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Do Solvated Electrons (e^-_{aq}) Reduce DNA Bases? A G4 and DFT-MD Study

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Abstract

The solvated electron (e^-_{aq}) is a primary intermediate after an ionization event that produces reductive DNA damage. Accurate determination of standard redox potentials (E°) of nucleobases and of e^-_{aq} determine the extent of reaction of e^-_{aq} with nucleobases. In this work, E° of e^-_{aq} and of nucleobases have been calculated employing the accurate *ab initio* Gaussian-4 theory including the polarizable continuum model (PCM). The Gaussian-4-calculated E° of e^-_{aq} (-2.86 V) is in excellent agreement with the experimental one (-2.87 V). The Gaussian-4-calculated E° of nucleobases in dimethylformamide (DMF) lie in the range (-2.36 V to -2.86 V); they are in reasonable agreement with the experimental E° in DMF and have a mean unsigned error (MUE) = 0.22 V. However, inclusion of specific water molecules reduces this error significantly (MUE = 0.07). Employing a model of e^-_{aq} -nucleobase complex with 6 water molecules, reaction of e^-_{aq} with the adjacent nucleobase is investigated using approximate *ab initio* molecular dynamics (MD) simulations including PCM. Our MD simulations show that e^-_{aq} transfers to uracil, thymine, cytosine and adenine, within 10 to 120 fs and e^-_{aq} reacts with guanine only when a water molecule forms a hydrogen bond to O6 of guanine which stabilizes the anion radical.

Graphical abstract

Keywords

Solvated electron; redox potential; DNA/RNA base anion; molecular dynamics; MD simulation; free energy of solvated electron

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Supporting Information: The Supporting Information is available free of charge on the ACS Publications website. The supporting information contains: Table S1 (Physical properties of solvated electron), atom numbering of bases, optimized structures of solvated electron with nucleobases and Cartesian coordinates of the optimized structures.

Introduction

The reaction of electrons with DNA represents one of the fundamental processes involved in radiation-induced damage to DNA.¹⁻⁷ The reactivity of a radiation-produced electron depends on its energy and local environment, i.e., whether it is in the gas phase (e^-_g), or in water either as a pre-solvated (e^-_{pre}) or fully solvated (e^-_{aq}) state.¹⁻¹² In the early physico-chemical stages, the interaction of ionizing radiation with water results in H_2O^{*+} and e^-_{pre} .¹³⁻¹⁵ H_2O^{*+} , being a strong Brønsted acid,² deprotonates to form $^{\bullet}OH$ and hydronium ion (H_3O^+) within 10^{-13} s (40 to 200 femtoseconds).⁹⁻¹¹ Within a picosecond, solvation of e^-_{pre} by its surrounding water molecules leads to the formation of a solvated or aqueous electron (e^-_{aq}).¹³⁻¹⁵ Owing to the fundamental importance of e^-_{aq} , many theoretical and experimental investigations have been carried out to elucidate its physical and chemical properties.^{5-7, 16-26}

The thermochemical properties of e^-_{aq} are critical to the understanding of its redox chemistry and as a consequence they have been of keen experimental and theoretical interest. Assuming a cavity model for e^-_{aq} , Jortner and Noyes²⁷ were the first to estimate its absolute solvation free energy (G°_{sol}), as -37.5 kcal/mol. Furthermore, they provided rough estimates for the absolute enthalpy (H°_{sol}) and entropy (S°_{sol}) of solvation of e^-_{aq} . Improved values of these thermodynamic parameters were obtained later as experimental techniques gradually developed (see Table S1 in the supporting information). Employing pulse radiolysis, Schwarz²⁸ estimated the H°_{sol} and S°_{sol} of e^-_{aq} as -34.0 kcal/mol and 16 cal/mol-K, respectively, which yields $G^\circ_{sol} = -38.8$ kcal/mol. Subsequent values for G°_{sol} , H°_{sol} , and S°_{sol} of e^-_{aq} have been near these with the most recent estimates based on experiments on the single ion hydration for proton and an electron, gave -34.4 kcal/mol, -30.2 kcal/mol and 14.2 cal/mol-K, respectively.²⁶ Therefore, the experimental values of G°_{sol} lie in the range -34.4 kcal/mol to -38.8 kcal/mol with an average of ca. -37 kcal/mol or -1.6 eV. This value not only gives the hydration free energy of electron solvation ($G^\circ_{sol} = -1.6$ eV) but also the magnitude of the adiabatic electron affinity (AEA) and the adiabatic ionization energy (AIE) of e^-_{aq} . In addition to experimental estimates, several works providing values for G°_{sol} , H°_{sol} , and S°_{sol} of e^-_{aq} using first-principle calculations including full solvent modeled by a dielectric continuum have been reported. For example, Zhan and Dixon²⁹ reported $G^\circ_{sol} = -35.5$ kcal/mol for e^-_{aq} . Very recently, Kumar et al.²⁶ calculated the G°_{sol} , H°_{sol} , S°_{sol} of e^-_{aq} as -37 kcal/mol, -31.7 kcal/mol and 17.9 cal/mol-K using high level Gaussian-4 quantum chemical calculations.

