Article

One-Electron Oxidation of Neutral Sugar Radicals of 2′-Deoxyguanosine and 2′-Deoxythymidine: A Density Functional Theory (DFT) Study

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Ⓢ *Supporting Information*

ABSTRACT: One electron oxidation of neutral sugar radicals has recently been suggested to lead to important intermediates in the DNA damage process culminating in DNA strand breaks. In this work, we investigate sugar radicals in a DNA model system to understand the energetics of sugar radical formation and oxidation. The geometries of neutral sugar radicals $C_{1'}{}^{\bullet}$, $C_{2'}{}^{\bullet}$, $C_{3'}{}^{\bullet}$, $C_{4'}{}^{\bullet}$, and $C_{5'}{}^{\bullet}$ of 2′-deoxyguanosine (dG) and 2′-deoxythymidine (dT) were optimized in the gas phase and in solution using the B3LYP and ωB97x functionals and 6-31++G(d) basis set. Their corresponding cations ($C_{1'}{}^{+}$, $C_{2'}{}^{+}$, $C_{3'}{}^{+}$, $C_{4'}{}^{+}$, and $C_{5'}{}^{+}$) were generated by removing an electron (one-electron oxidation) from the neutral sugar radicals, and their geometries were also optimized using the same methods and basis set. The calculation predicts the relative stabilities of the neutral sugar radicals in the order $C_{1'}{}^{\bullet} > C_{4'}{}^{\bullet} > C_{5'}{}^{\bullet} > C_{3'}{}^{\bullet} > C_{2'}{}^{\bullet}$, respectively. Of the neutral sugar radicals, $C_{1'}{}^{\bullet}$ has the lowest vertical ionization potential (IP^{vert}), ca. 6.33 eV in the gas phase and 4.71 eV in solution. $C_{2'}{}^{\bullet}$ has the highest IP^{vert}, ca. 8.02 eV, in the gas phase, and the resultant $C_{2'}$ cation is predicted to undergo a barrierless hydride transfer from the $C_{1'}$ site to produce the $C_{1'}$ cation. One electron oxidation of $C_{2'}{}^{\bullet}$ in dG is predicted to result in a low lying triplet state consisting of $G^{+\bullet}$ and $C_{2'}{}^{\bullet}$. The 5′,8-cyclo-2′-deoxyguanosin-7-yl radical formed by intramolecular bonding between $C_{5'}{}^{\bullet}$ and C_8 of guanine transfers spin density from $C_{5'}$ site to guanine, and this structure has IP^{vert} 6.25 and 5.48 eV in the gas phase and in solution.
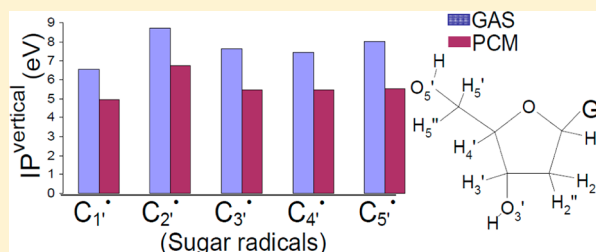
■ INTRODUCTION

The effects of ionizing radiation on DNA have been intensively investigated owing to the fact that DNA is the main target for biological important damage. Initially, radiation randomly ionizes each component of DNA and its surrounding, i.e., bases, sugar (deoxyribose), phosphate, and waters, producing highly reactive ion radical species.[1-12] The specific mechanisms of formation and reaction of these transient radical intermediates is of fundamental interest to understand the extent of DNA damage and related consequences. For example, the irradiation of DNA by a high-energy argon ion-beam (high linear energy transfer (LET) radiation) produced a far greater yield of neutral sugar radicals than ion radicals in the track core. Since these sugar radicals were formed in the track core, where excitations and ionizations are in proximity, it was proposed that excited-state cation radicals could be the direct precursors of the neutral sugar radicals.[13,14] On the basis of this hypothesis, the radical cations of nucleosides, nucleotides, and DNA and RNA oligomers were excited using UV−visible light to produce neutral sugar radicals, which were further characterized by the ESR (electron spin resonance) experiment as $C_{1'}{}^{\bullet}$, $C_{3'}{}^{\bullet}$, and $C_{5'}{}^{\bullet}$ sugar radicals.[15-23] This hypothesis was also supported by the excited state calculations of the radical cations of deoxyribonucleosides and several single-stranded dinucleosides.[17-19,23] $C_{5'}{}^{\bullet}$ sugar radical formation from one-electron oxidized 2′-deoxyguanosine (2′-dG$^{\bullet+}$) by proton coupled hole

transfer (PCHT) was proposed using theoretical calculations.[24] Using EPR/ENDOR sugar radicals at each of the carbon sites have been shown to result from direct radiation damage of nucleosides and nucleotides in the solid state.[25,26]

In the indirect effect of radiation, radicals are produced by the radiolysis of the water surrounding DNA, which reacts with DNA. The most important of these radicals is the hydroxyl radical ($OH^{\bullet}$), which readily reacts with DNA bases and the sugar phosphate backbone to produce base and sugar radicals.[1,27-33] The dominant reaction of $OH^{\bullet}$ is the addition reaction at C_4, C_5, and C_8 atoms of purines and C_5 and C_6 atoms of pyrimidines.[34-38] $OH^{\bullet}$ reacts with the sugar moiety by hydrogen abstraction and produces $C_{1'}{}^{\bullet}$, $C_{2'}{}^{\bullet}$, $C_{3'}{}^{\bullet}$, $C_{4'}{}^{\bullet}$, and $C_{5'}{}^{\bullet}$ sugar radicals. The rate of the hydrogen abstraction reaction by $OH^{\bullet}$ from different sites of the sugar unit depends on the accessibility of the sugar hydrogen atoms to the solvent, and the proposed order is H5′ > H4′ > H3′ ≈ H2′ ≈ H1′.[30-33] However, in several studies, $C_{1'}{}^{\bullet}$ sugar radical formation was observed predominantly.[39-44] For example, Bernhard and co-workers[39,40] report $C_{1'}{}^{\bullet}$ in abundance from X-irradiated DNA samples in aqueous solution or as a film, which is supported by work done by Greenberg and co-workers.[41,42] The relative

