Water mediated Electron Attachment to Nucleobases: Surface-bound vs Bulk Solvated Electrons

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We have investigated the electron attachment dynamics of uracil in water using accurate wavefunction and QM/MM methods. The initial electron attached state is found to be localized on the water and mixing of electronic and nuclear degrees of freedom leads to the transfer of electron from the water to the uracil. The water molecules around the uracil stabilize the uracil bound anion by creating an extensive hydrogen-bonding network. The presence of the bulk water environment accelerates the rate of electron attachment to uracil and the complete electron transfer from water to the uracil happens at a picosecond time scale. The degree of solvation of the aqueous electron can lead to a difference in the initial stabilization of the uracil bound anion but at a longer time scale the anion formed due to the attachment of both surface-bound and bulk solvated electrons behaves similarly.

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Radiation damage to genetic material is one of the active fields of chemical research with implication both in the cause and cure of cancer. High energy radiation can structurally alter DNA leading to base release, base damage, and strand break\(^1\). Creation of many of these local damage sites in the near vicinity leads to the formation of multiple damage sites (MDS)\(^2\). The formation of MDS can cause loss of genetic information, and they are often irreparable by the enzymatic repair process. The cause of the damage is, for a long time, attributed to ionization and excitation process created by the high energy radiation. But recent experiments have suggested a critical role played by the low-energy secondary electrons in the radiation damage process\(^3,4,5\). The secondary electrons are generated by the action of the ionizing radiation on the water surrounding the genetic materials. They can get attached to the base, sugar and phosphate group of the genetic materials causing structural distortion, ultimately leading the single and double-strand break. The ionizing radiation acting on the water initially produces pre-solvated electron (\(e_{\text{pre}}\)) in the water conduction band with a lifetime\(^6\) of 100 to 500 fs. The surrounding water molecules progressively orient itself along the (\(e_{\text{pre}}\)) due to the interaction of the charge with the induced or the permanent dipole moment of the water molecules and lead to partial and full solvation of the electron (\(e_{\text{aq}}\)). The partially solvated electron can exist in the surface of the water for a very short time and is transformed into bulk-solvated electron within a picosecond time scale. The role of surface (\(e_{\text{aq}^-}\)) and bulk (\(e_{\text{aq}}\)) solvated electron in electron attachment induced radiation damage is a matter of ongoing controversy\(^7\). The electron attachment process can be considered to be energetically favorable or unfavorable depending upon the interpretation of experimental data\(^8,9\). Very little has been known about the mechanism of the electron attachment process. Available theoretical calculations are limited\(^10,11,12\) and restricted mostly to micro-solvated DNA bases\(^13\). In this paper, we have taken uracil as a representative example to understand the mechanism of electron attachment to DNA bases in the presence of water.

The monohydrated uracil provides a very simple model to investigate the role of water in the process of electron attachment to the nucleobase. The electron attachment to monohydrated uracil at the neutral geometry leads to the formation of the dipole-bound state, which is vertically bound with a vertical detachment energy value of -0.069 eV. The additional electron is delocalized away from the nuclear framework (see the natural orbitals in Figure 1(a)). Consequently, the formation of the dipole-bound anion does not lead to any distortion from the neutral geometry. There also exists a valence-bound anionic state, which is adiabatically bound with AEA of 0.142 eV. The valence bound state shows a vertical detachment energy of -0.859 eV. The additional electron in the valence-bound state is localized on the nuclear framework and the formation of the valence-bound anionic state leads to geometric distortion of the uracil. The transition between the two anionic states is very feebly optically allowed with an oscillator strength of only 0.004. However, the molecular vibrations can result in the inter-conversion between the valence and the dipole-bound state of the anion. To understand that, we have plotted the adiabatic potential energy surface (PES) of the ground and first excited state of the anion along a linear transit from the dipole-bound to valence-bound geometry. The dipole and valence-bound state correspond to two different minima in the ground state adiabatic potential energy surface, and there exists an avoided crossing between the ground and first excited state of the anion. The nature of the electronic states changes very rapidly near the avoided crossing, which increases the derivative coupling term and leads to the breakdown of the Born-Oppenheimer approximation. In this kind of situation, it is
more advantageous to treat the two states in terms of diabatic potential energy surfaces which crosses each other along the path connecting the two minima and the dominant part of the coupling term is shifted to electronic Hamiltonian.

