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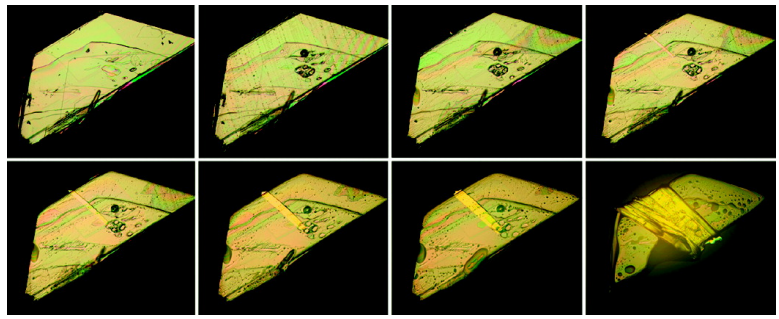

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Polymorphism and Phase Behaviors of 2-(Phenylamino)nicotinic Acid

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ABSTRACT: The discovery and phase transition studies of four polymorphs of 2-(phenylamino)nicotinic acid are described in this report. The four polymorphs were crystallized from solution under different conditions. All polymorphs differ in the degree of conjugation of the two aromatic rings and thus are of conformational polymorphism. Three of the four modifications have more than one conformer in the asymmetric unit. Due to the difference in conformation, all polymorphs display distinctive colors as well as different hydrogen-bonding arrangements. Phase behaviors of the four forms were studied by differential scanning calorimetry and hot-stage microscopy, indicating that metastable forms underwent phase transition to the stable one initiated by mechanical perturbation in solution or assisted by heating in the solid state. As such, this polymorphic system exhibits polychromism, conformational isomorphism, thermochromism, and mechanochromism. It may be valuable for further solid-state structure−property relationship studies.

1. Introduction

The ability of a given molecule to form multiple crystal structures is designated as polymorphism, and these solid-state forms are polymorphs.[1] Since polymorphs have different spatial arrangements of molecules, their physicochemical properties differ although the chemical composition is identical. The phenomenon of polymorphism was first recognized about 200 years ago.[2] Ever since then, the cases of polymorphism have increased dramatically, partially due to interest in the structure−property relationship of modifications of a polymorphic system.[3−5] The middle of the last century witnessed a waning in passion in polymorphism. Thanks to McCrone's unyielding compassion in this phenomenon,[1,6,7] and also the importance of polymorphism in the field of pharmaceuticals (individual cases of polymorphism of pharmaceuticals are numerous [8−16]), the study of polymorphism is now enjoying a renaissance.

Although McCrone audaciously claimed that every compound has different polymorphic forms, it is estimated that about 5,000−6,000 compounds (both inorganic and organic) out of some 400,000 in the Cambridge Structural Database (CSD) may be classified as polymorphic.[1,17] Extensive polymorphism of an organic compound is a rare situation. According to a survey done by Chen et al. in 2005,[18] for organic compounds in the CSD, only two systems were hexamorphic, one pentamorphic, 14 tetramorphic, and 102 trimorphic. 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY) was declared to be the first organic molecule to have more than five polymorphs. So far, ROY holds the record of polymorphs characterized by single-crystal X-ray diffraction at seven.[19,20] In 2005, four new polymorphs were reported for oxalyl dihydrazide (ODH).[21] The system described in this report is the newest addition to the "elite club" of organics with four or more polymorphs.

Among the generally accepted categories of polymorphism (packing, conformational, and pseudo polymorphism) (Note: Controversy is associated with the last definition. Indeed, pseudopolymorphism is not polymorphism according to the definition[22−25]), conformational polymorphism has attracted considerable attention due to the fact that it provides ideal systems for the study of structure−property relationships.[26] According to Bernstein, "conformational polymorphism is the existence of different conformers of the same molecule in different polymorphic modifications."[17] Generally, conformational polymorphs arise from the intrinsic conformational flexibility of molecules and are the results of the compromise between intra- and intermolecular interactions. In addition to the general definition of conformational polymorphism, Corradini added two special cases to the repertoire, conformational isomorphism and conformational synmorphism, the former being the existence of different conformers of a molecule in the same crystal structure and the latter describing the situation in which different conformers of a molecule are distributed randomly throughout the crystal lattice.[27−31] Since the first formal recognition of conformational polymorphism,[17,31] cases of this phenomenon have increased exponentially.

In this report, we will discuss our discovery of four conformational polymorphs of a diarylamine, 2-(phenylamino)nicotinic acid (2-PNA) (Scheme 1). Our interest in diarylamines is mainly due to their potential as nonsteroidal anti-inflammatory drugs as well as their possible polymorphic behavior.[32−34] Among the four conformational polymorphs, three are conformational isomorphs. In addition, phase transition between the metastable and stable forms was studied. It was found that either mechanical perturbation (mechanochromism[35]) in solution or heating in the solid state (thermochromism[36]) could initiate the phase transition.

2. Experimental Section

2.1. General. All solvents and reagents were purchased from commercial sources and used as received. The IR spectra were recorded using a FT-IR Nicolet 380 spectrometer. NMR spectra were obtained on a Varian INOVA spectrometer at an observation frequency 400 MHz. Thermal analyses were performed on a TA Instruments 2920 MDSC. A heating rate of 10 °C/min was employed.