Table 1. B3LYP/6-31++G(d) and ωB97x/6-31++G(d) Calculated Vertical and Adiabatic Ionization Potentials (IPs) in eV of DNA/RNA Bases, Furanose, and Deoxyribose (Sugar)

molecule	B3LYP/6-31++G(d)		experiment[a]		ωB97x/6-31++G(d)	
	IP^{vert}	IP^{adia}	IP^{vert}	IP^{adia}	IP^{vert}	IP^{adia}
guanine	7.99	7.64	8.24	7.77	8.14 (8.00)[e]	7.71 (7.57)[e]
adenine	8.24	8.05	8.44	8.26	8.42 (8.32)[e]	8.16 (8.05)[e]
thymine	8.98	8.74	9.14	8.87	9.13 (9.05)[e]	8.81 (8.76)[e]
cytosine	8.67	8.56	8.94	8.68	8.86 (8.78)[e]	8.74 (8.65)[e]
uracil	9.45	9.24	9.50	9.32	9.60 (9.50)[e]	9.30 (9.21)[e]
furanose	9.61	8.93		(ca. 9.3)[b]	10.18 (10.06)[c]	9.24 (9.05)[c]
1'-NH$_2$-furanose[d]	8.66	8.04			9.02 (8.97)[e]	8.21 (8.17)[e]

[a]References 82 and 83. [b]An experimental value for only the α-pyranose form (9.1 eV IP^{adia}) has been reported.[84] Calculations in ref 84 suggest that the furanose IP^{adia} will be 0.2 eV higher or 9.3 eV. [c]Calculated using the ωB97x/cc-pVTZ method.[84] [d]See Figure S1 in the Supporting Information. [e]Calculated using the ωB97x/cc-pVTZ method.

stability of the different sugar radicals have been calculated by several workers,[45−49] and the order is generally found to be $C_{1'}^{\bullet}$ > $C_{4'}^{\bullet}$ > $C_{5'}^{\bullet}$ > $C_{3'}^{\bullet}$ > $C_{2'}^{\bullet}$.

Carbon centered neutral sugar radicals in DNA/RNA are known to lead to base release, strand breaks, or cross-link formation.[50−58] It has also been reported that sugar radicals may be the locus for further oxidation by several chemical species.[27,28,30−33,50−60] In fact, double oxidation events have been suggested that involve first oxidation of the sugar to form the sugar radical with a second subsequent oxidation of the sugar radical to form a nonradical damage site. These nonradical double oxidized sugars are suggested to result in DNA strand breaks and are thus suggested to be important intermediates in DNA damage processes. In this context, the study of the ionization potential of these sugar radicals are of both chemical and biological interest.

Our goal in this work is to test the hypotheses put forward by Bernhard and co-workers[26] to account for the fact that stand breaks in DNA were found to be more abundant than sugar radicals trapped at low temperatures. They proposed that one electron oxidation of sugar radicals by one electron oxidized DNA bases leads to nonradical damage that results in DNA strand breaks. Our present work gives the energetics of the first step in the process, i.e., one electron oxidation of the sugar radicals of two model systems 2'-deoxyguanosine and 2'-deoxythymidine. The oxidation is found to be favorable for most of the sugar radical species but shows there would be a DNA base dependence for certain sugar radical oxidations. Most intriguing is our prediction that oxidation of the C2' radical of dG leads to a low lying triplet state consisting of G$^{+\bullet}$ and $C_{2'}^{\bullet}$.

■ METHOD OF CALCULATIONS

In this work, we employ both the B3LYP and ωB97x methods. B3LYP has been found to be an excellent and cost-effective choice for calculating various molecular properties of DNA bases in neutral and radical states.[5,61−73] The ωB97x functional, recently developed by Chai and Head-Gordon,[74] is also a good choice to describe the ionization energies of molecules. Therefore, in the present study, both methods are employed to calculate the ionization potentials of sugar radicals of 2'-deoxyguanosine and 2'deoxythymindine.

The geometries of the sugar radicals ($C_{1'}^{\bullet}$, $C_{2'}^{\bullet}$, $C_{3'}^{\bullet}$, $C_{4'}^{\bullet}$, and $C_{5'}^{\bullet}$) of 2'-deoxyguanosine and 2'-deoxythymidine in the gas phase and in solution were fully optimized using the B3LYP/6-31++G(d) and ωB97x/6-31++G(d) methods. The geometries of one-electron oxidized sugar radicals ($C_{1'}^{+}$, $C_{2'}^{+}$,

$C_{3'}^{+}$, $C_{4'}^{+}$, and $C_{5'}^{+}$) were optimized using the same methods and basis set in the gas phase and in solution by considering the corresponding optimized geometries of the sugar radicals as input. The effect of bulk aqueous solution was modeled through the use of the self-consistent reaction field and the integral equation formalism polarized continuum model (IEFPCM) having dielectric constant ε = 78.4 as implemented in the Gaussian09 program.[75] All the calculations were performed using the Gaussian09 suite of programs.[75] Gauss-View molecular modeling software[76] was used to plot the spin density distribution around the molecule, and JMOL molecular modeling software was used to draw the molecular structures.[77]