In addition to the AEA (1.6 eV) of e^-_{aq} , another important quantity of interest is its vertical detachment energy (VDE). Using liquid micro-jet photoelectron spectroscopy, the VDE was found to be in the range of 3.3 eV to 3.5 eV.^{18,21,22,23,30,31} Recently, liquid jet experiments reported the VDE of e^-_{aq} in the range of 3.42 – 3.45 eV.^{30,31} Using density functional theory (DFT) and considering the effect of full solvent through the non-equilibrated polarized continuum model (NE-PCM), the VDE of e^-_{aq} was calculated as ca. 3.4 eV.^{25,26} These two quantities, AEA and VDE, (see Figure 1A) are well-defined in literature as: (i) the AEA measures the binding energy of a gaseous electron when solvated in liquid water and (ii) the VDE is a measure of the instantaneous energy needed to remove an electron from liquid water to the gas phase.^{3-5,26}

In a recent report, Abel and coworkers used the VDE (3.3 eV) for e^-_{aq} to interpret the binding of e^-_{aq} with nucleobases.¹⁸⁻²⁰ Based on the VDE, they concluded that e^-_{aq} should not bind with nucleobases (see Figures 4, 5 and 13 in refs. 16 - 18) as nucleobases have electron affinities in the range ca. 1.7 - 2.2 eV.^{32,33} Their interpretation concerning the reactivity of e^-_{aq} with nucleobases is incorrect since it ignores the well-established experimental fact that the solvated electron, e^-_{aq} , efficiently adds to all the nucleobases.^{1-4,7,34,35} These include many works using pulse radiolysis that report near diffusion-controlled reaction rates ($3.8 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ to $1.8 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$; see Table 10.6 in ref 2) of e^-_{aq} with DNA/RNA components.^{2,7} Moreover, as emphasized in this work, the addition of e^-_{aq} to the nucleobases should follow its AEA and not its VDE.

In order to gain a deeper insight into the energetics of the reaction of e^-_{aq} with nucleobases, we have performed high level quantum chemical calculations employing the Gaussian-4 (G4) method to obtain the free energies (G°) for e^-_{aq} addition to the nucleobases. These values have led to the theoretical determination of one-electron reduction potentials (E° vs. NHE) of nucleobases. Furthermore, the thermodynamic work is complemented with *ab initio* molecular dynamics calculations which corroborate the experimental observation that e^-_{aq} efficiently reduces all five nucleobases.

Methods of calculation

In this study, we used the Gaussian-4 (G4) method to calculate thermodynamic properties by considering the effect of bulk water ($\epsilon = 78.4$) and n,n-DimethylFormamide (DMF; $\epsilon = 37.22$) as solvent via the integral equation formalism of the polarized continuum model (IEF-PCM) of Tomasi et al.³⁶ The cavity for IEF-PCM is formed using the UFF radii, which places a sphere around each solute atom, with the radii scaled by a factor of 1.1. G4 is an *ab initio*-based method that has been established to predict accurate thermochemical properties of molecules and was developed by Curtiss, Redfern, and Raghavachari.³⁷ The average absolute deviation in energies calculated at the G4 level including enthalpies, ionization energies, electron affinities, proton affinities and hydrogen-bond complexes for a data set of 454 experimental values is 0.83 kcal/mol and the root mean square deviation is 1.19 kcal/mol.³⁷ In this study, the geometries of DNA/RNA bases in their neutral and anion radical states were fully optimized in H₂O and DMF and frequency calculations confirmed these optimized structures as the minimum energy structures. All calculations were performed using the Gaussian09 suite of programs.³⁸

The thermodynamic properties (G°_{sol} , H°_{sol} and S°_{sol}) of the solvated electron, e^-_{aq} , were calculated employing the G4 method and the VDE was calculated using non-equilibrium PCM (NE-PCM).³⁹ These values are reported in our work (Table 2 in ref. 26) and we employ these values for e^-_{aq} in this present study.

The standard one-electron reduction potential E° vs NHE of DNA/RNA bases are calculated as

$$E^{\circ} = \frac{-\Delta G^{\circ}_{\text{sol}}}{F} - \text{SHE} \quad (\text{eq 1})$$

Where SHE is the absolute standard hydrogen electrode potential and F is the Faraday constant. The reference values of the absolute potential of the SHE in water varies in the range of 4.28 V to 4.44 V.⁴⁰ In this work, we used the IUPAC recommended value of SHE = 4.44 V.^{40, 41} We note that calculation of E° depends on the accuracy of calculated solvation free energy (G°_{sol}) and controlled by the chosen reference SHE value.⁴⁰ In the present study, the value of SHE = 4.44 V provides E° values in close agreement with experiment. The Faraday constant F is equal to 23.061 kcal·mol⁻¹·V⁻¹. The solvation free energy G°_{sol} and E° of one-electron reduced DNA/RNA bases are calculated using the direct method shown by Ho⁴² to obtain results that are comparable to those determined employing the complete thermodynamic cycle. The overall reaction of the solute in the solvent with the gas phase electron (e^{-}_{g}) is:

The free energy is calculated using $G^{\circ}_{\text{sol}} = G^{\circ}(M^{\bullet-}_{\text{sol}}) - G^{\circ}(M_{\text{sol}}) - G^{\circ}(e^{-}_{\text{g}})$. The free energy of the gas phase electron, $G^{\circ}(e^{-}_{\text{g}})$, of -0.867 kcal/mol is obtained from Fermi-Dirac statistics.⁴³ In the present work, the standard states chosen are: 1 atm, 1 mole, and 298 K.

