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2004 J. Phys. A: Math. Gen. 37 4977

(http://iopscience.iop.org/0305-4470/37/18/005)

INSTITUTE OF PHYSICS PUBLISHING JOURNAL OF PHYSICS A: MATHEMATICAL AND GENERAL

J. Phys. A: Math. Gen. **37** (2004) 4977–4984 PII: S0305-4470(04)68401-0

The salt dependence of the stretching transition of double-stranded DNA molecules

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Received 30 August 2003
Published 20 April 2004
Online at stacks.iop.org/JPhysA/37/4977 (DOI: 10.1088/0305-4470/37/18/005)

Abstract

We give a model for describing the elasticity of double-stranded DNA molecules on the basis of the ZZO model, which is related to the sodium ion concentration. The hydrogen-bond and the base-stacking interactions are taken into account in this model. The salt dependence of the stretching transition of double-stranded DNA molecules is discussed. As the salt concentration is increased, the stretching transition force increases nonlinearly. These results obtained by numerical calculations are in agreement with experimental measurements in DNA.

PACS numbers: 87.15.−v, 61.25.Hq, 36.20.Ey

1. Introduction

DNA is the basis of life. In cells, proteins apply forces to unzip and stretch DNA [1, 2]. With recent advances in nanomanipulation techniques, such as the use of optical traps, magnetic beads etc, these forces can be studied in single-molecule experiments [3–6]. Smith *et al* found that the double-strand DNA (dsDNA) molecule can overstretch 1.7 times of the B-form contour length and a phase transition appears from the B-form to a stretched or S-form when the force acting on it reaches about 65 pN. Before long, Wenner measured the elasticity and overstretching transition as a function of monovalent salt concentration by stretching single DNA molecules in an optical tweezers apparatus [7]. These experiments denote that the destabilizing of the DNA double helix by decreasing the salt concentration causes a decrease in the overstretching force [7, 8].

A number of theoretical models [9–15] have been formulated to model single DNA molecule experiments. In the low force region, its elastic response can be quantitatively predicted by the worm-like chain model (WLC) and freely-jointed chain model (FJC). In the high force region, the two-state model, the extensible worm-like chain (EWLC), and freely-jointed chain (EFJC) model have been applied successfully to the stretching of DNA

molecules. Recently Zhou *et al* (ZZO) proposed a new model [12, 13] based on bending and base-stacking interactions and provided a unified framework to understand systematically and quantitatively all aspects of DNA mechanical properties. Excellent agreements between theory and experimental results reported by several groups are obtained through this model. However, these models do not satisfactorily describe the influence of salt ion concentration on the stretching transition; because DNA is a very complicated nonlinear system and interacts with the environment, and the base-stacking and hydrogen-bond interactions change when the environment condition changes [16]. Therefore, this work is needed to study further the influence of salt ion concentration on the stretching transition. In this paper, we give a model of DNA including the hydrogen-bond and base-stacking interactions which are related to the sodium ion concentration on the basis of the ZZO model, and discuss the force–extension curves at different salt concentrations and compare them with experimental results.

2. Theoretical model

The B-DNA molecule is a double-stranded biopolymer with two complementary sugar-phosphate backbone chains twisted around each other to form a right-handed helix with one turn per 10.5 base pairs. Each chain is a linear polynucleotide consisting of four kinds of bases. The two chains are joined together by hydrogen bonds between pairs of nucleotides A–T and G–C. The distance between adjacent base pairs is about 0.34 nm.

