Redox-Mediated DNA Protection and Recognition of Defect Bases: Insights from Static QM Calculations and QM/MM Molecular Dynamics Simulations

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The ability of DNA to conduct charge has been documented extensively and it has been proposed that this ability can be employed by the cell for the recognition of DNA defects via charge transfer (CT) between base excision repair (BER) enzymes [1,2]. Exploiting differences in DNA redox chemistry introduced by the presence of a lesion, the defect is proposed to trap the migrating charge, thus disrupting DNA-mediated CT and initiating its repair process by base excision repair enzymes. For such a scheme, defect DNA fragments should have considerably different redox properties than their native counterparts.
8-oxoguanine (8OG), a product of guanine (G) oxidation, is the most abundant DNA lesion, and thus a highly relevant candidate for investigating this hypothesis. Recently, the ionization energies (IEs) and electron affinities (EAs) of native and 8OG-containing DNA models of up to 3 base pairs were determined by static DFT calculations under implicit solvation [3]. IEs were 0.2 eV lower for the defect fragments, while relative EA differences amounted to only 0.01 eV. Hole and excess electron distributions were consistent with these results (pronounced hole localization in 8OG, no differences for excess electron). In the context of a CT mechanism for the recognition of DNA damage, these findings strongly suggest that hole transfer is a more likely candidate than excess electron transfer. In fact, cyclic voltammetry experiments indicate that the detection of oxidative and bulky DNA lesions via hole transfer could be possible [4].
To gain more insight, it is essential to explicitly consider a biologically relevant environment (large DNA fragment, solvent, physiological ionic strength). Under this scope, we have performed QM/MM simulations of a native and a defect DNA 39mer in physiological conditions by means of hybrid DFT-based QM/MM simulations [5]. For the defect fragment, a G in a G-rich region was replaced by 8OG. Redox properties were determined using a theoretical method which is based on Warshel's theory on vertical energy gap distributions [6,7] and on Marcus Theory of electron transfer. The redox potential (E_{ox}) of 8OG-DNA is approximately 1 eV higher than that of its native counterpart. This outcome highlights 8OG's oxidizing power, and supports a potential DNA-mediated hole transfer scheme for the recognition of oxidative DNA lesions. In order to assess whether such a finding also applies to other DNA sequences and lesions, we are currently simulating the oxidation of an adenine (A)-rich region of the same DNA 39mer at the QM/MM level. In the defect fragment, one A is replaced by an isoguanine (IG) defect.

References

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