CRYSTAL GROWTH & DESIGN

Article

pubs.acs.org/crystal

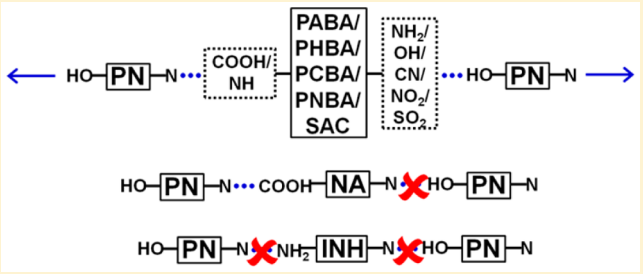
Multicomponent Adducts of Pyridoxine: An Evaluation of the Formation of Eutectics and Molecular Salts

Ramesh Ganduri, Suryanarayan Cherukuvada, and Tayur N. Guru Row*

Solid State and Structural Chemistry Unit, Indian Institute of Science, Bengaluru 560012, India

Supporting Information

ABSTRACT: Cocrystallization of pyridoxine (vitamin B_6) with several biologically important molecules was undertaken with the intent of successfully designing various hydrogen bonded adducts such as salts, cocrystals, and eutectics. Pyridoxine formed eutectics with isoniazid (an antitubercular drug) and nicotinic acid (vitamin B3) and molecular salts with para-aminobenzoic acid (a bioactive) and saccharin (an artificial sweetener), respectively, in accordance to our design strategy. A salt cocrystal, a precisely conjugate acid−base cocrystal, was obtained for the pyridoxine−para-nitrobenzoic acid combination. The role of supramolecular affinity of hydrogen bonding functional groups and ΔpK_a differences' leading to the formation of above diverse adducts was discussed. This study underpins the need for full-fledged supramolecular compatibility studies of multivitamin/drug combinations toward the development of optimal and/or synergistic combination formulations.



INTRODUCTION

Pyridoxine (abbreviated as PN, Figure 1), a form of vitamin B_6, is an essential organic nutrient which serves in many vital metabolic activities of living cells.[1] It is coadministered with several other B-complex vitamins and vitamin C in multivitamin therapy. Further, PN is advocated for prophylactic/supplemental use in tuberculosis treatment to prevent isoniazid-induced neuropathy.[1,2] It is administered as its hydrochloride salt in dietary and clinical conditions.[1] X-ray crystal structures were available for PN[3] and several of its salts including the hydrochloride salt.[4] Despite its combination with several vitamins and the antitubercular drug isoniazid (INH) in various pharmaceutical formulations, only a few studies on its interactions/compatibility with the latter have been undertaken in the literature.[5] Cocrystallization studies serve as an important methodology to probe the physical and supramolecular compatibility of a given combination, particularly multi-nutrient/drug combinations, and achieve an optimal formulation for the combination.[6−19] Friščić et al. emphasized the biological and pharmaceutical significance of cocrystallization through their studies on steroid hormones.[20,21] In their recent review, Sinha et al.[6] noted that in spite of the importance of cocrystallization studies on vitamins, they were found to be the least explored. In this background, we have performed cocrystallization of PN with nicotinic acid (vitamin B_3), bioactive para-aminobenzoic acid (PABA) and the antitubercular drug INH among other compounds (Figure 1). Although it is more practical to study the cocrystallization behavior of PN hydrochloride salt, native pyridoxine with an innocent pyridine N group amenable for molecular salt[22−27]/cocrystal formation was studied. The partner molecules for cocrystallization with PN were selected on the bottom line to corroborate the hypothesis that continuity of heteromolecular interactions leads to salt/cocrystal formation and discontinuity results in the eutectic for a particular combination.[7,28−31] A salt/cocrystal-forming combination features strong heteromeric interactions which outcompete homomeric interactions of individual components and in effect manifests distinct crystal packing as compared to that of the components. In the case of eutectic-forming combinations, heteromeric interactions are not strong enough to replace the homomeric interactions such that they prevail in a discontinuous/finite and random manner, and thus are largely ineffective in transforming the crystal packing of individual components.[7,28−31] The manifestation of molecular salt/cocrystal in this work is a matter of proton transfer/no proton transfer between the selected acidic compounds and basic PN. We obtained PN salts with para-amino, -hydroxy, -cyanobenzoic acids and saccharin (SAC), respectively, and PN−para-nitrobenzoic acid (PNBA) salt cocrystal and determined their X-ray crystal structures. PN−nicotinic acid (NA) and PN−INH combinations are eutectics by phase diagram analysis. We discuss the underlying reasons for the formation of these diverse supramolecular adducts of PN in this article.

RESULTS AND DISCUSSION

Cocrystallization experiments were carried out by the liquid-assisted grinding (LAG) method,[32,33] and preliminary charac-