2.1. ZZO model

In the ZZO model, the backbones of DNA are regarded as two wormlike chains characterized by a bending rigidity $k = k_B T l_p$, where k_B is the Boltzmann constant, T is the environmental temperature and l_p is the bending persistence length of the single-stranded DNA (ssDNA) chain. When one terminal of the DNA molecule is fixed and the other terminal is pulled with a force $\mathbf{F} = f\mathbf{z_0}$ along the direction of unit vector $\mathbf{z_0}$, the total energy of a dsDNA molecule under the action of an external force is expressed as

$$\begin{aligned} E &= E_b + E_{L-J} + E_f \\ &= \int_0^L \mathrm{d}s \left[k^* \left(\frac{\mathrm{d}\mathbf{t}}{\mathrm{d}s} \right)^2 + k \left(\frac{\mathrm{d}\theta}{\mathrm{d}s} \right)^2 + \frac{k}{R_0^2} \sin^4(\theta) + \rho(\theta) - f\mathbf{t} \cdot \mathbf{z_0} \cos\theta \right] \end{aligned} \tag{1}$$

where $k^* = k_B T l_p^*$ is the bending rigidity of dsDNA, l_p^* is its bending persistence length, $\mathbf{t}$ is the tangential vector of the central axis, s refers to the arclength of the backbone, L is the total contour length of the backbone and R_0 is the radius of B-DNA. θ is called the folding angle of the backbone with respect to the central axis. θ can vary in the range from $-\pi/2$ to $\pi/2$, with $\theta > 0$ corresponding to a right-handed double-helical configuration and $\theta < 0$ corresponding to a left-handed one (see figure 1 in [13]). The base-stacking energy density $\rho(\theta)$ originates from the weak van der Waals interaction between the adjacent nucleotide basepairs and is usually described in the Lennard-Jones form.

$$\rho(\theta) = \begin{cases} \frac{\rho_0}{r_0}\left[\left(\frac{\cos\theta_0}{\cos\theta} \right)^{12} - 2\left(\frac{\cos\theta_0}{\cos\theta} \right)^6 \right] & \theta \geqslant 0 \\ \frac{\rho_0}{r_0}[(\cos\theta_0)^{12} - 2(\cos\theta_0)^6] & \theta < 0 \end{cases} \tag{2}$$

where $r_0 = 0.34\ \mathrm{nm}/\langle\cos\theta\rangle_{f=0}$ is the backbone arclength between adjacent bases and θ_0 is a parameter related to the equilibrium distance between a DNA dimer. ρ_0 is the base-stacking energy density which is generally base-sequence specific.

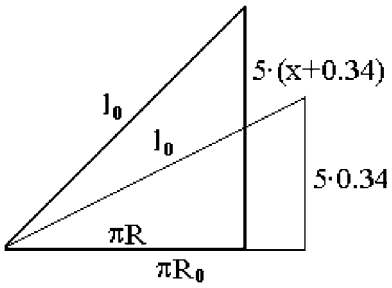

Figure 1. The relation between longitudinal stretching x and radius R of DNA.

2.2. The modified ZZO model

The mechanical properties of long dsDNA molecules are studied based on the ZZO model, where the base-stacking interaction is taken into account. Excellent agreement between theory and the experimental measurements is obtained. But hydrogen-bond interaction and the effects of environment, such as salt ion concentration of the solution, are not taken into account. The hydrogen bond plays a vital role in the stabilization of the DNA double-helix. On one hand, when the dsDNA chain is stretched by large external forces, there is a relative sliding of the two backbones so that the distance of the interstrand hydrogen-bond and hydrogen-bond energy change [16]. On the other hand, the DNA molecule is a strong polyelectrolyte, with negatively-charged groups distributed regularly along the chain's surface. As salt concentration changes, the electrostatic repulsion force between these negatively-charged groups will change so that the rigidity of the DNA chain changes and the stretching properties are influenced by them [17].

