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Near 0 eV Electrons Attach to Nucleotides

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Abstract: To elucidate the mechanism of the nascent stage of DNA strand breakage by low-energy electrons, theoretical investigations of electron attachment to nucleotides have been performed by the reliably calibrated B3LYP/DZP++ approach (*Chem. Rev.* **2002**, *102*, 231). The 2′-deoxycytidine-3′-monophosphate (3′-dCMPH) and its phosphate-deprotonated anion (3′-dCMP$^-$) have been selected herein as models. This investigation reveals that 3′-dCMPH is able to capture near 0 eV electrons to form a radical anion which has a lower energy than the corresponding neutral species in both the gas phase and aqueous solution. The excess electron density is primarily located on the base of the nucleotide radical anion. The electron detachment energy of this pyrimidine-based radical anion is high enough that subsequent phosphate−sugar C−O σ bond breaking or glycosidic bond cleavage is feasible. Although the phosphate-centered radical anion of 3′-dCMPH is not stable in the gas phase, it may be stable in aqueous solution. However, an incident electron with kinetic energy less than 4 eV might not be able to effectively produce the phosphate-centered radical anion either in solution or in the gas phase. This research also suggests that the electron affinity of the nucleotides is independent of the counterion in aqueous solution.

DNA strand breaks induced by low-energy electrons (LEE) are of great interest because LEEs are produced in significant numbers by ionizing radiation.[1] It is thought that there is an energy threshold for induction of DNA strand breaks by LEEs. Recently, both experimental and theoretical studies have demonstrated that at very low energies electrons may induce strand breaks in DNA via dissociative electron attachment.[2−13] To shed light on the nature of DNA strand breaks by LEEs, several different mechanisms have been proposed.[6,10,13]

For the nucleosides, both experimental and theoretical investigations[8,13] have suggested that the excess electron resides on the π^* orbital of the pyrimidine in the radical anion, forming a stable distonic radical anion. Subsequently, the glycosidic bond breaks to release the free pyrimidine anion and the 2-deoxyribose radical. To extend this mechanism to DNA, one must understand the details of electron binding to nucleotides since the negative charge associated with the phosphate might influence the electron affinities of the nucleotides.

On the basis of their theoretical study of the gas-phase sugar−phosphate−sugar model, Li, Sevilla, and Sanche[6] proposed that the near 0 eV electrons may be captured first by the phosphate, forming a phosphate-centered radical anion. Subsequent $C_{3'}-O_{3'}$ or $C_{5'}-O_{5'}$ σ bond breaking was estimated[6] to have an energy barrier of about 10 kcal/mol. It should be noted that the nucleic acid bases are excluded from the Li−Sevilla−Sanche model calculations. However, formation of a phosphate-centered radical anion has been questioned by Simons and co-workers.[10] The small value of the electron affinity of the sugar−phosphate−sugar (S−P−S) model seems to suggest that low-energy electrons might be trapped in the bases instead of by the phosphate groups.

Using the 2′-deoxycytidine-3′-monophosphate molecule as a model, Simons' group carefully examined the $C_{3'}-O_{3'}$ bond-breaking processes.[9,10,12] In harmony with experimental observations, they proposed that[10] very low energy electrons can attach to the π^* orbitals of the DNA bases and initiate $C_{3'}-O_{3'}$ bond cleavage in aqueous solution. The neutralized phosphate group cannot effectively host an electron with energy near 0 eV in the gas phase. However, for the determination of the electron affinities of DNA fragments, the method used (HF/6-31+G(d)) may yield results inconsistent with both experiments and higher level theories.[13]

