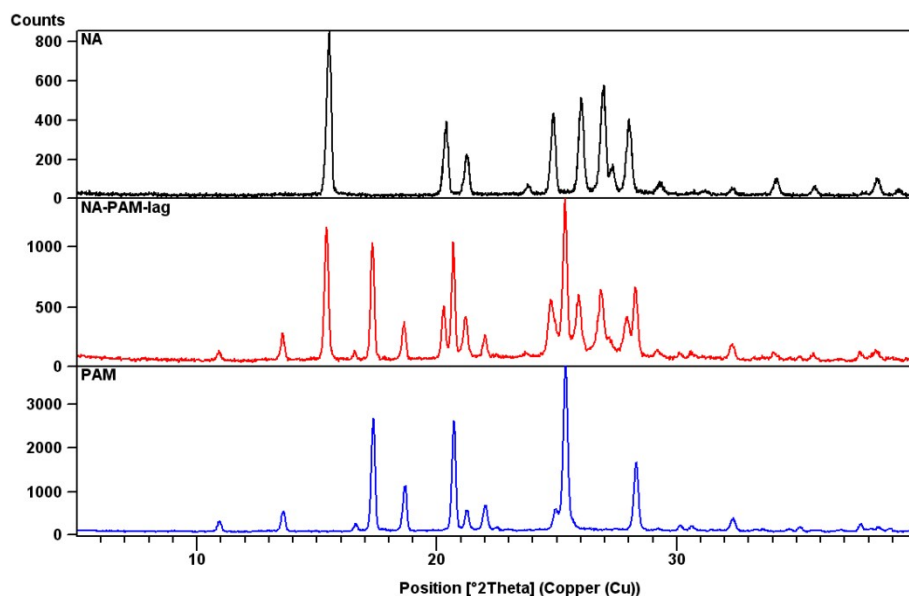


Electronic Supplementary Information†

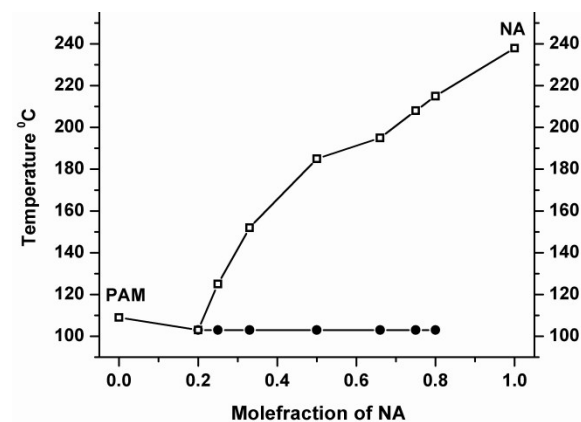
Manifestation of Cocrystals and Eutectics among structurally related molecules: Towards understanding the factors that control their formation

Ramesh Ganduri, Suryanarayan Cherukuvada, Sounak Sarkar and Tayur N. Guru Row*
Solid State and Structural Chemistry Unit, Indian Institute of Science, Bengaluru 560012, India

