The effect of DNA conformation changes on the coupling of the macromolecule deformation components

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Abstract

The model of the deformation of DNA macromolecule is developed with the accounting of two types of components of deformation: external and internal. External components describe the bend, twist and stretch of the double helix. The internal component - the conformational mobility inside of the double helix. In the work the deformation of DNA macromolecule is considered taking into account the coupling of the external component (of deformation) with the internal component (of conformational change). Under the task consideration the macromolecule twist-stretch coupling and coupling between twist and internal component are taken into account. The solution obtained in these conditions for the deformation components allows changing the character of respond in stretch component on unwind (overwind) in dependence on the applied force to twist component.

The changing of the character of deformation from compression to tension achieving of critical untwisting force (and vise versa the changing of the character of deformation from overwind to unwind at critical tension force) is known from the single molecular experiments [1–3]. The nature of such unexpected behavior of double helix have clarified in the present work by including in consideration the internal component. The obtained solutions and their conformity to experimental results show the essential role of coupling between internal and external components in the double helix conformational mechanics under action force in pN range.

1 Introduction

Determination of the deformation mechanism of DNA double helix is an important task for understanding the functioning of the macromolecule [4–6]. For a theoretical description of DNA double helix deformations, the model of the elastic rod or worm-like chain (WLC) model are commonly used. These models describe a macromolecule as infinitely long chain of homogeneous monomer links and the deformation of macromolecule is considered as the small displacement between adjacent links. The displacements are usually considered using the independent external components: bend, twist, stretch within the framework of the elastic rod model [7–8].
However, due to the DNA helical structure the deviations from equilibrium state usually accompany by the change in two or even all of three components. The single molecule experiments allow to measure twist under manipulating with stretching and vice versa stretch during twist manipulating [1–3,9], that confirms the existence of twist-stretch coupling. In the case of stretching force lower then critical value (about 35pN) the stretching induces the winding of the double helix (positive twist), while in the case of the force higher than critical one the stretching induces the unwinding of the double helix (negative twist).

This unexpected behavior have been modelled with the changing of coupling parameter under the force [9,10]. In the same time such changing could be induced by coupling with component associated with intrinsic conformational mobility of double helix. The approach allowing extract internal component for describing deformation of double helix during conformational transitions of B – A type was developed by S.N.Volkov [11–13]. This approach is appropriate for deformations accompanied with changing in internal conformation of double helix and could be generalized for deformations with coupled external components such as twist, stretch and bend.

Really, the molecular dynamics studies of twist-stretch coupling under the force shows that the intrinsic changes are similar to B – A transition with much more smaller amplitude [2]. Indeed, if unwouning of B-DNA tends to occur trough A-form, decreasing of twist accompany with inclination and decreasing of length. Also recent work [14] suggests that A- and B-forms helical structure of dsRNA and dsDNA are responsible for difference in sign of twist-stretch coupling due to additional inclination in A-form.

The switching mechanism between DNA conformations is sugar ring, that can transform only though specific pathway. In the present work the detailed study of coupling between elastic components and specificity of coupling with internal component due to the intrinsic flexibility of double helix (mainly associated with sugar ring) has been performed. The approach [11–13] is extended for tree coupled component (two elastic and one intrinsic). We argue that observed changing in the sings of coupling of elastic components under the force could be interpreted due to coupling with intrinsic component as rivalry to force influence. Similar behavior could be realized between other couples of the deformation components. The obtained quantitative results in framework of developed approach are in agreement with the experiment data on single-molecule studies of DNA mechanics and molecular modelling [2,3].

2 Model of DNA deformation.

Let us consider the role of the coupling between deformation components of macromolecules such as DNA. Deformation components of elastic rod such as bend, twist and stretch are mostly associated with local base pair step parameters as shift and/or roll, twist and stretch respectively (fig.1). Deformation energy of macromolecule in the model of an elastic rod is as follows:

\[ E_{WL} = \frac{1}{2} \sum_{n=1}^{N} \left\{ C_R (R_{n+1} - R_n)^2 + C_\phi (\phi_{n+1} - \phi_n)^2 + C_z (Z_{n+1} - Z_n)^2 \right\}, \]

where \( N \) is the number of monomer links of the molecular chain. \( R_n \) is dimensionless displacement of \( n \)-th link as whole from the equilibrium position (the direction of displacement is orthogonal to helix axis), \( \phi_n \) - turn of the \( n - th \) link as whole round the helix axis which
Figure 1: Schematic image of the mobility base pairs as a whole (link of molecular chain) in the elastic rod model. R - shelf of coordinate relating with bend, $\varphi$ - twist coordinate, $z$-stretch coordinate is measured in radian, $Z_n$ - dimensionless displacement of $n$-th link as whole along helix axis of macromolecular chain. $C_R, C_\varphi, C_z$ are bending, twist and stretching rigidity of the macromolecule chain, respectively.