■ RESULTS AND DISCUSSION

Suitability of the Method. We considered DNA/RNA bases (adenine (A), guanine (G), cytosine (C), thymine (T), and uracil (U)) and deoxyribose (sugar) moiety as test cases and calculated their vertical and adiabatic ionization potentials (IPs) using the B3LYP/6-31++G(d) method. The calculated IPs by the B3LYP/6-31++G(d) method were compared with the available experimental estimates of the IPs of theses bases and sugar; see Table 1. This test is necessary to establish the reliability of the chosen method because, to the best of our knowledge, the IPs of sugar radicals have not been determined experimentally. The IPs of DNA bases have been extensively studied using ab initio and DFT methods and well documented in the literature.[7,8,78−81] In Table 1, we compared our B3LYP/6-31++G(d) calculated IP values with experiment for method suitability purposes only, and for more details, see recent reviews.[7,8,79] From Table 1, we found that the vertical and adiabatic IP (IP^{vert} and IP^{adia}) of A, G, C, T, and U are in good agreement with the experimental IP values.[82,83] The maximum difference between theory and experiment for IP^{vert} is 0.27 eV and for IP^{adia} is 0.21 eV, respectively, see Table 1. Very recently, using tunable vacuum ultraviolet (VUV) synchrotron radiation coupled to an effusive thermal source, the ionization energy (AIE) of deoxyribose (sugar) gas phase has been reported to be 9.1($\pm$0.05) eV[84] in the pyranose form. However, the structure of furanose is appropriate for modeling the structure of deoxyribose (sugar) in DNA, thus, we calculated the vertical and adiabatic IPs of furanose using the B3LYP/6-31++G(d) method, and the values are IP^{vert} (9.61 eV) and IP^{adia} (8.93 eV), respectively. The corresponding values calculated using the ωB97x/cc-pVTZ method in ref 84 are 10.06 and 9.05 eV, respectively; see Table 1. Identical calculations for the pyranose form gave 9.6 and 8.8 eV, respectively.[84] In our calculation, we also considered deoxyribose (sugar) moiety with NH$_2$

substitution at the $C_{1'}$ site (see Figure S1 in the Supporting Information) and calculated the IPs using the B3LYP/6-31++G(d) and ωB97x/cc-pVTZ methods; see Table 1. As pointed out above, in comparison to experiment, the B3LYP/6-31++G(d) values are found to be good estimates.

The ωB97x/6-31++G(d) method was also used to calculate the ionization potentials of the test cases presented in Table 1; we find that the combination of ωB97x functional with 6-31++G(d) basis set provides the best estimate of the ionization potentials. The calculated IPs by the ωB97x/6-31++G(d) method are in close agreement with the experimental IPs values having a maximum difference of less than 0.1 eV, see Table 1. Since the B3LYP/6-31++G(d) method is also able to give good estimates of the IPs of molecules, we employ both methods to estimate the IPs of sugar radicals of 2'-deoxyguanosine and 2'-deoxythymidine.

Geometries and Relative Stabilities. The B3LYP/6-31++G(d) optimized geometries of sugar radicals ($C_{1'}{}^{\bullet}$, $C_{2'}{}^{\bullet}$, $C_{3'}{}^{\bullet}$, $C_{4'}{}^{\bullet}$, and $C_{5'}{}^{\bullet}$) of 2'-deoxyguanosine and their corresponding cations (one-electron oxidized sugar radicals) in the gas phase and in solution are presented in Figures S2 and S3 in the Supporting Information. From the calculation, it is evident that the optimized geometries of sugar radicals in the gas phase are similar to those optimized using the PCM model for solution effects. On the formation of $C_{1'}$ radical, a significant conformational change occurs at the $C_{1'}$ site of the sugar ring. The $C_{1'}$ atom, which was nonplanar (the sum of the three angles ($N9-C_{1'}-O + O-C_{1'}-C_{2'} + C_{2'}-C_{1'}-N9$) is ca. 329°) in the 2'-deoxyguanosine (see Figure S1 in the Supporting Information) becomes quite planar in gas phase, and the sum of the corresponding angle is ca. 349°. In $C_{2'}$ radical, $C_{2'}$ atom becomes completely planar, and the sum of the angles centering the $C_{2'}$ atom is ca. 360°. In $C_{3'}$, $C_{4'}$, and $C_{5'}$ radicals, the sum of the angles centering the $C_{3'}$, $C_{4'}$, and $C_{5'}$ atoms are 345, 357, and 353°, respectively. Thus, on radical formation, the $C_{2'}$, $C_{4'}$, and $C_{5'}$ radicals become planar, while $C_{1'}$ and $C_{3'}$ radicals have small nonplanarity. The B3LYP/6-31++G(d) calculation predicts the relative stability of the sugar radicals in the order $C_{1'}{}^{\bullet} > C_{4'}{}^{\bullet} > C_{5'}{}^{\bullet} > C_{3'}{}^{\bullet} > C_{2'}{}^{\bullet}$, which is in agreement with the earlier studies. On one-electron oxidation, large structural changes, mainly in the sugar moiety, are taking place. Cross-linking between $C_{2'}$ and C_8 (guanine) atoms was found on the formation of $C_{2'}$ cation in the gas phase; however, in solution, this cross-link is absent, and the the $O_{3'}$ atom makes a bond with the $C_{2'}$ atom; see Figure S3 in the Supporting Information. $C_{4'}$ and $C_{5'}$ cations show sugar ring fragmentation in the gas phase; see Figure S3 in the Supporting Information. The cross-link formation or sugar ring fragmentation is not unusual and has been found experimentally.[27,28,33] $C_{1'}$ and $C_{3'}$ cations were found to retain their parent neutral sugar radical structure and radical site becomes planar, i.e., the sum of the angles centering $C_{1'}$ and $C_{3'}$ atoms is 360°; see Figures S2 and S3 in the Supporting Information. Except for $C_{2'}{}^+$, the optimization of $C_{1'}{}^+$, $C_{3'}{}^+$, $C_{4'}{}^+$, and $C_{5'}{}^+$ in solution are found to retain their parent sugar radical structure; see Figures S2 and S3 in the Supporting Information. The relative vertical stabilities of the cations in the gas phase and in solution follow the order $C_{1'}{}^+ > C_{4'}{}^+ > C_{5'}{}^+ > C_{3'}{}^+ > C_{2'}{}^+$.