*Email: ssctng@sscu.iisc.ernet.in

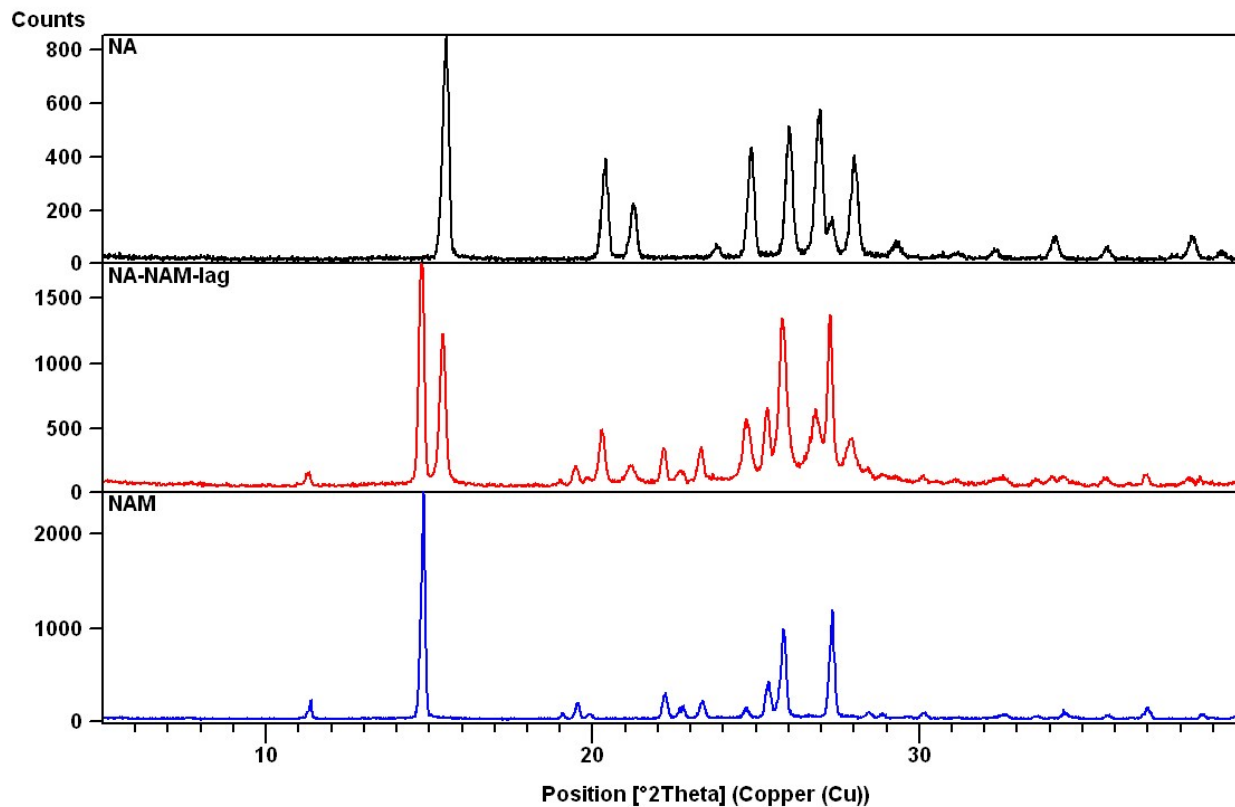


(a)

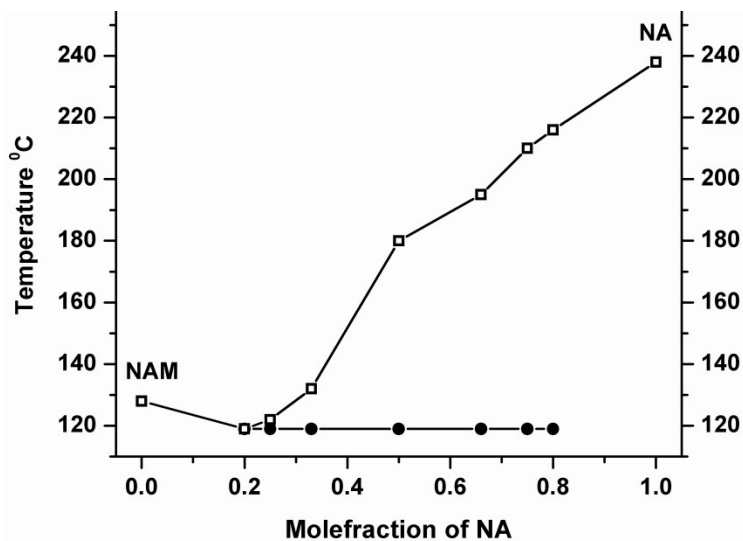


(b)

Figure S1 (a) PXRD pattern of 1:1 NA–PAM ground material (red) does not exhibit any new or distinct peaks characteristic of cocrystal formation and manifests as a summation of its parent components, NA (black) & PAM (blue). **(b)** Binary phase diagram analysis shows that the combination shows a eutectic point at 103 °C with a composition of 1:4. Solidus points are shown as filled circles and liquidus points as open squares.

