Conformational and Structural Stability of the Single Molecule and Hydrogen Bonded Clusters of Para Aminobenzoic Acid in the Gas and Solution Phases

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Keywords: DFT calculations, cluster stability, COMSO-RS, conformational analysis, crystal polymorphism, crystallisation, molecular and solid-state modelling, solution chemistry, solvent effects, , , para amino benzoic acid

Contents

List of Terms

B3LYP: Becke Three parameter Lee-Yang-Parr Functional

COSMO-RS: Conductor-like Screening Model for Real Solvents

TZVP: Valence-triple zeta plus polarisation basis set

BP86: Becke-Perdew 86 Functional

Abstract

The crystallographic structures of the α- and β- polymorphic forms of para aminobenzoic acid are deconstructed into their constituent hydrogen bonding molecular structural building blocks of monomers, dimers, tetramers and octamers, where they are analysed using ab-initio quantum mechanical calculations of their conformation and cluster stability in solution.

The molecular conformation found in the β-form is less stable than the same found in the α-form for both the gas and solution phases, suggesting that this causes a slight increase in the barrier to the crystallisation of the β-form in comparison to the α-form.

The solution populations of the self-associated OH…O H-bonding 'classic carboxylic acid dimer', present in the α- and not the β-structure, is calculated to dominate in acetonitrile, dimethyl sulfoxide, ethanol, ethyl acetate, methanol, nitromethane and water. It is observed that this classic dimer is least stable in water, compared to the other PABA crystallisation solvents, with the OH…N H-bonding interaction present in the β-form being the second most stable dimeric interaction.

These results are discussed in terms of the crystallisability and polymorphic behaviour of the α and β forms of PABA from the afore mentioned crystallisation solvents, whilst detailing how this approach could be reproducible for a range of polymorphic crystalline materials.

1 Introduction

Understanding and controlling the transition pathway associated with the directed assembly of molecules from their solvated state, via the crystallisation process into three-dimensional, ordered crystalline-solids, represents a significant Grand Challenge for the physical-chemical sciences[3, 4]. Crystallisation can be sub-divided into three-dimensional nucleation and two-dimensional, surface-mediated crystal growth stages, with the former directing a number of the important physico-chemical attributes of the product crystals, notably the crystal size distribution, crystallinity and polymorphic form[5-8].

Though the transition pathway from solvated molecules in solution to the phase separation of macroscopic crystals is still a matter of some debate, there has been experimental and theoretical evidence that solute molecules in the solution phase can be directed by this environment to adopt conformations and intermolecular structuring that can template the resulting crystallographic structure, and hence facilitate the nucleation of a material[9-14].

Smaller molecules with significantly lower degrees of conformational freedom, such as ibuprofen and aspirin, are observed to adopt molecular conformations close to their energetic minima in the their crystal structures and hence display little evidence of polymorphic behaviour[15, 16]. In comparison, more conformationally flexible molecules, such as benzophenone, l-glutamic acid and ritonavir, display complex polymorphic behaviour, with the metastable forms of these materials displaying more energetically favoured molecular conformations than the same in the stable forms[6, 8, 17, 18]. Hence it has been postulated that crystal structures which contain energetically favoured molecular conformations are likely to be easier to crystallise. This is likely to be associated with the fact that the molecule will have freedom to adopt low energy conformations in solution, and hence there would be an energy penalty associated with having to transition to a high energy conformation to form a solid-state structure.

Further to this, it has been observed for 5-fluoracil and tolbutamide that solvents which can facilitate formation of certain structural arrangements in solution prior to nucleation, which mimic a certain polymorph, can then template the polymorphic form which eventually nucleates[19, 20]. Indeed, there has been

significant research into using artificial templates which are thought to promote certain intermolecular interactions in solution, to either promote crystallisation or bias the crystallisation towards a particular polymorphic form[21, 22].

The identification of the influence of any conformational change that might take place during the crystallisation process is often achieved by a comparative examination of the conformation and intramolecular energy for a fully relaxed molecule, in the gas phase, or the same with a solution-state approximation, with that found within the solid-state structure, or structures in the case of polymorphic materials[6, 18, 23]. Quantifying the structural evolution over the full nucleation transition pathway is extremely challenging, even for the most sophisticated of simulations. However, relating the how pre-nucleation clusters can self-assemble in solution and template a crystalline form can provide useful information on the likely polymorphic direction of a solution crystallisation[24].

One hypothesis is that the crystallisation of a particular crystalline form may be directed by the relative stability of small cluster building blocks in solution such as dimers or tetramers, which then self-assemble to realise the structural motifs contained within the crystal structure, has been explored extensively in the field of coordination metal-ligand chemistry[25]. Such studies often focus on the self-assembly of complex structures[26-28] and, in particular, on tailor-made building blocks that have been designed to induce self-assembly[29, 30]. However, some more recent theoretical studies of organic materials have identified solute clusters in solution that resemble the crystalline form produced from different solvents[31-34].

In terms of understanding the nucleation transition pathway in a range of solvents, it is prudent to identify computationally efficient methods of modelling the stability of molecular clusters as a function of the solvation environment. Dielectric continuum treatment of the solvation environment can be a useful approximation to calculate solution thermodynamic properties[35, 36]. This approach encases the solute molecule within a solvation cavity in the shape of the molecule, with the solvent properties being treated as a continuum based on the dielectric constant of the solvent[37-39].

Klamt and co-workers have developed and expanded this approach to further treat the intermolecular interactions within solution using statistical thermodynamics calculations and have created the COnductor like Screening MOdel for Real Solvents (COSMO-RS)[40-42], which has been extensively used to calculate the thermophysical properties of solutions[43-49].

Drawing upon the above perspective, this paper uses electronic structure theory calculations to examine how the stability of the molecular conformation and the H-bonded crystallographic building blocks of para aminobenzoic acid (PABA) in solution can template the relative crystallisation rates of the α and β forms of the material. Recent studies have examined the link between OH…O H-bonding dimers in solution using molecular and intermolecular simulations[32, 34]. It can be observed that the packing of both forms of PABA contain different types of H-bonding interactions, hence the stability of all the different types of H-bonding clusters in solution are examined in this study.

The α- and β-forms of PABA are well characterised[50-57], though there have been more recent discoveries of a third polymorph[58] and a nitromethane solvate form[59]. Rosbottom et al characterised the solid-state chemistry of the α- and β-forms characterised in detail[1], with the α-form having two molecules in the asymmetric unit with its hydrogen bonding network being characterised by OH…O H-bonding dimers being linked by NH…O H-bonding interactions. In contrast, the β-form has one molecule in the asymmetric unit and its H-bonding network has a four membered H-bonding ring, containing two identical NH…O and two identical OH…N interactions. These are shown in Figure 1.

