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J. Am. Chem. Soc., **2008**, 130 (37), 12254-12255 • DOI: 10.1021/ja805000g • Publication Date (Web): 21 August 2008

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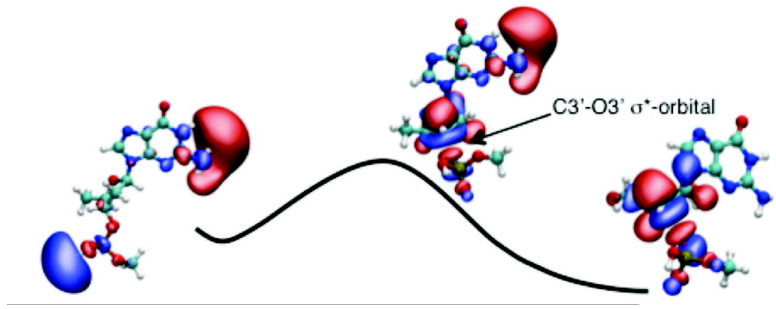

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Published on Web 08/21/2008

On the Effect of Low-Energy Electron Induced DNA Strand Break in Aqueous Solution: A Theoretical Study Indicating Guanine as a Weak Link in DNA

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Results from our density functional theory (DFT) calculations in this study indicate that low-energy electrons (LEEs) particularly attached to guanine nucleotides can induce strand breaks in aqueous solution.

LEEs are secondary electrons with kinetic energies below 20 eV, created in large amounts in the tracks of ionizing radiation.[1] DNA damage caused by LEEs has received much attention since being first reported by Sanche and co-workers.[2] It is now well established both experimentally and theoretically that LEEs can be responsible for a variety of damage within the DNA such as strand breaks, nucleobase damage, or base release through glycosidic bond cleavage.[3−10]

Most previous studies showing strand breaks by LEEs have been conducted with dry DNA or DNA in a sparse water environment. Theoretical studies, mostly with pyrimidine nucleotides, indicate that LEEs do not cause strand breaks in aqueous solution or at least the energy barriers when breaking the phosphodiester bonds are higher than those in the gas phase.[11−16] Experiments have also shown that for some nucleotides water molecules have a protective influence on the DNA.[17]

Several mechanisms for how LEEs create strand breaks have been proposed over the years. The first theoretical support for LEE-induced DNA strand breakage was presented by Li et al.[11] They calculated the energy barrier in the gas phase for breaking the C3′−O3′ or C5′−O5′ bond to be ∼10 kcal/mol, suggesting that the excess electron is already attached or transferred onto the deoxyribose and phosphate moieties of the DNA backbone. They did not include the nucleobase in their models.[11] Simons and co-workers proposed a mechanism, when the LEE is attached onto the base, by which the electron could migrate from the base through the glycosidic bond to the C−O phosphodiester bond.[12,13] Gu et al.[16] proposed an alternative mechanism by which the electron is directly transferred from the pyrimidine base to the C3′ through an S_N2-like mechanism. All calculated activation energies for breaking the C3′−O3′ or C5′−O5′ bond when an LEE is attached to cytosine, thymine, uracil, or adenine are in the range 7−15 kcal/mol in the gas phase and 13−30 kcal/mol in aqueous solution.[8,11−16]

However, the C3′−O3′ bond break with a guanine base has not until now been theoretically examined even though experiments have demonstrated several interesting properties for guanine. Ray et al.[18] highlighted the importance of guanine when capturing LEEs and showed experimentally that the LEEs can be more easily captured in a guanine-rich DNA sequence. Moreover, they suggested that guanine, due to its high dipole moment, could function as a gateway when capturing LEEs and concluded that when the electron is captured it is not located in the base but in the DNA backbone.[18] Experiments by Zheng et al.[19] showed that DNA strand breaks by LEEs are strongly suppressed when guanine and adenine are removed from the DNA sequence. Recently, Gu et al.[20] studied electron attachment with different DNA nucleotides in aqueous solution. They showed that the electron is attached onto the nucleobase for all nucleotides except for guanine where the electron is dipole-bound to the guanine and also situated near the 3′ phosphate moiety.

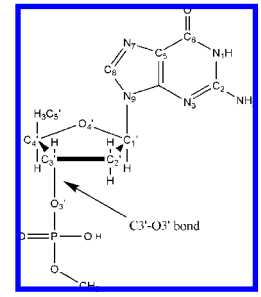

Figure 1. Guanine 3′-monophosphate (3′-GMPH).

In this communication we present DFT calculations of the C3′−O3′ bond break in aqueous solution for a 3′-guanine monophosphate radical anion, 3′-GMPH$^{-\bullet}$; cf. Figure 1. The GAUSSIAN 03 program[21] was used for all calculations. All geometries were optimized using the hybrid functional B3LYP[22,23] and a DZP++ basis set approach[24] (see Supporting Information for details). To obtain the effects of an aqueous solution a polarizable continuum model (IEF-PCM)[25] with the dielectric constant of water ($\varepsilon = 78.4$) was used. The effects of water were then further studied by surrounding the gas phase optimized guanine nucleotide with 21 water molecules and geometry optimizing the water with B3LYP/6-31G(d) while keeping the nucleotide fixed. The energies were obtained from B3LYP/DZP++ single-point calculations of the entire system. In our model we have protonated one of the oxygens in the phosphate group to resemble the situation of a closely located counterion. This is a good description of the situation in dry DNA where the motion of the ion is restricted, but in a biological situation this is not always the case and hence our model system is only valid in the time frame when the ion is in the vicinity of the phosphate.

