J|A|C|S
COMMUNICATIONS

Published on Web 10/17/2003

Density Functional Theory Studies of Electron Interaction with DNA: Can Zero eV Electrons Induce Strand Breaks?

Xifeng Li,[†] Michael D. Sevilla,*[,‡] and Léon Sanche[†]

Group of the Canadian Institutes of Health Research in the Radiation Sciences, Faculty of Medicine, Université de Sherbrooke, Quebec, J1H 5N4, Canada, and Department of Chemistry, Oakland University, Rochester, Michigan 48309

Received June 4, 2003; E-mail: sevilla@oakland.edu

Presented here are density functional theory (DFT) calculations suggesting near zero eV electrons can induce DNA strand breaks. Such breaks are considered to be the most potentially lethal form of cellular damage caused by any high energy radiation, such as X-rays, γ-rays,[1−3] or laser photons.[4] Until recently, strand breaks (single strand breaks (SSB) and double strand breaks (DSB)) induced by ionizing radiation have been attributed to[5] attack by water radicals such as OH$^{\bullet}$ or by direct ionization of the sugar phosphate backbone. However, recent reports[6,7] of direct damage by low energy electrons (LEEs) have sparked a need to elucidate alternative direct strand break mechanisms. Along these lines, Huels et al.[8] have proposed that formation and decay of well-localized transient anion states (resonances) within DNA is the principal mechanism leading to SSB and DSB by electron energies below 15 eV, whereas Pan et al.[9] demonstrated that dissociative electron attachment (DEA)[10] around 10 eV was implicated in this damage.

It is generally believed that there is an energy threshold for induction of DNA strand breaks by LEEs. Monte Carlo simulations have suggested[11] a threshold energy of 17.5 eV, which may include ionization and damages by both hydroxyl radical and LEEs. Prise et al.[12] reported that DNA strand breaks can be induced by photons with energy as low as 7 eV, near the minimum ionization energy. Boudaiffa et al.[6] reported that strand breaks can be induced by LEEs with energy as low as 5 eV. More recently, Barrios et al.[13] suggests that SSB can occur by 1 eV electrons via a "resonant capture mechanism", based on ab initio calculations using a model of base−deoxyribose−phosphate. It appears that the energy threshold may be very low for strand break induction by LEEs which can act directly on DNA.

Strand breaks caused by LEEs are of particularly interest because such electrons are produced in very large quantity (4×10^4/MeV deposited)[14] along all of the tracks of ionizing radiation, with an energy distribution lying mainly below 15 eV. The recent observation[15] of the effective destruction of gas phase uracil induced by electrons below 5 eV greatly increases the concern that LEEs can cause substantial DNA damage. Thus, it is of fundamental interest to ascertain if such processes as DEA[10] play a role in the formation of DNA strand breaks below 5 eV.

For this purpose, we select a model that consists of two deoxyribose (sugar) rings connected by a phosphate (Figure 1). In the model, the sites of bases on the sugar are replaced by amino groups, and the 3′- or 5′-ends are terminated with hydrogens; no counterion such as Na^+ or structural water is included. We seek to find those states on the DNA backbone which may directly interact with LEEs and form dissociative transient anion states, below 5 eV.

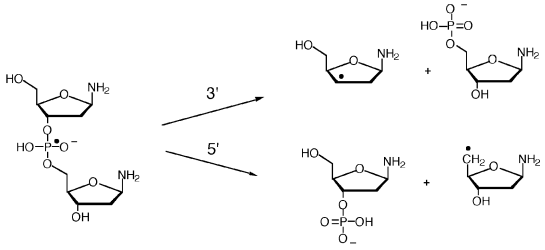

Figure 1. Sugar−phosphate−sugar model representing a section of DNA backbone. Electron-induced bond dissociations at the 3′ and 5′ ends of the model are investigated.

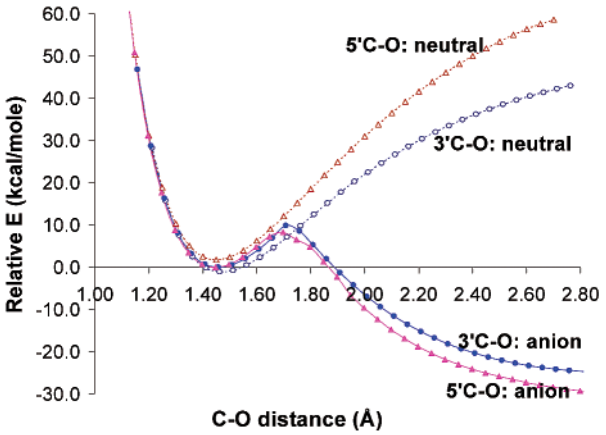

Figure 2. Adiabatic potential energy surfaces for 3′C−O and 5′C−O bond rupture. All energies are relative to the energies of the anions at equilibrium.

