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One-electron oxidation of ds(5'-GGG-3') and ds(5'-G(8OG)G-3') and the nature of hole distribution: a density functional theory (DFT) study†

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Of particular interest in radiation-induced charge transfer processes in DNA is the extent of hole localization immediately after ionization and subsequent relaxation. To address this, we considered double stranded oligomers containing guanine (G) and 8-oxoguanine (8OG), *i.e.*, ds(5'-GGG-3') and ds(5'-G8OGG-3') in B-DNA conformation. Using DFT, we calculated a variety of properties, *viz.*, vertical and adiabatic ionization potentials, spin density distributions in oxidized stacks, solvent and solute reorganization energies and one-electron oxidation potential (E^0) in the aqueous phase. Calculations for the vertical state of the -GGG- cation radical showed that the spin was found mainly (67%) on the middle G. However, upon relaxation to the adiabatic -GGG- cation radical, the spin localized (96%) on the 5'-G, as observed in experiments. Hole localizations on the middle G and 3'-G were higher in energy by 0.5 kcal mol⁻¹ and 0.4 kcal mol⁻¹, respectively, than that of 5'-G. In the -G8OGG- cation radical, the spin localized only on the 8OG in both vertical and adiabatic states. The calculated vertical ionization potentials of -GGG- and -G8OGG- stacks were found to be lower than that of the vertical ionization potential of a single G in DNA. The calculated E^0 values of -GGG- and -G8OGG- stacks are 1.15 and 0.90 V, respectively, which owing to stacking effects are substantially lower than the corresponding experimental E^0 values of their monomers (1.49 and 1.18 V, respectively). SOMO to HOMO level switching is observed in these oxidized stacks. Consequently, our calculations predict that local double oxidations in DNA will form triplet diradical states, which are especially significant for high LET radiations.

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Introduction

The direct interaction of ionizing radiation with DNA randomly ionizes and forms “holes” (cation radicals) on each of its components (*i.e.* bases, sugar and phosphate). The holes travel within DNA by tunneling and by thermally-activated hopping processes and localize on the DNA base having the lowest ionization potential (IP), guanine, forming the guanine radical cation ($G^{\bullet+}$).^{1–9} Electron spin resonance (ESR) and product analysis experiments showed that nucleophilic addition of a water molecule at the C8 site of $G^{\bullet+}$ followed by deprotonation leads to the formation of a highly reducing G8OH[•] intermediate;

subsequent one-electron oxidation of G8OH[•] followed by deprotonation produces 8-oxoguanine (8OG), which has a lower IP than G and acts as a global sink for hole traps in one electron oxidized DNA.^{10–14}

Factors such as base-pairing, stacking and solvation surrounding the DNA significantly affect the ionization potentials of bases in DNA. The photoionization of nucleosides and nucleotides in water has been studied in several pulsed laser experiments with 282,¹⁵ 266,^{16,17} 254¹⁸ and 193 nm¹⁹ photons, which bracketed the threshold ionization limit of DNA components between 4.40 and 6.42 eV, respectively. Microhydration of A and T has been shown to reduce the IP of these bases by *ca.* 0.7 eV compared to their gas phase values.²⁰ Under full aqueous solvation, Lebreton and coworkers²¹ established an ionization threshold of *ca.* 4.8 eV for guanine. Experimentally measured IPs were further supported by theoretical calculations carried out by Close and coworkers,^{22–24} Jungwirth and coworkers^{25–27} and Capobianco *et al.*,²⁸ including in aqueous solvent environments on DNA bases *via* either consideration of an explicit solvation model (polarized continuum model (PCM)) or by placing discrete

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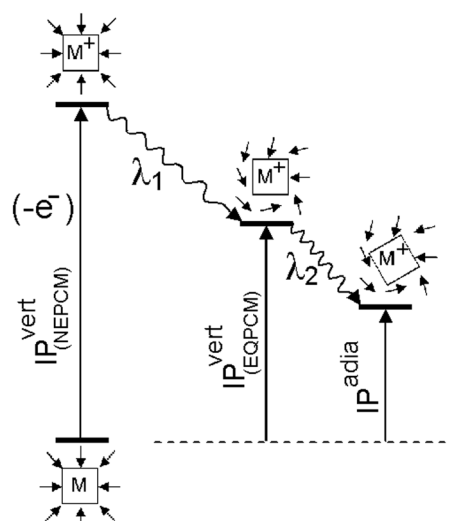
† Electronic supplementary information (ESI) available: Supporting information contains the following: (i) structure of ds(5'-GGG-3') and ds(5'-G8OGG-3'). (ii) Table. (iii) Scheme. (iv) Plots of MOs and (v) optimized geometries. See DOI: 10.1039/c9cp06244k

water molecules around bases. The ionization potentials of hydrogen-bonded GC and AT base pairs in the gas phase and in solution were calculated using HF and DFT methods by Colson *et al.*,^{29–31} Li *et al.*,^{32,33} Hutter and Clark,³⁴ Kumar and Sevilla⁹ and by Bravaya *et al.*³⁵ using the high level EOM-IP-CCSD/6-311+G(d,p) method. Their calculations showed that hydrogen-bonded DNA bases have lower IPs than monomeric bases.^{9,29–35} Theoretical calculations also showed that stacked DNA bases have lower IPs than monomeric bases,^{35–41} as found by *ab initio* EOM-IP-CCSD calculations by Krylov and coworkers^{35,40,41} of the IP_{vert} of stacked UU, AA, TT and AATT tetramers. Very recently, differential pulse voltammetry (DPV) measurements of guanine-rich single- and double-stranded oligonucleotides containing up to six consecutive guanines were reported by Capobianco *et al.*⁴² and they observed a progressive lowering of the first voltammetric peak potential as the number of guanines increased. Using photoelectron spectroscopy and MP2/aug-cc-pvdz calculations, the vertical IP of DNA in aqueous solution was very recently estimated by Jungwirth and coworkers⁴³ and they concluded that the lowest IP_{vert} (*ca.* 7 eV) corresponds to the guanine base in DNA.

