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April 3, 2023

Computational study of the stability of guanine through redox potential for potential existence in  
Martian brines

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## Abstract

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Martian brines consistent of sodium perchlorate and water could have the potential to sustain microbial life. However, perchlorate is a strong oxidizer with the ability to cause oxidative deoxyribonucleic acid (DNA) damage. The Martian brine environment can be computationally simulated to see if DNA is likely to be oxidized or if it can remain stable. Because guanine is the nucleotide most susceptible to oxidation, it can be used as the initial solute when modeling this type of environment. This research aims to use computational methods to study the redox potential of guanine in various solvation models to ultimately determine its stability in a Martian brine environment. TeraChem was used for the implicit solvation of guanine in water, approximating the redox potential to be 1.90 V. The redox potentials for adenine, cytosine, and thymine were also calculated in implicit solvation and it was verified that guanine has the lowest redox potential. AutoSolvate was then used for the explicit solvation model of guanine in water. The average energy value for the molecular dynamic simulation was -7677.24 Hartree. Future steps include the explicit solvation of guanine in sodium cations, perchlorate anions, and water. The same methods can be employed for this simulation. If it can be determined that guanine and DNA are not readily susceptible to oxidation in a Martine brines environment, then DNA has the potential to be stable on Mars. This information could help provide evidence for the potential existence of life on Mars or other brine-bearing worlds.

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## 1. INTRODUCTION

The existence and sustainability of life on Mars has long been an area of interest in scientific research. Notably, recent discoveries have found that Mars harbors salty brines formed on its northern and southern poles.<sup>1</sup> These brines consist of perchlorate ions ( $\text{ClO}_4^-$ ) as salts in solution with water, and due to their intense freezing point, liquid water thus has the potential to exist at subzero temperatures on Mars. These brines are consequently being investigated for their potential to host microbial life.<sup>2</sup> The perchlorate ions in the brines also have a variety of attributes that make them significant candidates for research due to their suggested compatibility with prebiotic chemistry and life forms.<sup>3</sup> Perchlorate is particularly known to be a strong oxidizer, having a comparable redox potential to oxygen at +1.287 V.<sup>4</sup> In fact, the oxidative powers of chlorine in general likely played a vital role in shaping both the planet's terrain<sup>5</sup> and the planet's atmosphere.<sup>1</sup>

However, perchlorate has historically been categorized as a chaotrope, meaning it is a weakly hydrated anion that has the ability to break secondary structure<sup>6</sup> and, in turn, impact molecular function and stability.<sup>3</sup> Perchlorate's strong oxidizing ability poses a risk to DNA and RNA because it can cause detrimental oxidative damage. The oxidation of DNA/RNA can distort the phosphoric backbone, preventing enzymes from binding and carrying out important biological functions.<sup>3</sup> It can also damage DNA/RNA via oxidative cleavage, and DNA that is already damaged or defective, is susceptible to further oxidation.<sup>7</sup> Therefore, to assess the potential for biomolecules like DNA and RNA to exist in a Martian environment, it is important to determine their stability in various concentrations of perchlorate and their likelihood of suffering from oxidative damage.

Typically, DNA oxidation initially occurs at guanine nucleotides, giving guanine the ability to act as an electron-hole sink and making it the most susceptible nucleotide to oxidative damage via perchlorate ions.<sup>8</sup> Therefore, focusing on guanine is a key preliminary step in determining the oxidative potential, or redox potential, of DNA. This study employs computational chemistry techniques to study the redox potential of water-solvated nucleotides and evaluate the susceptibility of DNA and RNA to oxidation in perchlorate solutions. By simulating the perchlorate Martian environment, this study aims to use quantum mechanical (QM) methods to examine the functionality of these structures, starting with a bulk solvation of nucleotides in water. Determining the possibility of stable guanine and DNA or RNA existing in Martian brines could ultimately lend credence to potential extraterrestrial life forms, and these findings can be extended to other brine-bearing worlds.

