ACCOUNTS
of chemical research

Elementary Lesions in DNA Subunits: Electron, Hydrogen Atom, Proton, and Hydride Transfers

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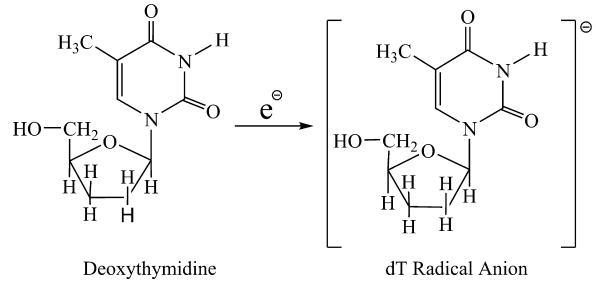
RECEIVED ON MARCH 5, 2008

CONSPECTUS

When DNA is damaged by ionizing radiation, the genes in a cell may acquire mutations or the cell could die. The smallest known DNA-damaging unit is an electron, often low-energy secondary electrons. Additional electrons and transfers involving hydrogen atoms, protons, and hydride anions can damage DNA subunits, including individual nucleobases and nucleoside pairs. Researchers would like to better understand the molecular mechanisms involved in DNA damage from ionizing radiation. In this Account, we highlight our theoretical investigations of the molecular mechanisms of DNA damage using quantum mechanical models. Our investigations use robust theoretical methods with computations conducted in the gas phase and with solution models.



We calculate adiabatic electron affinities (AEAs), which describe the energetics of electronic attachment to closed-shell DNA subunits, for the free bases, nucleosides, nucleotides, base pairs, and single and double DNA strand units. Electron affinities for free nucleobases yield the order uracil > thymine > cytosine > guanine > adenine and the same order for the DNA nucleosides, mononucleotides, and nucleoside 3′,5′-diphosphates. AEA values increase steadily with the size and complexity of the system because of greater hydration, glycosylation, nucleotide formation, and base pairing. We predict and experimental results partially confirm that most of the more complex and hydrated species are observable as radical anions. Our modeling studies indicate that depyrimidination reactions of radical anion nucleosides release cytosine more often than thymine. Recent experimental results support those findings.

Our theoretical studies of DNA base-pair radical anions predict increases in electron affinity accompanying H bonding and solvation. Electron addition facilitates some proton transfers in these pairs, which results in strongly perturbed pairing configurations. Of all nucleobase moieties within the more complex radical anion systems, thymine is best able to retain a negative charge. Charge and spin are well-separated in some of these systems.

Radical species derived via hydrogen abstraction from DNA subunits yield large AEA values because they form closed-shell anions. Our studies predict single-strand breaks following H abstraction from nucleotides. Some H-abstraction processes in the DNA base pairs lead to severe distortions in pairing configuration based on our calculations.

This body of systematic theoretical studies provides realistic descriptions of some events that lead to elementary DNA lesions, while providing rationalizations for many observed phenomena. Such approaches can lead to the design of new experiments, which would contribute to our understanding of the chemical physics of nucleic acids.

Introduction

DNA damage following the effects of ionizing radiation is a well-known phenomenon,[1] which, if unrepaired, may result in mutations or cell death. Perhaps the smallest DNA-damaging agent is the *electron*, produced as secondary electrons (often in the low-energy range) upon irradiation of DNA. This Account focuses on DNA damage arising from the addition of electrons and transfers involving hydrogen atoms, protons, and hydride anions in DNA subunits ranging from nucleobases to nucleoside pairs. Quantum mechanical models for

Published on the Web 02/20/2009 www.pubs.acs.org/acr
10.1021/ar800077q CCC: $71.50

molecular structure have been applied extensively in this laboratory to investigate such elementary processes, forming the subject matter of this Account. This research is applicable to present and future experiments on biomolecules in gas and solution phases.

Systems reviewed here are classified as (a) closed-shell DNA subunits, to which an electron attaches itself, (b) hydrogen-abstracted neutral radicals derived from DNA subunits, and (c) products of hydrogen atom and hydride anion addition to various subunits. This Account describes the systems in order of complexity, starting from free DNA bases, through nucleosides and nucleotides, to H-bonded base/nucleoside pairs.

Electron Addition. Secondary electrons arising from the effects of ionizing radiation on cellular components can cause lesions in DNA subunits. Solvated electrons arising from radiolysis of water can engender resonant phenomena involving attachment to DNA subunits.[2,3] Low-energy electrons may incorporate into DNA components, forming covalently bound anions, or be loosely located in a diffuse MO, yielding dipole-bound anions (notably in the gas phase). Attachment to DNA subunits can cause single- and double-strand breaks.[4] Other events following electron capture by DNA subunits include glycosidic bond cleavage[5] and base release.