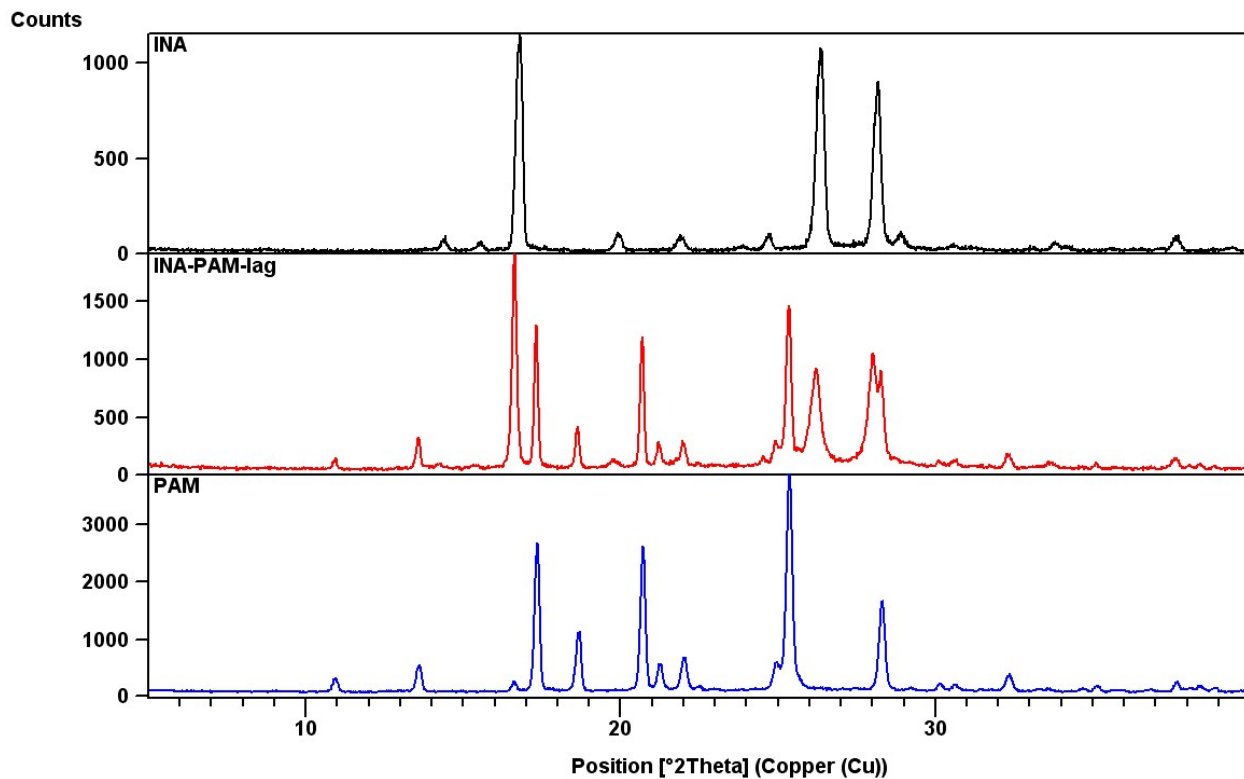


(a)

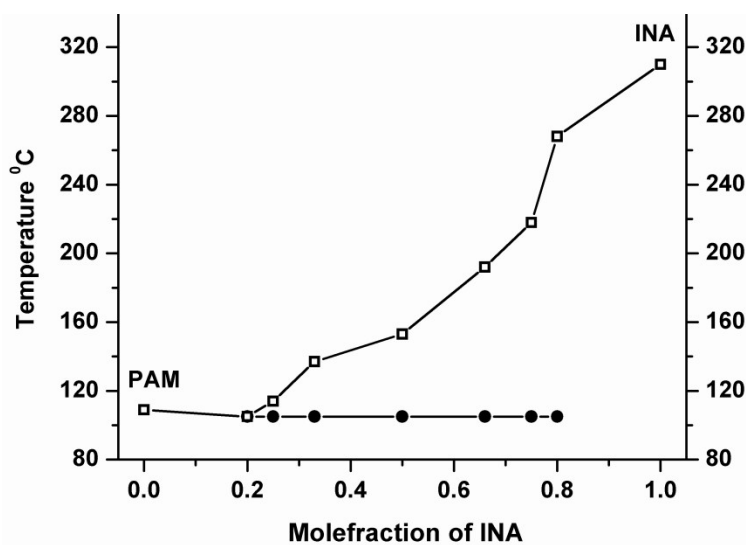


(b)