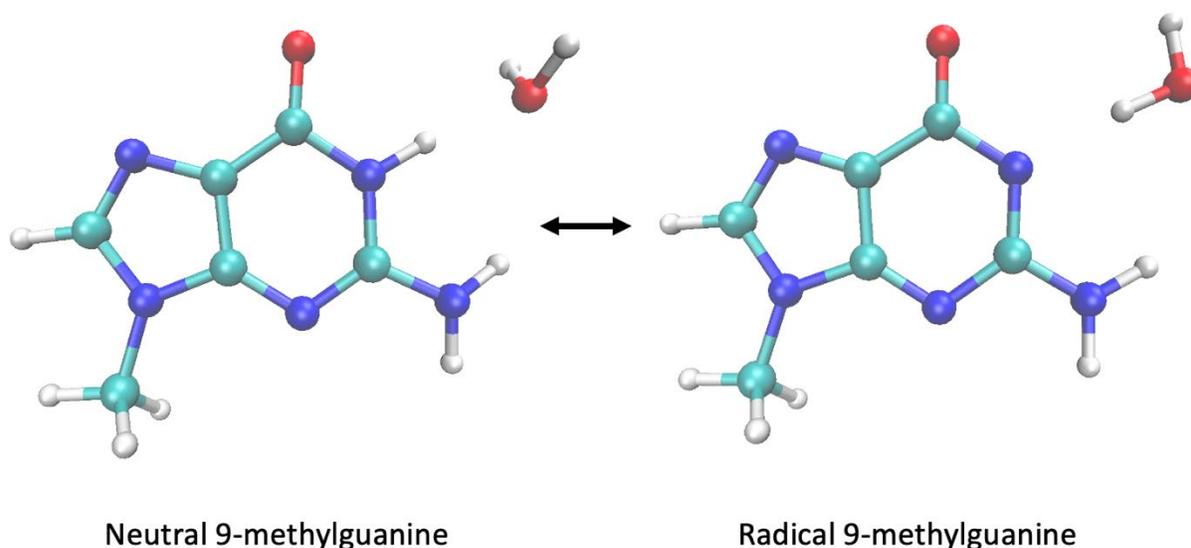
## 2. THEORY

### 2.1 Redox Potential

Redox potential is a thermodynamic property that quantifies a molecule's susceptibility to oxidation and occurs with the addition or loss of an electron. This property is crucial for understanding processes like catalysis, energy storage, and cellular metabolism.<sup>9</sup> Redox potentials can be approximated with density-functional theory (DFT), a widely used method in computational chemistry that employs QM and a uniform electron density approximation to solve the total energy of a system. The redox potential,  $E_{\text{red(aq)}}^{\circ}$ , can be calculated with Equation 1.

$$E_{\text{red(aq)}}^{\circ} = \frac{-(G_{\text{neu(aq)}}^* - G_{\text{rad(aq)}}^* - \Delta G_{\text{H}^+(\text{aq})}^*)}{nF} - \text{SHE} \quad (1)$$

Here,  $n$  is the number of electrons (1),  $F$  is Faraday's constant, and SHE is the potential of the standard hydrogen electrode (4.281 V).  $G_{\text{neu(aq)}}^* - G_{\text{rad(aq)}}^*$  is the change in Gibbs free energy between the neutral and radical forms of the molecule as seen in the redox reaction in Figure 1 between neutral 9-methylguanine and radical 9-methylguanine. The redox reaction in Figure 1 also involves the transfer of a proton, so the term  $\Delta G_{\text{H}^+(\text{aq})}^*$  needs to be included to account for the free energy change of the proton (270.29 kcal/mol).<sup>10</sup>



**Figure 1.** Molecular structure of the redox reaction between neutral 9-methylguanine and radical 9-methylguanine with one explicit water molecule.

## 2.2 Density Functional Theory

DFT is a QM method used to accurately model the electronic structure of molecules. It is based on the fact that the energy of a system can be expressed as a functional of particle density. DFT proves to be beneficial due to its low computational cost and sufficient accuracy.<sup>11</sup> It is consistent of an electron exchange term and a correlation term that are approximated by

mathematical exchange-correlation functionals. A common approach to DFT and modeling the electron exchange interaction is using the B3LYP functional. B3LYP is widely used for evaluating ground state properties of organic molecules because it shows good accuracy. This method works for closed shell systems with neutral molecules.<sup>12</sup> For open shell systems with charged or radical-containing molecules, the same functional can be used but in an unrestricted form (UB3LYP).<sup>13</sup> Basis sets are also used in DFT as a set of mathematical functions that describe the electronic wave function of molecules. With Gaussian basis sets, these functions are typically linear combinations of Gaussian functions that represent electron orbitals.<sup>14</sup> The basis set 6-31G\*\* is a time and cost-efficient basis set that uses polarization functions and works well with heavy atom and hydrogen-containing systems.<sup>15</sup>

