# Determination of Redox Potentials for the Watson−Crick Base Pairs, DNA Nucleosides, and Relevant Nucleoside Analogues

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Redox potentials for the DNA nucleobases and nucleosides, various relevant nucleoside analogues, Watson−Crick base pairs, and seven organic dyes are presented based on DFT/B3LYP/6-31++G(d,p) and B3YLP/6-311+G(2df,p)//B3LYP/6-31+G* levels of calculations. The values are determined from an experimentally calibrated set of equations that correlate the vertical ionization (electron affinity) energy of 20 organic molecules with their experimental reversible oxidation (reduction) potential. Our results are in good agreement with those estimated experimentally for the DNA nucleosides in acetonitrile solutions (Seidel et al. *J. Phys. Chem.* **1996**, *100,* 5541). We have found that nucleosides with *anti* conformation exhibit lower oxidation potentials than the corresponding *syn* conformers. The lowering in the oxidation potential is due to the formation of an intramolecular hydrogen bonding interaction between the 5′-OH group of the sugar and the N(3) of the purine bases or C(2)═O of the pyrimidine bases in the *syn* conformation. Pairing of adenine or guanine with its complementary pyrimidine base decreases its oxidation potential by 0.15 or 0.28 V, respectively. The calculated energy difference between the oxidation potential for the G·C base pair and that of the guanine base is in good agreement with the experimental value estimated recently (0.34 V: Caruso, T.; et al. *J. Am. Chem. Soc.* **2005**, *127,* 15040). The complete and consistent set of reversible redox values determined in this work for the DNA constituents is expected to be of considerable value to those studying charge and electronic energy transfer in DNA.

## 1. Introduction

Determination of accurate redox potentials for the DNA constituents is critical for the evaluation of thermodynamic and kinetic properties of their radical species, the possible charge transfer and oxidation reactions, and the design of electronic devices. Base pairing,[1−3] base stacking,[4−8] and solvent effects[8−16] are expected to modulate the local redox properties of the nucleobases in single- and double-stranded DNA helixes. Still, limited experimental information is available on the redox properties of DNA nucleobases, nucleosides, base stacks, and base pairs.[3,17−19] Only recently was the oxidation potential of the G·C base pair determined experimentally.[3] To our knowledge, direct experimental measurement of the redox properties for the A·T base pair has yet to be reported.

This contribution is focused on the reversible redox potentials of DNA nucleosides, various relevant nucleoside analogues, and the Watson−Crick base pairs. In addition, vertical ionization and electron affinity energies are presented for most of the DNA systems investigated. We make use of a free energy cycle for determining redox potentials, and the expected linear correlation of the ionization[20−22]/electron affinity[23] energy and the oxidation/reduction potential of a molecule to estimate the reversible redox potentials of the DNA model systems in solution. To this end, vertical ionization and electron affinity energies (VIE and VEA, thereafter) are calculated for 20 organic molecules at DFT/B3LYP/6-31++G(d,p) and B3YLP/6-311+G(2df,p)//B3LYP/6-31+G* levels of theory. These organic molecules were selected because their reversible redox potentials are known with good accuracy in *N*,*N*-dimethylformamide or acetonitrile solutions (DMF, $\epsilon = 36.71$ and ACN, $\epsilon = 36.64$, respectively).[24] Remarkably good linear correlations are obtained between the VIE/VEA and the oxidation/reduction potentials for these systems. The linear correlations are then used to determine the reversible redox potentials of the DNA building blocks by using the calculated VIE and VEA at the same level of theory. Redox potentials of seven organic dye molecules used by Seidel et al.[25] to estimate the redox potentials of the DNA bases are also

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**TABLE 1: Reported Irreversible Oxidation Potentials for the DNA Nucleosides**

| DNA system | $E°_{ox}$/V[a] | exptl conditions | ref |
|---|---|---|---|
| guanosine | 1.29 | aq solution at pH 7 | 19 |
| | 1.32 | aq solution at pH 6.24 | |
| | 1.49 | acetonitrile | 25 |
| | 1.52 | *N*,*N*-dimethylformamide | 34 |
| | 1.53 | aq solution at pH 6.5 | 30 |
| | 1.58 | aq solution at pH 1 | 27 |
| adenosine | 1.42 | aq solution at pH 7 | 19 |
| | 1.63 | aq solution at pH 6.5 | 30 |
| | 1.96 | acetonitrile | 25 |
| | 2.03 | aq solution at pH 1 | 27 |
| thymidine | 1.7 | aq solution at pH 7 | 19 |
| | 1.73 | aq solution at pH 6.5 | 30 |
| | 2.11 | acetonitrile | 25 |
| cytidine | 1.6 | aq solution at pH 7 | 19 |
| | 1.88 | aq solution at pH 6.5 | 30 |
| | 2.14 | acetonitrile | 25 |

[a] Oxidation potentials are reported versus NHE.[50]

determined to further corroborate the generality and accuracy of the set of equations proposed.

This work was motivated by the considerable need to know the redox properties of the DNA components with high accuracy in order to model and predict charge and energy transfer in DNA. A reasonable consensus between the experimental oxidation values reported by different groups does not exist. This is partially due to the use of significantly different experimental conditions (such as solvent, pH, detection method, etc.),[19,25−30] which make it very difficult to obtain a consistent and reliable set of redox properties. However, the reported redox values are sometime used in the literature as if they can be directly compared without appropriated solvent and/or pH corrections.

For instance, several of the oxidation potentials for the DNA nucleosides reported in the literature are shown in Table 1. The experimental values can differ by as much as ~0.7 V for a given nucleoside. On one hand, the discrepancy between the reported oxidation potentials for a given nucleoside is partially due to the different experimental conditions used. The use of different solvents can alter the voltages found for a given DNA nucleoside because the protonation−deprotonation equilibriums are solvent dependent. Besides, various tautomers could play an important role at different pH conditions.[31] On the other hand, the difference in redox values for a given nucleoside could also be attributed to unavoidable experimental uncertainties (i.e., irreversible electrochemistry, proton-coupled electron-transfer reactions, etc.) that preclude the determination of redox potentials under well-defined equilibrium conditions. In this regard, debates about the accuracy of the experimental redox values for the DNA nucleosides are currently under discussion.[32] Most experimentalists routinely use the redox values reported by Seidel et al.,[25] even though these values were determined under none-equilibrium, irreversible conditions. Such conditions are know to underestimated the redox potentials by as much as 0.3 V compared to the values expected for reversible, standard redox values.[33] Logically, the questions that arise are the following: What is the accuracy of the redox values reported in the literature and can a unified set of redox potentials be identified for all the DNA nucleosides?

With the above questions in mind, we have developed a semiempirical method to determine the reversible redox potentials of the DNA nucleosides in ACN or DMF solvent conditions. Strikingly, the calculated redox values for the DNA nucleosides are in good agreement (within 0.2 V or better) with the values estimated experimentally[25,34] from noneequilibrium, irreversible conditions in ACN or DMF solvents. The good agreement obtained between the calculated reversible redox values and the peak potentials estimated for the nucleosides[25,34] allows us to present the first complete and consistent set of reversible redox values for the nucleosides, the nucleoside analogues, and the DNA base pairs in ACN or DMF solvent conditions.