Figure S2 (a) PXR D pattern of 1:1 NA–NAM ground material (red) does not exhibit any new or distinct peaks characteristic of cocrystal formation and manifests as a summation of its parent components, NA (black) & NAM (blue). **(b)** Binary phase diagram analysis shows that the combination shows a eutectic point at 119 °C with a composition of 1:4.

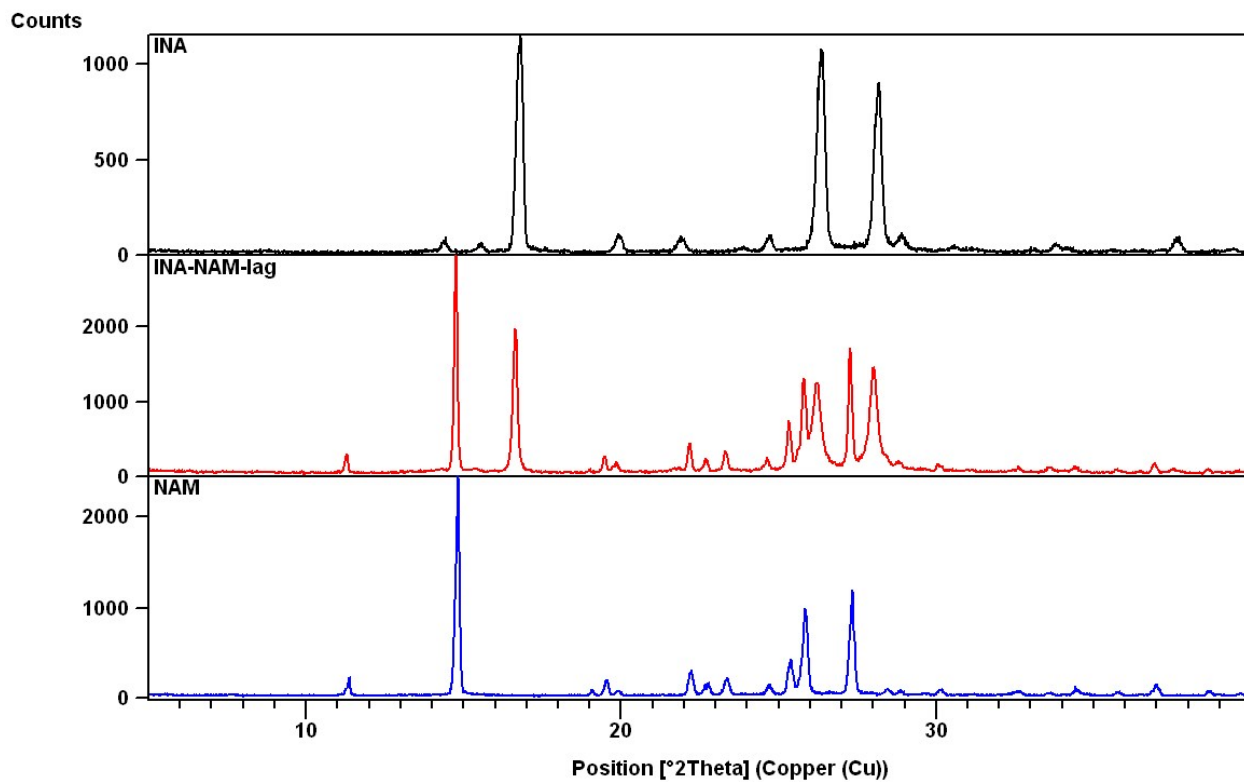


(a)

