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Structural and stereoisomer effects of model estrogen-DNA adducts

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An extensive conformational analysis has been carried out for two diastereoisomeric pairs of model estrogen-DNA adducts, N^2-(2-hydroxyestron-6(□,□)-yl)-2'-deoxyguanosine (2-OHE$_1$-6(□,□)-N^2-dG) and N^6-(2-hydroxyestron-6(□,□)-yl)-2'-deoxyadenosine (2-OHE$_1$-6(□,□)-N^6-dA), in a B-DNA duplex and at a primer-template junction in DNA polymerase □. *In vitro* primer extension studies in pol □□ (Terashima, et al. *Biochem.* 37:13807-13815, 1998) have shown that the dA adducts can incorporate dT, together with a small proportion of the incorrect base dC opposite the lesion, and they block less strongly than the dG adducts. Our searches revealed that the four-ring non-planar 2-OHE$_1$ moiety strongly prefers to reside in the minor groove of the dG adducts or the major groove of the dA adducts. No low-energy conformations involving intercalation of the 2-OHE$_1$ moiety were located in the search. This stems from the largely non-planar, non-aromatic nature of the 2-hydroxy estrone ring system, and implies that the proclivity for such bulky, non-planar adducts to reside at the DNA helix exterior is a plausible conformational feature of other structurally similar estrogen-DNA adducts. Possible structures of these adducts in pol □ were also investigated through molecular modeling. The estrone rings in the dA adducts can be comfortably accommodated on the major groove side of the templating base within the catalytically competent closed conformation of the polymerase, permitting Watson-Crick base pairing with incoming dTTP and maintaining a distance suitable for reaction between the □ phosphate and the primer terminus. However, the dG adducts cannot fit on the crowded minor groove side. These results can rationalize the observed greater proclivity for blockage by the dG adducts and the misincorporation of dC opposite the dA adducts. More broadly, our findings suggest how bulky estrogen-derived stable adducts may be accommodated within a model high fidelity polymerase for possible translesional synthesis or cause blockage that may lead to bypass by a low fidelity Y family polymerase. Different orientations of □ and □ stereoisomers found in both G and A adducts are intrinsic to the linkage site differences. These stereoisomer-dependent orientational differences could be expected to produce different biochemical effects, as has been observed in the stereochemistry-dependent differential treatment of adducts derived from polycyclic aromatic hydrocarbons.

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