Longest Relaxation Times of Double-Stranded and Single-Stranded DNA

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ABSTRACT: The longest relaxation times of double- and single-stranded lambda DNA (ds λ-DNA, ss λ-DNA) were studied by viscosity measurements in an oscillatory flow and by stress relaxation measurements. The results for ds λ-DNA agreed well with chain retraction experiments of stretched single molecules; both were close to the relaxation time calculated from the Zimm model. The relaxation time of ss λ-DNA is too small to be accurately measured by the stress relaxation experiments even in a very viscous solution. Such a small relaxation time makes it difficult to be studied in experiments of single molecule dynamics. For ds λ-DNA in the intermediate time scale, the stress relaxes in a power law manner toward the long time scale with an exponent of -0.95, which is in good agreement with the Brownian dynamics simulations.

Introduction

Recently the elastic properties of both double-stranded (ds) and single-stranded (ss) DNA have been studied with the development of new techniques to manipulate single DNA molecules.[1−4] In these studies, a DNA molecule is anchored to a surface at one end and stretched by a force at the other end. The inextensible wormlike chain is used to describe the elasticity of a semiflexible ds DNA chain with a persistence length of ∼53 nm, while the modified freely jointed chain is used for a flexible ss DNA chain with a persistence length of ∼0.75 nm.[3,5] A more recent experiment with ss DNA gave the persistence length ranged from 1.5 nm in 2 M NaCl to 3 nm in 25 mM NaCl.[6] The latter estimates that if the excluded volume effect is not considered for the more flexible ss DNA, the elasticity measurements of a single ss DNA results in a lower value for the Zimm relaxation time compared with that of ds DNA (see Supporting Information).[3,5] It was also found that the elastic behavior of ss DNA varies with salt concentration.[3,7] The different elastic properties of ds and ss DNA were used to study the replication and exonucleolysis of single DNA molecules.[8,9] Their different elastic properties also show a different effect on fluid flow properties, such as different turbulent drag reduction properties.[10] The dynamics of single ds DNA molecules in solution were extensively studied in various flows, including uniform,[11] elongational,[12,13] shear,[14] mixed,[15] and random flows.[16] Although ss DNA had been stretched by different methods, such as stretching in solution[3,7] or on surface,[17,18] there is no report on single molecule dynamics of this supposedly more flexible polymer in various flows.

The study on dynamics and conformations of a single polymer chain in various flows requires the longest relaxation time, which corresponds to the motion of the whole chain, to be precisely determined. Polymer relaxation times, corresponding to various modes of molecular motions of the chain, play a fundamental role in describing hydrodynamic properties of polymer solution. Experimental determination of the relaxation times may be achieved in different ways. One way is to study the frequency dependence of complex viscosity of a polymer solution which is subjected to a time-dependent shear flow.[19] However, a proper model is usually needed to draw the relaxation times from the measured complex viscosity.[20] Another way is to study the transient response of shear-induced properties (such as birefringence,[21] dichroism,[22] stress,[23] extension[12]) after abrupt cessation of the steady flow, which gives a direct measurement of the longest relaxation time.

In this paper, the longest relaxation times of ds and ss lambda DNA were determined by the viscosity measurements in an oscillatory flow as well as by the stress relaxation measurements. The results were compared with the relaxation time calculated from the Zimm model.

Experimental Part

A stock λ-DNA solution with a concentration of ∼0.5 mg/mL was obtained from New England Biolabs. All measurements were done in a mixed solvent consisting a TE buffer (10 mM Tris-HCl, 2 mM EDTA, and 10 mM NaCl) with appropriate concentration of sucrose. A solution of ds λ-DNA was prepared by diluting the stock solution by TE buffer with various concentrations of sucrose and heated to 65 °C for 10 min to free the DNA's complementary sticky ends. A solution of ss λ-DNA was prepared by diluting the stock solution by TE buffer with various concentrations of sucrose and heated to 85 °C for 15 min, followed by chilling on ice. The increase of the UV adsorption at 260 nm as well as the change of the mobility in pulse field gel electrophoresis proved the dissociation of two strands of ds DNA.