Loss of a Hydrogen Atom. A hydrogen atom in a DNA component may be abstracted by a hydroxyl radical (from radiation-induced ionization of water followed by deprotonation) or removed from a DNA subunit by radiation-induced electron loss and deprotonation. Abstraction at various sites on DNA leads to neutral radicals, which may capture electrons, forming closed-shell anions. These may protonate and restore the original component or undergo nucleobase loss and other damaging consequences.

Hydrogen Atom and Hydride Anion Additions. Although still speculative, the possible role of such processes for DNA damage has been discussed and investigated theoretically. Hydrogen atom addition to double bonds in DNA components gives neutral radicals, while the 2-fold process of H-atom addition followed by electron attachment is equivalent to hydride addition.

Theoretical Methods

Absolute energies, optimized structures, harmonic vibrational frequencies and zero-point vibrational energies (ZPVEs) were calculated using the density functional theory (DFT), notably the well-calibrated B3LYP density functional. This gave the most reliable predictions for electron affinities[6] in the context of the use of five exchange-correlation density functionals (B3LYP, B3P86, BHLYP, BLYP, and BP86). Double-ς quality basis sets with polarization, and diffuse functions (denoted as DZP++) were generally used, created by augmenting the Huzinaga–Dunning set of contracted double-ς 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 first-row atom. One diffuse *s* function was added to each H atom, while sets of *s* and *p* diffuse functions were centered on every heavy atom, with the even-tempered orbital exponents being determined by a well-known formula. Use of this B3LYP/DZP++ strategy has led to an average absolute error of 0.12 eV for theoretically computed adiabatic electron affinities for a large number of systems, as compared to critically reviewed experiments.[6]

All stationary points were confirmed as true minima or transition states by vibrational frequency analyses. Charge distributions were computed using natural population atomic charges derived from the natural bond order analysis of Weinhold et al.[7] An unrestricted DFT approach was used to treat radical systems having an unpaired electron, with the spin density at an atom being expressed as the difference between the $\propto$ and β spin orbital densities.

Hydration of DNA subunits was modeled by the Barone–Tomasi polarizable continuum model,[8] with a dielectric constant of 78.39 for water. Microsolvation, the more explicit consideration of hydration effects, involves attaching a finite number of H-bonded water molecules to the system of interest and subjecting the whole complex to structural optimization.

The energetics of electron attachment to each closed-shell DNA subunit system is measured by the adiabatic electron affinity (AEA), given as

$$\mathrm{AEA} = E(\text{optimized neutral system}) - E(\text{optimized anion})$$

with both neutral and anion geometries fully optimized and *E* standing for the total electronic energy.

The immediate ability of a system to capture an electron may be measured by the vertical electron affinity (VEA) given as

$$\mathrm{VEA} = E(\text{optimized neutral}) - E(\text{anion at optimized neutral geometry})$$

The vertical detachment energy (VDE), often the quantity most readily determined by experiment, describes removal of an electron from the anion and indicates radical anion stability with respect to electron detachment, being expressed as

VDE = *E*(neutral at optimized anion geometry) − *E*(optimized anion)

Electron Attachment to Closed-Shell DNA Subunits

Naturally occurring DNA subunits are ground-state closed-shell systems with varying capacities for electron capture. The adiabatic electron affinity, vertical electron affinity, and vertical detachment energy are the physical quantities of relevance here.

DNA Bases in the Gas Phase. Structures and International Union of Pure and Applied Chemistry (IUPAC) atom-numbering schemes for the major nucleic acid bases are portrayed in Figure 1. The existence of radical anions for adenine (Ade), guanine (Gua), thymine (Thy), cytosine (Cyt), and uracil (Ura) in *solution* and the *solid state* is well-known. Their existence in the gas phase, however, has been more elusive, and gas-phase data on nucleobase electron affinities is still scarce. Moreover, some aspects of the gas-phase experiments are not immediately relevant to the situation of DNA in nature with its aqueous environment. For example, a nucleobase radical anion in the gas phase may exist in a "dipole-bound" state, with the extra electron residing in a very diffuse orbital. Table 1 presents data on nucleobase electron affinities in the gas phase.[9−11]

The possibility of free nucleobase anions existing in valence-bound states has also been examined. Table 2 lists some theoretical estimates of nucleobase AEAs. Wetmore et al.[12] used the B3LYP/6-311+G(2df,p)//B3LYP/6-31+G(d,p) strategy to estimate valence-bound AEAs for the five major nucleobases. Russo et al.[13] used the B3LYP/TVZP approach to calculate AEA values without ZPVE corrections. Wesolowski et al.[14] used the B3LYP/DZP++ method with ZPVE corrections to obtain valence-bound AEA values. These results show that Ura and Thy yield small positive AEAs, while Gua and Ade have negative AEAs; the position of Cyt is borderline. However, DFT estimates suffer from the self-interaction error, resulting in poor absolute values, although relative trends can be reliable. Roca-Sanjuan et al.[15] used the CCSDT//CCSD/aug-cc-pVDZ strategy to predict negative AEA values for all five nucleobases. Note that all of these sets of theoretical nucleobase AEA values yield the same order Ura > Thy > Cyt > Gua > Ade.