Because this model is still too large (21 heavy atoms + 21 hydrogens), the layer treatment (ONIOM method) provided by the Gaussian 98 program[16] package is used to obtain a description of the full potential energy surface (PES). That is, the model is divided into a high layer that is treated at the DFT level of B3LYP/6-31+G-(d) for the critical bond cleavage atoms and a low layer treated by the AM1 method. For 3′C−O bond studies, the sugar that connects to the phosphate by 5′C is designated as the low layer, and the rest of the model is in the high layer. For the 5′C−O bond, the 3′-sugar is the low layer. We follow the adiabatic PES of both the neutral state and its anion, using the OPT= ModRedundant keyword with the S code. To verify the reliability of the ONIOM method, full DFT (B3LYP/6-31+G(d)) calculations were performed for the crucial point optimizations, such as the equilibrium and dissociated states, as well as for the calculation of a partial PES along the 3′C−O bond. Good agreement was found between both methods (see Supporting Information).

From the PESs of the 3′ and 5′C−O bonds shown in Figure 2, it can be seen that the activation barriers are around 10 kcal/mol for the anion's bond rupture at 3′ or 5′C−O, while the PESs of

[†] Université de Sherbrooke.
[‡] Oakland University.

10.1021/ja036509m CCC: $25.00

Table 1. Thermodynamic Data and Bond Distances for the Cleavage Process of the DNA Backbone Radical Anion Obtained by ONIOM(UB3LYP/6-31+G(d):AM1) and Full DFT Calculations

	ONIOM	UB3LYP/6-31+G(d)
	AEA (eV)	
gas phase	3′C, −0.003; 5′C, 0.077[a]	0.033 (0.88)[b]
	ΔE (kcal/mol)[c]	
3′C−O	−36.09	−37.17 (−44.64)[b]
5′C−O	−32.41	−37.75 (−44.19)[b]
	C−O distances: at equilibrium//at dissociative states (Å)	
3′C−O	1.458//3.447	1.435//3.837
5′C−O	1.445//5.058	1.444//3.607

[a] The AEAs from the ONIOM calculations differ from the differences in layering. [b] Values in parentheses are for solvation using the PCM model, water as solvent, $\epsilon = 78$. [c] Energy difference between the "dissociative state" and equilibrium anion.

their neutral states are in the typical Morse potential shape. The ΔE values from the equilibrium anion to the dissociative state for dissociation of 3′ and 5′C−O bonds calculated by the ONIOM method and by DFT are listed in Table 1. Both methods are in fairly good agreement and strongly suggest that bond dissociation is thermodynamically favorable. These results are surprising as they suggest that addition of near 0 eV electrons may cause bond ruptures, because the 10 kcal/mol activation barrier is very small.

In this work, the environment of DNA, such as the bases, structural water, and counterions, is not included, while it is clear that they will somewhat influence the overall energetics. Preliminary calculations show that the large exothermic energy release on strand breaking will be augmented by solvation of the systems (Table 1). In water solutions, LEEs will undergo energy degradation and become solvated. The process is exergonic with an absolute hydration free energy (ΔG) of about −35.5 kcal/mol.[17] The reaction between solvated electron and the negatively charged dialkyl phosphate has been found to be slow and the reaction with the bases has been found to be so fast that direct reaction of solvated electrons with the DNA backbone is not considered a cause of DNA strand breaks.[18] However, direct damage by low energy electrons before solvation is shown in this work to be a clear possibility even in solution.

Because the backbone is not the preferred site for attachment of a thermal electron, the electron must encounter the backbone before thermalization and the resulting anion is subjected to competitive electron transfer to neighboring bases, during strand breaking. However, recent measurement[9] of DEA within the sugar−phosphate unit of DNA indicates that transient anions formed at energies even up to 10 eV have lifetimes sufficiently long to dissociate before autoionization or electron transfer. Even though the bases have a deeper energy well than that of the backbone, electron transfer from these transient anions (i.e., electron autodetachment) to the bases is not necessarily favored, because the anion states may be more strongly correlated to energy levels closer both in space and in energy.[19] If an electron with sufficient kinetic energy attaches to DNA, it may lead to the formation of multiple resonant states, which decay into various damaged structures including strand breaks.[8] Because the minimum energy needed for the anion to surmount the activation barrier is only ∼0.5 eV, it is clear that DNA SSBs can be induced by very LEEs via a process which is thermodynamically highly favorable.