The viscosities of the solvent and the DNA solutions were measured at 22 °C with the Vilastic 3 viscoelasticity analyzer (Vilastic Scientific, Inc.) in an oscillatory flow at shear rate 1.0 s^{-1}. This rheometer requires a small sample volume of about 1.0 mL. The inner radius and the length of the capillary are 0.0512 and 6.324 cm, respectively. The real and the imaginary parts of the complex viscosity (or the so-called dynamic and storage viscosity) of the polymer solution, η' and η'', were measured in the wide range of the angular frequencies $\omega = 0.0628-6.28$ rad/s. The complex viscosity components for the solvent, η_s' and η_s'', were also measured. The values for the polymer complex viscosity were calculated as $\eta_p' = \eta' - \eta_s'$ and $\eta_p'' = \eta'' - \eta_s''$, respectively. Then the polymer relaxation time λ was calculated according to[24]

$$\lambda = \lim_{\omega \to 0} \left[\frac{1}{\omega} \left(\frac{\eta_p''}{\eta_p'} \right) \right] \tag{1}$$

The stress relaxation measurements were conducted on the stress-controlled rheometer AR1000N (TA Instruments) with a cone-and-plate geometry (with a cone diameter of 6 cm and a cone angle of

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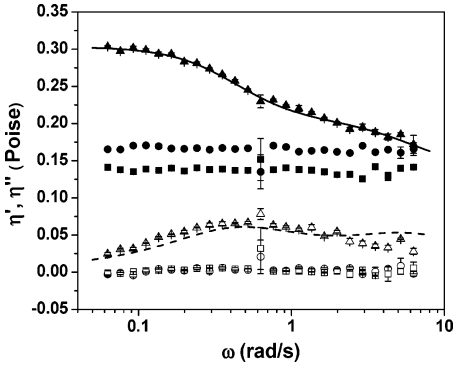

Figure 1. Complex viscosities of a 50.0% sucrose solution (■, □), ss λ-DNA (●, ○), and ds λ-DNA (▲, △) in 50.0% sucrose solution with a concentration of 48.9 μg/mL. The solid points denote the dynamic viscosity, and the open points represent the storage viscosity. The solid line is the best fit of the dynamic viscosity to a two-element Maxwell model for ds λ-DNA, and the obtained parameters are used to calculate its storage viscosity (the dashed line).

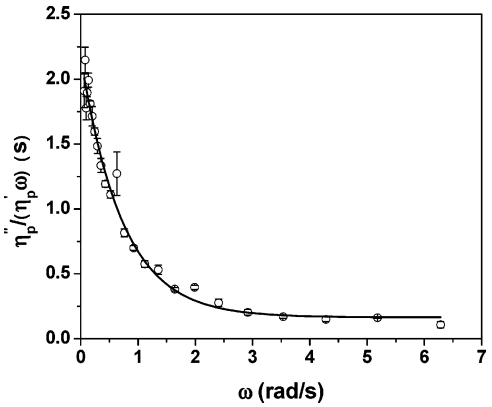

Figure 2. Angular frequency dependence of $\eta_p''/(\eta_p'\omega)$. The line is the best fit of the data by an exponential decay.

1°). DNA solutions were subjected to a shear flow with a shear rate of 10 s^{-1} for 1 min, and then the shear flow was abruptly stopped and solution stress was monitored. The whole setup was put into a box in order to maintain constant temperature. The measurements were conducted at 22 and 11 °C controlled within ±0.1 °C by circulating water under the lower steel plate and by blowing air at the controlled temperature.

Results and Discussion

Figure 1 shows the complex viscosity of ds λ-DNA and ss λ-DNA (with a concentration of 48.9 μg/mL) in a 50.0% sucrose solution. The solvent has $\eta_s' = 14$ cP and $\eta_s'' = 0$, since it is a Newtonian fluid and there is no energy storage during the oscillatory flow. For ss λ-DNA solution, the measured η' and η'' almost did not change with ω and $\eta'' = 0$ in the measured angular frequency range of 0.0628−6.28 rad/s, while the measured η' and η'' for ds λ-DNA solution varied with ω and showed typical variations of polymer complex viscosities in an oscillatory flow. Fitting η' function by a two-element Maxwell model[25] gave relaxation times of $\lambda_1 = 2.3$ s and $\lambda_2 = 0.16$ s. The calculated η'' according to the fitted parameters for η' coincided with the experimental data. On the other hand, by extrapolation of $\eta_p''/(\eta_p'\omega)$ to $\omega \rightarrow 0$ according to eq 1, the relaxation time of the ds λ-DNA solution was calculated to be $\lambda = 2.3$ s (Figure 2).