IPs of DNA and its bases in various configurations have been extensively studied using quantum chemical methods^{13,14,22,35} and an excellent agreement between theory and experiment has been achieved. However, in the context of ionization (oxidation event) of DNA, the nature of the hole distribution in DNA is of prime importance. There is a marked difference of opinion on whether the hole is localized on a single base^{28,38,39,44–51} or is delocalized over a few bases.^{42,52–56} Using theory and experiment, Saito and coworkers^{39,44} demonstrated that sequences of 5'-GG-3' and 5'-GGG-3' in DNA are the sites having the lowest IPs in DNA and the molecular orbitals, calculated by the HF/3-21G* method, are mainly localized on the 5'-G with a small amount residing on 3'-G in a stacked *N*-methylated GG/CC system. Barton and coworkers⁴⁵ showed that the photo-oxidation of a rhodium intercalator covalently attached to one end of the DNA produces long-range oxidative damage at the 5'-G of DNA containing 5'-GG-3' doublets. Recently, the one-electron oxidized DNA-oligomers were studied using an electron spin resonance (ESR) experiment at 77 K by Adhikary *et al.*⁴⁶ In this experiment, the site of hole localization was determined by use of oligomers with deuterium substitution at the C8 position of guanine at selected sites in the DNA sequences. ESR experiments⁴⁶ clearly showed that the hole is mostly localized at the 5'-G end in deuterium substituted oligomers containing -GGG- sequences. These experimental observations were further supported by several theoretical studies.^{28,37,38,47–49,51} Blancafort and Voityuk⁴⁷ used the CASSCF and CASPT2 levels of theories to calculate the Mulliken charges of one-electron-oxidized several G stacked nucleobases and they found that more than 95% of holes are localized on the 5'-G. Senthilkumar *et al.*⁴⁸ used DFT to calculate the charge distribution on 5'-XGGGY-3' (X, Y = A, C, T) duplexes and concluded that 5'-G is the most easily oxidized. However, there are a few studies that proposed the delocalized nature of the hole distribution in G-stacks.^{42,52–54} Liu and Schuster⁵² proposed that long-range

hole transfer in irradiated anthraquinone-linked duplex DNA oligomers is mediated *via* thermally activated polaron-like hopping in DNA, causing formation of 8OG at -GG- steps, revealed ultimately as strand breaks. From the progressive lowering of the oxidation potential as the number of stacked guanines increases up to six, Capobianco *et al.*⁴² proposed the delocalization of the hole on Gs.

To address the issue of the extent of hole (unpaired spin) localization immediately after ionization (vertical) and after relaxation (adiabatic), we considered double stranded ds(5'-GGG-3') and damaged ds(5'-G8OGG-3') (8OG = 8oxoG) in B-DNA conformations and calculated their vertical and adiabatic ionization potentials and spin density (hole) distributions within these stacks under the influence of an aqueous solution. From spin density plots, we analyzed the nature of hole distributions in -GGG- and damaged -G8OGG- stacks and the effect of solvent relaxation on the hole distributions in these stacks. In addition, we report separate reorganization energies of solvent (λ_1) and solute (λ_2) for stacks of -GGG- and -G8OGG- (Scheme 1). Another important aspect known as SOMO–HOMO level inversion, observed experimentally^{55–57} in several radicals and first shown by Coote and co-workers^{58–61} using *ab initio* and DFT calculations and later by us,^{9,61} is also found to occur for these systems. SOMO–HOMO level switching in radicals has important implications for the redox chemistry of radicals.^{55–61}



Scheme 1 Schematic diagram showing the procedure for calculation of the vertical and adiabatic ionization potentials of a molecule (M) (solute) in solution by one-electron oxidation of the parent solute molecule (M) under specific conditions. The different quantities depicted in the scheme are defined as: (a) $IP_{\text{vert}}^{\text{(NEPCM)}}$: this is the vertical IP in which the geometrical configuration of oxidized (M^+) is identical to that of the neutral (M) including solvent polarization shown by arrows. (b) $IP_{\text{vert}}^{\text{(EQPCM)}}$: this is the vertical IP in which the geometrical configuration of M^+ is identical to that of the parent M but the surrounding solvent is relaxed in response to the molecular charge formed on ionization. (c) IP^{adia} : this is the adiabatic IP in which M^+ and surrounding solvent are fully relaxed. (d) The difference between $IP_{\text{vert}}^{\text{(NEPCM)}}$ and $IP_{\text{vert}}^{\text{(EQPCM)}}$ gives an estimate of the solvent reorganization energy (λ_1). (e) The difference between $IP_{\text{vert}}^{\text{(EQPCM)}}$ and IP^{adia} gives solute reorganization energy (λ_2). The full reorganization energy, $\lambda_{\text{total}} = \lambda_1 + \lambda_2 = IP_{\text{vert}}^{\text{(NEPCM)}} - IP^{\text{adia}}$.

It is well known that holes produced in oxidized DNA end up on G, GG and GGG sites with the multiple G sites favored for hole localization.^{28,37,39,44–48} Moreover, 8OG owing to its lower redox potential¹¹ than those of G sites becomes favored for hole localization when present. Therefore, owing to computational limitations, we have chosen ds(5'-GGG-3') and ds(5'-G8OGG-3') systems as models of larger DNA systems,^{42,46} which have -GGG and -G8OGG- sequences, to investigate hole localization in DNA. We note that the sequence context around the GGG sites can influence the specific site of hole localization.⁴⁸

Methods of calculation

The initial structures of ds(5'-GGG-3') and ds(5'-G8OGG-3') were generated using the SPARTAN program.⁶² The anionic phosphate groups in these stacks were protonated to neutralize the system and 5'- and 3'-ends were terminated by OH groups. The structures thus generated were fully optimized in their neutral state by the ω B97XD density functional using the 6-31G** basis set. The fully optimized neutral state geometries of ds(5'-GGG-3') and ds(5'-G8OGG-3') were used for the calculation of the vertical and adiabatic ionization potentials of these stacks using similar calculation levels. All the calculations were carried out in the aqueous phase *via* the integral equation formalism of the polarized continuum model (IEF-PCM) by Tomasi *et al.*⁶³ For IEF-PCM calculations, the solvent was treated as a continuum and the cavity was generated using the default options set in the program. The complete methodology in the present work is abbreviated as ω B97XD-PCM/6-31G**. ω B97XD is a range-separated hybrid density functional with damped atom-atom dispersion corrections developed by Chai and Head-Gordon.^{64,65} This functional has been found to be reliable for the calculation of various properties of molecules in their ground and excited states in our recent works^{9,61,66,67} and by others.³⁵ Using the ω B97XD-PCM/6-31G** optimized geometries, the calculation level was further increased by calculating the ionization potentials using the 6-31++G** basis set. The complete optimization of structures with the 6-31++G** basis set is beyond our computational resources. All the calculations were carried out using the Gaussian 16 suite of programs.⁶⁸ Fig. S1–S13 and Tables S1–S3 are presented in the ESI.† We also carried out *ab initio* molecular dynamics (MD) simulation starting with the vertical radical cation of the -GGG- stack using the ω B97XD-PCM/6-31G** method. The details of the MD simulations and results are presented in the ESI.†

