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Predicting Nucleation of Isonicotinamide from the Solvent – Solute Interactions of Isonicotinamide in Common Organic Solvents

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Abstract

The interactions of isonicotinamide (INA) with seven common solvents (acetic acid, acetonitrile, acetone, chloroform, ethyl acetate, and methanol) have been studied to examine solute – solvent effects on the nucleation of INA from these solvents. In a simple model of 1:1 solute – solvent interactions, the strongest INA – solvent interaction is with acetic acid (binding energy, ΔE_{bind} = -64.05 kJ mol^{-1}) and the weakest is with chloroform (ΔE_{bind} = -24.85 kJ mol^{-1}). This arises since acetic acid and INA form a hydrogen bonding motif containing two moderate strength N-H···O hydrogen bonds, while chloroform and INA have a single weak C-H···O hydrogen bond. Taking acetic acid, chloroform, and methanol, the solvents with strongest, weakest and intermediate strength INA – solvent binding energy, the solvation of INA was studied to compare to the 1:1 model. Acetic acid has the strongest binding energy (-872.24 kJ mol^{-1}) and solvation energy (-341.20 kJ mol^{-1}) with chloroform binding energy (-517.72 kJ mol^{-1}) and solvation energy

(-199.05 kJ mol^{-1}). Methanol has intermediate binding energy (-814.19 kJ mol^{-1}) and solvation energies (-320.81 kJ mol^{-1}). These results further confirm the recent the findings which indicate that the key trends in solvent – solute interactions can be determined from a simple and efficient 1:1 dimer model and can be used to predict ease of nucleation with stronger binding energies correlating to slower, more difficult nucleation. A limit of this model is revealed by considering alcohol and acid solvents with longer alkyl chains.

Introduction

Crystallisation is defined as the phase change in which a crystalline material product is obtained from a solution.[1] Crystallisation is employed widely as a method of separation, isolation, and purification of molecules and is an important step in the generation of over 90% of all active pharmaceutical ingredient,[2] as well as for other fine chemicals and solid state materials. Crystallisation is generally thought to occur in two stages: nucleation and crystal growth.

Kashchiev defined nucleation as "the process of random generation of those nanoscopically small formations of the new phase that have the ability for irreversible overgrowth to macroscopic sizes".[3] The crystal growth step is the process of the growth of these nanoscopic nuclei formed by nucleation into macroscopic crystals. Thus, gaining a better understanding of the fundamentals of nucleation is crucial in the formation and control of producing crystalline material.

Currently the nucleation process is very poorly understood due to the difficulty in observing it.[4] This is related to (1) the rate at which the critical nuclei are formed, (2) their small size ranging from a few to a few hundred molecules in size and (3) the generally stochastic nature of the

process.[5] This can result in problems in crystallisation processes in controlling the form, shape and size of crystals,[6] where the choice of solvent can also have a substantial impact.[7–11]

The lack of understanding of the nucleation process means that crystallisation processes are generally developed by an empirical approach. This can lead to problems in control of the final product obtained. For example, in 1998 the formation of a new, undesired polymorph caused production delays in the HIV protease inhibitor Norvir.[12] The formation of this new polymorph had less than 50% bioavailability compared to the original polymorph and caused considerable financial loses to the manufacturer.[13] This is a potential problem for many crystallisation processes. For example, a recent report that involved polymorphic screening of 245 molecules found that approximately 50% exhibited polymorphic behaviour, while 90% showed multiple solid state forms including solvates, hydrates and amorphous forms.[14]

Computational modelling of molecular interactions can give detailed insight into the microscopic properties that are crucial to the nucleation of a molecule from a solvent. Experiments can measure macroscopic properties, such as nucleation time, metastable zone widths and interfacial energies, while modelling can be used to probe atomic level interactions that act as descriptors of these processes to screen for nucleation in different solvents. In several papers from Rasmuson and co-workers,[8–11] a computational approach to develop such descriptors to deepen the understanding of experimental nucleation behaviour has been presented. A model of the solvated molecule of interest is studied using density functional theory (DFT) and a simple model of a 1:1 solute – solvent heterodimer is found to reproduce the primary findings of the more complicated solvation shell model and rationalise the experimentally determined nucleation process, as measured by the induction times in different solvents. Six compounds have been reported to date: methyl, ethyl and butyl ester of *p*-hydroxybenzoic acid, salicylic acid, risperidone and

tolbutamide.[8–11] Generally, there is a correlation between the computed DFT 1:1 solute – solvent binding energies and the ease of nucleation measured experimentally. However, in their most recent work on tolbutamide,[11] Zeglinski et al demonstrated that tolbutamide can show deviations from this trend when toluene is used as the solvent. This may show up a limitation of this model, which we will further discuss. The deviation was attributed to the tolbutamide forming crystal-incompatible conformers in toluene solution due to intramolecular H-bonding, which inhibits the nucleation in comparison to solvents where crystal-compatible conformers can form.

Also within their work, Rasmuson and co-workers discuss a correlation between vibrational spectra and the strength of the solute – solvent interactions. [9,10] When comparing the Raman spectra of the solute in solution to the solid state spectra, they discovered that the magnitude of the shift of the carbonyl stretching mode of the solute within solvent increases with increasing solute – solvent interaction strength.

Generally, stronger solute – solvent interactions in both the 1:1 dimer and solvation shell models are consistent with longer measured nucleation times and, hence, increased difficulty in nucleating the solute. To further advance this method, a similar computational approach to calculate the binding energies of the isonicotinamide molecule (INA, Figure 1) in seven common organic solvents has been employed and, hence, used to predict the ease of nucleation of isonicotinamide from these solvents. Vibrational spectra of the solute – solvent interactions were also calculated and the shift in INA's carbonyl stretching mode was compared to the interaction strength to see if the correlation observed by Rasmuson's group [9,10] can be extended to computed vibrational spectra (in addition to experimental spectra). Isonicotinamide was chosen due to its increased complexity compared to salicylic acid, with an amine replacing the hydroxyl group of the acid of salicylic acid. This changes the possible hydrogen bonding motifs since the R-NH_2

contains two hydrogen bonding donors and one hydrogen bonding acceptor, whereas the R-OH has only one hydrogen bonding donor but two hydrogen bonding acceptors. The pyridyl nitrogen also adds another potential hydrogen bonding site compared to the phenyl ring of salicylic acid.

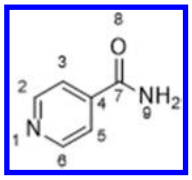


Figure 1: Atomic structure of isonicotinamide with atoms numbered for identification of bonds and torsion angles.

Isonicotinamide is a common model organic molecule widely used in crystal engineering, particularly in co-crystallisation.[15–17] The nucleation of its different polymorphs has been well studied,[18–22] however, the nucleation kinetics in different organic solvents has not been investigated in great detail, with only ethanol having been studied to date.[23] It has five known polymorphs,[24–26] which have been well studied. Kulkarni *et al.*[19] computed 1:1 solvent – isonicotinamide binding energies of isonicotinamide in order to understand which polymorph forms in which solvent. They found that in a hydrogen bond donating solvent, for example methanol, the solvent most favourably interacted with the NH_2 group of isonicotinamide (-5.12 kJ mol^{-1} per hydrogen bond)[18] and had no favourable interactions with the nitrogen in the pyridyl ring. In these solvents the chain motif of polymorphs forms I or IV[a] is most favourable. In hydrogen bond accepting solvents, however, the strongest isonicotinamide – solvent interaction was found with the nitrogen of the pyridyl ring (-16.8 kJ mol^{-1}) and so isonicotinamide molecules will form hydrogen bonded dimers as opposed to chains, thus favouring form II.

[a] For the naming of polymorphs I and II of isonicotinamide, the Aakeröy's naming system is followed.[24]

These results corresponded with the available experimental data.[25] To date, however, this remains the only work to study polymorph prediction using a simple solute – solvent interaction model; the majority of predictive polymorph work uses other methods, most commonly examining the crystal lattice energies.[27–29] However, irrespective of the stability of the different INA polymorphs, it is the fundamental isonicotinamide – solvent interactions that determine the nucleation time out of a solvent.

The aims of the present work are, therefore, to investigate the solute – solvent interactions of isonicotinamide in seven different organic solvents, that is, acetic acid, acetone, acetonitrile, chloroform, ethanol, ethyl acetate, and methanol. The binding energy of a single INA molecule with one solvent molecule (for each solvent) was studied to determine the most favourable interaction site. The solvation of isonicotinamide was also examined, which involved taking a single isonicotinamide molecule and surrounding it with enough solvent molecules to consider the molecule solvated. From a technical perspective, the influence of the DFT functional and the inclusion of explicit van der Waals interaction on the calculated binding energies was considered. Computed vibrational spectra were determined for isonicotinamide in each solvent to examine if the strength of the isonicotinamide – solvent interaction correlates with shifts in the position of the isonicotinamide carbonyl stretching peak. The influence of increasing alkyl side chains on the binding energies of a series of acids and alcohols was also studied to determine how increasing the side chain away from the interacting acid/alcohol group affected the interaction strengths.

The results of this paper show that isonicotinamide should nucleate most easily in chloroform, followed by acetonitrile, ethyl acetate, acetone, ethanol, methanol, and most difficult in acetic acid. This is in agreement with the available solvation data, in which INA dissolves most easily

in methanol and less so in chloroform. The simple 1:1 solvent – solute interaction model is therefore able to function as a reliable descriptor of solvation of isonicotinamide and other molecules. One limit to this model is when a series of alcohols and acids with long alkyl chains is considered, where the dimer model predicts very similar binding energies but in reality steric effects arising from the alkyl chains would reduce the strength of interaction between INA and the solvent.

Methodology

Turbomole code (version 6.4)[30] was used to perform all calculations using the following DFT hybrid functionals:

B3-LYP (which uses a mix of 80% LDA exchange, 72 % B88 exchange, and 20% Hartree-Fock exchange; and a mix of LDA (VWN) and LYP correlation)[31,32]

PBE0 (which uses a mix of 75% PBE exchange and 25 % Hartree-Fock exchange; and PBE correlation).[33]

The van der Waals (vdW) interactions were also included using the dispersion 3 (D3) model.[34] This allowed for the influence of the vdW interactions on the computed binding energies to be investigated. Also a direct comparison of two different hybrid DFT functionals was examined. A medium grid (option m3 in TURBOMOLE), and a triple zeta valence with polarisation functions (TZVPP) basis set[35] were employed. The gas-phase ground state geometry and energies for each solvent and isonicotinamide were individually determined. The different 1:1 solvent – solvent and 1:1 INA homodimer energies were calculated based on starting with different potential interaction sites in the molecules. The isonicotinamide – solvent 1:1 heterodimers were studied

with several different interaction sites. The electronic supplementary information presents the structures and binding energies for less stable solute – solvent interaction sites.

The binding energy between two molecules in a 1:1 dimer model is calculated from the formula:

$$\Delta E_{bind} = E_{INA-solvent} - (E_{INA} + E_{solvent})$$

where ΔE_{bind} is the computed binding energy, $E_{INA\text{-}solvent}$ is the calculated total energy of the isonicotinamide – solvent 1:1 system, E_{INA} is the ground state energy of isonicotinamide, and $E_{solvent}$ is the ground state energy of the solvent.

Standard counterpoise correction in TURBOMOLE was used to estimate BSSE in the solute – solvent heterodimers models. BSSE magnitudes range from 6-16 kJ mol^{-1} with the largest correction for INA – acetic acid. However, the inclusion of BSSE does not affect the trends in the INA – solvent interactions that are studied in this paper.

