DNA Lesion Can Facilitate Base Ionization: Vertical Ionization Energies of Aqueous 8-Oxoguanine and its Nucleoside and Nucleotide

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ABSTRACT

8-oxoguanine is one of the key products of indirect radiation damage to DNA by reactive oxygen species. Here, we describe ionization of this damaged nucleobase and the corresponding nucleoside and nucleotide in aqueous phase, modeled by the non-equilibrium polarizable continuum model, establishing their lowest vertical ionization energies of 6.8 - 7.0 eV. We thus confirm that 8-oxoguanine has even lower ionization energy than the parental guanine, which is the canonical nucleobase with the lowest ionization energy. Therefore, it can act as a trap for the cationic hole formed by ionizing radiation and thus protect DNA from further radiation damage. We also model using time-dependent density functional theory and measure by liquid jet photoelectron spectroscopy the valence photoelectron spectrum of 8-oxoguanine in water. We show that the calculated higher lying ionization states match well the experiment which, however, is not sensitive enough to capture the electron signal corresponding to the lowest ionization process due to the low solubility of 8-oxoguanine in water.

KEYWORDS: 8-oxoguanine, aqueous solution, photoionization, ab initio calculations

Introduction

Ionization of nucleobases is the initial key step leading to direct DNA damage and mutation.[1] Among the four nucleobases guanine has the lowest ionization energy.[2] Therefore, the positive hole created in the photoionization process tends to localize on the guanine base, which is also the most susceptible site for oxidative processes. Vulnerability of guanine to reactive oxygen species formed among others within indirect radiation damage of DNA leads to production of a variety of products, in particular 8-oxoguanine (8-OG).[3] This lesion is estimated to be generated at the rate of approximately 2000 per human cell per day.[4, 5] Its concentration in the cellular DNA is, in fact, a quantitative measure of the degree of damage that an organism has undergone.[6] The 8-OG lesions within DNA can cause serious problems.[7, 8] Because of an additional oxygen atom on the base it can form a Hoogsten base pair with adenine instead of forming the common guanine-cytosine Watson-Crick base pair. It is believed that this base pair mismatch is responsible for incorrect interpretation of genetic code, and consequently may lead to mutations.[9, 10] On the other hand, 8-OG is more susceptible to oxidation than the original base guanine. Because of this, it has been suggested that free 8-OG may serve as the trap for the positive hole and thus protect other bases including guanine from oxidation.[8, 11]

Further oxidation of 8-OG has been studied both by experimental[12, 13] and theoretical[14] groups. Additionally, there are experimental[11] and computational[15] studies of ionization, which may precede oxidation of guanine to 8-OG, however, the crucial knowledge of the vertical ionization energy (VIE) of 8-OG and its nucleoside and nucleotide in the context of the aqueous DNA environment has been missing, with only a single calculation on the parent species published most recently.[16] The principle aim of the present study is to fill this gap by establishing computationally accurate VIEs of the aqueous 8-OG base and its nucleoside and nucleotide.

Methods

Computational

The lowest VIEs of 8-OG and its singly ($8\text{-}OG^{1-}$) and doubly ($8\text{-}OG^{2-}$) deprotonated forms, as well as 8-oxo-2'-deoxyguanosine (8-OdGs) and the singly deprotonated 8-oxo-2'-deoxyguanosine monophosphate ($8\text{-}OdGMP^{1-}$) were evaluated as the difference between the ground state energy after and before ionization, at the optimal geometry of the closed shell species before ionization. For calculating higher VIEs for 8-OG, $8\text{-}OG^{1-}$, and $8\text{-}OG^{2-}$ excitation energies to the singly occupied molecular orbital of the ionized molecule (again at the geometry of the species before ionization) were added to the lowest VIE.[17, 18] By Gaussian broadening each of the calculated ionization energy by 1 eV[17, 18] this procedure allowed us to construct photoionization spectra comparable to experiment. For calculation of the spectra, we considered only the lowest in energy tautomer of $8\text{-}OG^{1-}$ and $8\text{-}OG^{2-}$, which should be dominantly populated (~90 %) at ambient conditions.[19] Additionally, test calculations for the second lowest tautomers showed that the spectra are very similar to those for the lowest tautomers.

Effects of solvation were taken into account within the non-equilibrium polarizable continuum model (NEPCM) accounting for the electronic but not nuclear relaxation of the solvent upon ionization of the solute, which is appropriate when modeling VIEs.[20-22] For the doubly charged $8\text{-}OG^{2-}$ species we checked the applicability of the continuum description of the solvent by performing also hybrid calculations with one to five explicit water molecules optimized around $8\text{-}OG^{2-}$ and then placed in the NEPCM cavity. Within this procedure, excitations originating from the explicit water molecules were excluded from the spectra and only excitations originating from the base were considered.