Received: April 20, 2015
Revised: June 2, 2015
Published: June 3, 2015

DOI: 10.1021/acs.cgd.5b00546
Cryst. Growth Des. 2015, 15, 3474−3480

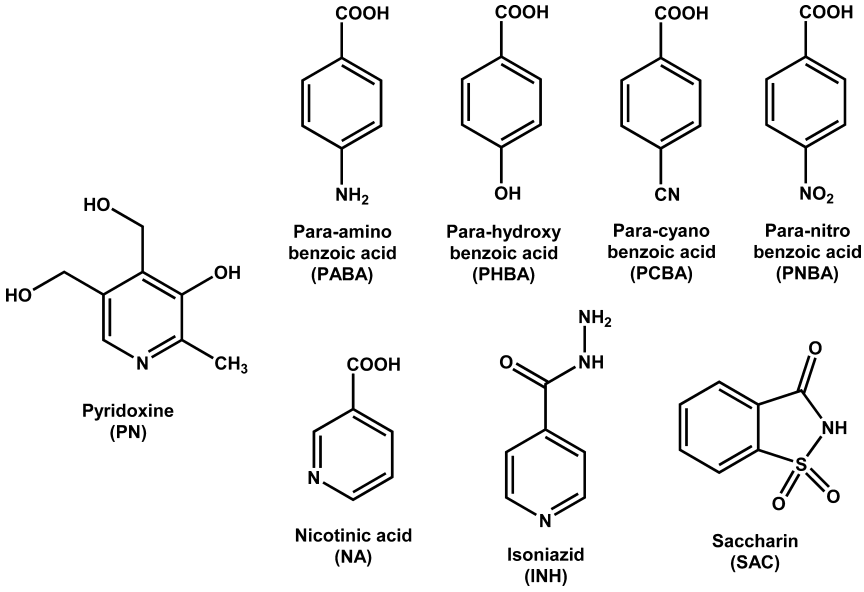
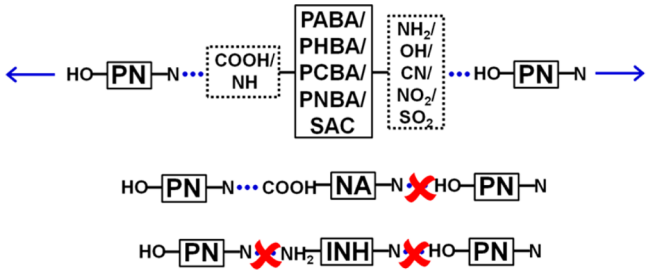


Figure 1. Molecular structures and acronyms of the compounds studied.

terization of the adducts was done by powder X-ray diffraction (PXRD) and thermal techniques (explained in Experimental Section; see Figures S1–S6 of Supporting Information for PXRD patterns). Single crystals were grown for combinations that exhibited distinct PXRD and thermal signatures characteristic of salt/cocrystal formation. PN can form molecular salts/cocrystals with compounds having complementary functionalities and eutectics with those having mismatched functionalities to it. All selected coformers have acidic functionality (Figure 1) and therefore can be thought to form salt or cocrystal (based on transfer or no transfer of proton) with basic PN. However, for supramolecular growth of a combination as a salt/cocrystal, heteromolecular interactions need to be propagated in the crystalline lattice. The repeating supramolecular unit for a binary salt/cocrystal could be in the order heterodimer to tetramer, and such units facilitated by auxiliary interactions grow into octamers and so on to build the salt/cocrystal.[7,28−31,34] Alternatively, the combination with finite heteromeric units and largely unaffected homomeric units manifests as a eutectic.[7,28−31] We anticipated the formation of a salt/cocrystal for PN−PABA/parahydroxy benzoic acid (PHBA)/para-cyanobenzoic acid (PCBA)/para-nitrobenzoic acid (PNBA)/SAC combinations and a eutectic for PN−NA/INH combinations and were successful in obtaining the respective adducts in accordance with our design schematics (Scheme 1). The one-to-one correlation between best hydrogen bond donor−acceptor pairs[7,28−31,35,36] in PN−PABA/PHBA/PCBA/PNBA/SAC systems resulted in their molecular salts as follows: protonated pyridoxine (PNH^+)··· deprotonated coformer heterodimeric units extend into a tetramer through $hydroxyl_{(PN)}$···$amine/hydroxyl/cyano/nitro/sulfonyl_{(coformer)}$ interactions, which repeats and grows through auxiliary interactions to form salts, respectively. On the other hand, in the PN−NA system, the heteromeric $hydroxyl_{(PN)}$···$pyridine_{(NA)}$ interactions are not strong enough to replace the homomeric interactions of NA (acid···pyridine) and PN (hydroxyl···hydroxyl). Further, the less robust $hydroxyl_{(PN)}$···$pyridine_{(NA)}$ interactions may not suffice to extend the plausible $pyridine_{(PN)}$···$acid_{(NA)}$ heterodimer into a tetramer and so on to result in a salt/cocrystal. Therefore, the PN−NA combination

Scheme 1. Propagation of Dominant Heteromeric Interactions (over Homomeric Ones) Ensures Supramolecular Growth of PN−PABA/PHBA/PCBA/PNBA/SAC Combinations into Their Respective Salts[a]



[a]The dominance of homomeric interactions in PN−NA and equivalence of homomeric and heteromeric interactions in PN−INH resulted in eutectics for the combinations.

makes a eutectic. In the PN−INH case, the heteromeric and homomeric interactions are almost equivalent (hydroxyl··· pyridine and hydrazide···pyridine) such that the system has no energetic drive to manifest into a salt/cocrystal. With the possibility of finite and random heteromeric interactions, the combination thus ends up as a eutectic.