The first solvation shells were examined for three solvents: chloroform, methanol and, acetic acid corresponding to the weakest, an intermediate, and the strongest isonicotinamide – solvent interactions, respectively. These were constructed starting with a single isonicotinamide molecule, surrounding it with four solvent molecules, relaxing the geometry, with B3-LYP functionals including van der Waals interactions. This was repeated with eight, twelve, and sixteen solvent molecules, each time relaxing the solvation shells and determining the binding energies. The binding energy (ΔE_{bind}), is the energy change upon binding the isonicotinamide molecule with the *n* solvent molecules, including the interactions of the *n* solvent molecules within the solvation shell, is computed from:

$$\Delta E_{bind} = E_{solvation-shell} - (E_{INA} + nE_{solvent})$$

where $E_{solvation\text{-}shell}$ is the calculated energy of the solute - solvent shell, $E_{isonicotinaimde}$ is the ground state energy of isonicotinamide, n is the number of solvent molecules in the solvation shell and $E_{solvent}$ is the ground state energy of one solvent molecule.

The solvation energy (ΔE_{solv}), is the energy of just the isonicotinamide – solvent interactions, with no solvent – solvent interactions, and was determined from the solvation shell structures using the following equation: [9,10]

$$\Delta E_{solv} = E_{solvation-shell} - (E_{INA}^{constrained} + E_{solvation-shell}^{constrained})$$

where $E_{solvation\text{-}shell}$ is the energy of the solvation shell, $E_{INA}^{constrained}$ is the energy of isonicotinamide in the geometry it adopts inside the solvation shell, and $E_{solvation-shell}^{constrained}$ is the energy of the geometry the solvation shell adopts upon solvating the isonicotinamide molecule. The constrained energies were determined by taking the relaxed geometry of the solvated isonicotinamide and removing the isonicotinamide molecule (, or the solvent shell,) and running a single point energy calculation to determine the energy of the isonicotinamide molecule (, or the solvent shell,) without relaxing the geometry.

The deformation energy (ΔE_{deform}), is the energy required to deform the isonicotinamide molecule as a result of solvation and is compared to the ground state energy of free isonicotinamide. It is defined as: [9,10]

$$\Delta E_{Deform} = E_{INA\ in\ shell}^{constrained} - E_{INA\ ground\ state}^{Relaxed}$$

The computed IR spectra were determined using the aoforce code in TURBOMOLE in which the second derivative of energy with respect to position is determined analytically to compute the vibrational frequencies.

The DFT calculations presented in this work are static 0 K calculations. While the solvation process is of course dynamic, which can be captured by molecular dynamics simulations,[11,36] we did not undertake such simulations. While there will be many different possible configurations of the solute – solvent system, in general the key interactions are those described by the static DFT calculations and this is therefore sufficient to capture the overall trends in INA-solvent interactions which is the focus of this work.

Results and Discussion

The effects of including or omitting the contributions due to van der Waals interactions had a small impact relative to the magnitude of the binding energy, being only 2-3 kJ mol^{-1}. Next comparing the B3-LYP energies to the PBE0 energies, the PBE0 energies was generally larger, by up to 20 kJ mol^{-1}. However, the trends in the binding energies (discussed below) are not affected. To demonstrate this, for the 1:1 interactions, B3-LYP and PBE0 functionals with van der Waals interactions were employed, to ensure that the functional does not affect the ordering, and to ensure a good description of the interactions. For the larger solvation models, due to the complexity and long computing times required, only the B3-LYP functional with vdW was considered.

Solvent – Solvent 1:1 Homodimer Interactions

For the solvent 1:1 homodimers, the order of interaction strength is: acetic acid > methanol > ethanol ≈ acetonitrile > ethyl acetate > acetone > chloroform. The choice of functional has no significant effect on the binding energies, with maximum differences being 6 kJ mol^{-1}, as shown

in Figure 2, and there is no impact on the ordering of the solvent-solvent interaction strengths. Similarly, for the inclusion of van der Waals interactions, there is no change to the trends despite changes of up to 9 kJ mol^{-1} in the magnitude of the energy.

The acetic acid dimer has a significantly stronger binding energy than the other solvent dimers because it contains two moderate hydrogen bonds, the geometric properties of these are described in Table S2 of the electronic supplementary information. Methanol has a strong binding energy due to the moderate O-H···O hydrogen bond present. It is surprising that ethanol, which contains a very similar hydrogen bond with almost identical donor acceptor distance, has a binding energy that is smaller by *ca.* 10 kJ mol^{-1}. A potential reason for this is the greater steric hindrance of the ethyl group than the methyl group. The energy differences between the acetonitrile, ethyl acetate and acetone dimers are also of note. Despite all three containing a pair of similar weak hydrogen bonds, there is some variation in energies. Acetonitrile is likely the strongest due to the hydrogen bonding interacting with a nitrile group. Chloroform has the weakest interactions due to it having a pair of weak electrostatic interactions and longer donor acceptor distances than the other solvents.

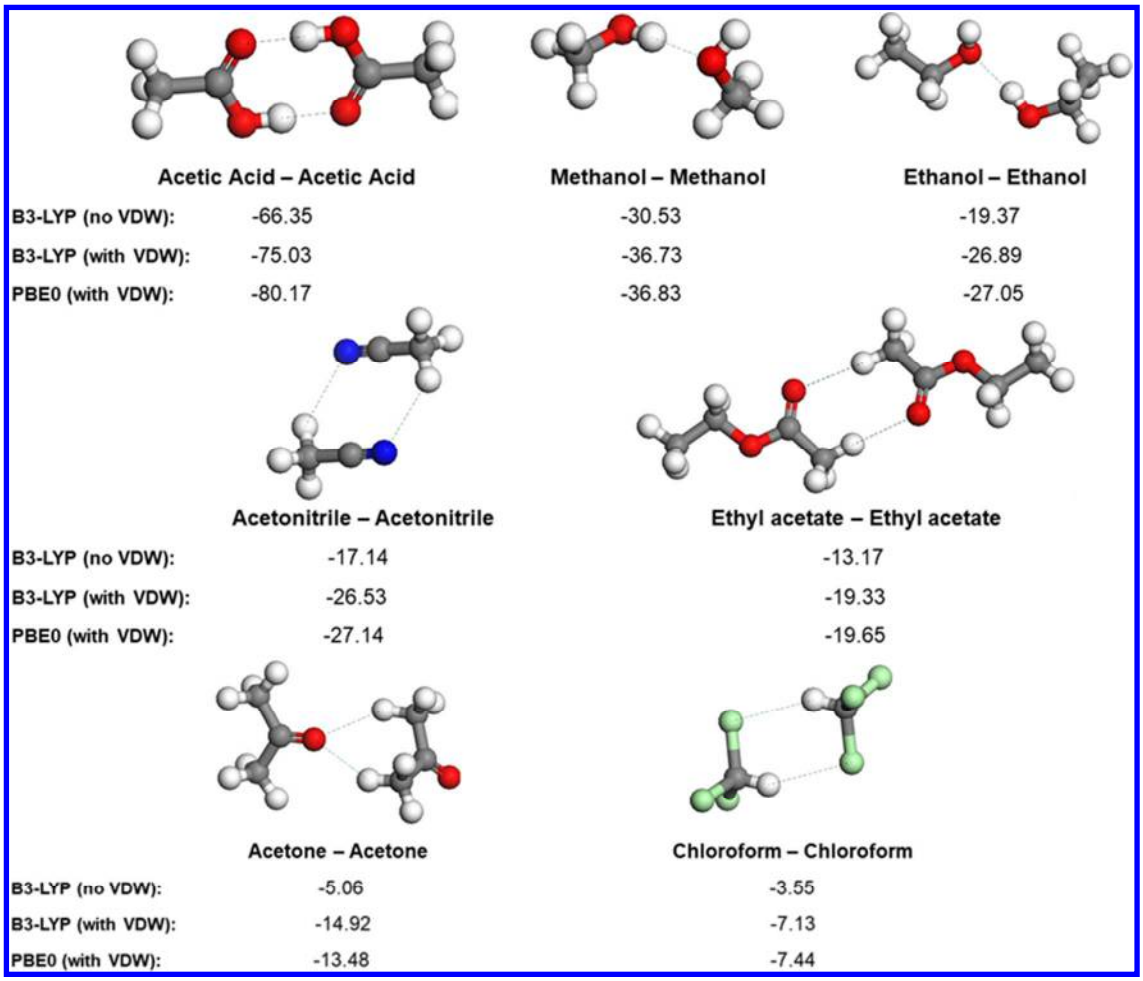


Figure 2: Atomic structures of the most stable solvent 1:1 homodimer interactions and their binding energies in kJ mol^{-1}. The comparison between using B3-LYP and PBE0 DFT functional as well as the comparison between inclusion and exclusion of van der Waals interactions is described in the text.

These solvent dimer energies are similar to the energies found by Khamar *et al.* [9] While the binding energies in this work are generally higher in magnitude than their values, the ordering of solvent dimer strengths is similar, except for ethyl acetate and acetone, which are reversed compared to their work; energy differences of this magnitude can be sensitive to the exact

computational set-up used.[37] They used the methanol tetramer as opposed to dimer since alcohols in the solid state can form $R_4^4(8)$ or $R_6^6(12)$ hydrogen bonding motifs, which was naturally significantly stronger than the dimer due to more hydrogen bonds being present.

Isonicotinamide 1:1 homodimer interactions

The isonicotinamide dimer binding energies were calculated to allow subsequent comparison of the isonicotinamide – isonicotinamide interactions with the isonicotinamide – solvent interactions and establish the relative strength of the interactions. The interaction sites used are based on the main interaction sites known in isonicotinamide polymorphs. These are:

1. All atoms in the amide functional group $C(O)NH_2$
2. The carbonyl C=O
3. The amine group NH_2
4. The aromatic nitrogen in the pyridine ring

The isonicotinamide 1:1 interaction with the most favourable interactions is that in which the two amide groups of each molecule interact, forming the well-known $R_2^2(8)$ hydrogen bonding motif described by Etter in the solid state structure of organic molecules[38] with computed binding energies of -52.10 kJ mol^{-1} (B3-LYP with vdW) and -67.98 kJ mol^{-1} (PBE0 with vdW), shown in Figure 3.