We employed the atom-centered density matrix propagation (ADMP) *ab initio* molecular dynamics (MD) method implemented in Gaussian-09 to simulate the dynamics of the reaction of e^{-}_{aq} with DNA bases. The working strategy of ADMP is equivalent to Born-Oppenheimer molecular dynamics but at substantially reduced computational cost. ADMP uses the extended Lagrangian approach to molecular dynamics using Gaussian basis functions and propagating the density matrix which is equivalent to Car-Parrinello molecular dynamics (CPMD).^{38,44} The B3LYP functional with 6-31++G** basis set including PCM was used in the ADMP simulations. We note that the use of PCM with ADMP has been successfully employed to explore the Menshutkin reaction of methyl chloride with ammonia by Patterson and coworkers.⁴⁵ All our simulations were run for 200 fs (up to 1.25 ps for guanine) with a time step of 0.1 fs using default values set in the program. The default values of fictitious electronic mass = 0.10000 amu, initial nuclear kinetic energy = 0.10000 Hartree and initial electronic kinetic energy = 0.00000 Hartree are used in the calculation.

We employed the dielectric continuum model combined with *ab initio* MD simulation. Implementation of the dielectric continuum models in the framework of time-dependent processes is an approximation since the nuclear motions of the specific molecules considered are instantaneously responded by the continuum. Clearly for the fast reactions considered in this work found by this method can be considered qualitatively instructive but not quantitative in nature. The aim of our MD simulations is to show that solvated electron initially trapped in a localized cavity is able to reduce the DNA bases. Our picture of the solvated electron is thus very different than the highly delocalized picture shown by Smyth and Kohanoff.⁴⁶ Our choice of 0.1 Hartree initial nuclear kinetic energy is the default value

set in the program and is sufficient to induce the molecular motions needed to induce transfer. A total of 12 MD simulations were performed. Even with this limited set of simulations there was consistency with each of the three pyrimidines (5 simulations), T (1), C(2), U(2), finding a fast transfer within 30 fs. For the purines (6 simulations), G(5), A(1), we found that all simulations showed a slower transfer time with the case of G needing a specific hydrogen bonding by water at N7 and O6 before transfer occurs.

Results and Discussion

Very recently, jointly with Bartels group, we calculated the various physical properties of the solvated electron (e^-_{aq}) employing a number of density functional theory (DFT) functionals as well as the G4 method.²⁶ Our calculated values were found to be in good agreement with those found by experiment.²⁶ In our approach, we considered the “cavity model” formed by four water molecules arranged in a tetrahedral conformation with one hydrogen atom of each water molecule pointed towards the cavity center binding the solvated electron. Assuming this model to represent the dominant structural motif of e^-_{aq} and taking into account the full effect of its solvation through PCM, we calculated the G°_{sol} , H°_{sol} and S°_{sol} of e^-_{aq} employing the G4 method.²⁶ The G4-calculated values of G°_{sol} of $4H_2O^-$ and $6H_2O^-$ are -35.9 kcal/mol (1.56 eV) and -37.0 kcal/mol (1.60 eV), respectively. The average of these G°_{sol} is 1.58 eV, when adjusted for the SHE= 4.44 V (eq 1), yields -2.86 V, for the E° of e^-_{aq} . (eq 1) yields -2.86 V, for the E° of e^-_{aq} . This value is in surprisingly good agreement with the reported E° vs NHE (-2.87 V) for e^-_{aq} ^{41,47,48} (see Table 1). The complete energetic cycle for the electron solvation based on its AEA (1.6 eV), VDE (3.4 eV) and the solvent reorganization energy (SRE) is shown in Figure 1(a). The solvent reorganization energy (SRE) is equal to the difference between the AEA and the VDE and is quite large (1.8 eV). The magnitude of the SRE is reasonable when one considers that after ejection of the electron from the cavity the remaining structure has 4 protons in a tetrahedral arrangement essentially pointing at each other.

The experimental reduction potentials E° vs NHE of DNA/RNA bases G, A, C, T, and U were measured by Seidel et al. using pulse polarography and cyclic voltammetry in DMF as G (< -2.76 V), A (-2.52 V), C (-2.35 V), T (-2.18 V), and U (-2.07 V)).⁴⁹ Using the G4 method, we calculated the reduction potentials of these bases in DMF and in water. Our G4-calculated E° vs NHE of G, A, C, T and U in DMF and in water are shown in Table 2.

