydrate (0.2 g, 1.1 mmol) in 10 mL of water was added to the mixture. The resulting system was refluxed overnight and then it was cooled to room temperature. Solids were precipitated from the reaction mixture to yield a crude product. The crude product was further purified by recrystallization and recovered as colorless crystals (0.5 g, yield%: 32).

^{1}H NMR (400 MHz, DMSO-d_6) *δppm* 9.89 (s, 1H), 8.04 (m, 1H), 7.89 (m, 1H), 7.58 (m, 1H), 6.81 (m, 1H), 6.68 (m, 1H), 6.54 (m, 1H), 2.84 (m, 3H), 2.76 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) *δppm* 169.8, 157.0, 153.9, 141.4, 138.3, 137.1, 128.6, 126.3, 125.2, 121.9, 113.1, 107.7, 21.3, 14.6; IR (KBr, cm^{-1}) 3249 (s), 3070-2765 (w),

1679 (s), 1578 (s), 1507 (s), 1241 (s), 1132 (s),781 (s); MS (MNa^+): 265.86; mp: 246.4 ºC.

1.4 Synthesis of 2-(3,4-dimethyl-anilino)-nicotinic acid (4)

2-Chloronicotinic acid (1.5 g, 9.5 mmol), 3,4-dimethyaniline (1.7 g, 14.3 mmol), pyridine (0.8 g, 9.5 mmol), and *p*-toluenesulfonic acid monohydrate (0.6 g, 3.2 mmol) were added to a round-bottom flask with 60 mL water. The resulting mixture was refluxed overnight. After completion of the reaction, the reaction mixture was cooled to room temperature and solid precipitated to yield a crude product. Pure product was obtained by recrystallization (0.5 g, yield%: 22).

^{1}H NMR (400 MHz, DMSO-d_6) *δppm* 13.49 (s, 1H), 10.31 (s, 1H), 8.36 (dd, J = 4.7, 2.0 Hz, 1H), 8.22 (dd, J = 7.7, 2.0 Hz, 1H), 7.50 (dd, J = 8.1, 2.2 Hz, 1H), 7.38 (d, J = 1.8 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.81 (dd, J = 7.7, 4.8 Hz, 1H), 2.19 (d, J = 13.5 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) *δppm* 169.2, 155.8, 152.8, 140.5, 137.4, 136.3, 130.0, 129.6, 121.4, 117.6, 113.4, 107.2, 19.6, 18.7; IR (KBr, cm^{-1}) 3319 (s), 2996-2857 (s), 2641 (s), 2578 (s), 1674 (w), 1616 (w), 1469 (m), 1433 (w), 1341 (s), 891 (s); MS (EI) 242.11; mp: 161.0 ℃.

Note: The melting points were measured with DSC, and the onset temperature was recorded.

Crystallization

Example: Compound **1** (50.0 mg) was suspended in 5 mL HPLC grade methanol. The suspension was stirred overnight and the remaining solid was removed by pipette filtration. A vial containing the clear solution was covered with perforated parafilm and left in a hume food. Slow evaporation led to single crystals in about a week.

Crystals of **1-A** were harvested from methanol (MeOH), ethanol (EtOH), *N,N*-dimethylformamide (DMF), dichloromethane (DCM), acetonitrile (MeCN), chloroform ($CHCl_3$), acetic acid (CH_3COOH), benzene, dimethyl sulfoxide (DMSO), or toluene; **1-H** crystals were grown from tetrahydrofuran (THF) or ethyl acetate (EtOAc); and crystals grown from acetone (CH_3COCH_3), ether (Et_2O), *iso*-propanol (*i*-PrOH) were a mixture of forms **1-H** and **1-A.** Pure **2-I** crystals were harvested from MeCN, and **2-II** crystals were grown from $CHCl_3$, *i*-PrOH, ether, DMF, DCM, THF, MeOH, CH_3COOH, DMSO, benzene or toluene; crystals grown from EtOAc were form **2-III** (structure was not determined because of poor crystal quality); crystals grown from acetone, ethanol were a mixture of forms **2-II** and **2-III**. Crystals of **3** and

4 grown from all the solvents other than water, pet ether, or hexane were the same form. No sufficient quantities of crystals suitable for characterization were obtained for each compound in water, pet ether, or hexane. The crystallization results are summarized in Table S1.