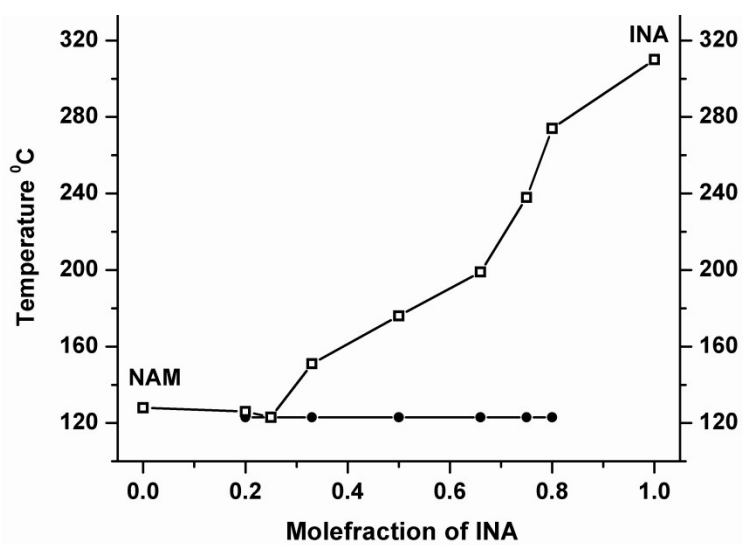


(b)

Figure S3 (a) PXR D pattern of 1:1 INA–PAM ground material (red) does not exhibit any new or distinct peaks characteristic of cocrystal formation and manifests as a summation of its parent components, INA (black) & PAM (blue). **(b)** Binary phase diagram analysis shows that the combination shows a eutectic point at 106 °C with a composition of 1:4.

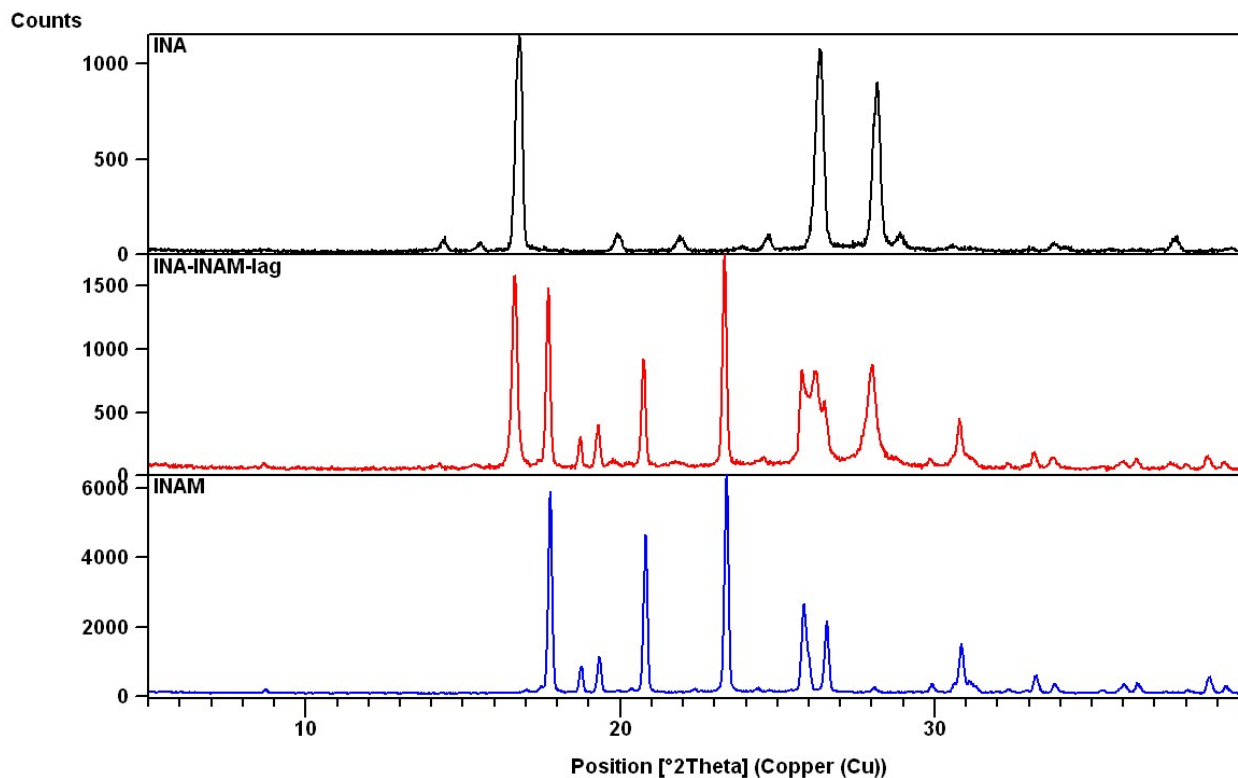


(a)