According to the theories of Rouse and Zimm,[26,27] the longest relaxation time of a non-free-draining polymer chain in a dilute solution can be calculated as

$$\lambda_{\text{Zimm}} = \frac{0.422\eta_s[\eta]M}{RT} \quad (2)$$

where $[\eta]$ is the intrinsic viscosity of polymer, M the molar mass, R the gas constant, and T the temperature. $[\eta]$ can be obtained by measuring a viscosity of a dilute polymer solution at different polymer concentrations, c, and extrapolating to zero concentration according to

$$[\eta] = \lim_{c\rightarrow 0} \frac{\eta/\eta_s - 1}{c} \quad (3)$$

We noted that in the recent study[28] Vilastic 3 was used to measure the intrinsic viscosity of ds λ-DNA, and a relatively low value was obtained. In our studies the measurements were conducted according to two protocols: (1) stretch protocol in which the shear rate is varied from 10 to 100 s^{-1} with the frequency fixed at 1 Hz ($\omega = 6.28$ rad/s) and (2) shake protocol in which the frequency is varied from 0.01 to 1.0 Hz ($\omega =$ 0.0628−6.28 rad/s) with the shear rate fixed at 1 s^{-1}. The former protocol was used in ref 28 at the fixed frequency of 2 Hz. Figure 3 shows the viscosity of ds λ-DNA solution at different polymer concentrations measured in the two protocols. The viscosity at $\omega \rightarrow 0$ (in fact, $\omega \rightarrow 0.0628$ rad/s) in the shake protocol and $\dot{\gamma} \rightarrow 0$ (in fact, $\dot{\gamma} \rightarrow 10$ s^{-1}) in the stretch protocol was used to calculate the intrinsic viscosity. It should be noted that the viscosity obtained in the stretch protocol is much lower than that obtained in the shake protocol due to shear thinning. In fact, by reducing the frequency to 0.02 Hz and the shear rate to 1 s^{-1} in the stretch protocol, the viscosity was found to be close to that obtained in the shake protocol, but the data were very noisy. Figure 4 shows the relative viscosity, η/η_s, of the polymer solutions as a function of concentration for both ds λ-DNA and ss λ-DNA obtained in both stretch protocol and shake protocol. The obtained intrinsic viscosities are summarized in Table 1. The Zimm relaxation time λ_{Zimm} in a solvent of viscosity 13.8 cP is calculated and also listed in Table 1. It should be noted that the intrinsic viscosity of ds λ-DNA obtained in shake protocol agreed well with the reference data,[29,30] while the stretch protocol underestimated the intrinsic viscosity of ds λ-DNA and thus gave a lower relaxation time due to rather high values of working frequency and shear rates. By assuming that the polymer relaxation time is proportional to the solution viscosity, λ_{Zimm} for a 48.9 μg/mL ds λ-DNA is calculated to be 2.51 s, which is close to the value obtained from the above viscosity measurements ($\lambda = 2.3$ s). The relaxation time of ss λ-DNA, however, is only about 1/8 (0.15 s vs 1.16 s) of that of ds λ-DNA in the solution of the same viscosity of 13.8 cP. In the solution of the same polymer concentration of 48.9 μg/mL, the relaxation time difference between ss λ-DNA and ds λ-DNA is even larger (0.18 s vs 2.51 s), since the viscosity of the solution of ss λ-DNA with the same polymer concentration is much lower. The relaxation time of polymer can also be calculated according to the Zimm model by using the Kuhn length and contour length of the DNA chain (see Supporting Information).[3,27] It gave λ_{Zimm} of 0.026−0.044 and 1.16 s in the solution viscosity of 13.8 cP for ss λ-DNA and ds λ-DNA, respectively, if the excluded volume effect is neglected. For ds λ-DNA, it agreed well with that calculated from the intrinsic viscosity because the Kuhn segment number is only 155 and the excluded volume effect is negligible, while for ss λ-DNA it is much smaller compared with that calculated from the intrinsic viscosity, which is due to the excluded volume effect of the flexible ss λ-DNA chain with a Kuhn segment number of 4527. Thus, the excluded volume effect plays a crucial role for ss λ-DNA.