The ωB97x/6-31++G(d) calculated geometries of sugar radicals and their cations in the gas phase and in solution are given in Figures S4 and S5 in the Supporting Information. The optimized geometries by the ωB97x/6-31++G(d) method are in close agreement with those optimized using the B3LYP/6-31++G(d) method. The ωB97x/6-31++G(d) method also shows that, on radical formation, the sugar radical sites become planar, and the sum of the angles centering the $C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, and $C_{5'}$ radical sites are 347, 360, 343, 354, and 352°, respectively, and on cation formation, the corresponding angles are 360, 357, 360, 360, and 358°, respectively. The optimization of the cations ($C_{1'}{}^+$, $C_{2'}{}^+$, $C_{3'}{}^+$, $C_{4'}{}^+$, and $C_{5'}{}^+$) by the ωB97x/6-31++G(d) method in the gas phase shows that $C_{1'}$ and $C_{3'}$ cations retain their parent sugar radical structure. However, $C_{2'}$, $C_{4'}$, and $C_{5'}$ cations show bond formation between $O_{3'}$ and $C_{2'}$ atoms of the sugar ring in $C_{2'}{}^+$ and $C_{1'}-O$ bond dissociation in $C4_{'}{}^+$ and $C_{5'}{}^+$. The optimization of cations in the solution using the PCM model retain their parent radical structure except for $C_{2'}{}^+$, which shows $O_{3'}$ and $C_{2'}$ bond formation as found in the gas phase; see Figures S4 and S5 in the Supporting Information.

Spin Density Distribution and Ionization Potentials. The B3LYP/6-31++G(d) calculated Mulliken spin density distributions in sugar radicals from 2'-dexoyguanosine are shown in Figure 1. In the Supporting Information the
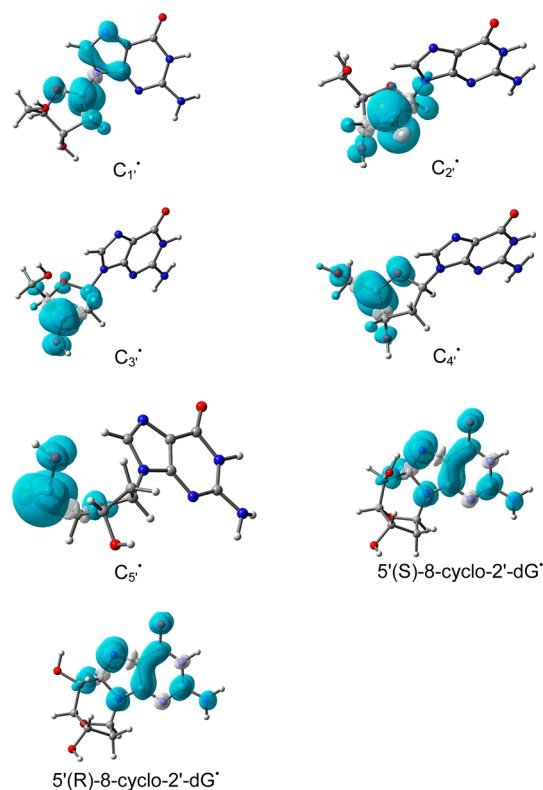
Figure 1. B3LYP/6-31++G(d) calculated Mulliken spin density distribution in sugar radicals ($dG(C_{1'}{}^{\bullet})$ − $dG(C_{5'}{}^{\bullet})$) and in 5',8-cyclo-2'-deoxyguanosin-7-yl radical in their two diastereoisomeric forms. Spin densities were calculated with 0.002 electron/bohr^3.

calculated atomic spin densities at each atom and the isotropic hyperfine coupling constants are given (Table S2). The spin density distribution of a molecule provides the distribution of the odd electron within the molecule and is usually in close accord with the singly occupied molecular orbital (SOMO). In our calculation, both the methods (B3LYP/6-31++G(d) and ωB97x/6-31++G(d)) showed that, for $C_{2'}$ and $C_{5'}$ radicals, the spin and SOMO distributions differ with each other. In these two cases ($C_{2'}$ and $C_{5'}$ radicals), the spin was localized on the $C_{2'}/C_{5'}$ atom, while the SOMO was localized on the guanine

Table 2. B3LYP/6-31++G(d) and ωB97x/6-31++G(d) Calculated Vertical and Adiabatic Ionization Potentials (IPs) in eV of Neutral Sugar Radicals of 2'-Deoxyguanosine (dG) in Gas Phase and in Aqueous Solution

sugar radical of dG	B3LYP/6-31++G(d)				ωB97x/6-31++G(d)			
	gas phase		aqueous phase[a]		gas phase		aqueous phase[a]	
	IP^{vert}	IP^{adia}	IP^{vert}	IP^{adia}	IP^{vert}	IP^{adia}	IP^{vert}	IP^{adia}
dG(C$_1$'$^{\bullet}$)	6.33	5.34	4.71	3.82	6.56	5.33	4.97	3.83
dG(C$_2$'$^{\bullet}$)	8.02[b]	c	6.41	c	8.71[b]	c	6.75	c
dG(C$_3$'$^{\bullet}$)	7.28	6.44	5.29	4.31	7.65	6.47	5.43	4.29
dG(C$_4$'$^{\bullet}$)	7.17	c	5.31	4.33	7.44	c	5.43	4.33
dG(C$_5$'$^{\bullet}$)	7.50	6.86	5.44	4.63	7.97	6.84	5.52	4.67

[a]Calculated using IEFPCM model with ε = 78.38. [b]Restricted open shell B3LYP/6-31++G(d) and ωB97x/6-31++G(d) calculated values are 7.98 and 8.66 eV, respectively. [c]Optimized structures underwent significant rearrangements that did not correspond to their parent sugar radical structure; see Figures in the Supporting Information.

