Kinetic Insights into the Role of the Solvent in the Polymorphism of 5-Fluorouracil from Molecular Dynamics Simulations

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We investigate the fundamental factors controlling polymorphism in 5-fluorouracil by performing molecular dynamics simulations of solutions of the compound in water, nitromethane, and wet nitromethane. Analysis of the effect of solvent on the initial aggregation of 5-fluorouracil molecules shows that the strong binding of water to the 5-fluorouracil molecule hinders the formation of the doubly hydrogen-bonded dimer and, by default, promotes close hydrophobic F···F interactions that are a feature of the unusual ($Z' = 4$) structure of form I. In contrast, doubly hydrogen-bonded dimers are observed to form readily in solution in dry nitromethane, consistent with the crystallization of the doubly hydrogen-bonded ribbon structure of form II from this solvent. When nitromethane is doped with water, the water forms hydrogen bonds to the solute, interfering with the formation of the doubly hydrogen-bonded dimers, which is consistent with the crystallization of form I from this hygroscopic solvent when it is not dried. Overall, the molecular dynamics simulations provide an atomistic picture of how solvent−solute interactions can significantly affect the initial association of 5-fluorouracil molecules to the extent that they determine the polymorphic outcome of the crystallization.

I. Introduction

Polymorphism, that is, the ability of some molecules to crystallize in more than one structure,[1] is a problem of major practical importance for the pharmaceutical and other industries based on molecular materials, which need to manufacture reliably in only one polymorphic form. Moreover, polymorphism raises fundamental questions concerning the factors that determine the outcome of crystallization procedures. The nature of the polymorph produced can be sensitive to a wide range of factors, such as solvent,[2] supersaturation,[3] seeding,[4,5] pressure,[6] and temperature, and new polymorphs continue to be discovered[7] or re-obtained[8] through novel crystallization methods. Developing an understanding of crystallization processes and mechanisms that lead to metastable polymorphs is essential if we are to predict polymorphism reliably.[9−11] Hence, there is considerable scientific and practical interest in obtaining insight into the early stages of molecular association in solution and nucleation[12,13] that affect polymorphic outcome.

We have recently obtained a new polymorph[14] of 5-fluorouracil that was originally synthesized in 1957[15] and is widely used as a pharmaceutical for the treatment of solid tumors.[16] The structure of the previously known polymorph was determined over 25 years ago[17] and invites rationalization as, unusually, it has four molecules in the asymmetric unit, with four fluorine atoms in close proximity (Figure 1a). Our earlier computational study[14] predicted that crystal structures of 5-fluorouracil in which all of the N−H···O═C hydrogen bonds were in doubly hydrogen-bonded pairs would, as expected, be competitive in stability with the known form. Following a series of crystallization experiments, form II was found, whose structure (Figure 1b) corresponds to that predicted to be the most stable in terms of lattice energy, although experimentally it was found to be thermodynamically less stable. The new form crystallized from nitromethane, and further crystallization experiments demonstrated that it could only be obtained from dry nitromethane. Experiments in which this hygroscopic solvent was not carefully dried resulted in form I, as did crystallization from most polar solvents in which 5-fluorouracil is soluble; and indeed form I is normally crystallized from aqueous solution. These observations led to the hypothesis that the difference in the solvation of the 5-fluorouracil molecules by nitromethane from that by polar molecules, such as water, is responsible for the growth of form II.

In this article, we seek a molecular mechanism to account for the factors controlling the polymorphism of 5-fluorouracil, by using molecular dynamics (MD) simulations to study the self-assembly of 5-fluorouracil molecules, contrasting the behavior in aqueous solution, in nitromethane solution, and in wet nitromethane solution. Molecular dynamics simulations are well established for simulating organic liquids and water[18] and have been used for estimating the enthalpies of solvation of solute molecules;[19] nevertheless, relatively few applications have focused on the initial stages of crystallization from solution, despite the obvious potential of MD to give such molecular-level insights.[20] The value of the method has been demonstrated in simulations of crystallization from solvents with model monatomic systems[21] and, more recently, of prenucleation processes in ZnS in aqueous solution.[22] Simulations of solutions of organic molecules have provided insight into how the hydrogen-bonded motifs in the crystal structures of 2-pyridone,[23] acetic acid,[24] and both polymorphs of tetrolic acid[25] can be related to the behavior in a nonpolar solvent model of carbon tetrachloride. This study uses molecular dynamics simulations to show how solvation effects in the prenucleation stage can control the polymorphic form, contrasting the behaviors in different solvents.

