Ab Initio Ionization Energy Thresholds of DNA and RNA Bases in Gas Phase and in Aqueous Solution

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Ionization energy thresholds have been calculated for the canonical DNA and RNA bases both in the gas phase and in aqueous solution at HF and MP2 levels of theory using standard 6-31++G(d,p) basis set. It is shown that the use of the spin projection procedure to correct the open-shell systems for contamination by higher spin states significantly improves the calculated ionization energies. This correction provides practically experimental accuracy to the calculated ionization energies in gas and in aqueous phase. The stabilization of the vertical and adiabatic radical cation energies by water solvation range from 2.15 to 2.58 eV, and from 2.12 to 2.79 eV, relative to the gas-phase results, respectively. The ab initio calculations show that long-range bulk polarization interactions have a significant role in the lowering of the first ionization energy of the DNA and RNA bases. Taking into account the stabilization of the free electron by the solvent, the adiabatic ionization energies in aqueous solution are estimated to be 5.27, 5.05, 4.91, 4.81, and 4.42 eV for uracil, thymine, cytosine, adenine, and guanine, respectively.

1. Introduction

It has been a goal for many decades to determine the first ionization energy thresholds of the canonical DNA/RNA bases (Figure 1) under physiological conditions. The major experimental difficulties in the determination of the minimum energy required to ionize the bases with one quanta of excitation are their very small photoionization yields ($10^{-2}-10^{-3}$)[1,2] and the high reactivity of the radical cation-hydrated electron pair formed in aqueous solution.[3] In this work, theoretical calculations are performed to estimate the threshold energies necessary to ionize the DNA and RNA bases by one photon in aqueous medium.

Experimentally, the ionization energy threshold of 2′-deoxyguanosine in aqueous solution has been estimated to be (4.8 ± 0.3) eV upon irradiation at different wavelengths, using as a probe the formation of oxidation products.[4] Further experimental evidence suggest that the DNA/RNA bases,[2,5−10] and even a wide range of purine containing dinucleotides,[11] have ionization energy thresholds in the vicinity of 4.7 eV in aqueous solution. However, the estimated ionization threshold energies of the DNA/RNA constituents in aqueous solution are still based on indirect experimental evidence.[4] Thus, a comprehensive and reliable computational study of the first ionization energies of the DNA/RNA bases is important because of the lack of direct and accurate experimental data.

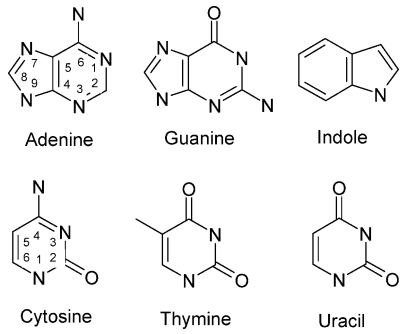

Figure 1. DNA and RNA base structures and standard numbering (hydrogen bonds not shown). The indole structure is also presented for comparison.

The physical and chemical factors which are important to provide an accurate description of the DNA and RNA ionization energy thresholds in aqueous solution include base pairing,[12] base stacking,[13] and solvation by water molecules. The solvent can control the stabilization component of the ionization energies with respect to two distinct types of solute−solvent interactions. These are the specific short-range hydrogen-bonding interactions and the long-range solvent polarization interactions.[14] In the former case, an explicit interaction with a limited number of solvent water molecules could influence the ionization energies by the reorientation of the solvent water dipoles in the stabilization process of the radical cation−electron pair formed.

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This case is currently under investigation.[15] In the latter case, the solvent polarization interactions could also have a significant effect on the solvation and stabilization of the radical cation and the ejected electron. This subject will be one of the principal concerns in this work. To describe the effects of the surrounding medium, a self-consistent reaction field method is used to account for nonspecific solvent interactions on the ionization energies and on the nuclear relaxation of the DNA/RNA bases. Relatively few accurate studies (mostly semiempirical calculations) of DNA base radicals under physiologically relevant conditions are available in the literature,[16−19] primarily owing to a lack of appropriate methods to deal with such large systems at a high level of accuracy. Therefore, the accurate ab initio study presented here should contribute to a better knowledge of the threshold energies necessary to ionize the DNA and RNA bases in aqueous phase.