2.2. Synthesis and Characterization. Synthesis of 2-PNA (Scheme 2):[37,38] 2-Chloronicotinic acid (3.83 g, 24.3 mmol), aniline (2.26 g, 24.3 mmol), pyridine (1.92 g, 24.3 mmol), and *p*-toluenesulfonic acid (1.0 g, 5.8 mmol) were added to a round-bottom flask, followed by

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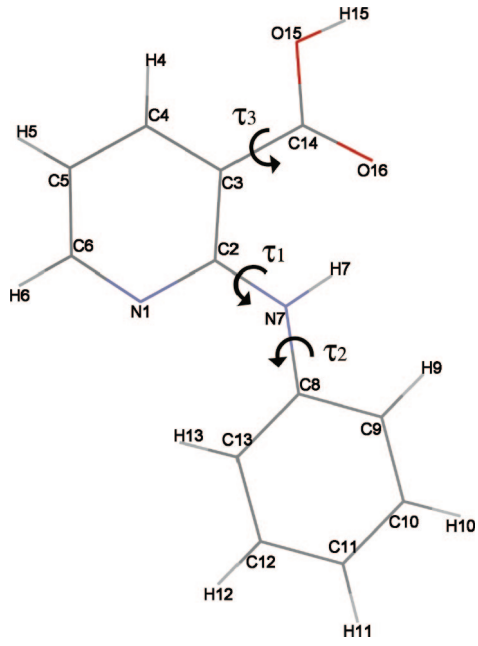
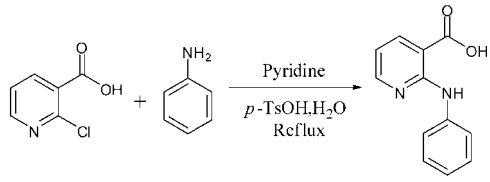
Scheme 1



Scheme 2



addition of 40 mL of H_2O. The resulting mixture was refluxed overnight. After the reaction, the mixture was cooled down to ambient temperature gradually. The product was collected as colorless crystals (4.0 g, 77%). Four different polymorphs were obtained by recrystallizing the product from different solvents. They all showed poor solubility in water. The most stable form melted at 160 °C while the other three forms transited to the most stable one during the heating. The thermal behaviors and phase transition are further discussed later in the report.

IR (cm^{-1}): 3417, 3270, 3063, 1645, 1652, 1597, 1582, 1558, 1520, 1248, 1143, 750. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.45 (s, 1H), 8.39 (dd, 1H), 8.26 (dd, 1H), 7.71 (d, 2H), 7.31 (m, 2H), 7.01 (t, 1H), 6.86 (m, 1H). ^{13}C NMR (DMSO-d_6, 400 MHz): δ 169.1, 155.6, 152.6, 140.7, 139.7, 128.8, 122.3, 120.1, 113.9, 107.7. MS (EI): m/z 214 (M^+); $C_{12}H_{10}N_2O_2$ (214).

2.3. Crystal Growth. The compound was recovered from the reaction mixture as colorless crystals which were designated as δ form (The polymorphs were named as α, β, γ, and δ in the order of density from highest to lowest). The δ form crystals were dissolved in different solvents (aqueous and organic) (Table 1) forming clear solutions at ambient temperature. The solutions were set for slow evaporation until single crystals were harvested with solvent remaining or totally evaporated. All crystallization experiments were conducted in an unmodified atmosphere. A typical example is given as the following: 130 mg of compound was dissolved in 5 mL of HPLC grade ethyl acetate in a glass vial at room temperature. The vial was sealed with aluminum foil with 30 holes poked with a needle. Crystals of form α were obtained in about a week through slow evaporation. Forms α, β, and δ can be produced consistently, while form γ has been obtained just once in spite of many trials.

2.4. Crystal Structure Determination. Crystal structures of the four polymorphs of 2-PNA were determined by single-crystal X-ray diffraction. For α, β, and δ forms, data collection was carried out at 90 K on a Nonius kappaCCD diffractometer with Mo Kα radiation (λ = 0.71073 Å), and data of the γ form were collected at 90 K on a Bruker-Nonius X8 Proteum with Cu Kα radiation (λ = 1.54178 Å).[39]

Table 1. Polymorph Screening of 2-PNA

solvent	polymorph
methanol	$\alpha/\beta/\delta$
ethanol	α
ethyl acetate	$\alpha/\beta/\gamma$
acetone	α/δ
dichloromethane	α
chloroform	α
benzene	α
toluene	α
hexane	α
isopropanol	α
water	α/δ
ethyl ether	α

Cell refinement and data reduction were done using SCALEPACK and DENZO-SMN.[40] Structure solution and refinement were carried out using the SHELXS97 and SHELXL97 programs, respectively.[41,42]

Powder X-ray diffraction (PXRD) was carried out for α, β, and δ forms, respectively. Because of limited amount of sample, no PXRD was conducted for the γ form. The PXRD data of ground fine powders were collected on a Rigaku Multiplex powder X-ray diffractometer with Cu Kα radiation (40 kV, 40 mA) between 5.0 and 40.0° (2θ) at ambient temperature.

2.5. Conformational Search. The energy of a 2-PNA single molecule of different conformations defined by three torsion angles, $\tau 1$, $\tau 2$ and $\tau 3$, was evaluated respectively with Gaussian 03 (Gaussian, Inc., Wallingford, CT). The molecule was optimized from various initial structures in order to identify the most stable conformation, which was then used for scanning each torsion angle with all bond lengths, bond angles, and other torsion angles fixed. The methods used for the structural optimization and conformational search were B3LYP/6-311G(d, p) and B3LYP/6-311++G(d, p), respectively. The same program and methods were also used for the NBO (natural bond orbital) analyses.