To check the reliability of the ω B97XD-PCM/6-31++G**// ω B97XD-PCM/6-31++G** methodology, we calculated the ionization potentials and relaxation energies λ_1 and λ_2 of the guanine and 8oxoguanine monomers and compared them to those calculated using the MP2/aug-cc-pVDZ method by Jungwirth and coworkers,^{26,69,74} and ourselves. We found that the calculated IPs and relaxation energies obtained with both methods are in excellent agreement, see Tables S2 and S3 in the ESI.†

The procedure for calculation of the vertical and adiabatic ionization potentials of a molecule (M) (solute) in the presence of a solvent (shown by arrows) is shown in Scheme 1. From Scheme 1, it is evident that in the calculation of the vertical IP, we considered the effect of solvent in two ways: (i) nonequilibrium solvent – in this case, only the fast electronic response of the solvent was considered, while the nuclear response was constrained to the optimized solute (M) with PCM before ionization.^{27,69} This protocol is known as nonequilibrated PCM (NEPCM) and implemented in the Gaussian program.⁶⁸ The vertical IP in this state is designated as $IP_{(NEPCM)}^{vert}$. (ii) Equilibrated solvent – in this case, solvent was allowed to relax but solute was constrained to the optimized solute (M) before ionization. This protocol is termed as equilibrated PCM (EQPCM) in this study. The vertical IP in this state is designated as $IP_{(EQPCM)}^{vert}$. The adiabatic IP (IP^{adia}) is calculated as the energy difference between the optimized solute (M) with a relaxed PCM (EQPCM) after and before ionization. The reorganization energies of the solvent (λ_1) and of the solute (λ_2) are estimated as: $\lambda_1 = IP_{(NEPCM)}^{vert} - IP_{(EQPCM)}^{vert}$; $\lambda_2 = IP_{(EQPCM)}^{vert} - IP^{adia}$. The sum ($\lambda_1 + \lambda_2$) gives the total reorganization energy (λ_{total}) due to relaxed solute and solvent, respectively.

Results and discussion

Aqueous phase ionization and oxidation potentials

The ω B97XD-PCM/6-31G** calculated vertical and adiabatic ionization potentials of ds(5'-GGG-3') oligos in the B-DNA conformation are given in Table S1 in the ESI.†

The calculated $IP_{(NEPCM)}^{vert}$, $IP_{(EQPCM)}^{vert}$ and IP^{adia} of ds(5'-GGG-3') at the ω B97XD-PCM/6-31++G**// ω B97XD-PCM/6-31G** level of theory are 6.64, 5.96 and 5.59 eV, respectively, see Table 1. Our calculated $IP_{(NEPCM)}^{vert}$ (6.64 eV) of ds(5'-GGG-3') by ω B97XD-PCM/6-31++G** is about 0.4 eV lower than the $IP_{(NEPCM)}^{vert}$ of a single guanine base in DNA dodecamer calculated using the *ab initio* MP2/aug-cc-pvdz level of theory considering the ONIOM approach in the Gaussian suite of programs⁶⁸ and

Table 1 ω B97XD-PCM/6-31++G**// ω B97XD-PCM/6-31G** calculated vertical and adiabatic ionization potentials and relaxation energies (λ_1 , λ_2 , and λ_{total}) of ds(5'-GGG-3') and ds(5'-G8OGG-3') oligos in eV. The estimated oxidation potential E^0 is given in volts

System	ω B97XD-PCM/6-31++G**// ω B97XD-PCM/6-31G** ^a						$E^{0,b}$	Exp. E^0
	$IP_{(NEPCM)}^{vert}$	$IP_{(EQPCM)}^{vert}$	IP^{adia}	λ_1	λ_2	λ_{total}		
ds(5'-GGG-3')	6.64	5.96	5.59	0.68	0.37	1.05	1.15	1.3 ^c
ds(5'-G8OGG-3')	6.43	5.74	5.34	0.69	0.4	1.09	0.90	1.18 ^d

^a All values in eV except E^0 in volt. ^b $E^0 = IP_{(NEPCM)}^{vert} - \lambda_{total} - SHE$; $IP^{adia} = IP_{(NEPCM)}^{vert} - \lambda_{total}$; SHE = 4.44 volt. ^c Estimated from DPV measurements showed lowering of 0.1 V oxidation potential per GG step in both single- and double-stranded DNA, *i.e.* 1.5 V(G)–0.2 V (GGG).⁴²

^d 8-OxoG (monomer).¹¹

estimated experimentally using valence photoelectron spectra of sheared herring sperm DNA at pH 7.7 by Jungwirth and coworkers.⁴³ This difference (0.4 eV) is evident as our calculated $IP_{(NEPCM)}^{vert}$ is of stacked -GGG-, while the latter is calculated for a single guanine in DNA. The calculated $IP_{(NEPCM)}^{adia}$ (5.59 eV), see Table 1, of -GGG- is *ca.* 1.1 eV less than the $IP_{(NEPCM)}^{vert}$. This lowering of IP results from the solvent and solute relaxation. The lower IP of stacked -GGG- in comparison to that of single guanine was also reported in earlier studies.^{37–39} Very recently, DPV (differential pulsed voltammetry) measurements showed a lowering of 0.1 V oxidation potential per GG step in single- and double-stranded DNAs containing up to six consecutive stacked guanines.⁴² This gives us an indication that the -GGG- sequence has a reduced oxidation potential between 0.15 and 0.2 V. The one-electron oxidation potential (E^0) of G is 1.49 V with (E_7) 1.29 V^{1,69,70} and thus the estimated E^0 of -GGG- should be *ca.* 1.3 V. The one-electron reduction potential (E^0) is calculated as $E^0 = (-\Delta G) - SHE$ (standard hydrogen electrode). The negative of free energy (ΔG) is simply the adiabatic ionization potential in the aqueous phase ($IP_{(NEPCM)}^{adia}$) referenced to the SHE rather than a vacuum.⁶⁹ Thus, our calculated E^0 of -GGG- is 5.59–4.44 V (SHE)^{71–73} = 1.15 V, which is in reasonable agreement with the experimental estimate of 1.3 V of the -GGG- stack, see Table 1. The calculations of E^0 using both methods are reported in the ESI† (see Table S1).