Compared to the dimer energy calculated by Kulkarni *et al*.,[19] where they found energies of -14.6 kJ mol^{-1} per hydrogen bond, our energies are significantly higher, -26.05 (B3-LYP) or -33.99 kJ mol^{-1} (PBE0) per hydrogen bond. The difference between these values is likely due to the different methods used.[37]

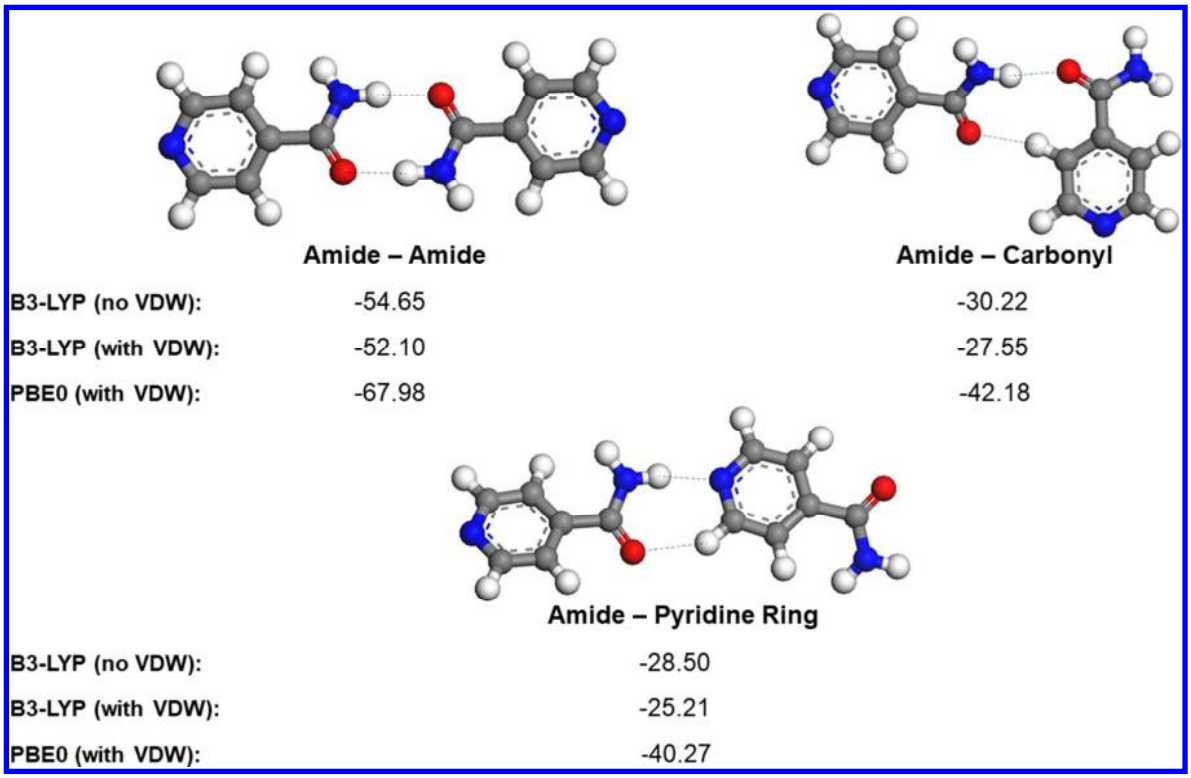


Figure 3: Atomic structures of the most stable isonicotinamide 1:1 homodimer interactions and their binding energies in kJ mol^{-1}. The three theoretical models are described in the text.

The interactions between the amide and carbonyl, which forms a $R_2^2(9)$ motif, and the amide pyridine ring interactions, which form a $R_2^2(7)$ motif, although quite favourable, are less energetically favourable than the amide – amide interaction, by as much as 25 kJ mol^{-1}. These results correlate with the experimental finding that form II is the most stable polymorph of isonicotinamide and it is the only polymorph with the dimer interaction built from amide-amide interactions.

In general, our results for the different interactions in INA dimers agree with the literature, where amide – amide interactions are generally stronger than the amide – pyridine or the amide – carbonyl interactions.[38] This is due to the amide – amide forming 2 strong N-H···O hydrogen

bonds compared to either the N-H···N or N-H···O hydrogen bond along with a weaker C-H···O hydrogen bond in the other cases. For the amide – amide interaction, both N-H···O hydrogen bonds can be classified as moderate according to Jeffrey's definition as the donor-acceptor distance is between 2.5 and 3.2 Å (see column 4 in Table S4 of the electronic supplementary information).[39] Both the amide – pyridine ring dimer and the amide – carbonyl dimer have one moderate and one weak hydrogen bond. This explains why the amide – pyridine ring and the amide – carbonyl interactions are similar in energies since they have two similar strength hydrogen bonds, one moderate and one weak, while being overall weaker than the amide – amide interaction which has 2 moderate interactions. For the PBE0 relaxed geometries, the same trend in the hydrogen bonding properties is seen, though the bond distances are shorter and the angles closer to linear, which is to be expected since the magnitude of the isonicotinamide – isonicotinamide interactions are larger. The B3-LYP geometric properties are presented for the remainder of this paper; the PBE0 geometries are available in the supplementary information.

The isonicotinamide molecules can also interact via π- π stacking of the pyridyl rings, however, when isonicotinamide dimers with π- π interactions were relaxed, they were either unstable or have negligible binding energies. Thus, the strongest interactions are through the amide groups. The strength of these interactions for pyridine rings is known to be quite weak,[40] with typical energies of < -20 kJ mol^{-1} found for the different possible orientations and so will be weaker than the amide – amide/pyridine/carbonyl interactions studied in this paper.

Interaction strengths of the isonicotinamide – solvent 1:1 heterodimers.

The interaction of the solvents with the possible interaction sites of isonicotinamide were studied, and the most stable structures for each solvent are shown in Figure 4. Other, less stable, isonicotinamide – solvent interactions are shown in Figure S2 in the electronic supplementary information. From these results, the isonicotinamide – solvent interactions are strongest in acetic acid and decrease in the order: methanol > ethanol > acetone > ethyl acetate > acetonitrile > chloroform (weakest). While the magnitudes of the PBE0 binding energies are again larger than the B3-LYP binding energies, both the ordering of the isonicotinamide – solvent interactions and the most favourable configuration of the INA – solvent interaction are the same for the two DFT functionals.

The isonicotinamide – isonicotinamide interactions are generally more favourable than the isonicotinamide – solvent interaction, with the exception of isonicotinamide – acetic acid. Based on these results, and previous work using this approach,[8–10] isonicotinamide is, therefore, expected to nucleate fastest from chloroform, slower from acetonitrile, ethyl acetate, acetone, ethanol, and methanol, and slowest from acetic acid. These different interaction strengths will result in different distributions of the solution species equilibrium. In solvents with weaker isonicotinamide – solvent interactions, equilibrium will favour isonicotinamide – isonicotinamide aggregation, leading to isonicotinamide clusters and, later, crystals. This will result in fast nucleation. In the solvents with strong isonicotinamide – solvent interactions, the equilibrium will favour formation of isonicotinamide – solvent aggregates and this delays the onset of nucleation.

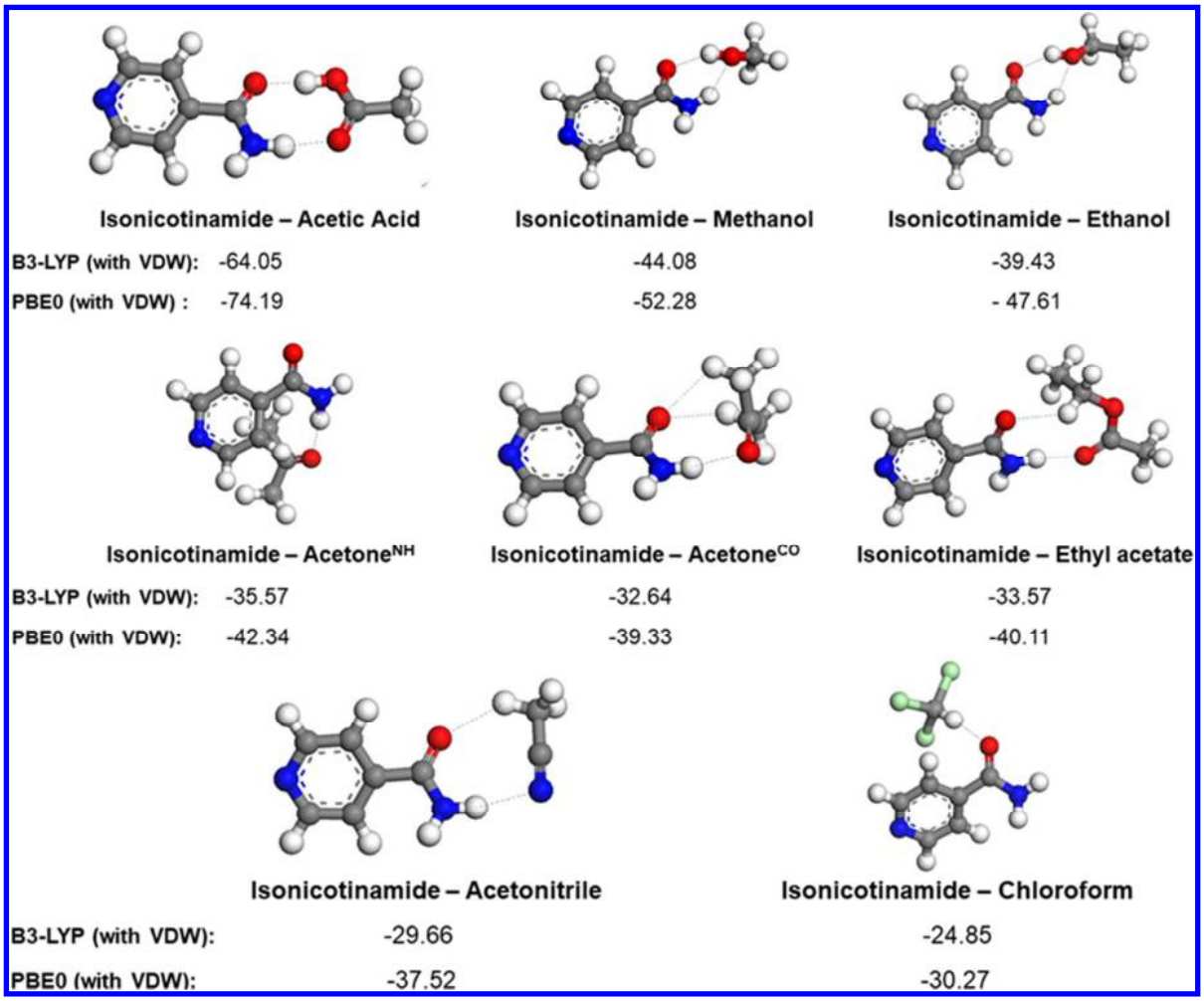


Figure 4: Atomic structures of the most stable isonicotinamide – solvent 1:1 heterodimer interactions and their binding energies in kJ mol^{-1}. Two interaction structures with acetone are presented, one through the NH (denoted $acetone^{NH}$) and the second through the CO (denoted $acetone^{CO}$) group. This facilitates the later discussion of the shift in the isonicotinamide carbonyl peak in different solvents.

While there are, at present, no direct measurements of nucleation times of INA (with the exception of in ethanol) to compare these theoretical predictions to, the trends in the interaction strength can be correlated to the available experimental solubility data for isonicotinamide in

these solvents. The solubility trend for isonicotinamide is: methanol (highest) > ethanol > acetone > acetonitrile > ethyl acetate > chloroform (lowest).[18, 22] (no data for isonicotinamide in acetic acid are available). This follows the trend in isonicotinamide – solvent interactions and show there is a correlation between solute – solvent interaction strength and solubility. We, therefore, predict the greatest solubility of INA to be observed acetic acid, out of the solvents considered in this study.

The isonicotinamide – acetic acid dimer has a significantly higher binding energy than the other isonicotinamide – solvent interactions because it contains two moderate hydrogen bonds. Thus, breaking the isonicotinamide – acetic acid interaction to facilitate isonicotinamide nucleation is the most difficult in this solvent. The isonicotinamide – methanol dimer also has similar moderate O-H···O and N-H···O hydrogen bonds present, but is approx. 20 kJ mol^{-1} weaker than the isonicotinamide - acetic acid interaction. This is because the D···A distances are longer, and thus, the interactions are weaker. For example, the O-H···O distance in the INA – acetic acid dimer is 0.24 Å shorter than the corresponding O-H···O distance in the INA – methanol dimer and is, therefore, stronger.