The valence and dipole-bound nature of the anionic states give us an obvious choice for the diabatic basis. We have generated the two diabatic states by fitting a harmonic potential to the valence-bound and dipole-bound part of the ground state adiabatic PES of the mono-hydrated uracil anion. At the dipole-bound geometry ($\lambda=0$) only one bound anionic state exists, and that is dipole-bound in nature. The second bound anionic state appears while transiting from the dipole-bound to the valence-bound geometry (around $\lambda=0.4$). This second bound anionic state is valence-bound in nature and is an excited state of the dipole-bound anionic ground state. Eventually, the valence-bound state becomes the ground state as the monohydrated uracil evolves towards the minimum energy structure. The rate of transition from the dipole-bound to valence-bound state is $1.2 \times 10^{11}$ sec$^{-1}$, which signifies the reduction of the nucleobases in water happens almost at near diffusion-controlled rates. However, the rate still one order of magnitude lower than the experimentally observed rates$^{14}$ for reduction of nucleobases in bulk water. The electron attachment process to uracil in bulk water can significantly differ from that observed in the simple micro-solvated model. To understand that we have simulated the electron attachment dynamics of both $e_{aq}$ (s) and ($e_{aq}$ (b)) in bulk-water using QM/MM molecular dynamics simulation.

The attachment of partially solvated electron to uracil leads to the formation of two vertically bound anionic states. The ground state has a VDE of $-0.089$ eV, and the additional electron is localized on the surface of the water (See Figure 2). The excited state is also surface-bound and has a VDE of $-0.023$ eV. The natural orbitals corresponding to the additional electron in both the anionic states are away from the nuclear framework of the nucleobase similar to the dipole-bound anionic state in micro-solvated uracil. Bound anionic state localized on the nucleobase first appears around 5 fs and has a VDE of $-0.036$ eV. The uracil-bound state initially appears as an excited state of the anion, and the corresponding natural orbital appears similar to the valence-bound state of mono-hydrated uracil anion. The ground state of the anion is still delocalized over the water surface with VDE of $-0.097$ eV. The transition between the water-bound state and uracil-bound

Figure 1: Uracil monohydrate anion (a) Natural orbital corresponding to the dipole-bound state. (b) Natural orbital corresponding to the valence-bound state. (c) Adibatic surface corresponding to the ground and first excited state (d) Diabatic dipole and valence-bound state
state is very weakly allowed (oscillator strength 0.003) as in the case of dipole, and valence-bound states monohydrated uracil anion. The uracil bound state almost immediately transforms (at 5.5fs) into the ground state with a VDE of –0.249 eV and the first excited state of the anion is localized at the water surface. The plot of detachment energy (see Figure S1) with respect to time shows the sign of avoided crossing similar to that observed in mono-hydrated uracil, indicating mixing of electronic and nuclear degrees of freedom, but the presence of multiple bound anionic states makes it difficult to use any sophisticated diabatization procedure. We have plotted the time evolution of the detachment energy for the lowest uracil-bound and water-bound states (Figure 2) by visual inspections of the natural orbitals corresponding to the electron attached states. It can be seen that the detachment energy of the water-bound state lowers down very slowly, whereas the detachment energy corresponding to the uracil-bound state shows a steep decrease and that leads to a flipping of the energy ordering of the two states.

The vertical attachment of $e_{aq}(b)$ to uracil in bulk water leads to the formation of multiple

![Figure 2: EA-EOM-DLPNO-CCSD natural orbitals depicting time evolution of anionic state formed by attachment of partially solvated electron to uracil](image)

stable bound anionic states as opposed to only two bound states observed for partially solvated electron. All of them are localized on the interior of bulk water, and the anionic ground state has vertical detachment energy (VDE) of –0.739 eV, which is much larger than that observed for partially solvated electron. The first four excited states of the anion are also bound and corresponding excitation energies are 0.338 eV, 0.513 eV, 0.627 eV, and 0.721 eV respectively.
Bound electron attached states which were localized on the uracil start to appear within 3 fs (Figure 4). Initially, the uracil-localized state appears as an excited state and is very weakly bound with vertical detachment energy of -0.146 eV.

