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# Structural Basis for the Mutagenic Properties of the UV-Induced DNA Photoproducts

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The (6-4) adduct is one of the major photoproducts induced by UV irradiation of DNA The (6-4) adduct is highly mutagenic and leads most often to a 3′-T→C transition with 85% replicating error frequency, whereas its Dewar valence isomer has low mutagenic potential and produces a broad range of mutations. In order to determine the origin of the mutagenic property of the (6-4) and Dewar product, we used NMR restraints and molecular dynamics to determine the solution structure of the (6-4)- and Dewar-lesion DNA decamer duplexes which contain mismatched base pairs between their 3′-T and the opposite G residues [(6-4)/GA and DW/GA].

In the (6-4)/GA duplex, normal Watson-Crick-type hydrogen bonding is retained at the 5′-T of the lesion site. The O2 carbonyl of the 3′-T forms hydrogen bonds with the imino and amino protons of the opposed G residue. This potential hydrogen bonding stabilizes the overall helix and restores the highly distorted conformation of the (6-4) adduct to the typical B-form-like DNA structure. This structural feature can explain the marked preference for the insertion of an A residue opposite the 5′-T, and a G residue opposite the 3′-T of the (6-4) lesion during translesion replication. Thus these insertions yield the predominant 3′-T→C transition.

In the DW/GA duplex, the helical bending and unwinding angles of the DW/GA duplex were much larger than those of DW/AA duplex. The DW/GA duplex showed the poorer stacking interactions at the two bases of the Dewar product and at the adjacent base pair than did the DW/AA duplex. This structural study implies that no thermal stability or conformational benefit is obtained by incorporating a G instead of an A opposite the 3′ T of the Dewar lesion. These properties may thus facilitate the preferential incorporation of an A in accordance with the A rule during TR and lead to the low frequency of 3′ T→C mutations observed at this site.