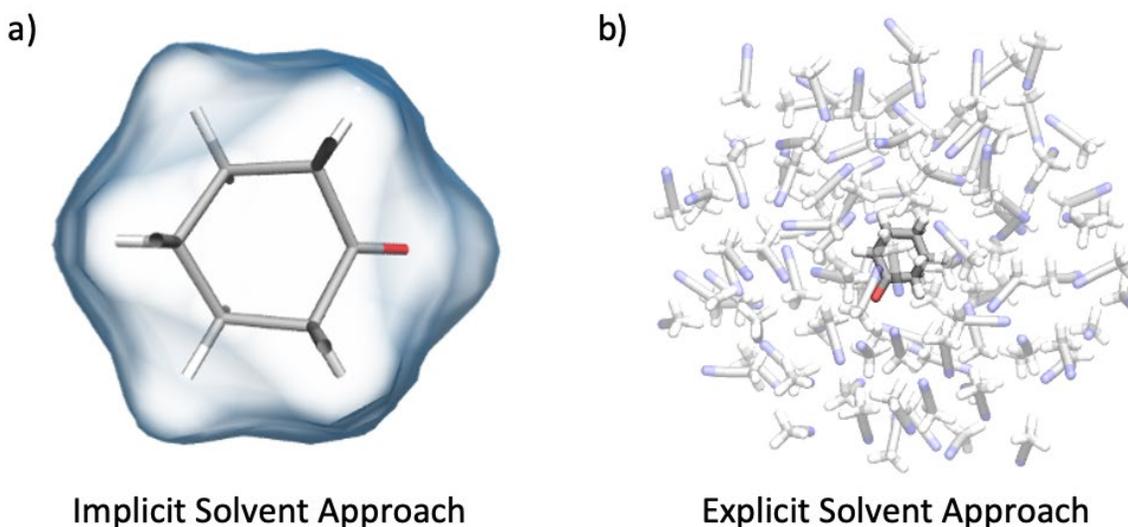
### **2.3 Implicit Solvation**

Implicit solvation uses a continuum model to simulate the general solvent dipoles that would exist in a solute-solvent environment (Figure 2a). No solvent molecules are present in an implicit solvent approach. These models are typically polarizable continuum models (PCMs) like SMD, based on DFT, and COSMO, a conductor-like screening model that works well with polar molecules.<sup>16</sup> The implicit solvent approach is efficient and works well when calculating solvation free energy values on large biomolecules. This model simplifies a physical solute-solvent environment and saves computational time by assuming the solute to be static.

### **2.4 Explicit Solvation**

An explicit solvation model simulates the individual atoms and bonds of the solvent as depicted in Figure 2b. While an implicit solvation model does not include individual molecules in the solvent, explicit solvation models directly include molecular structures in the solvent, considering electron structure and interactions. Explicit solvation models show improved accuracy

when predicting system properties due to the explicit inclusion of solvent-solute interactions, proton transfers, and hydrogen bonds.<sup>17</sup> However, the explicit solvent approach is costly because of its high degree of detail.<sup>9</sup> An explicit solvent model takes time to generate many frames or conformations of the structures in the environment. This process is meant to mimic the kinetics of physical molecules above 0 K.



**Figure 2.** Example depiction of implicit versus explicit solvation methods.

### 3. COMPUTATIONAL DETAILS

#### 3.1 TeraChem

TeraChem is a graphics processing unit (GPU) accelerated package for quantum chemistry (QC) calculations, meaning it performs significantly faster than other QC software. It has many other features that make it desirable including its ability to support various DFT functionals, basis sets, and types of energy calculations.<sup>18</sup> When given an input coordinate file, TeraChem can

perform efficient geometry optimization on a molecule in gas phase or in implicit solution, and it works well for large systems. With a variety of customizable parameters, TeraChem allows specification for basis set, method, charge, spin multiplicity, type of PCM model, etc.

### 3.2 AutoSolvate

AutoSolvate is an open-source tool for analyzing and predicting solution-phase molecular properties and running high-throughput QC calculations. It supports both command line input and graphical user interface (GUI), wrapping popular computation software such as TeraChem, AmberTools,<sup>19</sup> and Packmol.<sup>20</sup> AutoSolvate suggests task-specific workflows and writes input files for the supported software packages, giving it the ability to generate both implicit and explicit solvation models.<sup>17</sup> It is able to perform explicit solvation by doing charge fitting, generating force field (FF) parameters, and running molecular dynamic (MD) simulations. The user is required to input the charge, spin multiplicity, and coordinate file at the minimum.

