MOLECULAR MECHANISMS IN THE REPAIR OF THE CYCLOBUTANE PYRIMIDINE DIMER

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Exposure to far UV radiation induces DNA damage in the form of cyclobutane pyrimidine dimers (CPDs). Cyclobutane dimer lesions can be repaired by the enzyme photolyase, in which the absorption of a blue light photon initiates a sequence of photochemical events leading to the injection of an electron at the site of the CPD lesion in DNA. The electron catalyzes the repair of the cyclobutane dimer, splitting the CPD to is original pyrimidine units, and is subsequently recaptured by the photolyase protein. In this work we investigate the molecular mechanism of the repair of the cyclobutane dimer radical anion in aqueous solution using *ab initio* MD simulations. Umbrella sampling is used to determine a two-dimensional free energy surface as a function of the C5-C5 and C6-C6 distances. The neutral dimer is unable to surmount a large free energy barrier for repair. Upon addition of an electron, the splitting of the C5-C5 coordinate is virtually barrier less. Transition state theory predicts that the splitting of the C6-C6 bond is complete on a picosecond timescale. The free energy surface suggests that the splitting of the two bonds is asynchronously concerted. Our work is the first to explicitly include the electronic degrees of freedom for both the cyclobutane dimer and the surrounding water pocket. The ab initio simulations show that at least 30% of the electron density is delocalized onto the surrounding solvent during the splitting process. Simulations on the neutral surface show that back electron transfer from the dimer is critical for the completion of splitting: splitting of the C5-C5' and C6-C6' bonds can be reversed or enhanced depending on when electron return occurs. To maximize splitting yield, the back electron transfer should occur beyond the transition state along the splitting coordinate. Non-equilibrium trajectories are also conducted that begin with the electron added to a neutral unrepaired solvated CPD. Our results indicate that there are two sup-populations: the first population with the C5-C5' bond splitting spontaneously, as indicated by our two-dimensional free energy surface, and a second population where the C5-C5' bond remains intact over the first half of a picosecond.