Scheme 1. Reaction of C$_1$'$^{\bullet}$ with Oxygen to Form the Cation and Its Reaction with Water to Form the 2'-Deoxyribonolactone
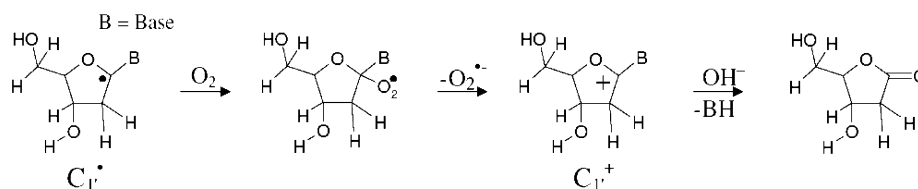
Table 3. B3LYP/6-31++G(d) and ωB97x/6-31++G(d) Calculated Vertical and Adiabatic Ionization Potentials (IPs) in eV of Neutral Sugar Radicals of 2'-Deoxythymidine in Gas Phase and in Aqueous Solution[a]

sugar radical	B3LYP/6-31++G(d)				ωB97x/6-31++G(d)			
	gas phase		aqueous phase[b]		gas phase		aqueous phase[b]	
	IP^{vert}	IP^{adia}	IP^{vert}	IP^{adia}	IP^{vert}	IP^{adia}	IP^{vert}	IP^{adia}
dT(C$_1$'$^{\bullet}$)	6.59	5.60	4.83	3.85	6.90	5.60	5.20	3.85
dT(C$_2$'$^{\bullet}$)	8.43		6.50		8.83		6.69	
dT(C$_3$'$^{\bullet}$)	7.38	6.56	5.26	4.37	7.70	6.22	5.38	4.34
dT(C$_4$'$^{\bullet}$)	7.65		5.42		7.94		5.53	4.44
dT(C$_5$'$^{\bullet}$)	7.77		5.32	4.55	8.07		5.43	4.61

[a]See Figures S6 and S7 in the Supporting Information. [b]Calculated using IEFPCM model with ε = 78.38.

base. This was observed for the C$_2$' radical by the B3LYP method and for C$_2$' and C$_5$' radicals by the ωB97x method. This discrepancy is often found to occur when two portions of a radical have energetically near equal IPs that are not well coupled electronically in the half filled orbital. This issue was overcome by the use of the restricted open shell method for these two cases; however, little difference (<0.05 eV) in IP between the restricted and unrestricted calculations was found (Table 2). For the C$_1$' radical, the most of the spin density (>90%) is located on the C$_1$' atom with a small delocalization on C5, C8, and N7 atoms of guanine, see Figure 1. Likewise, in C$_2$' to C$_5$' radicals, the spin density are localized on the single carbon site of the sugar ring. Thus, the present calculation suggests that further oxidation would be from the radical sites of these carbon-centered sugar radicals. Our theoretical predictions are further supported by several experiments that suggest the formation of carbon-centered sugar cations. Using quantitative kinetic measurements, the mechanism of C$_1$' radical oxidation of 2'-deoxyuridin-1'-yl radical has been explored in detail.[58] The C$_1$' radical reacts with O$_2$ to form peroxyl radical with rate constant 1×10^9 M^{-1} s^{-1}, which release O$_2^-$ with a rate constant of 1.5×10^4 s^{-1} to produce C$_1$' cation. The further reaction of C$_1$'$^+$ with water produces 2'-deoxyribonolactone as shown in Scheme 1.[27,58]

In addition, the formation of C$_2$' radical and its cation C$_2$'$^+$ were experimentally observed from the photoreaction of 2'-iododeoxyuridine by Sugiyama et al.[85] and C$_1$'$^+$ was produced by the 1',2'-shift of C$_1$'–H to C$_2$'. The oxidation of C$_4$' radical to give C$_4$'$^+$ by bleomycin/Fe^{2+}/O$_2$ complex has been supported by the experiments of Stubbe et al.[86] and Giese and co-workers.[87] The chemistry of C$_5$' radical proceeds as (i) formation of cross-link between C$_5$' and C8 atoms of purines with reaction rate constant ($k_c = 1.6 \times 10^5$ s^{-1}) and (ii) the formation of C$_5$'$^+$ by the oxidation reaction with K$_3$Fe(CN)$_6$, and the rate constant of the reaction was reported to be ca. 10^9 M^{-1} s^{-1}.[27,88]