AmberTools automatically generates FF parameters for common molecules.<sup>17</sup> The FF is a mathematical model or function used to describe the intermolecular forces of a molecule via the position and orientation of the atoms. These parameters involve the type of atom and the electronic structure and are crucial for both the solute and solvent when performing calculations, running MD simulations, or predicting molecular behavior. With unique molecules, customized FF parameters are required by the user. Within AutoSolvate there is NPT and NVT ensembles which are concepts from statistical mechanics.<sup>17</sup> The NPT ensemble entails a fixed pressure and temperature while the NVT ensemble implies a fixed volume and temperature.<sup>21</sup> The process is derived from the ideal gas law where  $PV = nRT$ , and one variable is changed while the other three parameters remain fixed. The NPT vs. NVT process is meant to mimic experimental reactions that would occur in a beaker where volume or pressure can be fixed.

## 4. METHODOLOGY

### 4.1 Implicit Solvation

To calculate the redox potential of guanine in an implicit water solution, TeraChem and its implementation of PCM were used to compare the neutral and radical forms of guanine. The original xyz coordinates used in this research for neutral 9-methylguanine and radical 9-methylguanine were obtained from a 2015 study by Thapa and Schlegel.<sup>10</sup> The coordinates notably each contain one explicit water molecule because the redox potential of guanine involves both a proton transfer and an electron transfer. The inclusion of the water molecule simulates any hydrogen bonding with the solute and shows its change in orientation and a depiction of these structures can be found in Figure 1.

TeraChem was used to optimize the geometry coordinates of both guanine molecules, then run an energy calculation at the B3LYP/6-31G\*\* level. The parameters required to run the energy calculation for the neutral 9-methylguanine included a spin multiplicity of 1, a charge of 0, and a COSMO specified solvation model with the dielectric constant for water as 78.39. For the neutral radical form of the 9-methylguanine, the parameters included a spin multiplicity of 2, a charge of 0, and the UB3LYP method. The computational output from TeraChem includes iterations of energy calculations for the provided molecule until the geometry is optimized. Geometry optimization is important for the static solute in the implicit solvation process. The final energy can be identified as the energy in the last step of the output file. The redox potential was calculated from the energy difference between the neutral and radical forms of the nucleotide as seen in Equation 1. The process was then repeated for the other nucleobases (9-methyladenine, 9-methylcytosine, and 1-methylthymine) with coordinates from the Thapa and Schlegel paper.<sup>10</sup>

## 4.2 Explicit Solvation

AutoSolvate was used for the explicit solvation models, following a three-step process: box generation, MD simulation, then microsolvated cluster extraction. The same coordinates from the geometry-optimized neutral 9-methylguanine were used, but the guanine residue required custom FF parameters with the assistance of AmberTools.<sup>22</sup> The AutoSolvate process begins with explicit box generation, or the creation of the solute-solvent environment. First, guanine was explicitly solvated in water. 7983 water molecules were auto-populated into a box, surrounding the solute, guanine. AutoSolvate uses a machine learning model that is trained to account for the closeness between molecules and can generate the initial structure for the solute-solvent environment. The box generation step creates the file types needed for future parameters including a .prmtop for compatibility with Amber parameter-topology and an input coordinate file in the form of a .inpcrd.<sup>17</sup>

Following the box generation step, AutoSolvate was then used to perform an MD run. The automatic MD simulation process begins with energy minimization, optimizing down the gradient until the ideal structure is reached. The system is then heated until it reaches the desired fixed temperature. The temperature used for the MD run was the average temperature on Mars at  $-60^{\circ}\text{C}$  (213 K).<sup>23</sup> This is followed by MM NPT equilibration, QM/MM energy minimization and heating, and QM/MM NVT equilibration. Because MM is a more low-level process and cannot give the most accurate description of the molecule, the QM/MM run proceeds automatically to get the desired conformation of the solute, guanine. Because AutoSolvate equilibrates in an iterative fashion, the steps, or frames, for heating, pressure, and volume equilibration were all specified. The following are the parameters that were used in the MD simulation: a charge of 0, spin multiplicity of 1, pressure as the default 1 bar, 10000 steps for the MM heat equilibration, 500000

steps for the MM NPT equilibration, 250 steps for QM/MM minimization, and 100 steps for both QM/MM heat and NVT equilibration. The steps for the MM computation should be high enough to allow for value convergence. The mmnpt.out file was then analyzed to determine if the appropriate parameters were reached. The MD simulation was considered successful because the temperature converged to a similar value as specified. The equilibration of density was used to determine if the system was pressure equilibrated.<sup>17</sup>

Finally, AutoSolvate can extract a cluster for microsolvation, a combination of an implicit and explicit solvent. This step generates a cluster that can be treated with entirely QM whereas the MD simulation treated only the solute with QM.<sup>17</sup> The trajectory file in the format of a .netcdf file was used as an input, and 500 microsolvated clusters were generated with a solvent shell radius of 6 Å. A visualization software called VMD was used to view the images of the xyz frames which were snapshots of the MD simulation at every 1000 steps, or 2 picoseconds (ps). The energy calculations were computed for all frames after the density was estimated to have reached an equilibrium. A python script was used to generate energy calculations via TeraChem for each microsolvated cluster. The resulting energies were compiled to calculate an average energy value of neutral 9-methylguanine in an explicit water solvation model.