Our values in DMF are in comparatively good agreement with experiment with a MUE (mean unsigned error) of 0.22 V. Using the M06-2X density functional and 6-31++G(d,p) basis set, Lewis et al.⁵⁰ calculated the E° vs NHE of G, A, C and T in water as -3.31 V, -2.86 V, -2.41 V and -2.31 V with MUE = 0.27 V. Crespo-Hernández et al.⁵¹ used gas-phase vertical electron affinities of G, A, C and T calculated at B3LYP/6-311+G(2df,p)//B3LYP/6-31+G* level of theory to estimate the E° vs NHE (G (ca. -3.0 V), A (-2.71 V), C (-2.56 V) and T (-2.32 V)) in acetonitrile (ϵ = 36.64) with MUE = 0.2 V.

From Table 2, it is evident that the G4-calculated reduction potentials of G, C, A, T and U in DMF/water are in the order $G < A < C < T < U$, which is in agreement with experiment. Both theory and experiment (Table 2) show that guanine has the least favorable reduction

potential (ca. -2.76 V to -2.86 V) which is close to the E° of e^-_{aq} (-2.87 V). Uracil has most favorable reduction potential. A comparison of the G4-calculated solvation free energy G°_{sol} along with E° vs NHE of all the bases and of e^-_{aq} is presented in Figure 1(b). We also used B3LYP/6-31++G** including PCM to calculate the E° vs NHE of isolated G, C, A, T and U in water. The B3LYP/6-31++G**-calculated E° values are found to be very close to the calculated G4 values, see Table 2.

Although, the calculated E° values in this work fit reasonably well to the experimental ones and to those determined using other methods reported, E° values obtained employing G4-approach were expected to improve this fit substantially. We believe that this discrepancy is a result of not accounting for the specific hydrogen bonding of water molecules to the DNA bases. The expected uncertainty with PCM can be improved by explicit addition of specific water molecules.^{6,52} To test this, we performed a G4 calculation on adenine with three waters of hydration with donor hydrogen bonds as shown in supporting information (Figure S3). For uracil, thymine and cytosine, we considered two explicit water molecules for the calculation of the E° using the G4 method (see Figure S3). For guanine, both 2 and 3 waters were considered. The G4-calculated E° values of guanine, adenine, uracil, thymine, and cytosine in the presence of the explicit water molecules are presented in Table 2. The inclusion of specific waters of hydration increases the reduction potentials (and electron affinities) of the various DNA bases and reduces the error in comparison to experiment significantly (MUE= 0.07 V).

The absolute potential for addition of e^-_{aq} to the DNA bases can be obtained by taking the E° values from Table 2, and subsequently correcting the experimental values from DMF to H_2O and adding the NHE voltage of 4.44 V. In Table S2, we present the details of this calculation and in Table 3 last column, we present these values. It is obvious from these E° values that all the DNA bases are capable of being reduced by e^-_{aq} with guanine favored but on the borderline unless specific waters of hydration are included. However, pulse radiolysis experiments clearly show that guanine (as a nucleobase, nucleoside, or in oligomers) reacts with e^-_{aq} at near diffusion controlled rates.^{2,7,53-57} Therefore, reaction of e^-_{aq} with guanine is both kinetically and thermodynamically accessible.

Modeling Reaction of e^-_{aq} with Nucleobases

To study the reaction of e^-_{aq} with G, C, A, T and U, we initially arranged four water molecules in a tetrahedral conformation forming a cavity near each of the bases. This cavity model, composed of four water molecules in a tetrahedral conformation, was recently studied by us and proposed to represent the dominant structural motif of e^-_{aq} .²⁶ The cavity model of e^-_{aq} has already been proposed in the literature.⁵⁸ The initial structure ($4H_2O$ -base) $^{\bullet-}$ (Base = A, T, G, C or U), thus generated, was fully optimized using the B3LYP/6-31++G** method including PCM to account for the full solvation effect. The spin density plot of the fully optimized structures showed that e^-_{aq} is completely localized in the cavity enclosed by $4H_2O$. Further, considering the fully optimized structures ($4H_2O$ -base), we placed two more water molecules near the four water cavity in a hydrogen bonded fashion and fully optimized the structures ($6H_2O$ -base) $^{\bullet-}$ using the B3LYP/6-31++G** method including PCM (see optimized structures in the supporting information). The spin density

plots of these fully optimized structures ($6\text{H}_2\text{O-base}^{\bullet-}$) again showed the complete localization of e^-_{aq} in the cavity, see Figures 2 - 8. The spin density plot of the fully optimized $\text{T-6H}_2\text{O}^{\bullet-}$ obtained using the B3LYP/6-31++G** method is shown in Figure 2, while the spin density plot for other optimized systems before and after electron transfer are also shown in Figure S2 in the supporting information. The optimized result for $\text{T-6H}_2\text{O}^{\bullet-}$ (Figure 2) appears in direct contrast with the experimental fact that all DNA bases react at diffusion controlled rates with e^-_{aq} .^{1-7,32-35,53-57} The unpaired electron spin distribution shown in Figure 2 appears anomalous since the stable position for the electron is actually on the thymine not in the water cavity as shown in the Figure. However, this metastable state converts to the stable molecular arrangement when molecular dynamics induces the electron transfer as described below.