To evaluate the lowest VIE, we used the unrestricted version of the second order Møller-Plesset (MP2) method with the aug-cc-pVDZ basis set. Higher spin components were annihilated via Schlegel's projection method (PMP2).[23] Previous calculations for isolated gas-phase nucleic acid bases showed that for purine nucleobases this approach provides ionization energies within 0.2 eV from the benchmark CCSD(T) values.[24] To obtain the higher ionization states, we additionally employed the time-dependent density functional approach (TDDFT) using the BMK functional,[25] as in our previous study on purines.[17] All calculations were performed using the Gaussian 03 program.[26]

Experimental

Valence photoelectron-spectroscopy measurements from 8-OG (2-amino-6,8-dihydroxpurine hydrochloride) aqueous solution were done at the U41-PGM undulator beamline of the synchrotron radiation facility BESSY II, Berlin. All the spectra were collected from a 20-μm vacuum liquid jet travelling at a velocity of approximately 40 ms^{-1}, with a temperature of 10^{o}C. Details of the technique and experimental setup were described in our previous papers.[27, 28] In short, photoelectrons were detected in the direction normal to both the synchrotron light polarization vector and the flow of the liquid jet. Photoelectrons pass through a 150 μm diameter orifice separating the main interaction chamber (at 10^{-4} mbar) from the differentially pumped detector chamber (at 10^{-8} mbar), which houses a hemispherical electron-energy analyzer. The distance of less than 0.5 mm between the liquid jet and the orifice ensures that the detected electrons did not suffered from inelastic scattering with water vapor near the jet surface.[27] The applied photon energy was 180 eV and the energy resolution of the beamline in this energy range was better than 50 meV. The resolution of the hemispherical energy analyzer of approximately 100 meV at 10 eV pass energy is constant with kinetic energy. The small focal size of 23x12

μm^2 of the incident photon beam matches the diameter of the liquid jet leading to an almost negligible photoelectron signal from water vapor (less than 5% of the total signal).

In order to achieve the highest possible concentration, 8-OG has been dissolved in water at basic pH. We found that at pH 12.6 500 mg of 8-OG is fully soluble up to 0.04 M, but this is not the case at lower pH. Adjustment of pH was made by addition of NaOH. The basic water solution, containing no 8-OG, was used to measure a reference photoelectron spectrum, and its subtraction from the solution spectrum yields the small signal due to ionization of 8-OG(aq). 2-amino-6,8-dihydroxpurine hydrochloride (purity >90%) was purchased from Toronto Research Chemicals Inc., and was used here without further purification. A consequence of the necessity to use a highly alkaline solution to increase solubility of 8-OG is that it becomes deprotonated. Indeed, since the pKas of the N1 and N9 sites are estimates as 8.7 and 11.9, respectively,[19] in our experiment 8-OG is in a mixture of about 83 % of $8\text{-}OG^{2-}$ and about 17 % of $8\text{-}OG^{1-}$.

Results and Discussion

Figure 1 shows the most stable aqueous structures of 8-OG, 8-OdGs, and $8\text{-}OdGMP^{1-}$. Note that both mono- and di-anionic nucleotides are present in the solution at neutral pH since the corresponding pKa_2 of phosphate is 7.2.[29] However, only the former is relevant in the DNA context. Table 1 presents the corresponding vertical ionization energies (VIE) calculated using the non-equilibrium polarizable continuum (NEPCM)[20-22] to model the aqueous environment (for details see Computational Methods). For reference we show also our previously calculated results for guanine and its derivatives[17] and compare results in water with those in the gas phase. In water, the lowest ionization always originates from the base, as demonstrated in Figure 2 which depicts the highest occupied molecular orbital (HOMO) of $8\text{-}OdGMP^{1-}$.