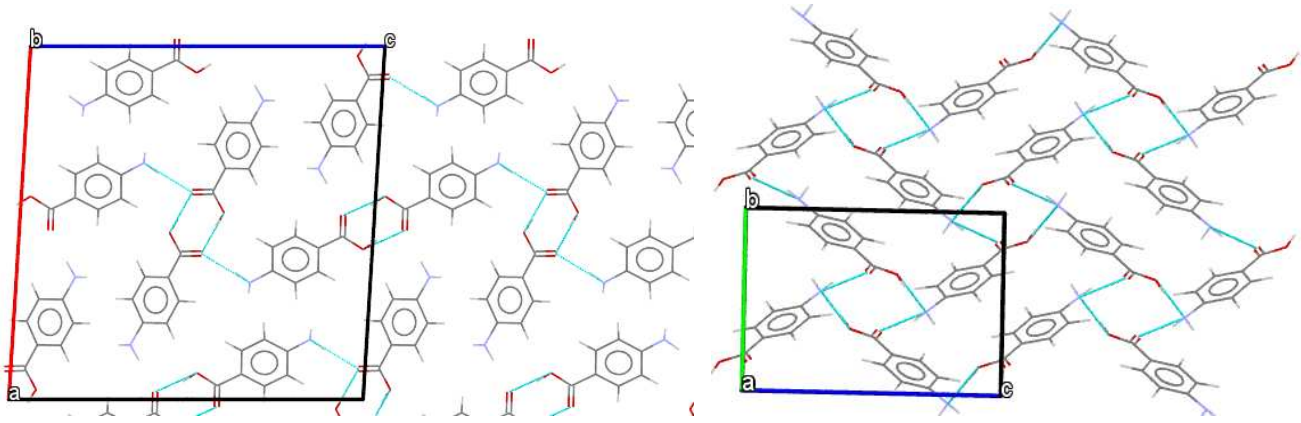


Figure 1: Intermolecular H-bonding crystal chemistry for α-PABA (left) and β-PABA (right)

Detailed theoretical and experimental studies of the solution and solid-state chemistry[1, 2], along with the nucleation behaviour[60-62], have concluded that the solvent influence on solution pre-clustering can impact upon the nucleation rate, critical cluster size and polymorphic form crystallised[8]. The observation that, despite the α- and β-polymorphs having an enantiotropic relationship with a well-defined transition temperature[56, 57], the α-form often dominates the crystallisation, is of particular interest.

Previous studies have identified that the OH…O H-bonding classic dimer found in the α-structure is important in stabilising the lattice energy of the α-form[1]. In addition, previous theoretical studies of PABA cluster stabilities in ethanol suggested that the classic OH…O dimer would be very stable in ethanol, correlating to experimental studies small angle X-ray scattering studies which suggested that a cluster forms with a shape consistent with two PABA molecules forming an OH…O H-bonding dimer[2]. One hypothesis is that this OH…O H-bonding dimer, that is present in the α form, drives this dominant crystallisation of the α-form[60, 61], and the impedance of this dimer by a solvent such as water can result in crystallisation of the β-form[62].

This study deconstructs the α- and β-crystal structures down to their single molecular structures, and then re-builds them based on molecular hydrogen-bonded building blocks of monomers, dimers and tetramers. The stability of the molecular conformation and the stability of increasing size building blocks of each form in the different solvent environments is examined using electronic structure theory and statistical thermodynamics calculations, to rationalise how the conformation energy and the energy of self-assembled pre-nucleation clusters in solution could template the crystallisation of particular polymorphic forms, through the overall methodology which is summarised in Figure 2. To our knowledge, this is the first time that such an approach has been applied on a polymorphic system, whereby the simulations can be related to the solution chemistry and solvent dependent polymorphic crystallisation of the system.

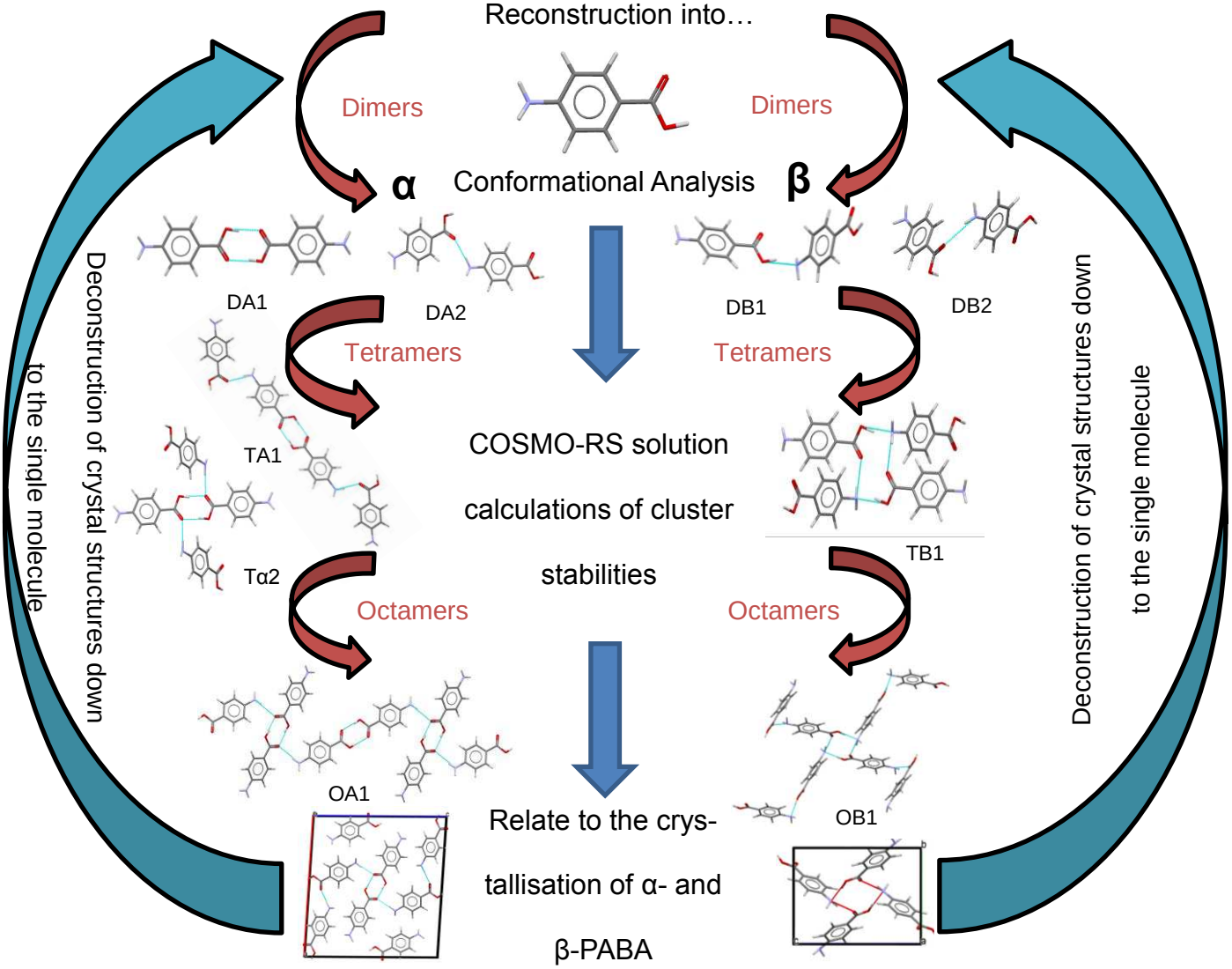


Figure 2: Work flow for the deconstruction of the crystal structures of α and β-PABA to the single molecule, and the subsequent reconstruction into H-bonding dimers, tetramer and octamers, highlighting the calculations carried out to examine their stabilities

2 Materials and Methods

2.1 Para Aminobenzoic Acid

This study focusses on the α- and β-forms of PABA. There are two structures of α-PABA (AMBNAC01 &06) and two structures of β-PABA (AMBNAC04 &08) in the Cambridge Structural Database with resolved atomic positions. The two different structures of α-PABA show practically identical intermolecular crystal chemistry, and this is the same in the case of the two different structures of β-PABA.