Similar to the solvent – solvent dimers, the isonicotinamide – ethanol interaction is weaker than the isonicotinamide – methanol interaction, by approx. 4.5 kJ mol^{-1}, despite similar O-H···O and N-H···O hydrogen bonds with similar geometric properties, as seen in Table 1. This is likely due to the greater steric hindrance of the ethanol ethyl group than the methanol methyl group.

Chloroform has the weakest interaction with INA, because it only forms a single C-H···O hydrogen bond, unlike the isonicotinamide interactions with acetone, ethyl acetate, and acetonitrile, which all form two similar interactions, with similar binding energies.

In their paper on salicylic acid, Khamar *et. al.*[9] found similar trends to our work. They found that salicylic acid interacted strongest with acetic acid, then methanol, and the weakest interaction was with chloroform. They did find ethyl acetate interacted more strongly than acetone but the difference was < 2 kJ mol^{-1}. These correlated well with their experimental nucleation findings[41] where the order of nucleation was chloroform (fastest) > ethyl acetate > acetonitrile > acetone > methanol > acetic acid (slowest), strengthening the validity of this methodology.

The geometry data in Table 2 shows the changes in the important distances and angles in our models of INA interacting with the solvents. There is a correlation between the strength of the interaction and the distortion to the geometry of the INA molecule. As the interaction strength of the INA – solvent interaction increases, the C=O bond length increases from 1.22 Å in the free INA and INA interacting with chloroform, acetonitrile and ethyl acetate to 1.23 Å for INA interacting with acetone^{CO}, ethanol and methanol, and up to 1.24 Å for INA interacting with acetic acid. Also the C–N_{Amide} bond length decreases from 1.37 Å in free INA to 1.34 Å when interacting with acetic acid.

Table 1: Key geometric parameters of the hydrogen bonds in isonicotinamide – solvent interactions, using the B3-LYP with van der Waals relaxed geometries. H is the hydrogen involved in bonding, A is the hydrogen bond acceptor, D is the hydrogen bond donor and the hydrogen bond angle is ∠DHA. Two interaction structures with acetone are presented, one through the NH (denoted acetone^{NH}) and the second through the CO (denoted acetone^{CO}) group. This facilitates the later discussion of the shift in the isonicotinamide carbonyl peak in different solvents.

Interaction	Bond Type	H···A Distance / Å	D···A Distance / Å	Hydrogen Bond Angle / °
INA – Acetic Acid	O-H···O	1.66	2.66	175
	N-H···O	1.83	2.84	169
INA – Methanol	O-H···O	1.90	2.79	151
	N-H···O	2.02	2.89	142
INA – Ethanol	O-H···O	1.90	2.79	150
	N-H···O	2.01	2.88	142
INA – Acetone^{NH}	N-H···O	1.99	2.99	172
	C-H···O	2.77	3.20	103
INA – Acetone^{CO}	N-H···O	1.99	2.96	160
	C-H···O	2.57	3.24	119
	C-H···O	2.68	3.33	118
INA – Ethyl acetate	N-H···O	1.92	2.93	170
	C-H···O	2.43	3.24	130
INA – Acetonitrile	N-H···N	2.13	3.12	167
	C-H···O	2.37	3.24	135
INA – Chloroform	C-H···O	2.09	3.16	173

Table 2: Key geometric parameters of the isonicotinamide molecule in the various 1:1 INA – solvent models, using the B3-LYP relaxed geometries. Atomic numbering is defined in Figure 1. Two interaction structures with acetone are presented, one through the NH (denoted acetone^{NH}) and the second through the CO (denoted acetone^{CO}) group. This facilitates the later discussion of the shift in the isonicotinamide carbonyl peak in different solvents.

Interaction	**N-$C_{pyridyl}$ Distances /Å**	**O=C–N Bond Angle /°**	**C=O Distance /Å**	**C–N_{Amide} Distance /Å**	**N–H_A Distance /Å**	**N–H_B Distance /Å**
Free INA	1.34 N-C_2 1.33 N-C_6	122	1.22	1.37	1.01	1.00
INA – Acetic acid	Both 1.33	122	1.24	1.34	1.02	1.00
INA – Methanol	1.34 N-C_2 1.33 N-C_6	122	1.23	1.35	1.02	1.00
INA – Ethanol	1.34 N-C_2 1.33 N-C_6	123	1.23	1.35	1.02	1.00
INA –Acetone^{NH}	1.34 N-C_2 1.33 N-C_6	124	1.22	1.36	1.01	1.01
INA – Acetone^{CO}	1.34 N-C_2 1.33 N-C_6	123	1.23	1.35	1.01	1.00
INA – Ethylacetate	1.34 N-C_2 1.33 N-C_6	123	1.22	1.35	1.01	1.00
INA – Acetonitrile	1.34 N-C_2 1.33 N-C_6	123	1.22	1.35	1.01	1.00
INA – Chloroform	Both 1.33	122	1.22	1.36	1.01	1.00

Correlating the binding energy with the shift in the isonicotinamide carbonyl stretching frequency

Now, the shift in the frequency of the C=O stretching mode in the amide group of INA upon interaction with each solvent is considered. This analysis is used since, in most cases, the most stable interaction site is at the carbonyl group in the amide and, thus, this functional group should be most strongly affected by the interaction with the solvent and can serve as a further descriptor of the strength of the INA-solvent interactions.

Figure 5 plots the binding energy of the solvent with INA in the 1:1 dimer model against the computed shift in the carbonyl C=O stretching frequency (presented in Table 3). These data show that the magnitude of the solute – solvent binding energy and the shift in the INA carbonyl stretching frequency are linearly correlated with a reasonable R^2 value of 0.9698. This scaling of carbonyl shift with binding energy agrees with the findings of Rasmuson *et al.* for both salicylic acid, risperidone and tolbutamide.[9-11] In this plot the INA – acetone^{CO} interaction is used, where acetone interacts through the carbonyl group of INA, even though this is not the most stable interaction site (Figure 4). However, the difference in energy between the two INA sites (CO and NH) is very small. Where acetone interacts through the NH group, there is no interaction at the carbonyl group and this interaction can only have a minor impact on the isonicotinamide carbonyl stretching mode, as evidenced by the small computed shift of only 11 cm^{-1}; the effect of this on the correlation is demonstrated in Figure S3 in the electronic supplementary information. Where the solvent interacts through the INA carbonyl group, the impact on the carbonyl stretching mode is significant, with shifts of up to 44 cm^{-1} for acetic acid. Our results indicate that in a solute molecule with multiple functional groups, such as INA, care must be taken when considering correlations between the solute – solvent binding energies and the shift in the

carbonyl stretching frequency, given that the most stable interaction site may not be at the carbonyl site.

Table 3: Computed INA - solvent binding energies (B3-LYP with van der Waals interactions) and the computed shift of the C=O peak in isonicotinamide. The free isonicotinamide C=O stretching mode lies at 1753 cm^{-1}. $Acetone^{NH}$ and $Acetone^{CO}$ denote INA-acetone interactions through the NH and CO groups in INA

Interaction	ΔE_{bind} **/ kJ mol^{-1}**	**Carbonyl C=O stretching mode / cm^{-1}**	**Shift in C=O stretching mode, $\Delta\nu$ / cm^{-1}**
INA – Acetic acid	-64.05	1709	-44
INA – Methanol	-44.08	1720	-33
INA – Ethanol	-39.43	1722	-31
INA – $Acetone^{NH}$	-35.13	1742	-11
INA – $Acetone^{CO}$	-32.64	1727	-26
INA – Ethyl acetate	-33.57	1722	-25
INA – Acetonitrile	-29.66	1731	-22
INA – Chloroform	-24.85	1730	-23

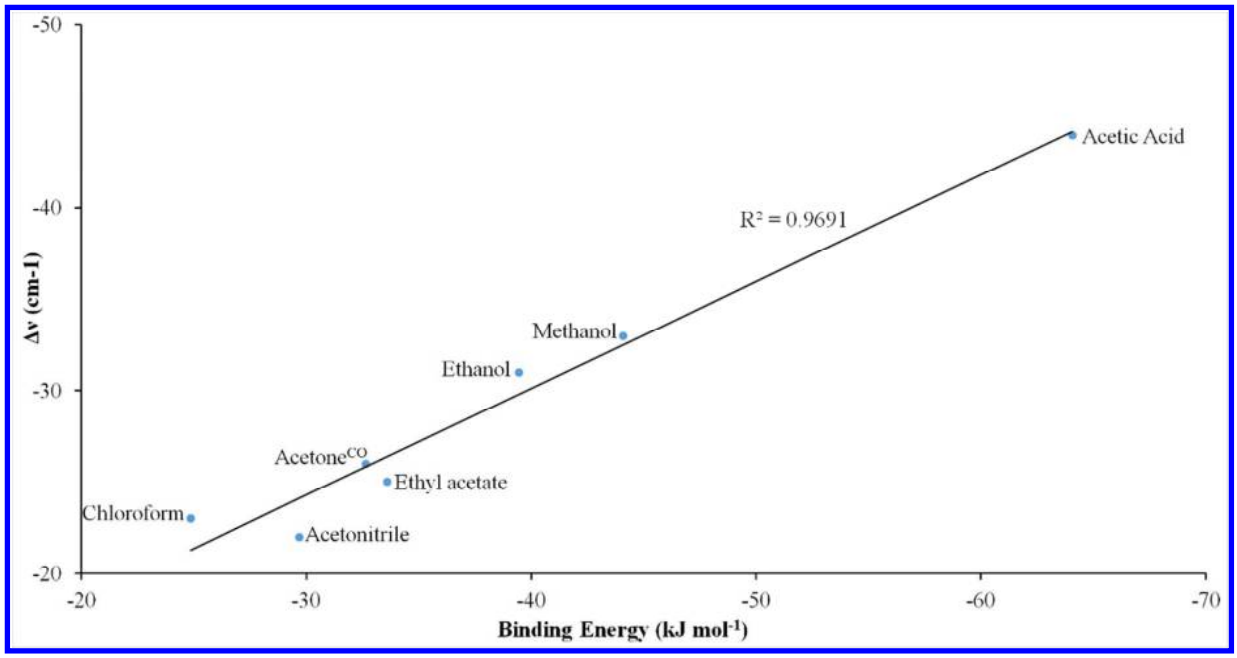


Figure 5: Relationship between the binding energies of the isonicotinamide – solvent dimers and the isonicotinamide carbonyl shift values with R^2 value, based on solute-solvent interactions at the carbonyl site.

Effects of alkyl chain length in acids and alcohols on the isonicotinamide – solvent binding energy.

Figure 6 shows the computed binding energies from B3-LYP and PBE0 for the INA – acid interactions where the acids are formic acid, acetic acid, propionic acid, butyric acid and *iso*butyric acid. For this series of acids, there is less than 1 kJ mol^{-1} of a difference in the INA – acid interaction strength on going from formic acid to butyric acid. This shows that the alkyl chain in these acids does not impact the binding energy, as the same $R_2^2(8)$ hydrogen bonding motif, with its strong interactions, is present. Table 4 shows that there are insignificant changes in the geometry around the hydrogen bonds.