## 2. Computational Methods

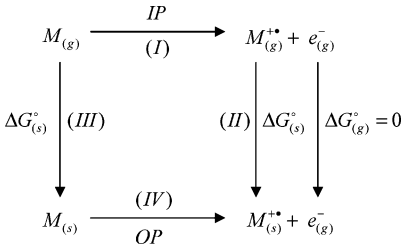
Results are presented based on DFT calculations for DNA monomers and base pairs, in addition to 7 organic dyes[25] and *20* organic molecules with known reversible redox properties in ACN or DMF solvents.[24] The underlying methodology is as follows. Selected organic molecules were fully optimized without any geometrical constraint. The closed-shell geometries were obtained by using the density functional computational approach with the B3LYP functional[35−37] and the 6-31++G(d,p) standard basis set, as implemented in the Gaussian 98 suite of programs.[38] The optimized structures were verified as true local minima on the potential energy surface by establishing that the matrix of the energy second derivatives (Hessians) does not show imaginary eigenvalues at the same level of theory. Herein we have concentrated on the most stable *syn* and *anti* gas-phase nucleoside conformations at the B3LYP/6-31++G(d,p) level of theory, which in general show C3′-endo (North) sugar conformations. A complete report of analogous calculations performed for others *syn* and *anti* nucleoside conformers showing C3′-endo and *C*2′-endo (South) sugar conformations is out of the scope of the present work. Such computational efforts will be presented in a forthcoming publication. The correction of the DNA dimers for basis set superposition error is negligible[39,40] and was therefore omitted in this work.

Gas-phase vertical ionization and electron affinity energies were calculated from the difference in total energy between the neutral molecule and its respective radical cation or anion, evaluated at the optimized geometry of the neutral molecule.[11] The adiabatic IEs were obtained in the same way, but using the total energy obtained from the optimized geometry of the radical cation.[11] The restricted formalism was used for the closed-shell systems, whereas the total energies for the radical cations and the radical anions were obtained by using unrestricted wave functions. The B3LYP/6-31++G(d,p) level of theory has been shown to provide reasonable values of VIE for related DNA systems,[1,11,12,14,15] and has been successfully used to estimate the redox potentials of other compounds in solution.[41,42]

In contrast, calculation of negative VEA for the DNA nucleobases at the DFT/B3LYP level of theory that includes extra diffuse functions in the basis set has been shown to be problematic.[43,44] Vera and Pierini have recently shown that reliable negative VEA for the DNA nucleobases can be obtained at the B3YLP/6-311+G(2df,p)//B3LYP/6-31+G* level of theory.[44] Thus, we performed additional calculations of VEA for the DNA nucleobases and base pairs using the methodology of Vera and Pierini.[44] This allowed us to better estimate the reduction potential of DNA systems.

Bulk solvent effects were studied by performing self-consistent reaction field (SCRF) calculations by using the PCM method[45] with the integral equation formalism (SCRF=IEFPCM)[46] on the gas-phase optimized geometries of the DNA/RNA nucleobases and N(9)- and N(1)-methylated purine and pyrimidine nucleobases, respectively. The dielectric constant of acetonitrile ($\epsilon = 36.64$) was used throughout. In ACN solutions,

**SCHEME 1: Free Energy Cycle for the Half-Wave Oxidation Potential (OP) of a Molecule (M) in Solution (s) and Its Relationship with the Gas-Phase (g) Ionization Potential (IP)**




the ionization energies were calculated by subtracting the total energies of the neutral molecule and radical cation obtained from single point IEFPCM calculations, using the corresponding gas-phase optimized geometries (IEFPCM/B3LYP/6-31++G(d,p)).

## 3. Results and Discussion

**3.1. Correlation of the VIE/VEA and the Redox Potentials for the Selected Organic Molecules.** A necessary condition for a correlation of redox data with any other parameter of electron-donating ability is that electrochemical equilibrium be achieved at the electrode. This is because the reversible half-wave potential is then related in a simple manner to the change in free energy involved in the electrode process. Typically, methods that do not involve any experimental data make use of a free energy cycle for determining redox potentials. For example, Scheme 1 depicts the free energy cycle for the oxidation half-wave potential of a molecule, M. The free energy change of the gas-phase oxidation potential of M is closely related to its ionization energy (Scheme 1, path I). Free energy changes associated with paths II and IV are the free energy of solvation and path III refers to the oxidation potential in solution. The normal hydrogen electrode (NHE) is frequently used as a reference potential ($H^+_{(s)} + e^- \rightarrow {}^1/_2H_{2\,(g)}$; $\Delta G^\circ = -4.44$ eV),[47] and thus the oxidation (reduction) potential refers to the free energy change for the net reaction resulting from addition of the NHE half-wave potential to the oxidation (reduction) half-wave potential. Note that path II involves an electron in the gas phase and thus its solvation free energy is not a relevant term in the cycle (Scheme 1). Thus, the oxidation potential of M in solution is determined as:

$$\Delta G^\circ_{ox}(\text{M vs. NHE}) = \text{AIE(M)} + \Delta G_{E,(g)}(\text{M} \rightarrow \text{M}^{+\bullet} + \text{e}^{-\bullet}) + \Delta G^\circ_{(s)}(\text{M}^{+\bullet}) - \Delta G^\circ_{(s)}(\text{M}) - 4.44 \quad (1)$$

where AIE is the adiabatic ionization energy of M in the gas phase; $\Delta G_{E,(g)}(\text{M} \rightarrow \text{M}^{+\bullet} + \text{e}^{-\bullet})$ is the total free energy of M derived from changes upon ionization (including thermal contributions); $\Delta G^\circ_{(s)}(\text{M}^{+\bullet})$ and $\Delta G^\circ_{(s)}(\text{M})$ are the solvation free energy of the oxidized and neutral form of M, respectively. All term in eq 1 are expressed in electronvolts.

To a first approximation, the gas-phase AIE of M might be replaced by its VIE if the relaxation energy term varies in a regular manner for the set of molecules investigated. This approximation has been shown to be satisfactory for other molecular systems.[20,23,48,49] In addition, for a series of similar compounds under similar experimental conditions, the variation in VIE might be expected to be more significant than variations in the other terms in eq 1. Under those conditions, a plot of $\Delta G^\circ_{ox}$ against VIE is expected to yield a straight line. Similarly, if $\Delta G^\circ_s$ is an approximately linear function of VIE, the linearity of $\Delta G^\circ_{ox}$ against VIE would be enhanced and we can write:

$$\Delta G^\circ_{ox}(\text{M vs. NHE}) = \text{VIE} + \text{constant} \quad (2)$$

An analogous relationship should hold between the half-wave reduction potential of M ($\Delta G^\circ_{red}$(M vs. NHE)) and the calculated vertical electron affinity (VEA):

$$\Delta G^\circ_{red}(\text{M vs. NHE}) = \text{VEA} + \text{constant} \quad (3)$$

To confirm the applicability of the approximations proposed above, we calculated the VIE and VEA of 20 organic molecules for which accurate reversible redox potentials are available in the literature.[24] The selection of this particular set of organic molecules is based on the following criteria: (1) the experimental reversible redox potentials are known with a high degree of accuracy; (2) the redox potentials of the molecules span a similar or wider range of potentials than those expected for the DNA nucleosides and base pairs; (3) some of the selected organic molecules include functional groups and heteroatoms similar to the DNA bases; and (4) the redox potentials of all the molecules are reported in the same ACN or DMF solvents used previously to estimated the redox potentials of the DNA nucleosides and base pairs.[3,25] The optimized geometries and coordinates of the selected organic molecules, and all other molecules investigated in this work, are included as Supporting Information.