2.2 Electronic Structure Theory Calculations

All electronic structure theory calculations were carried out using Gaussian09[63].

2.2.1 Gas Phase Geometry Optimisation of a Single Molecule

The single molecules of PABA from the 4 different crystal structures, totalling 6 molecules since there are two molecules in the asymmetric unit of α-PABA, were optimised in the gas phase with a density functional theory (DFT) approach, utilising a 6-31G* basis set and the Becke three parameter Lee-Yang-Parr (B3LYP) exchange-correlation function[64, 65]. This method has been widely used in the simulation of the stability and thermochemistry of small molecules and has recently been used to examine the stability of H-bonding clusters of ethanol and propan-1-ol[66-68].

2.2.2 Gas Phase Conformational Analysis of the COOH and NH_2 Groups

The dependence of the energy of a single molecule on the geometry of the COOH and NH_2 groups was calculated using the 'Redundant Coordinate Scan' option in Gaussian09. The torsions were defined as redundant coordinate dihedrals, whereby the COOH was rigidly rotated 360° in 10° steps and the hydrogens on the NH_2 group were bent into pyramidal positions approximately 40° above and below the nitrogen in 10° steps. The conformational energies were calculated using the B3LYP/6-31G* approach.

2.3 Solvent Continuum Calculations

2.3.1 Selection of Molecular Structural Building Blocks

The dimeric building blocks were selected based on the strongest H-bonding interactions found from a previous study of the intermolecular interactions within the crystallographic structures of the α- and β-polymorphic forms of PABA[1].

2.3.2 Polarised Continuum Solvent Geometry Optimisations

The monomers identified from the two crystal structures of α-PABA and the crystal structure of β-PABA were optimised using the 6-31G* basis set, utilising the B3LYP functional and compared to the same using the MP2/6-31G*. For both methods the torsion angles of the COOH and NH_2 groups were constrained using the 'redundant coordinate freeze option'. The Conducting Polarisable Continuum (CPCM) method[35] was selected and the dielectric constant of the solvent specified. The monomers and clusters were examined in the following solvents: water (H_2O), acetonitrile (ACN), di-methyl sulfoxide (DMSO), ethyl acetate (EA), ethanol (EtOH), methanol (MeOH) and nitromethane (NMe).

The resulting optimised geometries were then used to calculate a single point energy using the Becke-Parr 86 functional with a triple zeta plus polarisation basis set, utilising the COSMORS keyword, to produce inputs for subsequent solution population calculations.

The B3LYP/6-31G* approach was then repeated for the dimers, tetramers and octamers. The results from using the B3LYP functional were compared to those using the dispersion corrected M06-2X functional[69], as the latter has been shown[31, 70] to give much improved results when treating systems in which the dispersion force plays a significant role in the intermolecular interactions.

2.3.3 Calculations of Solution Populations of Monomers and Clusters

The solution populations were calculated within COSMOthermX15, using the COSMO files produced from Gaussian09 as input for the solute. The screening charge densities (σ) at the surface of the clusters,

calculated from the DFT optimisation, were used to calculate the interaction of the clusters with the surrounding solvent molecules, using a statistical thermodynamic ensemble[41] (full details provided in Section S1, supplementary material). The solvent's COSMO files were selected from the TZVP database provided in COSMOthermX15. The mixture calculation was selected and the concentration of the solute was set to infinite dilution at 25℃. The energy of the molecule or cluster in the solvent continuum and the chemical potential of the molecule or cluster was also extracted from the COSMOtherm output file.

3 Results and Discussion

3.1 Conformational Analysis of a Single Molecule of PABA

Table 1 shows the torsion angles for oxygen's in the COOH group and the hydrogens of the NH_2 group, away from the plane of the phenyl ring, for the six possible molecular conformers of PABA found from the α- and β-PABA crystal structures in the Cambridge Structural Database.

Table 1: Torsion angles of the NH_2 and COOH functional groups from the AMBNAC01, 04 and 06 crystal structures published in the Cambridge Structural Database. Two molecules shown for the two molecules in the asymmetric unit of the AMBNAC01 and 06 crystal structures. Two angles shown for the two C-C-N-H and C-C-C-O angles for the NH_2 and COOH groups respectively

Polymorph	Ref Code	C-C-N-H torsion (°)	C-C-C-O Torsion Angle (°)
α	AMBNAC01 (1)	24.33, -12.03	1.17, -3.40
α	AMBNAC01 (2)	-11.17, 27.76	2.87, 1.91
α	AMBNAC06 (1)	1.75, 0.002	1.34, -0.8
α	AMBNAC06 (2)	-1.91, 0.008	-2.97, -0.85
β	AMBNAC04	32.91, 26.84	10.40, 9.30
β	AMBNAC08	31.28, 24.61	10.87, 10.67

Table 1 shows that the molecular conformers in the α-PABA AMBANC01 and AMBNAC06 structures had planar COOH groups, however the NH_2 group in the AMBNAC01 structure was slightly more pyramidal than the same found in the AMBNAC06 structure. Though both of the α-PABA structures have two molecules in the asymmetric unit, in both cases the conformations of the two molecules in each crystal structure were found to be almost identical.

β-PABA has only one molecule in the asymmetric unit, and the molecular conformations found in the AMBNAC04 and AMBNAC08 structures were almost identical, with a slightly torsioned COOH group and a more pyramidal NH_2 group, in comparison to the α-PABA conformers. Geometry optimisation of these six conformers resulted in the same structure, suggesting this was the lowest energy molecular conformation, shown in Figure 3.