An example of these small changes is the increase in the O-H···O hydrogen bond from 1.65Å in INA – formic acid to 1.68 Å in the INA – *iso*butyric acid model. However, these changes have no impact on the binding energies, with < 1 kJ mol^{-1} energy difference between INA – formic acid and INA – *iso*butyric acid. There are no significant differences in the geometry of the INA molecule in the different INA – acid model as seen in Table S9 of the electronic supplementary information. Based on this, it could be expected that the nucleation rates will be similar in this group of acids. However, for the solvation models (see "Solvation of Isonicotinamide" section), the size of the alkyl group would play an important role, potentially limiting the number of solvent molecules that can solvate an isonicotinamide molecule, leading to weaker binding and solvation energies, *vide infra*. This would result in more favourable conditions for nucleation, contradicting the findings of the simple 1:1 model. This is a limitation to this heterodimer 1:1 interaction model which needs to be kept in mind.

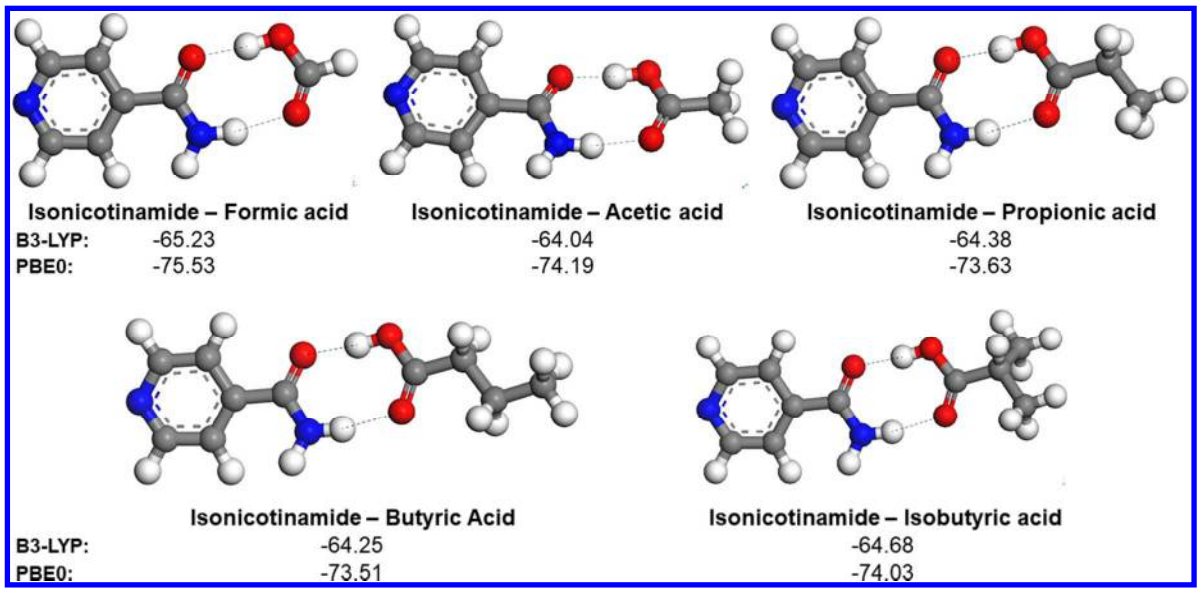


Figure 6: Atomic structures of the most stable 1:1 isonicotinamide – acid interactions and their binding energies in kJ mol^{-1}.

Table 4: Key geometric parameters in isonicotinamide - acid dimer hydrogen bonds using the B3-LYP relaxed geometries.

Interaction	Bond Type	H···A Distance / Å	D···A Distance / Å	Hydrogen Bond Angle / °
INA – Formic Acid	O-H···O	1.65	2.65	176
	N-H···O	1.89	2.89	168
INA – Acetic Acid	O-H···O	1.66	2.66	175
	N-H···O	1.83	2.84	169
INA – Propionic Acid	O-H···O	1.68	2.68	175
	N-H···O	1.85	2.86	168
INA – Butyric Acid	O-H···O	1.68	2.68	175
	N-H···O	1.85	2.86	168
INA – *Iso*butyric Acid	O-H···O	1.68	2.68	175
	N-H···O	1.85	2.86	169

For the isonicotinamide – alcohol interactions, methanol, ethanol, 1-propanol, 2-propanol, *n*-butanol, *iso*butanol, *sec*-butanol and *tert*-butanol, were investigated, Figure 7. Beyond ethanol, the identity of the alcohol has a small impact on the INA-alcohol binding energy. The energy of the isonicotinamide – methanol interaction is strongest, then, as the side chain lengthens, the energy reduces by up to 5.26 kJ mol^{-1} when going from methyl to ethyl. For larger groups, such as *iso*propyl or *n*-butyl groups, the effect is a change of < 2 kJ mol^{-1}, which is negligible. For the hydrogen bonding geometric properties, presented in Table 5, there are small changes in the bonding lengths. An example of these small changes is the increase in the O-H···O hydrogen bond distance from 1.90 Å in INA – methanol to 1.94 Å in the INA – *sec*-butanol model. However, these changes have only a small impact on the binding energies, with ~ 5 kJ mol^{-1} energy difference between the INA – methanol and INA – *sec*-butanol. There are no significant

differences in the geometry of the INA molecule in the different INA – acid models as seen in Table S12 of the electronic supplementary information. The overall result that alcohols have weaker interactions with INA than the acids, yet stronger than the other solvents considered persists. These small variations seen for the alcohols, which are not observed for the variation in acid chains, is likely because the alcohol interaction is significantly weaker than the acid interaction and, thus, it may allow for more impact of the alkyl group on the binding energy, though this is only observed going from methyl to ethyl side chain.

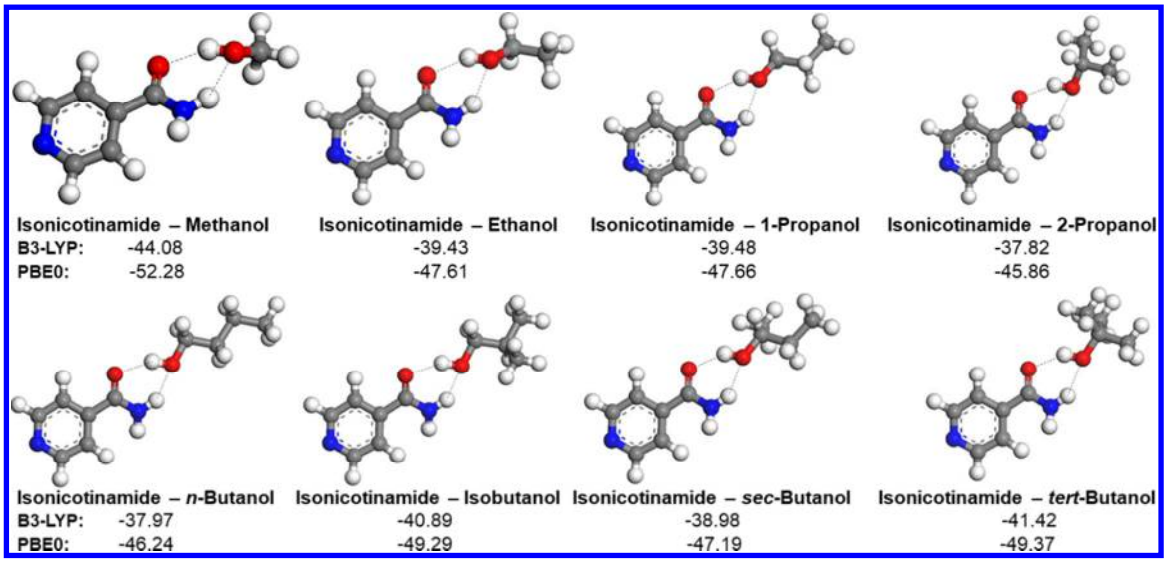


Figure 7: Atomic structures of the most stable 1:1 isonicotinamide – alcohol interactions and their binding energies in kJ mol^{-1}.

Table 5: Key geometric parameters in isonicotinamide – alcohol dimer hydrogen bonds, using the B3-LYP relaxed geometries.

Interaction	Bond Type	H···A Distance / Å	D···A Distance / Å	Hydrogen Bond Angle / °
INA – Methanol	O-H···O	1.90	2.79	151
	N-H···O	2.02	2.89	142
INA – Ethanol	O-H···O	1.90	2.79	150
	N-H···O	2.01	2.88	142
INA – 1-Propanol	O-H···O	1.91	2.79	149
	N-H···O	2.02	2.88	141
INA – 2-Propanol	O-H···O	1.92	2.81	150
	N-H···O	2.02	2.88	141
INA – *n*-Butanol	O-H···O	1.90	2.79	150
	N-H···O	2.03	2.88	140
INA – *iso*butanol	O-H···O	1.90	2.79	151
	N-H···O	2.04	2.89	140
INA – *sec*-Butanol	O-H···O	1.94	2.81	147
	N-H···O	2.01	2.87	142
INA – *tert*-Butanol	O-H···O	1.94	2.81	147
	N-H···O	2.00	2.87	141

Solvation of Isonicotinamide

To examine the solvation of INA the strongest, a moderate, and the weakest solvents from the dimer interaction model were chosen, namely, acetic acid, methanol, and chloroform. A solvation shell of each solvent around INA was built to examine the solute – solvent interactions, and study if the trends in the binding energy for dimer interaction model hold for a solvated isonicotinamide molecule. The binding, solvation, and deformation energies were determined, as defined in the methodology. Figures 8 – 10 show the computed solvation structures of INA with each solvent where 4, 8, 12 and 16 solvent molecules were used, with the latter leading to saturation in solvation of INA. Also shown are the computed binding energy, solvation energy and deformation energy in each case, using the B3-LYP functional. Tables S14 – 16 of the electronic supplementary information contain the key geometric features of the INA molecule within the solvation model to determine the effects of increasing the number of solvent molecules has on the INA geometry.

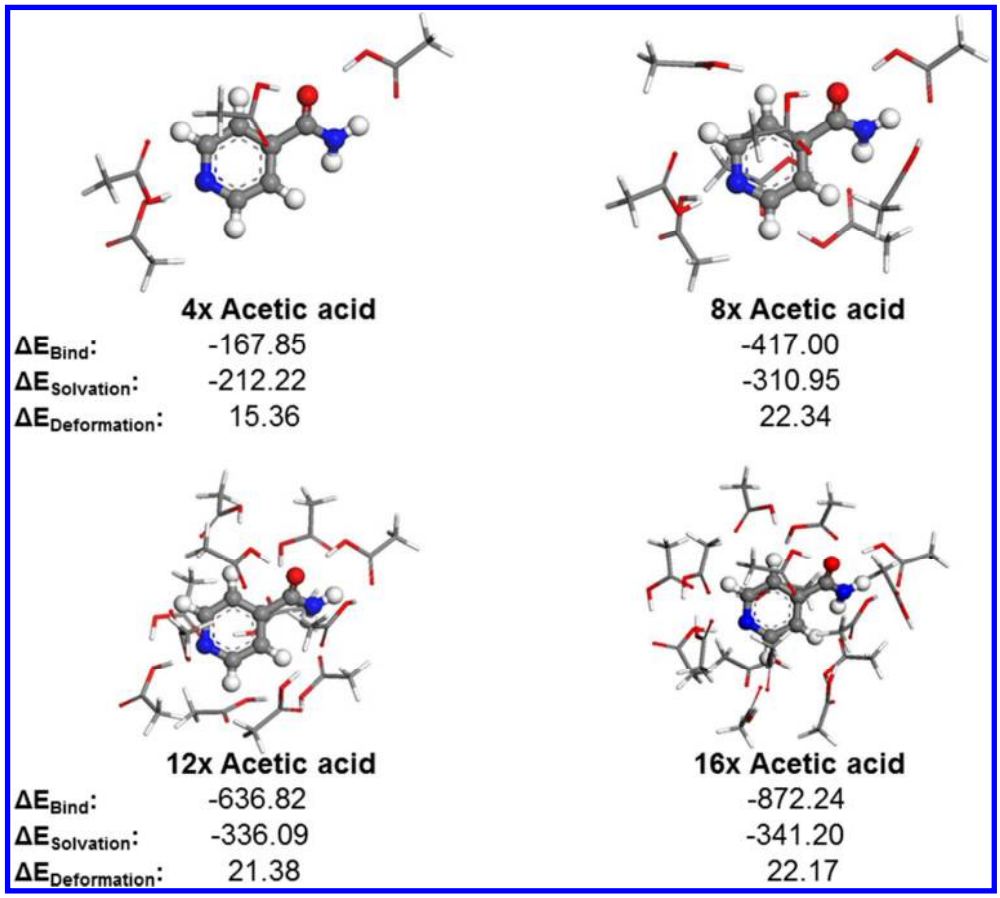


Figure 8: Atomic structures for the solvation model of isonicotinamide with acetic acid with corresponding binding energies (ΔE_{Bind}), solvation energies ($\Delta E_{Solvation}$), and deformation energies ($\Delta E_{Deformation}$), all in kJ mol^{-1} and using the B3-LYP functional.