ΔpK_a Rule and Nature of the Adducts Formed in This Study. The pK_a and ΔpK_a values of the compounds and the adducts resulting from our cocrystallization experiments are tabulated in Table 1. In PN−SAC and PN−NA systems, the ΔpK_a is ∼3 such that both the combinations can form salts as per the "ΔpK_a rule of three".[23,27,37−41] However, only the former formed a salt, while the latter gave a eutectic. For PN−NA, although $pyridinium_{(PN)}$···$carboxylate_{(NA)}$ heterodimers can form, the lack of viable interactions to propagate them into tetramers and so on should have resulted in eutectic for the combination (as explained above). This example illustrates the importance of secondary/auxiliary interactions even for the formation of a molecular salt (as observed in cocrystal-forming systems);[7,31,42] in other words, ionic heteromers of certain combinations may not be energetic enough to drive supramolecular growth of the combination as a salt. Furthermore, it

DOI: 10.1021/acs.cgd.5b00546
Cryst. Growth Des. 2015, 15, 3474−3480

Table 1. pK_a Values of Compounds and Nature of Adducts Formed

s. no.	partner	pK_a of acid partner	pK_a of PN	ΔpK_a = pK_a (base) − pK_a (acid)	adduct
1	PABA	4.87[54]	5.0[55]	0.13	salt
2	PHBA	4.57[56]	5.0	0.43	salt
3	PCBA	3.55[56]	5.0	1.45	salt
4	INH[a]	3.5[57]	5.0	1.5	eutectic
5	PNBA	3.43[56]	5.0	1.57	salt cocrystal
6	SAC[b]	1.8[58]	5.0	3.2	salt
7	NA	2.0[56]	5.0	3.0	eutectic

[a]Hydrazide nitrogen. [b]Imide nitrogen.

represents a less studied/reported case of eutectic formation for combinations with $\Delta pK_a \geq 3$, i.e., having potential for salt formation. On the other hand, the ΔpK_a of PN−PABA/PHBA/PCBA/INH/PNBA systems is between 0 and 3, the gray zone wherein the formation of salt/cocrystal for the combination cannot be predicted.[10,23,27,39−41,43−48] In addition, the possibility of a mixed-ionic complex[14,15,23,30,39,40,49−51] makes it less candid to anticipate the adduct in such cases. Accordingly, PN−PABA/PHBA/PCBA combinations formed salts, PN−INH formed a eutectic, whereas PN−PNBA gave a salt cocrystal (Table 1). The PN−PNBA salt cocrystal can be classified as a conjugate acid−base (CAB) cocrystal[11,52,53] since the adduct consists of PNBA and its conjugate base PNB^- in the crystal structure (described later). Crystal structures of PN−PABA/PHBA/PCBA/PNBA/SAC adducts (their crystallographic parameters are given in Table 2) are discussed next followed by binary phase diagrams of PN−NA/INH eutectics.

Crystal Structure Description. *1:1 PN−PABA/PHBA/PCBA/SAC Molecular Salts.* PN−PABA/PHBA/PCBA/SAC combinations formed salts in a 1:1 stoichiometry as per Scheme 1. PN−PABA/PHBA/SAC salts display cyclic tetramers composed of $PNH^+\cdots PAB^-/PHB^-/SAC^-$ dimers connected by hydroxyl$_{(PN)}\cdots$amine/hydroxyl/sulfonyl$_{(coformer)}$ interactions (Figure 2). PN−PCBA salt exhibits linear tapes composed of $PNH^+\cdots PCB^-$ dimers connected by methyl$_{(PN)}\cdots$cyano$_{(PCBA)}$ interactions (Figure 2) leaving a possibility of a synthon polymorph[60] with cyclic tetramers comprising $PNH^+\cdots PCB^-$ and hydroxyl$_{(PN)}\cdots$cyano$_{(PCBA)}$ dimeric units. The tetrameric units of all the salts propagate through auxiliary interactions involving additional hydroxyl groups of PN.

1:2 PN−PNBA Salt Cocrystal. Crystallization of 1:1 PN−PNBA ground mixture in methanol resulted in a 1:2 adduct containing protonated PN (PNH^+), PNB^-, and its conjugate acid PNBA. In the crystal structure, tetramers composed of $PNH^+\cdots PNB^-$ dimers connected by hydroxyl···nitro inter-

Table 2. Crystallographic Parameters of the Adducts[a]

adduct	1:1 PN−PABA	1:1 PN−PHBA	1:1 PN−PCBA	1:1 PN−SAC	1:2 PN−PNBA
formula	$2C_8H_{12}NO_3{-}2C_7H_6NO_2$	$C_8H_{12}NO_3{-}C_7H_5O_3$	$C_8H_{12}NO_3{-}C_8H_4NO_2$	$C_8H_{12}NO_3{-}C_7H_4NO_3S$	$C_8H_{12}NO_3{-}C_{14}H_9N_2O_8$
formula weight	306.31	307.29	316.31	352.36	503.42
crystal system	triclinic	monoclinic	triclinic	monoclinic	triclinic
T (K)	100	100	100	100	100
a (Å)	6.9930(7)	15.2676(15)	6.6720(5)	12.1306(3)	8.4250(5)
b (Å)	12.7693(8)	6.8912(7)	9.7266(5)	8.6404(2)	11.0485(5)
c (Å)	15.8817(15)	26.705(3)	12.2504(6)	15.1096(4)	11.9865(5)
α (deg)	89.049(6)	90	75.448(4)	90.00	95.465(4)
β (deg)	89.901(8)	95.223(10)	77.839(5)	110.143(3)	97.045(4)
γ (deg)	81.410(7)	90	76.928(5)	90.00	103.775(4)
volume (Å^3)	1402.1(2)	2798.0(5)	739.51(8)	1486.82(6)	1066.47(9)
space group	$P\bar{1}$	$C2/c$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
no. of independent general positions	2	8	2	4	2
Z'	2	1	1	1	1
Z''	4	2	2	2	3
Z	8	16	4	8	6
density (g cm^{-3})	1.451	1.459	1.421	1.574	1.568
μ (mm^{-1})	0.110	0.114	0.107	0.255	0.128
$F(000)$	648	1296	332	736	524
no. of measured reflections	23471	15977	13139	26607	18775
no. of unique reflections	5524	3203	3396	3415	4873
no. of reflections used	3476	2621	2874	3184	4197
$R_{\_all}$, $R_{\_obs}$	0.1383, 0.0826	0.0620, 0.0497	0.0519, 0.0426	0.0400, 0.0376	0.0554, 0.0476
$wR2_{\_all}$, $wR2_{\_obs}$	0.1799, 0.1550	0.1293, 0.1201	0.1067, 0.1013	0.1007, 0.0988	0.1268, 0.1208
$\Delta\rho_{min,max}$ (e Å^{-3})	−0.288, 0.291	−0.307, 0.329	−0.246, 0.309	−0.511, 0.521	−0.529, 0.610
GOF	1.091	1.057	1.037	1.032	1.055
CCDC no.	1057719	1057721	1057720	1057723	1057722