The $\omega B97XD-PCM/6-31++G^{**}/\omega B97XD-PCM/6-31G^{**}$ calculated $IP_{(NEPCM)}^{vert}$, $IP_{(EQPCM)}^{vert}$ and $IP_{(NEPCM)}^{adia}$ of ds(5'-G8OGG-3') are 6.43, 5.74 and 5.34 eV, respectively. It is evident from Table 1 that the IPs of the -G8OGG- stack are *ca.* 0.2 eV lower than the corresponding IPs of the -GGG- stack. Palivec *et al.*⁷⁴ calculated the $IP_{(NEPCM)}^{vert}$ (6.94 eV) of a single 8OG using the PMP2/aug-cc-pVDZ level of theory, which is *ca.* 0.5 eV higher than our calculated $IP_{(NEPCM)}^{vert}$ of ds(5'-G8OGG-3'), see Table 1. This difference is expected as our calculation of IP is for ds(5'-G8OGG-3'), which involves stacking and hydrogen-bonding interactions, while the calculations of Palivec *et al.*⁷⁴ are for a single 8OG. The lower IP of -G8OGG- than that of -GGG- (see, Table 1 and Table S1, ESI†) is in accord with experimental observations as 8OG is found to be a better hole trap (oxidation site) than G in DNA upon one-electron oxidation.^{10–14} The calculated E^0 of the -G8OGG- stack is

5.34–4.44 = 0.90 eV, see Table 1. Using kinetic rate measurement, Steenken *et al.*¹¹ measured the E^0 of 8-oxoG in aqueous solution as 1.18 V.

Relaxation energies and spin density distributions

The $\omega B97XD-PCM/6-31++G^{**}/\omega B97XD-PCM/6-31G^{**}$ calculated solvent relaxation energy (λ_1) values of ds(5'-GGG-3') and ds(5'-G8OGG-3') cation radicals are about the same and these are 0.68 and 0.69 eV, respectively, see Table 1. In this context, the solvent relaxation energy (λ_1) values for A, T, G, C and uracil nucleosides and nucleotides in PCM were estimated as 1.1 eV for all the bases by Schroeder *et al.*⁶⁹ using the MP2/aug-cc-pVDZ level of theory. Ours and Schroeder *et al.*'s⁶⁹ studies clearly indicate that the solvent response depends on the overall shape of the electronic distribution of solute on ionization and this is clearly evident from the fact that spin density distributions of ds(5'-GGG-3') and ds(5'-G8OGG-3') cation radicals calculated in NEPCM and EQPCM all have a π -type MO with delocalization on one base with lesser contributions from other bases, see Fig. 1–3 and Fig. S4 in the ESI.† The solute relaxation energy (λ_2) calculated at the $\omega B97XD-PCM/6-31++G^{**}/\omega B97XD-PCM/6-31G^{**}$ level of theory for ds(5'-GGG-3') and ds(5'-G8OGG-3') is 0.37 and 0.4 eV, respectively, see Table 1. Using the MP2/aug-cc-pVDZ level of theory,⁶⁹ λ_2 values of guanosine and 5'-guanosine monophosphate (5'-GMP) cation radicals in PCM were calculated as 0.44 and 0.45 eV, respectively, and these values are in good agreement with our calculated λ_2 (0.37 eV) of ds(5'-GGG-3'). The experimental λ_2 in the gas phase for the guanine cation radical is 0.47 eV and this is well-predicted by several theoretical calculations.⁷⁵

The spin density distributions of one-electron oxidized ds(5'-GGG-3'), calculated in NEPCM and EQPCM in the vertical states, and finally the optimized cation radical in the adiabatic state using $\omega B97XD-PCM/6-31G^{**}$ are shown in Fig. 1. From Fig. 1(a), we see that for NEPCM, the spin is delocalized over two bases with the middle G having 62% and 5'-G having 35% of the spin density. When the solvent is allowed to relax in the vertical state (EQPCM), the spin density distribution redistributes significantly in comparison to NEPCM (see Fig. 1(a)) and 5'-G has 85% and middle G has 15% of the total spin density, see Fig. 1(b). Changing from NEPCM to EQPCM in the vertical

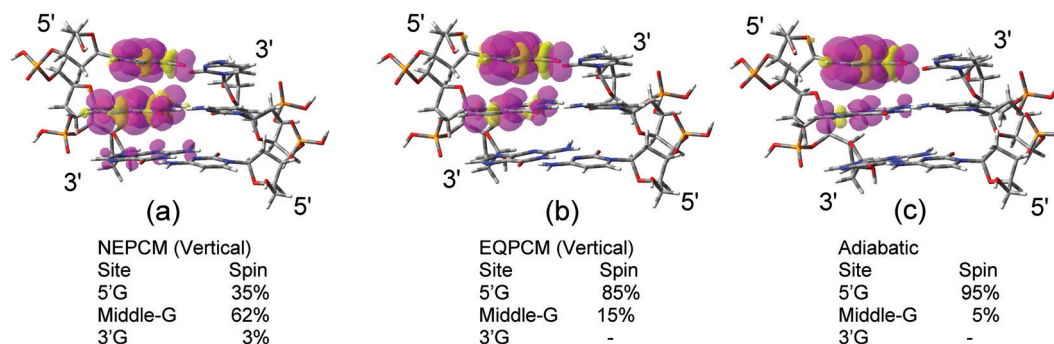


Fig. 1 Spin density plots of one-electron oxidized ds(5'-GGG-3') calculated using the $\omega B97XD-PCM/6-31G^{**}$ level of theory. (a) In NEPCM, (b) in EQPCM and (c) finally the fully optimized cation radical (adiabatic).