LeBreton and co-workers[16] have reported the ionization energy threshold of various DNA and RNA nucleotides in aqueous solutions using a combination of UV photoelectron data and theoretical calculations. These early investigations have been of great value to provide descriptions of electron distribution and semiempirical ionization energies for as many as 13 of the highest occupied molecular orbitals of various deoxy-nucleotides.[16,18,20−22] Colson and Sevilla have reviewed results from ab initio HF and MP2 calculations of the ionization energies in the gas phase, as well as effects of base−water interactions.[17] The available calculations have been mainly performed using small or modest basis sets and the Koopmans' approximation. For the calculation of adiabatic ionization energies of many-electron systems, the Koopmans' approximation within ab initio methods is rather inaccurate because it assumes that the remaining electrons do not reorganize when the electron is ejected. Then, it is not surprising that calculated ionization energies of organic molecules using Koopmans' approximation typically deviate from experimental values by 1−2 eV.[23] More recently, ab initio propagator calculations in the partial third-order (P3) approximation[24] with the 6-311G(d,p) basis set have been used to obtain a more accurate description of the ionization energy values of the DNA and RNA bases in the gas phase.[25] As the P3 method is not currently parametrized to treat molecules in aqueous solution, the scope of the present work is to find suitable methods for obtaining ionization energies in an aqueous environment.

In this report, spin-corrected ab initio calculations at the HF/ and MP2/6-31++G(d,p) level of theory are performed to have an accurate description of the first ionization energy thresholds of the canonical DNA/RNA bases in aqueous solution. Although the emphasis is on calculations of the ionization energy thresholds in aqueous solution, the ionization energies in gas phase are revisited taking into account the nonplanarity of the neutral bases and corrections for spin contamination of the open-shell systems by higher spin states. The indole molecule is used as a model compound to validate and probe the accuracy of the theoretical approach used to calculate the ionization energies because its experimental ionization energy threshold has been reported in aqueous solution.[26]

2. Computational Methods

All calculations were performed using the GAUSSIAN98 suite of programs.[27] All geometries of the DNA/RNA bases, indole, and their corresponding radical cations were optimized without symmetry restrictions (C_1 symmetry was assumed) by the gradient procedure at HF/6-31G(d), HF/6-31++G(d,p), MP2/6-31G(d), and MP2/6-31++G(d,p) levels of theory. The total energies of the open-shell systems were calculated using unrestricted wave functions at both levels of theory. The optimized structures were verified as local minima on the potential energy surface by establishing that the matrixes of the energy second derivatives (Hessians) at HF/6-31G(d) and HF/6-31++G(d,p) levels have zero imaginary eigenvalues. However, only the energies obtained using the 6-31++G(d,p) basis set at both levels of theory are presented in this work. The HF/6-31++G(d,p) and MP2/6-31++G(d,p) values of total energy were corrected for the zero-point energy (ZPE) contribution calculated at HF/6-31++G(d,p) level. The zero-point energies were scaled by the standard factor of 0.9153.[28]

To model the bulk solvent effects on the ionization energy values of the DNA/RNA bases and indole, the self-consistent isodensity polarizable continuum model, abbreviated as PCM method thereafter, of Tomasi and co-workers was employed.[29−36] This method was the best choice since it allows, with the same degree of accuracy, the evaluation of both direct (i.e., polarization) and indirect (i.e., relaxation) solvent effects. In the PCM method, the solvent cavities have a realistic molecular shape, and the reaction field is described in terms of apparent polarization charges or reaction field factors included in the solute's Hamiltonian. In this manner, it is possible to perform iterative procedures leading to the self-consistence between the solute wave function and the solvent polarization.[29−36] Thus, the gas-phase structures were further reoptimized using the PCM method at HF/6-31++G(d,p) level of theory. In addition, the single-point PCM/MP2/6-31++G(d,p) calculations were performed on the fully optimized base structures at PCM/HF/6-31++G(d,p). The dielectric constant of water ($\epsilon = 78.39$) was used throughout.

It is well known that Møller−Plesset perturbation calculations can be used successfully as a method for simple and efficient computations of electron correlation energies. For open-shell molecules, however, the unrestricted Hartree−Fock wave function is often contaminated by higher spin states.[37] To significantly remove the spin contamination errors in open-shell systems, we used the spin annihilation or projection procedure proposed by Schlegel,[38] herein referred to as PHF and PMP2.