Table 2 compiles the calculated VIE and VEA for the selected organic molecules together with the experimentally determined reversible redox potentials.[24] The calculated VIE of the selected organic molecules are compared with the corresponding experimental oxidation potentials in Figure 1. Similarly, the VEA are compared with the corresponding experimental reduction potentials in Figure 2. The good linear correlation ($r^2 = 0.96$)

**TABLE 2: Vertical Ionization and Electron Affinity Energies for Selected Organic Molecules at the B3LYP/6-31++G(d,p) Level of Theory and Their Experimental Reversible Oxidation and Reduction Potentials in DMF or ACN Solutions**

| system | VIE/eV[a] | VEA/eV[a] | $E^\circ_{ox}$/V[b] | $E^\circ_{red}$/V[b] |
|---|---|---|---|---|
| acenaphthene | 7.47 | −0.473 | 1.45 | n.d. |
| 2,4-dimethoxy-*N*,*N*-dimethylaniline | 6.75 | −0.389 | 0.51 | n.d. |
| 3,4-dimethoxy-*N*,*N*-dimethylaniline | 6.95 | −0.440 | 0.44 | n.d. |
| anthracene | 7.10 | 0.454 | 1.33 | −1.71 |
| azulene | 7.28 | 0.512 | 0.95 | −1.41 |
| benzaldehyde | 9.85 | 0.234 | n.d. | −1.69 |
| benzene | 9.21 | −0.613 | 2.54 | n.d. |
| methoxybenzene | 8.19 | −0.529 | 2.00 | n.d. |
| benzo[*a*]pyrene | 6.79 | 0.696 | 1.18 | −1.86 |
| 4,4′-dimethoxy-benzophenone | 7.81 | 0.201 | n.d. | −1.78 |
| 4,4′-dimethyl-benzophenone | 8.28 | 0.384 | n.d. | −1.66 |
| chrysene | 7.26 | 0.206 | 1.59 | −2.01 |
| dibenz[*a*,*h*]anthracene | 7.01 | 0.521 | 1.43 | −1.86 |
| fluoranthene | 7.60 | 0.620 | 1.69 | −1.50 |
| naphthalene | 7.90 | −0.081 | 1.78 to 1.94 | −2.25 |
| 1,5-dimethoxy-naphthalene | 7.08 | −0.424 | 1.52 | −2.52 |
| perylene | 6.64 | 0.897 | 1.09 | −1.43 |
| pyrene | 7.15 | 0.326 | 1.40 | −1.85 |
| tetracene | 6.55 | 1.023 | 1.01 | −1.34 |
| triphenylene | 7.60 | −0.075 | 1.79 | −2.22 |

[a] Gas-phase vertical energies at the B3LYP/6-31++G(d,p) level of theory. [b] Experimental redox potentials are reported versus NHE[50] in DMF or ACN solvents (see ref 24).

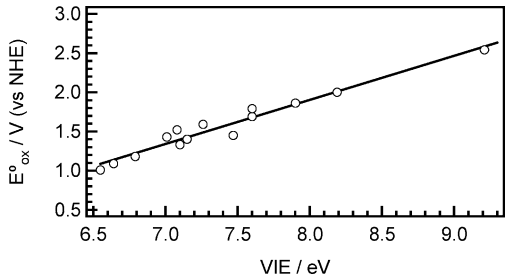



**Figure 1.** Reversible oxidation potentials of the 14 selected organic molecules[24] as a function of the vertical ionization energy.

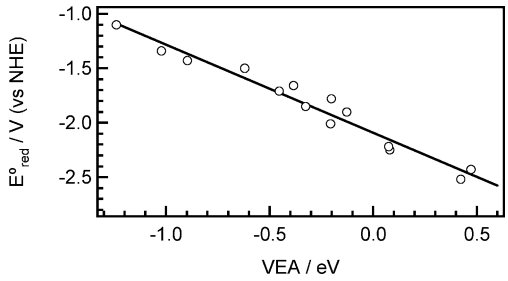



**Figure 2.** Reversible reduction potentials of the 14 selected organic molecules[24] as a function of the vertical electron affinity energy.

between these physical quantities is noteworthy, despite the fact that solvent effects are not taken into consideration,[22] and that the experimental data came from many different sources.[24] Because we are dealing with the one-electron oxidation/reduction potentials, the free energy change of oxidation/reduction can be readily substituted with the standard oxidation/reduction potential of M ($\Delta G^\circ = -nFE^\circ$) in eqs 2 and 3 above. The quantitative relationships are given by eqs 4 and 5

$$E^\circ_{ox} = (-2.59 \pm 0.26) + (0.56 \pm 0.03) \times \text{VIE} \quad (4)$$

$$E^\circ_{red} = (-2.09 \pm 0.03) \pm (0.81 \pm 0.05) \times \text{VEA} \quad (5)$$

where $E^\circ_{ox}$ and $E^\circ_{red}$ are the reversible halfwave standard oxidation and reduction potentials versus NHE, respectively,[24,50] and VIE and VEA are as defined above. The intercept and slope values, together with the estimated uncertainties ($1\sigma$) in parentheses, are obtained from a least-squares regression of the data, as shown in Figures 1 and 2.

Importantly, the good correlations obtained in Figures 1 and 2 support the rationale and approximations used above to obtain eqs 2 and 3. The linear relationships also confirm that the solvation energy terms, which are directly related to the dielectric constant of DMF and ACN solvents, vary in an approximately regular manner for all the molecules studied. This regular dependence also explains the deviation of the slope from unity in eqs 4 and 5, as described previously.[20] Standard redox potentials for the DNA nucleosides, nucleoside analogues, and base pairs were then determined by using the experimentally calibrated eqs 4 and 5 (Tables 4−6). The redox values determined for the DNA systems by using eqs 4 and 5 should be compared to those experimentally determined in similar solvents (ACN or DMF). We postpone the discussion of the redox potential of the DNA constituents for the next section.

Recently, it has been shown that calculations using DFT methods might underestimate the IE values.[51,52] However, it should be noted that the accuracy of the DFT calculations is not of major concern here because of the use of experimental data (redox potentials of the selected organic molecules) to calibrate the DFT calculations. Thus, if the VIEs/VEAs are underestimated in a similar manner for all the investigated molecules (the 20 organic compounds and the DNA systems), the calibration curves (eqs 4 and 5) should show a linear dependence, as observed.

