Solvation Effects on Dissociative Electron Attachment to Thymine

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Abstract

Ionizing radiation can excite the cellular medium to produce secondary electrons that can subsequently cause damage to DNA. The damage is believed to occur via dissociative electron attachment (DEA). In DEA, the electron is captured by a molecule in a resonant antibonding state and a transient negative ion (TNI) is formed. If this ion survives against electron autodetachment then bonds within the molecule may dissociate as energy is transferred from the electronic degrees of freedom into vibrational modes of the molecule. We present a model for studying the effect that transferring kinetic energy into the vibrational modes of a molecule in this way has on a DNA

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nucleobase. We show that when the base is in an aqueous environment, dissociation is affected by interactions with the surrounding water molecules. In particular hydrogen bonding between the nucleobase and the solvent can suppress the dissociative channel.

Introduction

Ionizing radiation can damage the DNA of cells and lead to diseases such as cancer. However, when properly targeted at unhealthy tissue, ionizing radiation can also be used to treat cancer.[1,2] To assess the dangers posed by involuntary exposure to radiation, and to refine techniques that use radiation in this way, requires a detailed understanding of the mechanisms that lead to DNA damage. These mechanisms can involve both direct damage to DNA by the incident radiation or damage caused by secondary species that form in the surrounding medium. The most abundant of these secondary species is the low-energy electron (LEE)[3] and Sanche *et al.* have shown that LEEs with energies as low as 0 eV can cause damage to plasmid DNA.[4,5] LEEs with energies around 20 eV, in particular, will travel about 20 nm before they stop and become solvated.[6] These solvated electrons can still react with the DNA bases[7,8] but once this species has formed the electron's reactivity is limited by diffusion. Given that the distance that an electron can travel is less than a μm, which is the size of a typical cell, the damage processes initiated by LEEs are thus essentially intracellular. Consequently, when a radiation field is targeted on a tumor, the LEEs produced damage the tumour and do not cause much damage to the surrounding healthy tissue.

It has been suggested that LEEs cause damage to DNA via dissociative electron attachment (DEA). Figure 1 shows, schematically, how the energies of the species that are relevant to DEA change as a function of the length of the bond that dissociates, for a molecule with a relatively large dipole moment.[9] This figure shows the potential energy curves for the neutral molecule and the transient negative ion (TNI) with a finite lifetime[10,11] as functions of the reaction coordinate - the distance between the N and H atoms. During the initial stage of the DEA process the electron is captured into the LUMO to form a TNI. This capture

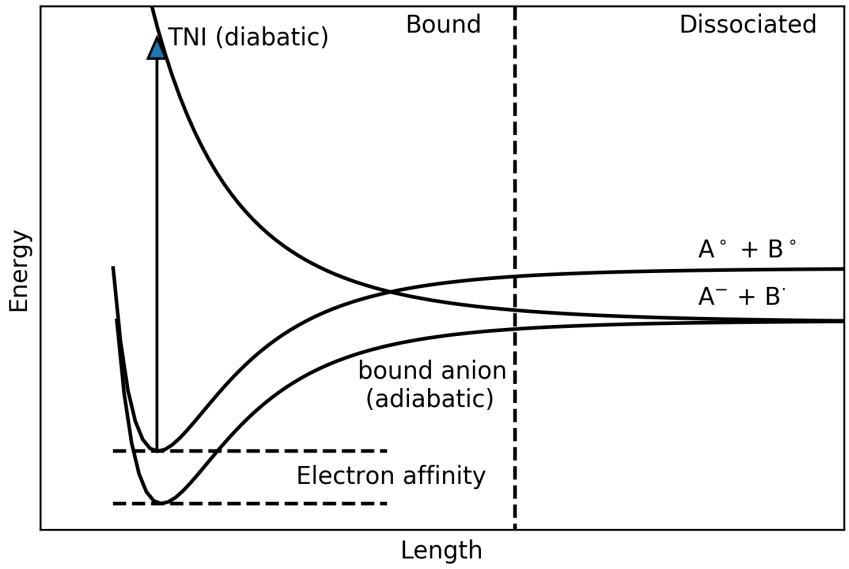


Figure 1: The potential energy surfaces (PES) that are relevant to the DEA process at relatively low electron energies. The curves in this figure are shown as a function of the N-H distance and excited state PES associated with higher energy processes are not shown for the sake of clarity.

