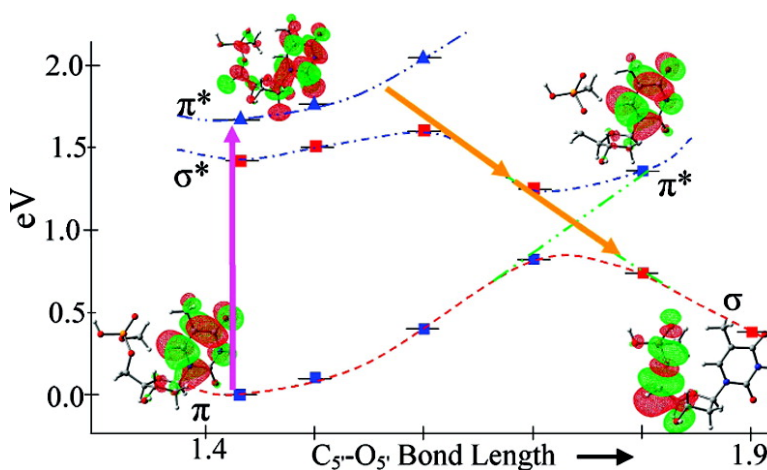


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J. Am. Chem. Soc., **2008**, 130 (7), 2130-2131 • DOI: 10.1021/ja077331x

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The Role of $\pi\sigma^*$ Excited States in Electron-Induced DNA Strand Break Formation: A Time-Dependent Density Functional Theory Study

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Low-energy electrons (LEEs) are increasingly recognized as a significant contributor to DNA damage and resultant cellular radiation damage.¹ LEEs below 15 eV are produced copiously (4×10^4 per MeV energy deposited) along the tracks of the energy deposited.^{1a} It is well-established that LEEs lead to induce a variety of damages within DNA such as single- and double-strand breaks (SSBs and DSBs) as well as base damage and release.^{1,2} Further, Illenberger and co-workers³ extensively studied the LEE induced fragmentation or dissociation of nucleobases and ribose derivatives.^{3a,b} In addition to these experimental^{2,3} efforts, a variety of theoretical^{4–8} efforts have been made in recent years to understand the detailed mechanisms of LEE induce strand breaks.

Simons and co-workers⁴ proposed the DNA base as the site for electron attachment as a shape resonance. Subsequent transfer of the electron from the base to the sugar phosphate bond is proposed to result in the C–O bond dissociation and a strand breaks. This concept was supported by theoretical calculations at the Hartree–Fock (HF) level⁴ and more recently supported by DFT calculations.⁷ An alternative mechanism was proposed by Li et al.^{5d} involving the direct addition of the electron to the sugar phosphate portion of the DNA, considered a sugar–phosphate–sugar (S–P–S) model, and found that C₃–O₃' and C₅'–O₅' bond dissociation to be ca. (~10.0 kcal/mol). However, the initial state was not a valance-bound state but a “dipole-bound” anionic state.^{5b} More recently, we investigated the LEE induced strand break mechanism by considering both vertical and adiabatic pathways for C₅'–O₅' bond dissociation after electron attachment to 5'-dTMPH.⁶ Surprisingly we found that the energy barrier for C₅'–O₅' bond breaking in the vertical state (~9.0 kcal/mol) is lower than the adiabatic state (~15.0 kcal/mol). Experiments by Sanche et al.⁹ support the possibility of LEE attachment on the base which initiates the SSB in DNA in gas phase. On the other hand, the recent experiments by Illenberger and co-workers³ led them to propose a direct mechanism of LEE induced SSB formation in which the excess electron directly attaches to the sugar phosphate group. We note LEE resonances form transient negative ions (TNI), which are equivalent to excited states of the electron adduct of the parent molecule. Since such resonances can be in the continuum, the study of molecular excited states by methods using compact basis sets¹⁰ that reject the continuum may provide insight on the nature and mechanism of LEE induced strand breaks.

In the present Communication, we used the time-dependent density functional theory (TDDFT) to study the lowest excited states of the 5'-thymidine monophosphate (5'-dTMPH) radical anion as a model of DNA. The ground-state geometries of 5'-dTMPH in neutral and in radical anionic states were fully optimized at the B3LYP/6-31G* level of theory and the vertical excited states of the 5'-dTMPH radical anion were calculated using B3LYP and BHandHLYP (BH&HLYP) functionals and the 6-31G* basis set as implemented in the Gaussian 03 program.¹¹ In recent years, TD-B3LYP has emerged as a prominent tool to study the excited states

of the molecules in their neutral,¹² cationic,¹³ and anionic^{13b} radical states. While several reports suggest the reliability of both of these methods,^{12–14} none have reported their use for shape resonances. We therefore have tested this approach by calculation of excitation energies for a number of DNA/RNA bases for which experimental shape resonance energies have been reported^{15a} (see Table 1 and Table S2 for details in Supporting Information). As seen in the Table 1 both methods give reasonable estimates for the shape resonance energies for DNA bases; however, TD-B3LYP fails¹⁶ for 5'-dTMPH radical anion. Therefore, we present TD-BH&HLYP results here.