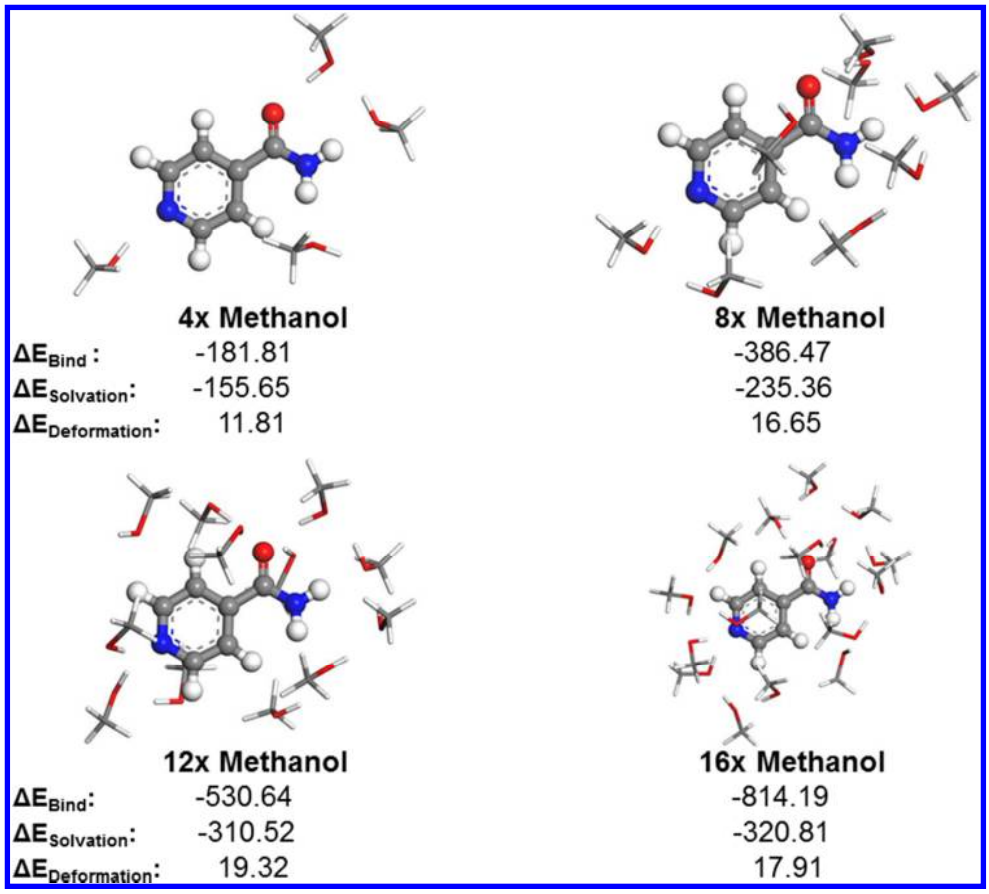


Figure 9: Atomic structures for the solvation model of isonicotinamide with methanol with corresponding binding energies, solvation energies, and deformation energies, all in kJ mol^{-1} and using the B3-LYP functional.

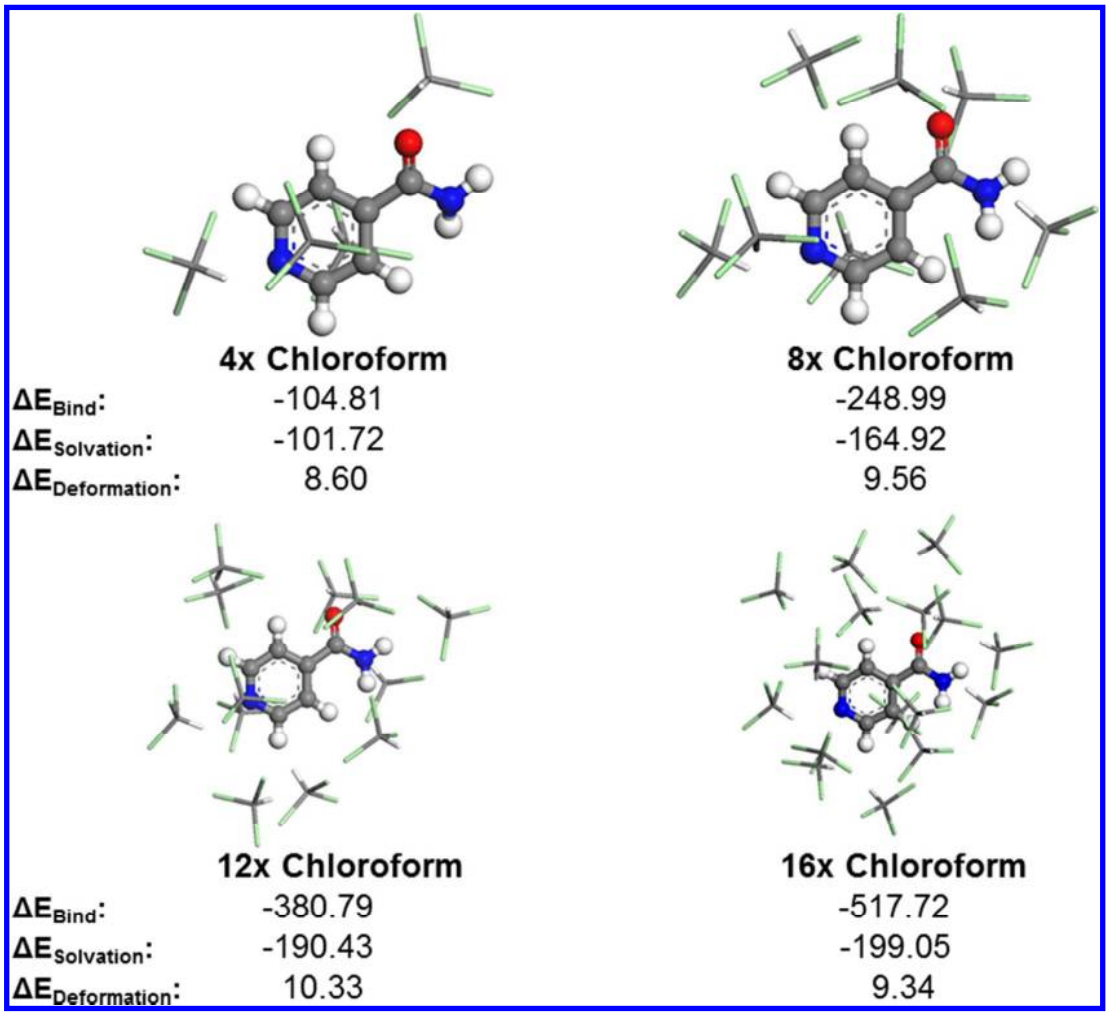


Figure 10: Atomic structures for the solvation model of isonicotinamide with chloroform with corresponding binding energies, solvation energies, and deformation energies, all in kJ mol^{-1} and using the B3-LYP functional.

Clearly the computed **binding energy** of each solvent with isonicotinamide increases as the number of solvent molecules in the shell is increased. However, the energies show that the binding energy change is smaller as more solvent molecules are added. This is due to weaker solute – solvent interactions upon addition of further solvent molecules since the strongest interaction sites were occupied preferentially by the first solvent molecules. Examining the 16 solvent molecules, the trends from the 1:1 heterodimer interactions are maintained, namely that

the INA – acetic acid interactions are significantly stronger than the INA – methanol and INA – chloroform interactions. This is found whether using the total binding energy or binding energy per solvent molecule.

The **solvation energy**, which is the strength of the isonicotinamide – solvent interactions within the solvation models as defined in the methodology, also shows the same trends as the binding energy. The acetic acid solvation models have much larger solvation energies than the INA-methanol model, which are in turn stronger than in the INA – chloroform model. While the solvation energy increases with increasing number of solvent molecules, the energy increase between 12 and 16 solvent molecules converges, a change of less than 10 kJ mol^{-1} between these solvation models, indicating that the isonicotinamide is solvated.

The **deformation energy** is the energy required to deform isonicotinamide from its gas phase geometry to the geometry within the solvated structure. For acetic acid this is ~22 kJ mol^{-1}, for methanol it is ~19 kJ mol^{-1}, and for chloroform it is ~9 kJ mol^{-1}. This reflects the greater distortion in INA when interacting with acetic acid solvent compared to methanol and chloroform. This is consistent with the results for salicylic acid.[9] The largest deformation energy for acetic acid arises due to stronger deformation of the isonicotinamide molecule to fit the more strongly interacting and therefore, closer bound, acetic acid molecules around isonicotinamide.

In Tables S14-16 of the electronic supplementary information, which include the ground state INA and the 1:1 heterodimer geometric data, the change in the C-O distance in INA is largest when the first solvent molecule interacts at the amide site and this changes very little as further solvent molecules are added. The remaining geometric properties show similar trends with the increasing number of solvent molecules within the shell, for example the C=O bond length increases and the C-N_{Amide} bond length shortens.

Conclusion

We have presented a study with hybrid DFT and van der Waals corrections of the interactions of isonicotinamide with a series of common organic solvents. We use a simple 1:1 solute – solvent dimer model and a solvation shell model to understand the interactions between INA and the solvent. Our results indicate that nucleation of INA will be slowest from acetic acid, due to its strong binding energy, and fastest for chloroform, due to the weak INA – chloroform interaction. This is because the acid of acetic acid can form a pair of strong O-H···O and N-H···O hydrogen bonds with the amide group of isonicotinamide while chloroform can only form weak C-H···O hydrogen bonds with isonicotinamide. This further confirms the application of this computational methodology to nucleation prediction. It also extends the scope of type of hydrogen bonding groups that have been studied, adding the R-NH_2 (two hydrogen bonding acceptors one hydrogen bonding donor) motif to the R-OH (one acceptor, two donors) and R-CO-R (two donors) motifs previously examined.