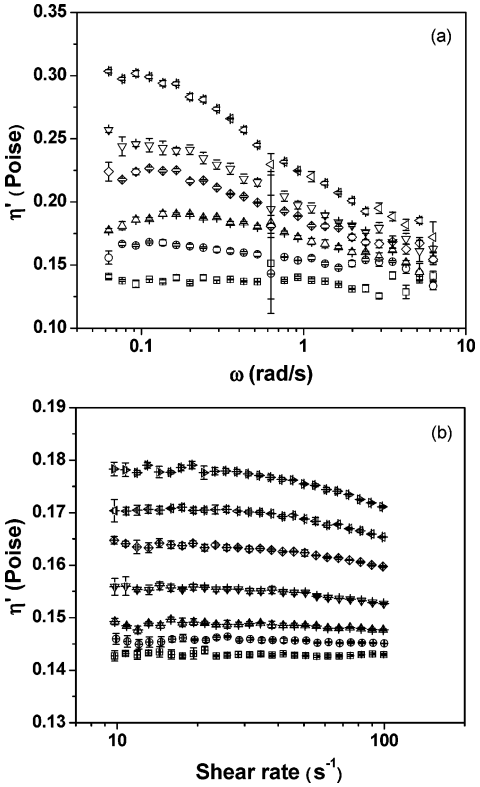

Figure 3. Viscosity of ds λ-DNA solution of different concentrations measured in shake protocol (a) and stretch protocol (b). From top to bottom, the data correspond to polymer solution with concentrations of 48.9, 38.4, 30.0, 19.9, 10.1, and 0 μg/mL in (a) and 50.0, 40.0, 30.0, 20.0, 10.0, 5.0, and 0 μg/mL in (b), respectively.

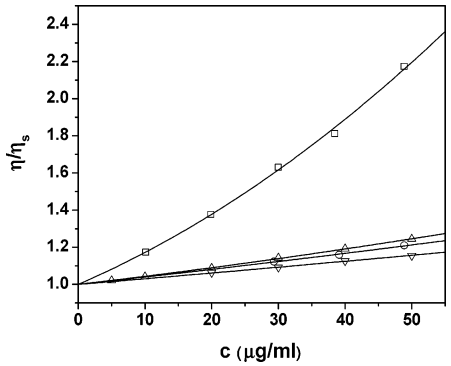

Figure 4. Polymer relative viscosity η/η_s as a function of concentration for both ds λ-DNA and ss λ-DNA obtained in both shake protocol (□, ds λ-DNA; ○, ss λ-DNA) and stretch protocol (△, ds λ-DNA; ▽, ss λ-DNA). The lines are calculated according to the obtained intrinsic viscosity.

Table 1. Intrinsic Viscosities of ds λ-DNA and ss λ-DNA

	shake protocol		stretch protocol	
sample	$[\eta]$ (mL/g)	λ_{Zimm} (s)[a]	$[\eta]$ (mL/g)	λ_{Zimm} (s)[a]
ds λ-DNA	15500	1.16 (2.51)[b]	4200	0.31
ss λ-DNA	3900	0.15 (0.18)[c]	3000	0.11

[a] λ_{Zimm} calculated according to eq 2 with solvent viscosity 13.8 cP for 50% sucrose solution. [b] The data in parentheses is corrected to 48.9 μg/mL ds λ-DNA solution with a relative viscosity of 2.16. [c] The data in parentheses is corrected to 48.9 μg/mL ss λ-DNA solution with a relative viscosity of 1.21.

The stress relaxation measurements for ds λ-DNA, and ss λ-DNA were conducted in sucrose solutions with different viscosities: (A) 50% sucrose solution at 22 °C with a viscosity of 15 cP; (B) 62.4% sucrose solution at 22 °C with a viscosity of 90 cP; (C) 62.4% sucrose solution at 11 °C with a viscosity of 192 cP. The stress relaxation of the corresponding sucrose solution was also measured, and a rapid decrease of the stress to 0 in 1−2 s was obtained, which is due to the fast viscous dissipation. Figure 5 shows the measured stress after the shear flow cessation for ds λ-DNA and ss λ-DNA in sucrose A, B, and C. The longest relaxation time was obtained by fitting the linear region in the semilogarithmic plot for stress relaxation due to an exponential decay, and the results are listed in Table 2. It should be noted that for ss λ-DNA in sucrose A and B the relaxation time cannot be measured since it is too small (on the order of the time scale for the disappearance of the inertia effect of the cone). For ss λ-DNA in sucrose C and ds λ-DNA in sucrose A, the relaxation time is about 3 and 4 s, respectively. However, these values are on the edge of the measurement resolution and hence are not very accurate. Only for ds λ-DNA in sucrose B and C is the relaxation time long enough to be accurately determined. As shown on the semilogarithmic plot (Figure 5a), on the long time scale ($t > \lambda$), a nice linear relationship was obtained, with $\lambda = 20.0$ and 33.6 s for ds λ-DNA in sucrose B and C, respectively. The calculated Zimm