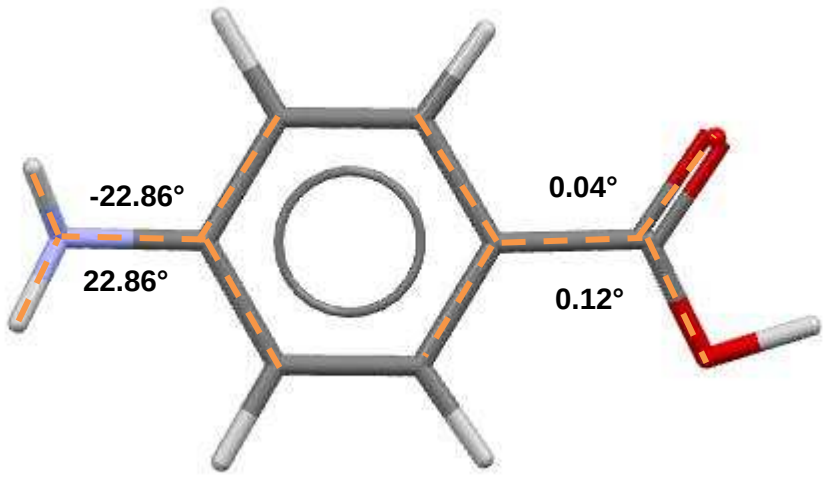
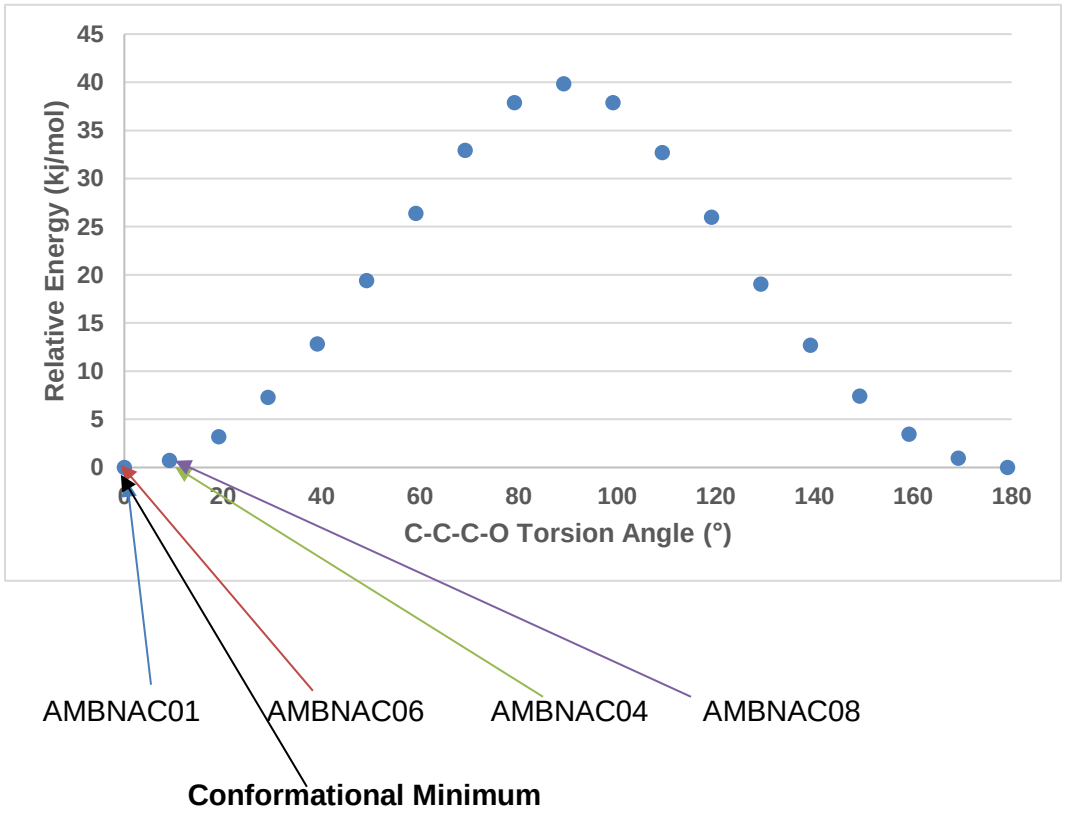


Figure 3: Most stable molecular conformation for a single molecule of pABA found from a 6-31G*/B3LYP gas phase geometry optimisation.

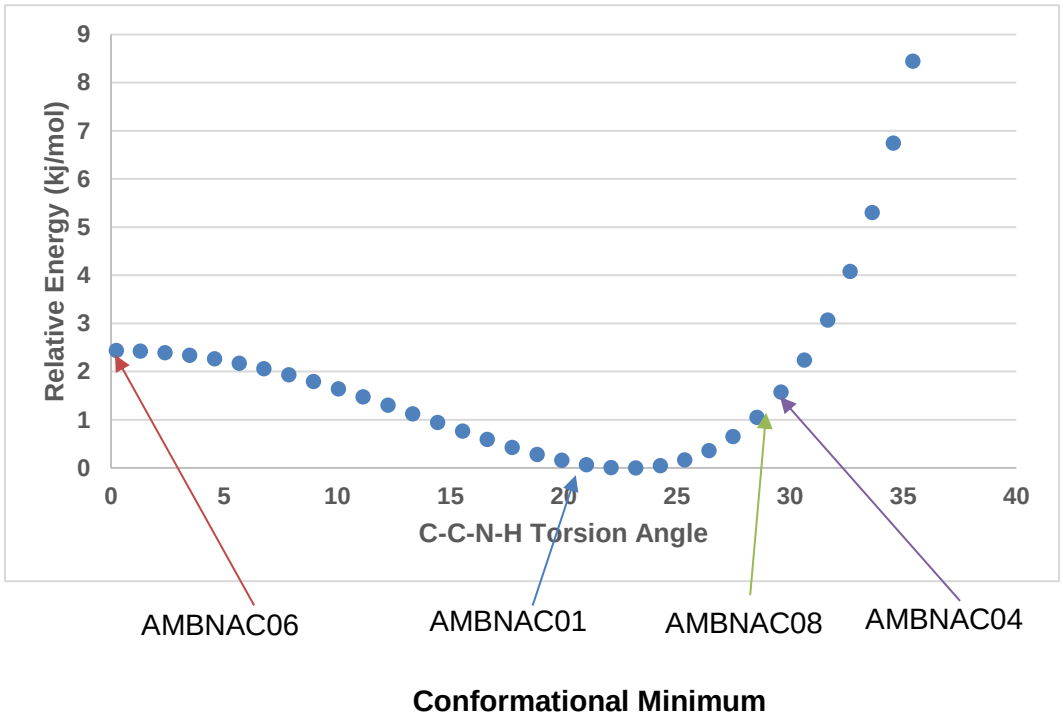
Figure 3 shows that the most stable molecular conformation found for PABA had a planar COOH group and a pyramidal shaped NH_2 group, with respect to the phenyl ring. These results are in good agreement with previously published gas phase electronic structure theory calculations of a PABA molecule[71, 72]. The

fact that each of the conformers in the different crystal structures optimises to the same conformer suggests that the energetic barriers to changes in molecular conformation are relatively low for PABA.

Since both the torsion angles for the COOH and NH_2 groups vary between the α-PABA and β-PABA conformers, the energetic dependence on the rotation of the COOH group and the pyramidilisation of the NH_2 was examined, shown in Figure 4.



(a)



(b)

Figure 4: Conformational energy scan of the (a) rigid rotation of the COOH group in 10° steps and (b) the pyramidal nature of the NH_2 group in 2° steps. The torsion angles for both of these groups found for the conformers in the crystal structures are also shown

Figure 4(a) shows that distortion of the COOH group away from its most stable planar orientation can significantly increase the energy of the molecule. The COOH geometry found in the AMBNAC01 and 06 α-PABA structures was found to be closest to the conformational minima, whilst the slight rotation of the COOH group found in the AMBNAC04 and 08 β-PABA structures resulted in a small energy penalty of less that 2kj/mol.

Figure 4(b) shows that the flattening of the NH_2 group to planar with respect to the phenyl ring, away from its slightly pyramidal optimal geometry, increases the energy of the molecule. Increasing the pyramidal nature of the group beyond 30° rapidly increases the energy of the molecule. The slightly pyramidal

NH_2 geometry in the AMBNAC01 α-PABA structure was found to be closest to the conformational minimum, with the planar AMBNAC06 α-PABA geometry and increased pyramidal AMBNAC04 and 08 β-PABA geometries each costing an energy penalty of approximately 2-2.5kj/mol.

