DNA Structure and Dynamics II

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Targeting Human Telomeric G-Quadruplex DNA by Berberine Analogues: A Comparative Biophysical Investigation
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Nucleic acids are potential target molecules in various anticancer therapies. Understanding how drug molecules interact with nucleic acid has become an active research area at the interface between chemistry, molecular biology, and medicine. Berberine is the most widely known alkaloid belonging to the protoberberine group, exhibiting myriad therapeutic applications. The anticancer potency of berberine is thought to emanate from its strong interaction with nucleic acids, and inhibition of the enzymes topoisomerases, telomeres. Berberine also binds strongly to the G-quadruplex structure, an alternative DNA structural motif. The capability of berberine analogs bearing substitution at 9 and 13-position to strongly bind G-quadruplex structure is studied for developing effective anti cancer therapies. Compared with berberine, these derivatives exhibit stronger binding affinity with G-quadruplex and the non cooperative binding affinity of berberine was propagated in the analogs also. The circular dichroism studies indicated that the alkylated bound quadruplex DNA has a fold similar to the unbound form. In all cases, the stoichiometry was found to be one mole of ligand binding per mole of quadruplex. Calorimetric results indicated that the interaction of these analogs with the quadruplex was entropy driven phenomenon. The negative heat capacity changes in all systems along with significant enthalpy-entropy compensation may be correlated to the involvement of multiple weak non-covalent forces in the complexation process. The amino alkyl substitution at 9-position were found to be more effective in stabilizing G-quadruplex structure compared to the phenyl alkyl substitution at 13-position. Detailed studies on these analogs stabilizing telomeric G-quadruplex-DNA through entropy driven process with high binding affinity shall be presented that enable consideration as a leads compounds for telomerase inhibition and anticancer therapy.

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Studying Ligand Binding and Site-Specific Mode of DNA Binding by Gamma-Butyrolactone Receptor Protein CprB from Streptomyces Coelicolor A3(2) using Two Different Fluorescence Techniques
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Quorum sensing is a cell density dependent phenomenon that utilizes inducers like γ-butyrolactones (GBLs) and their receptor proteins in Streptomyces species to control expression of a plethora of genes initiating antibiotic production and other secondary metabolic pathways. The receptor proteins regulate by binding to the DNA in the promoter regions of genes; release from the DNA takes place on binding to their specific GBL molecules, initiating the expression of the downstream genes.
Several cognate GBLs binding to the GBL receptor family of proteins remain elusive. Here, using the only structurally characterised member of this family, CprB from Streptomyces coelicolor A3(2) as a model system, we suggest tryptophan quenching as a method for ligand screening, showing that sequence effects on the physical properties of DNA molecules contribute nontrivially to the molecule’s behavior. Here we present the first results of a study of sequence effects on the formation and dynamics of plectonemes, the supercoiled structures produced when the DNA is put under torsional stress. Using, for the first time in this context, a fully sequence-dependent, non-cousregrained rigid base pair model for the DNA molecule, we examined the process of sliding a formed plectoneme along a DNA molecule in its entirety as a mechanism for plectoneme transport. We were able to map out the relevant energy landscapes and we find that we can rule out sliding as the dominant transporation mechanism.

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Sequence Dependent Plectoneme Dynamics
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In recent years, both theoretical and experimental indicators have been gathering, showing that sequence effects on the physical properties of DNA molecules contribute nontrivially to the molecule’s behavior. Here we present the first results of a study of sequence effects on the formation and dynamics of plectonemes, the supercoiled structures produced when the DNA is put under torsional stress. Using, for the first time in this context, a fully sequence-dependent, non-cousregrained rigid base pair model for the DNA molecule, we examined the process of sliding a formed plectoneme along a DNA molecule in its entirety as a mechanism for plectoneme transport. We were able to map out the relevant energy landscapes and we find that we can rule out sliding as the dominant transporation mechanism.

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Mismatched DNA Base Pairs Show Increased Conformational Fluctuations
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Base pair mismatches in DNA can have many adverse consequences, yet the exact mechanism by which mismatches are repaired is unknown. Both matched and mismatched DNA sequences were studied using molecular dynamics in biased and unbiased simulation. Significant differences were found between matched and mismatched pairs in structure, energy, and base flip work profiles. Mismatched pairs show greater movement perpendicular to the DNA strand and a lower free energy barrier for base flip than matched pairs. This supports experimental findings that the primary mechanism utilized by mismatch repair enzymes is to fully flip the base into the active site.

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The Study of Complexation Process between Cationic Gemini Surfactants and DNA using Structural and Spectroscopic Methods
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Dicationic (gemini) surfactants are intensively studied group of chemical compounds, because of the broad range of applications in medicine, chemical technology or pharmaceutical industry. In solution they can form with nucleic acids the complex structures (lipoplexes), which can be used as drug delivery systems.