The experimental electron affinities of hydrated Ura, Thy, and Cyt measured by Schiedt, Weinkauf, Neumark, and Schlag[11] were extrapolated to zero hydration levels to estimate gas-phase values (Table 2) corresponding to valence-bound anionic states. The agreement between the Neumark−Schlag experiments and our 2001 DFT predictions is very good, with both yielding electron affinities of very small magnitude.

Microsolvated DNA Bases. Including solvent effects makes theoretical models more realistic, considering the aqueous environment of DNA in nature. Treatments more definitive than general polarized continuum models involve attaching a finite number of solvent molecules to the molecule. Bowen[16] used photoelectron spectroscopy to study several hydrated Ade radical anions, reporting the trihydrate as the smallest adiabatically stable one. Electron capture by microhydrated Thy, Ura, and Cyt has been studied,[17−19] attaching one to five water molecules to the base through H bonding. For each degree of hydration, various structures were considered for both neutral and anion species. The lowest energy neutral system for each case was used as the basis for predicting the AEAs (Table 3). These B3LYP/DZP++ results predict that the AEA of each base generally increases steadily upon successive hydration. AEA values for the hydrated systems are appreciably higher than for the free bases, predicting that Ura, Thy, and Cyt should definitely yield valence-bound anions in solution. This concurs well with the photodetachment−photoelectron spectral study of Neumark[11] on hydrates of Ura, Thy, and Cyt, whose AEA values are recorded very approximately in Table 3, being taken from the broad peaks depicted diagrammatically in their paper. The order Ura > Thy > Cyt is followed at all hydration levels by both theoretical and experimental AEA values.

DNA Nucleosides. The structure and atom-numbering scheme for the DNA nucleoside 2′-deoxythimidine is depicted in Figure 2. Structures of other DNA nucleosides are analogous. No experimental or reliable theoretical estimates existed before 2004 for nucleoside electron affinities, prompting the systematic DFT study by Richardson et al.[20] of electron addition to the DNA nucleosides dA, dG, dT, and dC in the gas phase. The ZPVE-corrected AEAs values (Table 4) were positive for all four nucleosides, each higher than that for the corresponding free base, giving the order dT > dC > dG > dA (analogous to that for the free bases). Base glycosylation is thus predicted to raise electron affinities, even though the free sugar itself has a negative AEA value[20] of −0.4 eV. Sugar−base interactions thus contribute to nucleoside anionic stabilities exceeding those for the free bases or sugar. The relatively high AEA values for dT (0.33 eV) and dC (0.44 eV) coupled with their large VDE values (0.72 eV for dT and 0.94 eV for dC) predict that dT and dC should form observable radical anions, as later demonstrated in the PES study of Bowen,[21] who characterized covalently bound radical anions in the gas phase for dT and dC. Despite the high VDE value of 0.91 eV predicted[20] for dA, it is unlikely to yield a persistent

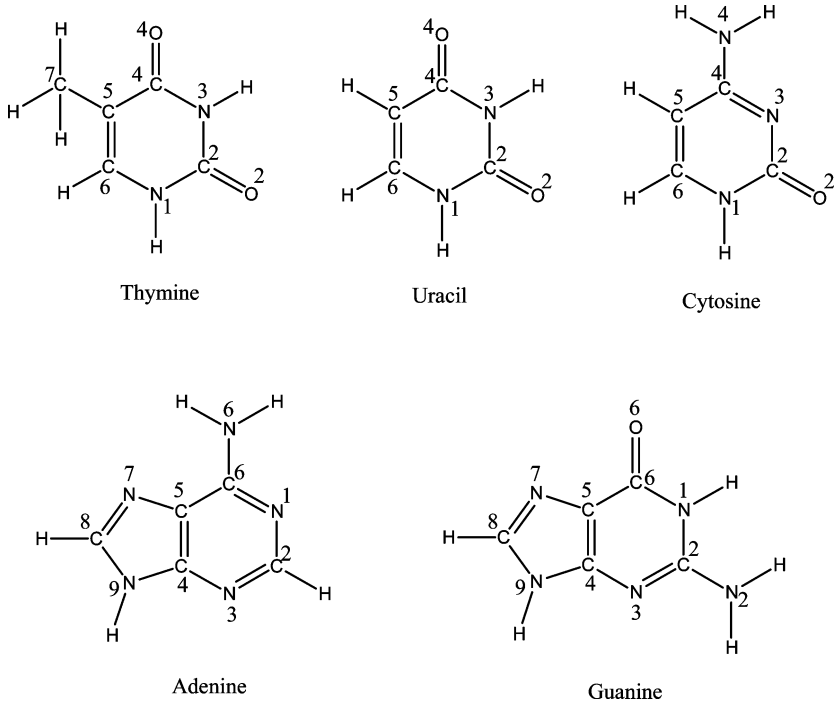


FIGURE 1. Structures and IUPAC numbering schemes for the major DNA and RNA bases.