The relatively low energy penalties between the conformers from the different crystal structures suggests that the conformation would be relatively fluid in solution. However, the most stable conformer was found to be the AMBNAC01 α-PABA conformer with a planar COOH and slightly pyramidal NH_2 group. The assertion that the NH_2 group is more likely to be pyramidal, rather than planar, is in good agreement with previously published core-level spectroscopy experimental results and periodic DFT calculations on the α-PABA structure[73].

Though the conformation will fluctuate in solution, we feel that these calculations give an indication of what the energy barriers to adopting the conformation in the crystal structure are likely to be, hence giving insight into what kind of barrier to crystallisation the conformation change from solution to crystal is likely to provide.

3.2 Stability of Crystallographic Building Blocks in Solution

3.2.1 Monomers

The solution populations calculated for the different monomers are shown in Figure 5.

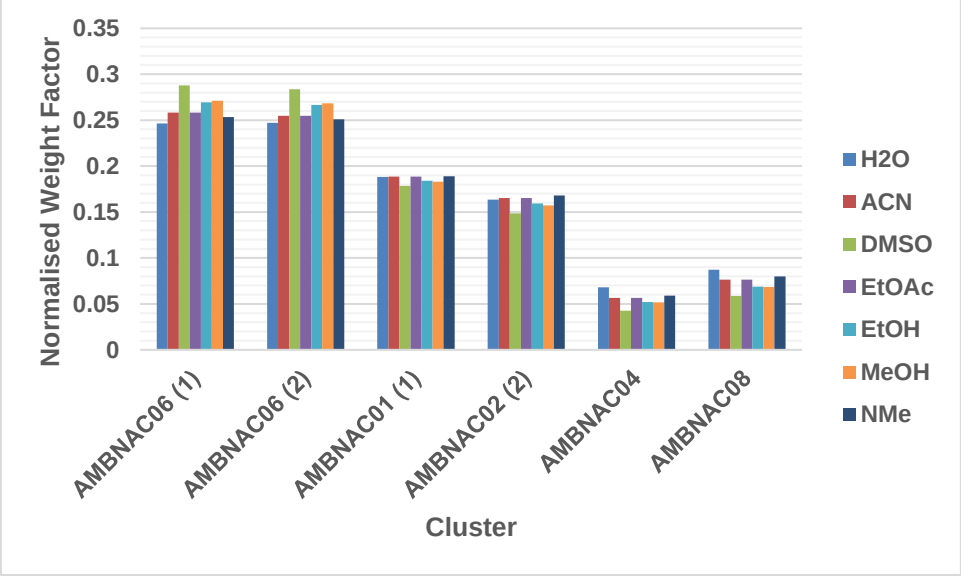


Figure 5: The normalised weight factors of the two molecules of the asymmetric unit of α-PABA from the two crystal structures of α-PABA and the single molecule from the asymmetric unit of the crystal structure of β-PABA, using the 6-31G*/B3LYP approach

Figure 5 shows that the two conformers from the AMBNAC06 α-structure were found to have the largest solution population, then the conformers from the AMBNAC01 α-structure and the conformers from the AMBNAC04 β-structures had the lowest solution populations of around 5%. Despite the conformational analysis suggesting that the AMBNAC01 conformers were more stable in the gas phase than the AMBNAC06 conformers, the AMBNAC06 were calculated to have slightly higher solution populations than the AMBNAC01. This could be due to the COSMO*therm* input files being created using the BP86/TZVP approach, which may not sufficiently account for increased stability of the slightly pyramidal NH_2 group in the AMBNAC01 structure. However, these free energy differences are extremely small, whereby the main finding here is that the β-conformer was calculated to be less stable in solution than the α-conformers, probably due to the combination of the rotated COOH group and increased pyramidilisation of the NH_2 group.

Hence, the energy barrier due to change in molecular conformation from liquid to solid-state is likely to be greatest for the β-structure. However, these calculations suggest that this energy barrier is likely to

be relatively low and may not be the directing factor in the crystallisation of the different polymorphic forms.

3.2.2 Identification of Putative Growth Units for Self-assembly from Solution

The above results has identified the stability of different conformers of the PABA molecule, and the energy penalty that they may occur when the molecule transitions from the solution to the solid-state crystal form. Crystal structures are a balance of conformational and packing energies, therefore, drawing upon previous studies of the solid-state chemistry, intermolecular synthon structure and solution structure present in the α- and β-PABA[1, 2], the following results deal with the solution stability of the H-bonded building blocks found in α- and β-PABA. These molecular building blocks are summarised in Figure 6.