(vertical arrow in Fig. 1) occurs vertically for a fixed value of the reaction coordinate in accordance with the Franck-Condon principle. The TNI that forms in this way is typically in an antibonding state and when it form the two molecular fragments are thus driven apart. Consequently, if the TNI survives against autodetachment of the electron, the molecule can break into fragments. The curve representing the TNI state is called, in collision theory, the *diabatic* state. It contrasts with the *adiabatic* state (the bottom curve) which results from the electron binding to the molecule due to the long-range electron-molecule interactions. The adiabatic state corresponds to the ground state anion, i.e. an eigenstate of the electronic Hamiltonian and can be computed using standard electronic structure calculations. This state is not populated during the electron collision event but is involved in vibrational Feshbach resonances that contribute indirectly to the DEA process.[9] Furthermore, for thymine in gas phase the adiabatic state only exists because this particular molecule has a large and permanent dipole moment of 4.13 D.[12] This large dipole moment ensures that the molecule has a very small adiabatic electron affinity of 0.07 eV.[13–15] For geometries close to the min-

imum the PES of the anion in gas phase is thus almost identical to that of the neutral molecule. When thymine is solvated in water, however, the adiabatic state is stablized by the field created by the surrounding water molecules and the minimum of the anionic PES is thus shifted downwards by about 1 eV.[16] Furthermore, the energy landscape for the TNI is also shifted downwards when the molecule is solvated.[17]

Theories to describe DEA were formulated many years ago.[18,19] Utilizing these theories is extremely challenging, however, and as a consequence only relatively simple molecules have been considered in simulations of DEA.[20] Typically a two step procedure is employed when such simulations are carried out. The first step of this procedure involves fixed-nuclei electron-molecule scattering calculations which have been accomplished in the past using *ab initio* R-matrix theory,[21–23] Schwinger's variational method,[24] Kohn's variational method,[25] and the finite-element discrete model.[26,27] These calculations allow one to identify the negative-ion resonances and to determine the fixed-nuclei scattering matrices. Once these quantities have been determined resonant R-matrix theory[28] or nonlocal complex potential theory[29] can be used to model the nuclear dynamics and to thus build a more complete picture of the DEA event.

Calculations similar to those described in the previous paragraph have been used to understand the process of DEA in uracil and thymine.[26] These calculations were, however, performed on isolated DNA fragments in gas phase. It is thus unclear whether this mechanism operates when the DNA is embedded in an aqueous environment as it would be in the cell.[30] When it comes to investigating this phenomenon a major problem is that studying DEA in fully solvated DNA using R-matrix theory is not currently possible. In fact modeling a single nucleobase with 5-water molecules, as was done in recent works by Smyth *et al.*[17] and by and Sieradzka and Gorfinkiel[31] are the current state-of-the-art. Smyth *et al.* found that the lifetime of the resonance in nucleobases is increased when the water molecules are present and that dissociation is thus about six times more likely in a micro-solvated environment than it is in gas phase.[17] However, these calculations assume that after dissociation the

fragments remain as such, and neither return back to the reaction zone nor interact with the cluster environment. In other words, the present status of R-matrix theory does not allow post-interaction processes, which could lead to chemical transformation of the fragments, to be included. The aim of this paper is thus to assess, using computer simulation, the role the environment plays in the DEA process, and to determine whether dissociation is facilitated or suppressed by the presence of explicit water molecules.

In the current study, we investigated the *final* stage of the DEA process for a DNA nucleobase in different environments. In other words, we investigated the events that occur after dissociation, which transfer the kinetic energy of the fragments into the surrounding solution. Simulations similar to those we ideally would like to carry out here are often performed by researchers investigating photochemical processes.[32] In these investigations the potential energy surface of the molecule in both its ground and excited state is mapped out and the process via which the reaction proceeds is then investigated by performing a quantum dynamics on this energy landscape. This approach is not adequate in the present case because we are not dealing with excited bound states, but with electronic resonances that have a finite lifetime. Although recent advances such as the complex absorbing potential method, do allow one to compute the electronic levels of these states these methods are not implemented in any of the standard electronic structure codes. Furthermore, high levels of theory, typically at the coupled clusters CCSD(T) level,[33] are required to obtain accurate models for the electronic structure of both the anion and the anionic resonances. Using a high level of theory is problematic because we wish to fully-solvate the nucleobase so the number of degrees of freedom in our model is enormous. We thus cannot possibly map out the potential energy surface and need instead to calculate the forces on-the-fly. Calculating forces in this way is possible using DFT, but extremely problematic for high-level quantum chemical methods.