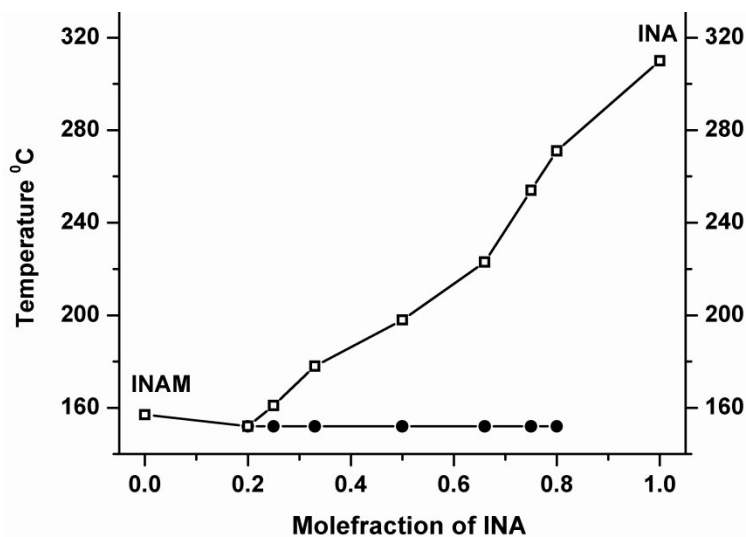


(b)

Figure S4 (a) PXR D pattern of 1:1 INA–NAM ground material (red) does not exhibit any new or distinct peaks characteristic of co-crystal formation and manifests as a summation of its parent components, INA (black) & NAM (blue). **(b)** Binary phase diagram analysis shows that the combination shows a eutectic point at 125 °C with a composition of 1:3.



(a)



(b)

Figure S5 (a) PXR D pattern of 1:1 INA–INAM ground material (red) does not exhibit any new or distinct peaks characteristic of cocrystal formation and manifests as a summation of its parent components, INA (black) & INAM (blue). **(b)** Binary phase diagram analysis shows that the combination shows a eutectic point at 153 °C with a composition of 1:4.