The gas-phase first ionization energies of the DNA/RNA bases and indole were calculated as follows. The vertical IEs were obtained from the difference in total energy between the neutral base and its radical cation, evaluated both at the optimized geometry of the neutral base. The adiabatic IEs were obtained in the same way, but using the total energy obtained from the optimized geometry of the radical cation. In aqueous solutions, the ionization energies were calculated by subtracting the total energies of the neutral molecule and radical cation obtained from the PCM model. To take into consideration the stabilization energy of the ejected hydrated electron, the experimental ground-state energy of the "quasi-free" electron in the liquid (−1.3 eV[39,40]) was added in the calculation of the ionization energies (IEs) according to the equation:

$$\mathrm{IE}_{\mathrm{cond}} = E_{\mathrm{n}} - E_{\mathrm{r}} + V \qquad (1)$$

where E_{n} is the total energy of the neutral molecule, E_{r} is the total energy of the radical cation in the condensed phase (vertical or adiabatic), and V is the hydrated electron stabilization energy as defined above.

3. Results and Discussion

3.1. Gas-Phase Ionization Energies of Indole and of the DNA and RNA Bases. The calculated vertical and adiabatic

TABLE 1: Calculated and Experimental Gas-Phase Ionization Energies of Indole and Canonical DNA/RNA Bases[a] (in eV)[e]

system	HF_{vert}	$MP2_{vert}$	HF_{adia}	$MP2_{adia}$	PHF_{vert}	$PMP2_{vert}$	PHF_{adia}	$PMP2_{adia}$	$IE_{vert.}$[b]	IE_{adia}[b]
U	8.77	10.35	8.15	9.47	8.48	9.43	8.10	9.36	9.50	9.32
Thy	8.16	9.50	7.78	9.00	8.21	9.07	7.79	8.74	9.14	8.87
Cyt	7.55	9.44	7.30	9.07	7.69	8.69	7.35	8.78	8.80	8.68
Ade	7.45	9.38	7.17	8.38	7.36	8.62	7.09	8.23	8.48	8.26
Gua	6.90	8.88	6.61	8.19	6.97	8.33	6.48	7.90	8.24	7.77
Ind	6.69	7.96	6.66	7.66	6.73	7.68	6.21	7.67	7.90[c]	7.76, 7.78[d]

[a] All calculations were done using the 6-31++G(d,p) standard basis set and the adiabatic energies are corrected for ZPE at HF/6-31++G(d,p) level of theory (see Computational Methods section for further details). [b] Taken from ref 41. [c] Taken from refs 42 and 43. [d] Taken from ref 44. [e] Ionization energies were calculated using the nonplanar optimized geometries and both standard and spin-corrected (PHF and PMP2) calculations are reported.

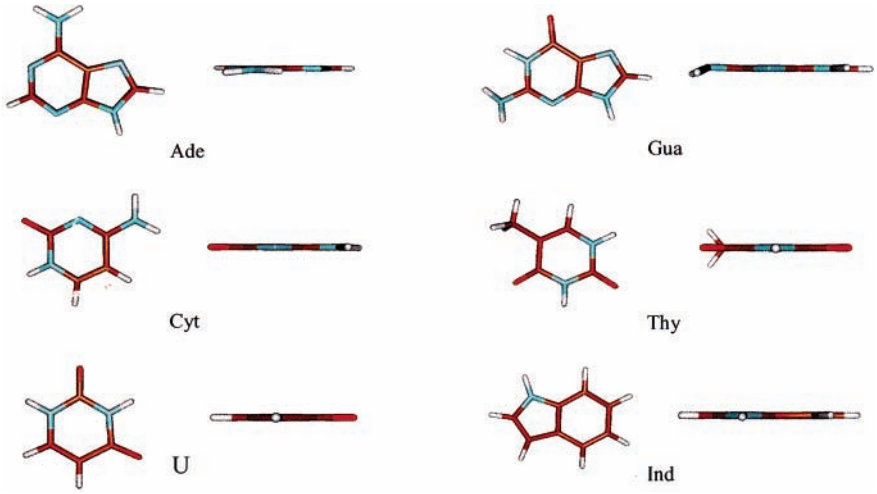

Figure 2. Optimized neutral geometries for the DNA and RNA bases and indole in aqueous solution at HF/6-31++G(d,p) level of theory. In the figure, oxygen atoms are depicted in red, nitrogen atoms in blue, carbon atoms in brown, and hydrogen atoms in white.