The B3LYP/6-31++G(d) and ωB97x/6-31++G(d) calculated ionization potentials of sugar radicals of 2'-deoxyguanosine in gas phase and in solution are presented in Table 2. From Table 2, it is evident that C$_1$' radical has the lowest vertical ionization potential in the gas phase and in solution and the calculated values are gas phase (solution) 6.33(4.71) eV by the B3LYP/6-31++G(d) and 6.56(4.97) eV by the ωB97x/6-31++G(d). For dG(C$_2$') radical, the restricted B3LYP/6-31++G(d) and ωB97x/6-31++G(d) calculations give the gas phase vertical IP as 7.98 and 8.66 eV, respectively, which is the highest among all the considered radicals; see Table 2. For this case, we found that the vertical triplet state of dG(C$_2$'$^+$) is more stable than the vertical singlet state of dG(C$_2$'$^+$), discussed later.
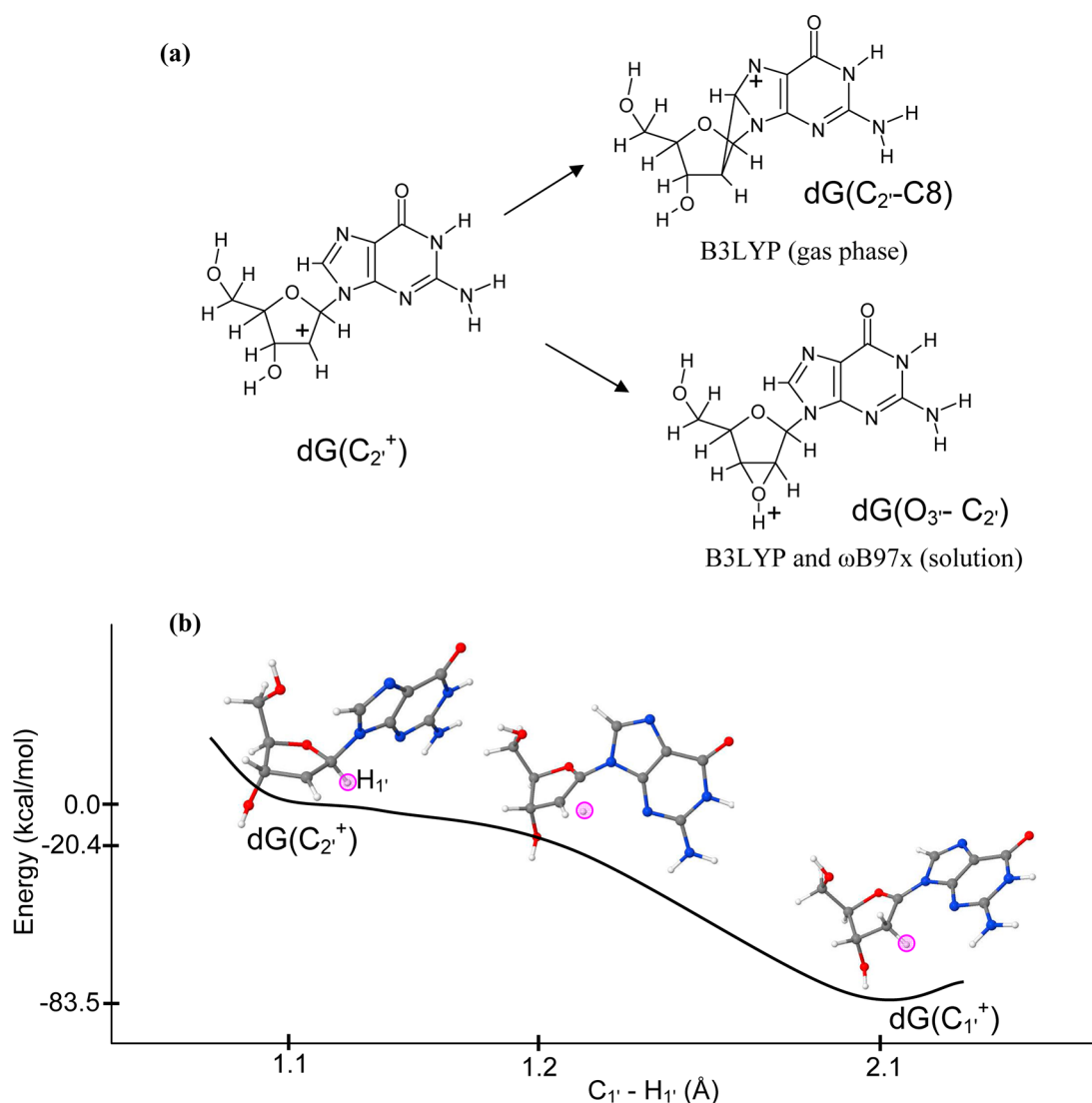
Figure 2. (a) Full optimization of dG(C$_{2'}$$^+$) in its singlet state resulted in a cross-link between C$_{2'}$−C8 by the B3LYP/6-31++G(d) in the gas phase and O$_{3'}$−C$_{2'}$ bond formation in solution (PCM) by the B3LYP/6-31++G(d) and ωB97x/6-31++G(d). (b) The ωB97x/6-31++G(d) constrained optimization of dG(C$_{2'}$$^+$) produced dG(C$_{1'}$$^+$) through H$_{1'}$ hydride transfer from C$_{1'}$ to C$_{2'}$ in solution using PCM model. Reaction proceeds barrierless in the gas phase and in solution. The pink circle shows the position of the transferring H$_{1'}$ atom during the reaction. Energies and distances shown are not to the scale.

Thus, the present calculation predicts that C$_{1'}$$^\bullet$ is the most probable site for oxidation followed by C$_{3'}$$^\bullet$, C$_{4'}$$^\bullet$, and C$_{5'}$$^\bullet$. The vertical ionization potential of C$_{2'}$$^\bullet$ in gas phase is 8.02−8.71 eV, and thus, it is the most difficult to oxidize. The IP of C$_{2'}$$^\bullet$ is also comparable to the IPs of guanine (7.99−8.14 eV) and adenine (8.24−8.42 eV); see Table 1, and thus, the ionization of purines in comparison to C$_{2'}$$^\bullet$ may be favored. The ionized C$_{2'}$$^\bullet$ radical (C$_{2'}$$^+$) is experimentally found to be highly reactive,[85] which is confirmed by our calculation as discussed in the next section. The vertical gas phase ionization potentials (IP^{vert}) of C$_{1'}$$^\bullet$, C$_{2'}$$^\bullet$, C$_{3'}$$^\bullet$, C$_{4'}$$^\bullet$, and C$_{5'}$$^\bullet$ lie in the order C$_{1'}$$^\bullet$ < C$_{4'}$$^\bullet$ ≈ C$_{3'}$$^\bullet$ < C$_{5'}$$^\bullet$ < C$_{2'}$$^\bullet$; see Table 2. The calculated adiabatic IPs of C$_{1'}$$^\bullet$, C$_{3'}$$^\bullet$, and C$_{5'}$$^\bullet$ are quite low in solution and they lie in the range 3.82−4.67 eV; see Table 2

A small delocalization of spin on N9, C4, C8, and N7 atoms of guanine is seen from the spin density distribution maps (Figure 1) of C$_{1'}$ radical and suggests that guanine may influence the IP of this sugar radical and perhaps others. Since guanine has the lowest IP and thymine has the highest IP of all

