

Conformation-Dependent Electronic Property of DNA

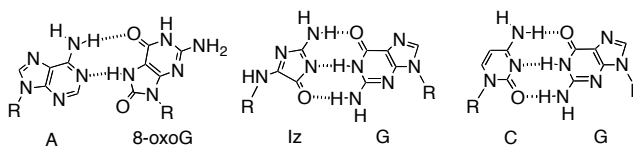
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The genome is assaulted constantly by oxidative stress. Reactive species attack duplex DNA and generate various oxidative lesions, which have been implicated in aging and carcinogenesis. Guanine is especially susceptible to one-electron oxidation because it has the lowest redox potential of the four bases. Interestingly, consecutive G sequences such as GG and GGG are hotspot sequences of oxidative DNA damage.¹ To explain such reactivity, we used an *ab initio* molecular orbital calculation (MO) and postulated that cation radicals formed in DNA migrate to the 5' side of GG or GGG sites in duplex DNA. The MO calculation clearly suggests that the stacking orientation of GG in B-DNA determines the reactivity of DNA. 8-oxoguanine (8-oxoG) is a typical oxidation product of GG sites, and the biological impact of 8-oxoG has been investigated extensively. The formation of 8-oxoG by forming Hoogsteen base pairs with adenine explains G-T transversion mutation. However, G-C transversion, which is also observed as G-T transversion, cannot be explained by 8-oxoG. We demonstrated that imidazolone (Iz) is formed from 8-oxoG in duplex DNA under oxidation conditions.² Importantly, the H-bonding donor and acceptor abilities of Iz closely resemble cytosine; *ab initio* calculations showed that the stabilization energy of Iz-G is similar to that of C-G.

We demonstrated that guanine is specifically incorporated opposite Iz by DNA polymerase I, indicating Iz-G base pair formation.^{2,3}



DNA can adopt a variety of secondary structures, which range from the canonical right-handed B form to the left-handed Z form. These conformations are assumed to play important biological roles. To determine the DNA local structure, we are interested in hydrogen abstraction by the uracil radical generated by photoirradiation of 5-halouracil. We examined the photoreactivity of 5-halouracil in various local DNA structures and showed that this method can be used to detect DNA structures.⁴ 5-Bromouracil (^{Br}U) also serves as an electron acceptor, which leads to guanine oxidation. Interestingly, this electron transfer is highly conformation dependent, and, in this transfer, guanine is oxidized efficiently to Iz in four-base -stacks in Z-DNA.⁵ Using the transition between right- and left-handed helices, we designed a molecular switch that is based on the characteristic properties of DNA and RNA; this switch indicates a completely inverted response to thermal stimuli.⁶ Using ^{Br}U, we also recently identified efficient electron transfer from protein and hypothesized that such a primitive DNA repair system existed at the origin of life.⁷

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