Table S1. Solvents Used for Crystallization and Crystal Forms Obtained for Compounds **1-4**.

	Solvent	**1**	**2**	**3**	**4**
Polar protic	MeOH	**1-A**	**2-II**	**3**	**4**
	EtOH	**1-A**	**2-II + 2-III**[a]	**3**	**4**
	CH_3COOH	**1-A**	**2-II**	**3**	**4**
	i-PrOH	**1-H + 1-A**	**2-II**	**3**	**4**
	H_2O	**N/A**	**N/A**	**N/A**	**N/A**
Polar aprotic	DCM	**1-A**	**2-II**	**3**	**4**
	Acetone	**1-H + 1-A**	**2-II + 2-III**[a]	**3**	**4**
	MeCN	**1- A**	**2-I**	**3**	**4**
	Et_2O	**1-H + 1-A**	**2-II**	**3**	**4**
	$CHCl_3$	**1-A**	**2-II**	**3**	**4**
	DMSO	**1-A**	**2-II**	**3**	**4**
	THF	**1-H**	**2-II**	**3**	**4**
	EtOAc	**1-H**	**2-III**[a]	**3**	**4**
	DMF	**1-A**	**2-II**	**3**	**4**
Apolar aprotic	Toluene	**1-A**	**2-II**	**3**	**4**
	Benzene	**1-A**	**2-II**	**3**	**4**
	Pet ether	**N/A**	**N/A**	**N/A**	**N/A**
	Hexane	**N/A**	**N/A**	**N/A**	**N/A**

a: high-quality single crystals were unavailable, and only PXRD was performed

N/A: not available

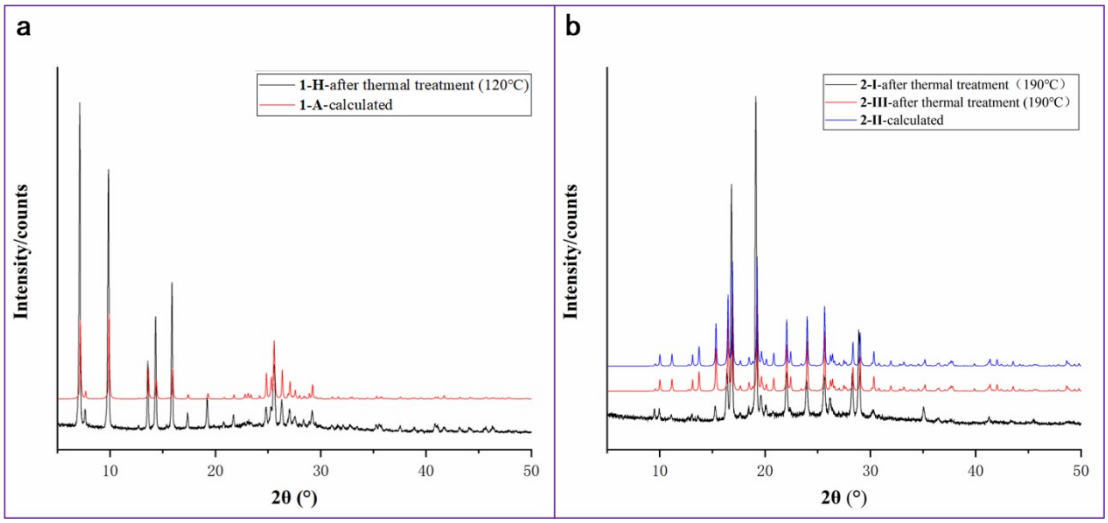


Figure S1. a) PXRD patterns of **1-A**, and **1-H** after thermal treatment at 120 ^{o}C for 12 hours; b) PXRD patterns of **2-II**, and **2-I** and **2-III** after thermal treatment at 190^{o} C.