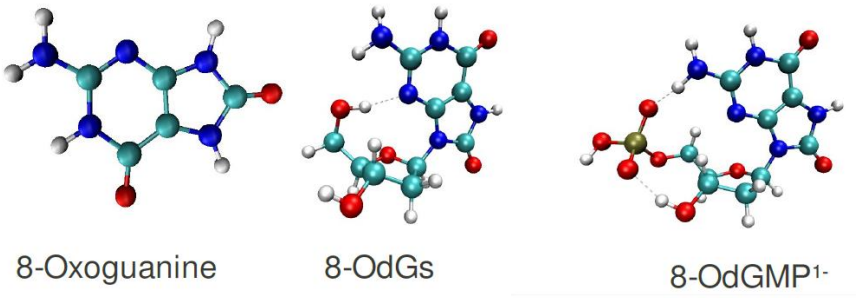

Figure 1: *Most stable aqueous-phase structures of 8-oxoguanine and its nucleoside and nucleotide.*

Table 1. *Vertical ionization energies (VIE) in eV calculated at the PMP2/aug-cc-pVDZ level in the aqueous phase employing NEPCM and in the gas phase.*

		nucleobase	deoxynucleoside	deoxynucleotide^{1-}
Aqueous phase	8-Oxoguanine	6.94	7.01	6.79
	Guanine	7.34	7.42[a]	7.08[a]
Gas phase	8-Oxoguanine	7.84	7.98	5.09
	Guanine	8.43	8.38[a]	5.18[a]

[a]VIE of the ribose analogues from Ref. [17], with that the difference between VIEs of deoxyribose vs. ribose containing nucleosides and nucleotides is negligible.

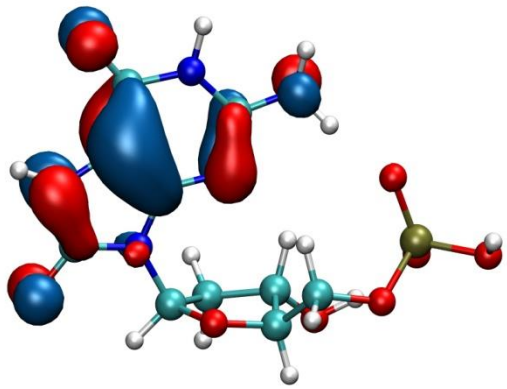

Figure 2: *The highest occupied molecular orbital (HOMO) of aqueous 8-OdGMP*$^{1-}$ *demonstrating that the lowest ionization originates from the base.*

Similarly to the canonical bases,[17, 18] we see from Table 1 the remarkable ability of the aqueous environment to screen the effect of the sugar and, in particular, of the phosphate on the ionization energy of 8-OG. While in the gas phase the phosphate anionic group strongly destabilizes the base leading to lowering of the VIE by almost 3 eV, in water this effect practically vanishes (Table 1). Most importantly, Table 1 demonstrates that in water 8-OG has VIE lower by about 0.4 eV than guanine, and this behavior is semi-quantitatively preserved also for the corresponding aqueous nucleosides and nucleotides.[17] Qualitatively, the reason for the lowering of VIE compared to guanine is the presence of the electronegative oxygen atom in 8-OG, which provides additional electron density and thus destabilizes the part of the molecules from which ionization originates. We also mention that the present value of VIE for 8-OG is very close to the value of 7.1 eV calculated most recently for the same species using a similar approach.[16] Finally, we have shown previously that in water the DNA environment has little effect on the VIE.[30] Our calculations thus support the hypothesis that not only free 8-OG but potentially also that produced in DNA could serve as a protective sink of the cationic hole upon prolonged exposure of DNA to ionizing radiation.[11] At the same time, lowering of the ionization

energy due to the presence of 8-OG increases the chance of moving the photoionization threshold of damaged DNA toward the edge of the terrestrial solar UV spectrum, as has already been suggested for undamaged DNA.[31]

In order to facilitate direct comparison with experiment (*vide infra*) we evaluated in addition to the lowest VIE also higher ionized states of 8-OG, 8-OG^{1-}, and 8-OG^{2-}. Each of these calculated peaks was then broadened with a Gaussian with a full-width-at-half-maximum (FWHM) of 1 eV to account for the experimental peak broadening assuming the same cross section for all transitions.[18, 32] The resulting spectra are presented in Figure 3 and compared to that of the aqueous canonical guanine base. We see that oxidation causes a shift to lower energies not only for the lowest ionization but also for the higher-lying ionized states. However, the shift for the lowest state is the largest, while that for the higher state gets to a large extent buried within the width of the higher energy peak (Figure 3). Furthermore, deprotonation directly on the base further shifts the ionization energies to even lower values. We mention in passing that this is different from the situation when deprotonation occurs on the phosphate moiety of the corresponding nucleotide, which has only a very small effect on the position of the lowest ionization peak.[17, 18]

For the singly and, in particular, the doubly deprotonated species, one may question the validity of the continuum approach to solvation due to potential strong perturbation of the solvent by the charged solute. In order to test this effect, we performed additional spectral calculations for 8-OG^{2-} including one to five explicit water molecules into the NEPCM cavity. The resulting spectra are presented in Figure 4. We see that in overall the continuum model performs surprisingly well even for 8-OG^{2-} with the lowest energy peak being practically unaltered and the higher peaks only moderately modified by including explicit water molecules.