first ionization energies in the gas phase for DNA/RNA bases and indole and a comparison with known experimental values[41−44] are presented in Table 1. All the calculated values follow the same order observed experimentally as I < G < A < C ≈ T < U, independent of the level of theory. These results suggest that qualitative predictions of the electronic properties of these systems in the gas phase can be obtained using either HF or MP2 level of theory. However, the MP2 calculations are in better agreement with the experimental results, showing that electron correlation plays a significant role in calculating accurate electronic properties of these biomolecules. The results of the ionization energy for all the bases in the gas phase are in good agreement with previous theoretical calculations[45,46] and in satisfactory agreement with the experimental results.[41−44]

A significant improvement of the calculated ionization energy values in the gas phase, relative to the experimental values,[41−44] is obtained upon correction of the open-shell systems for spin contamination effects (Table 1). The vertical and adiabatic ionization energy results, at the PMP2/6-31++G(d,p) level, are in very good agreement with the experimental values for all the bases (within 0.15 eV or less), whereas PHF theory underestimates the magnitude by approximately 1.2 eV. In indole, the vertical ionization energy obtained at PMP2/6-31++G(d,p) is in very good agreement with the experimental value (see Table 1). However, the PHF level of theory underestimated the ionization energy by ca. 1 eV. A similar result to that of the vertical ionization energy of indole was obtained for the adiabatic ionization energy (Table 1). To the best of our knowledge, the correction for contamination by higher spin states (≤0.6 eV for vertical and ≤0.2 eV for adiabatic IEs) has been performed for the first time on the calculated gas-phase radical cation energies of the DNA/RNA bases and indole. The nonplanar nature of the neutral DNA/RNA bases has only a negligible effect on the ionization energy calculations.

There does seem to be a small discrepancy in the adiabatic PMP2 values for cytosine and thymine in Table 1, since the computed values are nearly identical, whereas the experimental values have the IE of thymine 0.19 eV above cytosine. There are several reasons for small disagreements observed here. First of all, the experimental photoelectric spectra of cytosine are rather broad,[47] indicating the presence of several isomers. Also, the experimental data were taken at rather high temperatures, which could result in partial decomposition of the base. Though no error limits are given in the experimental paper,[47] it may just be that errors in measuring the IE of cytosine are greater than for the other bases. One must also consider the accuracy of the ab initio calculations. While the PMP2 calculations are useful in eliminating some of the contamination from higher order spin states, the results still contain a small amount of spin contamination. Further experimental and theoretical work is needed to resolve this apparent discrepancy.

3.2. Bulk Solvent Polarization Effects on the Radical Cation and First Ionization Energies of the DNA/RNA Bases and Indole. Although gas-phase calculations of the neutral DNA bases result in a partial sp^3 pyramidalization of the exocyclic amino groups,[48−50] the neutral DNA bases become nearly planar upon consideration of bulk solvent effects. The optimized geometries for the neutral bases, and indole, at the PCM/HF/6-31++G(d,p) level of theory are shown in Figure 2. The nonplanar character of the amino group is still observed in guanine and to a much lower extent in adenine. The nonplanarity of the bases is further reduced upon oxidation of the DNA/RNA bases in gas and in aqueous phase. The optimized coordinates obtained for the gas and the aqueous phase calculations are given in the Supporting Information section.

TABLE 2: Calculated Vertical and Adiabatic Ionization Energies in Aqueous Solution at MP2/6-31++G(d,p) Level of Theory[a] (in eV)[d]

system	HF_{vert}	PHF_{vert}	HF_{adia}	PHF_{adia}	$MP2_{vert}$	$PMP2_{vert}$	$MP2_{adia}$	$PMP2_{adia}$	IE[b]
U	4.78	4.36	4.40	3.99	5.87	5.55	5.51	5.27	
Thy	4.58	4.28	4.08	3.83	5.61	5.36	5.24	5.05	5.4
Cyt	4.38	3.57	4.09	3.68	5.94	5.24	5.13	4.91	5.5
Ade	3.96	3.38	3.70	3.35	5.96	5.08	5.07	4.81	5.0
Gua	3.69	3.30	3.24	2.87	5.09	4.77	4.72	4.42	4.8
Ind	3.54	3.16	3.13	2.13	4.79	4.46	5.24	4.36	4.35[c]−4.46

[a] The stabilization energy of the hydrated electron[39,40] has been taken into account in the calculations of the ionization energies and the adiabatic ionization energies are corrected for ZPE at HF/6-31++G(d,p) level of theory (see Computational Methods section for further details). [b] Taken from ref 16 for the base nucleotides. [c] Taken from ref 26. [d] Both standard and spin-corrected (PHF and PMP2) calculations are reported.