TGA

As shown in Figure S2, the dehydration of **1-H** correlates well with the first thermal event on DSC, with a weight loss of 6.5%, which matches well with the calculated theoretical loss of mass (6.8%) that would result from the loss of one water molecule per host molecule, thus further confirming the 1:1 stoichiometry of water and host molecule of **1-H**. The onset temperature of dehydration is approximately 73.2°C, in good agreement with the DSC endotherm. There is only one endothermic peak related to the dehydration of **1-H**, meaning that one equivalent of water molecule is lost from the crystal lattice in one single dehydration step.

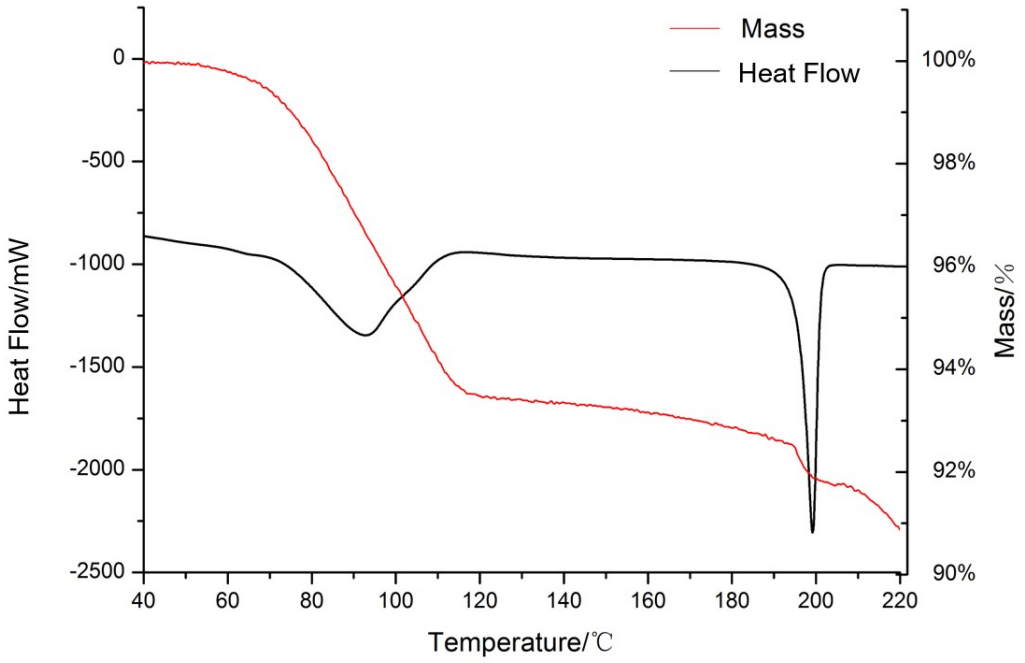


Figure S2. TGA-DSC thermographs of **1-H**.

Computational details

First principles calculations of the crystal structures of compounds **1-4** were carried out. To do partial optimization, all the atoms in each crystal were fixed except for H atoms. It is known that the hydrogen positions in the crystal structure solved by single-crystal XRD are manually assigned which may cause minor structural artifacts, so the partial optimization of only H atoms in the crystal will lead to more accurate hydrogen positions. The partial geometry optimizations were performed using the self-consistent charge density-functional tight-binding (SCC-DFTB) method with a dispersion correction using the DFTB+ program. The smart algorithm with the force convergence tolerance of 0.05 kcal/mol/Å was used and the SCC tolerance was set to 1.0×10^{-5} electrons. Then Hirshfeld surface analyses of the partially optimized crystals of **1-4** were performed by CrystalExplorer (Version 3.1), which can tell the relative

contributions of various intermolecular interactions existing in the crystals. Based on the partialy optimized crystals of **1**-**4**, the molecule in each crystal was taken for single-point calculation at the M062X/6-311++G (d, p) level of theory which was carried out using the Gaussian 09 software package. The full geometry optimizations and conformational searches of the molecules were also carried out at the M06-2X/6-311++G (d, p) level of theory, and a scan step size of 10 degrees was used.