3. Results and Discussion

3.1. Crystal Structures. As mentioned above, all of the crystallization experiments were performed in different solvents. As seen in Table 1, the crystallization of 2-PNA showed poor polymorphic selectivity in methanol, ethyl acetate and water. Three polymorphs were obtained nonconcomitantly from methanol and ethyl acetate, and two polymorphs were from water and acetone. In other organic solvents, however, only the α form was obtained—yellow crystals harvested from all of the solvents were the α form—and the colorless crystals originated from water and later from methanol and once from acetone were the δ form. The β polymorph was obtained from ethyl acetate and once from methanol, and the γ form was only encountered in ethyl acetate once.

Subsequently, the structures of all the four forms were determined. The crystallographic data are presented in Table 2. For complete CIF files, see Supporting Information. Two of the four polymorphs (δ and β) are triclinic with space groups $P1$ and $P\bar{1}$, respectively. The other two polymorphs (α and γ) are monoclinic with space groups $P2_1/c$ and $P2/c$, respectively. Three of the four have more than one crystallographically independent molecule in the asymmetric unit, and these molecules are conformationally different (i.e., conformational isomorphism[43]). The α form has one molecule in the asymmetric unit, β and δ have two, and γ has four. In contrast, the phenomenon of conformational isomorphism was not observed in the analogous compound 2-(2-methyl-3-chloroanilino)nicotinic acid, which has four polymorphs each with only one molecule in the asymmetric unit.[32] For both ROY and ODH, only one conformer exists in each crystal structure.[18−21]

The four polymorphs show distinctive colors (Figure 1). The polychromism (color polymorphism) is determined by the

Table 2. Crystallographic Data of Four Polymorphs of 2-PNA

	α	β	γ	δ
morphology	yellow blocks	light yellow blocks	colorless blocks	colorless plates
space group	$P2_1/c$	$P\bar{1}$	$P2/c$	$P1$
a/Å	15.837(3)	9.91110(10)	21.480(2)	5.2918(11)
b/Å	5.491(1)	10.1907(2)	7.2050(8)	9.0521(18)
c/Å	11.723(2)	11.2941(2)	28.057(3)	11.046(2)
α/deg	90	96.7598(6)	90	80.78(3)
β/deg	99.76(1)	114.2391(7)	110.467(3)	82.80(3)
γ/deg	90	96.6550(6)	90	79.88(3)
Z'	1	2	4	2
Z	4	4	16	2
V/Å^3	1004.7(3)	1015.79(3)	4068.1(7)	511.59(18)
D_{cal}/g·cm^{-3}	1.416	1.401	1.399	1.391
R_1	0.042	0.048	0.039	0.059
T/K	90	90	90	90

molecular conformational variance in the polymorphs. The yellow α form has the best π-conjugation between the two chromophores due to an almost planar conformation of the molecules; the colorless δ form has the worst π-conjugation between the two chromophores since the two aromatic rings are nearly perpendicular to each other; the other two forms show moderate π-conjugations within these two extremes, from light yellow to nearly colorless. The NBO analysis based on the second-order perturbation theory further epitomizes the influence of the molecular conformation on the π-conjugation. The donor−acceptor NBO stabilization energies between the lone pair electrons on N7 and the phenyl ring are 36.74 kcal/mol for the molecule in the α form, 33.09 and 31.68 kcal/mol in the β form, 29.77, 22.70, 19.83 and 25.43 kcal/mol in the γ form, and 26.40 and 17.31 kcal/mol in the δ form, respectively. The energy of the optimized single molecule of the lowest energy is 38.30 kcal/mol. Clearly, the molecule in the α form shows the largest degree of conjugation or delocalization of the lone pair electrons on N7 among the molecules in the four polymorphs, and the closest to the ideal conjugation of the molecule (36.74 vs 38.30 kcal/mol). One molecule in the δ form shows the smallest degree of conjugation (17.31 kcal/mol). The different conjugations are certainly a result of the molecular conformations. A similar phenomenon was reported for ROY.[44]

In all of the 2-PNA polymorphs, the −COOH adopts the *syn* conformation[45−47] with the carbonyl O forming an intramolecular hydrogen bond with the amino group of the diarylamine, leading to S(6) motif according to the graph set concept.[48−50] In addition, 2-PNA has three conformational degrees of freedom, designated as τ1, τ2 and τ3 (Scheme 1). The τ values are listed in Table 3. Clearly, the conformational flexibility arises mainly from differences in the torsion angles. A superposition of all different conformers in the polymorphs (Figure 2) graphically highlights the extent of conformational diversity.

Shown in Figure 3a, the molecules of the α polymorph form centrosymmetric dimers through intermolecular O−H···O hydrogen bonds between two carboxyl groups (O···O distance, O−H···O angle: 2.6407(13) Å, 173.7°) ($R_2^2(8)$ by the graph set). Each molecule has an S(6) hydrogen-bonding motif between the NH and carbonyl O (N···O distance, N−H···O angle: 2.6854(14) Å, 139.0°). The dimers further stack upon each other along the *b* axis, forming two types of one-dimensional columns slightly tilting from each other.