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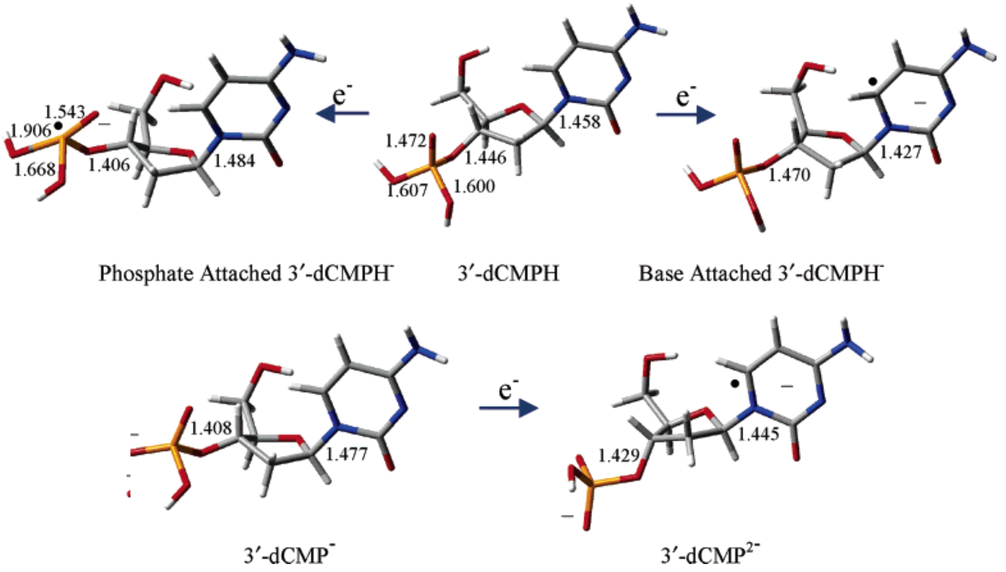

Figure 1. Optimized structures of neutral 3′-dCMPH, anionic 3′-dCMP$^-$, and the corresponding electron-attached radicals. Bond distances are in Ångstroms.

To elucidate the mechanism of the nascent stage of DNA strand breaks by LEEs, a reliable theoretical determination of the properties of the radical anions of the nucleotides is necessary. The success of this venture depends on the theoretical methods chosen. Recent development of carefully calibrated DFT methods[14] allows experiment-consistent EA_{ad} values close to zero (±0.3 eV) for the DNA and RNA bases, with the ordering U > T > C ≈ G > A.[15] With this reliable B3LYP/DZP++ approach accurate predictions of the electron affinities of the 2′-deoxyribonucleosides have also been achieved.[16] Here, we report theoretical investigations of low-energy electron attachment to nucleotides. The 2′-deoxycytidine-3′-monophosphate (3′-dCMPH) system and its phosphate-deprotonated anion (3′-dCMP$^-$) have been selected as models (Figure 1) because it is important to have a direct comparison with previous research. In this research 3′-dCMPH represents the nucleotide with a tightly bound counterion, while the 3′-dCMP$^-$ anion mimics the situation in which the counterion is far away from the nucleotide.

Geometries and vibrationally zero-point-corrected energies for 3′-dCMP were determined using the DZP++ B3LYP[17,18] approach. Each adiabatic electron affinity (EA_{ad}) was predicted as the difference between the total energies of the appropriate neutral and anion at their respective optimized geometries $EA_{ad} = E_{neut} - E_{anion}$.

The DZP++ basis sets were constructed by augmenting the Huzinage−Dunning[20−22] set of contracted double-ζ Gaussian functions with one set of p-type polarization functions for each H atom and one set of five d-type polarization functions for each C, N, O, and P atom [$\alpha_p(H) = 0.75$, $\alpha_d(C) = 0.75$, $\alpha_d(N) = 0.80$, $\alpha_d(O) = 0.85$, $\alpha_d(P) = 0.60$]. To complete the DZP++ basis, one even-tempered diffuse *s* function was added to each H atom while sets of even-tempered diffuse *s* and *p* functions were centered on each heavy atom. The even-tempered orbital exponents were determined according to the prescription of Lee and Schaefer.[23] The GAUSSIAN 98 programs[19] were used in the computations.