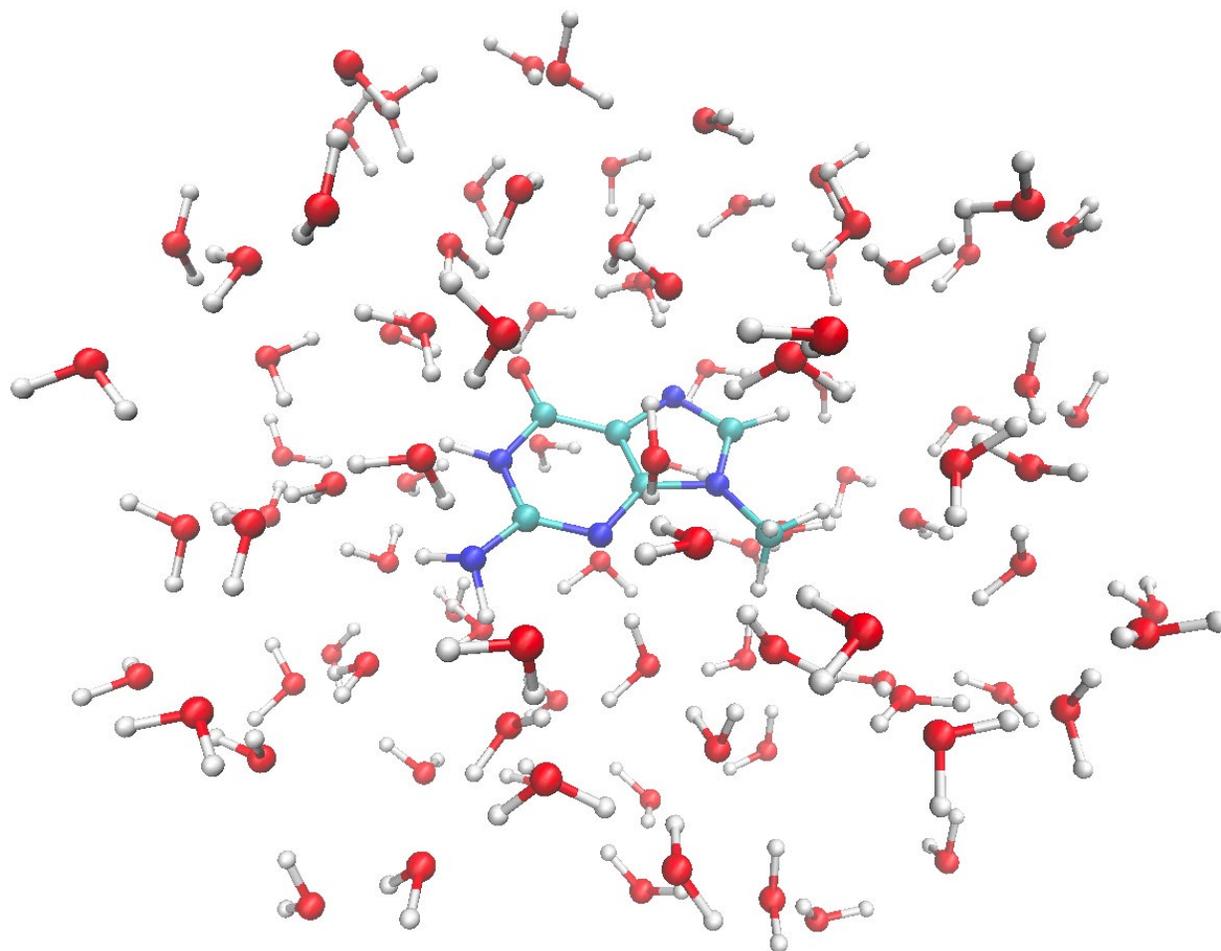
## 5. RESULTS

**Table 1.** Computed redox potential in Volts (V) for nucleobases compared to reference values.<sup>10</sup>

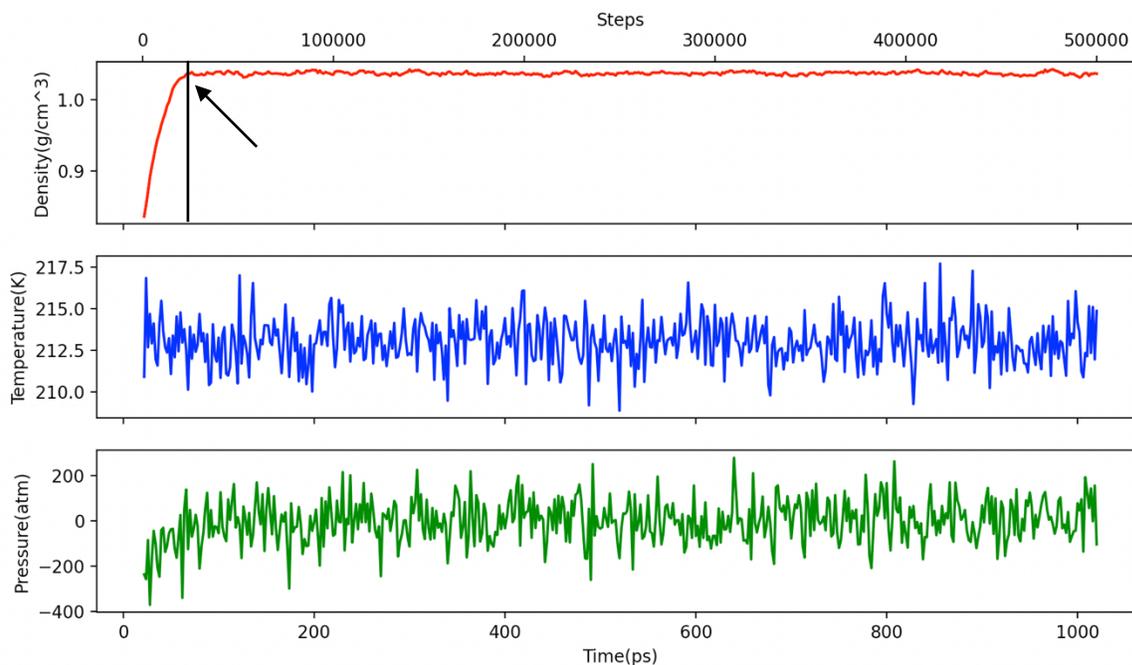
	Redox Potential (V)	
	Computed	Reference
<b>Guanine</b>	1.90	1.31
<b>Adenine</b>	2.15	1.70
<b>Thymine</b>	2.54	1.86
<b>Cytosine</b>	2.45	2.03

The calculated redox potentials for the implicit solvation model in Table 1 reasonably match the reference values and are sufficient preliminary results. Guanine notably has the lowest redox potential compared to adenine, thymine, and cytosine. This low redox potential verifies that guanine is the nucleotide most susceptible to oxidation. The deviation from the trend between thymine and cytosine should be further investigated. Any large difference between the computed and reference values could be due to the use of different implicit solvation models or different basis sets. The reference values were computed with an SMD solvation model while this study used COSMO supported on TeraChem.

The MD simulation for the explicit solvation of guanine in water took 1020 picoseconds (ps) to run. A microsolvated cluster was generated every 1000 steps creating 500 xyz coordinate files. An example snapshot of this explicit solvation cluster can be seen in Figure 3.