TABLE 1. Experimental Values of Adiabatic Electron Affinities Corresponding to Dipole-Bound Anionic States of the Nucleic Acid Bases in the Gas Phase[a]

base	Bowen[9]	Desfrancois[10]	Neumark and Schlag[11]
Ura	0.093 ± 0.007	0.054 ± 0.035	0.086 ± 0.008
Thy	0.069 ± 0.007	0.068 ± 0.020	0.062 ± 0.008
Cyt			0.230 ± 0.008[b]
Ade		0.012 ± 0.005	

[a] All values are in electrovolts. [b] For the normal amino-oxo tautomer. The value is 0.085 ± 0.008 eV for the amino-hydroxy tautomer.

anion because of its low AEA value of 0.06 eV. The study of Bowen[21] yielded AEA and VDE values in good agreement (except for the AEA of dG) with the results of our study and of a later DFT study on base release from nucleoside anions by Sevilla.

Electron capture by the nucleoside significantly perturbs[20] the geometry of the base moiety for dT, dC, and dA but less so for dG. The glycosidic bond appreciably lengthens upon anion formation in dT, dC, and dA but not in dG. The valence character of the singly occupied molecular orbital (SOMO) for the dT, dC, and dA anions predicts them as valence-bound; the diffuse SOMO for dG^- suggests that it is dipole-bound. These predictions were confirmed later in the PES study of Bowen.[21] Calculated charge and SOMO distributions of these nucleosides predict[20] that the extra electron resides chiefly on the base moiety rather than on the sugar moiety. Decomposition of the nucleoside anions was predicted[22] as more facile for the radical anion than for the neutral species, suggesting that base loss following electron capture could be a significant event leading to abasic sites in DNA.

Depyrimidination of DNA Nucleosides. Glycosidic bond cleavage in radical anion nucleosides was suggested in 2004 by Sanche et al.[5] as furnishing a new mechanism for base loss following DNA irradiation. This process yields the base (a closed-shell anion) and the sugar (a C1′ radical). Gu and coworkers[22] studied the radical anion nucleosides dT and dC, locating the transition states for glycosidic bond cleavage and specifying the stages along the reaction pathway. The transition-state SOMO is localized around the breaking bond. Cytosine release from the dC anion is predicted as less favored than thymine release from the dT anion, as confirmed by Sanche's group[23] through thin-film irradiation studies.

DNA Nucleotides in Gas and Solution Phases. Low-energy electron attachment to base π^* orbitals in nucleotides can cause DNA strand breaks through cleavage of the sugar−phosphate C−O bond, as discussed in the excellent Account of Simons.[24] This phenomenon has attracted much study using DFT.[25−28] B3LYP/DZP++ studies in the gas and solution phases[25,26] conducted in this laboratory yielded AEA values somewhat higher than subsequent photoelectron spectroscopy studies by Bowen et al.[29] coupled with theoretical calculations. The B3LYP/DZP++ study of Gu et al.[30] further predicted that C3′−O3′ bond cleavage would predominate over N-glycoside bond cleavage.

TABLE 2. Theoretical Adiabatic Electron Affinities of Nucleobases in the Gas Phase Corresponding to Valence-Bound Anions Compared to Values Extrapolated from Experimental Data on Hydrated Systems[a]

base	B3LYP/6-311+G(2d,f)[12]	B3LYP/TZVP[13]	CCSD(T)//CCSD/aug-cc-pVDZ[15]	B3LYP/DZP++[14]	experiment[11]
Ura	0.18	0.14	−0.05	0.24	0.15 ± 0.12
Thy	0.14	0.08	−0.09	0.20	0.12 ± 0.12
Cyt	−0.06	−0.12	−0.17	0.03[b]	0.13 ± 0.12
Gua	−0.27	−0.38	−0.44	−0.07[b]	
Ade	−0.40	−0.48	−0.84	−0.28	

[a] All values are in electrovolts. [b] The small magnitude of these values may indicate admixture with dipole-bound character.

TABLE 3. Adiabatic Electron Affinities for Microhydrated Nucleic Acid Bases Obtained from Theory and PES Experiments

base	base H_2O	base $(H_2O)_2$	base $(H_2O)_3$	base $(H_2O)_4$	base $(H_2O)_5$	free base
			B3LYP/DZP++ Values[a]			
Ura	0.45	0.51	0.64	0.63	0.74	0.24
Thy	0.38	0.43	0.56	0.55	0.65	0.20
Cyt	0.28	0.42	0.53	0.55	0.61	0.03
			Experimental Values[b]			
Ura	0.4	0.7	0.9	1.1	1.4	0.15 ± 0.12
Thy	0.3	0.6	0.8	1.0	1.2	0.12 ± 0.12
Cyt	0.3	0.4	0.6	0.8	1.0	0.12 ± 0.12

[a] Kim.[17−19] [b] Neumark and Schlag.[11]