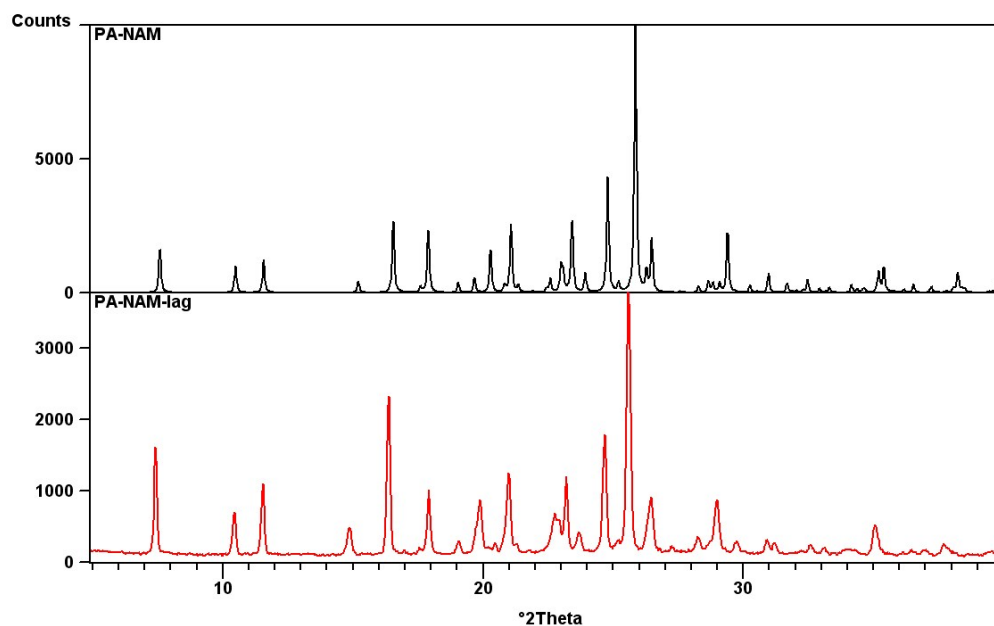


Figure S6 PXR D pattern of 1:1 PA–NAM ground material (red) exhibits complete match with the calculated diffraction pattern of 1:1 cocrystal (black). At higher angles, calculated (100 K) and experimental (298 K) diffraction peaks are slightly offset to each other due to temperature difference.

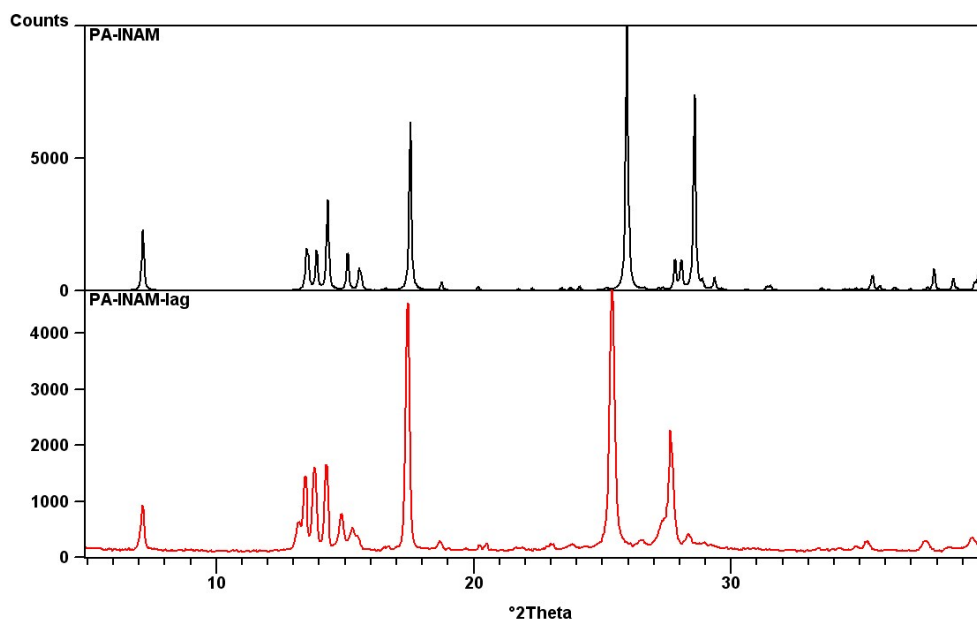
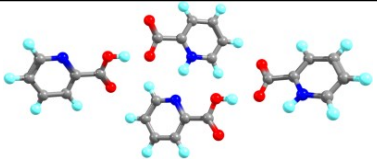
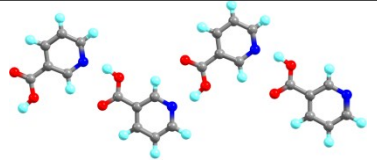
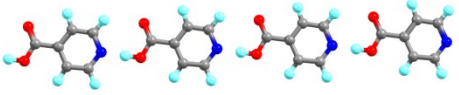
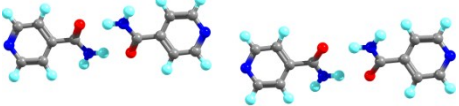
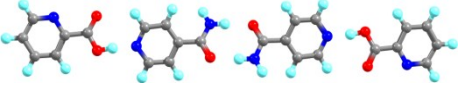
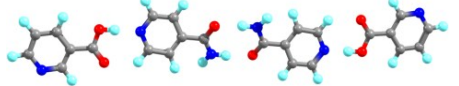
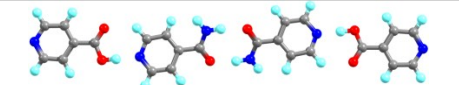


Figure S7 PXR D pattern of 1:1 PA–INAM ground material (red) exhibits complete match with the calculated diffraction pattern of 1:1 cocrystal (black).