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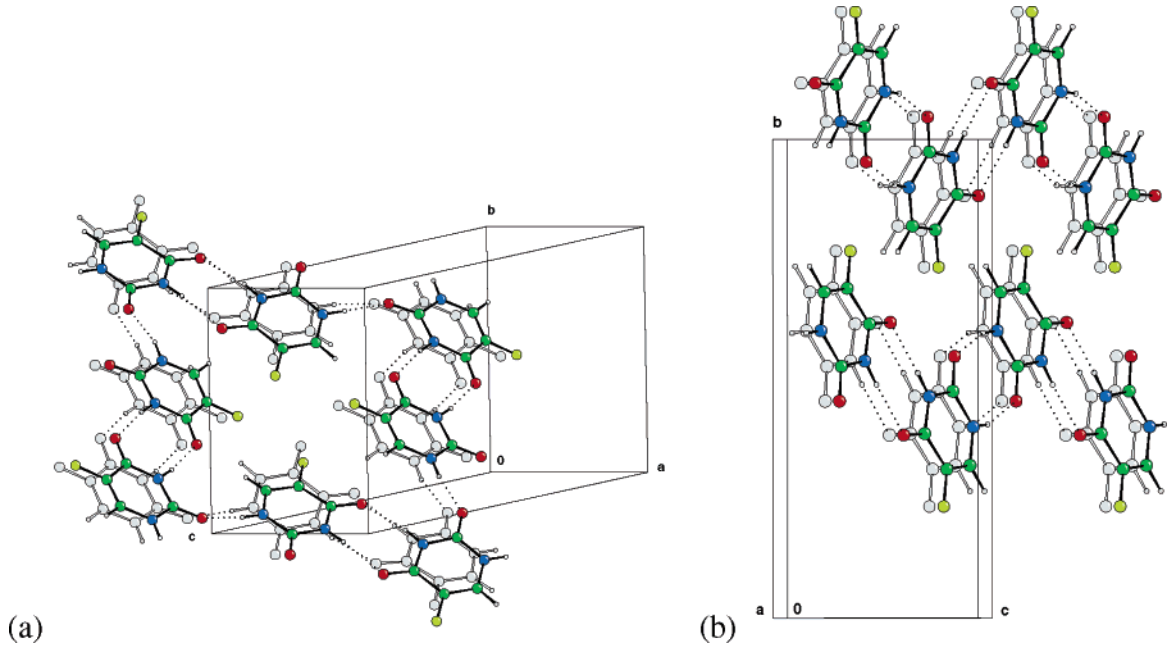
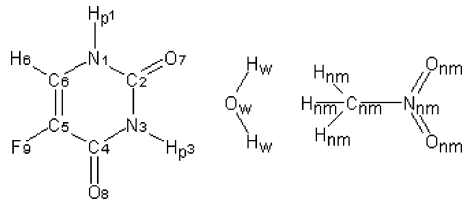


Figure 1. Crystal structure of 5-fluorouracil in (a) form I, showing two rippled sheets formed with close F···F contacts within each sheet, and (b) form II, showing two rippled sheets formed from chains of doubly hydrogen-bonded dimers.

CHART 1: Molecular Diagrams for 5-Fluorouracil, Water, and Nitromethane, Defining the Atomic Numbering and Atomic Types



II. Computational Details

All of our molecular dynamics (MD) simulations employ the DL_POLY[26] code implemented on the massively parallel, terascale computing facility HPCx at the CCLRC Daresbury Laboratory. 5-Fluorouracil molecules show very little flexibility, and so, they were modeled as rigid entities, using the ab initio MP2/6-31G**-optimized molecular structure. The intermolecular interactions for the molecules were described by the DREIDING force field,[27] which has been developed to simulate a wide range of organic molecules. The point charges on each atom were obtained from the ab initio MP2/6-31G** calculation on the optimized molecular structure in vacuo by electrostatic potential fitting using the CHELPG method within Gaussian 98.[28] The long-range electrostatic interactions were calculated using the Ewald summation.[29] Water molecules were modeled using the rigid SPC potential,[30,31] whereas the nitromethane intra- and intermolecular interactions were modeled using a set of potential parameters that previous studies[32,33] have shown describe correctly the behavior of this molecule in molecular dynamics simulations. The interaction parameters for the heteromolecular interactions (5-fluorouracil−water, 5-fluorouracil−nitromethane, and water−nitromethane) were obtained using the standard Lorentz−Bethelot combination rules, using the atomic-type definitions given in Chart 1. Hence, the model intermolecular potential was derived from appropriate available sources and was not adjusted for this particular study.

All the simulations were performed at ambient temperature and pressure. A 50 ps run for equilibration was applied first, during which all of the molecules were free to move, and equilibration was achieved. We then simulated the systems for 4 ns, in the NPT ensemble, using the Nosé−Hoover[34,35] thermostat and barostat to maintain the system at room temperature and pressure, and using time parameters in the range of 0.1−0.4 ps for the thermostat and barostat, depending on the system. The time step used to solve the equations of motion was 0.75 fs.

5-Fluorouracil form I is poorly soluble in all solvents, for example, approximately 2 mg mL^{-1} in nitromethane and about 10 mg mL^{-1} in water, which implies a ratio of several hundred water molecules to each 5-fluorouracil molecule in a saturated aqueous solution. The use of such low concentrations in simulations would require very large simulation cells in order to contain sufficient fluorouracil molecules to model any aggregation, which would make any molecular dynamics study unfeasible. Hence, the simulation cells were cubic boxes of side ca. 37 Å, and all simulations were performed with moderate numbers of molecules corresponding to high supersaturations. The solubility of form II has not been measured, although it is not expected to be significantly more soluble than form I. Hence, it is not possible to make use of the relative solubilities of the two polymorphs.