Given that the strongest interactions of INA with solvents are generally through the carbonyl group of INA, we computed the shift in the infra-red carbonyl stretching mode of isonicotinamide for the 1:1 isonicotinamide – solvent interactions. The magnitude of the shift in the carbonyl stretching mode correlates with the strength of the INA – solvent interaction; provided the solvent is interacting with the INA carbonyl group. This agrees and extends previous work by Rasmuson et al.[8,9]

One caveat is that if we consider a range of alcohols or acids with longer alkyl chains, the dimer binding energies are little affected. However, the steric hindrance of large alkyl groups will affect the explicit solvation, which leads to a limit of this simple model. It should however, be

suitable for predicting nucleation or solvation of organic molecules ordering in simple organic solvents. This, combined with the limitation noted by Zeglinski *et al.*[11] with respect to conformer species in solute and the hydrogen bonding propensity of the solvent show that while this is a quick and effective tool in predicting nucleation as shown in the five successful cases, the methodology needs to be used with care for predictions. It should however, be suitable for predicting nucleation or solvation of organic molecules ordering in simple organic solvents.

Finally, in explicit solvation models, the binding, solvation and deformation energies for acetic acid, methanol, and chloroform all show the same ordering as the dimer interaction model: acetic acid has the largest binding, solvation and deformation energies while chloroform has the weakest energies. Thus, this simple dimer interaction model can describe the complex behaviour in solvation models and solubility data, but is significantly easier, faster and cheaper to run.

Supporting Information

The Supporting Information contains geometric properties of the INA molecule from B3-LYP and PBE0 functionals, atomic structures for all solvent – solvent interactions studied, the geometric properties of the most favourable solvent – solvent hydrogen bonding interactions using both B3-LYP and PBE0 functional, the geometric properties of the INA – INA hydrogen bonding interactions using both B3-lyp and PBE0 functionals, atomic structures of all examined INA – solvent interactions, the geometric parameters of both the hydrogen bonding interactions and the INA molecule within the most favourable INA – solvent interactions using the PBE0 functionals, the geometric properties of the INA molecule in the most favourable INA – solvent interactions using both B3-LYP and PBE0 functionals, the graphical representation of the non-

correlating relationship between the strongest INA – solvent interaction and INA carbonyl stretching mode shift values, the hydrogen bonding geometric properties in the series of acid and alcohols with increasing alkyl chain length using the PBE0 functionals, the INA molecule's geometric properties in the series of acid and alcohols with increasing alkyl chain lengths using both the B3-LYP and PBE0 functionals, geometric properties of the INA molecule within the various acetic acid, methanol, and chloroform solvation models using the B3-LYP functional.

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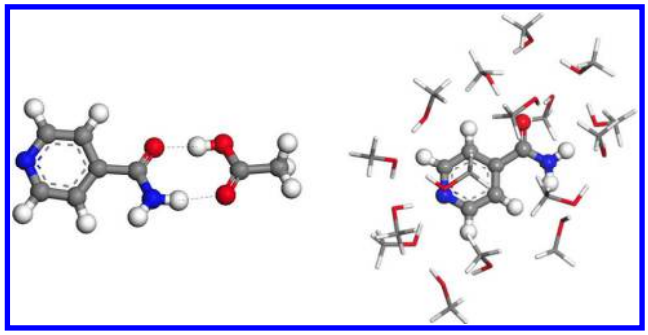
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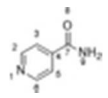


Figure 1. Atomic structure of isonicotinamide with atoms numbered for identification of bonds and torsion angles.

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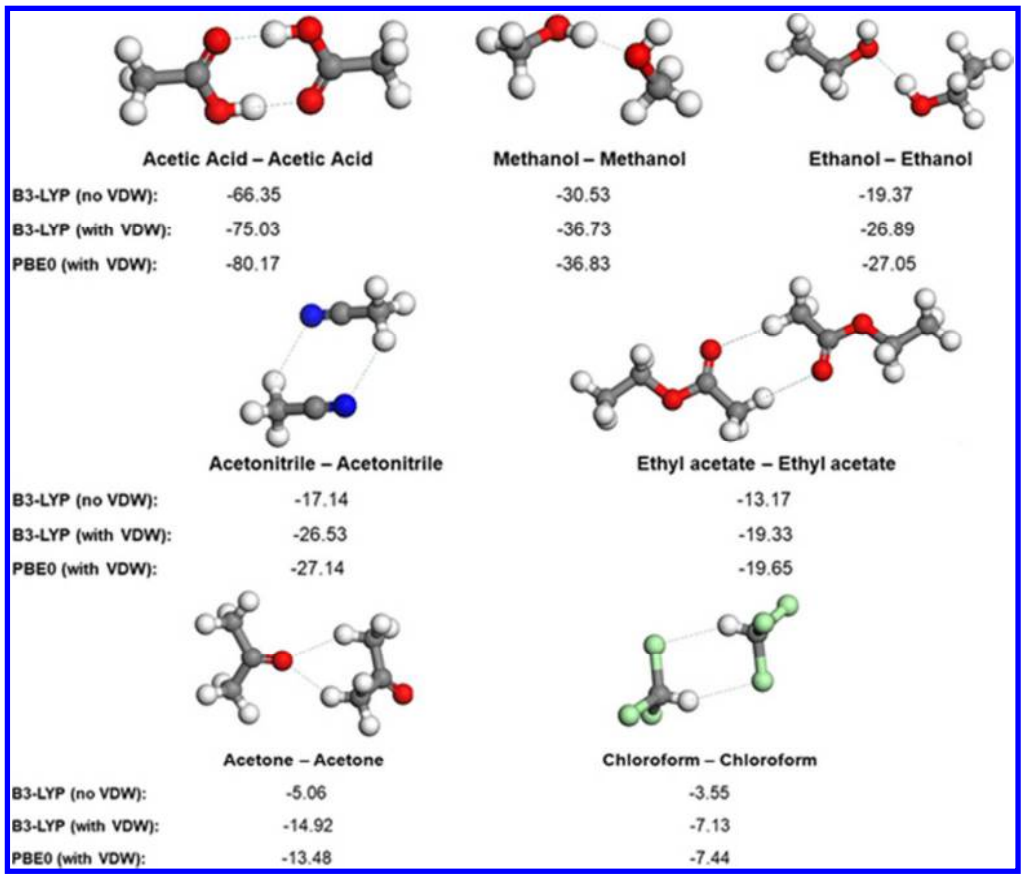


Figure 2: Atomic structures of the most stable solvent 1:1 homodimer interactions and their binding energies in kJ mol^{-1}. The comparison between using B3-LYP and PBE0 DFT functional as well as the comparison between inclusion and exclusion of van der Waals interactions is described in the text.

23x20mm (600 x 600 DPI)

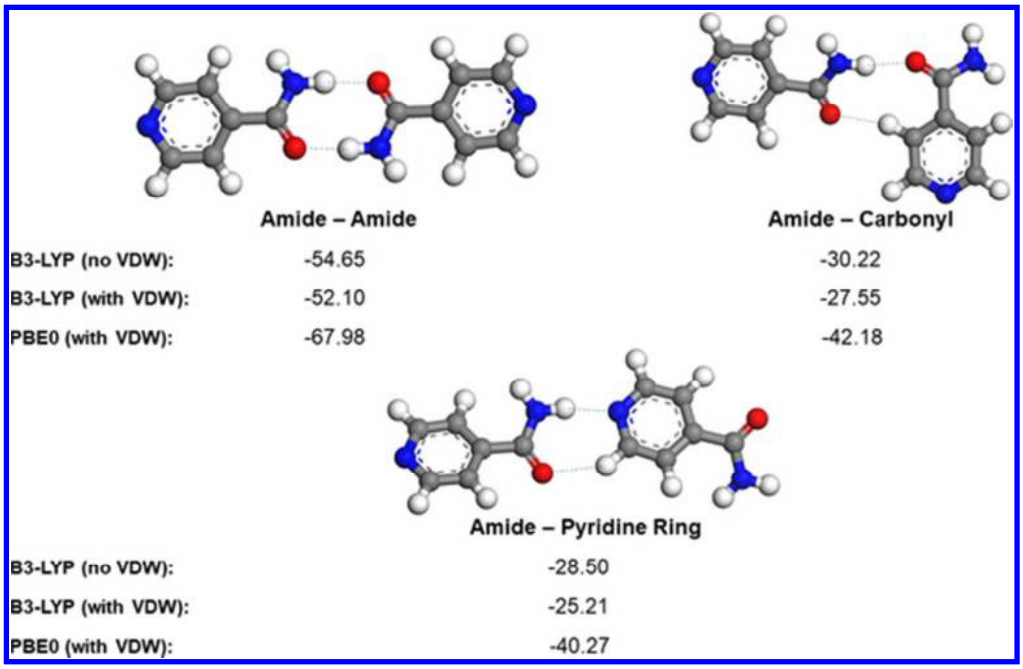
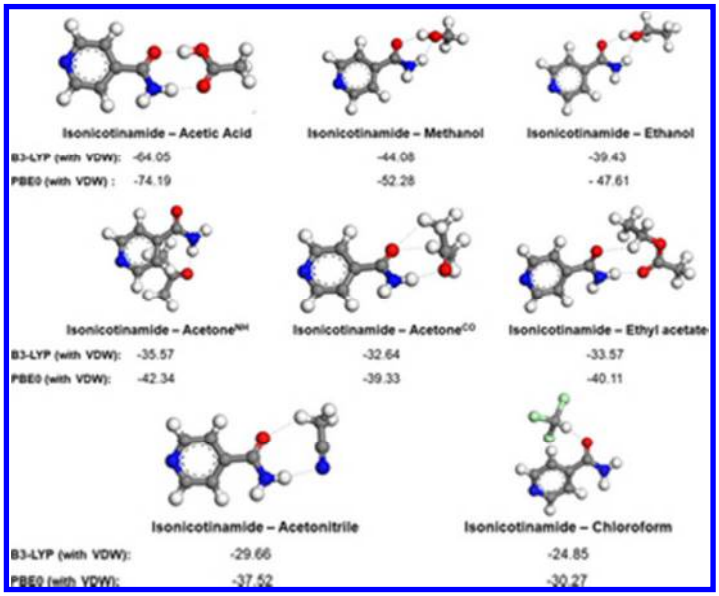


Figure 3: Atomic structures of the most stable isonicotinamide 1:1 homodimer interactions and their binding energies in kJ mol^{-1}. The three theoretical models are described in the text.

24x15mm (600 x 600 DPI)



Caption : Figure 4: Atomic structures of the most stable isonicotinamide – solvent 1:1 heterodimer interactions and their binding energies in kJ mol^{-1}. Two interaction structures with acetone are presented, one through the NH (denoted $acetone^{NH}$) and the second through the CO (denoted $acetone^{CO}$) group. This facilitates the later discussion of the shift in the isonicotinamide carbonyl peak in different solvents.