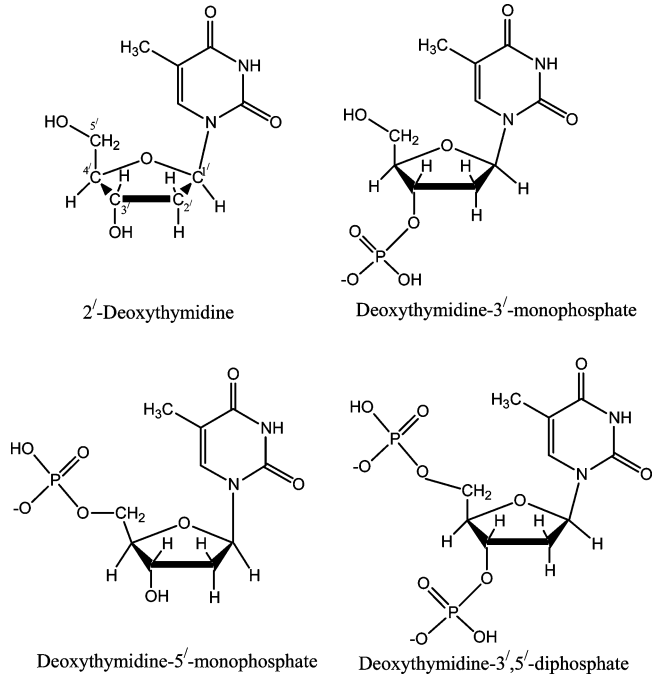


FIGURE 2. Structures of nucleosides and nucleotides as exemplified by deoxythymidine, deoxythymidine-3′-monophosphate, deoxythymidine-5′-monophosphate, and deoxythymidine-3′,5′-diphosphate.

Gu, Xie, and one of us have found[25] that the small positive VEA for deoxycytidine-3′-monophosphate (3′-dCMPH) implies its ability to capture near 0 eV electrons to form radical anions in the gas and solution phases, with excess electron density located on the base moiety. The high VDE indicates that this radical anion is stable enough to allow for DNA-damaging events, such as phosphate−sugar or glycosidic bond cleavage. The 3′-dCMPH radical anion has the excess charge on the anti-bonding orbital of the phosphate group. The phosphate-deprotonated nucleotide anion, not stable in the gas phase, may exist in solution, requiring electrons of energy above 4 eV to be formed. The nucleotide electron affinity is predicted to be independent of the counterion in solution, justifying use of the neutral 3′-phosphate-protonated nucleotide as a model here.

TABLE 4. Theoretical AEA Values for DNA Subunits[a]

	free base	nucleoside	3′-dNMP nucleotide	3′,5′-dNMP single-strand model
G	−0.07	0.09		0.36
C	0.03	0.33	0.44	0.44
A	−0.28	0.06		0.22
T	0.20	0.44	0.56	0.52

[a] All results are in electrovolts.

Electron attachment to solvated deoxythymidine-5′-monophosphate (5′-dTMPH) in neutral and deprotonated (5′-dTMP$^-$) forms was studied by Gu et al.[26] using the static isodensity surface-polarized continuum model. The AEA values of 2.00 eV for 5′-dTMPH and 1.95 eV for 5′-dTMP$^-$, as compared to only 0.28 eV for the gas-phase nucleotide, indicate dramatically increased electron-capturing ability upon solvation, with the extra electron located on the pyrimidine moiety. The significant VDE values in solution preclude electron auto-detachment, allowing for subsequent DNA damage routes. The B3LYP/6-31G** study of Sevilla on C5′−O5′ bond cleavage in 5′-TMPH indicates that adiabatic and vertical routes are both likely in the gas phase, unlike in solution.

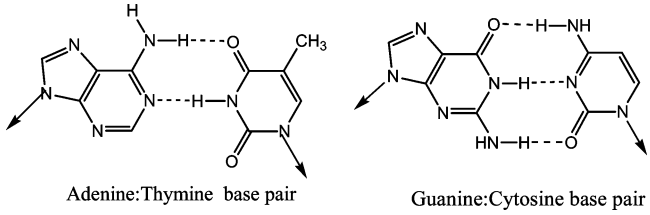


FIGURE 3. Two Watson−Crick DNA base pairs.

DNA Single Strands. Deoxynucleoside 3′,5′-diphosphates are the smallest units of single-stranded DNA. The theoretical values of Gu[30] for the gas-phase AEAs of the nucleoside 3′,5′-diphosphates (0.2−0.5 eV) follow the order 3′,5′-dTDP > 3′,5′-dCDP > 3′,5′-dGDP > 3′,5′-dADP, exactly corresponding to that followed by the free bases and deoxynucleosides (Tables 2 and 4). This study demonstrates that inclusion of phosphate groups increases electron affinity. Treatment of hydration effects through the polarizable continuum model further increases the electron affinities but preserves the order of Table 2. Predicted VDE values are smaller for purine nucleotides than for pyrimidine nucleotides, so that N-glycoside bond cleavage may be expected for the latter. The charge distributions predict that solvated 3′,5′-dGDP gives a phosphate-centered anion, while 3′,5′-dTDP, 3′,5′-dCDP, and 3′,5′-dADP give base-centered anions.