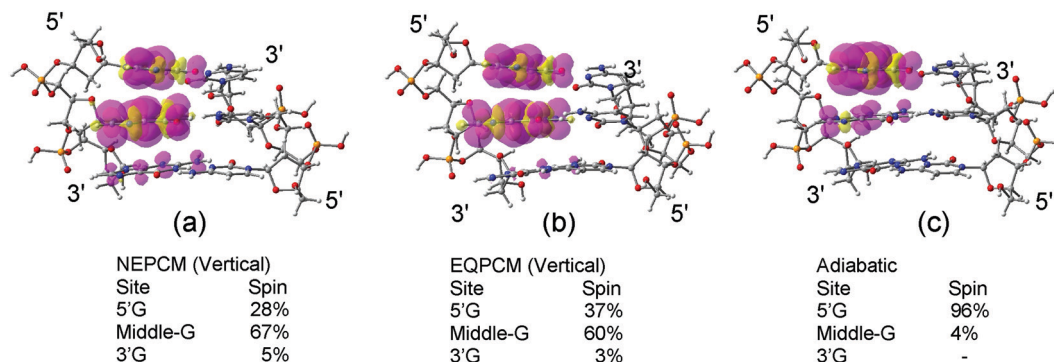


Fig. 2 Spin density plots of one-electron oxidized ds(5'-GGG-3') calculated using the ω B97xd-PCM/6-31++G**// ω B97xd-PCM/6-31G** method. (a) In NEPCM, (b) in EQPCM and (c) finally the fully optimized cation radical (adiabatic).

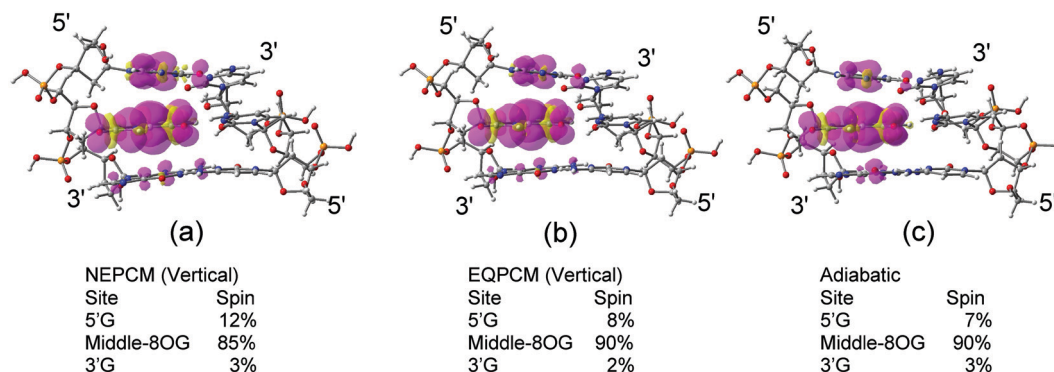


Fig. 3 Spin density plots of one-electron oxidized ds(5'-G8OGG-3') calculated using the ω B97xd-PCM/6-31++G**// ω B97xd-PCM/6-31G** method. (a) In NEPCM, (b) in EQPCM and (c) fully optimized cation radical (adiabatic).

state, the PCM-calculated solvent polarization shifts from the polarization inherent in the neutral structure to that for the cation radical. This has a significant effect on the spin distribution within the -GGG- stack. This occurs within a few picoseconds as the solvent equilibrates to the charge. Finally, for the full optimization of the radical cation (adiabatic state with PCM), 95% of the total spin is localized on the 5'-G, see Fig. 1(c).

The ω B97XD-PCM/6-31++G**// ω B97XD-PCM/6-31G** calculated spin density distributions in vertical and in adiabatic states of one-electron oxidized ds(5'-GGG-3') are presented in Fig. 2. In NEPCM, the spin is delocalized on 5'-G (28%) and on the middle G (67%), see Fig. 2(a). In EQPCM, the spins on 5'-G and the middle G are 37% and 60%, respectively, see Fig. 2(b). The ω B97XD-PCM/6-31++G**// ω B97XD-PCM/6-31++G** calculation shows that on solvent relaxation in the vertical state (EQPCM), spin density transfers from the middle G to 5'-G mildly in comparison to that of the ω B97XD-PCM/6-31G** method, see Fig. 1(b) and 2(b), but both methods propose the transfer of spin towards 5'-G. In the adiabatic state, 96% spin is localized on 5'-G only. The complete localization (95%) of total spin density on 5'-G in (5'-GGG-3') in the adiabatic state (Fig. 1(c) and 2(c)) is in agreement with several studies including both theory and experimental results.^{28,38,39,44–51} Our calculations predict a localized hole on 5'-G in an adiabatic radical cation -GGG-stack. Voityuk⁷⁶ also concluded that cation radical states in

DNA sequences are localized on a single G because of solvation and reorganization effects but the site was sequence dependent. For example, in the sequence AG₁G₂G₃, the hole initially was on both G₁G₂, and on full solvation, the hole localized only on G₂. Counter ions also affect the site of hole localization. For example, Barnett *et al.*⁷⁷ using QM/MM calculations reported that hydrated counter ions (*i.e.* Na⁺) strongly affect the energetics of electron hole states in DNA.

The spin density distributions in one-electron oxidized ds(5'-G8OGG-3') in NEPCM and in EQPCM in the vertical states and finally in the adiabatic state, calculated by both methods, are shown in Fig. 3 and Fig. S4 in the ESI.† From Fig. 3 and Fig. S4 (ESI†), we see that the spin is almost completely localized on 8OG in every case, *i.e.*, NEPCM (85%), EQPCM (90%) and for the adiabatic cation radical (90%), of the total spin, see Fig. 3 and Fig. S4 in the ESI.†

It is well known that DFT (such as B3LYP) suffers from self-interaction error (SIE), which leads to spin delocalization.⁵¹ However, in range separated hybrid DFT methods (ω B97xd), the problem of SIE is largely mitigated. Since the Hartree-Fock (HF) methodology is free from the SIE problem, we have checked whether our ω B97xd calculated spin densities shown in Fig. 1–3 are affected by SIE. We further calculated the spin densities using the HF-PCM/6-31++G**// ω B97xd-PCM/6-31G** level of theory. The calculated spin densities of ds(5'-GGG-3')

and $\text{ds}(5'\text{-G8OGG-}3')$ cation radical stacks are presented in Fig. S7 and S8 in the ESI.† The HF calculated spin density of $\text{ds}(5'\text{-GGG-}3')$ cation radical in NEPCM and in EQPCM shows that spin is mainly localized on the middle G, while in the adiabatic cation radical, the spin is localized on the $5'\text{-G}$, see Fig. S7 in the ESI.† For the $\text{ds}(5'\text{-G8OGG-}3')$ stack cation radical, spin is only localized on the 8OG. Thus, both HF and ωb97xd methods predict similar spin density distributions.

