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ORIGINAL PAPER

On the electron affinity of cytosine in bulk water and at hydrophobic aqueous interfaces

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Abstract In the past one possible mechanism of DNA damage in bulk water has been attributed to the presence of hydrated electrons in water. Recently, one important property of hydrated electrons, namely their binding energy, was reported to be smaller at hydrophobic interfaces than in bulk aqueous solution. This possibly opens up new reaction possibilities with different solutes such as the DNA at hydrophobic, aqueous interfaces. Here, we use QM/MM molecular dynamics simulation to study how the molecular environment at the vacuum-water interface and in the bulk alters the electron affinity of cytosine being a characteristic part of the DNA. The electron affinity at the interface is closer to the corresponding binding energy of the partially hydrated electron. The increased energy resonance makes the electron capture process more probable and suggests that hydrated electrons at hydrophobic interfaces may be more reactive than the fully hydrated ones. Additionally, we found that the relaxation of the anionic form after electron attachment also induces a proton transfer from the surrounding solvent that was confirmed by comparison with the experimental reduction potential.

Keywords Cytosine · QM/MM · Electron affinity

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Introduction

Approximately 50 years ago the hydrated electron was discovered in aqueous solution and since then it has opened various discussions on its reactivity and life time [1]. More recently its reactivity has been proposed as one posible additional mechanism for the damage of the DNA in radiation cancer therapy [2, 3]. This has triggered various experimental and theoretical studies on the nature of the electron in water and its possible reaction with parts of the DNA [3–19].

Recently, a new important contribution to the field has changed the way its reactivity in biological environments is understood: The binding energy of electrons (VBE) at the water-vacuum interface has been determined experimentally to be about 1.6 eV employing the liquid microjet technique in combination with a table top high harmonic light source [5]. Beyond its long life time the reduced binding energy in comparison to the energy of the completely hydrated electrons in bulk water (3.4 eV [5, 20, 21]) was surprising. This reduced electron binding energy possibly opens up the way to new reactions with molecules at hydrophobic interfaces that may have not been feasible or are very slow with fully hydrated electrons.

One of the possible reaction mechanisms for DNA damage besides others is the resonance dissociative electron attachment (RDEA) mechanism caused by hydrated electrons [9–11, 14, 22, 23]. In this mechanism a hydrated electron is transferred from the aqueous solution to one part

of the DNA forming an anion that undergoes barrier-less bond breaking leading to the observed damage in the DNA. Analysis of the different parts of the DNA and their electron affinity suggest that the first step in the electron transfer mechanism involves the base [11, 15]. The crucial part of the mechanism, therefore, is the relocation of the hydrated electron on the base. According to the RDEA mechanism this electron transfer becomes more likely if the energy difference between the neutral base and the formed radical anion (Franck-Condon region) matches the binding energy of the electron (VBE). Depending on the time scale of the process a relaxation of the anion and the surrounding water molecules may take place or not. In case of no relaxation the binding energy of the hydrated electron should match the vertical electron affinity (VEA) of the neutral form. If the surrounding solvent and the anion itself is allowed to relax VBE should match the adiabatic electron affinity (AEA). Therefore, for the electron attachment to occur the energetics of the neutral form and the respective anion are crucial.

According to Schaeffer et al. [15] the vertical electron affinity of a molecule can be determined by:

$$\mathrm{VEA} = \mathrm{E_n(neutral\ structure)} - \mathrm{E_a(neutral\ structure)} \quad (1)$$

where E_n and E_a are the absolute energy of the neutral and the anionic species at the conformation of the neutral molecule. If the anion radical is able to relax to its minimum during the attachment process one has to take the adiabatic electron affinity (AEA) into account that is defined as:

$$\mathrm{AEA} = \mathrm{E_n(neutral\ structure)} - \mathrm{E_a(anion\ structure)} \quad (2)$$

Therefore, a capture of the electron by DNA becomes probable if its VBE matches the magnitude of VEA assuming a fast attachment process or AEA if during the process a relaxation of the anion or the surrounding solvent takes place. The built anion radical often presents a very reactive species which may dissociate and break chemical bonds that lead to the observed DNA damage.