To understand the mechanism of DNA strand breaks, a knowledge of the potential energy surface (PES) along the C₅'–O₅' bond stretch in 5'-dTMPH is of utmost importance. For this reason, we scanned the PES by stretching the C₅'–O₅' bond (Figure 1) from the equilibrium bond length of the anion radical of 5'-dTMPH in the neutral geometry (vertical surface, Figure 1) and the optimized anion radical (adiabatic surface, see Figure S1 of Supporting Information) to 2.0 Å in steps of 0.1 Å using B3LYP/6-31G*. At each fixed C₅'–O₅' bond length on each PES, vertical excitation energies were calculated using TD-B3LYP and TD-BH&HLYP methods. In the present study, for the adiabatic surface, we find that TD-BH&HLYP predicts the three lowest excitation energies as $\pi(T) \rightarrow \pi(T)^*$, $\pi(T) \rightarrow \sigma(PO4)^*$ and $\pi(T) \rightarrow \sigma(S)^*$ type (here T, PO4, and S correspond to thymine, phosphate, and sugar in 5'-dTMPH) having transition energies 3.03, 3.40, and 3.85 eV, respectively. We found that these transitions are the dominant single excitation having ~61%, ~87%, and ~87% contribution, respectively. However, TD-B3LYP substantially underestimates these energies in the adiabatic and especially in the case of the TNI where it fails (see Supporting Information).

To understand LEE resonance interactions, it is important to investigate excited states of the TNI. TNI formation plays a key role in DEA mechanism of strand breaks as well as in resonance formation.^{2a,3,6} Thus, the excited states of 5'-dTMPH radical anion were also calculated at the geometry of the neutral 5'-dTMPH. These TD-BH&HLYP calculations show the same first three excited states as found for the adiabatic case but at lower energy and with an altered ordering (see Figure 1). TD-BH&HLYP predicts three lowest excited states as $\pi(T) \rightarrow \sigma(PO4)^*$, $\pi(T) \rightarrow \pi(T)^*$, $\pi(T) \rightarrow \sigma(S)^*$ in nature having excitation energies 1.42, 1.68, and 2.06 eV, respectively. The second $\pi(T) \rightarrow \pi(T)^*$ transition energy (1.68 eV) is in good agreement with the 1.71 ($\pi 2^*$) eV as predicted by ETS^{15a} for thymine (Table 1). This gives us confidence in the π^* surface. We note that the π^* MO also extends into the sugar phosphate (Figure 1). Experiments with DNA show that LEEs near 2 eV also induce SSB formation, and attachment to a π^* state is invoked.^{2b}

The ground-state singly occupied molecular orbital (SOMO) is of π type and localizes over the thymine ring as already found in the earlier studies.^{4–8} As the C₅'–O₅' bond stretches the barrier height increases and at the transition state (TS) we find the barrier

Table 1. Vertical Excitation Energies (ΔE , eV) of Transient Negative Ion (TNI) of DNA/RNA Bases Calculated Using TD-B3LYP/6-31G* and TD-BH&HLYP/6-31G* Methods and Their Comparison with Available Experimental Values^a

transition	molecule	ΔE		Exp ^{b,c}
		B3LYP	BH&HLYP	
$\pi \rightarrow \pi^*$	uracil	1.33	1.85	0.22 (π_1^*)
		4.27	4.73	1.58 (π_2^*)
$\pi \rightarrow \pi^*$	thymine	1.38	1.89	3.83 (π_3^*)
		3.86	4.46	0.29 (π_1^*)
$\pi \rightarrow \pi^*$	cytosine	1.55	1.91	1.71 (π_2^*)
		4.47	5.06	4.05 (π_3^*)
$\pi \rightarrow \pi^*$	adenine	0.88	1.0	0.32 (π_1^*)
		1.89	1.86	1.53 (π_2^*)
$\pi \rightarrow \pi^*$	5'-dTMPH ^d	1.16	1.68	4.50 (π_3^*)
		0.18	1.42	0.54 (π_1^*)
$\pi \rightarrow \sigma^{*e}$		0.70	2.06	1.36 (π_2^*)
				2.17 (π_3^*)
				(0.53 T) ^d
				(1.56 T) ^d
				(1.80 PO ₄) ^d
				(2.23 S) ^d

^a Transition energies of radical anions were calculated at the optimized neutral geometry of the molecules. ^b Energies of the shape resonances in the electron transmission spectroscopy (ETS) experiment; ref 15a. ^c π_1^* corresponds to the energy of the singly occupied molecular orbital (SOMO), and its difference with π_2^* and π_3^* orbital energies gives the estimate of the transition energies. ^d Scaled B3LYP orbital energies (VOE); ref 6. ^e Electron transfers from thymine (π) to PO₄ and sugar (σ) part of 5'-dTMPH.