The asymmetric unit of the β polymorph contains two symmetry independent molecules (A and B). Shown in Figure 3b, both conformers of the β polymorph form centrosymmetric dimers through $R_2^2(8)$ hydrogen-bonding motif based on intermolecular O−H···O hydrogen bonds between two carboxyls; a hydrogen-bonded S(6) loop exists between the NH and carbonyl O of each molecule. Because of the conformational difference, the packing pattern of these two dimers is slightly different. In dimer A, the donor−acceptor distance and angle of the hydrogen bond O−H···O are 2.6644(13) Å and 175.3°, respectively; the values of the N−H···O are 2.6943(14) Å and 136.5°. In dimer B, the distance and angle of the O−H···O are 2.6534(14) Å and 176.1°, while those of the N−H···O are 2.6905(14) Å and 138.7°.

In the γ polymorph, there are four symmetry independent molecules (A, B, C and D) in the asymmetric unit. Conformers C and A form one-dimensional chains along the *c* axis through C(6) hydrogen-bonding motifs based on intermolecular O−H···N hydrogen bonds between the OH of the carboxyl of conformer C and N of the pyridine ring of conformer A, while conformers B and D form another similar one-dimensional chain along the *c* axis (Figure 3c). Every two adjacent chains are antiparallel to each other. The S(6) hydrogen-bonding motif between the NH and carbonyl O persists in all conformers. Due to the conformational difference among the four conformers, the four intermolecular hydrogen bonds and the four intramolecular hydrogen bonds are slightly different in both lengths and angles as shown in Table 4.

In the δ polymorph, the asymmetric unit consists of two crystallographically independent molecules (A and B). The molecules form one-dimensional chains along the [122] direction through intermolecular O−H···N hydrogen bonds between the OH of the carboxyl of one conformer and N of the pyridine ring of the adjacent, different conformer (C(6) by the graph set) (Figure 3d). The chains further stack upon each other along the *a* axis. S(6) motif between the NH and carbonyl O persists in both conformers. Because of the two conformers, the two intermolecular hydrogen bonds and the two intramolecular hydrogen bonds are slightly different in geometry. When conformer A acts as the donor (O−H) and conformer B as the acceptor (N), the distance between O and N is 2.649(3) Å with the angle of O−H···N of 166.0°; conversely, when conformer B is the donor (O−H) and conformer A is the acceptor (N), the corresponding distance and angle are 2.685(3) Å and 172.2°, respectively. The intramolecular hydrogen bond in conformer A shows the distance between N and O to be 2.669(3) Å and the angle of N−H···O 133.7°; in conformer B, the corresponding values are 2.676(3) Å and 133.9°.

3.2. Phase Behaviors of Polymorphs.

3.2.1. Thermal Analyses. Differential scanning calorimetry (DSC) was conducted to investigate thermal properties of the four polymorphs, shown in Figure 4. The α form shows melting of the crystal (onset temperature of 155.6 °C), and no phase transition is detected. The β form shows two endothermic peaks. The one with the onset temperature of 147.2 °C appears to be a solid-to-solid phase transition to the α form, and the one of 156.1 °C is the melting of the transformed α form. Different from the β form, the γ form shows one broad exothermic peak with the onset temperature near 94.3 °C followed by one extra endothermic peak with the onset temperature of 153.2 °C. It is suspected that the first peak corresponds to a solid-to-solid phase transition to the α form, which melts as indicated by the second peak. Two endothermic peaks are observed of the δ form. The peak with the onset temperature of 150.8 °C is believed to be of a phase transition to the α form, while the other peak with the onset temperature of 155.7 °C coincides with the melting of the α form. As all of the DSC samples were cooled to ambient

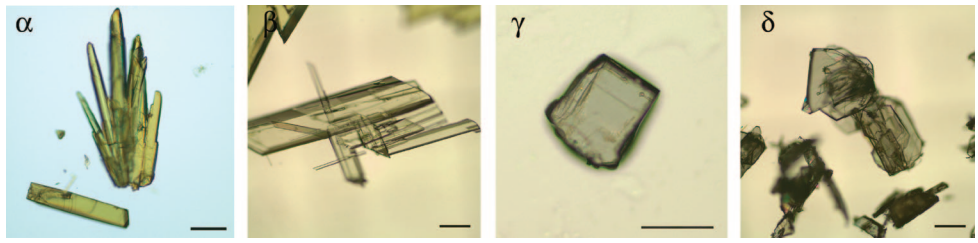


Figure 1. Crystals of the four polymorphs of 2-PNA. Scale bar: 0.2 mm.

Table 3. Torsion Angles as Defined in Scheme 1 of Molecules in Different Polymorphs. Multiple Conformers Exist in the *β*, *γ* and *δ* Forms. Values of the Optimized Single Molecule of the Lowest Energy Are Also Listed. Unit: Degree

	$\tau 1$	$\tau 2$	$\tau 3$
α	1.4	1.8	−178.2
β (A)	9.3	−163.4	−178.7
β (B)	3.8	156.8	179.8
γ (A)	11.2	−147.9	172.3
γ (B)	−15.5	132.6	−174.2
γ (C)	−0.3	−125.2	168.4
γ (D)	0.0	−139.4	173.7
δ (A)	18.6	−140.0	174.4
δ (B)	8.0	−110.6	171.1
single molecule	0.0	0.1	179.9

temperature after the heating, no thermal event was observed during the cooling, indicating supercooled liquids were likely formed.