In a recent review Schaeffer et al. [15] summarized the state of the art on the calculation of electron affinities of biomolecules employing various electronic structure methods and mircrohydration or continuum models to describe the solvent. These methods, however, are not suitable for hydrophobic interfaces as the water-vacuum interface that involves specific solute-solvent hydrogen bond dynamics and a non-uniform electrostatic potential.

In this study we use molecular dynamics simulations in combination with electronic structure methods (QM/MM methodology) to obtain the vertical and adiabatic electron affinity of cytosine as a representative of the DNA bases at the water-vacuum interface and in aqueous solutions. The selection of cytosine is not arbitrary since the base pairs are known to be the most probable regions within the DNA proned to the first electron transfer from the solvent [11, 15]. Recently, an experimental and computational study reported only a marginal effect of the surrounding sugar phosphate backbone for the opposite process - the vertical ionization potential - corroborating the importance of the base for electron transfer processes [24, 25]. In addition, cytosine possesses in comparison to the other bases the largest solubility in water, which makes a future experimental verification at the interface by the group of one of us feasible.

With the electron affinity at hand the probability of electron capture at the interface and in aqueous solution will be compared. We think that in the near future an experimental verification of the effect of the environment on the electron affinity would become possible confirming our results.

We are aware that the vacuum-water interface is not found in any biological environment but we do think that it serves as a model for biological interfaces as water-membrane or water-protein interfaces. If the magnitude of the electron affinity of a solute at the interface is closer to the corresponding binding energy of the electron, interface electrons would be more reactive than their fully hydrated counterparts leading to larger damage for biomolecules.

Methods

Although cytosine may display various tautomeric forms we considered only the keto form displayed in Fig. 1 which is most abundant in aqueous solution at physiological pH of 7 [26].

Prior to study the electron affinity in the condensed phase we explored the dependence of the electron affinity on the electronic structure method employed in vacuum. We restrict our exploration on DFT methods following the finding of Schaeffer et al. [15] who reported them as accurate and able to reproduce experimental data. Molecular dynamics simulations, additionally, require force evaluations every time step such that more exact electronic structure methods become prohibitive due to their computational cost. All calculations have been performed with the ORCA 2.9.1 program [27] and a detailed overview of the results for the adiabatic electron affinity can be found in the Supporting Information. We are aware that for the correct calculation of an anion in vacuum basis sets with diffuse function are needed. But since our main motivation is the study of the anion in condensed phases employing QM/MM simulations, diffuse functions have not been considered due to the resulting overpolarization of the wavefunction in presence of point charges. The obtained results for the adiabatic electron affinities show that semiempirical methods are not able to predict electron affinities correctly, that the adiabatic electron affinity depends only marginal on the basis set and

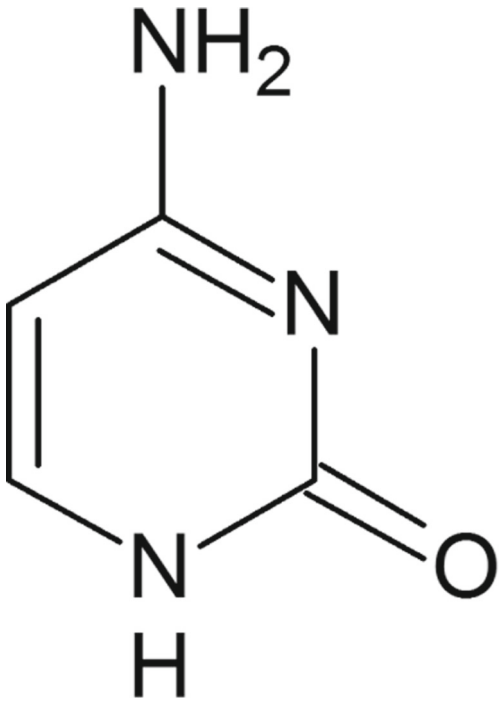

Fig. 1 Tautomeric form of cytosine used in this study

that pure functionals as BLYP and BP86 are not reliable due to the self-interaction error. We conclude in agreement with Schaeffer et al. [15] that B3LYP yields accurate results and that the SVP basis set presents the best compromise between accuracy and computational cost. Since pure functionals, however, present a lower computational cost than hybrid functionals we also studied if these methods are able to produce correct structures of the neutral form of cytosine. In fact the BLYP/SV(P) method yields the smallest RMSD to the B3LYP/SVP structure. Therefore, we chose the BLYP method in combination with the SV(P) basis set [28] to carry out the dynamics. Structures were extracted every 0.5 ps from the trajectories and the more accurate B3LYP method was employed with the SVP basis set to obtain the QM/MM energy (electrostatic embedding) of the neutral and the anion species. With the energies at hand the respective electron affinity was calculated.