To further evaluate the generality of the methodology used in this work, we have determined the reversible redox potentials of various fluorescent dyes used by Seidel and co-workers in their nucleoside quenching experiments.[25] The calculated oxidation potentials using eq 4 are compared with the reported experimental oxidation potentials in Table 3. The energy difference between the determined oxidation potentials and the corresponding experimental value is generally less than ~0.3 V, except for C-307 that shows a 0.4 V difference. It is interesting to note that for three out of seven dye molecules the energy difference is equal or less to 0.1 V. Similarly, with use of eq 5, the calculated reversible reduction values are in very good agreement with the experimental potentials (Table 3). In this case, the energy difference between the calculated reduction potentials and the experimentally estimated values is close to zero except for the C-124 dye, which shows a ~0.5 V energy difference. Even though the calculated VEA of C-124 is quite negative, the energy difference between the experimental and calculated value seems to not be due to the formation of a dipole-bound state. This is because formation of dipole-bound states typically underestimates the expected value for the valence VEA and thus a less negative reduction potential should be obtained from eq 5 compared to the experimentally determined value. This is clearly not the case for the reduction value determined for C-124 in Table 3. Nonetheless, the agreement between the experimental potentials and the calculated reversible redox potentials is very good, taking into consideration that the reported experimental values are peak potentials and not reversible half-wave values. Still, we argue that the values determined with eqs 4 and 5 provide the most accurate estimation of "reversible" redox potentials for this set of fluorescent dyes.

**3.2. Determination of the VIE and Oxidation Potentials for the DNA Monomers.** Once the generality and adequacy of the present methodology was confirmed in section 3.1, it seems reasonable to determine the reversible oxidation potentials of the DNA nucleosides and of the various nucleoside analogues by using eq 4. It should be emphasized that several of the organic molecules selected to generate the calibration curves have similar functional groups and heteroatoms as those of the DNA constituents. In addition, their redox values extend over a wider range of potentials than those expected for the DNA systems.

First of all, it is important to confirm the hypothesis that the gas-phase VIEs of the DNA bases vary in an approximately linear manner with the gas-phase AIE and the solvation energy term (eq 2). Thus, we have calculated the VIEs in ACN and the gas-phase AIEs of the nucleobases and N(1 or 9)-methylated nucleobases at the same level of theory used for the nucleosides and DNA base pairs (Table 4). A plot of the gas-phase VIEs of the nucleobases and N(1 or 9)-methylated nucleobases as a function of the gas-phase AIEs shows a remarkably good liner correlation at the B3LYP/6-31++G(d,p) level of theory (Figure 3A). Similarly, a good linear relationship is observed between the gas-phase VIEs and the VIEs in ACN (Figure 3B). Therefore, these linear relationships further support the approximations proposed in the derivation of eq 2 and show that they also hold for the DNA systems. Likewise, it is expected that linear relationships be obtained when calculating the adiabatic and solvated electron affinities for the DNA systems.

**TABLE 3: Determined Vertical Ionization and Electron Affinity Energies and Reversible Redox Potentials for Various Florescent Dyes and Their Experimental Peak Redox Potentials in DMF or ACN Solutions**

| system | VIE/eV[a] | VEA/eV[a] | $E°_{ox}$/V[b] | $E°_{red}$/V[b] |
|---|---|---|---|---|
| carbostyryl-124 (Ca-124) | 7.35 | −0.754 | 1.54 (1.19) | −2.70 (−2.24)[c] |
| coumarin-39 (C-39) | 6.76 | 0.112 | 1.20 (0.99) | −2.00 (−2.04) |
| coumarin-102 (C-102) | 6.80 | 0.060 | 1.22 (1.11) | −2.04 (−1.88 to −1.94) |
| coumarin-120 (C-120) | 7.58 | 0.067 | 1.65 (1.38) | −2.03 (−1.87 to −2.61) |
| coumarin-307 (C-307) | 7.90 | 0.860 | 1.83 (1.41) | −1.39 (−1.23 to −1.39) |
| 3-cyano-7-methoxycoumarin (C-3CN) | 8.49 | 1.240 | 2.16 (2.30) | −1.09 (−1.00 to −1.10) |
| 7-methoxycoumarin (C-3H) | 8.13 | 0.316 | 1.96 (2.04) | −1.83 (−1.62) |

[a] Gas-phase vertical energies at the B3LYP/6-31++G(d,p) level of theory. [b] Reversible oxidation potentials are determined in DMF or ACN solvents versus NHE with eq 4. [c] Experimental peak potentials are shown in parentheses and are taken form Seidel et al.[25]

**TABLE 4: Vertical and Adiabatic Ionization Energies and Estimated Reversible Oxidation Potentials for the DNA Nucleobases and N-Methylated Nucleobase Analogues in Vacuum and in ACN Solvent Conditions**

| nucleobase[a] | VIE/eV | $VIE_{ACN}$/eV[b] | AIE/eV | $E°_{ox}$/V[c] |
|---|---|---|---|---|
| U | 9.47 | 7.33 | 9.25 | 2.71 |
| T | 9.01[d] | 7.01 | 8.78 | 2.46 |
| C | 8.69[d] | 6.85 | 8.57 | 2.28 |
| A | 8.26[d] | 6.43 | 8.07 | 2.04 |
| G | 7.98[d] | 6.21 | 7.65 | 1.88 |
| 1-MetU | 9.06 | 7.1 | 8.88 | 2.48 |
| 1-MetT | 8.78 | 6.81[e] | 8.47 | 2.33 |
| 1-MetC | 8.53 | 6.67[e] | 8.31 | 2.19 |
| 9-MetA | 8.09 | 6.37 | 7.88 | 1.94 |
| 9-MetG | 7.83 | 6.15 | 7.49 | 1.79 |

[a] Optimized in the gas phase at the B3LYP/6-31++G(d,p) level of theory. [b] Single point calculations in acetonitrile at the IEFPCM/B3LYP/6-31++G(d,p) level of theory. [c] Reversible oxidation potentials in DMF or ACN solvents versus NHE are determined from the gas-phase VIEs (second column) with eq 4. [d] From ref 12. [e] From ref 56.

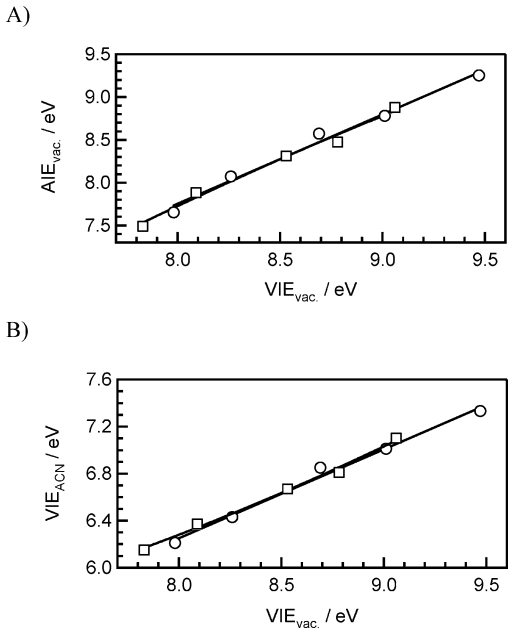



**Figure 3.** Gas-phase vertical ionization energies of the DNA and RNA nucleobases versus (A) their gas-phase adiabatic ionization energies and (B) their adiabatic ionization energies in acetonitrile. From left to right: guanine, adenine, cytosine, thymine, and uracil. Circles are for the N(9)-H and N(1)-H and squares are for the N(9)-$CH_3$ and N(1)-$CH_3$ purine and pyrimidine nucleobases.