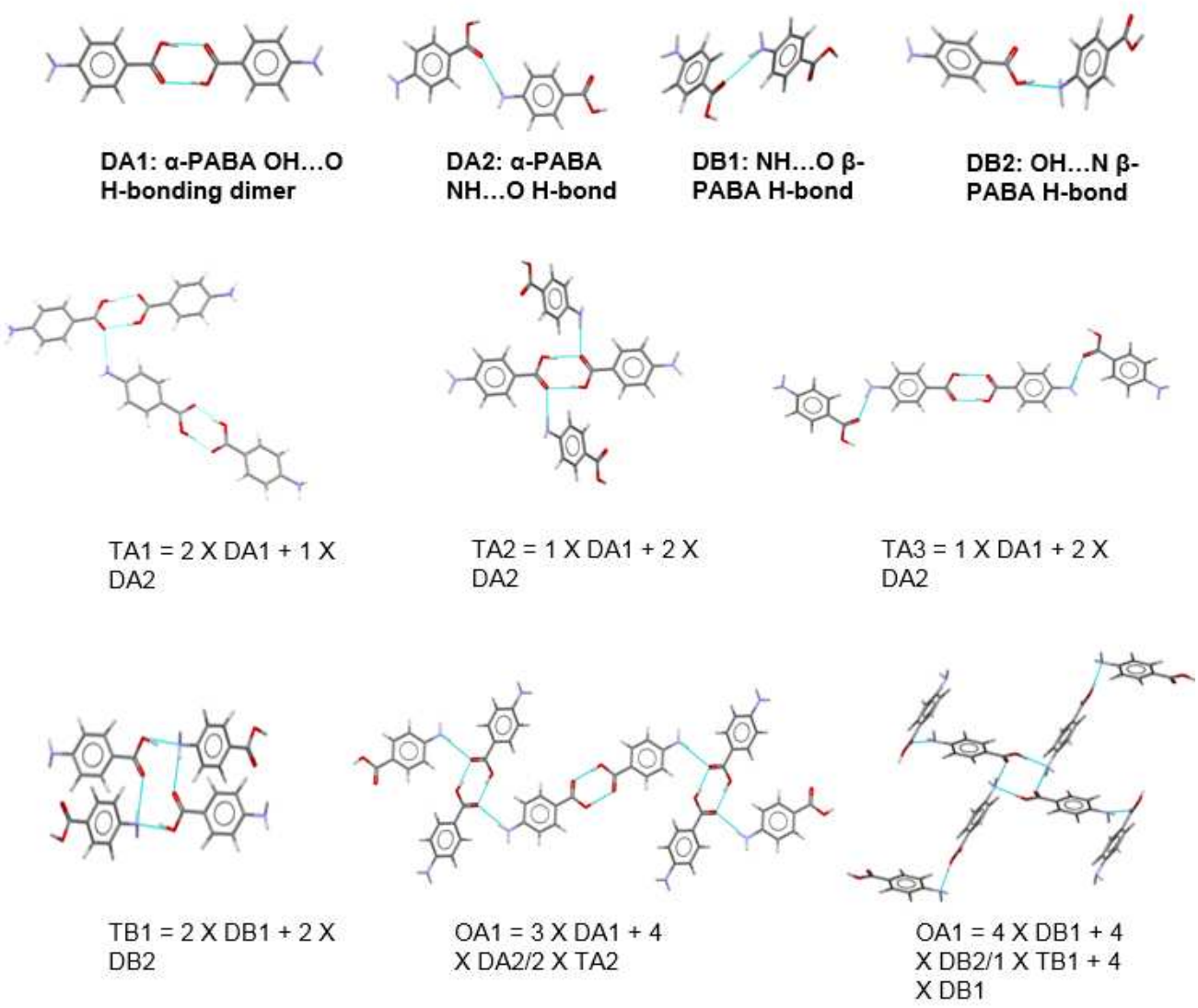


Figure 6: The 4 dimers, 4 tetramers and 2 octamers depicted from the crystal structure of α- and β-polymorphs of PABA. These clusters are based on the H-bonding interactions that have been found to be important in the stabilisation of the α- and β-structures of PABA in previous studies[1, 2]

The building blocks shown in Figure 6 were examined using the COSMO-RS approach to estimate their relative populations in solution (normalised weight factors).

3.2.3 Dimers

A previous study[1] has shown that the DA1 dimer was found to be the strongest synthon from the solid-state structures of α- and β-PABA, and that the stability of such 'classic carboxylic acid dimers' in solution can template the nucleation of specific crystalline forms of small organic molecules[31, 32, 34]. Figure 7 shows a comparison of the normalised weight factors of the H-bonded dimers, shown in Figure 6.

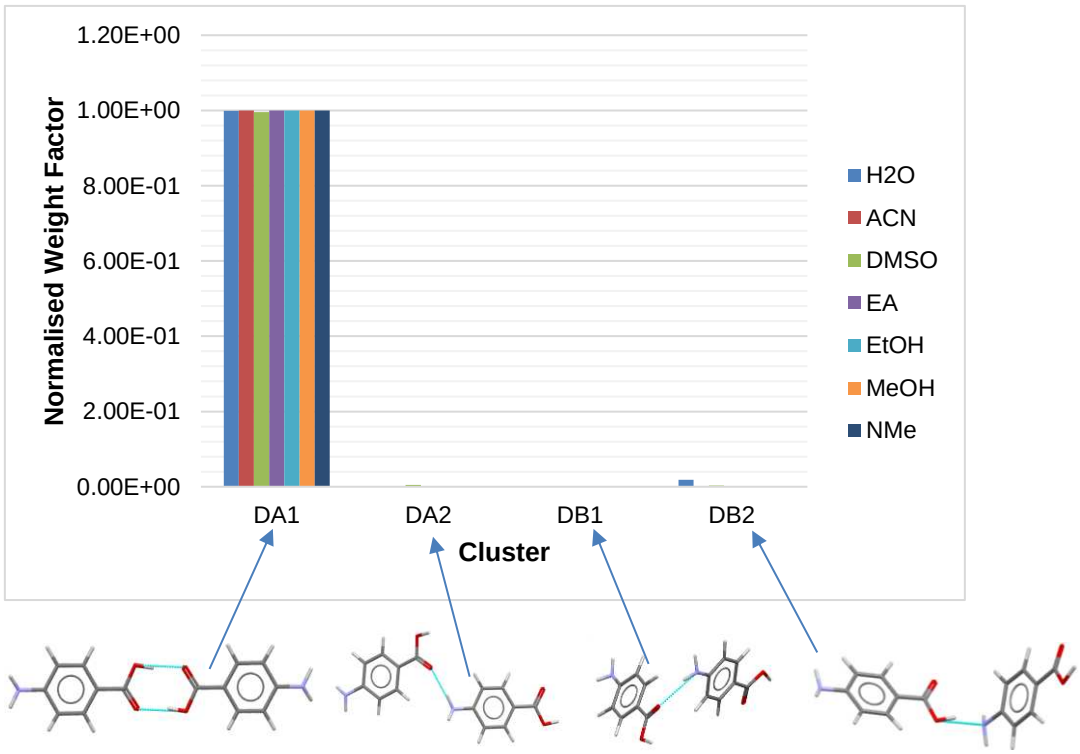


Figure 7: Comparison of the normalised weight factors of DA1 with the other dimers identified in Figure 6 showing that the DA1 dominates the calculated solution populations in all of the solvents studied here

Figure 7 shows that the DA1 dimer dominates the solution populations in all solvents when compared to the other dimers. The comparison of DA1 with DB2 in water show that there is a small amount of the DB2 dimer predicted to be present in that solution, but the DA1 dimer is still clearly predicted to be the most stable dimeric building block in solution which exists in either the α- or the β-structure.

When DA1 is not considered, the DB2 cluster is generally predicted to have the highest solution population in comparison to the other dimers, shown in Figure 8.

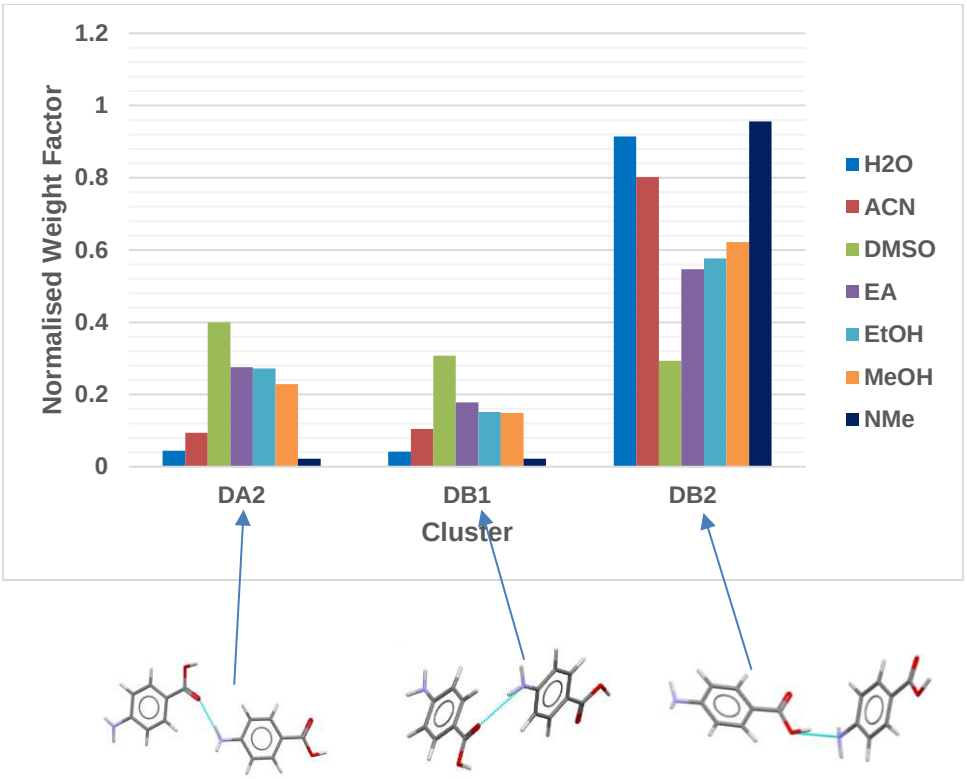


Figure 8: Solution populations of DB2 in comparison to the other dimers except DA1, showing that the DB2 dimer is the second most stable dimer and has particular stability in water, possibly templating the formation of β-PABA in water