To study the electron affinity in aqueous solution cytosine was centered in a cubic water box with 5 nm box length. For the water-vacuum interface simulations one side of the cubic box was increased to 15 nm, the water box centered in the middle and cytosine was placed at the water-vacuum interface. The QM/MM molecular dynamics simulations were performed using the GROMACS 4.5.3 program [29] in combination with the ORCA 2.9.1 program [27] for the electronic structure calculations. For all simulations classical water molecules were described by the SPC/E water model and the cytosine molecule was treated quantum mechanically except for the Lennard-Jones parameter which were taken from the AMBER99 force field.

The employed time step in the molecular dynamics simulations was 1 fs in combination with the reaction field method ($\epsilon = 78$) for the electrostatics with a cutoff radius of 1.0 nm and a shifting function starting at 0.9 nm. For the Van-der-Waals interactions the employed cutoffs were 0.9 and 0.8 nm respectively. The temperature was maintained constant with the v-rescale method [30] recently implemented in gromacs which creates the correct NVT ensemble.

Results and discussion

In this first part we use the vertical electron affinity to validate our simulation parameters and study qualitatively the influence of the environment. In vacuum vertical electron affinities may be positive or negative depending on the interaction of the excess electron with the neutral molecule according to Jordan et al. [3, 31, 32]. For favorable interactions positive electron affinities arise, whereas when the potential is not attractive negative electron affinities are to be expected. These vertical negative electron affinities can be observed experimentally when metastable states are formed that result from longer-range contributions producing an energy barrier that prevents the electron to escape. For the case in vacuum these barriers may arise from a centrifugal potential or longer-range repulsive Coulomb repulsion in anionic molecules [32]. This study focuses on condensed phases and it is expected that the electron may also experience barriers originated from the neighboring solvent molecules and their associated electrostatic potential such that an escape of the electron would be hindered in comparison to the situation in vacuum.

However, since the nature of this barrier is unknown, in this first part we only use the vertical electron affinity to validate our simulation parameters assuming that although the vertical electron affinity may present negative values the electron is trapped on the molecule and is not able to escape.

To calculate the vertical electron affinity of cytosine in aqueous solution molecular dynamics simulations of the neutral form applying the QM/MM methodology (BLYP/SV(P) for the QM part) were carried out. In a second step the vertical electron affinity (VEA) was obtained as an ensemble average from the trajectories calculating the energy of the neutral and the anionic form for the same structure with the QM/MM methodology and the B3LYP/SVP method. Additionally, we also employed the smaller SV and larger DZP basis set to exclude possible basis set effects but the observed changes in the reported

values were in the order of 0.1 eV. It is known that DFT methods may overbind the anionic state but since we are focused on the relative value of the two molecular environments and not the absolute electron affinity we expect the effect to be present in both environments and therefore cancel out for the comparison.

It is expected that a correct description of the electrostatics in the aqueous phase is crucial for the interactions of the anion with its environment. Therefore, the dependence of the vertical electron affinity on the employed cuttoff radius to define the sphere of point charges representing the water molecules included in the electronic structure method was studied. Figure 2 shows the average vertical electron affinity of cytosine from 80 structures of the last 40 ps of a QM/MM molecular dynamics simulations (50 ps in total) calculated with the B3LYP/SVP method. As can be seen the values approach a constant value at 1.6 nm indicating that larger cutoffs are not needed to account for longer range electrostatics. The large change observed at shorter distances can be understood analyzing the radial distribution function between cytosine and the surrounding water molecules (see Supporting Information). At short distances the solvation of the cytosine molecule is partial and only some specific water molecules in certain positions are included. The variability of the VEA value on the position of specific water molecules was already reported by Schaeffer et al. [15] and confirmed by Smyth et al. [19].

Therefore, the employed cutoff for the sphere of point charges included in the electronic structure calculation was set to 1.6 nm for all further calculations.