[a]Z' = number of formula units in the asymmetric unit; Z'' = no. of crystallographically nonequivalent molecules of any type in the asymmetric unit;[59] $Z = Z'' \times$ no. of independent general positions of the space group.

DOI: 10.1021/acs.cgd.5b00546
Cryst. Growth Des. 2015, 15, 3474−3480

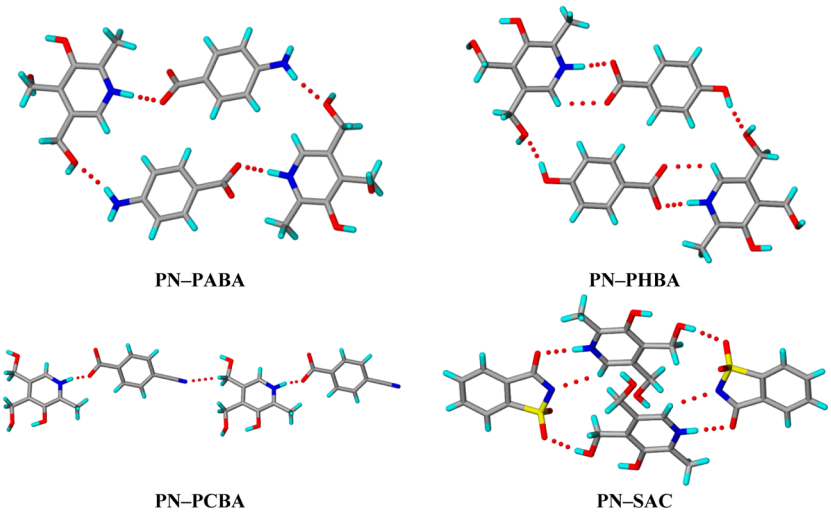


Figure 2. Tetrameric units in the crystal structures of PN−PABA/PHBA/PCBA/SAC salts.

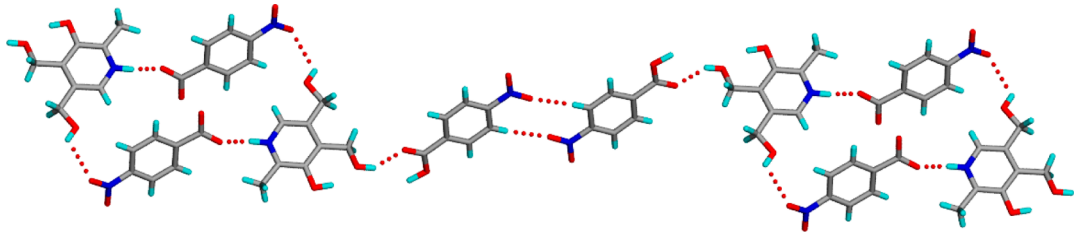


Figure 3. Tetramers composed of $PNH^{+}\cdots PNB^{-}$ dimers extend through PNBA C−H···O dimers in a 1:2 PN−PNBA salt cocrystal.

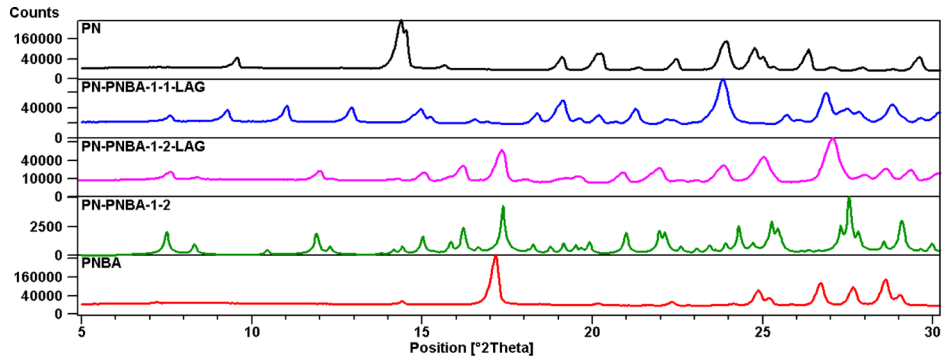


Figure 4. PXRD patterns of PN−PNBA system. Individual patterns, including both polymorphs of PNBA, are given in Figures S7−S12, Supporting Information.