DNA Base Pairs in the Gas Phase. Figure 3 depicts the two canonical Watson−Crick base pairs Gua/Cyt and Ade/Thy. Electron attachment to the Gua/Cyt and Ade/Thy pairs in the gas phase has been examined[31−33] using DFT approaches. In the study of Richardson et al.,[31] electron capture by the Gua/Cyt pair strongly perturbs the geometry, where puckering of the cytosine base and amino group pyramidalization indicate a valence-bound radical anion. H-bond lengths are also subject to major changes. Excess charge is located on the cytosine base in the Gua/Cyt anion and on the thymine base in the Ade/Thy anion (studied by Richardson et al.[32]), as expected from the higher electron affinities of Cyt and Thy over Gua and Ade in isolation.[14] Our ZPVE-corrected AEA values are 0.60 eV for Gua/Cyt and 0.36 eV for Ade/Thy, with the latter comparing well with the B3LYP/6-31+G(d) values for Ade/Thy and Ade/Ura. Our B3LYP/DZP++ AEA values for the base pairs are higher than those for the free bases,[14] indicating that H-bonding of one base to another increases the electron affinity relative to each isolated base. Both base pair anion radicals should be observable, as confirmed for the Ade/Thy pair in a subsequent PES study by Bowen's group.[33] The latter synergistic study also yielded good agreement between theoretical and experimental VDE values, besides predicting a barrier-free proton transfer within this Ade/Thy anion pair. Our B3LYP studies[31,32] further indicated that electron attachment actually stabilizes the base pairs, where pairing energy increases from 27 to 38 kcal/mol for the Gua/Cyt pair and from 14 to 17 kcal/mol for the Ade/Thy pair.

Microsolvated Ade/Ura Pair. The study of Kim[34] on the microhydrated adenine−uracil base pair and its radical anion is the first of its kind on a DNA base pair. A total of 5 monohydrated and 14 dihydrated structures were located for the neutral pair and its radical anion. Monohydration improves the electron-capturing ability of the Ade/Ura pair from 0.40 to 0.51 eV (AEA values). Dihydrates yield electron affinities larger than monohydrates. The extra electron in all of the hydrated radical anions is localized primarily on the uracil moiety, in line with the higher electron affinity of free Ura with respect to free Ade.[14]

dG/dC and dA/dT Nucleoside Pairs. The theoretical study of Gu et al.[35] yielded a positive AEA value of 0.80 eV for dG/dC, higher than for the Gua/Cyt base pair[31] or for the isolated nucleosides[20] dG (0.09 eV) and dC (0.33 eV). This demonstrates that electron-capturing ability improves with H bonding and glycosylation. The added electron resides mainly on the cytosine base moiety. Electron attachment triggers a low-barrier N1(dG)−N3(dC) proton transfer in the dG/dC$^-$ pair, resulting in a distonic radical anion, with spin and charge separated. Formation of the d(C + H)$^\bullet$ nucleoside radical within the pair could also lead to the formation of an abasic site.

The AEA value of 0.60 eV for the dA/dT nucleoside pair as predicted by Gu et al.[36] is appreciably higher than that (0.36 eV) for the gas-phase Ade/Thy base pair,[32] indicating again that glycosylation increases electron affinity. Electron attachment perturbs the pairing configuration, altering the H-bond lengths. The positive values for both the VEA (0.2 eV) and VDE (1.1 eV) confirm that the dA/dT pair radical anion would be stable enough to allow for subsequent glycoside bond cleavage.

Ade/5′-dTMPH Pair. Electron capture by the adenine/deoxythymidine-5′-monophosphate pair was studied in the gaseous and solution phases by Gu et al.[37] using the B3LYP/DZP++ method and, in the latter case, with the static IPC model. The gas-phase AEA value of 0.8 eV for this pair is appreciably higher than that for dA/dT[36] (0.6 eV), pointing to an effect of the phosphate group. H bonding in this pair increases the electron affinity relative to the isolated thymidine. The extra electron resides primarily on the thymine moiety, as for the Ade/Thy[32] and dA/dT[36] anion pairs. Solution effects greatly enhance electron-capturing ability, with the AEA increasing to 2.0 eV and the VEA increasing to 1.7 eV, along

with even greater localization of an excess negative charge upon the thymine moiety.

Hydrogen-Abstracted Radical Species

Abstraction of a hydrogen atom from DNA subunits leads to the formation of a neutral radical. This may occur from the direct effects of radiation or electron bombardment or by action of the radicals created during the radiolysis process *in vivo*. Hydrogen-abstracted radicals have a strong propensity for capturing electrons to create closed-shell anions. Each radical studied is labeled in terms of the atom of the base from which the hydrogen is removed, with this applying also to the corresponding anions.