Why does the hole localize on $5'\text{-G}$?

The question arises: why is $5'\text{-G}$ localization chosen over other G sites in the -GGG- stack. Previous works^{37,47,48,51,76} on G stacks show that localization on a single G occurs on relaxation of solvent and structure. So, it would seem likely that the $5'\text{-G}$ site is the energetically favored position. To test this, we performed calculations that localized the holes first to the central G and subsequently to the $3'\text{-G}$. The procedures used for these two calculations are: (i) to localize the hole on the central G, we replaced the central G with the bond lengths found for the $5'\text{-G}$ cation radical and the $5'\text{-}$ and $3'\text{-Gs}$ were kept in the neutral geometry. All angles, dihedrals and other bond distances were optimized, except for bond-lengths constituting the middle guanine (assumed to be the cation radical) in $5'\text{-GGG-}3'$, using the $\omega\text{b97xd-PCM/6-31G}^{**}$ level of theory. This partially optimized geometry was then fully optimized at the same level of theory. The spin density (hole) was found to localize on the middle G but the energy of this structure (Fig. 4(b)) was 0.5 kcal mol^{-1} higher in energy than that found for the hole at the $5'\text{-G}$ site shown in Fig. 4(a). (ii) The second calculation was performed using the same procedure of optimization used in (i) for the cation radical on the $3'\text{-G}$ in $5'\text{-GGG-}3'$. We found that this structure (Fig. 4(c)) is $0.36\text{ kcal mol}^{-1}$ higher in energy than that found for the hole at the $5'\text{-G}$ site (Fig. 4(a)). The spin density plots for all three structures are presented in Fig. 4. So, there appears to be a small energetic preference for the hole-localization at the $5'\text{-G}$ site over the

middle and $3'\text{-G}$ sites. The coordinates of the optimized structures are provided in the ESI.†

Experimental work employing ESR reported the distribution of localized holes in one-electron oxidized $\text{d}[\text{GGGCCC}]_2$ and $\text{d}[\text{TGGGCCCCA}]_2$ by selective deuterium substitution at the C8 position of guanine (8-deuterioguanine (G^*)).⁴⁶ In these experiments, three independent dsDNA oligomers with G^* substitutions at each G in $\text{d}[\text{GGGCCC}]_2$ were investigated, specifically, (i) $\text{d}[\text{G}^*\text{GGCCC}]_2$ (ii) $\text{d}[\text{GG}^*\text{GCCC}]_2$ and (iii) $\text{d}[\text{GGG}^*\text{CCC}]_2$.⁴⁶ From the ESR experiment at 155 K, it was found that $60\% \pm 10\%$ ($\text{d}[\text{G}^*\text{GGCCC}]_2$)⁺ oligomers have a $5'\text{-G}^*$ localized hole, while $15\% \pm 10\%$ ($\text{d}[\text{GG}^*\text{GCCC}]_2$)⁺ oligomers have a hole localized on the middle G^* . Finally, $20\% \pm 10\%$ ($\text{d}[\text{GGG}^*\text{CCC}]_2$)⁺ oligomers have a $3'\text{-G}^*$ localized hole.⁴⁶ The addition of a T before the $5'\text{-G}$ in ($\text{d}[\text{TGGGCCCCA}]_2$)⁺ was found to shift localization from the $5'\text{-G}$ to the central G, as expected.⁴⁶

Our calculations for the one-electron oxidized -GGG- stack predict three structures separated by less than 0.5 kcal mol^{-1} , see Fig. 4. Thus, each one is expected to be present in experiments at 155 K ⁴⁶ with small differences in energy leading to relative Boltzmann populations of each structure shown in Fig. 4. The calculated Boltzmann population of structure shown in Fig. 4(a) is 66%, for the structure shown in Fig. 4(b), it is 14%, and for the structure shown in Fig. 4(c), it is 20%. These calculated populations are approximate as they are calculated using the electronic energy only, but they agree well with the ESR study,⁴ perhaps, fortuitously owing to the errors inherent in both experiment and theory.

SOMO–HOMO level switching

Conventionally, it is supposed that the singly occupied molecular orbital (SOMO) should be the highest occupied molecular orbital according to the aufbau principle. However, in recent years, many studies including theory and experiment pointed out the violation of the aufbau principle for many radicals in which the SOMO is found to be energetically lower in energy than the doubly occupied HOMO.^{9,55–61,78–80} Thus, electron

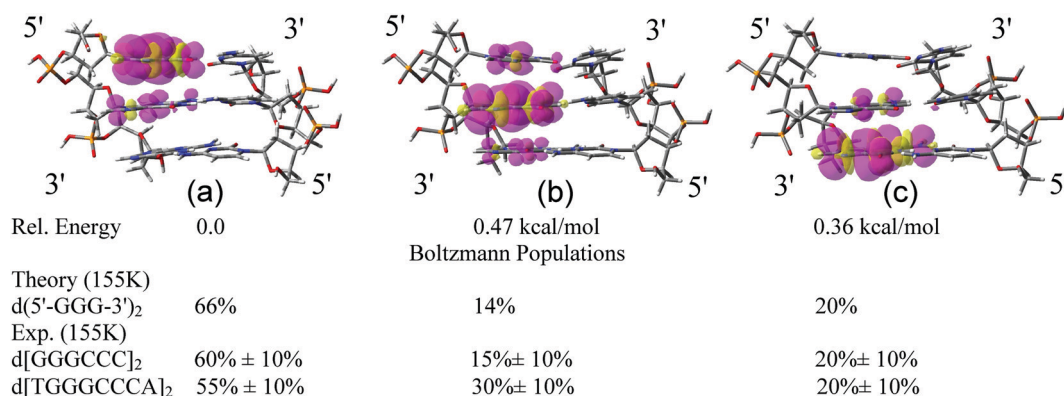
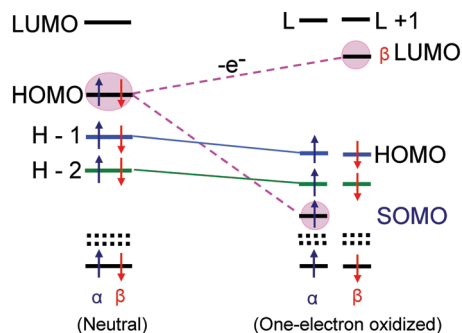