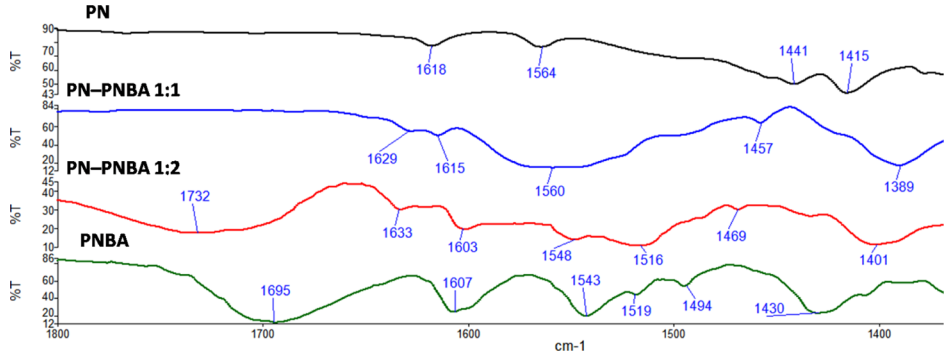


Figure 5. IR patterns of PN−PNBA system. Individual spectra are given in Figures S13−S16 of Supporting Information.

actions propagate through hydroxyl···carboxylic acid interactions involving PNBA molecules (Figure 3).

We anticipated a 1:1 adduct; however, the outcome was a conjugate acid−base (CAB) pair cocrystal, a category of salt

DOI: 10.1021/acs.cgd.5b00546
Cryst. Growth Des. 2015, 15, 3474−3480

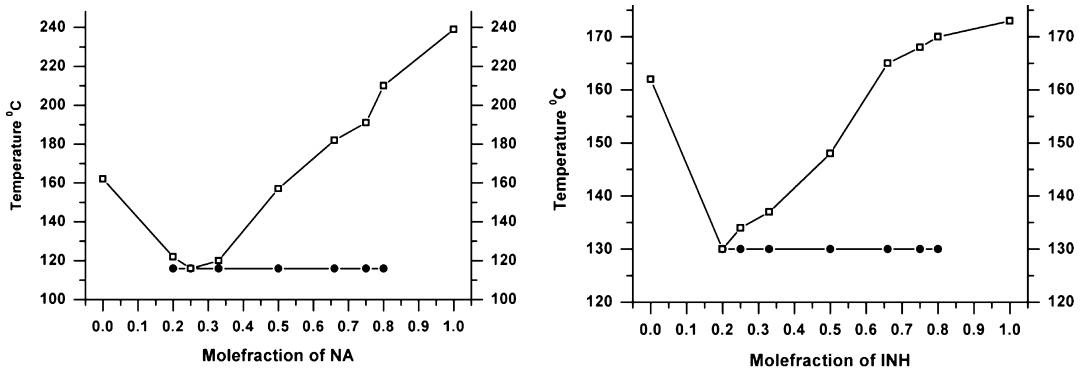


Figure 6. Binary phase diagrams of (a) PN−NA and (b) PN−INH eutectic systems. Solidus points are shown as filled circles and liquidus points as open squares.

cocrystal.[11,52,53,61−64] It appears that CAB cocrystals are a nemesis to crystal engineering[65,66] because of the associated unpredictability, although Sun et al.[11,52,53] achieved some control on their design and formation. It is of interest to note that the experimental PXRD pattern of a 1:1 ground mixture is different from that of the parent materials and also did not match the calculated X-ray diffraction pattern of the 1:2 PN−PNBA adduct (Figure 4). This supports our premise about the formation of a unique 1:1 PN−PNBA adduct. We have performed IR spectroscopy, which is known to establish the nature of an adduct,[17,37−40,67] on the material in the lack of single crystals to determine its structural integrity. IR spectrum of 1:1 PN−PNBA ground material is devoid of the distinct C═O stretching vibration of PNBA's carboxylic acid (∼1700 cm^{-1}) and manifested two peaks around 1550 and 1400 cm^{-1} characteristic of asymmetric and symmetric stretch of the COO^- group,[17,37−40,67] thus indicating salt formation for the 1:1 adduct (Figure 5). We were able to reproduce the 1:2 PN−PNBA salt cocrystal (as checked by PXRD, Figure 4) by methanol-assisted grinding of 1:2 stoichiometric mixture of the components. IR spectrum of the adduct features peaks of both C═O and COO^- groups (Figure 5), further confirming it to be a CAB cocrystal.

PN−NA and PN−INH Eutectics. Binary phase diagrams of PN−NA and PN−INH combinations exhibit 'V'-type pattern characteristic of a eutectic system[28−31,42,68−70] (Figure 6). The eutectic compositions of the combinations are found to be 3:1 and 4:1, with melting temperatures 116 and 130 °C, respectively.

CONCLUSIONS

Diverse adducts of pyridoxine were designed and successfully obtained in this study. A relatively less studied case of eutectic formation for the combination having potential for salt formation was also reported. The importance of secondary/auxiliary interactions, which were established to be crucial in steering cocrystal vs eutectic formation,[7,28−31,42] was demonstrated to be critical also in salt vs eutectic settings. Altogether, the utility of cocrystallization studies in unraveling mutual interactions and supramolecular compatibility of a given combination of materials was demonstrated through combinations of the essential nutrient pyridoxine and some biologically important molecules. Such studies are significant since they facilitate the understanding, sometimes postfacto rationalization, of synergism/antagonism in properties exhibited by a particular combination. The unintentional eutectic formation in drug-excipient formulations leading to enhancement of solubility for some combinations, and compromised stability for some others,[71−74] can also be the case with combinations having the potential for salt/cocrystal formation in the formulation environment. Multivitamin formulations can be synergistic since many of the vitamin components are ionic and also have potent hydrogen bonding functionalities amenable to form different adducts. In the context of anti-TB, anti-HIV, antimalarial, and cardiovascular drugs being formulated in combinations[75−80] with the likelihood to form such adducts, cocrystallization studies can pave the way for the optimization and improvement of combination formulations.