This is because the relaxation effects in the determination of electron affinities are expected to be lower than those for ionization energies.

The optimized geometries of the DNA nucleosides are shown in Figure 4 and the corresponding VIE and oxidation potential in Table 5. Strikingly, the first ionization energy and oxidation potential depend on the orientation of the base around the N-glycosidic bond (Table 5 and Figure 4). In general, nucleosides with *anti* conformation show lower VIE and oxidation potentials than the corresponding *syn* conformers. As observed in Table 5, the oxidation potential of the nucleosides decreases by ∼0.2 V (∼0.3−0.4 eV for the VIE) going from *syn* to *anti* conformation. The increase in VIE and oxidation potential for the *syn* conformations is primarily due to the formation of an intramolecular hydrogen bond between the N(3) of the purine bases (C(2)═O for the pyrimidine bases) and the 5′-OH group of the sugar (Figure 5). To further corroborate this hypothesis we have performed additional VIE calculations on the *syn* dGuo conformer, where the hydrogen of the 5′-OH group of the sugar was rotated by 175° around the 5′-C−O bond to break its intramolecular interaction with the N(3) atom (geometrical coordinates are given as Supporting Information). The VIE of the modified *syn*-dGuo conformation decreases to 7.54 eV upon rotation of the hydrogen thus showing that the intramolecular H-bond is the main reason for the increase in VIE and oxidation potential of the syn conformations. The VIE and oxidation potential of the modified *syn*-dGuo conformation is almost identical to that of the *anti* conformation, showing that noncovalent hydrogen bonding interactions can modulate the redox properties of the nucleic acids. This observation is particularly important for experimental and theoretical studies where the redox potentials (and probably any other electronic property) of the DNA monomers are determined in aqueous solution.

Intramolecular hydrogen bonding interactions have been previously observed for the most stable guanosine enol conformer in the gas phase and in ab initio calculations.[53] Our gas-phase calculations predict that the *syn* conformer is more stable than the *anti* conformer by 5.9 kcal/mol for dAdo, 5.2 kcal/mol for dGuo, 4.2 kcal/mol for dCyd, and 0.4 kcal/mol for dThd at the B3LYP/6-31++G(d,p) level of theory. However, in single- and double-stranded DNA such intramolecular hydrogen bonds are not possible. Nonetheless, our results for the *anti* and *syn* conformation suggest that intermolecular hydrogen bond interactions between the bases and water molecules in DNA might modulate the local redox potentials of the bases. In this regard, it is worthwhile to note that inclusion of explicit water molecules and counterions is essential for a proper and accurate description of the energetics and dynamics of charge transport in DNA.[54] In fact, such intermolecular hydrogen bonds between water molecules and the nucleic acids have been observed by infrared spectroscopy.[55]

Importantly, our calculations show that N-glycosidic bond formation decreases the VIE and oxidation potential of the bases. Recently, the vertical ionization energy of the nucleobases has been determined at the level of theory used in this work (see Table 4).[12] A decrease in VIE by as much as 0.4 eV for adenine, 0.6 eV for cytosine, 0.4 eV for guanine, and 0.7 eV for thymine

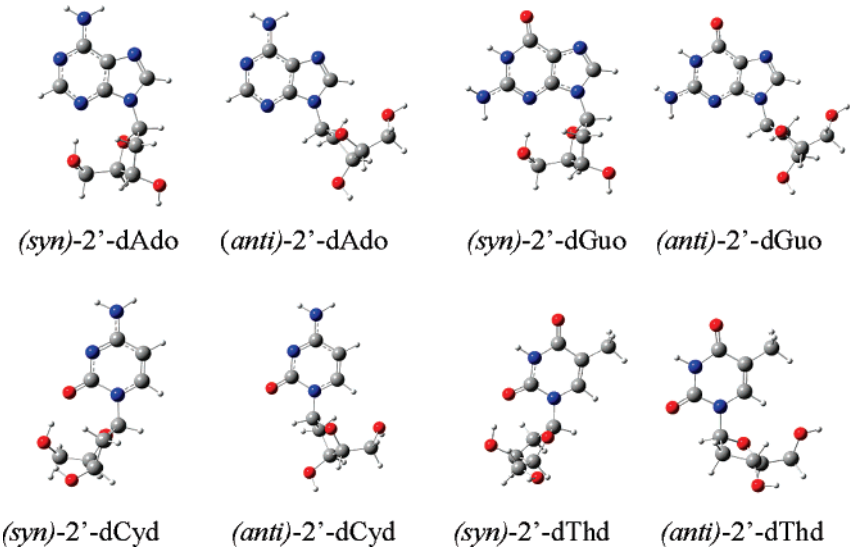



**Figure 4.** Optimized geometries for the DNA nucleosides at the B3LYP/6-31++G(d,p) level of theory. Carbon, hydrogen, nitrogen, and oxygen atoms are depicted in gray, white, blue, and red, respectively.

**TABLE 5: Ionization Energies and Estimated Reversible Oxidation Potentials for DNA Nucleosides and Nucleoside Analogues**

| system[a] | *syn*-VIE/ eV[b] | *anti*-VIE/ eV[b] | *syn*-$E°_{ox}$/ V[c] | *anti*-$E°_{red}$/ V[c] |
|---|---|---|---|---|
| 2′-deoxyadenosine | 8.19 | 7.86 | 2.01 | 1.83 |
| 2′-deoxycytidine | 8.48 | 8.09 | 2.18 | 1.96 |
| 2′-deoxyguanosine | 7.95 | 7.57 | 1.88 | 1.66 |
| 2′-deoxythymidine | 8.62 | 8.31 | 2.25 | 2.08 |
| 2′-deoxyinosine | 8.45 | 8.09 | 2.16 | 1.96 |
| 2′-deox-2-aminopurine | 8.04 | 7.91 | 1.93 | 1.86 |
| 8-oxo-2′-deoxyguanosine | 7.67 | 7.70 | 1.72 | 1.74 |
| 8-oxo-2′-deoxyadenosine | 8.15 | 8.14 | 1.99 | 1.98 |
| 5-methyl-2′-deoxycytidine | 8.26 | 7.83 | 2.05 | 1.81 |

[a] See the Supporting Information for optimized coordinates. [b] Gas-phase vertical energies at the B3LYP/6-31++G(d,p) level of theory. [c] Reversible oxidation potentials are determined in DMF or ACN solvents versus NHE with eq 4.