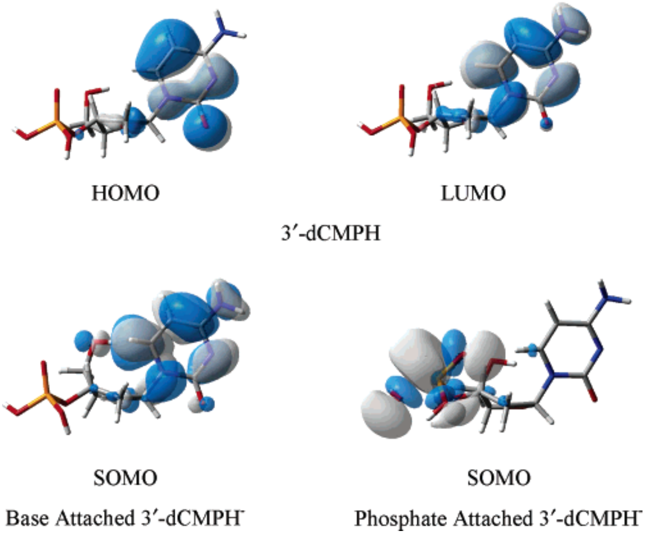
HOMO LUMO
3′-dCMPH
SOMO SOMO
Base Attached 3′-dCMPH- Phosphate Attached 3′-dCMPH-

Figure 2. Singly occupied molecular orbitals (SOMOs) of the two different 3′-dCMPH radical anions and related MOs of the neutral 3′-dCMPH molecule.

The EA_{ad} of 3′-dCMPH is predicted to be 0.44 eV, about 0.11 eV higher than that of the nucleoside 2′-deoxycytidine (dC).[16] The singly occupied molecular orbital (SOMO, Figure 2) of the 3′-dCMPH radical anion (base-attached 3′-dCMPH$^-$) demonstrates that the excess electron resides on the π^* orbital of the base. The vertical electron affinity (VEA) determines the necessary energy needed for a fast electron capture step in the formation of anions.[7] The positive VEA value of 0.15 eV for 3′-dCMPH suggests that 3′-dCMPH can capture near 0 eV

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electrons. Moreover, the vertical detachment energy (VDE) is predicted to be substantial (1.28 eV) based on the optimized structure of the base-attached 3′-dCMPH$^-$ anion. For comparison, the VDE of dC$^-$ is only 0.72 eV.[16] With a VDE value of 1.28 eV, the 3′-dCMPH radical anion should undergo the subsequent phosphate−sugar C−O σ bond-breaking[6,7,9−12] or the glycosidic bond cleavage[5,8,13] processes instead of autodetachment.

To elucidate the possibility of electron capture by the phosphate group, as suggested by the sugar−phosphate−sugar model investigation,[6] the phosphate-centered 3′-dCMPH radical anion (phosphate-attached 3′-dCMPH$^-$) has also been shown to be a local minimum on the potential-energy surface. The SOMO of the phosphate-attached 3′-dCMPH$^-$ anion clearly demonstrates that the excess electron resides in the antibonding orbital between the P and O atoms of the phosphate group. This conclusion is further supported by the significant elongation of the P−O bonds in the phosphate-attached 3′-dCMPH$^-$ radical (Figure 1). The adiabatic EA for the formation of the phosphate-attached 3′-dCMPH$^-$ anion has been evaluated to be negative (−0.14 eV), qualitatively consistent with the theoretical value[6] (−0.003 to 0.033 eV) based on the sugar−phosphate−sugar model. The VEA for phosphate-attached 3′-dCMPH cannot be meaningfully predicted because this anion is not stable, collapsing to the lower energy base-attached 3′-dCMPH$^-$.

Solvent effects remarkably improve the electron capture ability of 3′-dCMPH. For the formation of the base-centered 3′-dCMPH radical anion, the EA$_{ad}$ and the VEA values are 2.18 and 1.72 eV, increased by 1.85 and 1.57 eV, respectively, due to solvent effects. Solvent effects also increase the electron detachment energy of the 3′-dCMPH$^-$ radical anion. The VDE of the base-attached 3′-dCMPH$^-$ is predicted to be 2.97 eV in aqueous solution.

