Differential Cocrystallization Behavior of Isomeric Pyridine Carboxamides toward Antitubercular Drug Pyrazinoic Acid

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Supporting Information

ABSTRACT: Pyrazinoic acid, the active form of the antitubercular pro-drug Pyrazinamide, is an amphoteric molecule containing carboxylic acid and pyridine groups and therefore can form both salts and cocrystals with relevant partner molecules. Cocrystallization of pyrazinoic acid with isomeric pyridine carboxamide series resulted in a dimorphic complex with isonicotinamide and in eutectics with nicotinamide and picolinamide, respectively. It is observed that with alteration of the carboxamide position, steric and electrostatic compatibility issues between molecules of the combination emerge and affect intermolecular interactions and supramolecular growth, thus leading to either cocrystal or eutectic for different pyrazinoic acid−pyridine carboxamide combinations. Intermolecular interaction energy calculations have been performed to understand the role of underlying energetics on the formation of cocrystal/eutectic in different combinations. On the other hand, two molecular salts with piperazine and cytosine and a gallic acid cocrystal of the drug were obtained, and their X-ray crystal structures were also determined in this work.

INTRODUCTION

Pyrazinoic acid (also called Pyrazinecarboxylic acid or Pyrazinic acid; abbreviated as POA; Figure 1) is the active form of the pro-drug Pyrazinamide, which is one of the front-line drugs used in the treatment of tuberculosis.1 POA is an amphoteric molecule and therefore can exist both in ionized and un-ionized forms. The two known polymorphs of it manifest in an un-ionized state,2 leaving a possibility for a zwitterionic polymorph3 upon solid form screening. Investigations on various supramolecular solid forms have become important for organic compounds in general and drugs in specific from both fundamental and application aspects.4 New polymorphs, amorphous forms, salts, cocrystals, eutectics, etc. are of particular interest to modulate the physicochemical properties of the compound of interest and achieve desired properties.5,6 An ionizable molecule can combine with different partners to form a salt/molecular salt, cocrystal, or even salt cocrystal.5,6 Further, on the basis of the $pK_a$ difference between the molecules, a salt-cocrystal continuum6b,d,7 can manifest, which is an interesting topic to understand the role of functional groups in affecting the nature of the hydrogen bond. This is important because the nature of the hydrogen bond can dictate the functional properties of a material,4a,c,5e,g,6c,7a,8 and therefore the study of salts and cocrystals of a compound is necessary toward property modulation along desired lines. In the

Figure 1. Molecular structures and acronyms of the compounds studied in this work.
present case, the pro-drug Pyrazinamide, being the marketed drug form, was well explored, but the active Pyrazinonic acid did not receive proper attention in terms of supramolecular solid form diversity. POA, of its carboxylic acid and pyridine groups, is amenable to both salt and cocrystal formation. Further, it makes a good model system to study the formation of cocrystal and eutectic. In practice, the ΔpKₐ value for the POA−INAM system is between 0 and 3 (Table 1), which is the gray zone where the extent of proton transfer is unpredictable. In the POA−nicotinamide and POA−cytosine systems also fall into the gray zone and form molecular salts.

### Crystal Structure Description

**Polymorphs of POA−INAM Mixed-Ionic Complex.** A dimorphic 1:1 adduct of POA and INAM was obtained when their ground mixture was crystallized from 1,4-dioxane. Both the polymorphs crystallized in the space group PI with one as a Z'= 1 structure (designated as POA−INAM-α) and the other as Z'= 2 structure (designated as POA−INAM-β) and could be identified and isolated based on their crystal habits (see Experimental Section). Both these polymorphs show partial proton transfer in the carboxylic acid−pyridine heterosynthons having partial proton transfer and crystallized as an anhydrous dimorphic system, which we designate as POA−INAM-α and -β polymorphs. The ΔpKₐ values for the POA−INAM system is between 0 and 3 (Table 1), which is the gray zone where the extent of proton transfer is unpredictable. The POA−piperazine and POA−cytosine systems also fall into the gray zone and form molecular salts. The POA−gallic acid system, with a ΔpKₐ = −3.91, is the only combination in this study that obeys the ΔpKₐ rule by forming a cocrystal (Table 1). Crystallographic parameters of these adducts are given in Table 2 and their crystal structures are described next.