We studied the association of 5-flurouracil molecules in aqueous solution by using an initially random configuration of 16 5-fluorouracil molecules in the simulation box of water molecules, corresponding to a ratio of 1:97, approximately 6 times the saturated concentration. In contrast, in our simulations of nitromethane solutions, the 16 solute molecules were randomly dispersed in the simulation cell with 480 nitromethane molecules. The nitromethane solutions experimentally used in the growth of 5-fluorouracil crystals are usually contaminated through contact with air, typically containing 0.1−1% of water molecules (which corresponds to 4−40 water molecules per 5-fluorouracil molecule), and as noted, only nitromethane solutions that are carefully treated to avoid the presence of water crystallize form II. The effect of the hygroscopicity of nitromethane was modeled in a "wet nitromethane simulation" in which 4 water molecules per fluorouracil were added to the solution of 16 5-fluorouracil molecules in 496 nitromethane molecules. The properties of all of the systems simulated are summarized in Table 1. The number of solvent molecules was

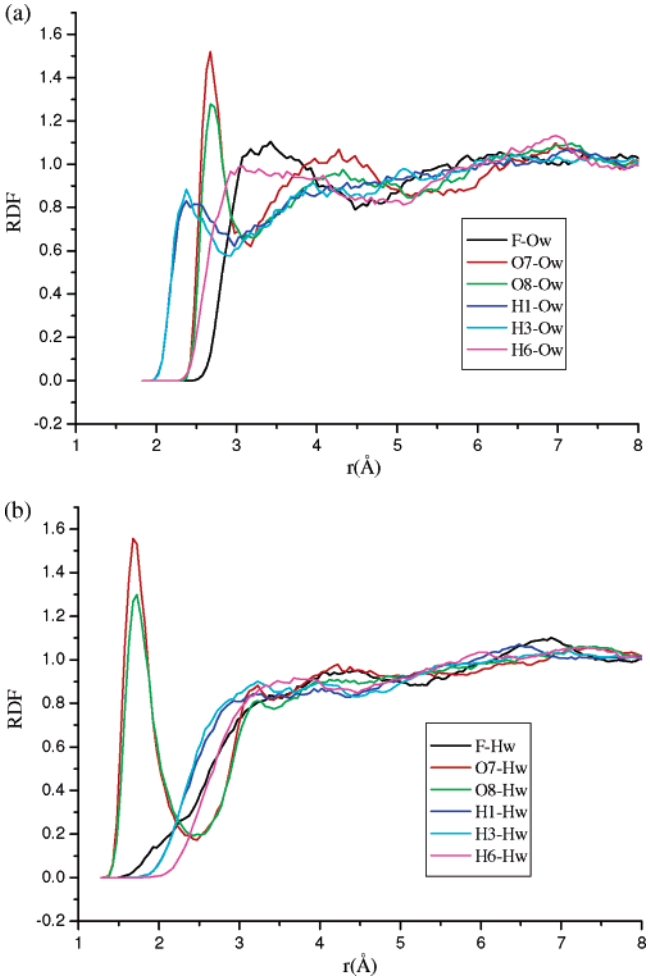


Figure 2. RDFs between atoms in 5-fluorouracil molecules and atoms in water molecules in aqueous solution: (a) with O_w and (b) with H_w.

TABLE 1: Molecular Dynamics Simulation Details

	aqueous solution	nitromethane solution	wet nitromethane solution
number of 5-fluorouracil molecules	16	16	16
number of water molecules	1550	0	64
number of nitromethane molecules	0	480	496
equilibrated cell size	36.9 Å	36.4 Å	36.7 Å
simulated time	4 ns	4 ns	4 ns

chosen in every case to make the volume of the unit cells approximately the same in all of the simulations.

We note that the heavy supersaturation used in these simulations is an advantage for the purpose of this work, as it enhances solute−solute interactions and hence prenucleation events. Even using such supersaturations and modeling the system using terascale computers, it is still not possible to observe the formation of large clusters of solute molecules in solution, because of the extremely long simulation times and large system sizes that would be required to observe the formation of critical nuclei.

The simulations were visualized using Materials Studio, available from Accelrys.[36] Various radial distribution functions[29] (RDFs) were calculated throughout the duration of the production run by evaluating a histogram of the distances between every pair of atoms of defined atomic types and atomic numbering (as defined in Chart 1) every 10 time steps. The RDFs shown are those obtained by averaging all of the histograms and normalizing to the RDF of an ideal gas of the same density.

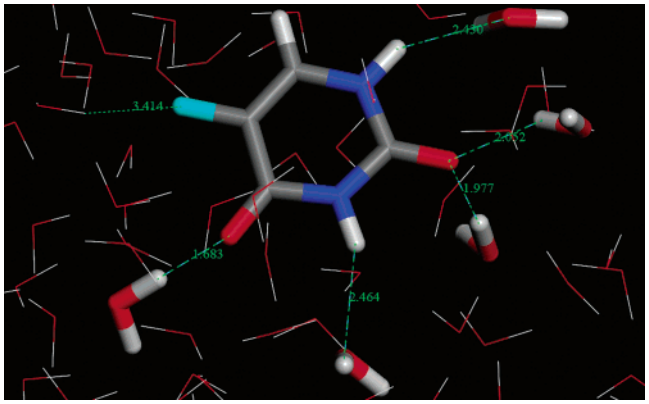


Figure 3. Snapshot showing the hydrogen-bond networks around the 5-fluorouracil molecules typically observed in the aqueous solution simulations. Hydrogen bonds (distances less than 2.5 Å) are shown as blue lines. The atom closest to the F atom is at 3.4 Å.