While the electron affinities of the DNA bases are higher than that of the phosphate, as the C−O bond extends, the electron affinity of the backbone eventually becomes higher than that of the bases (at ca. 1.9 Å).[13] This means electron transfer to the bases will not be favored beyond a certain C−O internuclear distance.

As direct evidence of the proposed mechanism, we note that the radicals associated with cleavage of the 3′C−O and P−O bonds have been reported in ESR experiments[20,21] on DNA irradiated at low temperatures; furthermore, the mechanism of formation of these radicals was attributed to LEEs. This experimental evidence for P−O fragmentation provides impetus for future theoretical work, because the cleavage of the 3′CO-P, P-O5′C, or even the 5′C−4′C bonds would result in immediate DNA strand breaks. Experimental and theoretical investigations are now underway to test the energetics of these fragmentation routes.

Acknowledgment. L.S. is the Canada Research Chair in the Radiation Sciences. This research was supported by the Canadian Institutes of Health Research (CIHR), the National Cancer Institute of Canada, and the NIH NCI Grant RO1CA45424, in joint efforts between the CIHR Group in the Radiation Science of the Université de Sherbrooke and Department of Chemistry, Oakland University. We also acknowledge use of the MACI cluster of the University of Calgary for part of this work.

Supporting Information Available: Optimized geometry, figure comparing PES, figure showing ONIOM layer definition (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) von Sonntag, C. *The Chemical Basis for Radiation Biology*; Taylor and Francis: London, 1987.

(2) Becker, D.; Sevilla, M. D. *Advances in Radiation Biology*; Academic Press: New York, 1993; pp 121−180.

(3) Fuciarelli, A. F.; Zimbrick, J. D. *Radiation Damage in DNA: Structure/Function Relationships at Early Times*; Battelle: Columbus, OH, 1995.

(4) Douki, T.; Angelov, D.; Cadet, J. *J. Am. Chem. Soc*. **2001**, *123*, 11360.

(5) O'Neil, P. Radiation-induced damage in DNA. In *Radiation Chemistry*; Elsevier Science: Dordrecht, The Netherlands, 2001; pp 585−622.

(6) Boudaiffa, B.; Cloutier, P.; Hunting, D.; Huels, M. A.; Sanche, L. *Science* **2000**, *287*, 1658.

(7) Boudaiffa, B.; Cloutier, P.; Hunting, D.; Huels, M. A.; Sanche, L. *Radiat. Res*. **2002**, *157*, 227−234.

(8) Huels, M. A.; Boudaiffa, B.; Cloutier, P.; Hunting, D.; Sanche, L. *J. Am. Chem. Soc*. **2003**, *125*, 4467−4477.

(9) Pan, X.; Cloutier, P.; Hunting, D.; Sanche, L. *Phys. Rev. Lett*. **2003**, *90*, 208102−1.

(10) Sanche, L. *Scanning Microsc.* **1995**, *9*, 619.

(11) (a) Charlton, D. E.; Humm, J. L. *Int. J. Radiat. Biol*. **1988**, *53*, 353−365. (b) Nikjoo, H.; Martin, R. F.; Charlton, D. E.; et al. *Acta Oncol*. **1996**, *35*, 849−856.

(12) Prise, K. M.; Folkard, M.; Michael, B. D.; Vojnovic, B.; Brocklehurst, B.; Hopkirk, A.; Munro, I. H. *Int. J. Radiat. Biol.* **2000**, *76*, 881.

(13) Barrios, R.; Skurski, P.; Simons, J. *J. Phys. Chem. B* **2002**, *106*, 7991.

(14) LaVerne, J. A.; Pimblott, S. M. *Radiat. Res*. **1995**, *141*, 208−215.

(15) Hanel; et al. *Phys. Rev. Lett*. **2003**, *90*, 188104.

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(17) Zhan, C. G.; Dixon, D. A. *J. Phys. Chem. B* **2003**, *107*, 4403−4417.

(18) von Sonntag, C. *The Chemical Basis for Radiation Biology*; Taylor and Francis: London, 1987; Chapter 7, p 167.

(19) Sanche, L. *Surf. Sci.* **2000**, *451*, 82−90.

(20) Becker, D.; Razskazovskii, Yu.; Callaghan, M.; Sevilla, M. D. *Radiat. Res*. **1996**, *146*, 361−368.

(21) Becker, D.; Bryant-Friedrich, A.; Trasko, C. A.; Sevilla, M. D. *Radiat. Res*. **2003**, *160*, 174−185.

JA036509M