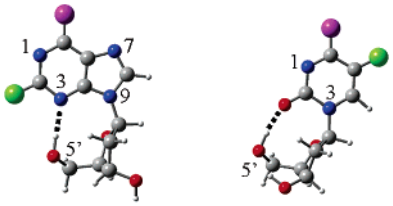



**Figure 5.** Generic base−sugar interactions for the *anti* (right) and *syn* (left) nucleoside conformations optimized in the gas phase at the B3LYP/6-31++G(d,p) level of theory. An intramolecular hydrogen bond is formed between the N(3)-purine or the C(2)═O-pyrimidine and the 5′-OH group of the sugar in the *syn* conformation. Carbon, hydrogen, nitrogen, and oxygen atoms are depicted in gray, white, blue, and red, respectively. dAdo: green = hydrogen and violet = $NH_2$. dGuo: green = $NH_2$; violet = oxygen. dCyd: green = hydrogen; violet = $NH_2$. dThd: green = $CH_3$; violet = oxygen.

upon N-glycosidic bond formation is evidenced by comparing the VIE values reported in Table 5 for the *anti* nucleoside conformers with those for the nucleobases (Table 4). Significantly, the lowering in VIE upon N-glycosidic bond formation is significantly higher than that obtained previously for cytosine ($\Delta$VIE = 0.3 eV) and thymine ($\Delta$VIE = 0.4 eV) bases with N1-methylated bases as models of the nucleosides.[56] Likewise, by using eq 4 and the VIE values of the nucleobases,[12] the oxidation potentials of adenine, cytosine, guanine, and thymine are determined as 2.04, 2.28, 1.88, and 2.46 V, respectively (Table 4). The oxidation values of the nucleobases are consistently higher than those of the *syn* and *anti* nucleosides (Table 5). Thus, the results show that the VIE and oxidation potentials are also modulated by covalent substitutions. This is further supported by the calculations reported below for various nucleoside analogues (see also Table 5).

The estimated reversible oxidation potentials follow the trend observed experimentally for the DNA bases in solution: G < A < C ≈ T.[19,25] The energy difference between the reversible values determined for the *anti* nucleoside conformations in this work and those estimated experimentally from peak potentials[25] in identical solvent conditions is 0.17 V for dGuo (or 0.14 V from the dGuo oxidation value in DMF reported in ref 34), 0.13 V for dAdo, 0.18 V for dCyd, and 0.03 V for dThd. The observed energy difference between the calculated and experimental values is proposed to be primarily due to the fact that the experimental values are irreversible, peak potentials. It is known that if the redox reaction is coupled to chemical reactions, both the peak currents and peak potentials can be affected, making it impossible to measure standard (reversible) oxidation potentials under well-defined equilibrium conditions. In such cases, the estimation of the standard oxidation potentials from peak potentials can deviate by as much as 0.15 to 0.3 V.[21,33] This is in agreement with the energy difference estimated above between the reversible oxidation potentials and the experimental peak potentials reported previously.[25] Thus, we argue that the oxidation potentials reported in Table 5 for the DNA nucleosides in ACN or DMF solutions are the most accurate set of values available at present.

Much less experimental information is available on the oxidation potentials of the other relevant DNA derivatives studied in this work (Figure 6). To our knowledge, only one experimental value has been reported for the oxidation potential of 8-oxodAdo (0.96 V)[57] and 2dAP (1.34 V[58]), none for 5-MetdCyd, two values for dI (1.39[59] and 1.5 V[60]), and three values for 8-oxodGuo (0.58,[57] 0.74,[61] and 1.09 V[34]). However, most of the experimental oxidation potentials for the nucleosides analogues were measured under solvent conditions other than DMF or ACN, and thus cannot be directly compared with the values reported in Table 5. Sheu and Foote[34] reported a 1.09 V oxidation potential for 8-oxodGuo in DMF, which is 0.62 V lower than the theoretical estimate. This difference cannot be easily explained by considering the experimental errors incurred

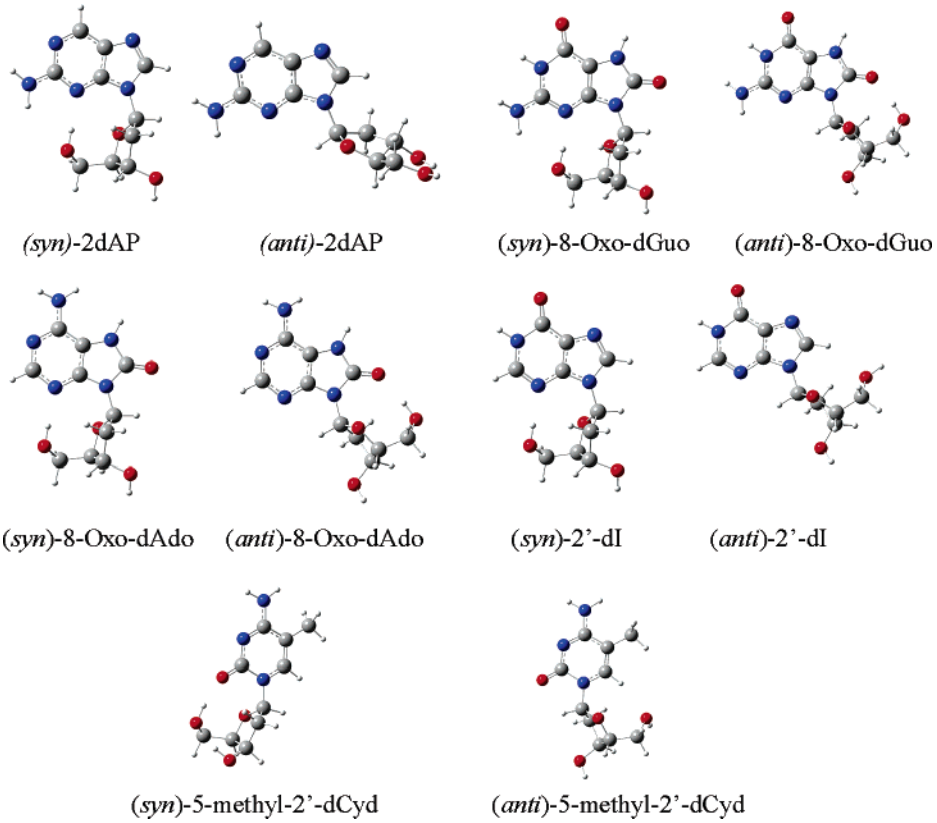



**Figure 6.** Optimized geometries for various DNA nucleoside analogues at the B3LYP/6-31++G(d,p) level of theory. Carbon, hydrogen, nitrogen, and oxygen atoms are depicted in gray, white, blue, and red, respectively.

in using irreversible measurements to estimate reversible oxidation potentials. Deprotonation of the 8-oxodGuo is expected to significantly lower the redox potential in aqueous solution (p$K_a$ of 6.6),[61] but its relevance on the oxidation potential of 8-oxodGuo in DMF is unknown. On the other hand, the fact that solvent effects are not taken into account in the determination of VIE in our calculations seems not to be the major reason for this discrepancy. This is because for the DNA nucleosides, and for the GC base pair (vide infra), a fairly good agreement of the reported oxidation values with experimental results was obtained. In any case, the values reported in Table 5 permit a direct comparison of the oxidation properties of the DNA nucleosides with those of the nucleoside analogues for the first time because they were determined under identical conditions.