### RESULTS AND DISCUSSION

All selected coformers have complementary basic or acidic groups (Figure 1) which can form either a salt or a cocrystal or even a eutectic with amphotropic POA. In practice, the ΔpKₐ rule is used as a guide to assess the formation of salt or cocrystal for an acid−base combination (here carboxylic acid−pyridine/amine, Figure 1) according to which a salt forms when ΔpKₐ > 3 and a cocrystal when ΔpKₐ < 3.5d,7e,11 Cocrystallization experiments were carried out by liquid-assisted grinding (LAG) method, and characterization of the adduct was done by powder X-ray diffraction, IR spectroscopy, and thermal techniques (the characterization is detailed in the Experimental Section; see Supporting Information, SI, for PXRD patterns and IR spectra). The pKₐ and ΔpKₐ values of the compounds and the results of cocrystallization experiments are tabulated in Table 1. It is expected that all coformers, barring picolinamide and nicotinamide, can form either cocrystal or salt with POA due to steric compatibility for heteromolecular interactions and packing. Indeed, both picolinamide and nicotinamide formed eutectics with POA, and the issues with respect to eutectic formation are discussed later. Among the other adducts obtained, all are either hydrated salt or cocrystal, except for the POA−isonicotinamide combination. It is a mixed-ionic complex,7a,13 having partial proton transfer and crystallized as an anhydrous dimorphic system, which we designate as POA−INAM-α and -β polymorphs. The ΔpKₐ value for the POA−INAM system is between 0 and 3 (Table 1), which is the gray zone where the extent of proton transfer is unpredictable. The POA−nicotinamide and POA−picolinamide systems are reported in this article.
Table 2. Crystallographic Parameters of the Adducts

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<th>adduct</th>
<th>POA–INAM-α</th>
<th>POA–INAM-β</th>
<th>2POA−PPZ−2H2O</th>
<th>POA−CYT−H2O</th>
<th>POA−GA−H2O</th>
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<td>formula</td>
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<td>a (Å)</td>
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<td>b (Å)</td>
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<td>9.944(4)</td>
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<td>c (Å)</td>
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“Z” = number of formula units in the asymmetric unit; “Z” = no. of crystallographically nonequivalent molecules of any type in the asymmetric unit;¹⁷ Z = Z” × no. of independent general positions of the space group.
Figure 2. In both POA−INAM mixed-ionic complex polymorphs, tetrameric units of POA−INAM acid-pyridine heterodimers and INAM amide homodimers make infinite tapes, which extend into a sheet structure making them 2D isostructural. Unique POA−INAM heterodimers of β polymorph are shown in different color.

Figure 3. Linear tapes of $N^+$−H⋯O− bonded POA and PPZ molecules supported by water mediated C⋯H⋯O bonds propagate into a sheet through O⋯H$_{\text{(water)}}$−$N_\text{(POA)}$, $N^+$−H⋯N and C⋯H⋯O$^-$ interactions in POA−PPZ salt dihydrate. Symmetry independent water molecules are shown in different color.

Figure 4. Carboxylate-aminopyrimidinium heterodimers of POA and CYT molecules extend into a sheet structure through N⋯H−N and C⋯H–O interactions with adjacent dimers and multiple hydrogen bonds involving water molecules in POA−CYT salt hydrate.
tetrameric motifs in a coplanar geometry for POA-pyridine carboxamide combinations (Scheme 1). In POA-INAM combination, the para location of the amide group renders the anti-NH donor free to participate in strong hydrogen bonds (N—H···O, see Figure 2; Scheme 1a) and thus facilitates the progression of tetramers leading to cocrystal formation in accordance to the previous reports.9a,19 In the case of POA-PAM and POA-NAM systems, the anti-NH donors in the tetrameric motifs are sterically crowded and thus become unavailable for propagation (Scheme 1c,e). As per Etter’s hydrogen-bond rules,22 a strong donor like NH will not remain idle but participates in hydrogen bonding with a strong acceptor (here carboxyl oxygen). In the alternate way of cocrystal formation for POA-pyridine carboxamides through tetramers composed of acid–amide dimers, the anti-NHs are hydrogen-bond locked (Scheme 1b,d,f). The extension of any of the two POA-PAM and POA-NAM tetramers through out-of-plane twisting of carboxamide group or via weak C—H···O/N interactions would need twisted acid moiety or additional oxygen containing moiety as observed in acid–PAM/NAM cocrystals.21,22 Thus, POA-PAM and POA-NAM systems having steric hindrance coupled with weak stabilization

Figure 5. Linear tapes of POA and GA molecules connected by acid-pyridine synthon and C—H···O bonds extend into a sheet structure through O—H···O and C—H···O interactions also including water molecules in POA-GA cocrystal hydrate.

