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1989-Pos Board B126
Packing and Phase Transitions in DNA Duplexes and Tetraplexes: Similarities and Differences
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We have mapped the thermodynamic potentials that drive transitions of DNA in uni- and di-valent salt solutions. The successive mesophases, with measured free energies of deformation and transition, allow computation of interaction potentials as well as transition entropies and enthalpies. We have been able to measure transitions of DNA tetraplexes and duplexes and to compare entropic and enthalpic contributions. Changes in fluctuation free energies are much greater at DNA-ordering transitions for tetraplexes than for duplexes, indicating strong entropic contributions. Disordering due to fluctuations is much greater in the less-ordered (cholesteric) phase, seen in broadening of x-ray scattering peaks. This indicates attraction in the more-ordered phase, where packing is stricter, and the effect of fluctuations is much smaller. This attraction is stronger for quadruplexes than for duplexes.
We can read two kinds of information from the x-ray data: the degree of ordering, and the change in density. These changes are much bigger in tetraplexes than in double helical DNA.
In addition, we also observe that upon decreasing the applied osmotic stress on the less-ordered phase, there is spontaneous disassembly of tetraplexes. This second transition, from a stack of tetramers to monomers, also depends on temperature, allowing us again to measure transition entropy and free energy.
Lowering the temperature in the cholesteric phase favors tetraplex formation. The critical osmotic pressure for the formation of tetraplexes, just as the critical osmotic pressure for inducing the higher-density packing, depends strongly on the temperature.
Out next goal is to compare tetraplexes, which lack a linking backbone, with quadruplexes (where the bases are linked) so as to see the stabilizing contributions of a polymer backbone.

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The Relationship between Electrophoretic Mobility and Polyelectrolyte Charge
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Many textbooks state that the electrophoretic mobility of a polyelectrolyte is proportional to its effective charge divided by its frictional coefficient. We have tested this relationship by analyzing the mobilities of single- and double-stranded DNA molecules containing the same number of bases or base pairs and different numbers of negatively charged phosphate linkers. Small organic molecules containing different numbers of charged residues were also analyzed,using data taken from the literature. In each case, the free solution mobilities of the charge variants of a given molecule were divided by the mobility of the charge variant with the highest number of charged residues, measured under the same conditions. The mobility ratios were then plotted as a function of the fractional charge of each molecule. The results indicate that the fractional mobilities of polyelectrolytes of the same size are proportional to the logarithm of the fractional charge, not the first power of the charge as commonly assumed. The Manning theory of DNA electrophoresis and electrophoretic theories based on the zeta potential both predict a logarithmic dependence of the mobility on charge density. The experimental mobility ratios will be compared with the predictions of these two theories.

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Enhanced Sampling of DNA Step Parameters: Impact of Methylation on DNA Shape and Flexibility
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We present a novel approach for the selection of DNA step parameters as reaction coordinates in umbrella sampling simulations. Simplified representation of DNA that uses only three atoms per base, allowed for highly efficient calculations of the step parameters and their Cartesian derivatives in the molecular dynamics simulations. Good correlation between the actual and calculated twist, roll, tilt, rise, slide and shift was obtained. The method is illustrated through its application to the unmethylated and methylated DNA systems. Impact of the methylation on the shape and flexibility of DNA depending on the location of the methyl group is discussed.

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Three-Dimensional Modeling of Single Stranded Hairpin DNA Aptamers
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Aptamers are short oligonucleotides that are selected for affinity binding to a wide range of targets and provide a number of advantages over antibodies including robustness, low cost, and reusability [1,2]. The relatively simple chemical structure of aptamers allows the insertion of electrochemical or fluorescent reporter molecules as well as surface-binding agents in specific locations on the oligonucleotide. During probe-target binding, the conformation change of the aptamer may be exploited to generate an analytical signal. The robustness and simplicity of aptamers has allowed for multiple uses of aptamer-based biosensors and a number of direct detection strategies employing aptamers have been proposed. However, in order for commercialization of these devices to become feasible, significant improvements in optimization for consistency and reproducibility must be done. Overcoming these challenges has been hampered by a lack of complete understanding of the molecular-level biophysics involved [3]. In this regard, computational studies can complement experimental studies in improving our understanding about the structure, molecular-level interactions, dynamics, and solvent effects of biomolecular complexes [4,5]. Here, we present a method to predict the three-dimensional structure of single stranded DNA aptamers from their sequence.
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Resolving the DNA Binding Mode of a Rotationally Flexible Binuclear Ruthenium Complex
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Binuclear ruthenium complexes demonstrate slow dissociation upon binding to DNA, and they are considered as potential DNA-targeted therapeutic drugs. Quantitative investigations of their properties, such as binding affinity, binding mode and kinetics, require approaches beyond traditional experimental techniques. In particular, previous reports showed that the rotationally flexible binuclear ruthenium complex Δ,Δ-[μ-bipb(phen)$_4$Ru$_2$]$^{4+}$ (Δ,Δ-Pi) strongly condenses DNA. However, the strong DNA condensation poses a challenge in bulk experiments such that even the DNA-ligand binding mode could not be resolved. We examined the kinetics of ΔΔ-Pi interactions with single λ-DNA molecule as a function of a constant applied force of 30 pN and ligand concentration of 5 nM using dual-beams optical tweezers. We find that Δ,Δ-Pi exhibits characteristics of threading intercalation into DNA base pairs. DNA elongation measurements, as monitored over tens of minutes, illustrate two distinct phases during association; rapid intercalation that is analogous to classic intercalation, followed by very slow intercalation that approaches equilibrium with a rate that is comparable to that observed for other threading intercalators. We investigated ΔΔ-Pi dissociation after reaching the equilibrium extension by rinsing the binding ligands from the surrounding solution, and observed that the DNA-ligand complex extension decreases to the DNA-only extension over a timescale longer than the association process. Interestingly, the dissociation measurements fit well to a single rate that is slower than the dissociation rate measured for the previously reported binuclear ruthenium complex Δ,Δ-[μ-bidppz-(phen)$_4$Ru$_2$]$^{4+}$ (Δ,Δ-P), which is a threading intercalator. Further measurements of force-dependent intercalation thermodynamics and kinetics will allow us to fully quantitatively characterize the complex binding mechanism of this unusual intercalator.