Polymorph discovery by controlling the self-association in solution

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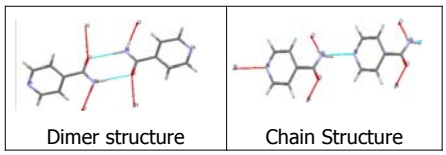
Introduction

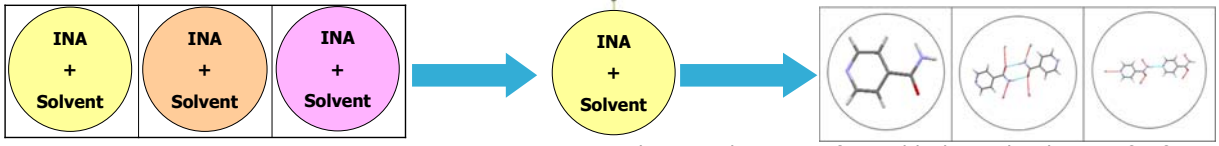
- We are working to establish a systematic method for the discovery and reproducible preparation of new polymorphs based on speciation.
- We believe that the self-association is a key factor in polymorph crystallization.
- The crystal nucleation of isonicotinamide (INA) is a most interesting process because of the strongly differing packing of form II and the other forms. While metastable form (Form I, III, IV and V) arrange in head-to-tail chains of INA molecules, stable forms (Form II) arranges in dimers in which structures the pyridine group is not hydrogen bonding. Therefore we performed a study on the crystallization behavior of isonicotinamide from different solvents.



Experimental method

- The first step is to identify the different type of association of INA in solution using different solvent. In the second step the effect of association on the crystallization behavior of INA was studied.

Step I: Study of different association in INA solution



Clear solution of INA in different solvents

In-situ Raman and FTIR analysis

Preferential hydrogen bonding motifs of INA in solutions which was identified after Raman and FTIR analysis

Step II: Effect of association on the Crystallization of INA

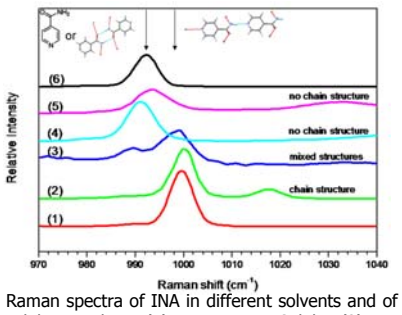
Crystallization of INA solution which has different self associated INA

CRYSTALLINE Setup Multiple reactor system

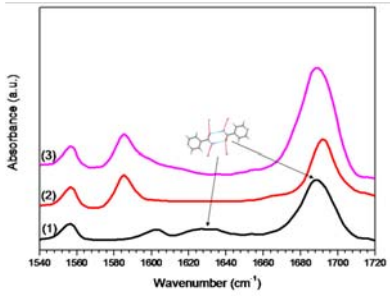
Crystallization outcome of INA. specific solvents lead to specific polymorphic forms.

Results

- The difference in association within the crystal structure of the stable and metastable forms makes an excellent opportunity to study the effect of association in solution on the crystallization behavior since this association in solution can also be analyzed using Raman and IR.



Raman spectra of INA in different solvents and of solid samples. (1) Form IV Solid; (2) In nitrobenzene; (3) In methanol; (4) In acetone; (5) In chloroform (6) Form II solids.



FTIR spectra of solutions of INA in (1) methanol, (2) nitromethane and (3) chloroform.

Spectroscopy results for the association of INA in solvents and the form obtained from crystallization experiments

Solvents	HB[i]	Raman	FTIR	Summary	Crystalli-zation
		Chain	Dimer		
Nitrobenzene	SA	Yes	No	Chain	IV
Nitromethane	SA	Yes	No	Chain	I
Acetone	WA	No	Yes	Dimer	II
Dioxane	WA	No	Yes	Dimer	II
Chloroform	WA	No	No	Single molecule	VI (New)
2-Propanol	SD	Yes	Yes	Chain/ Dimer	II
Methanol	SD	Yes	Yes	Chain/ Dimer	II
Ethanol	SD	Yes	Yes	Chain/ Dimer	II

[i] *Hydrogen bonding (HB) capabilities of the solvent: Strong acceptor (SA), weak acceptor (WA), strong donor (SD).*

Conclusion

- We demonstrated that the structural outcome of the crystallization process of INA is directed by the association and self-association processes in solutions which are largely influenced by the hydrogen bonding capacity of the solvent.
- We can now explore the solvent-solute phase in a more rigorous way and can identify the different self association processes going on in that solvent.
- Not only the published forms of INA were found, but also new form was identified.
- This new systematic method could also be applied to discover new multicomponent crystals such as salts and co-crystals.

Reference: S. A. Kulkarni, E. S. McGarrity, H. Meekes and J. H. ter Horst, Chemical Communications, 2012, 48, 4983-4985.

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