With all this in mind we have thus used molecular dynamics on the Born-Oppenheimer surface for the ground state anion in our studies. We began by studying the nucleobase

in gas phase to validate this approach and then progressed to modeling the nucleobase in the condensed phase. The potential energy surface for the ground (adiabatic-weakly-bound) state anion, unlike that for the TNI, has a minimum for the bound geometry so the chemical bond will not break spontaneously. We thus generated a bond fragmentation event by simply increasing the kinetic energy of the atoms in the molecule that are involved in the dissociating coordinate. In other words, instead of setting the initial velocities in these simulations from a Maxwell-Boltzmann distribution, the initial velocities of particular atoms were set to specific values so as to reflect the increase in the total energy of the molecule that occurs as a consequence of the electron attachment. The justification for increasing the kinetic energies is that during the DEA event the electronic excitation energy is converted into kinetic energy of the molecular fragments. The reason this conversion takes place is clear from Figure 1. When the electron is attached the ground state system is vertically excited onto the energy landscape for the TNI. The geometry of the neutral molecule has a high energy on this new landscape and large forces are thus applied onto the nuclei. These large forces cause bonds to break and the nuclei to accelerate away from each other. We argue in this work, therefore, that, by artificially increasing the velocities on atoms and by performing simulations on the ground state of the anion, we can mimic the behavior that follows a DEA event. We justify this statement by noting that as the N-H bond is stretched during our ground state simulations the excess electron is transferred from a π^* antibonding orbital to the σ^* orbital that is intimately related to the rupture of the N-H bond.[26] By investigating how this system reattains equilibrium we can thus understand the final stages of the DEA process in solution. What we see is that 'caging' effects due to the aqueous environment can disrupt the DNA dissociation process and thus increase the energy required to break bonds. Furthermore, hydrogen bonding between the DNA and water molecules can strongly affect this process. Although there are several assumptions in these simulations the results are in agreement with recent experimental work by Kočišek *et al.*[34] who demonstrated that when microsolvated DNA bases capture LEEs the excess energy of

these species is rapidly transferred to the surrounding waters. Moreover, our results resolve the discrepancy between experiment, which predicts that the dissociation rate is lowered when the base is solvated, and R-matrix theory,[17] which predicts that the lifetime of the resonance increases when the molecule is solvated. The R-matrix result alone suggests that the dissociation rate would increase when the molecule is solvated as a consequence of the resonance's longer lifetime. In these calculations, however, caging due to the surrounding waters as we observe in our calculations is not considered as it is not possible to include this effect in R-matrix calculations.

Method

All simulations were performed using a combination of Density Functional Theory (DFT) and Molecular Dynamics (MD). The electronic structure of the DNA and water was calculated at the DFT level of theory, using the Gaussian and plane waves method (GPW),[35] GTH pseudopotentials,[36] and a TZVP-GTH basis set. The PBE functional and Grimme's DFT-D3[37] van der Waals dispersion correction was used to calculate forces[38] and classical trajectories were determined for the atoms using a timestep of 0.5 fs. These calculations were performed using the ab initio quantum module Quickstep (QS) of the open source computer code CP2K.[39]

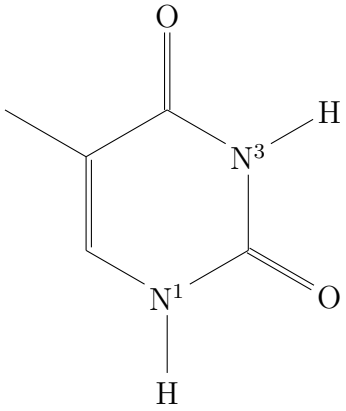


Figure 2: The structure of the thymine nucleobase. The bond that dissociates in our simulations is the one involving N^3.

As is commonplace in works of this type we investigated the dissociation of the nucleobase with the highest electron affinity; namely, thymine.[40,41] This nucleobase was placed in a cubic box of size 25 Å and its geometry was optimized. A vibrational analysis of the molecule in its optimised geometry was then performed in order to identify the normal modes. An analysis of the vibrational modes of the molecule showed that the N-H bond involving the N^3 nitrogen atom in Figure 2 is the highest frequency mode of the molecule. This bond is not the bond that would, in the nucleotide, attach the base to the sugar but experimental[42–44] and theoretical[26] studies have shown that LEEs can either cause this bond or the bond involving the N^1 nitrogen atom to break and that the physics of these two DEA channels are different. When hydrogen loss occurs from N^1 the electron is captured into the lowest σ^* unoccupied orbital in a process that is assisted by the interaction with the dipole-supported state. By contrast when hydrogen loss occurs occurs from N^3 the electron is captured in the unoccupied π^* orbital and there is then a transition into the second σ^* state due to vibronic coupling. When performing gas phase calculations of cross sections researchers have typically focused on what happens to N^1 and studied the DEA process for this bond using either the nonlocal complex potential[29] or resonant R-matrix[28] approach. Studying how N^3 behaves is more difficult because, although the narrowness of the π^* resonance allows us to make assumptions that make the calculation more straightforward to perform, it is unfortunately necessary to include vibronic coupling between the σ^* and π^* resonances, which makes the problem more complicated. In spite of this, in this work we have studied what happens after the bond involving atom N^3 breaks instead of studying the bond involving N^1 that has been examined in previous works.[17,26] The reason for doing so is that our use of ground state density functional theory ensures that we are adding the electron into the LUMO of the molecule, which has a strong π^* character. As discussed above the bond involving N^3 breaks when the electron is captured in a π^* orbital on the TNI, while the bond involving N^1 only breaks when the electron is captured in the σ^* orbital. We thus assumed that the electron is captured into the LUMO, which has strong π^* character. Given that we are forced to use