29x24mm (300 x 300 DPI)

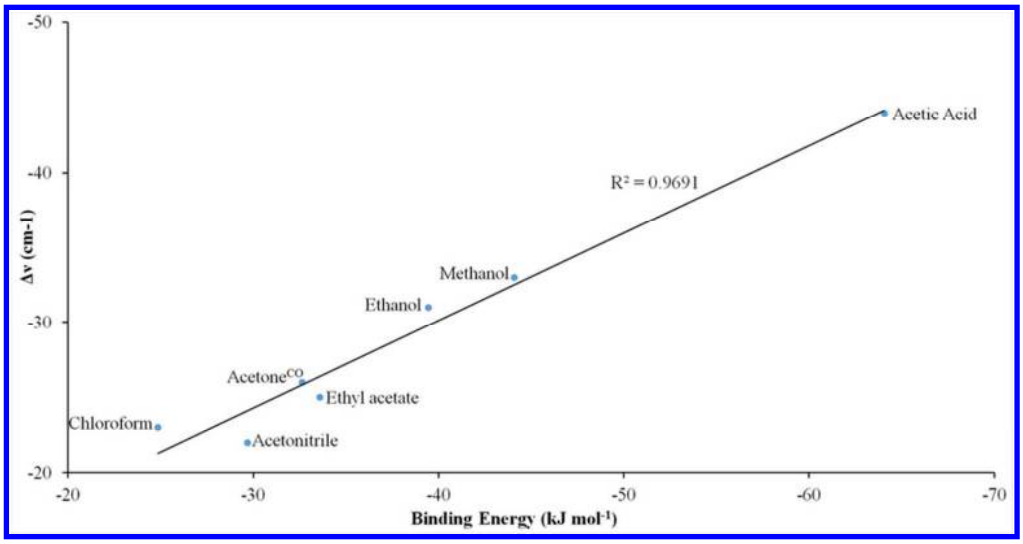


Figure 5: Relationship between the binding energies of the isonicotinamide – solvent dimers and the isonicotinamide carbonyl shift values with R^2 value, based on solute-solvent interactions at the carbonyl site.

38x19mm (600 x 600 DPI)

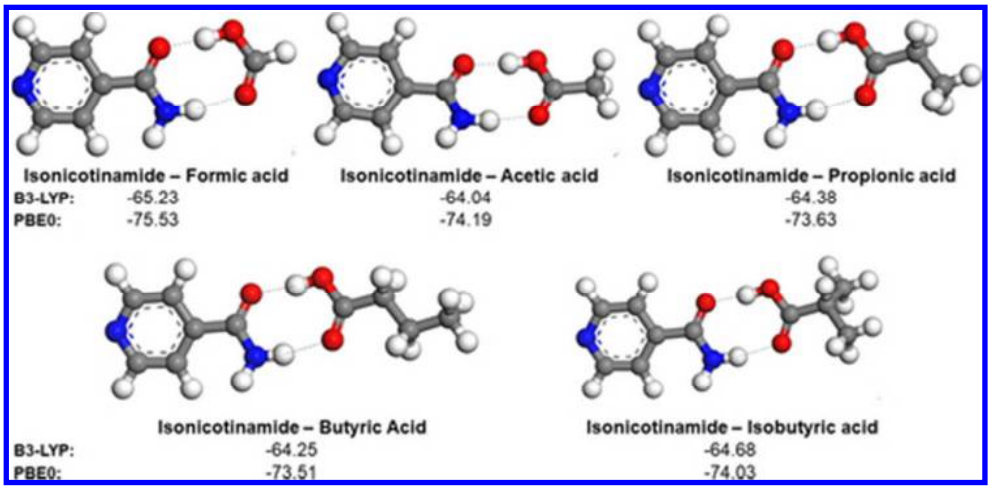


Figure 6: Atomic structures of the most stable 1:1 isonicotinamide – acid interactions and their binding energies in kJ mol^{-1}.

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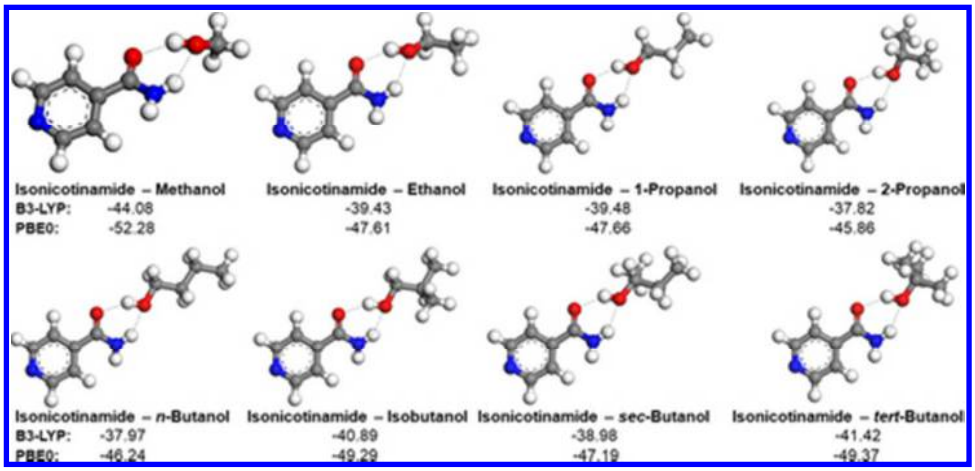


Figure 7: Atomic structures of the most stable 1:1 isonicotinamide – alcohol interactions and their binding energies in kJ mol^{-1}.

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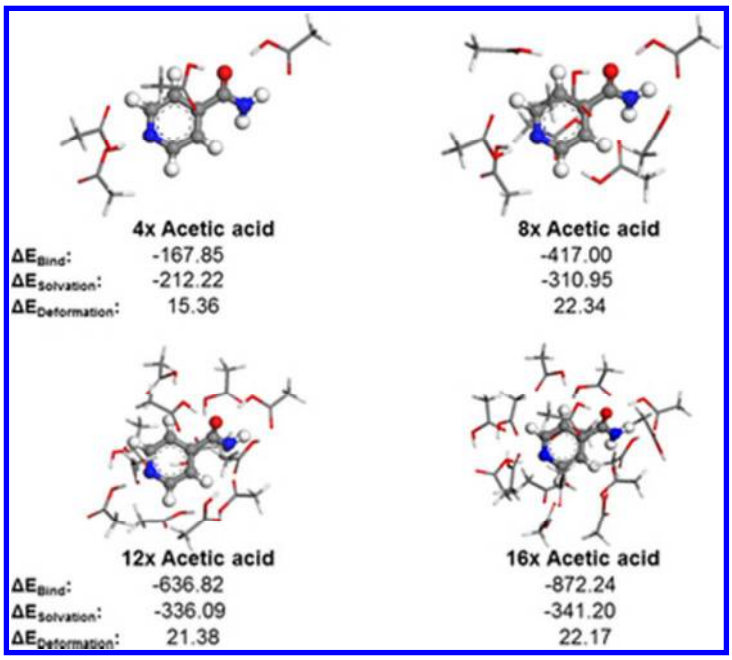


Figure 8: Atomic structures for the solvation model of isonicotinamide with acetic acid with corresponding binding energies (ΔE_{Bind}), solvation energies ($\Delta E_{Solvation}$), and deformation energies ($\Delta E_{Deformation}$), all in kJ mol^{-1} and using the B3-LYP functional.

30x26mm (300 x 300 DPI)

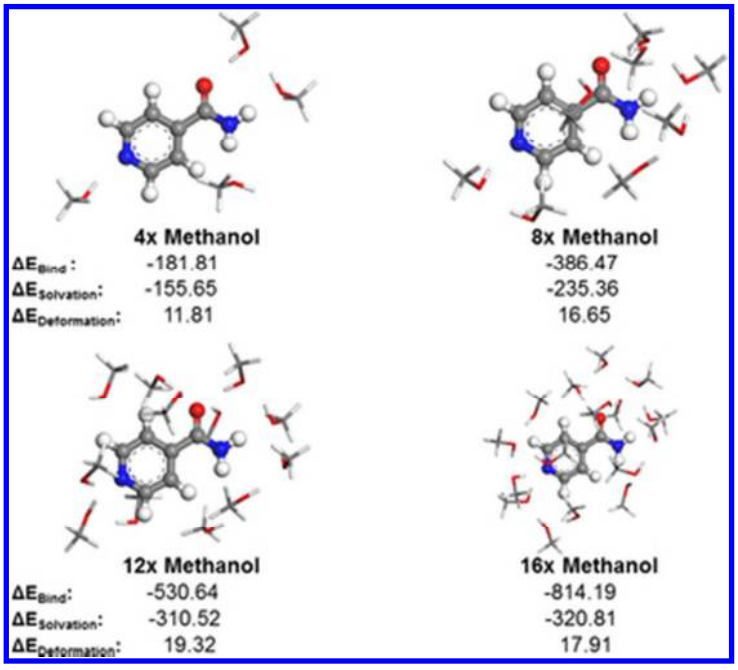


Figure 9: Atomic structures for the solvation model of isonicotinamide with methanol with corresponding binding energies, solvation energies, and deformation energies, all in kJ mol^{-1} and using the B3-LYP functional.

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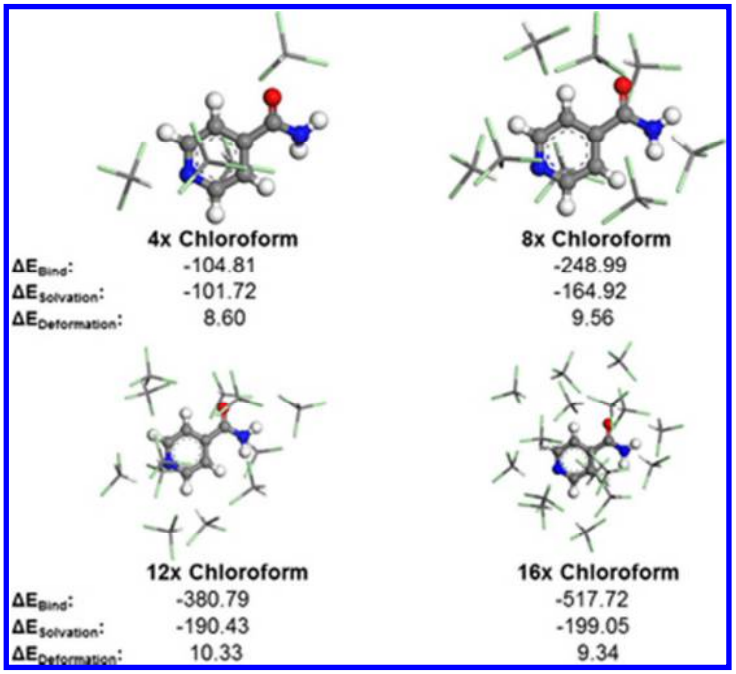
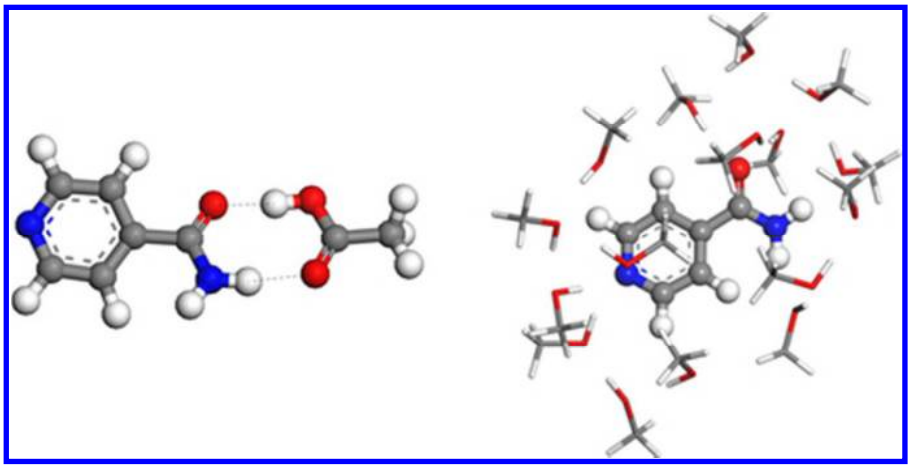


Figure 10: Atomic structures for the solvation model of isonicotinamide with chloroform with corresponding binding energies, solvation energies, and deformation energies, all in kJ mol^{-1} and using the B3-LYP functional.

30x27mm (300 x 300 DPI)



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