For the sake of describing the transverse interaction energy due to the hydrogen bonds within each base pair, some potential forms have been employed, including the Morse potential, Toda lattice potential, Lennard-Jones potential and ϕ^4 potential [18–20]. In the present paper, we will adopt the Morse potential

$$V_M = D_0[(\mathrm{e}^{-\alpha y} - 1)^2 - 1] \tag{3}$$

where y is the stretching of the hydrogen bond, D_0 is the depth of the Morse potential well, typically of the order of 0.04 eV, depending on the type of base pair (adenine–thymine or guanine–cytosine) as well as on the ionic strength [21]. The covalent bond length remains fixed during the course of stretching DNA molecules because the energy of the covalent bond outclasses that of the hydrogen bond and van der Waals interactions. When the longitudinal average extension of a base is x, the relation between radius R and average extension x of DNA molecules is (see figure 1)

$$l_0^2 = (\pi R_0)^2 + (5 \times 0.34)^2 = (\pi R)^2 + [5(x + 0.34)]^2. \tag{4}$$

The average extension of the interstrand hydrogen bond is (see figure 2)

$$y = \sqrt{[l_1 - 2(R_0 - R)]^2 + (5x)^2} - l_1 \tag{5}$$

where $x = 0.34\big(\frac{\cos\theta}{\langle\cos\theta\rangle_{f=0}} - 1\big)$, $\langle\cos\theta\rangle_{f=0} = 0.573\,84$, l_0 is the total length of five phosphate groups and $l_1 = 0.29$ nm is the bond length of the hydrogen bond.

Because the cations neutralize charges of the phosphate group and decrease electrostatic repulsion between interstrands, the potential well becomes deeper and DNA is more stable when salt concentration increases. The transverse electrostatic energy between a pair of

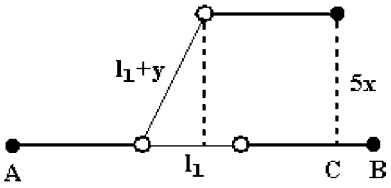

Figure 2. The relation between longitudinal stretching x and hydrogen-bond stretching y of DNA where $B = 2R_0$, AC $= 2R$, ○ (bases) and ● (phosphate groups).

phosphate groups on a base-pair plane is expressed as

$$\frac{(q-\Delta q)^2}{8\pi\varepsilon R_0} \cong \frac{q^2}{8\pi\varepsilon R_0}\left(1-\frac{2\chi}{q}C\right) \tag{6}$$

where ε is the absolute dielectric constant of the aqueous solution and q is the charge of a phosphate group. Δq is the part of the charge neutralized by cations and is proportional to the salt concentration C: $\Delta q = \chi C$ when salt concentration is not high enough. Thus the change of the depth of the transverse hydrogen bonds potential well resulting from the effect of salt is

$$\Delta E \cong \frac{q^2}{8\pi\varepsilon R_0}\frac{2\chi}{q}C = \frac{q\chi}{4\pi\varepsilon R_0}C. \tag{7}$$

The depth of the Morse potential well at salt concentration C is given by

$$D = D_0 + \frac{\chi q}{4\pi\varepsilon R_0}C = D_0(1+\lambda C) \tag{8}$$

where $\lambda = \frac{\chi q}{4\pi\varepsilon R_0 D_0}$, χ is a ratio constant and C is expressed in moles per litre.

The effects of salt on the longitudinal stacking interaction can be studied by a cylinder model [20] in which DNA is considered as an infinitely long uniformly negatively charged cylinder of radius R_0, immersed in an infinite medium with a fixed dielectric constant $\varepsilon = 80$. In the solution there are positively and negatively charged counterions and their diameter approaches zero but the charge density at every point remains fixed. The bulk concentrations of these mobile ions at infinity are equal to C. Under the Debye–Huckel approximation, the dimensionless equilibrium electrostatic potential $u(r) = eU(r)/k_BT$ satisfies the linear Poisson–Boltzmann equation

$$u''(r) + r^{-1}u'(r) = \kappa^2 u(r) \qquad u'(R_0) = 2q^* R_0^{-1} \qquad u(\infty) = 0 \tag{9}$$

where $q^* = \frac{l_D}{d}$, $l_D = \frac{e^2}{4\pi\varepsilon k_B T}$, $\kappa^2 = 8\pi l_D C$, $d = 0.17$ nm (for B-DNA). The solution of equation (9) is

$$u(r) = -2q^*[\kappa R_0 K_1(\kappa R_0)]^{-1}K_0(\kappa r) \tag{10}$$

where $K_m(x)$ is a modified Bessel function. Because the counterions exist around DNA, the electrostatic energy of DNA with length L is

$$E_0 = 2N(-e)U(R_0) = \frac{4e^2 N K_0(\kappa R_0)}{\varepsilon d\kappa R_0 K_1(\kappa R_0)}. \tag{11}$$