Nucleic Acid Base Radicals. The energetics of H atom loss from pyrimidine nucleobases has been studied by Sevilla using theoretical methods. The studies of our group[38,39] on hydrogen-abstracted cytosine and adenine have yielded AEA values for the neutral radicals, which, as expected, are much larger than those for the bases themselves. Cytosine gives the five radicals studied by Luo et al.,[38] with AEA values ranging between 2.2 and 3.0 eV and following the order N1 > N4a > N4b > C6 > C5. The VDE values are also large (2.7−3.2 eV). Hydrogen atom removal from adenine yields the five radicals studied by Evangelista et al.,[39] with electron affinities between 1.0 and 3.2 eV, giving the order N9 > N6 > C8 > C2. In general, nitrogen-centered radicals have higher electron affinities than carbon-centered ones.

Deoxyadenosine Radicals. A total of 11 neutral radicals may result from abstraction of an available hydrogen from 2′-deoxyadenosine. The energies of radical formation obtained by Evangelista and Schaefer[40] are spread over a range of 26 kcal/mol, giving the radical stability order as C (aliphatic) > N (amino) > O (hydroxyl) > C (aromatic). Radical centers on the sugar moiety tend toward sp^2 planarity. The adenine base rotates away from an *anti* conformation in the C1′ radical, implying the possibility of base pair dissociation and strand opening. The C4′, C5′, and C2′ radicals can undergo decomposition reactions following electron capture, which may lead to base loss. Radicals produced on the adenine moiety generally lie higher in energy, following the order N6 > C8 > C2. ZPVE-corrected AEA values of all of these radicals are large, ranging from 1.0 to 3.2 eV and yield the order C4′ < C2 < C1′ < O3′ < O5′ < N6 < C8. The spin density is chiefly localized around the formal radical center for the aliphatic radicals but is delocalized for the N6-amino radicals. The ribose ring is always positively charged in all radicals, while accepting a negative charge in some of the analogous anions.

Deoxyadenosine-5′-phosphate Radicals. The neutral radical derived from one-electron oxidation of the 5′-dAMP anion moiety in DNA has been implicated in strand scission of nucleic acids.[41] The results of this group[42] indicate that the electron hole is present on both phosphate and adenine moieties, as demonstrated by the charge redistributions and geometry changes. In our study, the weak C5′−O5′ bond in the radical implies the possibility of a single-strand break. The calculated VDE and adiabatic detachment energy for the 5′-dAMP anion fall below the values obtained by Wang et al.[43] using photoelectron spectroscopy. Conformational differences in the sugar may explain this, as well as the possibility of experimental uncertainty; analysis of such photodetachment data can be in some cases perilous.

Hydrogen atom abstraction from a 5′-dAMP anion moiety within DNA may be the initial step in the oxidative strand scission of DNA.[44] Hydrogen abstraction does not significantly affect the electron distribution in this nucleotide.[42] The negative charge in the radical anions is distributed mainly on the phosphate and then on the base. Nitrogen-centered anions display spin delocalization around the base moiety, while carbon-centered anions do not. Spin and charge centers are well-separated in these distonic radical anions.

Gua/Cyt Radical Pairs. Radical forms of the Gua/Cyt pair may arise through hydrogen atom abstraction from either base in the pair. Dissociation energies of various (Gua-H)•−Cyt and Gua−(Cyt-H)• pairs as obtained by Bera and Schaefer[45] have been compared to those of the closed-shell Gua/Cyt pair. Abstraction from nitrogen rather than carbon leads to lower energy radical pairs. Hydrogen abstraction from the H bonds severely distorts the pairing configuration, resulting in backbone shifts, ring distortions, and departures from planarity.

Ade/Thy and Ade/Ura Radical Pairs. For both of these pairs, removal of hydrogen from even one hydrogen bond greatly affects pairing stability, because only one H bond remains and base pair dissociation energies are appreciably lowered. Hydrogen-abstracted radicals for these pairs are labeled here according to the base and the atom losing the hydrogen. The radical energetics predicted for the Ade/Thy pair by Lind et al.[46] follow the order A (C5) > A (N9) > U (N1) > A (N6b) > A (N6a) > A9 (C2) > U (N3), largely analogous to that for the Ade/Ura pair studied by Kim et al.[47] Interestingly, the Ade/Ura (N3) pair develops a substantial carbon H bond, leading to a dissociation energy comparable to that of the intact Ade/Ura pair itself (12.9 kcal mol^{-1}). Hydrogen atom addition to the Ade/Thy and

Ade/Ura pairs does not perturb the pairing configuration as much as for the Gua/Cyt pair.