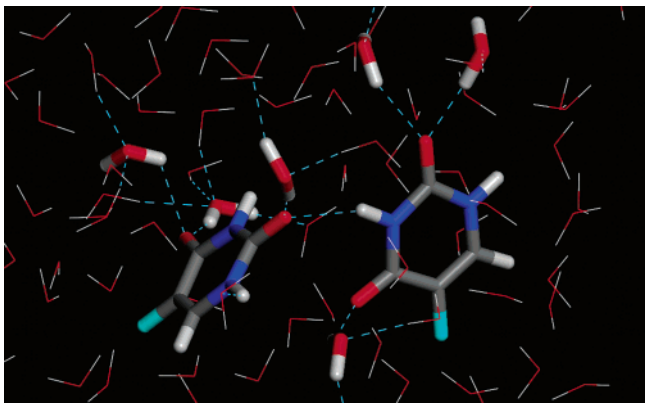


Figure 4. Snapshot showing a single hydrogen bond formed between 5-fluorouracil molecules in aqueous solution. The water molecules that are hydrogen-bonded to the 5-fluorouracil molecules are shown in the thicker stick format and appear to prevent the formation of a double hydrogen bond.

III. Results

IIIa. 5-Fluorouracil in Aqueous Solution. The nature of the hydration of 5-fluorouracil in aqueous solution is indicated by the differences in radial distribution functions for water and 5-fluorouracil atoms shown in Figure 2. It is clear first that the oxygen atoms of fluorouracil interact strongly with the water molecules: The RDFs show sharp peaks at an O···H_W distance of 1.6 Å (O refers to both O7 and O8) (Figure 2b) and at an O···O_W distance of 2.7 Å (Figure 2a). The interaction between the F atoms and the water molecules is much weaker: there is no peak at all in the F···H_W RDF (Figure 2b), and the water oxygens do not approach the F atoms more closely than 3 Å. The visualization of the simulations showed that the occasional contacts between F and H_W are of short duration, as the persistent features of the hydration structure involved the water H_W being hydrogen-bonded to other waters or the oxygens of 5-fluorouracil.

The differences in the nature of the interactions between the O and F atoms of 5-fluorouracil and the water molecules result in the hydration of 5-fluorouracil showing hydrophilic (O) and hydrophobic (F) regions. This feature is illustrated in Figure 3, which shows a typical snapshot of a hydrated 5-fluorouracil molecule where one can clearly see the presence of O···H_W hydrogen bonds leading to a hydrogen-bonded network of water

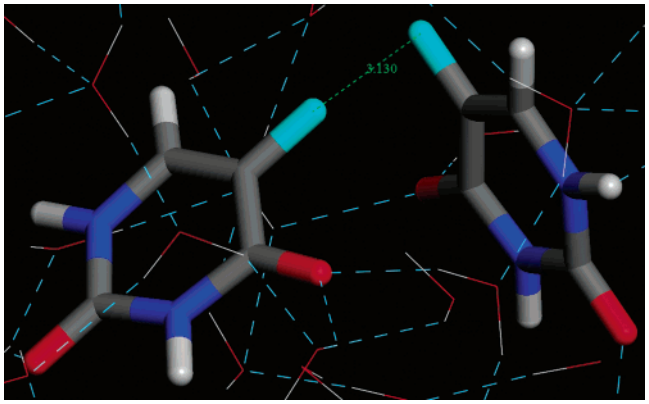


Figure 5. Snapshot from association of 5-fluorouracil in water. Hydrogen bonds are shown in broken blue lines, and the close F···F contact is shown in green.

molecules around most of the 5-fluorouracil molecule, but with a small surrounding, water-free region around the F atom.

The effect of these solute−water interactions on the solute−solute interactions is illustrated in the snapshots in Figures 4 and 5.

Figure 4 shows the formation of a single CO···H hydrogen bond between 5-fluorouracil molecules while the adjacent hydrogen-bond donors and acceptors are hydrogen-bonded to water molecules. We did not observe the formation of any 5-fluorouracil doubly hydrogen-bonded dimers in aqueous solution, implying that the additional solute−solute hydrogen bonds could not be formed by displacement of the water molecules. Indeed, during the simulation, any one 5-fluorouracil molecule did not form hydrogen bonds with more than one other 5-fluorouracil molecule at the same time. Figure 5 illustrates the other dominant close contact between 5-fluorouracil molecules in aqueous solution, that of F···F contacts in a large water-free cavity. These contacts cause the peak in the F···F RDF for van der Waals contact between 5-fluorouracil molecules in Figure 6, which is the most well-defined contact between the associating solute molecules in water.