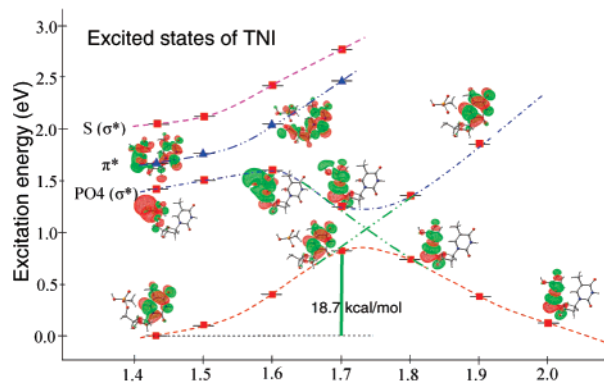


Figure 1. Lower curve: Potential energy surface (PES) of the 5'-dTMPH transient negative ion (TNI); calculated in the neutral optimized geometry of 5'-dTMPH with C₃-O_{5'} bond elongation. SOMO is shown at selected points. Upper curves: calculated vertical excitation energies of the radical anion at each point along the PES, MOs involved in excitations are also shown. Energies and distances are given in eV and Å, respectively. The lowest $\pi\pi^*$ state (triangles) and lowest $\pi\sigma^*$ states (square) are shown.

height 18.7 kcal/mol (TNI) versus 23.34 kcal/mol for the adiabatic surface (see Figure S1). These values are higher and likely to be more reliable than the B3LYP/6-31G* calculated values of 9 and 14.8 kcal/mol reported earlier.⁶ The second and third excited states show bound character while the first $\pi(T) \rightarrow \sigma(PO_4)^*$ state shows a dissociative nature. The fall off in the $\sigma(PO_4)^*$ surface on shortening the bond should possibly continue to rise to show the full antibonding nature reported earlier by Simons.⁴ Such dissociative nature of $\pi \rightarrow \sigma^*$ excited states in similar systems is well-known.^{18,19}

Our TD-BH&HLYP calculations suggest that an excess electron of ca. 2 eV could directly attach to the sugar-phosphate group ($\pi(T) \rightarrow \sigma(PO_4)^*$) and initiate strand breaks in 5'-dTMPH (Figure 1). However, generally, such dissociative states are not accessed

directly but can be populated by vibronic coupling with a $\pi(T) \rightarrow \pi(T)^*$ state.^{18,19d} Thus, while the $\pi \rightarrow \sigma^*$ transitions are difficult to observe, $\pi \rightarrow \pi^*$ transitions are bright^{15b} and readily populated. A π^* and σ^* coupling would then lead to a rapid dissociative process resulting in DNA strand cleavage.

Acknowledgment. This work was supported by the NIH NCI under Grant No. R01CA045424. The authors are grateful to the Arctic Region Supercomputing Center (ARSC) for generously providing the computational time to perform these calculations.