Once the influence of the long range electrostatics on the vertical electron affinity has been studied, the influence of the neighboring water molecules treated as point charges or quantum mechanically was addressed. Treating

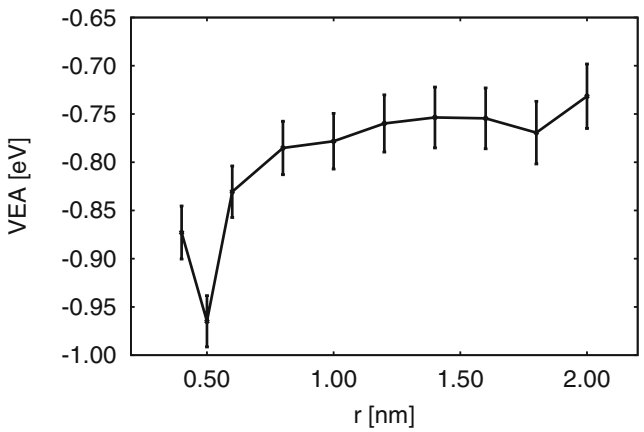

Fig. 2 Mean vertical electron affinity of cytosine in aqueous solution as function of the cutoff radius specifying the neighboring point charges of the classical water molecules considered in the electronic structure calculation

the surrounding water molecules quantum mechanically, in principle, would describe the electronic response of the solvent electron density due to the instantaneous formation of the anion. We took one representative structure and included the next 33 neighboring water molecules in the first solvation shell into the QM region. A 1-ps molecular dynamics simulations of the neutral system was performed to relax it in the next local minimum and the electron affinity was calculated in three different ways: **i.** with the water molecules in the first solvation shell described quantum mechanically, **ii.** with the water molecules in the first solvation shell described quantum mechanically and the rest of the water molecules as point charges and **iii.** with all water molecules as point charges (see Fig. 3). It was found that in all cases the values of the VEA did not change considerably (see Supporting Information).

Figure 3 displays the influence of the three different descriptions on the probability density of the single occupied molecular orbital (SOMO) of the anion. This orbital describes the spacial distribution of the attached electron without any relaxation of the solute or the solvent nuclei. First, one clearly observes that the SOMO is located on the DNA base with no participation of the solvent. This holds for all three different representations of the environment and confirms the almost constant VEA value obtained in the three cases. Second, as can be seen in Fig. 3 there are only minor changes in the location of the SOMO when the description of the surrounding water molecules are varied as described.

Finally, we also studied the dependence on the total simulation time extending it to 150 ps and calculating the vertical electron affinity of cytosine in the bulk from 500 structures extracted from the QM/MM molecular dynamics simulation. The obtaind value is -0.77 ± 0.02 eV (error corresponds to the error of the mean value) and lies in the error range of the previously reported ones. To compare qualitatively if the hydrophobic interface alters the obtained value we performed the same calculation for the respective simulation at the vacuum-water interface calculating the energy of the anion and the neutral form with the B3LYP/SVP method employing the QM/MM methodology and a cutoff of 1.6 nm. During the simulation at the vacuum-water interface a small translations of the cytosine molecule away from the surface could be observed, but this did not affect the value of the vertical electron affinity. The average value for the vertical electron affinity at the interface is -0.93 ± 0.02 eV. In an effort to determine if the energy difference to the bulk originates from the different number of hydrogen bonds at the interface we calculated the average number of hydrogen bonds in both molecular environments. However, no significant difference could be observed. Therefore, the most probable origin for the