IIIb. 5-Fluorouracil in Nitromethane Solution. The NPT simulations of 5-fluorouracil in pure nitromethane solution, from which form II crystallizes, demonstrate that the behavior of 5-fluorouracil in this solvent is very different from that observed when the solvent is water. Figure 7 shows the RDFs for the interactions between 5-fluorouracil and the nitromethane solvent. The first peaks in the $H_P\cdots O_{NM}$ (where H_P refers to both H1 and H3) and $O\cdots H_{NM}$ RDFs are at around 2.3 Å, compared to the simulation in water, where the first $O\cdots H_W$ peak is at 1.6 Å and is sharper. Similarly, the $O\cdots O_{NM}$ peak is far broader and at a larger separation than the $O\cdots O_W$ peak, confirming that the interactions with nitromethane are weaker and more variable in structure than the well-defined hydrogen-bonded geometry seen in water. As might be expected from the weak polarity of methyl hydrogen atoms, the hydrogen atoms of nitromethane approach both the 5-fluorouracil oxygen and fluorine atoms at their similar van der Waals contact distances.

Figure 8 shows a snapshot of a solvated 5-fluorouracil molecule, with the hydrogen atoms forming hydrogen bonds with the oxygen atoms in nitromethane, which also emphasizes that the poorer hydrogen-bonding ability of nitromethane results in a less-structured solvation environment. As a result, we can regard 5-fluorouracil as more evenly solvated and less strongly bound by nitromethane, thus making it easier to displace nitromethane than water from the solvation sphere.

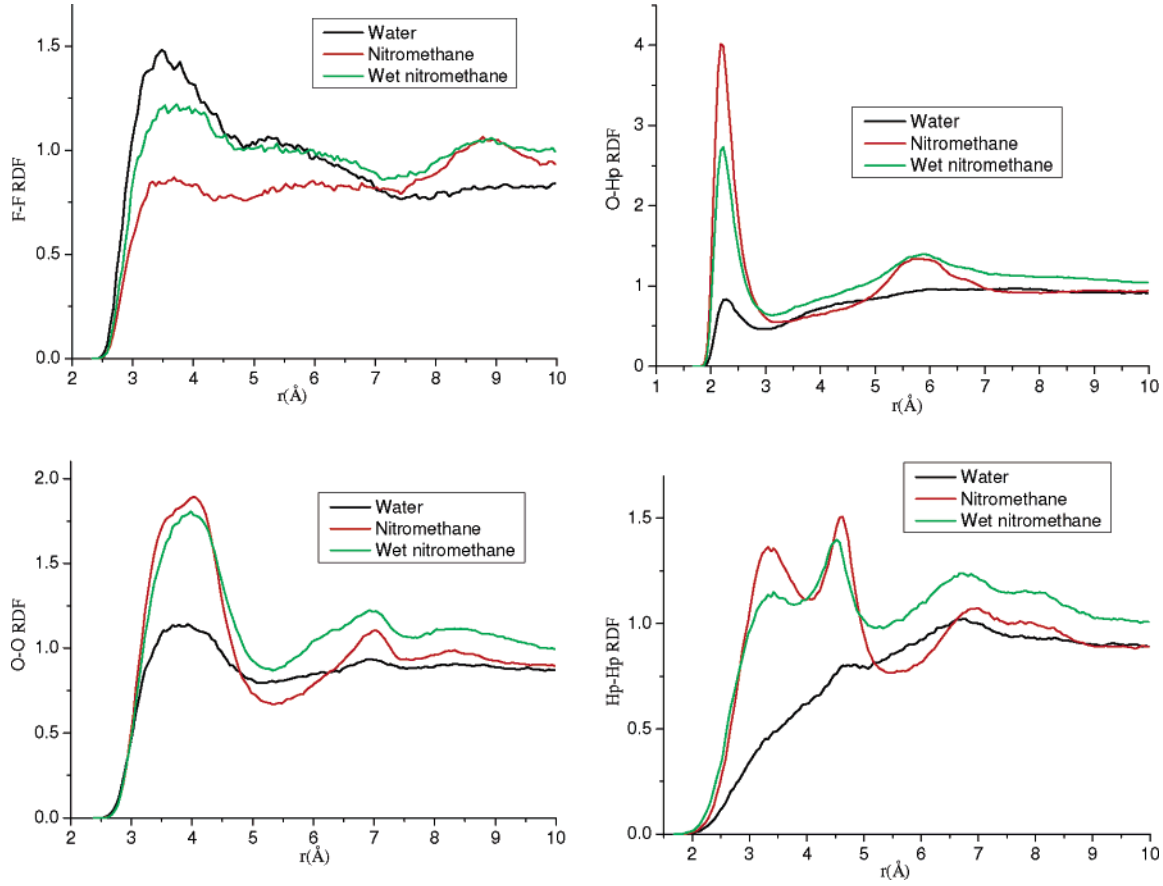


Figure 6. Contrasting RDFs for 5-fluorouracil···5-fluorouracil interactions in water (black), nitromethane (red), and wet nitromethane (green).