the bases, comparing 2′-deoxythymidine with 2′-deoxyguanosine should provide a good test of the effect of the base on the IP of the sugar radicals. The calculated vertical and adiabatic IPs of 2′-deoxythymidine in the gas phase and in solution by the B3LYP and ωB97x methods are presented in Table 3. From Table 3, we see that IP of the sugar radicals of 2′-deoxythymidine are generally only slightly higher than the IPs of sugar radicals of 2′-deoxyguanosine; see Table 2. This small effect is reflected in the small delocalization of spin found for the C$_{1'}$ radical in dT (Figure S9, Supporting Information) which is similar to that found for the C$_{1'}$ radical in dG (Figure 1). The dT(C$_{1'}$$^\bullet$) has the lowest and dT(C$_{2'}$$^\bullet$) has the highest IP as found for the other two cases (Tables 2 and T1 in the Supporting Information). The high reactivity of dT(C$_{2'}$$^+$) is also evidenced. The optimization of dT(C$_{2'}$$^+$) by both the methods show rearrangement that transfers the thymine base from C$_{1'}$ to C$_{2'}$ through N1−C2 bond formation in the gas phase; see Figure S6 in the Supporting Information. In solution, however, a barrierless hydrogen atom transfer from C$_{3'}$ to C$_{2'}$

occurs resulting in $C_{3'}^+$; see Figure S7 in the Supporting Information. This reaction, i.e., the formation of $dT(C_{3'}^+)$ from $dT(C_{2'}^+)$ through 1,2-shift of $C_{3'}-H$ to the $C_{2'}$ carbocation, has been proposed from experimental studies for $dU(C_{3'}^+)$ formation from $dU(C_{2'}^+)$ via 1,2-shift of $C_{3'}-H$ to the $C_{2'}$ carbocation.[85]

We note that we also considered another model by replacing the guanine base with NH_2 group at the $C_{1'}$ atom of the sugar ring; see Figure S1 and Table T1 along with discussion in the Supporting Information. This was less informative as the NH_2 group actually lowered the IPs more than the guanine.

$1',2'$-Hydride Shift of $C_{1'}-H$ to $C_{2'}$ in $C_{2'}^+$ Singlet State. As we mentioned, $C_{2'}^\bullet$ has the highest IP among all the sugar radicals considered in the present study, and its cation is highly reactive. The full optimization of $C_{2'}^+$ by the B3LYP method in its singlet state results in a cross-link between C8(guanine) and $C_{2'}$ of the sugar ring in the gas phase and bond formation between $O_{3'}$ and $C_{2'}$ atoms in solution, which is obtained by both B3LYP and ωB97x methods; see Figure 2a. The $O_{3'}$ and $C_{2'}$ bonding is not possible in DNA because $O_{3'}$ is rigidly attached to the phosphate group. This bonding is also absent in the optimized radical structure; therefore, we optimized the $C_{2'}^+$ structure in the gas phase and in solution by constraining the $O_{3'}-C_{3'}-C_{2'}-C_{1'}$ as present in $C_{2'}^\bullet$. This constrained optimization by the ωB97x/6-31++G(d) shows a barrierless transformation of $C_{2'}^+$ to $C_{1'}^+$ by hydride transfer, see Figure 2b. Our calculation supports the experimental observation of the formation of $C_{1'}^+$ from $C_{2'}^+$ by the $1',2'$-shift of $C_{1'}-H$ to $C_{2'}$ by Sugiyama et al.[85] The B3LYP/6-31++G(d) method shows the cross-linking of C8(guanine) and $C_{2'}$ in the solution. This calculation clearly provides evidence that $C_{2'}^+$ is a very short-lived species if formed and is highly reactive and able to oxidize $C_{1'}$ or the purine base.

$C_{2'}^+$ Triplet State in $dG(C_{2'}^+)$. Another interesting aspect of $dG(C_{2'}^+)$ is that the vertical triplet state (T) lies lower in energy than the singlet state (S) as calculated by both the ωB97x/6-31++G(d) and B3LYP/6-31++G(d) methods; see Figure 3. This is a consequence of the low IP of G, which
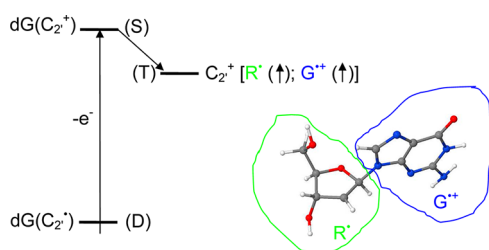
Figure 3. Schematic diagram of the vertical ionization of $C_{2'}^\bullet$ of 2′-deoxyguanosine in the doublet (D) state. The vertical triplet state (T) is lower in energy than the singlet (S) state of $dG(C_{2'}^+)$ as calculated by both the ωB97x/6-31++G(d) and B3LYP/6-31++G(d) methods. In the triplet state, spins (shown by upward arrows) are localized on guanine (G) and deoxyribose (R) making a diradical.

transfers an electron to the $C_{2'}$ site and is therefore not expected for $dT(C_{2'}^+)$. In the triplet state spins (shown by upward arrows in Figure 3) are localized on guanine (G) and at $C_{2'}$ in the deoxyribose (R) effectively making a diradical. Thus, after intersystem crossing to the triplet state, the reactivity of $dG(C_{2'}^+)$ would be determined by the diradical nature of the intermediate. The formation of $dG(C_{1'}^+)$ and the $dG(C_{2'}-C8)+$

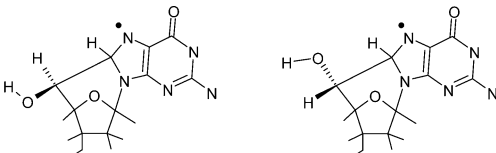might be explained by hydrogen atom shift and radical–radical reaction, respectively.

Cyclization of C5′ and C8. The cyclization of C5′ and C8 has been observed experimentally.[50,51] The underlying mechanism of this cyclization is the initial formation of the $C_{5'}$ radical, which binds with C8 atom of guanine or adenine with cyclization rate constant of $1.6 \times 10^5\ s^{-1}$. The cyclic radical structure has two diastereoisomeric forms: (i) $5'(S)$,8-cyclo-2′-deoxyguanosin-7-yl and (ii) $5'(R)$,8-cyclo-2′-deoxyguanosin-7-yl. Using the B3LYP/6-31++G(d) and ωB97x/6-31++G(d) methods, we optimized the geometries of these two isomers in their radical and cation states. Our structural optimization showed that the sugar ring of these cyclic structures adopt the O-exo conformation (Figure S8 in the Supporting Information) as found in earlier studies using NMR spectroscopy[89] and theory.[90,91] The calculated spin density distribution of these two isomers in their radical state are shown in Figure 1. From Figure 1, it is clearly evident that spin density in these isomers resides mainly on the guanine base. Thus, on cyclization, spin density is transferred from the $C_{5'}$ site to the guanine in these two isomers. The calculated IPs of these two isomers in the gas phase and in solution lie in the range ca. 4.3−6.3 eV; see Table 4. From the IP values, it is inferred that these cyclic radical structures in DNA would undergo electron transfer to one electron oxidized bases in DNA.