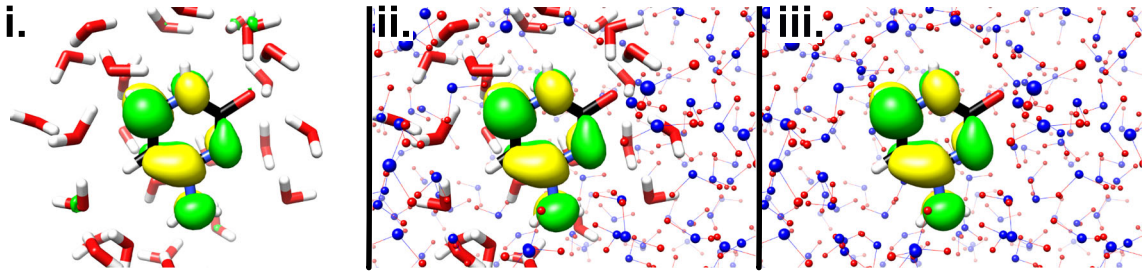

Fig. 3 Representative structures of the single occupied molecular orbital (SOMO) of the anion (isovalue = 0.035 $a_0^{-3/2}$) with different descriptions of the molecular environment: **i.** Water molecules in the first solvation described quantum mechanically **ii.** Water molecules in the first solvation described quantum mechanically and the rest of the water molecules as point charges and **iii.** all water molecules described as point charges

observed difference is the change in the electrostatics due to the absence of half of the surrounding water molecules at the interface.

The observed increased magnitude of the vertical electron affinity of cytosine at the interface can be interpreted with respect to its reactivity towards hydrated electrons under the assumptions raised in the beginning of this section. According to the Resonant Dissociative Electron Attachment (RDEA) mechanism the electron capture process at the interface would be more likely since the magnitude of the vertical electron affinity is closer to the electron binding energy than in the bulk.

Once the simulation parameters were validated and the qualitative influence of the environment addressed we focused on the adiabatic electron affinity that accounts for the relaxation of the anion and the surrounding solvent during the electron attachment process. In an effort to calculate the value for cytosine at the interface and in aqueous solution we carried out the same simulations described above but starting from the anionic form. The total simulation time for the anion was reduced to 50 ps since no appreciable difference in extending the simulation time for the VEA values could be observed. From this 50-ps QM/MM molecular dynamics simulations we extracted 200 structures from the last 40 ps and calculated with the B3LYP/SVP method the corresponding energy of the anion averaged over all structures. Subtracting the ensemble average of the neutral form from this values yields the value for the adiabatic electron affinity. At the interface the AEA of cytosine was determined as 5.42 $\pm$ 0.05 eV and in the bulk as 5.59 $\pm$ 0.06 eV confirming the smaller value at the interface due to a possible destabilization of the anion.

During the relaxation of the solute and the solvent in the anionic form the extra electron could become delocalized over the solvent molecules. Therefore, we took one representative structure of the neutral and the anionic form and included the 33 nearest water molecules into the QM region. The rest of the water molecules were represented as point charges within the QM/MM methodology. From each representative structure we first performed a 2-ps molecular dynamics simulation with the new QM region ($\simeq$ 100, atoms) and the same simulation parameters to allow the system to relax. From the last snapshot we then recalculated the AEA value obtaining a value of $\simeq$ 3.0 eV (although one has to keep in mind that this corresponds to one structure only).

To elucidate the origin of the difference to our previous result we calculated the probability density of the SOMO orbital for the relaxed anion after 2-ps from the molecular dynamics simulations. As can be seen in Fig. 4 the additional electron becomes delocalized over the surrounding water molecules. We performed an additional calculation at 1.5-ps to see if this also holds for another conformation during the molecular dynamics simulations and found that delozalization over the water molecules is still present although less pronounced and the adiabatic electron affinity increases slightly (see Supporting Information). Additionally, we also studied the effect of the point charges replacing

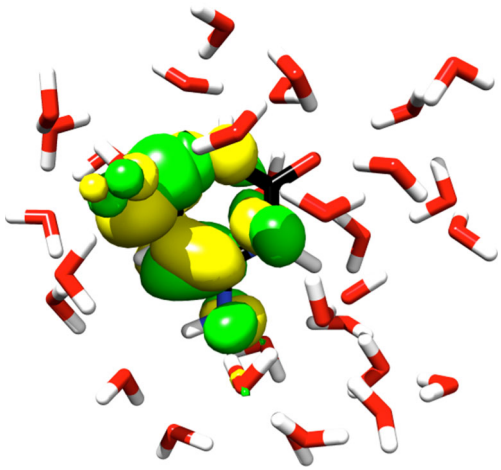

Fig. 4 Representative structure of the single occupied molecular orbital (SOMO) (isovalue = 0.035 $a_0^{-3/2}$) taken after 2 ps from the molecular dynamics simulation of the anionic state including 33 water molecules in the QM region

them with a continuum model (COSMO as implemented in ORCA) in the same structure including the 33 water molecules after 2-ps of molecular dynamics simulations of the anionic and the neutral state. The resulting adiabatic electron affinity and the probability density of the SOMO, however, differ only marginally from the results with the point charges (see Supporting Information).