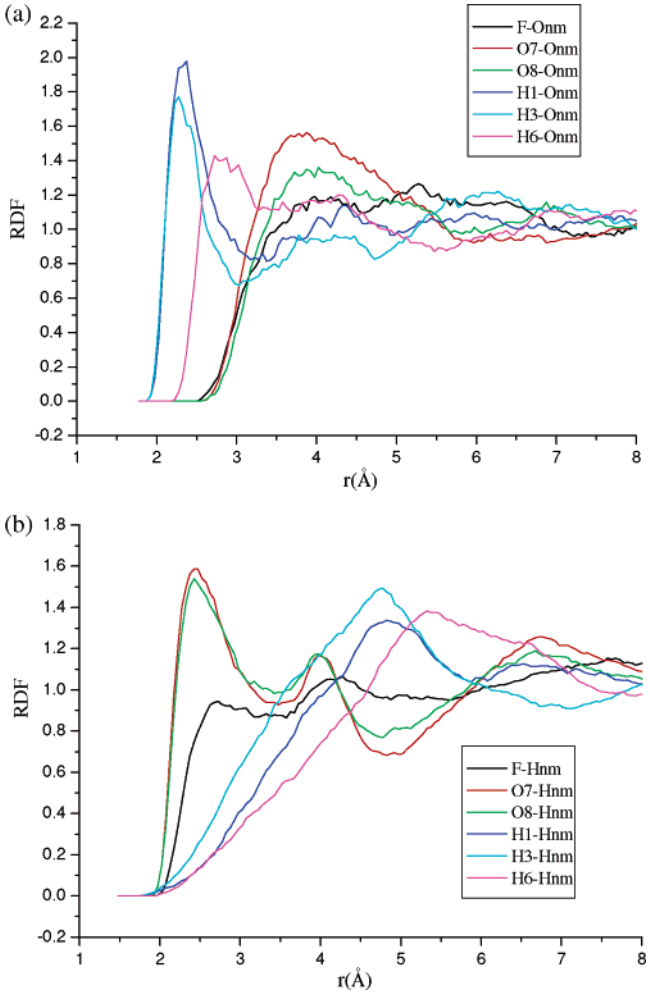


Figure 7. RDFs between atoms in 5-fluorouracil and solvent atoms in nitromethane solution: (a) with O_{NM} and (b) with H_{NM}.

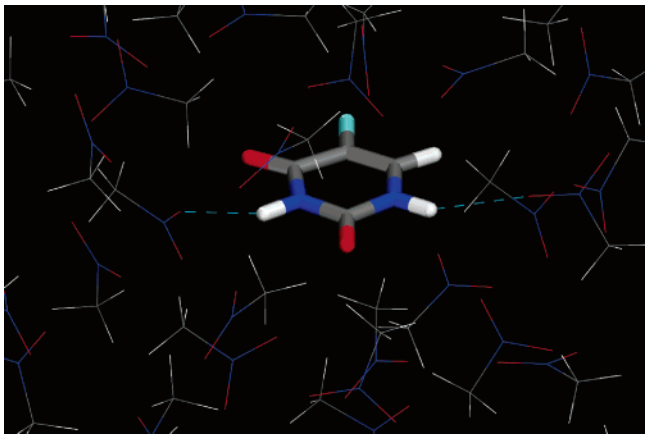


Figure 8. Snapshot of a 5-fluorouracil molecule solvated in nitromethane. Hydrogen bonds are shown as blue lines.

The association of the 5-fluorouracil molecules in nitromethane solution is primarily through O···H−N hydrogen bonds, which explains the very large peak in the O···H RDF between 5-fluorouracil molecules seen in Figure 6. The simulations reveal frequent formation of doubly hydrogen-bonded dimers, and even trimers, in nitromethane solutions, as seen in the snapshots in Figure 9.

This feature is apparent in the RDFs in Figure 6, where the H_P···H_P RDF shows three prominent peaks at around 3, 4.5, and 7 Å, and the O···O RDF shows peaks around 3−4 and 7

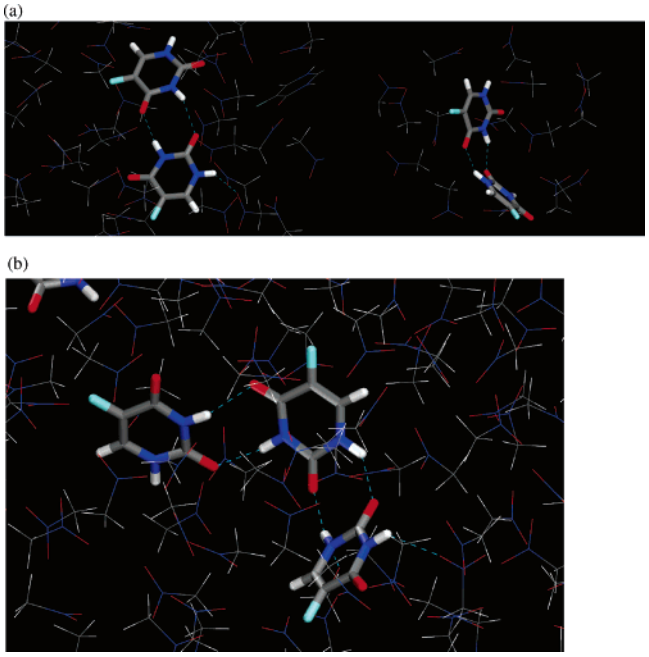


Figure 9. Snapshots of doubly hydrogen-bonded (a) dimers and (b) trimer of 5-fluorouracil in nitromethane solution.

