# Electronic Supplementary Information (ESI)

# Isonicotinamide self-association: the link between solvent and polymorph nucleation

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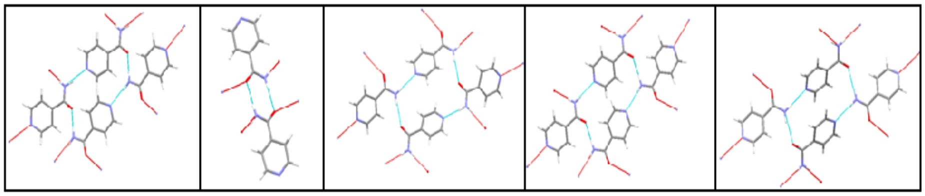
## 1. The Hydrogen bond motifs in the Isonicotinamide crystal structures



**Form I** **Form II** **Form III** **Form IV** **Form V**

Figure 1: The hydrogen bond motifs in the INA crystal structures. While form I, III, IV and V arrange in head-to-tail chains of INA molecules, form II arranges in INA dimers in which structure the pyridine group is not hydrogen bonding.

## 2. Raman Spectra of different forms of Isonicotinamide

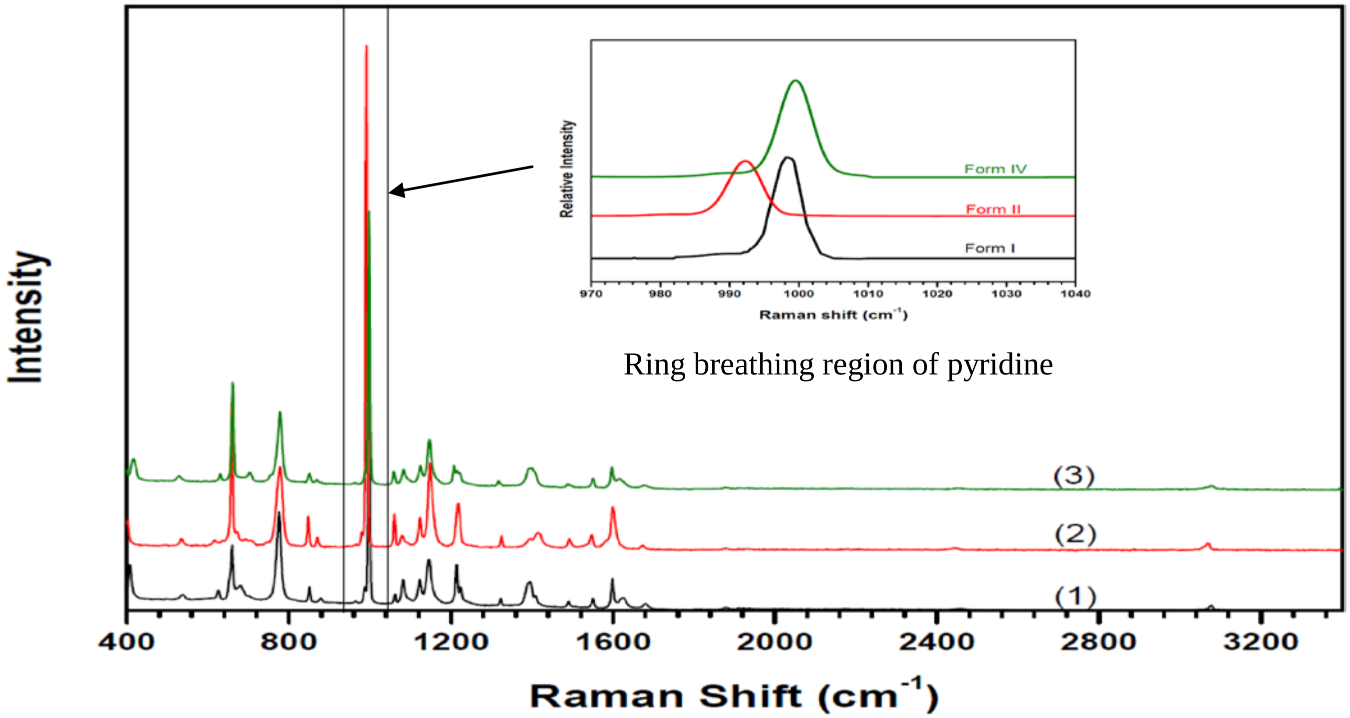


Figure 2: Raman spectra of solids samples of Isonicotinamide polymorphs, (1) Form I (2) Form II (3) Form IV.