DFT calculations: We have considered combinations of isonicotinamide with all three pyridine carboxylic acids as representatives to understand the cocrystal/eutectic-forming nature of these structurally related entities. Further, the fact that isonicotinamide forms a cocrystal with pyrazinoic acid (containing pyridine-carboxylic acid functionality)¹ gives credence to the selection. Since the primary supramolecular units for both parent components and combinations are tetrameric units, we have calculated energies of homo- and hetero-tetramers. The starting geometry of tetrameric units in case of parent components was taken from their respective crystal structures reported in the Cambridge Structural Database (CSD refcodes: picolinic acid – PICALA02; nicotinic acid – NICAC02; isonicotinic acid – ISNICA; isonicotinamide – EHOWIH).² It is to be noted that the crystal structure of PA is a spatial average of neutral molecules and zwitterions arranged alternately rendering the hydrogen to have 50% occupancy on carboxylic oxygen and pyridine nitrogen respectively.³ For the cocrystal combination PA-INAM, the most robust tetrameric motif consisting of hetero acid-pyridine dimer and homo amide-amide dimer^{1,4} was taken from the crystal structure obtained in this work whereas in eutectic combination of NA-INAM and INA-INAM, tetrameric motif similar to that of PA-INAM was considered as the most probable starting geometry. The initial geometries of eutectic combinations NA-INAM and INA-INAM, and also the parent acid PA (due to biasness in the structure caused due to disorder in proton position), were optimized using the M062X/6-311+ (d, p) level⁵ of theory in the Gaussian 09 package.⁶ For other cases (NA, INA, INAM, PA-INAM), the crystalline geometry was considered in which their X-H (X=C,N,O) bond lengths were constrained to the values reported by neutron diffraction experiments in literature.⁷ The basis set superposition error (BSSE) corrected energies using the counterpoise method⁸ was estimated for the all the individual tetramers (both optimized and crystalline geometry). The energy calculations were performed at wB97xD/cc-pvDZ^{9,10} level of theory. The obtained stabilization energy values of all tetrameric motifs are given in Table 1.

Table 1 : Calculated stabilization energy values of tetrameric motifs.

Compound	Tetrameric motif	Stabilization energy (kJ/mol)
PA*		-238.45
NA†		-169.08
INA†		-192.42
INAM†		-145.23
PA-INAM†		-175.18
NA-INAM*		-183.43
INA-INAM*		-181.13

* Indicates optimized geometry.

† Indicates crystalline geometry with X-H bond lengths constrained to neutron bond lengths.

References :

1. K. D. Prasad, S. Cherukuvada, R. Ganduri, L. D. Stephen, S. Perumalla and T. N. G. Row, *Cryst. Growth Des.*, 2015, **15**, 858.
2. Cambridge Structural Database, ver. 5.37, ConQuest 1.18, <http://www.ccdc.cam.ac.uk/>
3. H. Hamazaki, H. Hosomi, S. Takeda, H. Kataoka and S. Obha, *Acta Crystallogr.*, 1998, **C54**, IUC9800049.
4. C. B. Aakerøy, A. M. Beatty and B. A. Helfrich, *J. Am. Chem. Soc.*, 2002, **124**, 14425.

5. Y. Zhao and D. G. Truhlar, *Theor. Chem. Account.*, 2008, **120**, 215.
6. Frisch, M., Trucks, G., Schlegel, H. B., Scuseria, G., Robb, M., Cheeseman, J., Scalmani, G., Barone, V., Mennucci, B. & Petersson, G. (2009). Inc., Wallingford, CT 200), Gaussian 09 package, http://www.gaussian.com/g_tech/g_ur/m_citation.htm
7. F. H. Allen and I. J. Bruno, *Acta Crystallogr.*, 2010, **B66**, 380.
8. S. F. Boys and F. Bernardi, *Mol. Phys.*, 1970, **19**, 55.
9. J. D. Chai and M. H. Gordon, *Phys. Chem. Chem. Phys.*, 2008, **10**, 6615.
10. T. H. Dunning, Jr., *J. Chem. Phys.*, 1989, **90**, 1007.