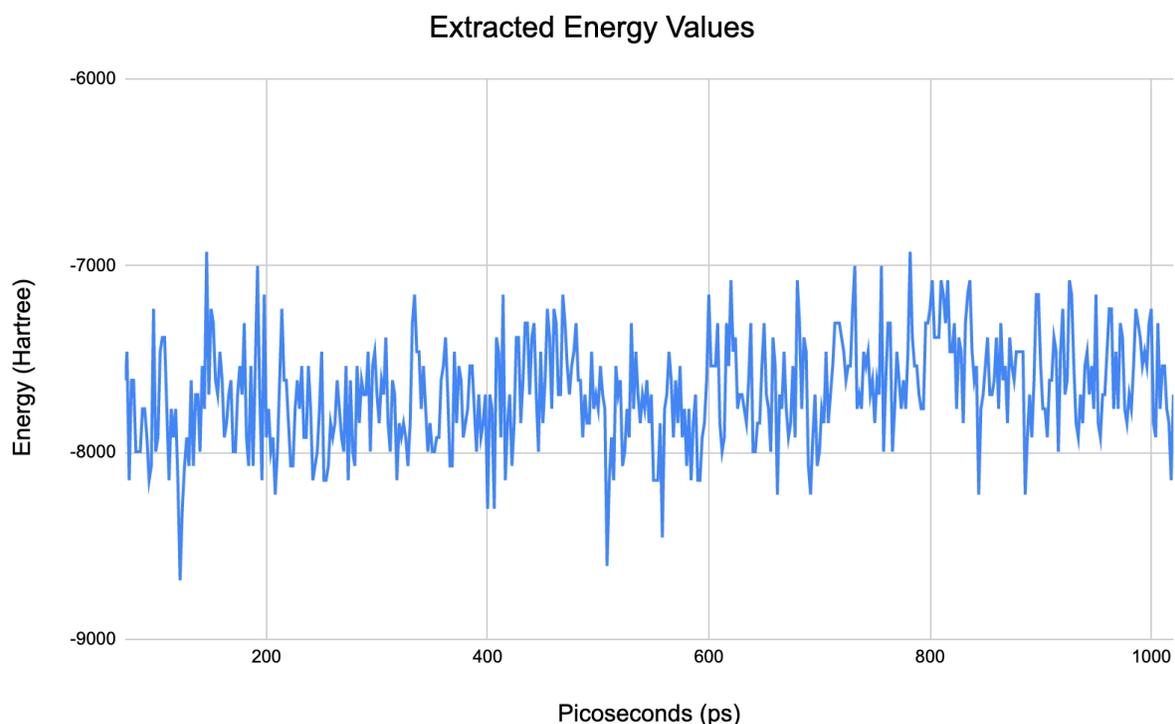


**Figure 3.** Optimized microsolvated cluster from the last step of the MD simulation with 9-methylguanine (blue) as the solute in the middle and water (red and white) as the surrounding explicit solvent. The solvent shell radius is 6 Å.



**Figure 4.** Graphs of density, temperature, and pressure over time from the MD simulation of the explicit solvation model of guanine in water at 213 K. Density equilibration estimated at around 25000 steps.

Using both the mmnpt.out output file and the graph of density equilibrating over time in Figure 4, it was estimated that density equilibration occurred at around 25000 steps. Therefore, the energy values were calculated for frames 25 through 499 which spans from 72 ps to 1020 ps. A graph of the energies for each microsolvated cluster can be found in Figure 5. The average energy value for the explicit solvation was -7677.24 Hartree and had a standard deviation of 284.70 Hartree.

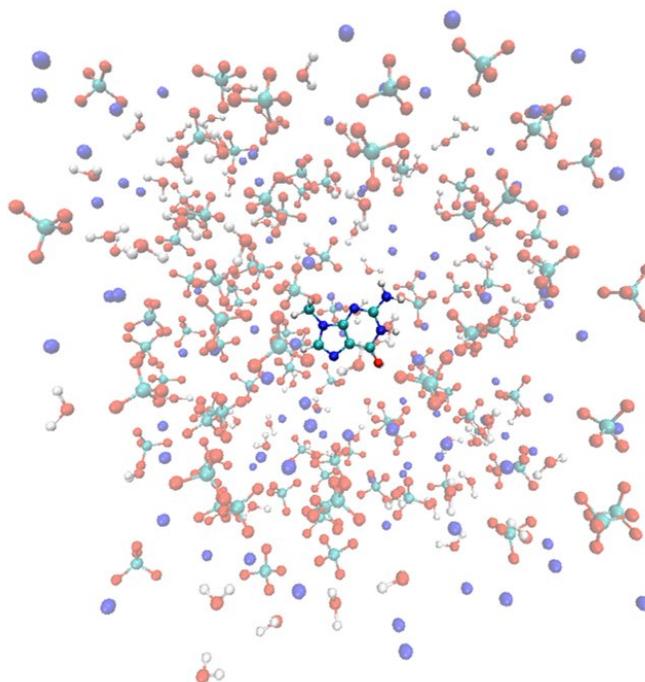


**Figure 5.** Line plot of extracted energy values taken every 2 ps (1000 steps) from step 25000 to 500000 from neutral 9-methylguanine explicit water solvation.