From the results above it becomes evident that for the relaxation of the anionic state the surrounding water molecules has to be described quantum mechanically. The difference between the value of 5.6 eV obtained with the point charge description and 3.0 eV with inclusion of the water molecules in the QM region has to be related to the anionic state since for the vertical electron affinity the inclusion of the 33 surrounding water molecules did not alter the results. The description of the neighboring water molecules as point charges over-stabilizes the anionic state through an over-polarization of the electron density of the cytosine anion in the molecular dynamics simulations, or through the overestimation of the interaction of the negative charged cytosine molecule with the surrounding water molecules treated as point charges, or the combination of both.

Additionally, by detailed inspection of the relaxed anionic state with the 33 water molecules in the QM region we found that the imine nitrogen atom of cytosine abstracts a proton from its neighboring water molecule during the molecular dynamics simulations (see Fig. 4) reducing its distance from initially 1.7 to 1.3 Å that is close to a nitrogen hydrogen bond distance (N-H $\simeq$ 1.0 Å). This presents the first steps towards a protonation of this nitrogen atom that possesses the largest basic character.

In an effort to verify the quality of the AEA results we searched for an experimental value but with no success. The obtained AEA value, however, can be compared to the experimental reduction potential of cytosine with respect to the standard hydrogen electrode (SHE) [33].

$$\mathrm{CYT} + \mathrm{e}^- \rightarrow \mathrm{CYT}^- \quad \mathrm{E}^0_{\mathrm{CYT/CYT^-}} = -1.09\mathrm{V} \tag{3}$$

The reduction potential together with a free energy value for the standard hydrogen electrode ΔG_{SHE} of −4.33 eV (−418 kJ/mol) yields an adiabatic electron affinity of 3.24 eV,

$$\begin{aligned} AEA &= G_{\mathrm{CYT}} - G_{\mathrm{CYT^-}} = -\left(G_{\mathrm{CYT^-}} - G_{\mathrm{CYT}}\right) \\ &= -\left(\Delta G_{\mathrm{SHE}} - E^0_{\mathrm{CYT/CYT^-}} \times \frac{F}{N_A e}\right) \end{aligned} \tag{4}$$

where F is the Faraday constant (96485 J mol^{-1} C^{-1}), N_A the Avogadro number and e the elementary charge.

This value is very close to our value including the 33 water molecules. Additionally, in the publication of the experimental reduction potential the authors [33] speculate that the formation of the anion might be accompanied with a protonation of cytosine which confirms our observation of the reduced nitrogen hydrogen distance and the onset of its protonation.

Finally, one can conclude that once the anion is formed it relaxes through structural changes in cytosine and a reorientation of the solvent molecules accompanied with the transfer of a proton from the neighboring water molecules.

Conclusions

The performed QM/MM simulations of cytosine in bulk water and at the vacuum(air)-water interface show that its electron affinity is significantly altered depending on the molecular environment. Assuming a trapped electron on the solute and no relaxation the interface increases the vertical electron affinity (VEA) bringing the value closer to the binding energy of the partially hydrated electron at the interface. Even when the relaxation of the surrounding water molecules are considered the interface seems more favorable for the electron capture process. Therefore, when the electron affinity of cytosine and the binding energy of the electron is compared in both molecular environments, the reaction seems much more probable (resonant process) at the interface than in solution. This indicates a higher reactivity of electrons at the interface than the fully hydrated counterparts.

Water molecules and their reorientation in the adiabatic picture stabilize the anionic form. Additionally, this relaxation is also accompanied by a proton transfer from the surrounding water molecules to the basic imine nitrogen atom as was confirmed through the experimental reduction potential.

We want to emphasize that the results found here may also be relevant for other hydrophilic-hydrophobic interfaces in aqueous systems - such as the interface between proteins or lipid membranes and water. It is, for example, tempting to look at electrons at the protein-water interface or at any other water-hydrophobic biointerfaces in a very similar way as we look at the vacuum/air-water or nonpolar medium-water interface [34].

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