Å, which is consistent with the ranges of H_P···H_P and O···O distances in the various doubly hydrogen-bonded dimers that can be formed by 5-fluorouracil, as can be seen from the distances found for each doubly hydrogen-bonded motif in crystal structures, reported in Table 2.

The F···F distances between fluorouracil molecules in nitromethane are fairly evenly distributed with perhaps a small peak around 9 Å close to the F···F distance in the dimers seen in crystal structures (Table 2). Thus, the simulations suggest the common and rapid formation of a second hydrogen bond between 5-fluorouracil molecules once they have diffused into contact, which is consistent with the solvating nitromethane molecules being readily displaced.

IIIc. 5-Fluorouracil Molecules in Wet Nitromethane Solution. The differences between water and nitromethane as solvents are clearly demonstrated by the addition of water as an impurity into the nitromethane simulations. Although nitromethane is hygroscopic, the water molecules tend to form hydrogen bonds either to other water molecules or to the solute molecules in clusters (Figure 10), which then move through the solution as relatively stable entities.

Figure 6 shows that even the small amount of water near associating 5-fluorouracil molecules has a large effect on the solution behavior, which is explained by the snapshot in Figure 10. One water molecule hydrogen-bonded to 5-fluorouracil adjacent to a single hydrogen bond between associated 5-fluorouracil molecules prevents the formation of the second hydrogen bond that would otherwise easily form in nitromethane solution. Because there are many hydrogen bonds between 5-fluorouracil and water molecules relative to the density of water molecules, the pathway to form doubly hydrogen-bonded dimers is blocked, causing them to be observed only in water-free regions.

IV. Discussion

The simulations and the RDFs in Figure 6 clearly show that the marked differences in the solvation of 5-fluorouracil in water and nitromethane solutions produce different structures for the first association of 5-fluorouracil molecules. Nitromethane

TABLE 2: Intermolecular Distances (in Å) within the Doubly Hydrogen-Bonded Dimers Found in Real and Hypothetical Crystals of 5-Fluorouracil, Illustrating the Types of Distances that Would Be Found in the Three Doubly Hydrogen-Bonded Dimer Structures of 5-Fluorouracil

structure[a]	double-hydrogen-bond motif	first O···O	second O···O	third O···O	first H_P···H_P	second H_P···H_P	third H_P···H_P	F··F
form II	N3−H3···O8/N3−H3···O8	3.614	3.613	7.374	2.733	6.157	9.773	8.618
	N1−H1···O7/N1−H1···O7	3.257	6.778	11.072	3.051	4.33	7.44	11.086
form I	N3−H3···O18/N13−H13···O8	3.472	3.724	7.53	2.634	6.158	9.858	8.533
			3.692			6.139		
	N33−H33···O28/N23−H23···O38	3.462	3.739	7.584	2.749	6.238	9.895	8.547
			3.743			6.217		
CA13	N3−H3···O7/N3−H3···O7	3.631	3.694	7.526	2.546	4.362	8.01	10.956
	N1−H1···O7/N1−H1···O7	3.438	6.887	11.206	2.784	4.369	7.937	11.115

[a] Forms I ($Z' = 4$) and II are X-ray experimental structures, whose hydrogen atoms positions have not been corrected for the systematic error in their determination, and CA13 is a hypothetical low-energy crystal structure exhibiting a different hydrogen bonded motif found from computational crystal structure prediction.[14]

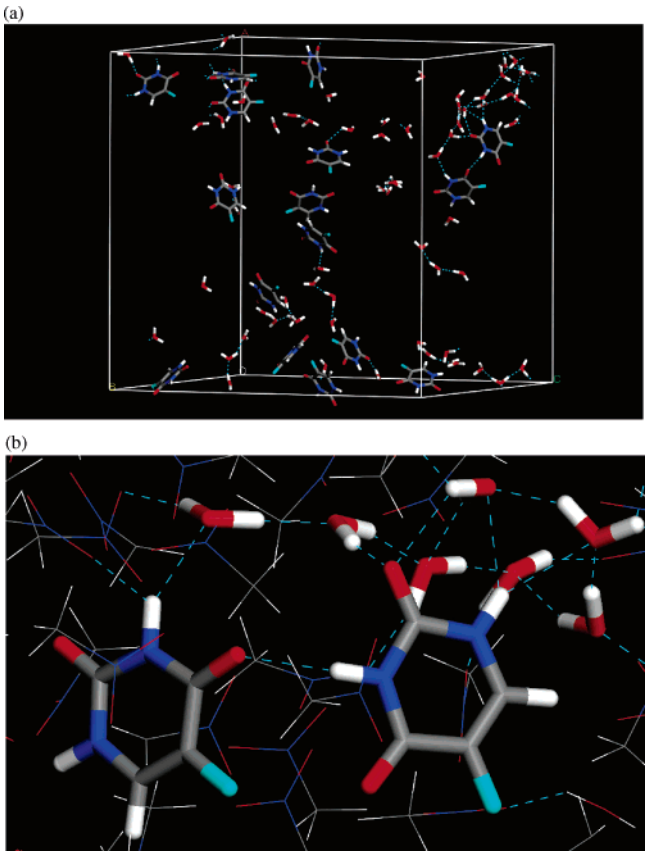


Figure 10. (a) Snapshot of 5-fluorouracil in wet nitromethane. Nitromethane molecules are not shown for clarity. (b) Closeup of a singly hydrogen-bonded dimer of 5-fluorouracil, showing how the presence of the water molecules inhibits the formation of a second hydrogen bond.