As $\kappa R_0 \ll 1$ (at low salt concentration), we have

$$E_0 = \frac{4e^2 N}{\varepsilon d}\ln\frac{2}{\kappa R_0} = -\frac{4e^2 N}{\varepsilon d}\ln\left(2\pi l_D R_0^2\right) - \frac{4e^2 N}{\varepsilon d}\ln C. \tag{12}$$

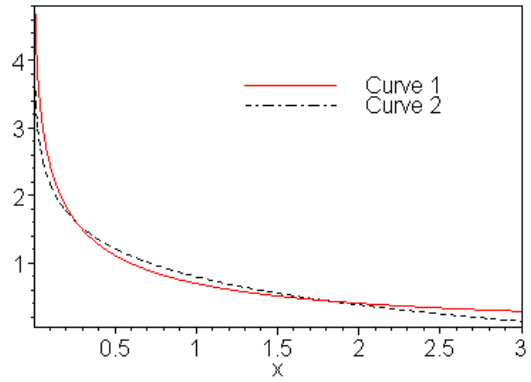

Figure 3. The numerical fitting at high salt concentration. Curve 1: $\frac{K_0(x)}{xK_1(x)}$; curve 2: $0.8-0.6\ln(x)$; $x = \kappa R_0$.

Therefore the change of the depth of the longitudinal stacking potential well resulting from the effect of salt concentration is

$$\Delta E \sim \ln C. \tag{13}$$

$\kappa R_0 \ll 1$ is not correct at high salt concentration. However, through the numerical fitting (see figure 3), we can get the relation between the electrostatic energy of DNA and salt concentration, which is still expressed as equation (13).

Through the above analyses, the relation between the change of the depth of the longitudinal stacking potential well and salt concentration is approximately expressed as equation (13). We take ρ_0 as the potential well depth of van der Waals at salt concentration $C_0 = 1$ mol l^{-1}, then the depth at salt concentration C is represented as

$$\rho = \rho_0(1 + \mu \ln C) \tag{14}$$

where μ is a ratio constant.

When the influence of salt on hydrogen-bond and stacking interaction is taken into account, the total energy of a dsDNA molecule under the action of an external force is expressed as

$$E_b = \int_0^L \mathrm{d}s \left[k^* \left(\frac{\mathrm{d}\mathbf{t}}{\mathrm{d}s}\right)^2 + k\left(\frac{\mathrm{d}\theta}{\mathrm{d}s}\right)^2 + \frac{k}{R_0^2}\sin^4(\theta) + \tilde{\rho}(\theta) + \tilde{v}(\theta) - f\mathbf{t}\cdot\mathbf{z_0}\cos\theta \right] \tag{15}$$

where $\tilde{\rho}(\theta)$ and $\tilde{v}(\theta)$ are the hydrogen-bond and stacking interaction energy densities including the effect of salt, respectively,

$$\tilde{\rho}(\theta) = \begin{cases} \frac{\rho_0}{r_0}(1 + \mu \ln C)\left[\left(\frac{\cos\theta_0}{\cos\theta}\right)^{12} - 2\left(\frac{\cos\theta_0}{\cos\theta}\right)^6\right] & (\theta \geqslant 0) \\ \frac{\rho_0}{r_0}(1 + \mu \ln C)[(\cos\theta_0)^{12} - 2(\cos\theta_0)^6] & (\theta < 0) \end{cases} \tag{16}$$

$$\tilde{v}(\theta) = \frac{D_0}{r_0}(1 + \lambda C)[(\mathrm{e}^{-\alpha y} - 1)^2 - 1]. \tag{17}$$