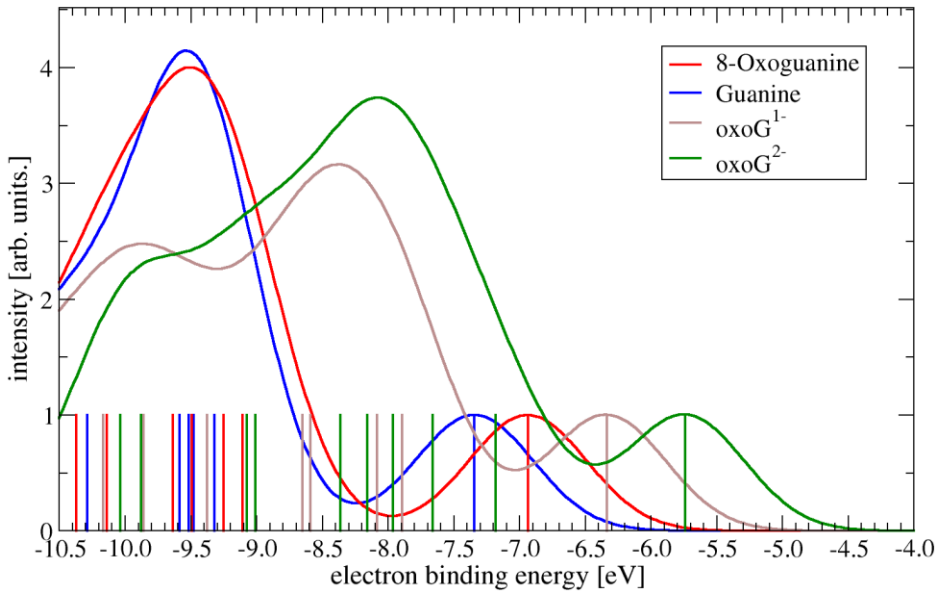

Figure 3: *Photoionization spectrum of aqueous 8-oxoguanine (red) compared to that of the canonical guanine base (blue) in water. In addition, spectra of the singly and doubly deprotonated 8-oxoguanine are depicted in brown and green.*

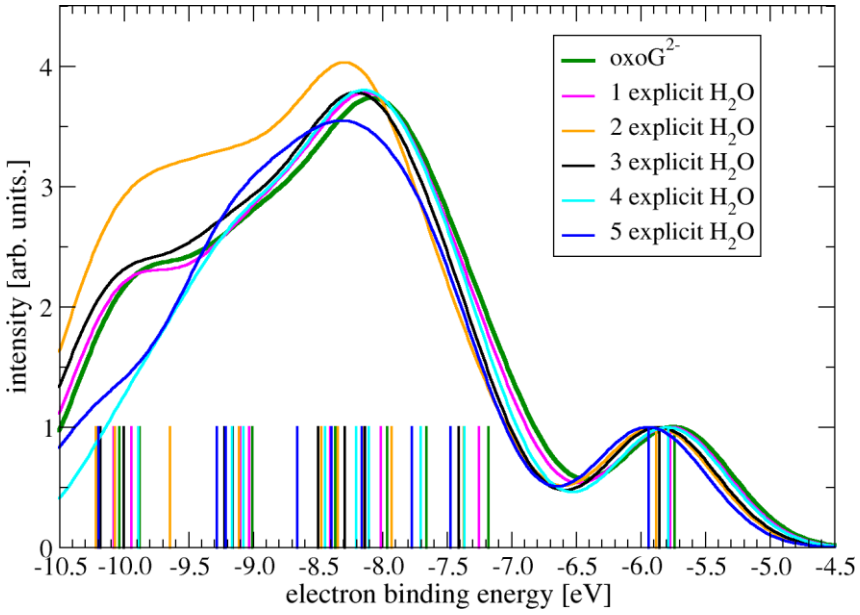

Figure 4: *Photoionization spectrum of aqueous doubly deprotonated 8-oxoguanine, 8-OG^{-2}, with 0 – 5 explicit water molecules included into the NEPCM solvent cavity.*