■ CONCLUSIONS

From the present study, we found that each of the neutral sugar radicals (except for $C_{2'}$) have lower IPs than the DNA bases and thus can be a locus for oxidation. $C_{1'}$ radical has the lowest ionization potential (6.33 eV IP^{vert}), while $C_{2'}$ radical has the highest ionization potential (8.02 eV IP^{vert}). Our calculations predict that not only is the $C_{2'}$ radical far more difficult to be oxidize than the other sugar radicals but its cation ($C_{2'}^+$) is highly reactive and undergoes barrierless hydride transfer from $C_{1'}$ or $C_{3'}$ resulting in the formation of $C_{1'}^+$ and $C_{3'}^+$. This reaction has been found experimentally by Sugiyama et al.[85] Another intriguing feature is that, for $dG(C_{2'}^+)$, the triplet state lies lower and that it is a diradical in nature with spin localizing on both the base and the sugar; see Figure 3. This theoretical finding is considered significant, and the triplet (diradical) should live long enough for hole transfer to neighboring bases or sites of lower ionization potential to take place as shown in the schematic diagram in Figure 4. This theoretical prediction needs experimental verification. Thus, the overall conclusions we have for $C_{2'}^+$ are that it is a very reactive species and that different reaction paths are possible as explained above.

The calculated IP of the sugar radicals by both methods employed, B3LYP and ωB97x, are in close agreement particularly the adiabatic ionization potentials. Except for $C_{2'}^\bullet$, the B3LYP/6-31++G(d) calculated vertical ionization potential values of $C_{1'}^\bullet$, $C_{3'}^\bullet$, $C_{4'}^\bullet$, and $C_{5'}^\bullet$ are slightly less than the likely more reliable ωB97x/6-31++G(d) values, see Tables 2, 3, and T1 in the Supporting Information. Both the methods are found to be suitable for the calculation of the ionization potentials of molecules. The reactivity of the $dG(C_{2'}^+)$ to produce $dG(C_{1'}^+)$ by hydride transfer is well reproduced by the ωB97x/6-31++G(d) method; see Figure 2b. The B3LYP/6-31++G(d) method predicts the cross-linking between $C_{2'}$ and C8. For $dT(C_{2'}^+)$, both the methods show $d(C_{3'}^+)$ formation by barrierless hydride transfer from $C_{3'}$ to $C_{2'}$ in solution (Figure S7 in the Supporting Information), which is observed experimentally.[85] The $C_{5'}$ sugar radical is formed in significant

Table 4. B3LYP/6-31++G(d) and ωB97x/6-31++G(d) Calculated Vertical and Adiabatic Ionization Potentials in eV of 5′,8-Cyclo-2′-deoxyguanosin-7-yl Radical in Gas Phase and in Aqueous Solution

5′(S)-8-cyclo-2′-dG-7-yl radical   5′(R)-8-cyclo-2′-dG-7-yl radical

| 5′,8-cyclo-2′-deoxyguanosin-7-yl radical | B3LYP/6-31++G(d) | | | | ωB97x/6-31++G(d) | | | |
| | gas phase | | aqueous phase[a] | | gas phase | | aqueous phase[a] | |
	IP^{vert}	IP^{adia}	IP^{vert}	IP^{adia}	IP^{vert}	IP^{adia}	IP^{vert}	IP^{adia}
5′(S)	6.34	5.89	4.66	4.31	6.38	5.85	4.70	4.29
5′(R)	6.25	5.90	4.58	4.29	6.33	5.88	4.64	4.28

[a]Calculated using IEFPCM model with ε = 78.38.
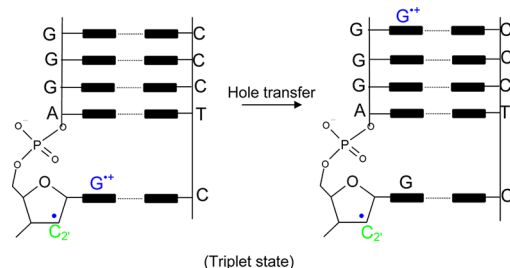
Figure 4. Proposed schematic of possible hole transfer in the triplet state of dG(C$_{2'}^+$) after one electron oxidation of dG(C$_{2'}^\bullet$).

amounts by radiation[92] and is known to undergo facile attack at C8 in guanine to produce a cyclized species, the 5′,8-cyclo-2′-deoxyguanosin-7-yl radical in two diastereoisomeric (R) and (S) forms.[50,51] The ionization potentials of these radicals (Table 4) are relatively low 6.25−6.28 eV (gas phase IP^{vert}) and 4.58−4.70 eV (solution IP^{vert}), and in keeping with these low IPs, these cross-links in DNA are readily further oxidized to form the diamagnetic products, i.e., 5′,8-cyclo-2′-deoxyguanosine isomers.

ASSOCIATED CONTENT

S Supporting Information

B3LYP/6-31++G(d) and ωB97x/6-31++G(d) optimized geometries of sugar radicals of 2′-deoxyguanosine and 2′-deoxythymidine and their corresponding cations, 5′-8-cyclo-2′-dG in their radical and cation states. Calculated vertical ionization potentials (IPs) for sugar radicals for a 1′-NH2-furanose model system. Mulliken spin density distribution in sugar radicals (dT(C1′●)−dT(C5′●)). Calculated isotropic hyperfine couplings for the sugar radicals of 2′-deoxyguanosine (dG). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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