The electron attachment ability of the phosphate group is also improved in aqueous solution. The EA for the formation of phosphate-attached 3′-dCMPH$^-$ has been predicted to be 1.20 eV, corresponding to a 1.40 eV increase due to solvent effects.

The 3′-dCMP$^-$ anion is not expected to capture an excess electron to form the dianion (3′-dCMP^{2-}) in the gas phase since the EA$_{ad}$ and VDE predicted for 3′-dCMP$^-$ is negative (−1.75 and −1.59 eV, Table 1). Although the current method used does not describe the dianion in any theoretical rigor,[24] the negative EA$_{ad}$ and VDE values reflect this metastable property qualitatively. However, solvent effects reverse this situation, and the dianion is a stable species in solution. Our theoretical results (Table 1) show that the EA$_{ad}$ and VEA values of 3′-dCMP$^-$ are positive (2.17 and 1.79 eV, respectively) in aqueous solution. This stabilization effect is also demonstrated by the increased VDE value of the solvated 3′-dCMP^{2-} radical dianion (2.27 eV).

Table 1. Electron Attachment Energies for 3′-dCMPH and the Anion 3′-dCMP$^-$ (in eV). Values with Zero-Point Vibrational Corrections Are Given in Parentheses. See Figure 1 for the Naming of the Different Species

	EA$_{ad}$	VEA[a]	VDE[b]
gas phase			
3′-dCMPH → base-attached 3′-dCMPH$^-$	0.33 (0.44)	0.15	1.28
3′-dCMPH → phosphate-attached 3′-dCMPH$^-$	−0.20 (−0.14)	c	2.63
3′-dCMP$^-$ → 3′-dCMP^{2-}	−1.84 (−1.75)[d]	−2.13[d]	−1.59[d]
S−P−S → S−P−S$^-$	−0.003; 0.033[e]		
aqueous solution[f]			
3′-dCMPH → base-attached 3′-dCMPH$^-$	2.18	1.72	2.97
3′-dCMPH → phosphate-attached 3′-dCMPH$^-$	1.20	c	4.04
3′-dCMP$^-$ → 3′-dCMP^{2-}	2.17[d]	1.79[d]	2.27[d]
S−P−S → S−P−S$^-$	0.88[e]		

[a] VEA = E(neutral) − E(anion), with the energies evaluated based on the optimized neutral structures. [b] VDE = E(neutral) − E(anion), with the energies taken from the optimized anion structures. [c] The anionic phosphate-attached 3′-dCMPH$^-$ collapses to the more stable base-attached 3′-dCMPH$^-$. [d] Calculated as E(anion) − E(dianion). All gas-phase dianion results should be treated with caution; see text. [e] Reference 6. [f] PCM model, using water as solvent with $\epsilon = 78$.

It is interesting to note that in aqueous solution the EA$_{ad}$ and VEA values of the neutral 3′-dCMPH are essentially the same as those of the anionic 3′-dCMP$^-$. This similarity seems to suggest that the electron affinities of the nucleotides are independent of the counterion in aqueous solution.

In conclusion, our theoretical investigation reveals that the 3′-dCMPH nucleotide is able to capture near 0 eV electrons to form a radical anion which lies energetically below the corresponding neutral species both in the gas phase and in aqueous solution. The excess electron is mostly located on the base of the nucleotide radical anion. The electron-detachment energy of this pyrimidine-based radical anion is sufficiently high that it is able to undergo subsequent phosphate−sugar C−O σ bond-breaking[6,7,9−12] or glycosidic bond-cleavage[5,8,13] processes before the autodetachment. Although the phosphate-centered radical anion of 3′-dCMPH is not stable in the gas phase, it should be viable in aqueous solution. This research also suggests that the electron affinities of the nucleotides are independent of the counterion in aqueous solution.

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Supporting Information Available: Complete ref 19. This material is available free of charge via the Internet at http://pubs.acs.org.

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