For instance, our calculations suggest that charge transfer in DNA between 2dAP and the nucleic acids should occur by both hole and electron-transfer mechanisms. On the basis of the oxidation potentials determined for the DNA monomers in the *anti* conformation (Table 5), our results predict that both dGuo and dAdo should transfer a hole to photoexcited 2dAP, whereas dCyd and dThd should transfer an electron. Furthermore, our results suggest that dI should quench photoexcited 2dAP by the electron-transfer mechanisms. Importantly, these predictions are in complete agreement with experimental observations by Zewail and co-workers,[32] even though the experiments were performed in aqueous solutions.

The results reported in Table 5 also suggest that 5-MetdCyd has an oxidation potential comparable to that of dGuo and dAdo in DMF and ACN solutions. This observation suggests that 5-MetdCyd might compete with dGuo and dAdo for hole-trap in DNA. Interestingly, it has been reported that cytosine methylation defines hotspots for oxidative damage to DNA.[62] In addition, it has been suggested that 5-methylation of cytosine reduces its ionization potential from 8.79 to 8.50 eV,[56] which could lead to a rate acceleration for the electrochemical oxidation of its complementary guanine base.[18] The lowering in ionization energy observed by Close upon cytosine 5-methylation[56] is in good agreement with the lowering observed here for the nucleoside (Table 5). However, recent experiments by Kanvah and Schuster have not provided evidence that cytosine methylation is a general cause of enhance oxidative damage in DNA.[63]

Similarly, it has been suggested that 8-oxodGuo is a better hole-trap than dGuo.[34,64] Our results suggest that the 8-oxodGuo monomer could be a better hole-trap than dGuo in the *syn* conformation but that in the *anti* conformation both nucleosides have similar oxidation potentials (Table 5). A plausible explanation for the latter apparent disagreement with experiments is that in aqueous solutions an intermolecular hydrogen bond may be formed between a water molecule and dGuo and 8-oxo-dGuo in the *anti* conformations, making the oxidation potential of the latter lower than that of dGuo. In fact, the likelihood of intermolecular hydrogen bonding interaction between water molecules and the N(3) atom of guanine has been documented,[65,66] thus it is reasonable to suggest that the N(3) of dGuo and 8-oxodGuo should serve as a hydrogen acceptor in aqueous solutions. However, it seems clear that further experimental and theoretical efforts are mandatory in order to solve the apparent discrepancies observed above. In particular, future computational works directed at understanding the microscopic factor that influences the redox potentials of the DNA monomer in aqueous solutions, as well as the ionization and the electron affinity energies, should include explicit water−base interactions in their efforts. Work in this area is currently underway in our and other groups.[4,14−16]

As observed for the natural nucleosides, the first ionization energy and oxidation potential depend on whether or not an intramolecular hydrogen bond between the sugar and base

**TABLE 6: Calculated Reversible Oxidation Potentials and Vertical Ionization Energies for the Watson−Crick DNA Base Pairs**

| system | VIE/eV[a] | $E°_{ox}$/V[b] |
|---|---|---|
| G·C | 7.25 | 1.48 |
| 9-MetG·1-MetC | 7.07 | 1.38 |
| A·T | 7.83 | 1.81 |
| 9-MetA·1-MetT | 7.59 | 1.68 |

[a] Gas-phase vertical energies at the B3LYP/6-31++G(d,p) level of theory. [b] Reversible oxidation potentials are determined in DMF or ACN solvents versus NHE with eq 4.

analogue is formed (Table 5). In general, our gas-phase calculations predict that the *syn* conformer is more stable than the *anti* conformer by 4.9 kcal/mol for d2AP, 0.5 kcal/mol for 8-oxodAdo, 4.2 kcal/mol for 2′-dI, and 7.4 kcal/mol for 5-methyl-2′-dCyd at the B3LYP/6-31++G(d,p) level of theory. Interestingly, our calculations predict that the *anti* conformer of 8-oxodGuo is more stable than the *syn* conformation by 0.01 kcal/mol in the gas phase, but this is smaller than the accuracy of our calculations.

**3.3. Determination of VIE and Oxidation Potentials for the DNA Base Pairs.** The VIE and reversible oxidation potentials for the Watson−Crick DNA base pairs and their N-methylated derivatives are reported in Table 6. In the latter base pairs, the methyl group models the lowering in VIE observed in the nucleobases upon N-glycosidic bond formation (vide supra). The VIE values obtained for the base pairs are in favorable agreement with those calculated by others at a similar level of theory.[1,67] N-Methylation at the N(9)-purine and the N(1)-pyrimidine positions decreases the VIE of the G·C and A·T base pairs by 0.18 and 0.23 eV, respectively, at the B3LYP/6-31++G(d,p) level of theory (Table 6). The lowering in VIE of the base pairs by N-methylation is significant and of the same order as that observed for adenine and guanine bases upon Watson−Crick base pair formation. It is plausible that formation of the N-glycosidic bond would further lower the VIE of the base pairs.

Formation of Watson−Crick base pairs also lowers the one-electron oxidation potential, as expected. Base pair formation of 9-MetAde or 9-MetGua with the complementary pyrimidine nucleoside (modeled by its N-methylated analogues in Table 6) decreases its oxidation potential by 0.15 or 0.28 V, respectively. In particular, the energy difference between the oxidation potential for the G·C base pair and that of the guanine base is in remarkably good agreement with the value estimated by Peluso and co-workers using voltammetric measurements (0.34 V).[3] We expect that closer agreement to the experimental value could be obtained if nucleoside base pairs instead of N-methylated base pairs are used. To our knowledge, the experimental oxidation potential for the A·T base pair has yet to be reported, and the calculated value might be used to guide the experiments. Importantly, the calculations presented in this work show the sensitivity of the electronic properties of the DNA bases to covalent and noncovalent interactions.

**3.4. Determination of VEA and Reduction Potentials for DNA Nucleosides, Nucleoside Analogues, and Base Pairs.** The determination of accurate negative electron affinities has been a real challenge in computational chemistry,[44] and the DNA monomers are not an exception. The estimated vertical electron affinities of the nucleosides, nucleoside analogues, and DNA base pairs at the B3LYP/6-31++G(d,p) level of theory are reported in Table 1S (Supporting Information). The values are in stark contrast with the best theoretical estimates of vertical valence electron affinities reported by Sevilla and co-workers

**TABLE 7: Electron Affinities and Estimated Reduction Potentials for DNA Nucleobases, Watson−Crick Base Pairs, and *N*-Methylated Derivatives**

| system | VEA/eV[a] | $E°_{ox}$/V[b] |
|---|---|---|
| Gua | −1.25[c] | ∼−3.0[c] |
| Ade | −0.76 | −2.71 |
| Cyt | −0.58 | −2.56 |
| Thy | −0.29 | −2.32 |
| 9-MetAde | −0.69 | −2.65 |
| 1-MetCyt | −0.58 | −2.56 |
| 1-MetThy | −0.30 | −2.33 |
| Ade·Thy | −0.12 | −2.19 |
| 9-MetAde·1-MetThy | −0.13 | −2.20 |