The bulk solvent polarization effects on the first ionization energies of the DNA/RNA bases, and indole, are presented in Table 2. Indole was used as a model compound to validate the theoretical approach used because its ionization energy threshold in aqueous solution has been determined experimentally.[26] Our calculations gave a value of 4.36 eV, in excellent agreement with those obtained experimentally (4.35 eV),[26] and by semiempirical methods, 4.64 ± 0.5 eV.[16] Further support of the procedure used in this work comes from our calculated adiabatic ionization energy for guanine, which is in good agreement with the experimentally estimated ionization threshold of 2′-deoxyguanosine, in the range of 4.8 ± 0.3 eV to 4.9 ± 0.5 eV, in aqueous solution at pH 6.3.[4]

The spin-corrected and uncorrected (or standard) values of the ionization energies at the HF and the MP2 level of theory are presented in Table 2. After correction for spin contamination of the open-shell systems by higher states, the calculated ionization energies follow the experimentally expected trends (I < G < A < C < T < U). Taking into consideration the bulk water solvation, the stabilization energy of the adiabatic radical cation range from 2.12 to 2.79 eV relative to the gas-phase values. Using eq 1, vertical and adiabatic aqueous ionization energies were calculated for the DNA/RNA bases and indole, taking into consideration the stabilization of the ejected electron by the water solvent (Table 2). The values are in the range of 5.55−4.77 eV and 5.27−4.42 eV in the condensed phase for vertical and adiabatic ionization energies, respectively. The lowering of the adiabatic energies upon formation of the radical-cation-hydrated electron pair range from 3.48 to 4.05 eV at the MP2/6-31++G(d,p) level of theory, in good agreement with the widely used 3.50 eV value.[51] These results show the significant role of bulk water solvation on the lowering of the first ionization energy of the bases. In addition, the calculations suggest that the ionization energies of these molecules in aqueous solution, within the PCM method, have values similar to photon energies in the wavelength range of 240−280 nm.

In native DNA, the lowering of the ionization energy of the bases might be more pronounced. Recent theoretical calculations indicate that hydrogen-bonding and base-stacking interactions decrease the threshold ionization energies compared to those of the free bases by 0.5−0.7 eV.[12,13,52] Lowering the ionization energy values of the free bases by 0.5−0.7 eV leads to a threshold wavelength in the range of 260−300 nm. These wavelengths are within the UV−B range occurring in the solar spectrum, further emphasizing the importance of global efforts to reduce the depletion of the atmospheric ozone layer. However, the accessibility of the water molecules to the bases in single- and double-stranded DNA/RNA might be diminished because of the effective shielding obtained by base-stacking and base-pairing interactions between the bases. In this work, it is shown that bulk water solvation is one of the most significant factors that contributes to the lowering of the DNA/RNA bases ionization energy thresholds. Thus, the aqueous phase ionization values reported here should be considered a lower limit in ionizations in single- and double-stranded DNA/RNA bases under physiological conditions.

4. Conclusions

In this work, a comprehensive ab initio study of the DNA and RNA bases, and of their cationic radicals, is presented. The reliability of the spin-corrected MP2/6-31++G(d,p) calculations is confirmed by the good agreement with existing experimental gas-phase data, and by the agreement of our ionization energy thresholds of guanine and indole with experimentally determined values in aqueous solution. Furthermore, it is demonstrated that long-range bulk polarization interactions have a significant role in the lowering of the first vertical and adiabatic ionization energies of the DNA and RNA bases, and a quantitative estimate of this stabilization energy is given for each base. The spin projection procedure was used to correct the open-shell systems for contamination by higher spin states. It was shown that this correction is important to obtain good agreement with the experimental results and to preserve the expected energy trends of the ionization energy thresholds in aqueous phase. Finally, the new results presented in this work support the idea that the solar energy thresholds reaching the earth's surface might induce deleterious damage and photochemical oxidation of the DNA/RNA constituents under physiologically relevant conditions.

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Supporting Information Available: Optimized coordinates of the DNA and RNA bases (neutral bases and radical cations) in gas and in aqueous phase at MP2/6-31++G(d,p) and HF/6-31++G(d,p) levels of theory, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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