The anionic ground state is still localized on the water, and the transition from water-bound the anionic state to uracil-bound anionic state is very weakly optically allowed with an oscillator strength of 0.002, similar to that observed for the mono-hydrated uracil model. Within 6 fs, the uracil-bound state becomes the ground state with VDE of -0.988 eV, which is also much higher than that observed for the first appearance of the nucleobase-bound ground state for the attachment of partially solvated electrons to uracil. The water-bound states appear as the first excited state at 6 fs with an excitation energy of 0.121 eV. The plot of the detachment energy with respect to time shows avoided crossing similar to the partially solvated uracil anion (Figure S1). The detachment energy corresponding to the diabatic uracil-bound anionic state formed due to the attachment of bulk solvated electron increases much steeply than that in partially solvated one. The detachment energy of $e_{\text{aq}}^-(b)$ increases up to 500 fs around after which they reach their equilibrium value of 4-5 eV, which is much larger than the detachment energy (3.3 eV) of an electron in bulk water. It indicates the feasibility of reduction of nucleobases in bulk water. The fluctuations in the detachment energy are more prominent for the partially solvated electron that reaches its equilibrium value around 1000 to 1500 fs (See Figure 3(c) ), which is consistent with the experimental time scale of conversion of the partially solvated electron to bulk solvated electron. Although, the quantitative trends in the detachment energy are initially different for partially

Figure 3: The upper panel depicts time evalultion of detachment energy of the valence and dipole states for the attachment of (a) partially solvated (b) bulk solvated (c) both on a longer time scale. The lower panel depicts the radial distribution function (RDF) plot for (d) O1 of uracil and H of water (e) O2 of uracil and H of water

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solvated and bulk solvated uracil anion, in the longer time scale (above 1.5 ps) both lead to similar detachment energy values.

The very high detachment energy of nucleobase in bulk water can be rationalized in terms of the local structure of the water distribution around the uracil anion. Figure 3(d) and 3(e) present the radial distribution function plot for O of uracil and H of water for the attachment of $e_{aq}^{-}(b)$ to uracil. The radial distribution function of both the uracil oxygen with the hydrogens of water shows a very sharp peak around 2 Å for the anionic nucleobase. The peak appears in addition to the standard hydrogen bonding peak at 3 Å present for solvated neutral nucleobases. It indicates the formation of a short-range local structure around the bulk solvated uracil as it evolves from the neutral to anionic state. The local structure of water preferentially stabilizes the uracil anion through its hydrogen bonding network and leads to high detachment energy in solvated nucleobases. A similar trend is observed for the attachment of partially solvated electron to uracil.

Based on our theoretical calculations, we have proposed a two-step mechanism of reduction of nucleobases in water:

$$U \left( H_2O \right)_n + e \xrightleftharpoons[k_{-1}]{k_1} U \left( H_2O \right)_n ^{+} \xrightarrow[k_2]{k_3} U^- \left( H_2O \right)_n$$

**Figure 4:** EA-EOM-DLPNO-CCSD natural orbitals depicting time evaluation of anionic state formed by attachment of bulk solvated electron to uracil
In the first step, the pre-solvated electron reacts with the solvated uracil and the resulting gets solvated to give a uracil water anionic complex, where the extra electron is localized on water. In the second step, the electron transfer happens from the water to the nucleobase in the activated complex. Subsequently the complex decomposes into uracil anion and water. The solvation of pre-solvated electron takes place in the picosecond timescale. To explain the experimentally observed rate of nucleobases in order, using the above mechanism, the electron transfer from water to uracil needs to happen at the picosecond time scale. The calculated rate of electron transfer from water-bound state to uracil bound state is \(2.1 \times 10^{12} \text{ sec}^{-1}\), which is consistent with the proposed mechanism.