interacts only weakly with 5-fluorouracil, and so, the solute molecules have a strong tendency to associate as doubly hydrogen-bonded dimers as they would in the gas phase. The polar water molecules strongly hydrogen bond to the C═O groups of fluorouracil, producing a stable hydration sphere around most of the molecule except the hydrophilic F region. Thus, when the 5-fluorouracil molecules associate by forming a single hydrogen bond, the formation of a second hydrogen bond requires displacement of the strongly bound water, which becomes sufficiently unlikely that no doubly hydrogen-bonded 5-fluorouracil dimers were observed in the aqueous simulation. This barrier to the formation of the doubly hydrogen-bonded dimers occurs even when the water is present only at low levels representing a wet nitromethane solution. In aqueous solution, the other predominant mode of association is through close F··F contacts, with the hydrophobicity of the F atoms forming water-free regions.

There is a compelling correlation between the initial self-assembled structures for 5-fluorouracil seen in the simulations and structures of the polymorphs (Figure 1) that crystallize from water and dry nitromethane. In nitromethane solution, the formation of doubly hydrogen-bonded dimers predominates, and it seems almost certain that any nucleus that appears in nitromethane will consist of chains of doubly hydrogen-bonded dimers, some of which would therefore lead to the growth of form II. Once a nucleus containing the doubly hydrogen-bonded ribbons of form II has formed and started to grow, there will be a large kinetic barrier to breaking these double hydrogen bonds to rearrange to the structure of form I, and so, form II can be formed as a persistent metastable crystal.

The unusual, but thermodynamically more stable, structure of form I contains C4═O8···H3−N3 double hydrogen bonds, which the simulations strongly suggest must be formed later in the association process in water, with the initial associations being more likely to be the formation of close F···F contacts and single hydrogen bonds. The large peak for short F···F distances in aqueous solution in Figure 6 and the cluster of close F···F contacts in form I (Figure 1) suggest that the prenucleation events involve the association of F atoms, driven by the difficulty of displacing the hydrogen-bonded waters. The F···F aggregation is the byproduct of other forces, induced by the tendency of water-free regions to aggregate. This reflects the smaller atomic charge on F (−0.18 e) than on the carbonyl oxygens (ca. −0.65 e).

The effect of the strong solute-water interactions in preventing the formation of the doubly hydrogen-bonded dimers, which is apparent in the wet nitromethane simulations, is fully consistent with the recent discovery of form II[14] from only dry nitromethane. Very small quantities of water in this hygroscopic solvent are enough to inhibit the growth of form II from nitromethane. This strongly corroborates the inference that significant differences in the hydrogen bonding involved in the solute−solvent interactions can lead to very different prenucleation behavior in water and nitromethane, resulting in different polymorphs.

The picture emerging from these simulations, that the initial association of the molecules in solution determines the polymorphic outcome of 5-fluorouracil, is consistent with recent experimental studies of polymorphic systems.[12,14] In the case of tetrolic acid, FTIR spectroscopy has established that doubly hydrogen-bonded dimers are common in solvents that give rise to the α polymorph, which has a hydrogen-bonded dimer motif, whereas only single hydrogen bonds predominate in solutions that produce the β polymorph with a catemer hydrogen-bonded

motif.[37] Solution NMR studies on two organic compounds[38] suggest that the structures of the aggregates formed in solution are similar to the structures of dimer motifs found in the final solid material. Obtaining experimental insights into the structures of nucleating entities to understand how this leads to polymorphism is very challenging.[12] Cases such as 5-fluorouracil, where the polymorphic form is determined by the nature of the solvent and the hydrogen bonding between nearest neighbors differs between polymorphs, are particularly suited for molecular dynamics simulation studies of the initial associations. However, other types of polymorphism, where the polymorphic outcome is determined by the degree of supersaturation[3,39] or agitation or where the differences between the strongest nearest neighbor contacts in the polymorphs is smaller and so more susceptible to change as the nucleus grows, will present a major challenge to simulation and experiment for years to come.

V. Conclusions

By contrasting molecular dynamics simulations in two different solvents, we have provided a clear explanation at the molecular level of how the differences in the initial association of fluorouracil molecules can rationalize the polymorphic outcome. We have shown that the nature of the solvent is able to influence significantly the nature of the initial 5-fluorouracil intermolecular interactions, so that crystals grown from aqueous solution will have the polymorphic form I, whereas in nitromethane, the prenucleation self-assembly leads to the formation of form II. In addition, the wet nitromethane simulations show how easily impurities can influence this association and therefore change the polymorph grown.

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