ground state methods it thus seemed more reasonable to model the process via which the bond involving N^3 breaks as the orbitals involved in this particular DEA process are more similar to the ground state. The fact that our initial resonant state is actually quasibound, rather than bound, should not affect our main conclusions since we are interested mostly in what happens to the fragments after the TNI has been stabilized and the N-H bond has broken. The fate of these fragments is largely determined by the interaction between the fragments of the dissociated anion and the surrounding water molecules. The results of this paper would thus probably be similar had we chosen to study the other N-H bond in the molecule. The only differences would be in the threshold for dissociation and the DEA cross section enhancement.[31]

To investigate the process after the breaking of the N-H bond we first equilibrated the nucleobase in a gas phase environment and a fully solvated environment. In this second simulation we used a periodic cubic box of 14.6 Å containing the nucleobase and 64 water molecules all of which were modeled explicitly using DFT. The neutral nucleobase was equilibrated for 2 ps in gas phase and 10 ps in condensed phase. For the condensed phase we also further pre-equilibrated the water in this simulation by performing a 2 ns molecular dynamics simulation using the OPLS classical force field.[45,46] To simulate the effect of the additional energy that would be introduced due to a dissociative electron attachment event we vertically attached an excess electron to the system and introduced additional vibrational energy to the N-H bond. We can increase the vibrational energy of a molecular bond by increasing the velocities and hence the kinetic energies of the constituent atoms. For the N-H bond, the new velocities of the Nitrogen, $\mathbf{v}_N$, and Hydrogen atoms, $\mathbf{v}_H$, were calculated using:

$$\begin{aligned} \mathbf{v}_N &= \mathbf{v}_N^{(0)} + \eta_N \hat{\mu} \\ \mathbf{v}_H &= \mathbf{v}_H^{(0)} + \eta_H \hat{\mu} \end{aligned} \tag{1}$$

where $\mathbf{v}_N^{(0)}$ and $\mathbf{v}_H^{(0)}$ are the velocities these atoms had after equilibration and where $\hat{\mu}$ is the director of the bond connecting atom N to atom H. $\eta_{N,H}$ is the extra velocity, which enters

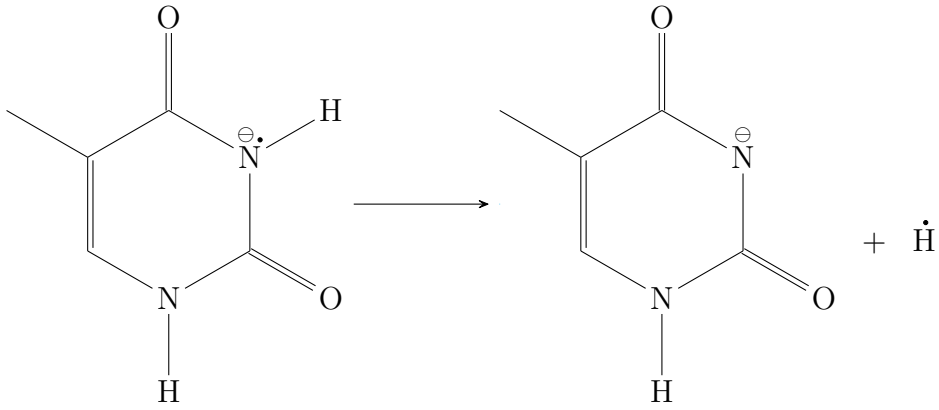
the bond by virtue of our simulated DEA event. These two quantities were calculated by solving the following pair of simultaneous equations:

$$\begin{aligned} \mathrm{KE} &= \frac{1}{2} m_N \left[(\mathbf{v}_N^{(0)} + \eta_N \hat{\mu})^2 - (\mathbf{v}_N^{(0)})^2 \right] + \frac{1}{2} m_H \left[(\mathbf{v}_H^{(0)} + \eta_H \hat{\mu})^2 - (\mathbf{v}_H^{(0)})^2 \right] \\ 0 &= m_N \eta_N + m_H \eta_H \end{aligned} \tag{2}$$

The second of these equations ensures that the total change in the momentum of the bond is zero, while the first measures the total kinetic energy (KE) that we wish to introduce.

Results and Discussion

To simulate the effect of a DEA event in the gas phase nucleobase, an energy of 1 eV was introduced to the N-H bond. This additional energy caused the H atom to briefly detach from the nucleobase. However, the N-H bond quickly reformed as the system returned to equilibrium and the excess energy redistributed among the other vibrational modes. By contrast when an energy of 2 eV was introduced, the bond broke and never reformed. We thus infer an energy of between 1 and 2 eV must be introduced into the bond in order for the following process to take place.