Molecular Dynamics

Thymine- $6\text{H}_2\text{O}^{\bullet-}$ —From the analysis of the trajectory of thymine- $6\text{H}_2\text{O}^{\bullet-}$ we find that the solvated electron which was initially (at 0 fs) localized in the cavity, transfers from the cavity to thymine with time. By 22 fs, around half of e^-_{aq} is transferred and by 30 fs it is completely localized on the thymine base (see Figure 3). The total spin density plot at various time scales are shown in Figure 3. The structure at 30 fs from the MD simulation was further considered for the full geometry optimization using the B3LYP-PCM/6-31++G** method. In the fully optimized structure, the water molecules are arranged around the thymine in a hydrogen bonded fashion (Figure 3e) and extended from the N1 to O4 site of the thymine base (see Figure S1 in the Supporting information for atom numbering). Comparison of the optimized structures of the solvated electron and base (0 fs, Figure 3 (a)), to the transferred structure with the electron moved to the thymine base (Figure (3e)), the latter is found to be stabilized by an additional -0.88 eV (see Table 3).

Recently, Smyth and Kohanoff studied the excess electron attachment with solvated DNA bases using *ab initio* CP2K molecular dynamics.⁴⁶ For thymine solvated by 64 water molecules, they also found that within 25 fs the excess electron completely localizes on the thymine base. This result is in good agreement with our calculations employing our much smaller system (see Figures 2 and 3). We note here that Smyth and Kohanoff considered a delocalized distribution of the solvated electron on water and thymine.⁴⁶ However, in our approach, we considered a localized solvated electron model residing in the cavity. Our MD simulation shows that cavity of the solvated electron is quickly lost (within 30 fs) owing to the nuclear motion as the electron transfers to thymine.

Cytosine- $6\text{H}_2\text{O}^{\bullet-}$ —From the time evolution of the total spin density of cytosine- $6\text{H}_2\text{O}^{\bullet-}$, we found that the solvated electron remains localized in the cavity up to 14 fs (see Figure 4). At 15 - 20 fs, the solvated electron completely transfers from the cavity to the cytosine base. The transferred structure at 20 fs was then fully optimized and this structure is shown in Figure 4(d). In this fully optimized structure, the waters form a hydrogen bonding network around the cytosine base extending from O2 to N4. Also, the fully optimized structure (Figure 4(d)) is 0.64 eV more stable than the initial structure at 0 fs ((Figure 4 (a)), see Table 3).

Uracil-6H₂O[•]—For uracil, we placed the 6H₂O[•] structure in two positions, first near the O4-N3 and second near the O4-C5 sites of uracil. Subsequently, each initial structure was optimized and thereafter the MD calculation was performed employing this optimized structure. The simulations of uracil-6H₂O[•] in both structural arrangements showed a very fast transfer (within 5 -10 fs) of the solvated electron from the cavity to the uracil base. The result of 6H₂O[•] placed near O4-N3 site of uracil is presented in the supporting information (Figure S4), while the result of 6H₂O[•] placed near O4-C5 site of uracil is discussed below. From the simulation, it is found that within 8 -10 fs, spin density is completely transferred to the uracil base. On full optimization of the 10 fs structure, the excess electron remains completely localized on uracil base. In the optimized structure (Figure 5d), five water molecules are arranged in a hydrogen bonding fashion around O4 of uracil and one water molecule moves towards C6 and is stabilized through hydrogen bond formation with the π_z -orbital on C6 of uracil. We note that the first structure (6H₂O[•] placed near the O4-N3, Figure S4 in the supporting information) maintains all the waters near O4-N3 and does not lead to the hydrogen bond formation at C6. There is a slight energy difference (ca. 4 kcal/mol) between these two structures with the C6 hydrogen bonded form favored. The fully optimized structure (Figure 5(d)) is stabilized by -0.93 eV over structure at 0 fs (Figure 5(a)).

Adenine-6H₂O[•]—MD simulation of adenine-6H₂O[•] shows that the solvated electron remains localized mainly in the cavity for up to 100 fs. A small transfer of spin density within this time period takes place to adenine which is evident from the total spin density plot (see Figure 6 (a) and (b)). By 120 fs, almost ca. 75% spin density localizes on adenine and ca. 25% remains in the cavity. The geometry optimization completely localizes spin density on adenine and one water molecule hydrogen bonds with the N7 site of adenine. Compared to the pyrimidines (T, C and U) adenine shows a comparatively slow reaction with the solvated electron. In comparison to the optimized structure at 0 fs (Figure 6(a)), the fully optimized structure (Figure 6(d)) is stabilized by -0.25 eV, see Table 3.