Fig. 4 Spin density distribution plots of one-electron oxidized $\text{ds}(5'\text{-GGG-}3')$ calculated using the $\omega\text{b97xd-PCM/6-31G}^{**}$ method. (a) Fully optimized cation radical (adiabatic) in which spin is localized on $5'\text{-G}$. (b) Fully optimized cation radical (adiabatic local minimum) in which spin is mainly localized on the middle G. (c) Fully optimized cation radical (adiabatic local minimum) in which spin is mainly localized on the $3'\text{-G}$. The relative stability values of structures (b) and (c) with respect to the most stable structure (a) are 0.5 and 0.4 kcal mol^{-1} , respectively. A comparison of the Boltzmann population of each structure is also given along with the experimental values found for the two oligomers at 155 K.⁴⁶



Scheme 2 Diagram showing the electronic configuration (α - and β -MOs) of a neutral parent molecule and its one-electron oxidized radical. In the neutral molecule, each MO is doubly occupied; however, on one-electron oxidation (removal of an electron), α - and β -MOs rearranged independently. Removal of an electron from the HOMO of the neutral molecule splits the HOMO of the neutral molecule into β -LUMO and α -SOMO, with the SOMO buried below the filled MOs. As expected, the SOMO and the β -LUMO have near identical wave functions. HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital; and SOMO = singly occupied molecular orbital. Blue and red arrows represent α and β spin of an electron, respectively.

addition or removal to such types of radicals produces poly-radicals, which have interesting conductive and magnetic properties.⁶⁰ Scheme 2 shows diagrammatically how one electron oxidation can lead to SOMO to HOMO level switching. The ω b97xd-PCM/6-31G** calculated MOs of neutral and one-electron oxidized ds(5'-GGG-3') are presented in Fig. S2 in the ESI,[†] while the ω b97xd-PCM/6-31++G** calculated MOs are presented in Fig. 5. In Fig. 5, we see that the HOMO of neutral ds(5'-GGG-3') is mainly delocalized on 5'-G and on the middle G. On one-electron oxidation (electron removal), the resulting SOMO (see Fig. 5), according to the aufbau principle, should be the highest occupied MO. But, from the analysis of the MOs of the one-electron oxidized -GGG- stack, we see that the SOMO is buried below two levels of doubly occupied MOs, see Fig. 5. The burial of the SOMO below the HOMO has important consequences and it dictates that second ionization will not occur from the SOMO but from the HOMO, which produces a diradical in the triplet^{9,61} or in the open-shell singlet^{60,81} ground state. Similarly, SOMO to HOMO level inversion for one-electron oxidized ds(5'-G8OGG-3') was also found and the results are presented in Fig. S3 and S6 in the ESI.[†] Simultaneous two-electron oxidations within DNA were proposed earlier by Bernhard to account for products formed in nonradical processes.^{82,83}

To test our hypothesis that SOMO to HOMO level inversion leads to a triplet state on further oxidation, we performed single point calculations for the energies of doubly oxidized ds(5'-GGG-3') and ds(5'-G8OGG-3') stacks in singlet and in triplet states using the ω b97xd-PCM/6-31G** and ω b97xd-PCM/6-31++G** levels of theory using the optimized structures of ds(5'-GGG-3')^{•+} and ds(5'-G8OGG-3')^{•+}. Our calculations show that indeed the triplet states of ds(5'-GGG-3')²⁺ and ds(5'-G8OGG-3')²⁺ are more stable than their singlet state by 10–20 kcal mol⁻¹ (see Fig. S10–S13 in the ESI[†]).

Conclusions

The present study shows that stacks of -GGG- in ds(5'-GGG-3') have a lower ionization potential than single guanine in DNA⁴³ by ca. 0.3 V. However, the presence of the damaged base, 8OG, in ds(5'-G8OGG-3') results in a low ionization potential (see Table 1) and thus acts as a global sink and hole trap, as found experimentally.^{10–14} The degree of solvent relaxation and its effect on spin localization/delocalization on ionization were for the first time calculated by us for ds(5'-GGG-3') and ds(5'-G8OGG-3') considering NEPCM and EQPCM approaches, as shown in Scheme 1. Our calculations using ω b97xd-PCM/6-31G** and ω b97xd-PCM/6-31++G** levels of theory show that the solvent relaxation energy (λ_1) values for ionized -GGG- and -G8OGG- stacks are the same (ca. 0.7 eV, see Table 1), as the nature of spin density distributions in both the systems is similar (π -MOs delocalized on base, see Fig. 1–3). This supports the conclusion drawn in an earlier study by Schroeder *et al.*⁶⁹ for one-electron oxidized nucleosides and nucleotides. The one-electron oxidation potential (E^0) values of G and 8OG have been estimated using theory^{69,84} and experiment^{1–5,11,69,70} but not for -GGG- and -G8OGG- stacks in DNA. Our calculated E^0 values of -GGG- and -G8OGG- stacks are 1.2 V and 0.9 V, respectively, which are lower than those of their corresponding monomers by ca. 0.3 V.