As we are in gas phase we can calculate the energy of reaction for this process exactly. We did this using a TZVP-MOLOPT-GTH basis set and the PBE functional and found that it was equal to 1.67 eV. This behavior is consistent with the experimental findings,[47–50] which

show that hydrogen atoms are released when DNA components interact with electrons of energies below 3 eV. In particular, Ref.[50] shows that the resonant capture of 1.8 eV electrons may lead to the break of the N^3-H bond, whereas 1 eV induces the loss of H from N^1 but it is not sufficient for N^3. More important for the present purpose is that this value is in agreement with the value that we obtained by arbitrarily increasing the vibrational kinetic energy of the N-H bond, which suggests that we can safely use this method to investigate the ease of bond breaking in a condensed phase environment where the bond dissociation energy cannot be calculated by any other means.

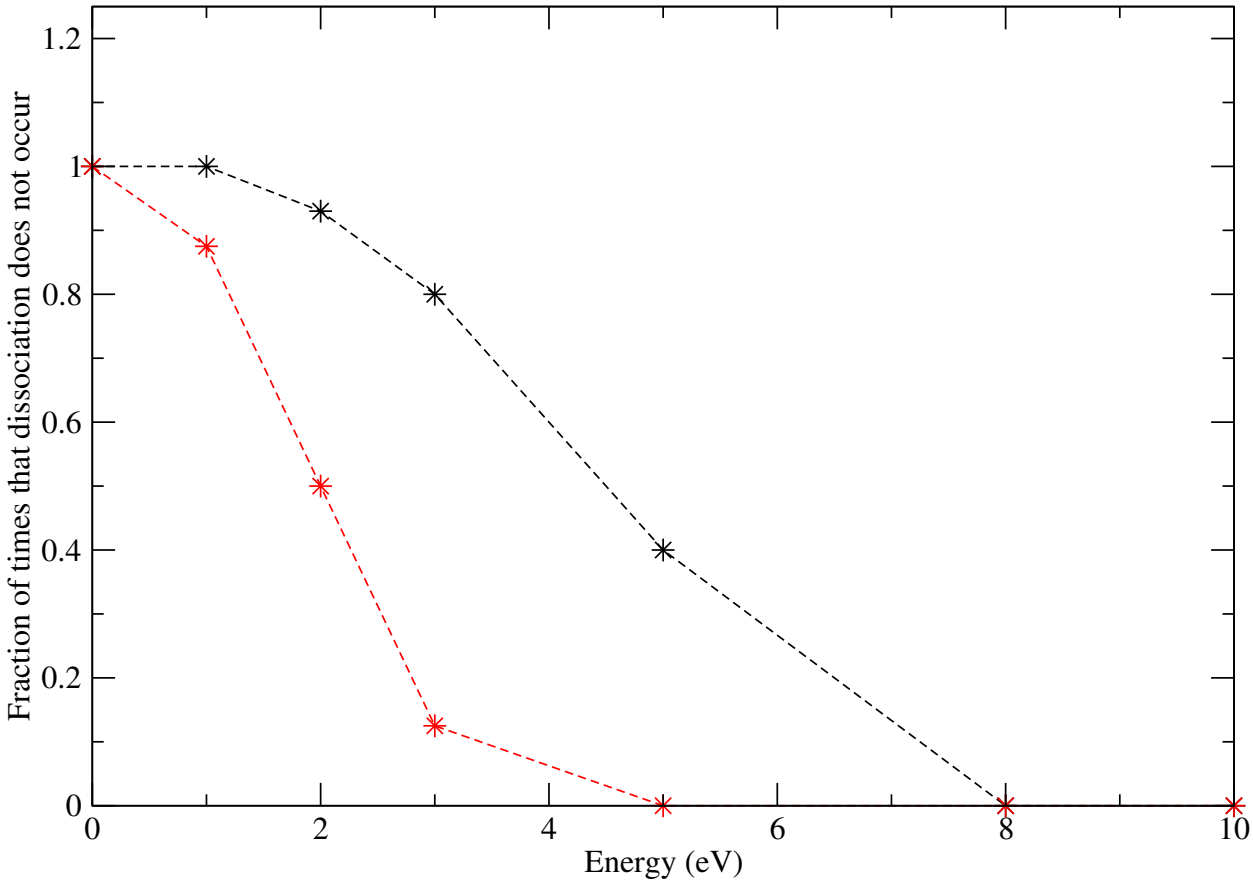


Figure 3: The fraction of times the nucleobase was observed to not dissociate when particular values for the additional vibrational energy from the DEA event were added. The red line shown in this figure is the fraction of times that the nucleobase was observed to not dissociate when the DEA energy was added to a configuration which did not have a hydrogen bond between the N-H and a water, while the black line is the same quantity for simulations in which the initial configuration was hydrogen bonded.