Guanine-6H₂O[•]—We ran three MD trajectories by placing the 6 H₂O cavity containing cluster near the N7-C8, O6-N7, and O6-N2 sites of guanine. The simulations were carried out up to 1.25 ps with a time step of 0.25 fs. In all of the three trajectories considered, we found that the solvated electron is localized in the cavity and only a very small fraction (ca. 20%) of total spin density is transferred to guanine up to 1.25 ps. The result of 6 H₂O located near to the N7-C8 site of guanine is shown in Figure 7. The total spin density plot (Figure 7a) of guanine-6H₂O[•] at 0 fs shows the complete localization of the solvated electron in the cavity. After ca. 400 – 1250 fs, a very small spin density transfer from the water cavity to guanine is evident. In Figure 7b and c, the total spin density plot at 625 fs and 825 fs are shown.

From our simulations, we found that with time one of the water molecule (pink highlighted in Figure 7b and c) moves away from the guanine; while the other water molecule moves towards the N7 site of the guanine (see Figure 7b and c). Since the distant water molecule (pink highlighted) was interacting very weakly with rest of the molecular system, we considered moving this water molecule towards O6 of guanine to increase the stabilization

of the anion radical. To perform this structural modification, we took the structure at 625 fs, shown in Figure 7b, and manually moved the water molecule (pink highlighted) near the O6 atom of guanine without disturbing the configuration of the remainder of the system. We used this modified structure for MD simulation and results are presented in Figure 8. The total spin density plot at 0 fs shows that solvated electron is localized in the cavity (Figure 8(a)) and within 60 fs the spin density transfers to guanine, see Figure 8(b). From this result, we infer that a donor hydrogen bonding water network around guanine is essential to stabilize the guanine anion radical for rapid electron transfer. Thus, we infer that the driving force for transfer of the solvated electron is only significant when specific waters are included around guanine as it is evident from E° vs NHE values calculated including 2 and 3 water molecules (see Figure S3e). The optimized structure shown in Figure 8(b) is more stabilized than initial optimized structure at 0 fs shown in Figure 7(a) by 0.19 eV, see Table 3. This value, 0.19 eV, is the same as that found in Table 2 for the increase in E° of guanine after addition of 2 or 3 waters (0.18 or 0.22 eV). This shows that hydrogen bonding to water increases the electron affinity of the guanine and facilitates the transfer of the electron to the base.

In Table 3, we present the relative stability of the solvated base anion radicals with respect to the solvated electron residing in the cavity near to base (optimized 0 fs initial structure in each case). From Table 3, we found that relative stability of the solvated base anion radicals is in the order $G^{\bullet-}-6H_2O < A^{\bullet-}-6H_2O < C^{\bullet-}-6H_2O < T^{\bullet-}-6H_2O < U^{\bullet-}-6H_2O$ which is in excellent agreement with the trends obtained from the experimental E° vs. NHE presented in Table S2 in the supporting information. The solvation free energy G°_{sol} calculated using the B3LYP-PCM/6-31++G** method is in excellent agreement with those determined experimentally using the standard reduction potentials (E°) given in Table 2.

Conclusions

From the present study, we arrive at the following points.

1. Reduction potential of e^-_{aq} : Our earlier work showed that the G4-calculated thermodynamic properties of e^-_{aq} ($G^\circ_{sol} = -1.58$ eV, $H^\circ_{sol} = -1.33$ eV and $S^\circ_{sol} = 19.1$ cal/mol deg) are in excellent agreement with those available from experiment, see Table 1 and Table S1 in the supporting information. The value for the free energy results in a calculated value for the reduction potential of -2.86 V for e^-_{aq} in excellent agreement with the experimental reduction potential E° vs NHE (-2.87 V) of e^-_{aq} .
2. One-electron Reduction potential of nucleobases: The G4-calculated reduction potentials E° vs. NHE of DNA/RNA bases are in reasonable agreement with those determined experimentally in DMF. The maximum difference between the theoretical and experimental values of the reduction potential for a particular nucleobase is ca. 0.3 V while the MSE is -0.22 V showing that the theory predicts values that are about 0.2 V too low. Other workers have reported similar results (Table 2). We find that inclusion of specific waters of solvation leads to significant reduction of the error to less than 0.1 V (see Table 2 and Figure S3 in the supporting information).

3. e^-_{aq} can reduce all nucleobases: From a comparison of the E° vs NHE of DNA/RNA bases with respect to that of the solvated electron (see Tables 1 and 2 and Figure 1b), it is evident that solvated electron can reduce all the DNA/RNA bases and contradicts Abel's reports¹⁸⁻²⁰ that fully solvated electrons cannot reduce DNA/RNA bases.
4. MD simulation using the cavity model for e^-_{aq} : Our approximate *ab initio* molecular dynamics (ADMP) simulations of the reaction of the solvated electron with DNA/RNA bases predicts that the reaction of the solvated electron with C, T, U and A should be fast with the solvated electron transferring from its cavity to the base within 10 – 120 fs. While these times must be considered estimates, they clearly show a difference in reaction time for purines vs. pyrimidines. We note that the experimentally obtained second order rate constants for the reaction of e^-_{aq} with all DNA bases employing pulse radiolysis are near diffusion controlled (ca. $1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$).^{2,7} Thus, e^-_{aq} reacts with each nucleobase essentially within the encounter time period.