In addition, no phase transition of each polymorph was observed from 90 K to room temperature. Table 5 lists unit cell parameters of the four forms that were indexed at 90, 180, and 295 K, respectively. There are only small differences in each parameter, which were most likely caused by the thermal expansion of unit cell volume. The crystal structures at ambient condition are indeed of those measured at 90 K, albeit the small variation in cell parameters. It should be noted that the subtle difference between the indexed and fully solved values at 90 K is due to the methodology (i.e., indexing vs solving the structure), not a reflection of physics. Moreover, Figure 5 shows the powder X-ray diffraction patterns of α, *β*, and *δ* forms collected at room temperature as well as simulated patterns of all forms that are based on the single crystal structures determined at 90 K. The similarity of each form between the experimental and simulated patterns further indicates the thermodynamic stability at low temperature. The comparison also suggests that each crystallization batch was most likely of one single polymorph, not a mixture of multiple polymorphs. The slight shift of experimental patterns to the left as compared to the simulated ones confirms the increase in unit cell dimensions (Table 5), because the experimental patterns were collected at room temperature while the simulated ones were based on the structures that were determined at 90 K.

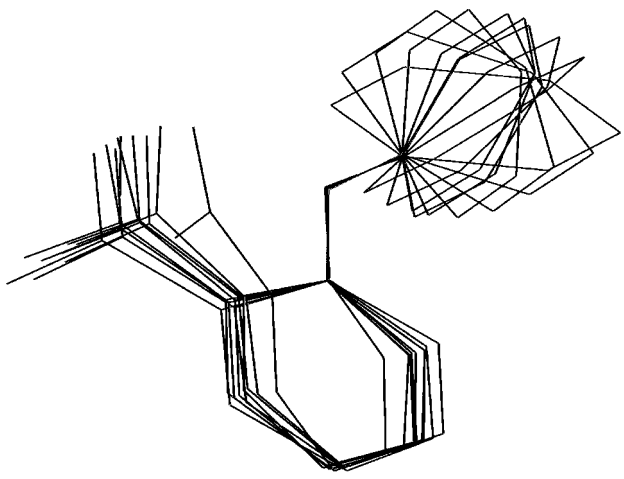


Figure 2. Superposition of nine conformers in the asymmetric units of the four polymorphs. For clarity, hydrogen atoms are not shown.

3.2.2. Mechanochromism and Thermochromism. Phase transition induced by mechanical perturbation was first observed, unintentionally, during the data collection of the *δ* crystals from methanol. When some crystals were taken away from the solution by a spatula, in less than a minute, the colorless crystals remaining in the vial all yellowed (Figure 6a). Interestingly, crystals immersed in oil (Paraton, Exxon) remained colorless even after poking. The yellow crystals were identified as the α form. Another batch of colorless crystals in the absence of solvent did not transform to the yellow α form. As such, the phase transition was likely triggered by physical perturbation of the spatula used to pick the crystals. Moreover, the phase transition required assistance by a suitable solvent. Under similar conditions, the same type of phase transition was observed in the *β* crystals (Figure 6b). Without mechanical perturbation, once again, no phase transition was observed. For the metastable form *γ*, the same transition was not conducted because the crystals were harvested with all solvent evaporated and efforts to obtain the form failed. The poor polymorphic selectivity shown in Table 1 (e.g., α, *β* and *δ* forms from methanol) may thereby be a result of the uncontrolled manner of solvent evaporation during the crystallization experiments. Further kinetics studies of crystal growth under refined conditions are needed.

Phase transitions from the metastable forms to the most stable form were further examined on a polarized, hot-stage microscope. Their phase behaviors echo the DSC experiments (Figure 4). The α form underwent melting with no other phase transition being observed. When metastable forms were heated on the hot stage, they all transformed into the α form at various temperatures. The light yellow crystals of the *β* form underwent phase transition becoming the yellow α form around 140 °C (Figure 7a). The phase transition of the *γ* form took place at a much lower temperature, 101 °C (Figure 7b), appearing to be in agreement with the DSC result. The colorless *δ* crystals started turning into yellow crystals at around 141 °C (Figure 7c). Then at 160 °C, all of the newly transformed yellow crystals melted, indicating the most stable α form was indeed the final crystal. Three movies showing the phase transition of the *β*, *γ*, and *δ* forms are available in Supporting Information. Both solvent-mediated and heat-assisted phase transitions can happen quickly consuming the original crystal completely within minutes after the new phase is initiated. The mechanism seems to be a first-order, nucleation-and-growth process.[51] More experiments to examine the kinetics and mechanism will be conducted.