The neutral thymine was equilibrated in the condensed phase for 2.5 ps and subsequent production calculations were run for 7.5 ps. During these production calculations we observed that the nucleobase fluctuated between configurations in which the hydrogen of the N-H bond was hydrogen bonded to a water molecule and configurations in which this hydrogen bond was absent. A number of previous works have shown that hydrogen bonds between the nucleobase and the water molecules can affect barriers for dissociation reactions.[51–53] We therefore investigated DEA events for configurations in which the hydrogen bond between the N-H bond and the surrounding waters was present and configurations where this bond was absent. We took 15 configurations in which the hydrogen bond was present and 8 configurations in which the hydrogen bond was absent. We then vertically attached an additional electron to these configurations and added various amounts of vibrational kinetic energy to the N-H bond using the method described in the previous section. The final result from these simulations is shown in Figure 3, which portrays the fraction of configurations which did not dissociate as a function of the kinetic energy added. It is clear from this figure that as the amount of vibrational energy that is added to the N-H bond increases the likelihood for bond breaking increases. What is surprising, however, is that this probability is dependent on whether or not the nucleobase is initially hydrogen bonded to a surrounding water molecule. The red line shown in this figure is the fraction of times that the nucleobase was observed to not dissociate when the DEA energy was added to a configuration which did not have a hydrogen bond between the N-H and a water. The black line shows the same quantity but for simulations that were started from a configuration in which there was a hydrogen bond between the N-H and a water. Figure 3 thus shows that dissociation of the N-H bond is observed in 90 % of simulations in which 3 eV is added to the N-H bond and which start from configurations which do not have a hydrogen bond. By contrast, when the hydrogen bond is present dissociation is only observed in 20 % of the simulations in which 3 eV is added to the N-H bond. In other words, dissociation of the N-H bond requires more energy when the hydrogen is H-bonded to a water molecule than when it is not.

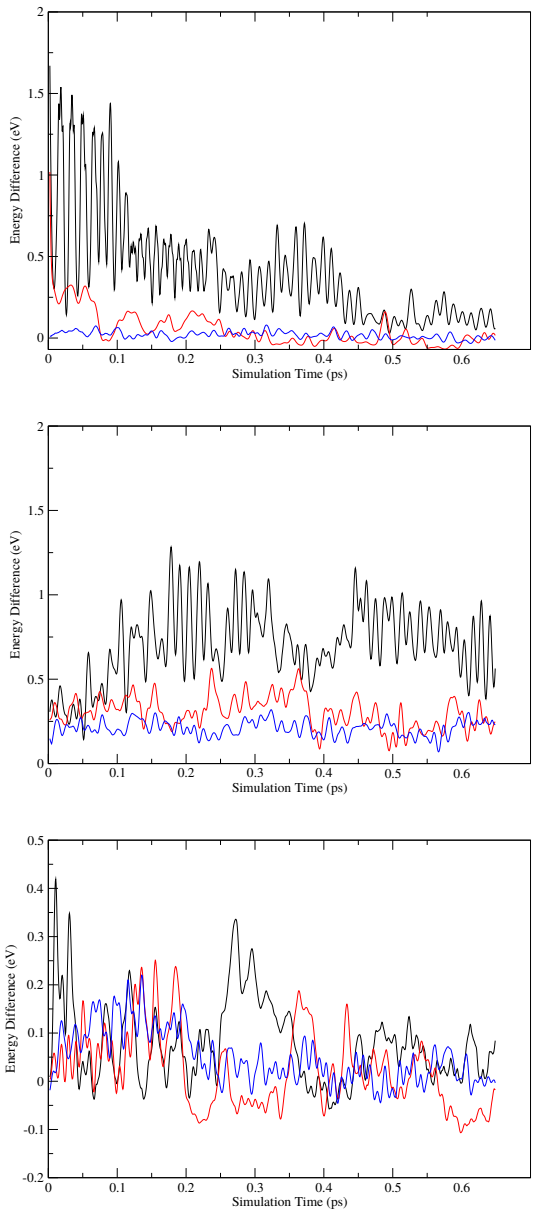


Figure 4: Running averages for the change in the kinetic energy of the N-H bond (top panel), the remainder of the nucleobase (middle panel), and the closest water molecule to the N-H bond during simulations in which 3 eV was added to the N-H bond at time $t = 0$. The black lines show the behaviour of these groups of atoms when a hydrogen bond is present in the initial configuration. The red lines show the behaviour when this hydrogen bond is absent. The blue lines show what happens in simulations when no additional kinetic energy is added to the N-H bond.