Figure 8 shows that the DB2 dimer was predicted have the greatest solution population, when compared to the DA2 and DB1 which both contain the NH…O H-bonding interaction. The DB2 dimer is particularly dominant in water and nitromethane. Interesting both of these solvents display unusual polymorphic behaviour in comparison to the other solvents studied, with water being the most reliable solvent for producing the β-form[62] and nitromethane being recently found to produce a solvate structure[59].

Since it has been highlighted that DFT calculations of organic materials can often poorly estimate the effects of dispersion interactions[74, 75], a comparison of the results using the B3LYP and dispersion corrected M06-2X functional revealed negligible changes in the solution population results (supplementary materials). Hence, the B3LYP functional was used for the solution population calculations of the tetramers and octamers.

The free energy change from two monomers to the four H-bonding dimers, in aqueous solution, was also calculated (Figure S1 in supplementary material). The free energy change for each of the four dimers was negative, suggesting they are plausible building blocks for embryonic solution clusters. It was also found that the free energy change for the DA1 cluster was most favoured, followed by the DB2 cluster, suggesting that the populations shown in Figure 8 are representative of the free energy calculations.

3.2.4 Tetramers and Octamers

The normalised weight factors of the tetramers and octamers are shown in Figure 9.

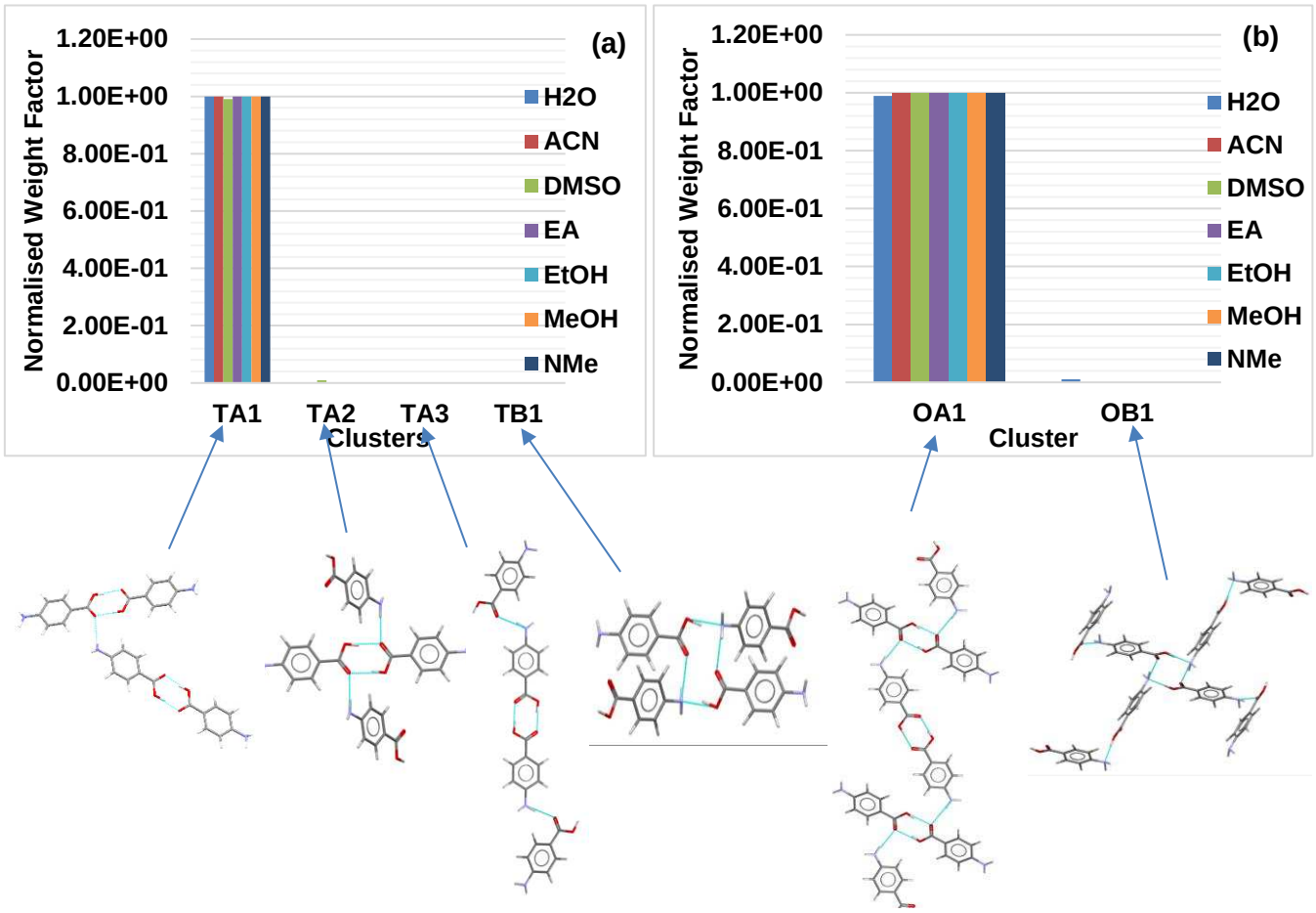
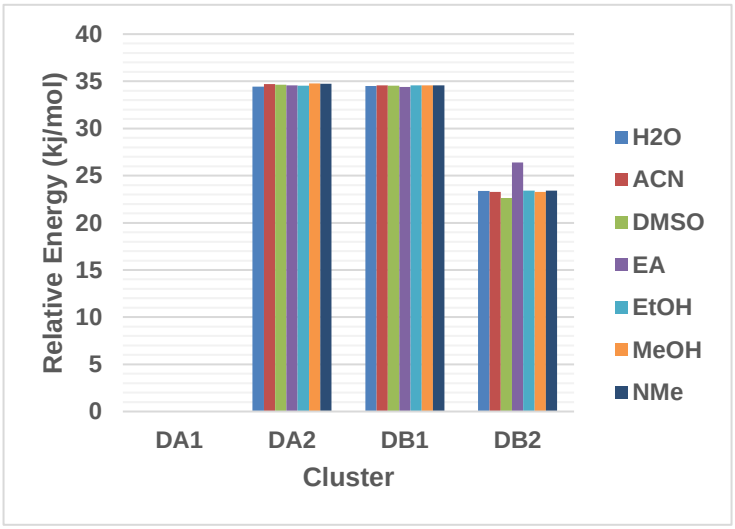