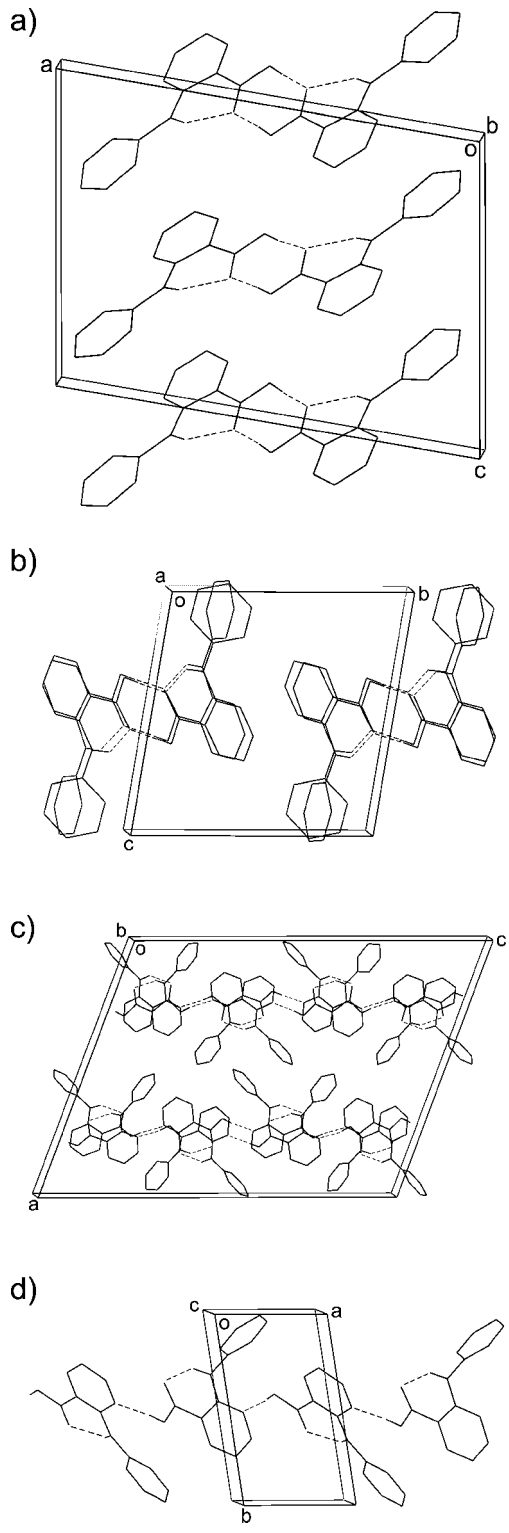


Figure 3. Crystal packing of the α (a), *β* (b), *γ* (c), and *δ* forms (d). For clarity, hydrogen atoms not participating in the hydrogen-bonding interactions are omitted.

3.3. Conformational Polymorphism. The polymorphism of 2-PNA arises from the intrinsic conformational flexibility of the molecule. To further understand the polymorphic formation, conformational scans of single 2-PNA molecule were conducted for *τ*1, *τ*2 and *τ*3, respectively, as illustrated in Figure 8. The global minimum of *τ*1 was identified at 0° (Figure 8a); two local minima were found at ±115°, but these local minima are not energetically feasible because of the large energy increase (about 88 kJ/mol). In addition to the global minimum located at 0°, two energetically possible local minima of *τ*2 (Figure 8b) were discovered at ±140° (about 17 kJ/mol increase). For *τ*3 (Figure 8c), besides the global minimum at ±180°, two energy local minima were located at ±30° (about 32 kJ/mol increase). Upon examining the torsion angles in the polymorphic structures (Table 3), it appears that the polymorphism is indeed a result of the conformational flexibility of the single molecule. The *τ*1 and *τ*3 angles of all nine conformers are close to their global minimum values. The *τ*2 values show a relatively large distribution around the local minima at ±140° as well as one instance at the global minimum (1.75° of the α form). It is likely

Table 4. Donor−Acceptor Distances and Angles of Hydrogen Bonds of Four Conformers in Form *γ*

donor···acceptor	distance/Å	angle/deg
(C) O−H···N (A)	2.7039(19)	170.1
(A) O−H···N (C)	2.6915(18)	175.6
(A) N−H···O	2.6338(18)	139.6
(C) N−H···O	2.6897(19)	136.6
(B) O−H···N (D)	2.6979(19)	174.1
(D) O−H···N (B)	2.6454(19)	172.3
(B) N−H···O	2.6672(19)	133.4
(D) N−H···O	2.6592(19)	139.4

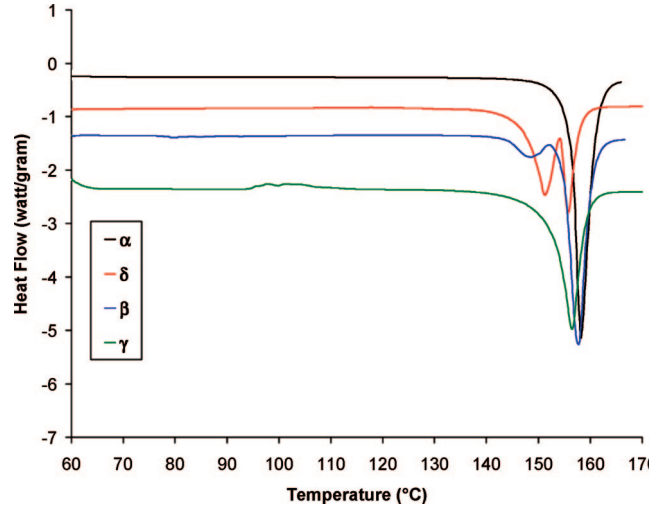


Figure 4. DSC thermographs of the four polymorphs.

Table 5. Unit Cell Parameters Indexed at Different Temperatures[a]

	α	*β*	*γ*	*δ*
a/Å	15.86	9.89	21.56	5.29
	15.87	9.95	21.59	5.31
	15.93	10.01	21.60	5.34
b/Å	5.52	10.14	7.24	9.04
	5.51	10.22	7.30	9.19
	5.53	10.30	7.38	9.20
c/Å	11.77	11.27	28.17	11.02
	11.79	11.35	28.19	11.18
	11.90	11.45	28.21	11.18
α/deg	90	96.83	90	80.93
		97.30		80.61
		98.10		81.21
β/deg	99.49	114.27	110.51	82.76
	101.17	114.59	110.57	82.47
	101.02	115.15	110.70	81.95
γ/deg	90	96.65	90	79.96
		96.15		79.84
		95.47		80.12

[a] The three numbers in each data field are of 90, 180, and 295 K, respectively.