3. The effect of salt on the force-stretching property

In this section we investigate the force–extension property versus salt concentration under the actions of external forces based on equation (15). According to the path integral method,

the Schrödinger-like equation governing the evolution of the 'wavefunction' $\Psi(t, \theta, s)$ of the system is expressed as

$$-\frac{\partial \Psi(\mathbf{t}, \theta, s)}{\partial s} = \hat{H}\Psi(\mathbf{t}, \theta, s) = \left[-\frac{\partial^2}{4l_p^* \partial \mathbf{t}^2} - \frac{\partial^2}{4l_p \partial \theta^2} + \frac{l_p}{R_0^2}\sin^4\theta - \frac{f\cos\theta}{k_B T}\mathbf{t}\cdot\mathbf{z_0} + \frac{\tilde{\rho}(\theta) + \tilde{v}(\theta)}{k_B T}\right]\Psi(\mathbf{t}, \theta, s). \tag{18}$$

We choose the combination of the spherical harmonics functions, $Y_{\mathrm{lm}}(\mathbf{t})$, and the eigenfunctions of the one-dimensional infinitely deep square potential well of width a, $f_n(\theta)$, as the base functions [13] of equation (18). To simplify the calculation, m can be set to $m = 0$. Thus we have

$$\Psi(\mathbf{t}, \tilde{\theta}, s) = \sum_{nl} C_{nl}(s) Y_{l0}(\mathbf{t}) f_n(\tilde{\theta}) \tag{19}$$

where $Y_{l0}(\mathbf{t}) = Y_{l0}(\vartheta, \varphi)$, $f_n(\tilde{\theta}) = \sqrt{\frac{2}{a}}\sin\left(\frac{n\pi}{a}\tilde{\theta}\right)$, $\tilde{\theta} = \theta + \frac{\pi}{2}$. According to equation (19), the matrix form of equation (18) can be expressed as

$$\langle i'|\hat{H}|i\rangle = \delta_{l,l'}\delta_{n,n'}\left[\frac{l(l+1)}{4l_p^*} + \frac{n^2\pi^2}{4l_p a^2}\right] - \frac{f}{k_B T}[\delta_{l+1,l'}a_{l,0} + \delta_{l-1,l'}a_{l-1,0}]\langle n'|\sin\tilde{\theta}|n\rangle + \delta_{l,l'}\langle n'|\left[\frac{\tilde{\rho}(\tilde{\theta}) + \tilde{v}(\tilde{\theta})}{k_B T} + \frac{l_p}{R^2}\cos^4\tilde{\theta}\right]|n\rangle \tag{20}$$

where $a_{l,0} = \sqrt{\frac{(l+1)^2}{(2l+1)(2l+3)}}$.

The ground-state eigenvalue g_0 of equation (18) can be obtained through diagonalization methods according to equation (20). The force–extension curves versus salt concentration can be obtained by differentiation of the g_0 with respect to f:

$$\langle z\rangle = \int_0^L \langle \mathbf{t}\cdot\mathbf{z_0}\cos\theta\rangle\,\mathrm{d}s = -Lk_B T\frac{\partial g_0}{\partial f}. \tag{21}$$

In the numerical calculation, we have used the following values for the various parameters [12, 13, 22]: $l_p = 1.5\,\mathrm{nm}$, $l_p^* = 46\,\mathrm{nm}$, $\theta_0 = 62^\circ$, $R_0 = 1\,\mathrm{nm}$, $\alpha = 15\,\mathrm{nm}^{-1}$, $D_0 = 1.5478 k_B T$ and $\rho_0 = 8.5 k_B T$. To avoid flush-off of computer memory, the boundary of the square well is chosen to be slightly less than π and set as $a = 0.95\pi$. Our results indicate that μ must be adjusted to the order of 0.03 and λ should be adjusted to the order of $0.1\,\mathrm{l\,mol}^{-1}$ to obtain reasonable fitting with experimental measurements.

