MOLECULAR DYNAMICS SIMULATIONS OF NITROGEN MUSTARD CROSSLINKED DNA

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The nitrogen mustard based DNA alkylating agents were the first effective anticancer drugs and remain important drugs against many forms of cancer. There is strong evidence that the effectiveness of these drugs for killing cancer cells is related to their ability to form interstrand DNA crosslinks. Our goal is to develop new analogs of the nitrogen mustard drugs designed to increase the fraction of interstrand crosslinks resulting from the initially monoalkylated DNA. To study the effect of variation in the crosslinker length and composition on the second alkylation step, we have performed molecular dynamics simulations of five different crosslinking agents bound to DNA. These include the active metabolites of three anticancer drugs and two proposed analogs with increased crosslinking lengths. In unconstrained simulations we find that monoalkylated DNA with different crosslinking agents adopt conformations similar to non-alkylated DNA. However, we find large structural and free energy differences for short-length crosslinking agents when distance constraints are included in the simulations to force the monoalkylated structure to adopt the conformation necessary for the second alkylation reaction to form the crosslink. The significance and relevance of simulation data to the experimental observations will also be discussed. (Work performed under contract W-7405-ENG-48 from US Dept. of Energy).