## 3. FTIR Spectra of different forms of Isonicotinamide

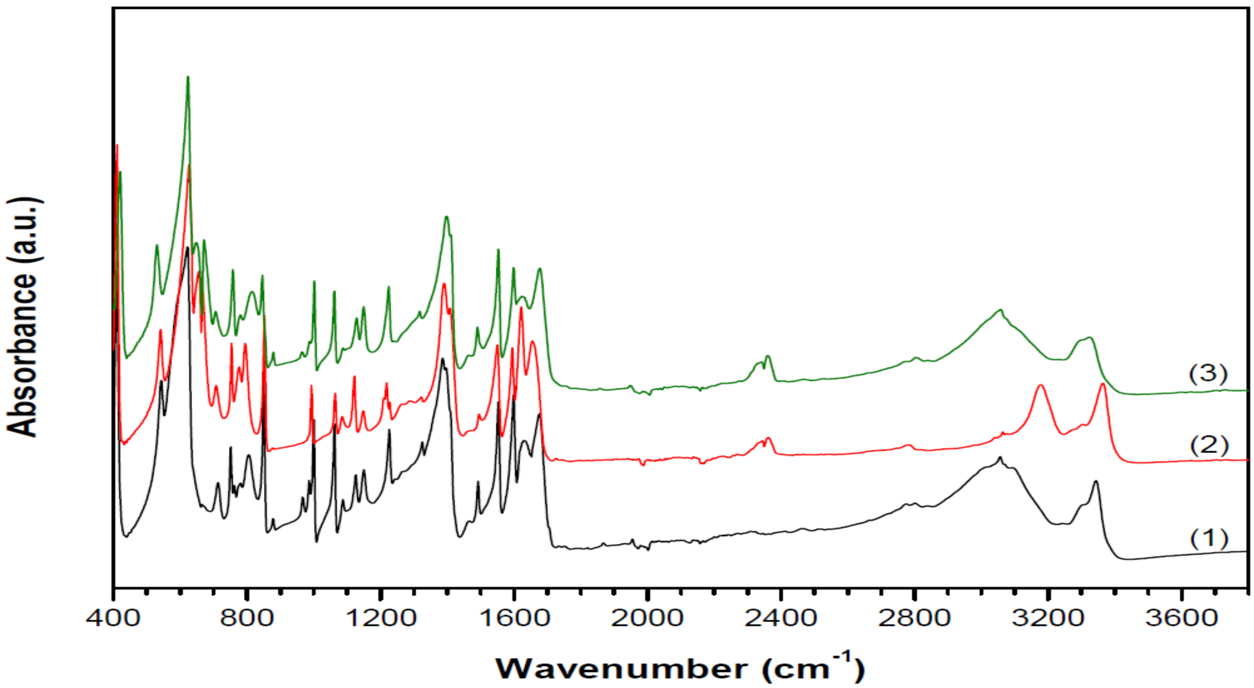


Figure 3: FTIR spectra of solids samples of Isonicotinamide polymorphs, (1) Form I (2) Form II (3) Form IV.