EXPERIMENTAL SECTION

Materials. All compounds were commercially available (Sigma-Aldrich and Alfa Aesar, Bengaluru, India) and 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 using a mortar-pestle for 15 min with 1−2 mL of methanol added. The ground materials were analyzed by PXRD and thermal techniques to ascertain the formation of the adduct. The molecular salt exhibited a distinct PXRD pattern and melting behavior, but eutectics showed only a depression in the melting point compared to the parent materials.

Evaporative Crystallization. *1:1 PN−PABA Salt.* A ground mixture of PN (17 mg, 0.1 mmol) and PABA (14 mg, 0.1 mmol) was dissolved in 4 mL of isopropanol and left for slow evaporation at room temperature. Colorless needle crystals were obtained after a few days upon solvent evaporation. m.p. 111 °C.

1:1 PN−PHBA Salt. A ground mixture of PN (17 mg, 0.2 mmol) and PHBA (14 mg, 0.1 mmol) was dissolved in 5 mL of methanol and left for slow evaporation at room temperature. Colorless plate crystals were obtained after a few days upon solvent evaporation. m.p. 142 °C.

1:2 PN−PNBA Salt Cocrystal. A ground mixture of PN (17 mg, 0.1 mmol) and PNBA (17 mg, 0.1 mmol) was dissolved in 4 mL of isopropanol and left for slow evaporation at room temperature. Colorless plate crystals were obtained after a few days upon solvent evaporation. m.p. 186 °C; m.p. of 1:1 PN−PNBA: 160 °C.

1:1 PN−PCBA Salt. A ground mixture of PN (17 mg, 0.1 mmol) and PCBA (15 mg, 0.1 mmol) was dissolved in 3 mL of acetonitrile and left for slow evaporation at room temperature. Colorless needle crystals were obtained after a few days upon solvent evaporation. m.p. 151 °C.

1:1 PN−SAC Salt. A ground mixture of PN (17 mg, 0.1 mmol) and SAC (18 mg, 0.1 mmol) was dissolved in 5 mL of water and left for

DOI: 10.1021/acs.cgd.5b00546
Cryst. Growth Des. 2015, 15, 3474−3480

slow evaporation at room temperature. Colorless plate crystals were obtained after a few days upon solvent evaporation. m.p. 148 °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 were performed using CrysAlisPro (version 1.171.36.32),[81] and OLEX2 (version 1.2)[82] 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 normalized to neutron distances. All C−H atoms were fixed geometrically. The WinGX package[83] was used for final refinement and production of the 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. X'Pert HighScore Plus (version 1.0d)[84] 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 a 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[85] was used to prepare packing diagrams.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

PXRD patterns, IR spectra, and CIFs. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.5b00546.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ssctng@sscu.iisc.ernet.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

R.G. thanks the CSIR for Junior Research Fellowship and S.C. thanks the UGC for the Dr. D. S. Kothari Postdoctoral Fellowship. T.N.G. thanks the DST for the J. C. Bose Fellowship. We thank the Institute for providing infrastructural facilities.