To investigate how the presence of the hydrogen bond is affecting the dissociation process

we calculated the kinetic energy of the N-H bond, the kinetic energy of the remaining atoms of the nucleobase and the kinetic energy of the water molecule that was closest to the hydrogen of the N-H bond separately. For each of these groups of atoms we then evaluated the following quantity:

$$E_{\text{excess}}(t) = E(t) - E_0$$

In this expression E_0 is the total kinetic energy the atoms in the part of the system of interest had before the vibrational energy from the modeled DEA process was added. $E(t)$ is then the energy those atoms had at a time t ps after the addition of the vibrational energy. The value of $E_{\text{excess}}(t)$ thus gives a measure of how much the kinetic energy deviates from an unperturbed, equilibrium value. Furthermore, because the value of E_0 is taken prior to the modeled DEA event we can, when comparing curves started from different initial conditions, deconvolute the effect of the modeled DEA process from the stochastic effects.

Figure 4 shows how the value of a running average of $E_{\text{excess}}(t)$ changes after a simulated DEA event in which 3 eV of energy is inserted into the N-H bond. The black lines show what happens when a hydrogen bond is present in the original configuration and the red lines show what happens when no such hydrogen bond is present in the original configuration. For comparison we have also included blue lines that show the running average for $E_{\text{excess}}(t)$ that we observed during a similar length of time of an equilibrium simulation. It is clear from Figure 4 that the presence of the hydrogen bond strongly affects the way the system re-approaches equilibrium. First and foremost, the top plot in Figure 4 shows that the kinetic energy of the N-H bond decays much more slowly when there is a hydrogen bond between the H of this bond and the water molecules. When the hydrogen bond is absent (red line), the N-H bond breaks early in the simulation. The excess kinetic energy that was added to the N-H bond is thus converted into the potential energy that allows the bond breaking reaction to occur. By contrast, when the hydrogen bond is present, we observe in the trajectories that, although the initial 3 eV of vibrational energy causes the H atom to detach, it rapidly reattaches itself to the nitrogen. The fact that, as shown in the top panel of Figure 4, the

kinetic energy of the N-H bond decays more slowly in this second, hydrogen-bonded, case is consistent with these observations.

The top panel of Figure 4 shows that in both the hydrogen-bonded and non-hydrogen bonded cases, the kinetic energy of the N-H bond does eventually relax down to a value that is consistent with equipartition. The added energy must therefore leave this degree of freedom. In the non-hydrogen bonded case we have already discussed how this energy must be used to break the chemical bond. In the hydrogen bonded case, however, the bond does not break, so the energy must therefore go elsewhere. The middle panel in Figure 4 shows that a considerable portion of this energy moves into the remaining atoms of the nucleobase. The bottom panel, meanwhile, shows that kinetic energy from the N-H bond takes a number of brief excursions into the degrees of freedom that belong to the nearest water molecule. Similar increases are not observed in the non-hydrogen bonded case and what we thus believe is that the hydrogen bond serves both as a channel to transfer energy to the surrounding solution and as an obstacle that reflects energy back into the nucleobase. The hydrogen bond thus has a caging effect on the dynamics of the hydrogen atom of the N-H bond. This process of caging channels kinetic energy out of this bond and into the surroundings and is thus what prevents the bond from breaking. Whether or not the hydrogen bond is present in solvated nucleobases, is therefore crucially important in terms of understanding whether or not the nucleobase will dissociate via DEA.