Figure 4 shows the force–extension curves of dsDNA as a function of salt concentration according to equation (21). In figure 5 we also give the experimental results [7] for comparisons. At certain salt concentration (10 mM), the relation between force and extension of a dsDNA molecule has four regions. In the low force region, it requires only a small force (<10 pN) to change the molecule from the random coil form to its native B-form conformation. In the moderate force region (10–45 pN), the DNA displays a linear stretching behaviour and the length of the molecule changes slightly. If the external force is increased further, a force plateau appears and the dsDNA chain becomes highly extensible up to a new conformation, the S-DNA. The contour length of S-DNA is about 1.7 times the B-form. The plateau signifies a phase transition from the B- to S-DNA. A larger increasing force is needed for further extension when exceeding the phase transition stretching force. These results agree with experimental results [3, 5].

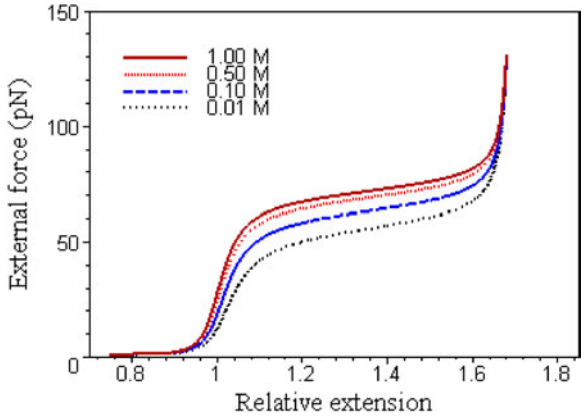

Figure 4. Force–extension curves of dsDNA at several salt concentrations according to equation (21).

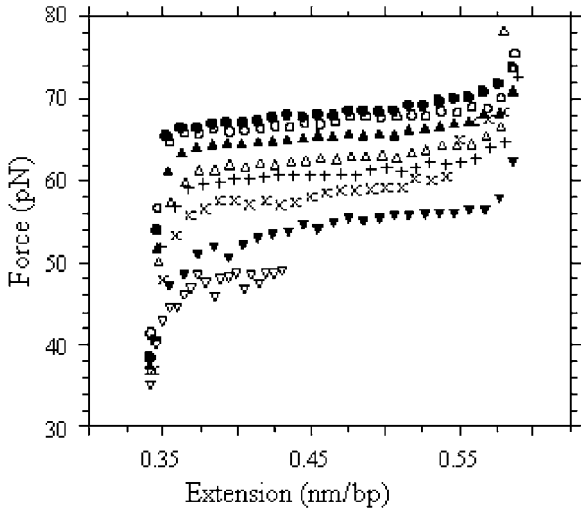

Figure 5. Overstretching portions of the DNA force–extension curves as a function of salt concentration [7]; 1 M (●), 0.5 M (○), 0.25 M (▲), 0.1 M (△), 0.05 M (+), 0.025 M (×), 0.01 M (▼) and 0.0026 M (▽).

With increasing salt concentration, the stretching force evidently increases. The reason is that the cations neutralize charges of the phosphate group so that the electrostatic repulsion decreases, and the hydrogen-bond and base stacking interactions increase, which causes the increase in stretching force. With the salt concentration increasing further, the change of curve slows, which indicates that the counterion has already reached saturation. These results agree with experimental results [7].

4. Conclusion

In summary, we give the modified ZZO model and stress the important role of the hydrogen-bond and salt. The force–extension curve of dsDNA is obtained at various salt concentrations. The results show that the stretching force increases nonlinearly with salt concentration in

agreement with experimental measurement. The salt effect on the stretching force is easily understood. The repulsion between the charged phosphate groups promotes stretching, but this repulsion is shielded by the addition of salt.

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