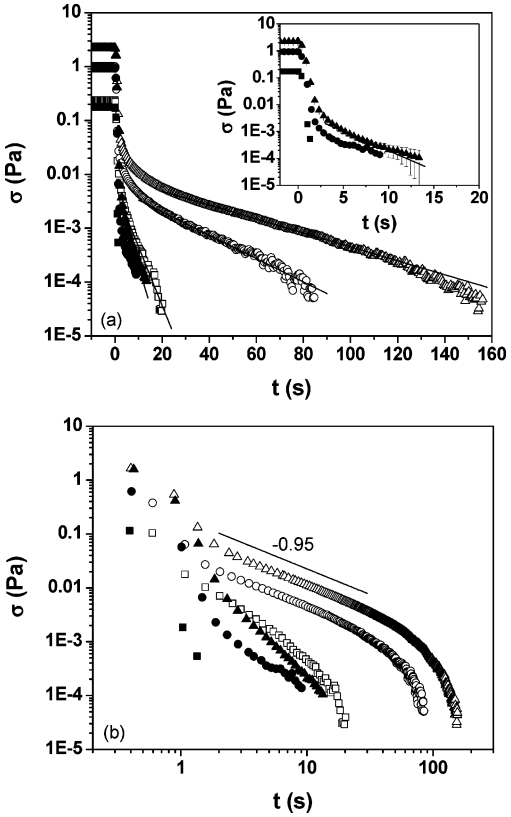

Figure 5. Measured stress after stopping the steady shear flow for ds λ-DNA (□, sucrose A; ○, sucrose B; △, sucrose C) and ss λ-DNA (■, sucrose A; ●, sucrose B; ▲, sucrose C) on a semilogarithmic (a) and a logarithmic (b) scale plot. The inset in (a) is the magnification at a short time scale for ss λ-DNA.

Table 2. Relaxation Times of ds λ-DNA and ss λ-DNA Obtained from Stress Relaxation

solvent viscosity (cP)	ds λ-DNA		ss λ-DNA	
	λ (s)	λ_{Zimm} (s)[a]	λ (s)	λ_{Zimm} (s)[b]
15	(4.0)	2.77		0.19
90	20.0	16.59		1.15
192	33.6	36.77	(3.0)	2.55

[a] λ_{Zimm} calculated according to eq 2 after corrected to 50.0 μg/mL ds λ-DNA solution with a relative viscosity of 2.20. [b] λ_{Zimm} calculated according to eq 2 after corrected to 50.0 μg/mL ss λ-DNA solution with a relative viscosity of 1.21.

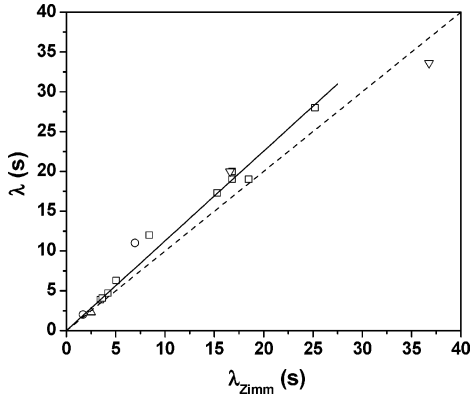

Figure 6. Comparison of λ_{Zimm} with the relaxation time of ds λ-DNA obtained in different methods: chain retraction (□,[11−13,31−33] ○[15]), viscosity (△), and stress relaxation (▽). The solid line denotes the best fit of all data obtained by chain retraction. The dash line shows the relaxation time equal to λ_{Zimm}.

relaxation times λ_{Zimm} of the same polymer solutions are also listed in Table 2. The measured relaxation times and the Zimm relaxation times agreed well within the experimental error. It should be indicated that, in another experiment on the stress relaxation of a high molar mass ($M_w = 1.8 \times 10^7$) polyacrylamide (PAAm) in 65.5% sucrose solution after cessation of the steady shear at different shear rates between 1 and 100 s^{-1}, the obtained relaxation time did not show any dependence on the shear rate, although the measured relaxation time is much bigger than the Zimm relaxation time, which is due to the polydispersity of the PAAm sample.[31]