We also attempted to obtain a photoelectron (PE) spectrum of 8-OG aqueous solution experimentally (for details see Experimental Methods) in order to benchmark the calculations. Due to the high pH of 12.6 employed in the experiment to increase solubility, the investigated species is actually a mixture of of doubly (8-OG^{2-}) and singly (8-OG^{1-}) deprotonated forms, denoted further as 8-$OG^{1-/2-}$. Still, because of the very low solubility in water even at higher pH, signal-to-noise in our spectra allows to unequivocally identify only states with energies larger than the lowest ionization energy, which have larger integrated ionization probability. Results are shown in Figure 5 presenting the PE spectrum from the 0.04 M 8-$OG^{1-/2-}$ basic aqueous solution (in red) along with the water reference (in blue) spectrum, both measured under identical experimental conditions at a photon ionization energy of 180 eV. Despite using high pH, the signal corresponding to the lowest ionization energy of 8-$OG^{1-/2-}$(aq) is within the experimental noise level, and cannot thus be quantified here. Yet, there seems to be an indication of small above-zero signal from the base in the differential PE spectrum (in black) near 8.2 eV electron binding energy, which correlates well with the second ionization peak of the calculated spectrum of both 8-OG^{1-} and 8-OG^{2-}. This signal is observable here due to the larger integrated ionization probability than for lowest ionization energy. The experimental signal intensity in the differential spectrum near 9-10.5 eV electron binding energy, which has been successfully used in previous studies to single out solute contributions,[32,33] is in agreement in position, albeit stronger in intensity, compared to the calculated additional peak arising from the higher VIEs for both 8-OG^{-1} and 8-OG^{-2} (Figure 3). Note that analysis of the experimental spectrum for binding energies larger ~10.5 eV is not feasible because the water signal fully overwhelms that from 8-$OG^{1-/2-}$ and, consequently, the differential spectrum only reports noise.

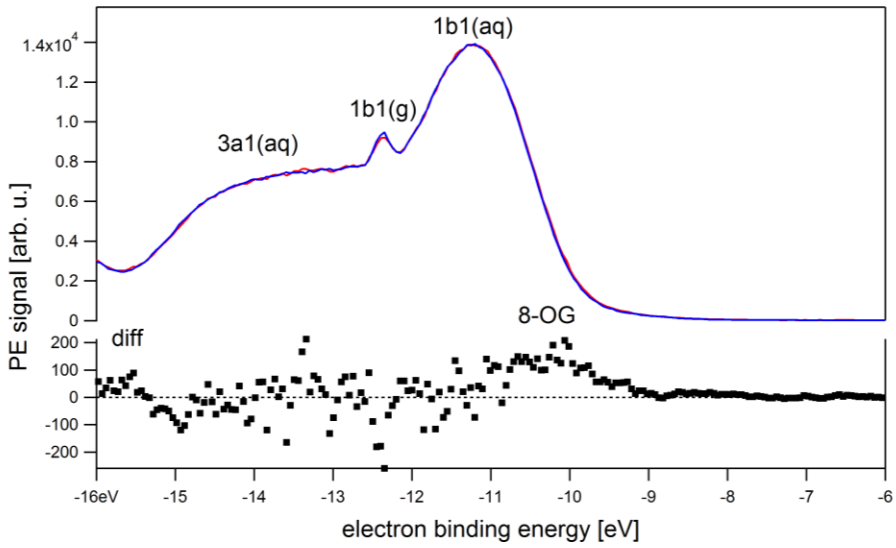

Figure 5: *Photoelectron spectrum from 0.04 M 8-oxoguanine (i.e., mixture of its singly and doubly deprotonated forms 8-OG^{1-2-}), aqueous solution (red) and of a reference spectrum from liquid water at pH 12.6 (blue), both measured at 180 eV photon energy. The differential spectrum, solution minus water signal, is shown at the bottom (in black squares). Top labels indicate the water valence orbitals which are ionized. The small narrow peak, 1b$_1$(g), arises from ionization of gas-phase water's highest occupied molecular orbital.*

Conclusions

In summary, using quantum chemical calculations we have shown that 8-oxoguanine, which is a primary product of radiation damage to DNA, has in the aqueous environment ionization potential lower by about 0.4 eV compared to the canonical guanine base. The calculated photoelectron spectra agree semi-quantitatively with results from liquid microjet photoelectron spectroscopy experiments where, however, only the higher ionization states between 8 and 10.5 eV of can be discerned due to the low solubility of 8-oxoguanine in water, leading to small electron signal intensity. Moreover, the necessity to use high pH conditions in

the experiment to increase solubility of the base results in formation of a mixture of singly and doubly deprotonated 8-oxoguanine. The present results strongly support the hypothesis[11] that due to its low ionization potential 8-oxoguanine can serve as a sink to the cationic hole and, therefore, help to protect DNA from further radiation damage.

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