Scheme 1. Plausible Tetrameric Motifs for POA–INAM (a, b), POA–PAM (c, d) and POA–NAM (e, f) Combinations

| (a) POA–INAM tetrameric motif composed of acid–pyridine and amide–amide dimers | (b) POA–INAM tetrameric motif composed of acid–amide dimers |
| (c) POA–PAM tetrameric motif composed of acid–pyridine and amide–amide dimers | (d) POA–PAM tetrameric motif composed of acid–amide dimers |
| (e) POA–NAM tetrameric motif composed of acid–pyridine and amide–amide dimers | (f) POA–NAM tetrameric motif composed of acid–amide dimers |

“In all motifs, except (a), the strong anti-NH donors (marked in red) are either sterically crowded or hydrogen bond locked such that the propagation of the combination as a cocrystal does not take place. The (a) motif is the repeating unit which propagates via sterically free anti-NH in POA–INAM dimorphic mixed-ionic complex (see Figure 2).
of heteromeric motifs cannot form cocrystals and therefore manifested as eutectics, respectively.

Further, the formation of POA−INAM cocrystal and nonformation of POA−PAM/NAM cocrystals can be rationalized from the crystal structure analysis of parent pyridine carboxamides. In the crystal structure of INAM, amide homodimers extend into tapes through weak phenyl−pyridine (C−H···N) dimers involving the strong pyridyl group (Figure 6).

![Figure 6. Formation of POA−INAM mixed-ionic complex takes place due to the dominance of strong heteromeric (acid−pyridine) interactions over the weak homomeric (phenyl−pyridine) interactions (marked in red) in INAM (CSD refcode: EHOWIH).](image)

Combination of POA, having strong acid group, with INAM can easily replace/displace the weak phenyl−pyridine synthons by the strong and robust acid−pyridine heterosynthon (in accordance to best hydrogen bond donor−acceptor criterion).19

Thus, the propagation of tetrameric motifs composed of acid−pyridine and amide dimers through anti N−H···O interactions leads to cocrystal formation in POA−INAM (Scheme 1a and Figure 6). On the other hand, the crystal structures of PAM and NAM are sustained by strong N−H···O/N interactions at the primary level of organization.20 These strong homomeric interactions cannot be replaced by almost equivalent heteromeric interactions (O−H···N and N−H···O) to form cocrystals with POA unless the latter interactions are propagated in the combination. Hence, POA−PAM and POA−NAM form eutectics with finite and discrete heteromeric units as per Scheme 1c−f.

To corroborate the formation of cocrystal/eutectic in POA−pyridine carboxamide series, energy calculations (detailed in Experimental Section) were performed on primary dimeric and tetrameric supramolecular motifs of both parent compounds and their combinations. In the case of the parent compounds, the motifs present in their crystal structures were taken for calculations. For combinations, various plausible motifs (given in the SI, also including the ones depicted in Scheme 1) were considered. It has been proposed that a cocrystal can form if it is thermodynamically more stable than the sum of its component crystal structures.24 Conversely, a eutectic (or even a physical mixture in the worst case) can form when there is no energetic advantage. However, energy values of different cocrystal systems in the literature showed mixed results, which is not surprising since the energy landscape of a combination is widespread, spanning a 30 kJ/mole window.24 There can be cocrystals which have higher stabilization energy (in other words, low energy) as compared to individual compounds, cases with low stabilization (or high energy) and some in borderzone arena. This lends support in a semiempirical way to the manifestation of cocrystals having high, intermediate, and low melting points and solubilities, as compared to their parent compounds.5 In our study, although there is energetic advantage for the three combinations compared to individual components (stabilization energy of heterodimers is 5−20 kJ/mole greater than that of homodimers; similarly heterotetramers 20−45 kJ/mole > homotetramers; Table 3, see SI for motifs), only POA−INAM combination formed cocrystal and POA−PAM and POA−NAM combinations formed eutectics. This shows that the energetic advantage of a combination over parent compounds is not sufficient to establish/conclude cocrystal formation. On the other hand, stabilization energy values of POA−NAM are greater than those of POA−INAM and not significantly lower for POA−PAM (Table 3), such that the nonformation of cocrystals in these cases is justified. It is interesting to note that the tetrameric motif composed of acid−pyridine dimers (Scheme 1a,c,e) has less stabilization energy as compared to the motif composed of acid−amide dimers (Scheme 1b,d,f) in all combinations (acid−pyridine 75−90 kJ/mole < acid−amide; Table 3), yet has manifested in POA−INAM polymorphs. This is in contrast to the domination of acid−pyridine synthon over the acid−amide one.9b,10a,25 It appears that even though the tetrameric acid−amide motif is low in energy, the unavailability of anti-NH group for propagation renders the motif finite such that it cannot make cocrystal growth units. For this reason, both POA−INAM polymorphs should have organized with tetrameric acid−pyridine units having anti-NH available for propagation (Scheme 1a) and not with tetrameric acid−amide units having anti-NH locked (Scheme 1b). In POA−PAM and POA−NAM systems, the anti-NH in both acid−amide and acid−pyridine tetramers is locked (Scheme 1), thus leading to nonformation of cocrystals. To sum up, the obtained energy values do not validate the formation/nonformation of cocrystal in POA−pyridine carboxamide series. We surmise that reliable computational methodologies to predict or validate the formation of a cocrystal need to be developed.