Our calculations which find a stable initial metastable state with the electron in a water cavity next to the DNA base suggest there is a barrier for transfer of the electron from the water cavity to the DNA bases. This is clearly reasonable since a vertical electron transfer from the water cavity to the thymine base would leave the water cavity in a highly unstable arrangement (by ca. 1.8 eV) with four protons pointed inward toward each other. Thus, only on molecular rearrangement, can the electron transfer as shown in our molecular dynamics simulations.

5. MD simulation of the reaction of e^-_{aq} with G: For guanine, our ADMP simulation did not show the transfer of the solvated electron from cavity to guanine up to 1.25 ps. From reduction potential E° vs NHE of G (-2.76 V to -2.86 V) and the solvated electron (-2.87 V) it appears that reaction between G and the solvated electron is not very favorable thermodynamically until discrete water molecules are employed stabilize the guanine especially by hydrogen bonding to O6 of guanine. The increase in the favorability of electron addition to guanine by inclusion of hydrogen-bonded waters is shown both by the MD simulations and the calculations of the redox potentials provided in Table 2. This is a general trend for all DNA bases which increase in reduction potential by ca. 0.2 V with addition of 2-3 waters of hydration.
6. The Reaction of the Solvated Electron with dsDNA: The reaction of the solvated electron with dsDNA is of obvious fundamental interest from a biological point of view. The present study confirms that all the DNA/RNA bases are efficiently reduced by the solvated electron. In DNA, the bases are stacked and the dielectric constant (ϵ) within DNA is estimated to be about 4.0^{59, 60} with the DNA solvated by water with a dielectric constant of 78. Furthermore, DNA is a highly dynamic structure which readily undergoes various breathing, twisting, unzipping and other motions. The dynamic nature of the DNA structure would allow both solvent and solvated electron accessibility and is expected to effect the rate and extent of reaction of the aqueous electron with DNA. A variety of experimental studies show

that aqueous electrons react with dsDNA with rates of ca. $1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ based on the individual concentration of nucleotides making up the DNA polymer.^{2,7, 54–57} This rate is about two orders of magnitude lower than that found for the individual bases (ca. $1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$) but is in accordance with the diffusion controlled reaction with a polymer.^{2,7, 54–57} Thus, strong experimental evidence for the reaction of the aqueous electron reaction with dsDNA exist in the literature. We note further that aqueous electrons do not cause strand breaks in dsDNA to a significant extent, but cause stable base damage product formation.² The base damage molecular products have been found to be predominantly dihydropyrimidines and other hydrogen atom adducts owing to protonation of the anion radicals.

Recent studies show that the level of hydration of DNA is critical to the reaction of the aqueous electron with DNA. For example, Falcone et al.³⁵ studied the reaction of solvated electron with hydrated DNA (hydrated from 2.5 to 367 waters per nucleotide (Γ)). In this study, they observed the predominant formation of 5,6-dihydropyrimidines at low hydration ($\Gamma < 22$); whereas, at high hydration ($\Gamma \approx 30$), an almost five-fold decrease in the yields of the 5,6-dihydropyrimidines and a corresponding increase in hydrogen (H_2) yields were found. These results are not yet explained and work is currently underway in our laboratory to gain further insight on the reaction of solvated electron with DNA in aqueous phase.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Schematic diagram showing the energetic cycle for the adiabatic electron solvation (AEA), the photoejection of the solvated electron (e^-_{aq}) into the gas phase (VDE), and the solvent reorganization to equilibrated water (SRE = 1.8 eV). The VDE has the same geometry for the upper state as in the ground state. The difference between AEA and VDE gives the value of SRE. The SRE shows the solvent after photoejection of the electron is unstable by ca. 1.8 eV over a stable water phase geometry. (b) A comparison of the G4-calculated solvation free energy G°_{sol} along with E° vs NHE of all the bases and solvated electron.

Figure 2. Total spin density plot of T-6H₂O^{•-}. The structure is optimized to a local minimum using the B3LYP/6-31++G** method including PCM.

Figure 3.

Total spin density plot of T-6H₂O* at different time during MD simulation. (a) 0 fs (initial optimized starting structure for simulation), (b) 22 fs, (c) 23 fs, (d) 30 fs and (e) fully optimized structure. Structure (e) is stabilized by -0.88 eV over structure (a), see Table 3.

Figure 4.

Total spin density plot of $\text{C-6H}_2\text{O}^*$ at different time during MD simulation. (a) 0 fs (initial optimized starting structure for simulation), (b) 10 - 14 fs, (c) 15 - 20 fs and (d) fully optimized structure. Structure (d) is stabilized by -0.64 eV over structure (a), see Table 3.

Figure 5.

Total spin density plot of $\text{U-6H}_2\text{O}^+$ at different time during MD simulation. (a) 0 fs (initial optimized starting structure for simulation), (b) 7 fs, (c) 8 - 10 fs and (d) fully optimized structure. Structure (d) is stabilized by -0.93 eV than structure (a), see Table 3.