**Computational Details:** The geometry of the micro-solvated uracil has been optimized using the RI-MP2/aug-cc-pVDZ level of theory. The adiabatic potential energy surface corresponding to the linear transit from dipole-bound to valence-bound geometry has been calculated using EA-EOM-DLPNO-CCSD method with NORMALPNO settings. The intermediate geometries were obtained by varying the linear transition parameter \(\lambda\) from 0 to 1 in the following formula:

\[
R = (1-\lambda) R_{DB} + \lambda R_{VB}
\]

where \(R\) is the geometrical parameter (bond length, bond angle and dihedral angle) for the intermediate geometry, \(R_{DB}\) is the parameter for the dipole-bound geometry, and \(R_{VB}\) is the parameter for the valence-bound anion geometry. The coupling elements between two diabatic states are obtained by fitting a simple avoided crossing model potential defined as follows:

\[
V = \begin{pmatrix}
V_1 & W \\
W & V_2
\end{pmatrix}
\]

Where the diagonal elements are chosen to be harmonic potential in the coordinate \(\lambda\) with the form:

\[
V_i = \frac{1}{2} \omega_i (\lambda - \lambda_i^0)^2 + V_i^0
\]

And the off-diagonal element is assumed to be constant. We have calculated the rate of transition of an electron from dipole-bound to valence-bound state using the Marcus theory:

\[
k = \frac{2\pi}{h} |W|^2 \sqrt{\frac{1}{4\pi k_BT \lambda_R} e^{-\Delta G^0/4k_BT}}
\]

Where \(\Delta G^0\) is the free energy change between the valence and dipole-bound state (\(E_{VB} - E_{DB}\), ignoring the entropy contribution), \(\lambda_R\) is the reorganization energy.

The classical molecular dynamics simulations on the uracil are performed in NAMD using a charm compatible forcefield. The TIP3P model has been used for the water. Uracil was solvated with 2460 water molecules (TIP3P) in a cubic box of 40 Å, and minimization was performed keeping the uracil fixed and using the non-bonded cutoff 12 Å. The minimized structure was heated up to 300 K using Langevin Thermostat. After the heating was complete, the system was equilibrated for 500 ps using the time step for integration as 2 fs. Periodic boundary condition and particle-mesh Ewald technique (PME) was applied during the equilibration run. Subsequently, a
10 ns Production run was carried out in constant pressure (1 bar) - constant temperature (300 K) condition with Nosé-Hoover Langevin piston pressure control. From the Production run, 10 snapshots were generated in a regular interval of 1 ns.

The snapshot after the equilibration run and the snapshot after 1ns of production run were taken for mixed quantum-classical QM/MM simulation using ORCA-NAMD QM/MM interface. The uracil is treated as the QM region at BP86 and def2-SVP basis set, and waters are treated at the MM level using the same forcefield as that of the classical MD simulations. The timestep for integration was taken as 0.5 fs, and the QM/MM simulations were run for 2ps in both the cases. In each case, 4000 snapshots were generated from the QM/MM trajectory in an interval of 0.5 fs. The single point QM/MM calculation on each snapshot was performed using ORCA with uracil treated using EA-EOM-DLPNO-CCSD method with NORMALPNO setting, and the TIP3P model has been used for the water. The aug-cc-pVDZ basis sets with additional 5s 5p 4d diffused functions added on the carbonyl oxygen of uracil have been used for all the calculations, except the potential energy surface of microsolvated uracil and rates of electron transfer in bulk water, which are calculated using aug-cc-pVTZ basis sets with additional 5s 5p 4d diffused functions. The snapshots from the QM/MM simulations using geometry from the equilibration run lead to partially solvated electrons, and snapshot from the QM/MM simulation on the geometries from the production run leads to bulk solvated electrons. Multiple trajectories were considered for the analysis. More details on standardizing the QM/MM protocol has been provided on the supporting information.

Supporting Information
The Supporting Information is available

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