On the other hand, we suspect the role of pK_a on the differential cocrystallization behavior of pyridine carboxamides with POA. There is a gradual decrease in ∆pK_a values in POA−pyridine carboxamide series (POA−INAM 0.77 > POA−NAM 0.4 > POA−PAM −1.73; Table 1) which indicates diminishment

![Table 3. Stabilization Energy Values of Dimeric and Tetrameric Motifs in kJ/mol](image)
of electrostatic interactions from the cocrystal-forming combination to the eutectic-forming combination. It is not out of place to draw such a relationship between electrostatic interactions (dictated by pK As here) and cocrystal/eutectic formation in light of the role of electrostatic force compatibility (dictated by inductive strength) of hydrogen bonding functional groups in their formation (interaction of the high +I group with the high +I group resulted in cocrystals and that with weak +I group in eutectics).10b However, this observation needs to be substantiated by relevant investigations. It is worth studying a series with pK As in all, this study strengthens the role of steric factors and their formation (interaction of the high +I group with the high +I group resulted in cocrystals and that with weak +I group in eutectics).10b However, this observation needs to be substantiated by relevant investigations. It is worth studying a series with pK As

### CONCLUSIONS

Cocrystallization of pyrazinoic acid with isomeric pyridine carboxamides was performed to probe and establish the role of the position of hydrogen bonding functionality (carboxamide here) on the formation of cocrystal vs eutectic as the two alternatives of a cocrystallization experiment. As such, both cocrystals and euctectics have formed in different combinations, and the first case of polymorphism in a mixed-ionic complex was noted in this study. The higher ΔpK_a value and steric comfort in POA–PPZ and the multiple hydrogen bond sites offered by CYT and GA in POA–CYT and POA–GA systems were responsible for strengthening and sustaining heteromolecular interactions to result in their respective salts and cocrystal. The variation in steric compatibility and electrostatic complementarity at the supramolecular level, stemming from the differences in functional group position (carboxamide) and pK_a (pyridine) among isomeric pyridine carboxamides, was found to influence supramolecular growth and packing and thus dictate the formation of cocrystal/eutectic for the POA–pyridine carboxamide series. All in all, this study strengthens the role of steric factors and their consequent effect on cocrystallization and adds to the existing knowledge and understanding of the phenomenon.

### EXPERIMENTAL SECTION

**Materials.** Commercially available pyrazinoic acid and other compounds (Sigma-Aldrich, Bengaluru, India) were used without further purification. Solvents were of analytical or chromatographic grade and purchased from local suppliers.

**Methods.** Liquid-Assisted Grinding and Characterization of Adduct. Compounds in molar ratios combined on the 100 mg scale were manually ground with 1–2 mL of solvent (methanol and/or water) added using a mortar-pestle for 15 min. The ground materials were analyzed by powder X-ray diffraction (PXRD), IR spectroscopy, and thermal techniques to ascertain the formation of the adduct. The cocrystal or molecular salt exhibited distinct PXRD patterns, IR spectra, and melting behavior, but eutectics showed only a depression in melting point compared to the parent materials.36,10c

**Evaporative Crystallization.** POA–INAM. A ground mixture of POA (12 mg, 0.1 mmol) and INAM (12 mg, 0.1 mmol) was dissolved in 3 mL of hot 1,4-dioxane and left for slow evaporation at room temperature. Two different morphologies of crystals (plates of α polymorph and blocks of β polymorph, both of which are colorless) were obtained after a few days of solvent evaporation. mp 180 °C.