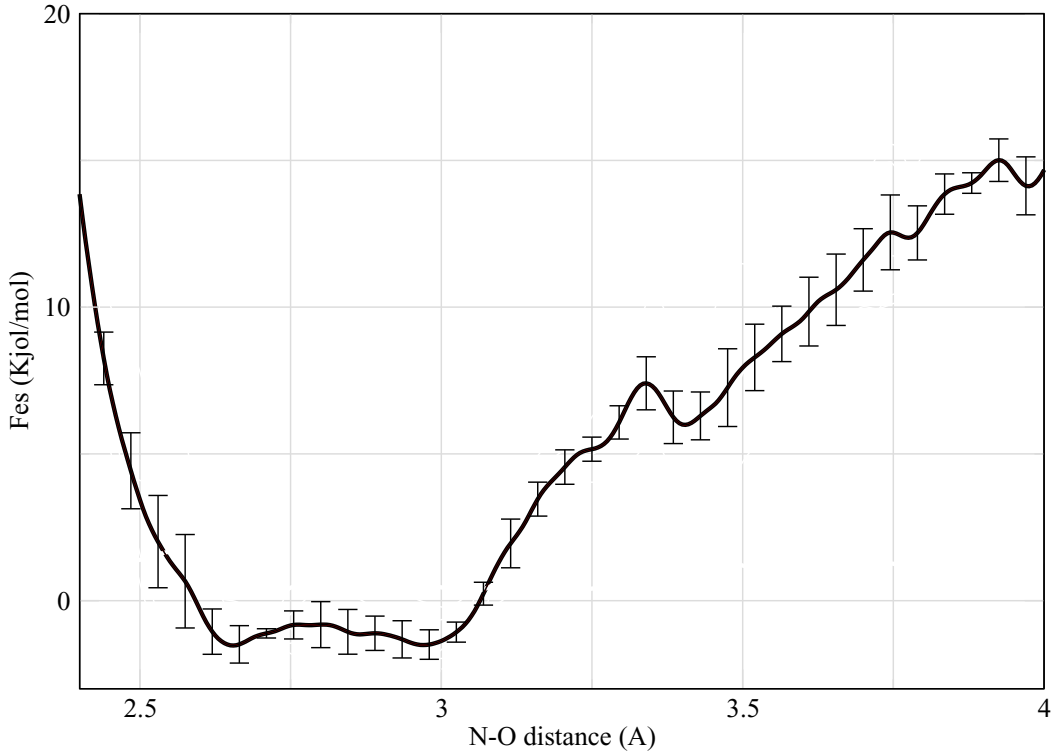


Figure 5: The free energy as a function of the distance between the nitrogen atom of the N-H bond and the oxygen atom of the nearest water molecule. The free energy landscape is very flat for values for this distance between 2.5 and 3.0 Å which suggests that this hydrogen bond is rather labile. The free energy increases when this distance is longer 3.0 Å, however, so the hydrogen bond is likely to be present in any equilibrium configuration.

To investigate the propensity with which the N-H bond forms hydrogen bonds to the solvent molecules we performed well-tempered metadynamics simulations[54,55] at 300 K. These calculations allowed us to extract the free energy of the system as a function of the shortest distance, x, between the oxygen atoms of the water molecules and the nitrogen atom of the N-H bond. Gaussian hills of width of 0.2 Å were added to the bias potential every 5 fs. The initial height of these Gaussians was set equal to 1.2 kJ mol^{-1}, while the well-tempered factor was set equal to 10. The resulting free energy landscape, which was extracted by reweighting,[56,57] is shown in Figure 5 together with error bars on the estimates of the free energy

that were calculated using block averaging. It is clear that the hydrogen bond between the N-H group of the nucleobase and the nearest water molecule is very labile. The free energy surface is very close to flat for values of this distance between 2.5 Å and 3.0 Å and only rises significantly once this distances is greater than 3.1 Å. The flat region covers the range of distances over which we would say the hydrogen bond is present. Furthermore, when the free energy does begin to rise it does so slowly. We would thus expect large fluctuations in the length of this hydrogen bond but that the system should overall prefer to be in configurations in which there is a hydrogen bond between the N-H group of the nucleotide and one of the surrounding water molecules. Combining this result with what we have seen in the rest of this paper we thus would expect the breaking of the N-H bond to be suppressed by the hydrogen bonding network on most occasions when a DEA event occurs for a molecule in solution.

Conclusion

In this study, we have modeled the dynamics of the final step in the DEA mechanism for a nucleobase in aqueous solution. In agreement with other studies we found that breaking the N-H bond and releasing a hydrogen atom requires only 1.67 eV in gas phase[47–49] but that this reaction is strongly affected by the aqueous environment. When there is a hydrogen bond between the N-H of the nucleobase and a surrounding water molecule, there is no guarantee that the bond breaks even when up to 5 eV of additional energy is inserted into the bond. The reason for this is that this hydrogen bond rapidly channels kinetic energy away from the N-H, into the surrounding water molecules and back into the nucleobase. This result is in agreement with recent experiments by Kočišek *et al.*[34] In their experiments they observed that the dissociation channels of nucleobases were suppressed by the surrounding water molecules. Furthermore, much as we have seen in this work this suppression was ascribed to a transfer of energy away from the bond.

Recent findings from R-Matrix calculations performed on micro-solvated nucleobases have suggested that water molecules in the environment increase the DEA cross section.[17] This led the authors, Smyth *et al.*, to suggest that DEA is more likely to occur in solution. Our results do not contradict this suggestion. Instead we argue that the enhanced levels of electron capture observed in solution, do not necessarily lead to an increase in the amount of damage caused because the additional energy that is introduced by the formation of the TNI is dissipated rapidly in the environment. As a consequence this energy does not cause bonds to dissociate. It is important to note that this dissipation of energy only occurs when explicit hydrogen bonds are formed between water molecules and the DNA. It is difficult to incorporate such interactions in continuum models, which suggests that when it comes to investigating why reaction barriers in solvated DNA are higher than those in dry DNA,[58–63] using an explicit treatment of the aqueous environment is essential. In future work we will model how the energy from a DEA event is dissipated in nucleotides and in longer DNA strands in explicit water, which will allow us to better understand the most important damage channel for DNA.

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