Deprotonated Gua/Cyt and Ade/Ura Pairs. H-atom abstraction followed by electron attachment is equivalent to deprotonation. This group has studied[48] 10 such anionic species of the Gua/Cyt pair. The most favored structure (dissociation energy of 42 kcal/mol) involves a very short NH···OC hydrogen bond at the cytosine O2 site (refer to Figure 1). A reverse wobble structure involving two new H bonds was located following deprotonation from the N1 guanine site. AEA values for the H-abstracted Gua/Cyt radicals range from 1.9 to 3.7 eV. The small dissociation energies for some deprotonated pairs suggest that even very low-energy secondary electrons (0−3 eV) may be able to split the base pairing.

The deprotonated Ade/Ura base pair was studied theoretically by Kim et al.[49] Proton transfer following electron attachment to the H-atom abstracted pairs was predicted for pairs deprotonated at the adenine N9, N6, and C2 sites, where the uracil N3 proton shifts to the adenine N1 site. The Ade/Ura pair anions are tightly bound and allow for facile C−H and N−H bond dissociations.

Hydrogen Atom and Hydride Anion Additions

The addition of a hydrogen atom to a double bond in a DNA base yields a neutral radical, in itself potentially damaging to DNA. Furthermore, an electron may easily attach to this neutral radical, forming a closed-shell anion. These two steps are equivalent to the direct addition of a hydride anion to the double bond.

Adenine. The energies and structures of eight hydrogen-added radicals and their corresponding closed-shell anions derived from adenine have been examined by Evangelista and Schaefer.[50] Therein, the C8 adenine site is predicted to be the most favored for hydrogen addition. Radical stability consistently depends upon the topology around the site of hydrogen attachment and the scope for spin delocalization. The least stable C4- and C5-added radicals distort the co-planarity of the adenine rings to an interesting "butterfly" shape. Electron attachment to all of these radicals yields covalently bound anions, with the most stable one arising from hydride addition to the C8 site. Anion formation distorts the ring structure appreciably. The AEA values range from near 0 to 2.0 eV. The positive VDE values (0.5−2.1 eV) should allow for detection of these anions in the gas phase via photodetachment experiments.[6]

Protonated Guanine. Guanine has the highest proton affinity among the nucleic acid bases, with the proton attaching to the N7 site. Nine protonated guanine tautomers were studied by Zhang et al.[51] The N7 site was predicted as most favored for protonation in the gas phase; the PA of 228.1 kcal/mol compares very well to an experimental estimate of 227.4 ± 0.1 kcal/mol.[52] Electron addition to these protonated guanines leads to nine neutral radicals, with the C8-hydrogenated tautomer being the most stable. Further addition of an electron gives the hydride-added closed-shell anions (studied for the first time), with AEA values ranging from 0.1 to 3.1 eV, where the C2 site is most favored for hydride addition.

Gua/Cyt Pair. Hydrogen atom addition to the Gua/Cyt pair has been studied by Zhang et al.,[54] predicting that appendage to the C8 guanine site leads to the lowest energy base pair radical among the 12 studied. Dissociation energies of these (Gua + H)•−Cyt and Gua−(Cyt + H)• radical pairs were compared to the normal Gua/Cyt pair dissociation energy. Addition of a H atom to the pair most often destroys its planarity. A "butterfly" shape for the guanine moiety results from H-atom addition to the C4 and C5 sites. Loss of one H bond upon H-atom addition to the cytosine N3 site shifts the entire backbone of the resulting pair.

The 2008 study of Zhang et al.[54] shows that H-atom addition plus electron attachment to the Gua/Cyt pair results in a proton transfer in the H-bonding region. The 14 conventional hydride addition products are well-defined structures but allow for proton migration and charge transfer, leading to the corresponding proton-transferred anionic base pairs. Proton transfers for two cases have low barriers, and the resultant pairs may be sufficiently long-lived for DNA damage to occur even before dissociation.

Concluding Remarks

This Account provides a comprehensive discussion of theoretical work on elementary DNA lesions and amply testifies to the ability of computational methods to furnish reliable descriptions of electron attachment to DNA components and to characterize other processes, such as hydrogen atom abstraction and addition. The role of such processes for DNA damage is well-borne out in many of these studies and is predicted with a good level of confidence for many situations not yet studied experimentally. This generates confidence that such a strategy of study may be extended to other systems relating to nucleic acid chemistry. It is hoped that such approaches will not only clarify many essential details regarding the molecular basis of DNA lesions but also provide a basis for the design of future experiments, which will add confirmatory and new knowledge concerning the chemical physics of biomolecules in the gas phase.

This research was supported by the U.S. National Science Foundation (Grant CHE-0749868). We are greatly indebted to our gifted co-workers Professor Jiande Gu, Dr. Yaoming Xie, Dr. Steven Wesolowski, Dr. Partha Bera, Dr. Martin Kim, Professor Nancy Richardson, Dr. Maria Lind, Dr. Holly Wang, Dr. Steven Wheeler, Professor Q.-S. Li, Dr. Francesco Evangelista, Dr. Ankan Paul, Mr. Ruobing Hou, Dr. David Zhang, Dr. Matthew Leininger, and Dr. Plamen Pentchev, for their critical contributions to the research described in this Account.

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FOOTNOTES

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