2POA–PPZ–2H_2O. A ground mixture of POA (24 mg, 0.2 mmol) and PPZ (4.5 mg, 0.1 mmol) was dissolved in 5 mL of hot methanol and left for slow evaporation at room temperature. Colorless plate crystals were obtained after a few days of solvent evaporation, mp 230 °C.

POA–CYT–H_2O. A ground mixture of POA (12 mg, 0.1 mmol) and CYT (11 mg, 0.1 mmol) was dissolved in 3 mL of hot methanol and left for slow evaporation at room temperature. Colorless plate crystals were obtained after a few days of solvent evaporation, mp 260 °C.

POA–GA–H_2O. A ground mixture of POA (12 mg, 0.1 mmol) and GA (18 mg, 0.1 mmol) was dissolved in 5 mL of hot isopropanol and left for slow evaporation at room temperature. Colorless plate crystals were obtained after a few days of solvent evaporation, mp 215 °C.

**Single Crystal X-ray Diffraction.** X-ray reflections were collected on an Oxford Xcalibur Mova E diffractometer equipped with an EOS CCD detector and a microfocus sealed tube using Mo Kα radiation (λ = 0.7107 Å). Data collection and reduction was performed using CrystAlisPro (version 1.17.136.32,26) and OLEX2 (version 1.2.12) was used to solve and refine the crystal structures. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms on heteroatoms were located from difference electron density maps and all C—H atoms were fixed geometrically. The WinGX package28 was used for final refinement and production of CIFs and crystallographic table.

**Powder X-ray Diffraction.** PXRD were recorded on PANalytical diffractometer using Cu—Kα X-radiation (λ = 1.5406 Å) at 40 kV and 30 mA. Diffraction patterns were collected over 2θ range of 5–40° using a step size of 0.06° 2θ and time per step of 1 s. XPert HighScore Plus (version 1.0d)29 was used to collect and plot the diffraction patterns.

**IR Spectroscopy.** IR spectra were recorded using PerkinElmer Frontier FT-IR spectrometer on samples dispersed in potassium bromide pellets.

**Thermal Analysis.** The melting behavior of the combinations was analyzed on a Labindia visual melting range apparatus (MR 13300710).
equipped with a camera and an LCD monitor. Solidus–liquidus events of different compositions of eutectic-forming combinations were monitored and based on the merger of solidus and liquidus points the eutectic composition was determined.

**Packing Diagrams.** X-Seed was used to prepare packing diagrams.

**Energy Calculations.** The motifs present in crystal structures of polymorphs, which matched with commercial materials by PXRD (commercial forms are supposedly stable, i.e., low energetic in nature), of respective parent compounds (CSD refcodes: Pyrazinic acid, PYAZAC; Picoliminamide, PICAMD02; Nicotinamide, NICOAM02; and Isonicotinamide, EOHWI) were taken for calculations. For combinations, various plausible motifs were considered and compared with that of present in the crystal structure of pyrazinic acid–isonicotinamide mixed-ionic complex. All the geometries were optimized using the M062x/6-31++ (d, p) level of theory in the Gaussian 09 package. The basis set superposition error (BSSE) in the energies of dimers and tetramers was corrected using the M062x/6-31++ (d, p) level of theory in the Gaussian 09 package. The stabilization energy of the adduct was calculated by subtracting the amount of the individual energies of fragments from the adduct energy.

**ASSOCIATED CONTENT**

- Supporting Information
  
  - PXRD patterns and IR spectra of compounds, energy calculations on dimeric and tetrameric motifs, and CIF files.
  
  This material is available free of charge via the Internet at http://pubs.acs.org.

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**Notes**

The authors declare no competing financial interest.

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**REFERENCES**


**NOTE ADDED AFTER ASAP PUBLICATION**

This paper was published ASAP on January 12, 2015, with ChemDraw figures of dimeric and tertrameric motifs missing in the second column of Table S1 in the Supporting Information. The corrected version was reposted on January 23, 2015.