The relaxation time of ds λ-DNA was recently studied by the chain retraction of stretched single molecules by Chu's and our groups in solutions of different viscosity.[12−14,16,32−34] In Figure 6, the results obtained from the chain retraction and the above measurements are compared with λ_{Zimm}. It can be seen that the relaxation time of ds λ-DNA obtained from the both stress relaxation and chain retraction agreed well with λ_{Zimm}. This is because in the region of relative extension less than 0.3 the square of the molecular extension is directly related to the stress in the solution, and hence the chain retraction experiments yield the same relaxation time as the stress relaxation measurements. The results from the single polymer chain retraction experiments is slightly increased (13%), since the length of ds λ-DNA increased from 16.4 to ∼21 μm after staining by YoYo, which should increase the longest relaxation time. However, the increase would be about $[(21/16.4)^{1.66} - 1] = 51\%$, as follows from the scaling law $\lambda \sim L^{1.66}$ (L is the contour length of DNA).[35] The discrepancy with the observed increase in λ is probably due to the stiffness of DNA chain that might be changed slightly after staining by YoYo, and a simple scaling by length is not enough to explain the increase of the relaxation time. Another possible explanation is derived from the increase of the radius of gyration R_g of ds DNA after it is stained by dye. Although the contour length of ds DNA increases by 30−40% after staining with dye,[1,36] a recent study shows that R_g of a ds DNA with ∼1400 base pairs is only increased by ∼5% after staining with dye of the similar molar ratio between base pairs and dye as in the chain retraction experiments. If the same increase in R_g for ds λ-DNA is assumed, an increase of 15% in relaxation time as calculated by the scaling law $\lambda \sim R_g^3$ is obtained, which agrees well with the above results. In earlier studies by birefringence relaxation,[21] flow dichroism,[22] creep recovery,[23] light scattering,[37] and onset of birefringence response in an elongation flow,[38] the relaxation time of ds DNA with different length also agreed well with λ_{Zimm} (Figure S1). It indicates that ds DNA can be well explained by the Zimm model for non-free-draining chains in a solution.

It should be also noted that for ds λ-DNA in sucrose B and C, in the intermediate time scale ($2 \text{ s} < t < \lambda$), the stress relaxes in a power law manner toward the long time scale with an exponent of −0.95 (Figure 5b). Brownian dynamics simulations of the polymer stress relaxation indicated that the exponent in the power law relaxation in the intermediate time scale is −0.50 for flexible chains[39−41] and −1.25 for stiff ones.[42,43] For ds λ-DNA with 48 502 base pairs, the contour length L, the persistence length L_p, and the base pair length b are 16.4 μm, 53 nm, and 0.338 nm, respectively.[1,3] The dimensionless bending energy E ($= L_p/b$) is 157, and the number of Kuhn segments N [$= L/(2L_p)$] is 155. So, it corresponds to the case of a semistiff ($E \approx N$) chain in the Brownian dynamics simulations.[43] The simulation gave the power law exponent close to −1.0, which is directly verified by the stress relaxation experiments for a semiflexible ds λ-DNA. The flexibility of ds DNA can be tuned by adjusting the polymer length or salt concentration. Thus, it provides a possibility to study the power law exponent covering all the flexibility regimes from stiff to flexible chains.

Conclusions

The longest relaxation times of ds λ-DNA and ss λ-DNA were studied by the viscosity measurements in an oscillatory flow and by the stress relaxation measurements. The results for ds λ-DNA agree well with the chain retraction experiments of stretched single molecules, and both are close to the relaxation time calculated from the Zimm model, indicating that ds λ-DNA can be well explained by the Zimm model for non-free-draining chains in a solution. A calculation from the Zimm model provides the relaxation time of ss λ-DNA of about 1 order of magnitude smaller than that of the ds λ-DNA. The relaxation time of ss λ-DNA is too small to be accurately measured by the stress relaxation experiments even in a very viscous solution. Such a small relaxation time makes it difficult to be studied in experiments on single molecule dynamics. For ds λ-DNA in the intermediate time scale ($2 \text{ s} < t < \lambda$), the stress relaxes in a power law manner toward the long time scale with the exponent of −0.95, which is in a good agreement with the Brownian dynamics simulations.

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Supporting Information Available: Comparison of the Zimm relaxation times for ds λ-DNA, ss λ-DNA, and PAAm calculated from both the intrinsic viscosities and the elastic properties. This material is available free of charge via the Internet at http://pubs.acs.org.

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