■ REFERENCES

(1) Combs, G. F., Jr. *The Vitamins*, 4th ed.; Academic Press: UK, 2012.
(2) Snider, D. E., Jr. *Tubercle* **1980**, *61*, 191.
(3) Longo, J.; Franklin, K. J.; Richardson, M. F. *Acta Crystallogr., Sect. B: Struct. Sci. Online* **1982**, *38*, 2721.
(4) Cambridge Structural Database, ver. 5.35, ConQuest 1.16, www.ccdc.cam.ac.uk.
(5) Roy, J.; Mahmud, M.; Sobhan, A.; Aktheruzzaman, M.; Al-Farroque, M.; Ali, E. *Drug Dev. Ind. Pharm.* **1994**, *20*, 2157.
(6) Sinha, A. S.; Maguire, A. R.; Lawrence, S. E. *Cryst. Growth Des.* **2015**, *15*, 984.
(7) Cherukuvada, S.; Nangia, A. *Chem. Commun.* **2014**, *50*, 906.
(8) Surov, A. O.; Voronin, A. P.; Manin, A. N.; Manin, N. G.; Kuzmina, L. G.; Churakov, A. V.; Perlovich, G. L. *Mol. Pharmaceutics* **2014**, *11*, 3707.
(9) Jiang, L.; Huang, Y.; Zhang, Q.; He, H.; Xu, Y.; Mei, X. *Cryst. Growth Des.* **2014**, *14*, 4562.
(10) Delori, A.; Galek, P. T. A.; Pidcock, E.; Patni, M.; Jones, W. *CrystEngComm* **2013**, *15*, 2916.
(11) Sun, C. C. *Expert Opin. Drug Delivery* **2013**, *10*, 201.
(12) Almarsson, Ö; Peterson, M. L.; Zaworotko, M. J. *Pharm. Pat. Anal.* **2012**, *1*, 313.
(13) Brittain, H. G. *Cryst. Growth Des.* **2012**, *12*, 5823.
(14) Cherukuvada, S.; Nangia, A. *CrystEngComm* **2012**, *14*, 2579.
(15) Grobelny, P.; Mukherjee, A.; Desiraju, G. R. *CrystEngComm* **2011**, *13*, 4358.
(16) Cheney, M. L.; Weyna, D. R.; Shan, N.; Hanna, M.; Wojtas, L.; Zaworotko, M. J. *J. Pharm. Sci.* **2011**, *100*, 2172.
(17) Schultheiss, N.; Newman, A. *Cryst. Growth Des.* **2009**, *9*, 2950.
(18) Bhatt, P. M.; Azim, Y.; Thakur, T. S.; Desiraju, G. R. *Cryst. Growth Des.* **2009**, *9*, 951.
(19) Aitipamula, S.; Chow, P. S.; Tan, R. B. H. *CrystEngComm* **2009**, *11*, 1823.
(20) Ardila-Fierro, K. J.; André, V.; Tan, D.; Duarte, M. T.; Lancaster, R. W.; Karamertzanis, P. G.; Friščić, T. *Cryst. Growth Des.* **2015**, *15*, 1492.
(21) Friščić, T.; Lancaster, R. W.; Fábián, L.; Karamertzanis, P. G. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 13216.
(22) Black, S. N.; Collier, E. A.; Davey, R. J.; Roberts, R. J. *J. Pharm. Sci.* **2007**, *96*, 1053.
(23) Sarma, B.; Nath, N. K.; Bhogala, B. R.; Nangia, A. *Cryst. Growth Des.* **2009**, *9*, 1546.
(24) Braga, D.; Chelazzi, L.; Grepioni, F.; Dichiarante, E.; Chierotti, M. R.; Gobetto, R. *Cryst. Growth Des.* **2013**, *13*, 2564.
(25) Tao, Q.; Chen, J.-M.; Lu, T.-B. *CrystEngComm* **2013**, *15*, 7852.
(26) Kaur, R.; Lalithalakshmi, B. V.; Guru Row, T. N. G. *Cryst. Growth Des.* **2014**, *14*, 2614.
(27) Lemmerer, A.; Govindraju, S.; Johnston, M.; Motloung, X.; Savig, K. L. *CrystEngComm* **2015**, *17*, 3591.
(28) Cherukuvada, S.; Row, T. N. G. *Cryst. Growth Des.* **2014**, *14*, 4187.
(29) Prasad, K. D.; Cherukuvada, S.; Stephen, L. D.; Row, T. N. G. *CrystEngComm* **2014**, *16*, 9930.
(30) Prasad, K. D.; Cherukuvada, S.; Ganduri, R.; Stephen, L. D.; Perumalla, S.; Row, T. N. G. *Cryst. Growth Des.* **2015**, *15*, 858.
(31) Kaur, R.; Gautam, R.; Cherukuvada, S.; Row, T. N. G. *IUCrJ.* **2015**, *2*, 341.
(32) Friščić, T.; Trask, A. V.; Jones, W.; Motherwell, W. D. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7546.
(33) Shan, N.; Toda, F.; Jones, W. *Chem. Commun.* **2002**, 2372.
(34) Thakur, T. S.; Desiraju, G. R. *Cryst. Growth Des.* **2008**, *8*, 4031.
(35) Etter, M. C. *J. Phys. Chem.* **1991**, *95*, 4601.
(36) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120.
(37) Johnson, S. L.; Rumon, K. A. *J. Phys. Chem.* **1965**, *69*, 74.
(38) Stahl, P. H.; Wermuth, C. G., Eds. *Handbook of Pharmaceutical Salts, Properties, Selection and Use*; Wiley-VCH: New York, 2002.
(39) Bhogala, B. R.; Basavoju, S.; Nangia, A. *CrystEngComm* **2005**, *7*, 551.
(40) Childs, S. L.; Stahly, G. P.; Park, A. *Mol. Pharmaceutics* **2007**, *4*, 323.
(41) Cruz-Cabeza, A. J. *CrystEngComm* **2012**, *14*, 6362.
(42) Seaton, C. C.; Parkin, A. *Cryst. Growth Des.* **2011**, *11*, 1502.
(43) Elacqua, E.; Bučar, D.-K.; Henry, R. F.; Zhang, G. G. Z.; MacGillivray, L. R. *Cryst. Growth Des.* **2013**, *13*, 393.
(44) Seaton, C. C.; Munshi, T.; Williams, S. E.; Scowen, I. J. *CrystEngComm* **2013**, *15*, 5250.
(45) Cherukuvada, S.; Bolla, G.; Sikligar, K.; Nangia, A. *Cryst. Growth Des.* **2013**, *13*, 1551.
(46) Stilinović, V.; Kaitner, B. *Cryst. Growth Des.* **2012**, *12*, 5763.
(47) Bekö, S. L.; Schmidt, M. U.; Bond, A. D. *CrystEngComm* **2012**, *14*, 1967.
(48) Cheney, M. L.; Shan, N.; Healey, E. R.; Hanna, M.; Wojtas, L.; Zaworotko, M. J.; Sava, V.; Song, S.; Sanchez-Ramos, J. R. *Cryst. Growth Des.* **2010**, *10*, 394.