The spin density in the -GGG- cation radical stack using NEPCM in the vertical state (see Fig. 1(a) and 2(a)) is delocalized on 5'-G (ca. 30%) and on the middle G (65%). But, as solvent relaxes (EQPCM) in the vertical state, the spin density in the -GGG- cation radical stack transfers from the middle G towards 5'-G, see Fig. 1(b) and 2(b); and, finally, in the adiabatic state, the spin -GGG- cation radical is almost completely localized on the 5'-G (90%), as observed in previous studies.^{39,44–51} Localization of the hole on the 5'-G in the ds(5'-GGG-3') cation radical is found to be energetically preferred to the hole localization on the middle G by only 0.5 kcal mol⁻¹ and by 0.4 kcal mol⁻¹ compared to the hole localization on the 3'-G (Fig. 4). The calculated relative populations show a preference for hole localization at the 5'-G but show significant hole localization at both middle G and 3'-G, as found in ESR experiments at 155 K.⁴⁶

Our calculated localized spin density at the 5'-G site in one-electron oxidized -GGG- stacks does not agree with the proposal of Capobianco *et al.*⁴² that the reduction in redox potential with the number of Gs was a result of the delocalization of the hole over the guanine-rich single- and double-stranded oligonucleotides containing up to six consecutive guanines. This work and our previous theoretical work³⁷ agree that the drop in oxidation potential with number of Gs is expected but show that the hole is localized in the adiabatic state in each case. In the context of delocalized spin in the vertical states, an important question arises: are vertical states chemically reactive? Vertical ionized states are very short lived and usually react only after they are thermalized, which occurs on the timescale of 10⁻¹²–10⁻⁹ s.^{85,86} It is interesting that this work confirms that the hole can localize at each of the Gs in GGG with the 5' site favored. For oxidized -G8OGG- stacks, the spin is localized mainly on 8OG in vertical and in adiabatic states. Finally, we have previously found that

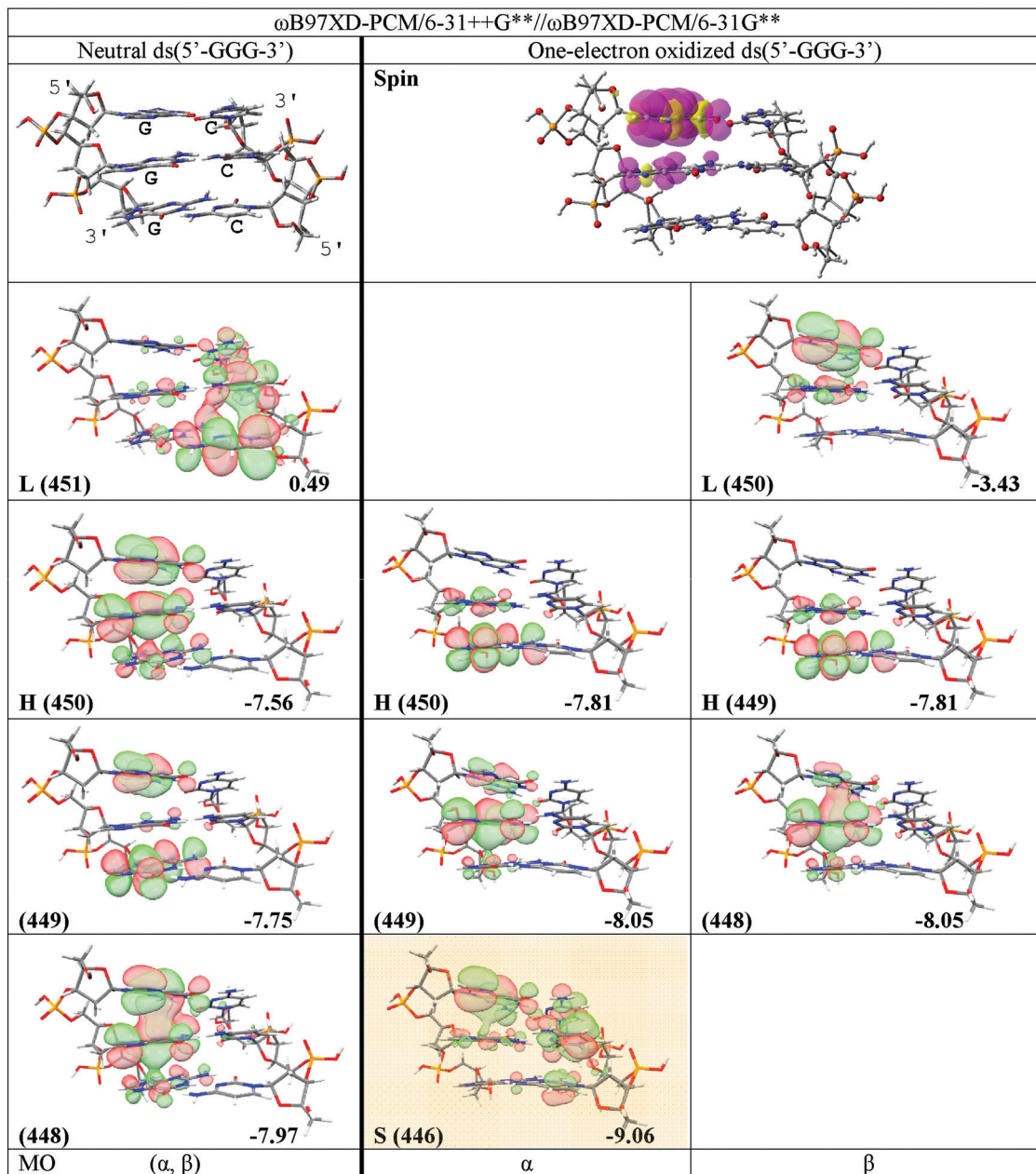


Fig. 5 ω b97xd-PCM/6-31++G**// ω b97xd-PCM/6-31G** calculated molecular orbital of optimized neutral ds(5'-GGG-3') and spin density and α - and β -MOs of optimized one-electron oxidized ds(5'-GGG-3') are shown. MO energies are in eV. In the figure, H, L and S designate the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO) and singly occupied molecular orbital (SOMO), respectively. Note that the SOMO is below four filled single occupied MOs.

SOMO to HOMO level inversion is a general phenomenon that occurs in many radicals^{9,58–61} including one-electron oxidized DNA systems (Scheme 2 and Fig. 5). In this work, we find that the SOMO is buried below several levels of doubly occupied HOMOs. This has important implications in high LET (linear energy transfer) radiation, which often produces two one-electron ionizations within a short-range.^{87,88} For such species with their SOMO buried beneath their HOMO, a second ionization forms a triplet state, whose chemistry is likely to be quite different than that of the doublet state resulting from a single oxidation.⁶¹

Conflicts of interest

The authors declare that there are no conflicts.

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