## 6. DISCUSSION

These results provide increased knowledge regarding the redox potential of guanine in various solvation models. This research also provides a workflow to ultimately determine the redox potential of DNA in explicitly solvated perchlorate anions to simulate a true Martian brine environment. Following the microsolvated cluster extraction of 9-methylguanine in an explicit water solvation model, the redox potentials should be calculated at each trajectory and averaged over all frames with equilibrated density. This process is complicated because it requires the reorientation of the explicit water molecule, as the redox potential is calculated from the difference in energy after both a proton and electron are transferred.

However, the biggest challenge for the present work was accurately representing the perchlorate ions in the explicit solvation model. In the next stage for determining the redox potential of guanine in a Martian brine environment, a solvation box needs to be generated with water, sodium cations, and perchlorate anions as seen in Figure 6.

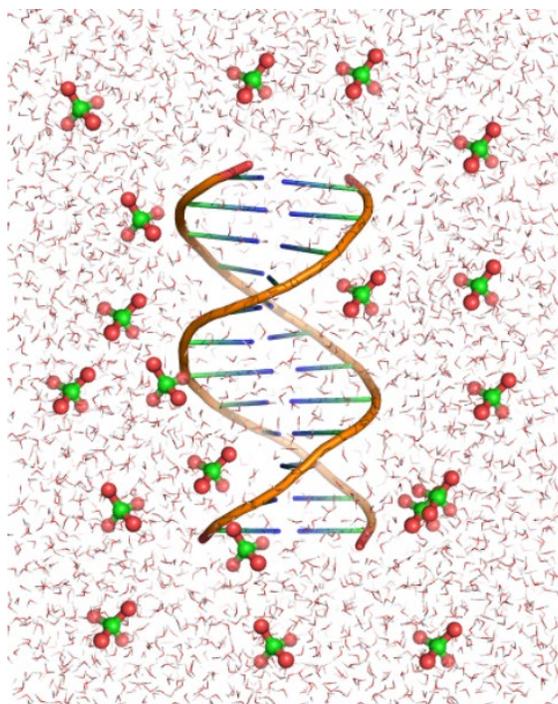


**Figure 6.** Preliminary box generation for explicit solvation of 9-methylguanine (center) in water (red and white), sodium ions (dark blue), and perchlorate ions (red and teal).

Preliminary steps have been taken in this study to simulate the brines environment, but there is a specific need to correct the FF parameters for the perchlorate anion as well as correctly model its tetrahedral bond angle. The MD simulation process follows a similar methodology, but the box needs to be generated with Packmol<sup>20</sup> to populate the environment with water, sodium cations, and perchlorate anions. Water molecules should be explicitly included in the environment

because they are present in the Martian brines and contribute to electrostatic effects. The inclusion of water molecules will improve the accuracy of the results. After the step of microsolvated cluster extraction, the charged ions will affect the overall charge of each cluster due to an imbalanced number of anions and cations included in the specified solvent shell radius. Instead of bulk calculating the energies for a neutral system (charge 0, spin multiplicity 1), the number of cations, indicated by sodiums, and anions, indicated by chlorines, need to be counted for each cluster. Then, the parameters for each energy calculation can be made specific to the frame to achieve the correct energy values. The redox potential can then be computed by subtracting the difference in energy values for each frame, and the average value will be considered the redox potential for the system.

Once guanine is used as the solute, the next step will be to perform an explicit solvation calculation of DNA's redox potential in a solution of water, perchlorate, and sodium as seen in Figure 7. Calculating the redox potential for the simulated DNA strands would help determine the ability for DNA to remain stable in a Mars-like environment. The difference between the redox potential of DNA and guanine in the same solute-solvent environment could also provide interesting insights to how the molecules would respond in Martian brines.



**Figure 7.** Example depiction of DNA modelled in a solvent box containing perchlorate ions and water molecules.

Because the redox potential is greatly dependent on the solution environment, the perchlorate concentration could also be manipulated to find the most stable state for guanine or the DNA strand. It is also important to study the lowest concentration of perchlorate that still affects the redox potential of the solute and find the threshold for the amount of perchlorate where guanine would be entirely susceptible to oxidation.

Overall, this research importantly shows how computational chemistry can be used to simulate explicit solvation environments and how quantum mechanical methods can be used to calculate the energy and redox potential of these systems. It also provides knowledge on how AutoSolvate can be used to simulate the Martian brine environment with perchlorate anions to ultimately determine the stability of guanine or DNA. If it can be determined that DNA is not

easily susceptible to the strong oxidizing ability of perchlorate, it would provide evidence that a Martian environment could be capable of sustaining DNA without causing oxidative damage. This possibility could indicate that Mars either had or currently has the ability to contain life and could thus be a prebiotic environment.

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