## 4. PXRD data of different forms of Isonicotinamide

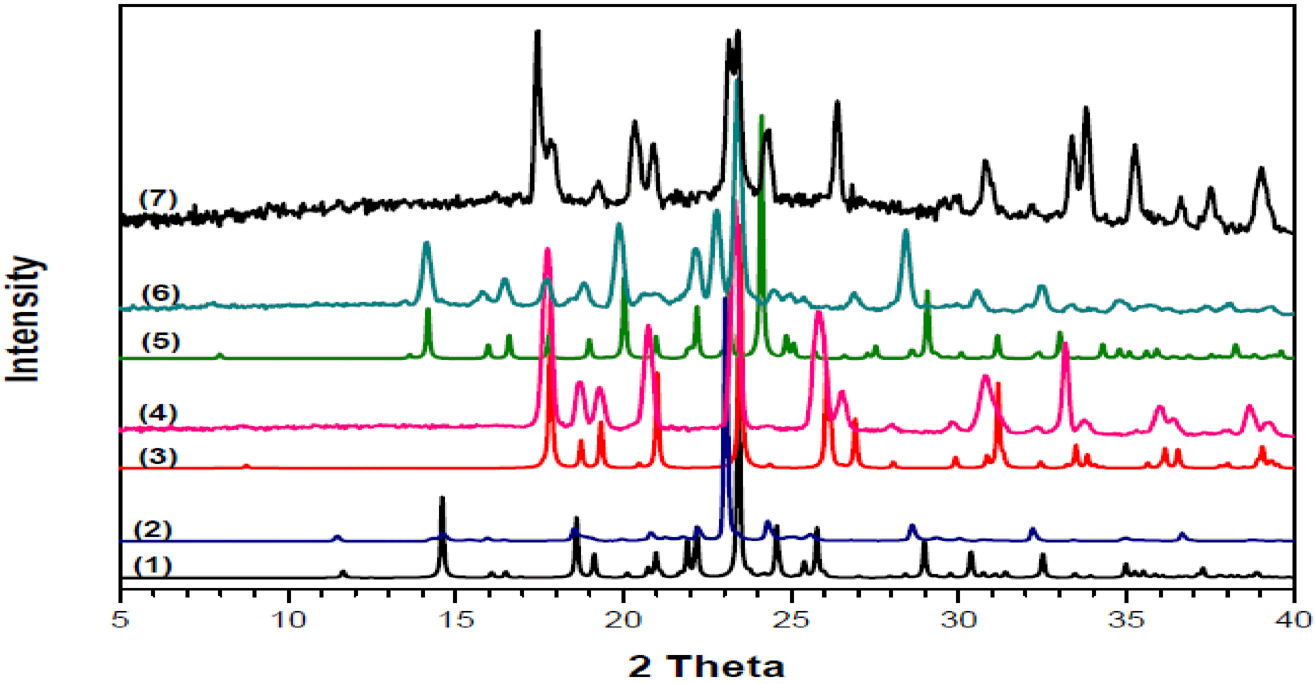


Figure 4: PXRD of solids samples of Isonicotinamide polymorphs, (1) Form I_CSD (EHOWIH.search1.cif) (2) Form I Solids (3) Form II_CSD (EHOWIH2.search1.cif) (4) Form II Solids (5) Form IV_CSD (isonicotinamid_form IV.cif) (6) Form IV Solids (7) New form VI Solids.

The single crystal data have smaller d-values than the powder data. This suggests that the single crystal data have been obtained at low temperatures, which is quite commonly done in order to diminish the thermal motion of the atoms. The deviations in shift for various individual peaks are due to the anisotropic contraction of the unit cell on lowering the temperature.

## 5. Experimental details

The INA solubility was measured to be 70, 103, 44, 18, 3 and 11 mg/ml solvent in ethanol, methanol, 2-propanol, dioxane, nitromethane and nitrobenzene, respectively at a temperature of 25 °C. The cooling crystallization experiments (3ml, Crystalline, Avantium, Amsterdam) were carried out using different concentrations of INA in methanol (100 to 135 mg/ml), ethanol (70 to 105 mg/ml), 2-propanol (40 to 90 mg/ml), nitromethane (2, to 10 mg/ml) and nitrobenzene (10 to 26 mg/ml). A Hololab series 5000 Raman spectroscopy (Kaiser Optical System, Inc.) and a NIR-FTIR spectrometer (Bruker Optics GmbH, Germany) facilitated the recording of Raman and IR spectra. The starting suspension was heated to 60°C to establish a clear solution and then cooled down to 5°C with different cooling rates while stirring (700 rpm). The polymorphic forms were identified by in situ Raman spectroscopy[1] directly after the formation of the first crystals as well as by XRPD afterwards.

## 6. Simulation details

In the quantum mechanical calculations (Amsterdam density functional theory code ADF-2010.1)[2], the molecules were treated using the B3YLP-D3 dispersion corrected exchange correlation functional with the TZ2P basis set. Association energies $\Delta E = 2E_{AB} - (E_A + E_B)$ were calculated, where $E_{AB}$ is the geometry optimized energy of species $A$ and $B$ in vacuum, and $E_A$ is the energy of a single molecule in vacuum. The hydrogen bonding strengths were then computed by subtracting the dispersion correction energies.

**References:**

1. T. Ono, J. H. ter Horst and P. J. Jansens, *Crystal Growth & Design*, 2004, **4**, 465-469.
2. C. Fonseca Guerra, J. G. Snijders, G. te Velde and E. J. Baerends, *Theoretical Chemistry Accounts*, 1998, **99**, 391-403.