Figure 9: (a) Comparison of the normalised weight factors of the H-bonding tetramers identified in Figure 6; (b) comparison of the normalised weight factors of the two H-bonding octamers identified in Figure 5. These results show that as the size of the clusters increases, the population of the tetramers and octamers containing the OH…O H-bonding dimers becomes even more enhanced in comparison to those which do not contain this interaction

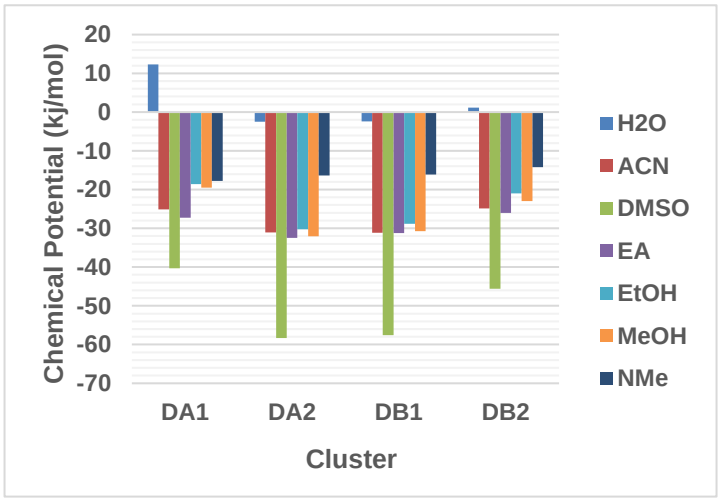
The TA1 cluster, which is made up of two DA1 like H-bonding dimers that are linked by an NH…O H-bond, were calculated to dominate in solution over the other clusters examined. This domination of these OH…O and NH…O H-bonding clusters is also reflected in the domination of the α-H-bonding octamer over the β-H-bonding octamer. The high stability of the clusters of increasing size that are reflective of the α-crystal structure may be indicative that the self-assembly of the α-structure in solution is favoured over the β-structure self-assembly, resulting in the dominant crystallisation of the α-form.

3.3 Cluster Energetics

Equation S7 (supplementary material) indicates that the population of the different clusters is dependent on the energy of the cluster in the continuum (E_{cosmo}) and the chemical potential (μ^s). The E_{cosmo} energetics and the chemical potentials for the dimers are shown in Figure 10.



(a)



(b)

Figure 10: (a) E_{cosmo} for the dimers showing that the free energy of the DA1 dimer is over 20kj/mol more stable than the next most stable dimer in all solvents; (b) the chemical potentials for the dimers showing that the DA1 has a particularly unfavourable chemical potential in water

Figure 10(a) reveals that the energy of the DA1 dimer in the continuum for all the solvents is much more stable than for the other dimers tested. This suggests that the energy of interaction between the molecules in the DA1 results in its domination of the Boltzmann populations. Further to this, Figure 10(b) shows that the chemical potentials for DA1 are in general lower than for most of the other clusters studied. Indeed, the chemical potential calculated for the DA1 cluster in water was found to be positive,

suggesting that the DA1 dimers interactions with the surrounding solution are unfavourable, but this is compensated by the favourable interaction energy between the PABA molecules within the dimer.

3.4 Impact upon the Direction of Polymorphic Form

The examination of the conformation and cluster stability of PABA in solution suggests that both of these pose a greater barrier to the crystal nucleation of β-PABA from solution, compared to α-PABA. Further scrutiny of the H-bonding ring structure in β-PABA (Figure 1) shows that the directionality of the DB1 and DB2 synthons indeed distorts the conformation of the COOH and NH_2 groups to a conformation that was calculated to be less stable in solution than the α-PABA conformation. Hence, it is likely that the COOH group on the molecule in the β-form rotates to this unfavourable conformation to maximise the OH…N and NH…O H-bonding interactions. However, since the energy barriers to distorting the conformation in solution were calculated to be low, it is more likely that the clustering of the solute in solution directs the nucleation to a greater extent than the molecular conformation.

The calculated dominant stability of the OH…O H-bonding dimers, along with the tetramers and octamers containing such H-bonding motifs, probably directs the dominant nucleation of the α-form observed from most organic solvents. A comparison to p-aminophenol[76] shows that replacing the COOH group with an OH group results in a packing structure which more closely resembles the β-PABA structure, rather than α-PABA. It can be observed that in small molecules which contain a carboxylic group, such as ibuprofen[77] and aspirin[78], their crystal structures contain the classic OH…O H-bonding interaction. However, as molecules go up in molecular weight and have other competing intermolecular interactions which they can form, the propensity for the OH…O dimers to direct the packing structure may well be reduced. However, from the limited structures examined we can suggest that small molecules are likely to pack in motifs that facilitate the formation of these strong H-bonding dimer interactions.

It is interesting to note the role that the NH…O interactions play in linking the OH…O H-bonding dimers in the α-structure to form H-bonding chains through the structure. These chains will create a cooperative H-bonding effect which can enhance the packing energy of the α-like clusters as they increase in size,

where such cooperative H-bonding stabilisation has been seen in similar organic molecules[79, 80]. In contrast, the β-form does not have any infinite chains of H-bonds within its structure, suggesting that clusters which resemble the β-form would be much less likely to benefit from such cooperative H-bonding effects. Hence, the H-bonding cooperativity would be likely significant role in the rapid self-assembly of the α-form in solution, and have a much lesser effect on stabilising solute clusters which resemble the β-form in solution.

Drawing upon the more detailed examination of the COSMO-RS calculations, the OH…O H-bonding dimers were found to be least stable in water, due to unfavourable interactions of this dimer with the surrounding solution. We speculate that the observation of crystallisation of the β-form from aqueous solutions[54, 62] can be related to these unfavourable interactions of this dimer with the surrounding water, hence impeding the nucleation of the α-form.

4 Conclusions

This study has revealed that even for a small molecule, such as PABA, the molecular conformation, crystal packing and solute clustering in solution can impact upon the polymorphic direction of solution crystallisation. These simulations have revealed that the crystal packing of the α-form structure is less likely to distort the PABA molecule away from its most favoured conformation, whilst the directional OH…N and NH…O H-bonding ring interactions present in the β-form structure distort the NH_2 and COOH torsion angles away from their most favoured conformation. As a caveat to this, the OH…O H-bonding dimer that has been identified as a key synthon for the α-form structure was found to dominate the solution populations, in comparison to the other identified key synthons from the α- and β-forms.

These results suggest that the energetic barrier to solution crystallisation of α-PABA would be lower than β-PABA, reflected in the experimentally observed dominant crystallisation of this form from solution, even in environments where the β-form is expected to be thermodynamically stable. Indeed these calculations also suggest that the formation of the OH…O H-bonding carboxylic acid dimer would be least stable in

water, reflecting experimental observations that the kinetic barrier to nucleation is higher in water when compared to acetonitrile and ethanol[60], along with water being the only solvent to reliably crystallise the β-form[62].

The flexibility of such simulations to be able to treat a wide variety of elements indicates that the methods here could be expanded to a wide variety of polymorphic materials. The early indication of barriers to crystallisation of certain molecules, or polymorphs of a particular molecule, can be vital in the design of crystallisation of a high value crystalline material. Indeed, folding the influence of different solvent into the model can further assist in the decision making associated with the manufacturing and processing of a high value crystalline material.

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