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Phase diagram of mechanically stretched DNA: The salt effect

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ABSTRACT

The cations, in the form of salt, present in a solution containing DNA play a crucial role in the opening of the two strands of DNA. We use a simple non-linear model and investigate the role of these cations on the mechanical unzipping of DNA. The Hamiltonian is modified to incorporate the solvent effect and the presence of these cations in the solution. We calculate the melting temperature as well as the critical force that is required to unzip the DNA molecule as a function of salt concentration of the solution. The phase diagrams are found to be in close agreement with the experimental phase diagrams.

1. Introduction

The stability of the double stranded DNA (dsDNA) molecule is primarily due to the hydrogen bonding present between the bases of the complimentary strands. The bases along the strands give rise to the stacking interaction between the nearest base pairs which contributes to the rigidness of the molecule. In addition to this, the presence of the cations (Na^+ or Mg^{2+}) in the form of salt (in the solution) plays a crucial role in the stability of these molecules. The stability of the strand can be monitored by changing the temperature, by applying the force on either of the ends or by changing the pH of the solution. A systematic investigation done in the past has shown that the melting temperature of a dsDNA increases with the salt concentration [1–8]. Since the two strands of the dsDNA are negatively charged, to neutralize the Coulombic repulsion between the phosphates, cations like sodium or magnesium ions are required. The concentration of these ions contributes not only to the stability of the molecule but also plays an important role in the folding kinetics of the molecule. To understand the mechanism theoretically, the counterion condensation model (based on the two state ion distribution) [9], and the Poisson–Boltzmann model (based on mean field calculations) [10,11] have been used. Recently, the tight bonding approximation (TBA) [12], and Peyrard–Bishop–Dauxious (PBD) [3] models are also used to study the helix–coil transition in these molecules. Most of these studies focused primarily on the thermal stability of the dsDNA molecule as a function of salt concentration of the solution.

In recent years, using single molecule force spectroscopy (SMFS) experiments, e.g. optical and magnetic tweezers, atomic force microscope, etc., the forces exerted by single stranded binding (SSB) proteins in maintaining the open regions of ssDNA have been measured directly [4,6–8]. These groups have experimentally measured the force required to destabilize the dsDNA molecule as a function of concentration of salt in the solution. In addition to this, several groups have measured the effect of these cations on the stretching behavior of dsDNA [13,14]. However, the theoretical understanding of these results is also important in order to get a precise idea of the physical processes that are involved in these transitions. To investigate the various issues related with the helix to coil transition in dsDNA various theoretical models have been developed. These models can be classified under the Poland–Scheraga (PS) model [15–17] which considers a dsDNA chain with regions of denaturated loops, or the Peyrard–Bishop–Dauxois (PBD) model [18] which is a Hamiltonian based model. There is another class of theoretical model in which dsDNA is modeled by two self avoiding or directed walks on a square lattice [19–22] to

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study the thermal as well as mechanical denaturation of the dsDNA molecule. In this paper, we investigate the effect of salt present in the solution, on the force induced unzipping of a heterogeneous dsDNA molecule using the PBD model, which has been discussed in Section 2. In this section, we also discuss the method to calculate the melting temperature (T_m) and the forces required to unzip the chain. The method developed in Section 2, has been extended to study the thermal and force induced melting of dsDNA in Sections 3 and 4, respectively. Section 5 summarizes the results followed by brief conclusions.

2. The model

In this section, we briefly discuss the basic features of the PBD model, which considers the stretching between corresponding bases only. Although the model ignores the helicoidal structure [23–27] of the dsDNA molecule, it has enough details to analyze mechanical behavior at few Å scale relevant to molecular-biological events. The Hamiltonian for the considered system of N base pairs unit is written as,

$$H = \sum_{i=1}^{N} \left[\frac{p_i^2}{2m} + V_S(y_i, y_{i+1}) + V_M(y_i) + V_{\text{sol}}(y_i) \right] \tag{1}$$

where y_i represents the stretching from the equilibrium position of the hydrogen bonds, $p_i = m\dot{y}_i$ represents the momentum while m is the reduced mass of a base pair (taken to be the same for both AT and GC base pairs). The stacking interaction between two consecutive base pairs along the chain is represented by,

$$V_S(y_i, y_{i+1}) = \frac{k}{2}(y_i - y_{i+1})^2[1 + \rho e^{-b(y_i + y_{i+1})}], \tag{2}$$

where k represents the single strand elasticity. The anharmonicity in the strand elasticity is represented by ρ while b represents its range. These parameters are assumed to be independent of sequence heterogeneity. The sequence heterogeneity has an effect on the stacking interaction along the strand. This can be taken care of through the single strand elasticity parameter k.

The hydrogen bonding between the two bases in the ith pair is represented by the Morse potential,

$$V_M(y_i) = D_i(e^{-a_i y_i} - 1)^2, \tag{3}$$

where D_i represents the potential depth, roughly equal to the bond energy of that pair and a_i represents the inverse of the width of the potential well. The heterogeneity in the sequence is taken care of by the values of D_i and a_i. In the stability of the dsDNA molecule the role of hydrogen bonds is the key factor. In most of the previous studies, the hydrogen bond interaction and the effects of surroundings, such as salt concentration of the solution, are taken as constant [18,23]. As the DNA molecules are strong polyelectrolytes, having negatively charged phosphate groups, it would be interesting to analyze its role in the melting or unzipping profiles. The salts present in the solution neutralize the negative charge of the phosphate groups, therefore, the increase in their concentration will reduces the electrostatic repulsive forces between these negatively charged groups. At higher concentrations, the stability of the molecule increases, thus more energy is required to break the hydrogen bonds. In the PBD model, the stability in hydrogen bonds is represented by the depth of the Morse potential, D_i. Thus, this parameter should be a function of salt concentration of the solution. Experimental observations on short oligomers predict that the melting temperature of dsDNA scales non-linearly with the $\ln[Na^+]$ present in the solution [2,28]. Keeping these factors in the background, we modify the potential depth as,

$$D_i = D_0 \left[1 + \lambda_1 \ln\left(\frac{C}{C_0}\right) + \lambda_2 \ln^2\left(\frac{C}{C_0}\right) \right]. \tag{4}$$

Here, the concentration, C is expressed in moles per liter and C_0 is the reference concentration chosen to be 1 mole/liter. λ_1 & λ_2 appearing in the potential are solution constants [2,3,29].

An additional term in the Hamiltonian is the solvent term which simulates the formation of hydrogen bonds with the solvent, once the hydrogen bonds are stretched by more than their equilibrium values. We adopt the solvent term from Refs. [30,31]:

$$V_{sol}(y_i) = -\frac{1}{4} D_i \left[\tanh(\gamma y_i) - 1 \right]. \tag{5}$$

The "tanh" term in the potential enhances the energy of the equilibrium configuration and the height of the barrier below which the base pair is closed. The small barrier basically determines the threshold stretching of hydrogen bonds about which a base pair may be temporarily broken, re-bonded and then fully broken. This comes to the broken state at a length greater than ∼2 Å. As the solvent role is to stabilize the denatured state, this form of potential can be a good choice. The term, γ is the solvent interaction factor and it reduces the height of the barrier appearing in the potential [30–33]. We tune various values of γ from 0.1 to 1.0 and plotted the effective potential, as shown in Fig. 1(B). We found that for larger values of γ, the unzipping transition is more favorable. As the broken state occurs ∼2.0 Å, the value of γ should be chosen which reflects the breaking around 2.0 Å. We found $\gamma = 1.0$ Å^{-1} as a suitable choice for our calculations.