Figure 6.

Total spin density plot of A-6H₂O⁺ at different time during MD simulation. (a) 0 fs (initial optimized starting structure for simulation), (b) 100 fs, (c) 120 fs and (d) fully optimized structure. Structure (d) is stabilized by -0.25 eV than structure (a), see Table 3.

Figure 7.

Total spin density plot of G-6H₂O⁺ at different time during MD simulation. (a) 0 fs (initial optimized starting structure for simulation), (b) 625 fs and (c) 825 fs. The 6H₂O is located near the N7-C8 site of guanine.

Figure 8.

Total spin density plot of G-6H₂O* at times during MD simulation. (a) 0 fs and (b) 60 fs. The 0 fs structure is generated from the 625 fs simulation (Figure 6(b)) by moving one water molecule (pink highlighted) to hydrogen bond with O6 of guanine. Structure (7c) is stabilized by -0.19 eV than structure shown in Figure 6(a), see Table 3.

Table 1

G°_{sol} (kcal/mol), H°_{sol} (kcal/mol) and S°_{sol} (cal/mol deg) of Solvated Electron (e^-_{aq}) Calculated Using the G4 theory incorporating PCM along with Experimental Data.

e^-_{aq}	G°_{sol} (kcal/mol)	H°_{sol} (kcal/mol)	S°_{sol} (cal/mol deg)	E° vs NHE (V)
4H ₂ O ^{•-}	-35.9	-29.8	20.3	-2.88
6H ₂ O ^{•-}	-37.0	-31.7	17.9	-2.84
Average	-36.45	-30.8	19.1	-2.86
Ref. 29	-35.5			-2.90
Exp	-34.4 ^a	-30.2 ^a	14.2 ^a	-2.95 ^a , -2.87 ^b

^aRef. 26 and the supporting information for complete analysis.

^bRef. 40, 43, 47, 48.

Table 2

E° of G, A, C, T and U in water and in DMF calculated using G4 theory and different theoretical methods along with the experimental E° values in DMF.

Base	E° vs NHE (V)				
	Theory				Exp. ^a
	G4				
	ε=78		ε=37	B3LYP ^b	
	No water	Waters (n) ^d	“DMF” ^f	No water	DMF
G	-2.84 (-3.31) ^c	-2.62 (3); -2.66(2)	-2.86(ca.-3.0) ^g	-2.89	<-2.76
A	-2.78 (-2.86) ^c	-2.57(3) ^e	-2.81 (-2.71) ^g	-2.78	-2.52
C	-2.44 (-2.41) ^c	-2.31 (2)	-2.48 (-2.56) ^g	-2.49	-2.35
T	-2.42 (-2.31) ^c	-2.34 (2)	-2.45 (-2.32) ^g	-2.37	-2.18
U	-2.33	-2.05 (2)	-2.36	-2.30	-2.07
MUE ^h	0.24(0.20) V	0.07 V	0.22 (0.20V)	0.16 V	

^aRef 49.

^bUsing 6-31++G** basis set. Present calculation.

^cRef. 50. E° vs NHE was calculated using SHE = 4.36 V and MUE = 0.27 V.

^dn = number of explicit water molecules. See Figure S3 in the supporting information.

^eE° calculated in DMF is -2.54 V and corrected for water ($\epsilon = 78.4$)

^fNo explicit DMF molecules were considered.

^gRef. 51. E° vs NHE calculated in acetonitrile ($\epsilon = 36.64$) using SHE=-4.44 V.

^hMUE(mean unsigned error) when compared to experiment. For H₂O experimental values the DMF experimental values were employed with 0.03V added.

Table 3

B3LYP-PCM/6-31++G** calculated relative stability of solvated nucleobase anion radicals ($B^{\bullet-}-6H_2O$) with respect to the solvated electron localized in a cavity ($B-6H_2O^{\bullet-}$)^a.

Base	Figure	E(eV) ^b	G° _{sol} (eV) ^b	Exp. G°(eV) From E° ^c
G ^{•-} -6H ₂ O	7(c)	-0.19	-0.096	ca. -0.1
A ^{•-} -6H ₂ O	5(d)	-0.25	-0.33	- 0.32
C ^{•-} -6H ₂ O	3(d)	-0.64	-0.72	- 0.49
T ^{•-} -6H ₂ O	2(e)	-0.88	-0.70	- 0.67
U ^{•-} -6H ₂ O	4(d)	-0.93	-0.94 MUE= 0.11	- 0.77

^aThe optimized 0 fs structure in each case and shown in Figures 2 - 6.

^b E = TE($B^{\bullet-}-6H_2O$) – TE($B-6H_2O^{\bullet-}$) and G° = G($B^{\bullet-}-6H_2O$) – G($B-6H_2O^{\bullet-}$). TE = total energy and G = free energy calculated using the B3LYP-PCM/6-31++G** method.

^cFrom experimental values in Tables 2 and S2 with G° = - E°