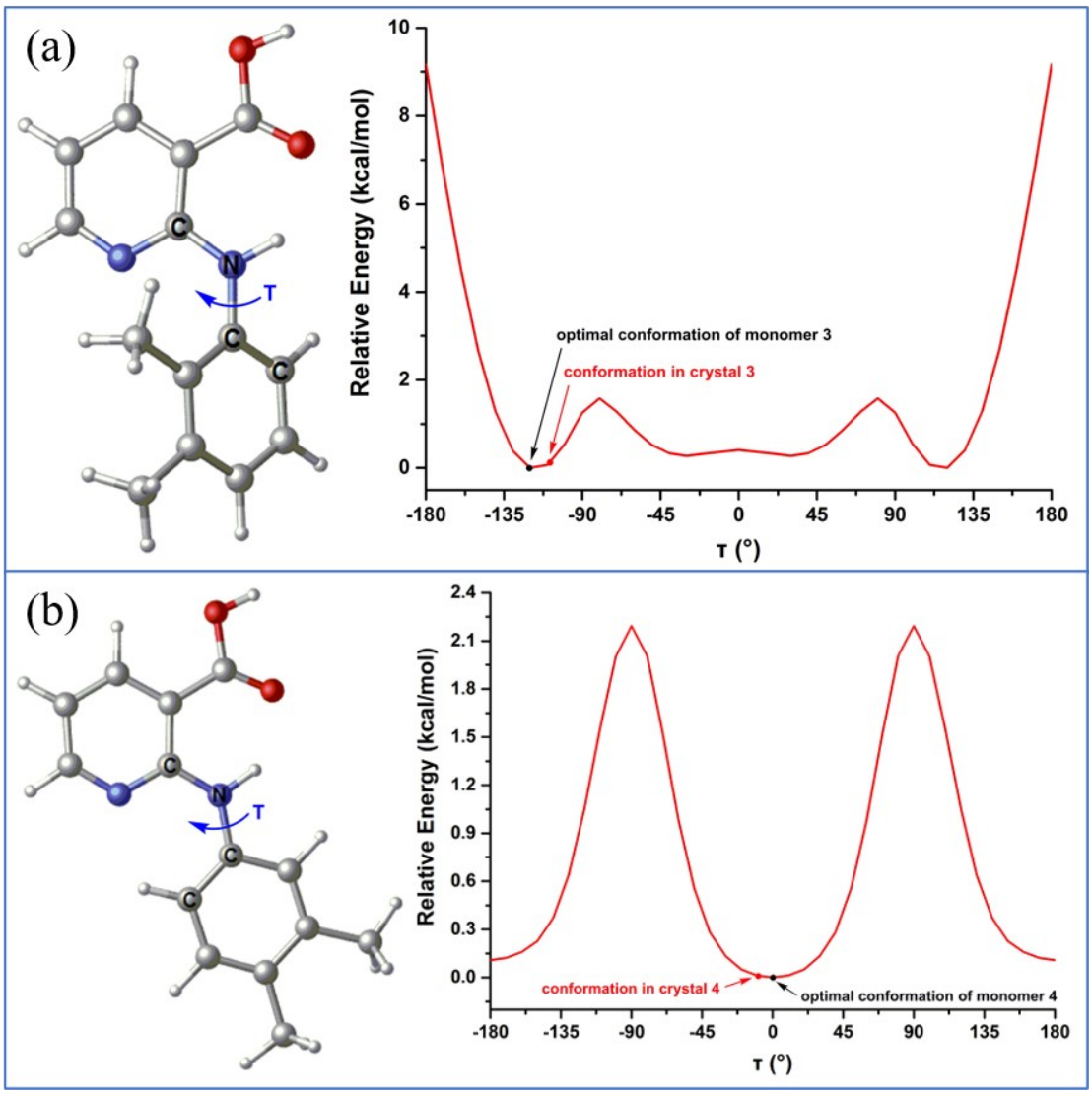


Figure S3. Potential energy surface scan of **3** (a), and **4** (b).