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Comment on "Theoretical Study of Polaron Formation in Poly(G)-Poly(C) Cations"

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In a recent report, Boyd and co-workers have employed density functional theory (DFT) to investigate polaron formation in poly(G)-poly(C) cation radical.[1] Their results report that the hole in the poly(G)-poly(C) cation radical is delocalized over a number of guanine residues.[1]

In their presentation of the theoretical results regarding delocalization of the spin and charge on the guanine residues in the poly(G)-poly(C) cation radical, Boyd and co-workers [1] have discussed experimental work from our laboratory [2] in which we directly determined the site and extent of hole localization at each individual G moiety in the GGG sequence of an one-electron oxidized double stranded (ds) DNA oligomer, (d[TGGGCCCA]$_2$). However, they have not represented our work accurately as described below.

In our work, the G moiety at each site of the GGG sequence has been selectively replaced by 8-deuteroguanine (G*) in d[TGGGCCCA]$_2$ - for example, d[TG*GGCCCA]$_2$, d[TGG*GCCCA]$_2$, and d[TGGG*CCCA]$_2$.[2] After one-electron oxidation, the site of the hole localization at each individual G moiety in the GGG sequence of (d[TGGGCCCA]$_2$)$\cdot^+$ was determined directly by employing electron spin resonance (ESR) spectroscopy at low temperatures.[2] Our findings show that for ca. 60% of these oligomers the hole is localized at the 5′G site, while for ca. 20% of oligomers the hole is localized at the middle G, and in the remaining (ca. 20%) of oligomers, the hole is localized at the 3′G site at 77 K.[2] Therefore, these numbers are not representative of delocalization of the hole over the entire GGG sequence, but, represent the preferential site of localization of the hole in GGG sequence. We also found that, owing to the facile intra-base pair proton transfer from the N1 site in guanine to the N3 site in the complementary base paired cytosine in (d[TGGGCCCA]$_2$)$\cdot^+$, the cation radical (G$\cdot^+$:C) exists in the intra-base pair proton transferred form (G(N1-H)$\cdot$:C(+H)$^+$).[2, 3] which localizes the hole to a single G moiety.

Selective substitution of an H-atom by the D-atom has negligible effects on the electronic properties such as ionization energy, or the spin density distribution in a radical. A deuteron shows hyperfine couplings that are only 15% (1/6.514) of that of a H-atom in the same environment and the change in ESR spectrum on deuteration at C8-H in G allows for the identification of the hole at a specific G site in the sequence.[2, 4] Thus the factors controlling hole localization in the GGG sequence in (d[TGGGCCCA]$_2$)$\cdot^+$ - for example, DNA electronic structure and conformation, proton transfer between base pairs, counter-ion location, solvation shells etc. are not affected by selective substitution of G (C8-H) by G* (C8-D)[2] and hole localization at each G site in the GGG sequence for each deuterated and undeuterated oligomer studied should be identical. Hence, the statement by Boyd and coworkers that the hole distribution in (d[TGGGCCCA]$_2$)$\cdot^+$ with G hydrogen atoms at C-8 differs from the corresponding hole distribution in the GGG oligomers with G*, i.e., G with deuterium atoms at C-8 (C8-D), misinterprets our work.

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If the hole is delocalized over the entire GGG sequence and not localized on the individual G moiety in the GGG sequence, the ESR spectrum of $(d[TGGGCCCA]_2)^{\cdot+}$ would differ from that of one-electron oxidized guanine (G(N1-H)·) in dGuo and this would be reflected by a change in the C8-H hyperfine coupling constant (HFCC) values to smaller values. However, the ESR spectrum of $(d[TGGGCCCA]_2)^{\cdot+}$ at 77 K matches that of one-electron oxidized guanine radical in dGuo.[3] Most telling is that in an X-ray irradiated single crystal of guanine:HCl:H_2O, the hole is found to be localized on one single guanine at 15 K and this clearly argues against hole delocalization in guanine stacks.[5]

The experimental observations mentioned above are also supported by a number of theoretical calculations using CASSCF, CASPT2 and DFT level of theories.[6] Very recently, the extent of hole delocalization in A- and G-stacked systems were studied using M06-2X/6-31G* method.[7] The geometries of both the stacks in neutral and cation radical states were fully optimized in the B-DNA conformation. The calculations showed that in A-stacks hole is delocalized over 2 to 3 adenine bases in the A-stack, while in optimized G-stacks (GG and GGG) hole is predominantly localized on a single guanine. M06-2X/6-31G* calculated isotropic hyperfine coupling constants (HFCC) in MHz of the C8-H atom have similar values for the G cation radicals for G (−22.43), GG (−20.84), or GGG (−19.63) stacked in the B-DNA conformation. These couplings are from one of the Gs in the stack and are found to be in very good agreement with the corresponding experimental value of −21.5 MHz found in ESR studies of one electron oxidized G ($G^{\cdot+}$ and G(N1-H)·) in dGuo in D_2O.[4a] Therefore, from theory and ESR spectral studies, the hole is found to be located on a single guanine moiety in stacked GG, and GGG sequences in the B-DNA conformation.[7]

Regarding the theoretical studies of intra-base pair proton transfer (PT) reaction in $G^{\cdot+}$-C, Boyd and coworkers have discussed only early studies [1, 8] carried out in the gas-phase which reported the PT from N1 atom in $G^{\cdot+}$ to N3 atom in C in $G^{\cdot+}$-C was an endothermic process. More recent work shows that, the PT reaction in $G^{\cdot+}$-C is exothermic when the effect of full solvation (first hydration layer) was considered, the calculation was done at the B3LYP/6-31+G** level of theory[9] and latter, this was also confirmed by the MP2 level of theory.[10] The proton-transferred G(N1-H)·:C(+H^+) + 11H_2O was found more stable than $G^{\cdot+}$:C + 11 H_2O by 1.2 [9] to 1.7 [10] kcal/mol. We do agree that this value is so small that various dynamic environmental factors considered by Boyd and coworkers, such as counter ions, conformations and hydration environments can dynamically alter these energetics and an equilibrium clearly exist between ($G^{\cdot+}$:C) and (G(N1-H)·:C(+$H)^+$) at room temperature.[1, 2] with the deprotonated form favored at low temperatures as found in our experimental work.[2,3] We note that many studies of photo-injection of holes into ds DNA oligomers containing GGG sequences in aqueous solutions at room temperature find the preferential formation of 8-oxo-G and associated DNA strand cleavage at the 5′-end of the GGG sequences suggesting preferential hole localization at the 5′-end.[11 - 14]

In conclusion, our experimental work at low temperatures shows that the hole in contiguous G sequences in ds DNA oligomers is localized to a single G.[2, 3] Delocalization of the hole is initially feasible, especially if in a stack of G moieties, uniform geometry is maintained (see supporting information of Ref. 7); but, upon adiabatic relaxation, various factors, such as, relaxation, polarization, and proton transfer, result in hole localization.

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