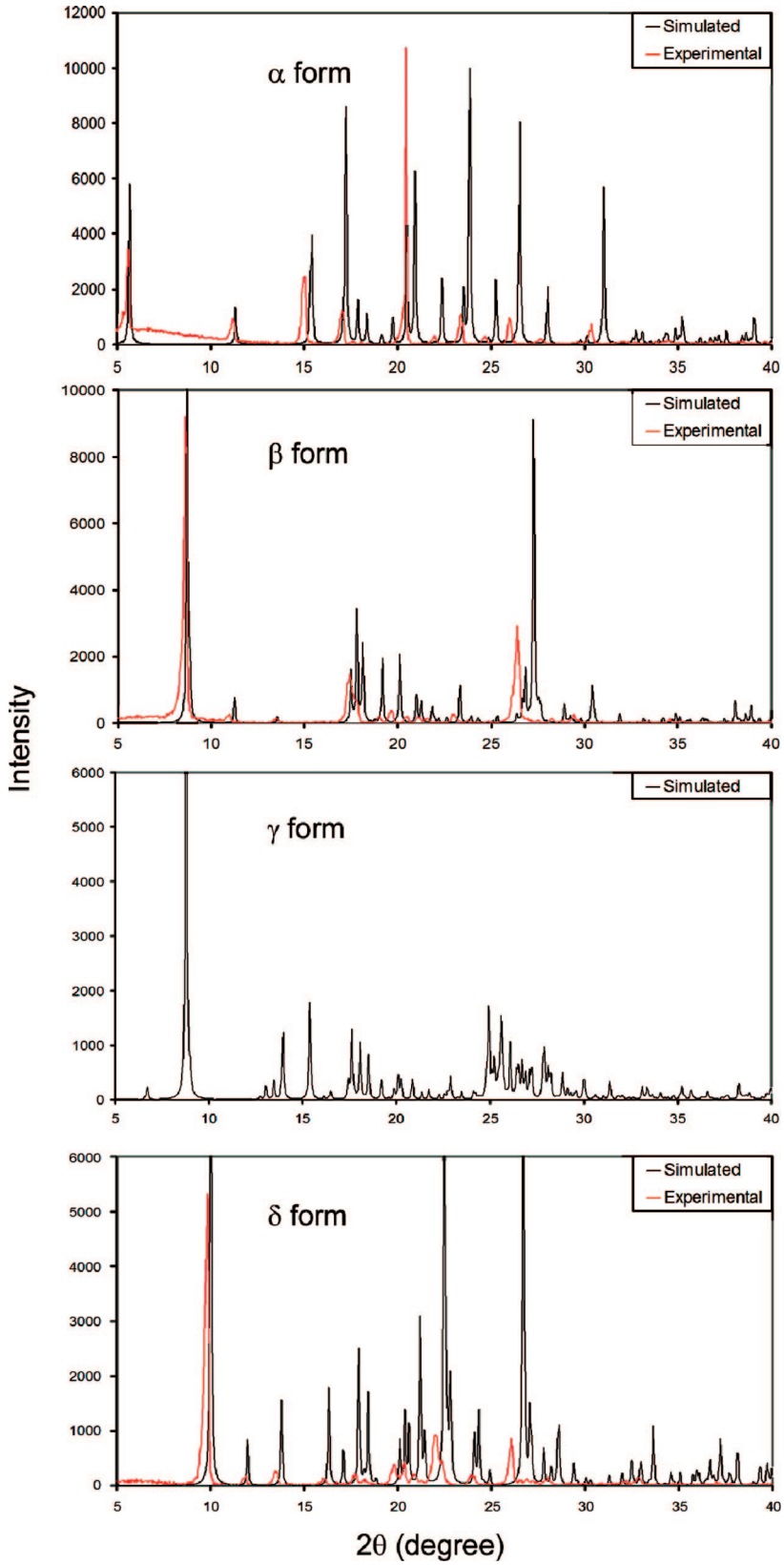


Figure 5. Experimental and simulated powder X-ray diffraction patterns of 2-PNA polymorphs. No experimental pattern of the γ form was collected due to limited sample amount.

that the large variation of $\tau 2$ around $\pm 140°$ may be due to the small energy barrier (less than 22 kJ/mol). Moreover, the discovered polymorphs seem to traverse all possible conformational flexibilities as identified by the torsion angles.

Despite the conformational polymorphism being dominant in the crystal system, intermolecular interactions and consequent close contacts among molecules may also play an important role in leading to the polymorphs of 2-PNA. The subtle

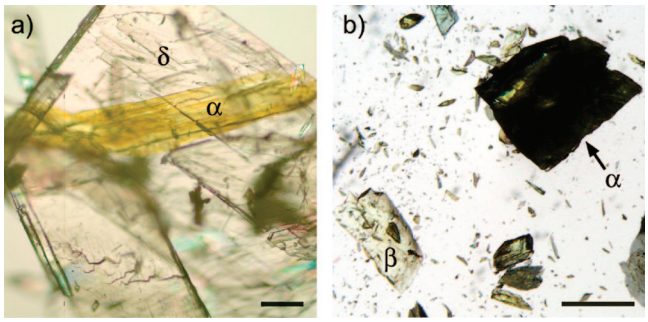


Figure 6. Solvent-mediated phase transition at room temperature: from δ to α (a) and from β to α (b). Scale bar: 0.2 mm.