[a] Gas-phase vertical energies at the B3LYP/6-311+G(2df,p)//B3LYP/6-31+G* level of theory. [b] Reduction potentials are estimated in DMF or ACN solvents versus NHE with eq 5. [c] Estimated by using the VEA reported in ref 43.

for the nucleobases: −0.80 V for A, −0.63 V for C, −1.25 V for G, and −0.28 V for T.[43] The reason for the lack of self-consistency among different DFT (B3LYP functional) calculations has been discussed previously, and the interested reader is referred to refs 43 and 44 for details. In short, it is known that the formation of dipole-bound states precluded the reliable determination of VEA for the DNA bases at the B3LYP/6-31++G(d,p) level of theory due to the extra diffuse function in the basis set. Similarly, our estimated VEA values for the DNA base pairs are in discrepancy with those reported previously (see ref 2), due to the formation of dipole-bound states, as suggested by inspection of the relevant molecular orbital (not shown). Therefore, we conclude that reliable reduction potentials for the DNA nucleosides and base pairs cannot be obtained at the B3LYP/6-31++G(d,p) level of theory. Our calculations, as well as those by others,[44] thus suggest that caution should be taken when estimating VEA at the DFT level of theory. Regardless, the dipole-bound VEA are include in Table 1S (Supporting Information) because such dipole-bound states have been observed in the gas-phase studies on nucleic acids,[68−71] whereas in solution only valence states are expected.

Vera and Pierini have recently investigated the feasibility of DFT methods with the B3LYP functional to accurately determined negative electron affinities of ground-state anions, including the DNA nucleobases.[44] It was found that the B3YLP/6-311+G(2df,p)//B3LYP/6-31+G* level of theory could satisfactorily reproduce the VEA for a wide range of molecular anions. Thus, in Table 7 we present calculations for the DNA nucleobases, the Watson−Crick base pairs, and the corresponding N-methylated derivatives using this approach in an attempt to better estimate the reduction potentials for these systems. Our results for the VEA of adenine, cytosine, guanine, and thymine bases are in very good agreement with those of Vera and Pierini.[44] Similarly, our gas-phase results for the nucleobases are in good agreement with those of Sevilla and co-workers,[43] with the exception of guanine. For the latter nucleobase the calculated VEA value at the B3YLP/6-311+G(2df,p)//B3LYP/6-31+G* level of theory represents the dipole-bound and not the valence state of the radical anion, as previously reported.[44] Thus, the calculation of VEA for the valence state of the guanine radical anion is particularly problematic even at the B3YLP/6-311+G(2df,p)//B3LYP/6-31+G* level of theory. This problem persists for the N-methylated guanine and guanine base pair (not shown). Thus, for the guanine systems we are not able to report reliable reduction potential values. More recently, Schaefer and co-workers has used a carefully calibrated theoretical method[72] based on the B3LYP/DZP++ level of theory to estimated the adiabatic electron affinities of the DNA

nucleosides.[73,74] The authors calibrated the exponents of the diffuse functions using the directions of Lee and Schaefer.[75] Unfortunately, to our knowledge, this method has yet to be applied to the calculation of VEA of the DNA nucleobases.

Having in mind the above limitations, Table 7 reports the estimated values for the reversible reduction potentials of the DNA nucleobases and base pairs, and corresponding N-methylated derivatives, using eq 5. These reduction potentials are presented as estimated values because eq 5 was calibrated with experimental data and the B3LYP/6-31++G(d,p) level of theory but not the B3YLP/6-311+G(2df,p)//B3LYP/6-31+G* level. Nonetheless, our results for adenine, cytosine, and thymine are in very good agreement (within 0.2 V) with those estimated by Seidel and co-workers from nucleoside quenching experiments.[25] The reduction potentials of the guanine base pair are not reported in Table 7 due to contaminations of the radical anion by dipole-bound states (vide supra). However, we can roughly estimate the reduction potential of guanine by using the most accurate vertical electron affinity value reported for guanine (−1.25 eV).[43] A reduction potential of ca. −3.0 V is estimated for guanine, and it is included in Table 7.

In general, N-methylation has a negligible effect on the VEA and reduction potentials of the nucleobases and base pairs (Table 7). This is in contrast to the great sensitivity observed for the VIE and the oxidation potentials of the nucleobases and nucleosides in the previous section. On the other hand, the reduction potentials and VEA of the nucleobases are modulated by base pairing formation. The reduction potential of adenine and 9-methyladenine increases by ∼0.6 V upon base pair formation. These results further show the sensitivity of the DNA electronic properties to covalent and noncovalent interactions.

## 4. Conclusions

The redox potentials of the DNA bases are fundamental physical properties essential to understand charge transfer and damage processes (by radiation or photons) occurring in DNA. Here we have presented benchmark calculations permitting the determination of a complete and accurate set of reversible redox potentials. The reported values are based on experimentally calibrated data using a critically compiled set of reversible redox potentials for 20 organic molecules.[24] Our calculations show that base pairing and covalent and noncovalent (hydrogen bonding) interactions modulate the redox potential of the DNA bases. Significantly, our results for the DNA nucleosides and G·C base pair are in good agreement with those estimated experimentally in identical solvents.[3,25]

Vertical electron affinities and reduction potentials for the nucleobases, DNA base pairs, and corresponding N-methylated derivatives were successfully determined by using the B3YLP/6-311+G(2df,p)//B3LYP/6-31+G* methodology.[44] The only exception was the guanine nucleobase and its base pair, for which contamination of the radical anions by dipole-bound states precluded the estimation of valence bound VEA and consequently its reduction potentials. In an attempt to partially overcome the limitations observed in the calculations of the reduction potential of guanine, we have estimated its reduction potential (∼3.0 V) using its most accurate VEA value reported in the literature.[43] It was further shown that the reduction potentials of the adenine and thymine increase upon base pair formation, whereas methylation at N(9) and N(1), respectively, did not appreciably affect its value at the selected level of theory. Similar results are expected in the case of guanine and cytosine bases.

Although our calculations are directly relevant to monomeric and single DNA base pairs in ACN or DMF solutions, they might also aid in elucidating how the redox properties of the bases modulate electronic energy relaxation in DNA.[32,76] Recent experimental evidence suggests that the long-lived, excited states formed in DNA base stacks have significant charge-transfer character and control the fate of excess electronic energy in DNA double helixes.[77−79] With an accurate knowledge of the local and dynamical redox properties of the bases in double-stranded DNA, an in-depth understanding of the interplay between electronic energy relaxation and charge transfer in DNA might be possible. It would be desirable to determine the redox properties for nucleoside base stacks and more complex DNA systems that include explicit solvent effects. Work in this area is currently underway. The straightforward method presented in this work should be extendable to other molecular systems for which determination of experimental "reversible" redox potentials is not feasible. Results of such studies might prove fruitful in elucidating charge/electron transfer and electronic energy relaxation processes in general.

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**Supporting Information Available:** Tables including the optimized structures of the selected organic molecules at the B3LPY/6-31++G(d,p) level of theory, containing the VEA of all the DNA constituents studied in this work at the B3LYP/6-31++G(d,p) level of theory, and giving geometrical coordinates of the neutral molecules optimized at the B3LYP/6-31++G(d,p) level of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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