DOI: 10.1021/acs.cgd.5b00546
Cryst. Growth Des. 2015, 15, 3474−3480

(49) Li, Z. J.; Abramov, Y.; Bordner, J.; Leonard, J.; Medek, A.; Trask, A. V. *J. Am. Chem. Soc.* **2006**, *128*, 8199.
(50) Aakeröy, C. B.; Hussain, I.; Desper, J. *Cryst. Growth Des.* **2006**, *6*, 474.
(51) Boenigk, D.; Mootz, D. *J. Am. Chem. Soc.* **1988**, *110*, 2135.
(52) Perumalla, S. R.; Sun, C. C. *CrystEngComm* **2013**, *15*, 5756.
(53) Perumalla, S. R.; Sun, C. C. *CrystEngComm* **2012**, *14*, 3851.
(54) Hollingsworth, C. A.; Seybold, P. G.; Hadad, C. M. *Int. J. Quan. Chem.* **2002**, *90*, 1396.
(55) Bilski, P.; Li, M. Y.; Ehrenshaft, M.; Daub, M. E.; Chignell, C. F. *Photochem. Photobiol.* **2000**, *71*, 129.
(56) Lide, D. R., Ed. *CRC Handbook of Chemistry and Physics*, 90th ed. (CD-ROM Version 2010), CRC Press/Taylor and Francis: Boca Raton, FL, 2010.
(57) Becker, C.; Dressman, J. B.; Amidon, G. L.; Junginger, H. E.; Kopp, S.; Midha, K. K.; Shah, V. P.; Stavchansky, S.; Barends, D. M. *J. Pharm. Sci.* **2007**, *96*, 522.
(58) Williamson, D. S.; Nagel, D. L.; Markin, R. S.; Cohen, S. M. *Food Chem. Toxicol.* **1987**, *25*, 211.
(59) van Eijck, B. P.; Kroon, J. *Acta Crystallogr., Sect. B: Struct. Sci. Online* **2000**, *56*, 535.
(60) Aitipamula, S.; Chow, P. S.; Tan, R. B. H. *CrystEngComm* **2014**, *16*, 3451.
(61) Qiu, Y.; Chen, Y.; Zhang, G. G. Z., Eds. *Developing Solid Oral Dosage Forms. Pharmaceutical Theory and Practice*; Academic Press: New York, 2009.
(62) Pop, M.; Sieger, P.; Cains, P. W. *J. Pharm. Sci.* **2009**, *98*, 1820.
(63) Harrison, W. T. A.; Yathirajan, H. S.; Bindya, S.; Anilkumar, H. G.; Devaraju. *Acta Crystallogr., Sect. C: Struct. Chem. Online* **2007**, *63*, o129.
(64) Chierotti, M. R.; Gaglioti, K.; Gobetto, R.; Braga, D.; Grepioni, F.; Maini, L. *CrystEngComm* **2013**, *15*, 7598.
(65) Desiraju, G. R.; Vittal, J. J.; Ramanan, A. *Crystal Engineering: A Textbook*; World Scientific: Singapore, 2011.
(66) Clarke, H. D.; Arora, K. K.; Bass, H.; Kavuru, P.; Ong, T. T.; Pujari, T.; Wojtas, L.; Zaworotko, M. J. *Cryst. Growth Des.* **2010**, *10*, 2152.
(67) Silverstein, R. M.; Webster, F. X.; Kiemle, D. J. *Spectrometric Identification of Organic Compounds*; John Wiley & Sons: Hoboken, NJ, 2005.
(68) Zhang, S.; Harasimowicz, M. T.; de Villiers, M. M.; Yu, L. *J. Am. Chem. Soc.* **2013**, *135*, 18981.
(69) Stahly, G. P. *Cryst. Growth Des.* **2009**, *9*, 4212.
(70) Davis, R. E.; Lorimer, K. A.; Wilkowski, M. A.; Rivers, J. H.; Wheeler, K. A.; Bowers, J. *ACA Trans.* **2004**, *39*, 41.
(71) Bi, M.; Hwang, S.-J.; Morris, K. R. *Thermochim. Acta* **2003**, *404*, 213.
(72) Sakata, Y.; Tanabe, E.; Sumikawa, T.; Shiraishi, S.; Tokudome, Y.; Otsuka, M. *Int. J. Pharm.* **2007**, *335*, 12.
(73) Žalak, S.; Khan, M. Z. I.; Gabelica, V.; Tudja, M.; Meštrović, E. *Chem. Pharm. Bull.* **1999**, *47*, 302.
(74) Weng, T. H.; Williams, M. G. U. S. Patent 5512300, 1996.
(75) Blomberg, B.; Spinachi, S.; Fourie, B.; Laing, R. *Bull. World Health Organ.* **2001**, *79*, 61.
(76) Wertheimer, A. I.; Morrison, A. *Pharm. Ther.* **2002**, *27*, 44.
(77) Sanz, G.; Fuster, V. *Nat. Clin. Pract. Cardiovasc. Med.* **2008**, *6*, 101.
(78) Kumar, V.; Prasad, B.; Singh, S. *Drug Disc. Today: Ther. Strategies* **2008**, *5*, 63.
(79) http://apps.who.int/medicinedocs/pdf/s6172e/s6172e.pdf.
(80) http://apps.who.int/iris/bitstream/10665/93142/1/EML_18_eng.pdf?ua=1.
(81) *CrysAlisPro*, ver. 1.171.36.32; Agilent Technologies UK Ltd: Yarnton, England, 2011.
(82) Dolomanov, O. V.; Blake, A. J.; Champness, N. R.; Schröder, M. *J. Appl. Crystallogr.* **2003**, *36*, 1283.
(83) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.
(84) *X'Pert HighScore Plus, The Complete Powder Analysis Tool*; PANalytical B.V.: Almelo, the Netherlands, 2003.
(85) Barbour, L. J. *X-Seed, Graphical Interface to SHELX-97 and POV-Ray, Program for Better Quality of Crystallographic Figures*; University of Missouri-Columbia: Columbia, MO, USA, 1999.

DOI: 10.1021/acs.cgd.5b00546
Cryst. Growth Des. 2015, 15, 3474−3480