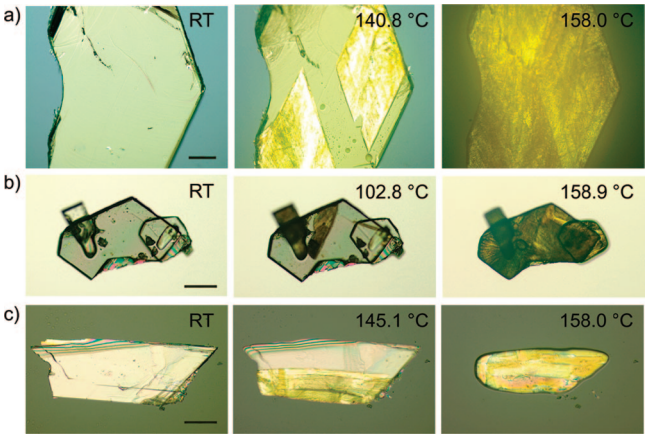


Figure 7. Temperature-induced phase transition: β to α (a), γ to α (b), and δ to α (c). Scale bar: 0.2 mm.

differences in torsion angles are very likely a result of molecular packing. The interplay between molecular conformation and intermolecular arrangements may lead to more forms than what we have discovered. Moreover, the *anti* conformation of the carboxyl group may be expected to appear in the new forms, although all the conformers in the four polymorphs have a *syn* conformation.

4. Conclusions

Compounds with extensive polymorphism are scarce; extensive polymorphic systems with an assembly of conformational polymorphism, conformational isomorphism, polychromism, mechanochromism and thermochromism are even rarer. 2-PNA is one of them.

Four polymorphs of 2-PNA have been obtained as crystalline solids with distinctive colors by crystallization from various solvents. Structure determination indicates they are conformational polymorphs due to the conformational flexibility around the secondary amino group. Conformational analysis of the molecule suggests that the polychromism is related to the degree of conjugation of the two aromatic rings through the lone pair of the bridging amino group. All four polymorphs have different hydrogen-bonding arrangements. Phase behaviors of the crystals show that metastable forms can undergo the solid-to-solid phase transition to the most stable form initiated by mechanical perturbation (mechanochromism) in solution or assisted by heating in the solid state (thermochromism).

Therefore, due to the interesting structural and phase properties, the crystal system may provide an excellent case understanding crystal growth and crystal packing.

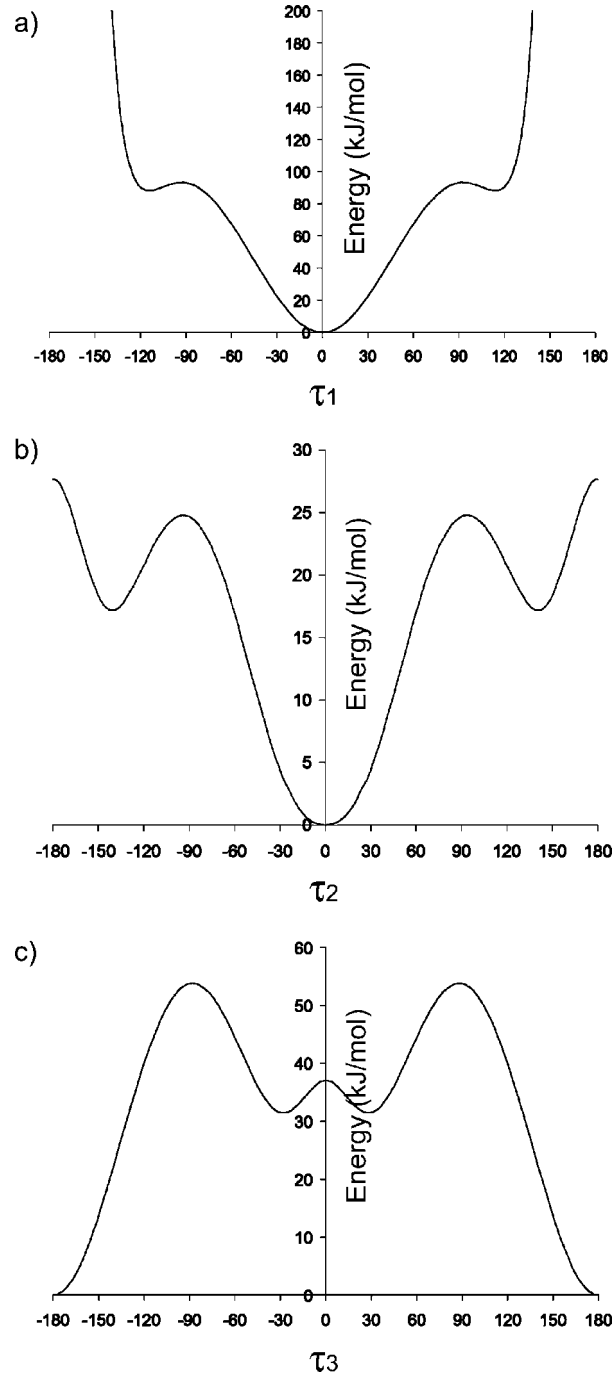


Figure 8. Conformational search of τ1 (a), τ2 (b) and τ3 (c) of single 2-PNA molecule.

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Supporting Information Available: Crystal structures of the four polymorphs in the form of crystallographic information files (CIF) and movies of phase transition in the AVI format. This material is available free of charge via the Internet at http://pubs.acs.org.

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