Supporting Information Available: Full reference 11, tables of excitation energies, and figures showing energy level diagram and orbitals of 5'-dTMPH radical anion. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Boudaïffa, B.; Cloutier, P.; Hunting, D.; Huels, M. A.; Sanche, L. *Science* **2000**, *287*, 1658. (b) Swiderek, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4056 and references therein.
- (2) (a) Zheng, Y.; Cloutier, P.; Hunting, D. J.; Wagner, J. R.; Sanche, L. *J. Am. Chem. Soc.* **2004**, *126*, 1002. (b) Martin, F.; Burrow, P. D.; Cai, Z.; Cloutier, P.; Hunting, D.; Sanche, L. *Phys. Rev. Lett.* **2004**, *93*, 068101.
- (3) (a) Bald, I.; Kopyra, J.; Illenberger, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 4851. (b) Ptasińska, S.; Denifl, S.; Gohlke, S.; Scheier, P.; Illenberger, E.; Märk, T. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1893. (c) König, C.; Kopyra, J.; Bald, I.; Illenberger, E. *Phys. Rev. Lett.* **2006**, *97*, 018105.
- (4) (a) Simons, J. *Acc. Chem. Res.* **2006**, *39*, 772 and references therein. (b) Berdys, J.; Anusiewicz, I.; Skurski, P.; Simons, J. *J. Am. Chem. Soc.* **2004**, *126*, 6441.
- (5) (a) Li, X.; Sevilla, M. D. *Adv. Quantum Chem.* **2007**, *52*, 59. (b) Li, X.; Sevilla, M. D.; Sanche, L. *J. Am. Chem. Soc.* **2003**, *125*, 13668.
- (6) Kumar, A.; Sevilla, M. D. *J. Phys. Chem. B* **2007**, *111*, 5464.
- (7) (a) Bao, X.; Wang, J.; Gu, J.; Leszczynski, J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 5658. (b) Gu, J.; Wang, J.; Leszczynski, J. *J. Am. Chem. Soc.* **2006**, *128*, 9322.
- (8) Gu, J.; Xie, Y.; Schaefer, H. F. *J. Am. Chem. Soc.* **2005**, *127*, 1053.
- (9) Zheng, Y.; Wagner, J. R.; Sanche, L. *Phys. Rev. Lett.* **2006**, *96*, 208101.
- (10) Li, X.; Cai, Z.; Sevilla, M. D. *J. Phys. Chem. A* **2002**, *106*, 1596.
- (11) Frisch, M. J.; et al. *Gaussian03*, revision B.04; Gaussian, Inc.: Pittsburgh, PA, 2003.
- (12) (a) Ismail, N.; Blancafort, L.; Olivucci, M.; Kohler, B.; Robb, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 6818. (b) Grimme, S.; Waletzke, M. *J. Chem. Phys.* **1999**, *111*, 5645.
- (13) (a) Kumar, A.; Sevilla, M. D. *J. Phys. Chem. B* **2006**, *110*, 24181. (b) Hirata, S.; Head-Gordon, M.; Szczepanski, J.; Vala, M. *J. Phys. Chem. A* **2003**, *107*, 4940. (c) Hirata, S.; Lee, T. J.; Head-Gordon, M. *J. Chem. Phys.* **1999**, *111*, 8904.
- (14) (a) Piacenza, M.; Sala, F. D.; Fabiano, E.; Maiolo, T.; Gigli, G. *J. Comput. Chem.* **2008**, *29*, 451. (b) Dierksen, M.; Grimme, S. *J. Phys. Chem. A* **2004**, *108*, 10225. (c) Huenerbein, R.; Grimme, S. *Chem. Phys.* **2007**, doi: 10.1016/j.chemphys.2007.08.005.
- (15) (a) Aflatouni, K.; Gallup, G. A.; Burrow, P. D. *J. Phys. Chem. A* **1998**, *102*, 6205. (b) Burrow, P. D.; Gallup, G. A.; Scheer, A. M.; Denifl, S.; Ptasińska, S.; Märk, T.; Scheier, P. *J. Chem. Phys.* **2006**, *124*, 124310.
- (16) B3LYP underestimates the long-range coulombic interaction in charge transfer states involving hole and electron separation.¹⁷ The use of increased HF exchange (50% in BH&HLYP) over B3LYP (20%) is found to better describe excited states involving charge transfer.^{14b,c,17} Charge separation is not induced in the 5'-dTMPH radical anion on excitation; only electron transfer between nominally neutral portions of the molecule occurs.
- (17) (a) Dreuw, A.; Weisman, J. L.; Head-Gordon, M. *J. Chem. Phys.* **2003**, *119*, 2943.
- (18) (a) Domcke, W.; Sobolewski, A. L. *Science* **2003**, *302*, 1693. (b) Sobolewski, A. L.; Domcke, W.; Dedonder-Lardeux, C.; Jouvet, C. *Phys. Chem. Chem. Phys.* **2002**, *4*, 1093. (c) Sobolewski, A. L.; Domcke, W. *Eur. Phys. J., D* **2002**, *20*, 369.
- (19) (a) Ashfold, M. N. R.; Cronin, B.; Devine, A. L.; Dixon, R. N.; Nix, G. D. *Science* **2006**, *312*, 1637. (b) Ullrich, S.; Schultz, T.; Zgierski, M. Z.; Stolow, A. *Phys. Chem. Chem. Phys.* **2004**, *6*, 2796. (c) Satzger, H.; Townsend, D.; Zgierski, M. Z.; Patchkovskii, S.; Ullrich, S.; Stolow, A. *Proc. Nat. Acad. Sci. U.S.A.* **2006**, *103*, 10196. (d) Lippert, H.; Ritze, H.-H.; Hertel, I. V.; Radloff, W. *Chem. Phys. Chem.* **2004**, *5*, 1024. (e) Hünig, I.; Plützer, C.; Seefeld, K. A.; Löwenich, D.; Nispel, M.; Kleinermanns, K. *Chem. Phys. Chem.* **2004**, *5*, 1427. (f) Nielsen, S. B.; Sølling, T. I. *Chem. Phys. Chem.* **2005**, *6*, 1276.

JA077331X