Figure 2 shows the C3′−O3′ bond rupture with an excess electron attached. The excess electron here is considered to be adiabatically attached in which case the nucleotide geometry is relaxed after electron attachment. The choice of basis set with diffuse functions is important in producing a dipole bound state to the guanine (this is further discussed in the Supporting Information). Bond distances for the optimized structures can be found in the Supporting Information.

Table 1 shows the activation energies for the radical anion 3′-GMPH$^{-\bullet}$. The transition state energy is 10.3 kcal/mol in the gas phase with an imaginary frequency of 727.3i cm^{-1} and a C3′−O3′ bond distance of 1.72 Å. In comparison with previous results for other nucleotides in the gas phase the energy barrier for GMPH$^{-\bullet}$ is comparable with the lowest calculated energy barriers. Interestingly, for GMPH$^{-\bullet}$ in aqueous solution the energy barrier is lowered to 5.3 kcal/mol. For the other nucleotides only much higher barriers

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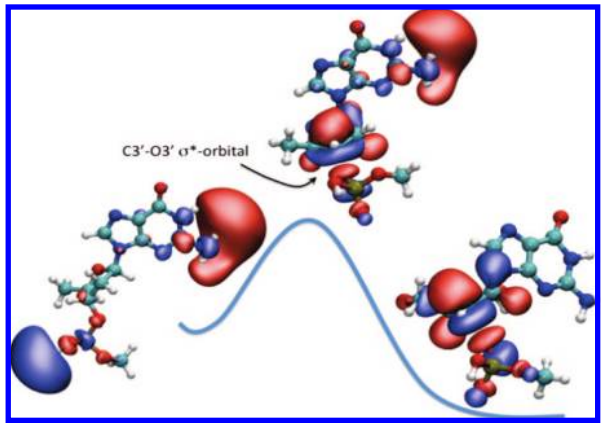

Figure 2. Schematic energy profile along the C3′−O3′ reaction coordinates showing the SOMO for the guanine radical anion at the reactant, transition state, and when the C3′−O3′ distance is 2.26 Å. VMD software[26] was used for molecular visualization. The red and blue colors of the orbitals show the different signs of the wave function.

Table 1. Transition State Energies (in kcal/mol) of Radical Anions Relative the Reactant in Different Environments[a]

	gas phase	water ($\epsilon = 78$)	explicit water[b]
ΔE_{TS}	10.28 (8.56)	5.25 (3.53)	6.54

[a] All energies were obtained with the DZP++ basis set. Energies including zero-point energy correction are in parentheses. [b] 21 water molecules included.

have been observed with energies in the range 13−30 kcal/mol.[8,12−16] The transition state energy in aqueous solution was also calculated with the 6−311++G(2d,2p) basis set to 5.1 kcal/mol which is very close to the DZP++ energy.

The singly occupied molecular orbital (SOMO) for the 3′-GMPH$^{-\bullet}$ (cf. Figure 2) shows that the excess electron is partly dipole-bound to the guanine base and partly in the vicinity of the phosphate group (near the P−OH oxygen) at the equilibrium geometry. This is in agreement with the result in the gas phase presented by Gu et al.[20] At the transition state the excess electron when located near the phosphate is easily transferred to the antibonding σ^*-orbital of the C3′−O3′ bond as can be seen in Figure 2. This can explain the low energy barrier in the gas phase. Furthermore, when the C3′−O3′ bond is broken the excess electron is no longer bound to the base but to the deoxyribose and the phosphate moiety.

In an aqueous solution we do not observe the excess electron near the phosphate; see Figure 3. This result differs from what Gu et al.[20] obtained when they applied a PCM model to their 2′-deoxyguanosine-3′,5′-diphospate radical anion, 3′,5′dGDP$^-$. Even though the same molecule was not used, we expected to see similar behavior of the excess electron. This led us to set up new calculations with 21 explicit water molecules surrounding the 3′-dGMP to more accurately describe the solvent; see Figure 3. These calculations give an energy barrier that agrees with the one obtained with the IEF-PCM model as can be seen in Table 1. The mechanism by which the excess electron is transferred from the base to the C3′−O3′ bond is not yet fully understood, and further calculations are needed.

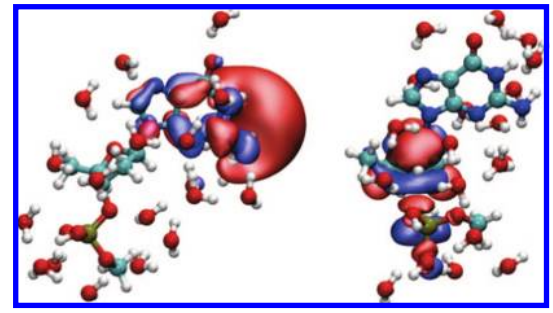

Figure 3. SOMOs for the reactant (left) and transition state (right) geometries. VMD software[26] was used for molecular visualization.

Our results presented here reveal low activation energies for the phosphodiester bond rupture induced by LEEs in both the gas phase and aqueous solution. In conclusion, compared with previously calculated phosphodiester bond rupture for thymine, cytosine, and adenine, DNA strand breaks would most likely occur when an LEE is attached to the guanine nucleotide.

Acknowledgment. The Swedish Science Research Council (VR) is gratefully acknowledged for financial support. We also acknowledge the National Supercomputing Center (NSC) and the Center for Parallel Computing (PDC) at the Royal Institute of Technology for grants of computing time.

Supporting Information Available: Full ref 21, computational details, figures showing geometries and orbitals, and tables of energies. This material is available free of charge via the Internet at http://pubs.asc.org.

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JA805000G