The bending rigidity is related to the persistence length $P = C_R l / k_B T$, where $l = L/N$ - the average value of the link length $l \sim 0.34 \text{nm}$, $k_B$ is the Boltzmann constant, $T$ is temperature. According to various experiments bending rigidity is $C_R = (85 \div 100) \text{kcal/mol}$, that is typical for angle about $6^\circ$ \[15\] between normals to plan base pairs of adjacent links and/or angel associated with shift. Torsion rigidity constant is defined less precisely and strongly depends on the sequence of base pairs, $C_\varphi \approx (64 \div 170) \text{kcal/mol}$. Thermal deviation of torsion between adjacent base pairs of DNA is in the range of $(3.4^\circ \div 5.5^\circ)$ \[16\]. Stretching rigidity, $C_z \sim S \cdot l = 50 \text{kcal/mol}$ where $S \sim 10^3 \text{pN}$ is the stretch modulus of dsDNA or thermal deviation $(0.02 \div 0.04) \text{nm}$ \[1\].

In the model WLC \[7, 8\] all the deformation components vary independently. However, for the large amplitudes of macromolecule deformation, coupling between components can provide a significant contribution to the total energy of the system. Lets examine the linear coupling of two of any elastic components of the elastic rod ($u, v \{R, \varphi, Z\}$). In this case the potential energy of the deformation can be written as:

$$E = \frac{1}{2} \sum_{n=1}^{n=N} \left[ C_u (u_{n+1} - u_n)^2 + C_v (v_{n+1} - v_n)^2 + 2 \gamma_{uv} (u_{n+1} - u_n)(v_{n+1} - v_n) \right],$$  \hspace{1cm} (2)

where $C_u, C_v = \{C_R, C_\varphi, C_z\}$, are the rigidity constants of the macromolecule, $\gamma_{uv} = \{\gamma_{R\varphi}, \gamma_{Rz}, \gamma_{\varphi z}\}$, ($\gamma_{uv} = \gamma_{vu}$) are the coupling parameter between $u$ and $v$ components.

Let us consider uniform deformation of the macromolecule chain. Assume $u_{n+1} - u_n = u$, $v_{n+1} - v_n = v$. Introduce the variables of the deformation of the chain is uniform, the energy will be splitted into $N$ separated terms. Taking this in consideration and introducing, the density of energy (2) in new variables has the following form:

$$\varepsilon(u, v) = \frac{E}{N} = \frac{C_u u^2}{2} + \frac{C_v v^2}{2} + \gamma_{uv} u v.$$  \hspace{1cm} (3)

The energy (3) consist of two parts $\varepsilon(u, v) = \varepsilon_0(u, v) + \varepsilon_{corr}(u, v)$, where harmonic part $\varepsilon_0(u, v) = C_u u^2/2 + C_v v^2/2$, and correlated part $\varepsilon_{corr}(u, v) = \gamma_{uv} u v$. We can find minimum of the energy
Figure 2: Shift of deformation energy minimum in u-component in response to deformation in v-component $v = v_a$. Small interrelations $|\gamma_0| < \sqrt{1/2}$ correspond to grey area. Large interrelations correspond to $\sqrt{1/2} < |\gamma_0| < 1$ ($v_a = 0.2$ for solid lines, and $v_a = 0.4$ for dotted lines); $\sigma = \sqrt{C_u/C_v}$; maximums of energy correspond to $v_a^2/2$.

(3) as follows, in the other words it is equations of stationary state:

$$\frac{\partial \varepsilon(u, v)}{\partial u} = C_u u + \gamma_{uv} v = 0; \quad (4)$$

$$\frac{\partial \varepsilon(u, v)}{\partial v} = C_v v + \gamma_{uv} u = 0. \quad (5)$$

The system has antiviral decision in the case of zero determinate of coefficients. It gives following circumstance: $C_u C_v - \gamma_{uv}^2 = 0$, then $v = v_a$ is any deformation, $u$ is determined proportionally to $v_a$:

$$u = -\frac{\gamma_{uv} v_a}{C_u} \quad (6)$$

However, in the case when $C_u C_v - \gamma_{uv}^2 \neq 0$ and $\gamma_{uv} = \gamma_0 \sqrt{C_u C_v}$ and $(-1 \leq \gamma_0 \leq 1)$, stationary state is determined by zero deviations from equilibrium state. Minimum of energy for unstressed state of the system with coupling stays the same as for system without coupling and realize for $u_0 = 0, v_0 = 0, E_0 = E(u_0, v_0) = 0$. In the same time minimum of energy will be shifted under an external action. As a result uniformly stressed state of chain with $v = v_a$ will have minimum of energy in $u = u_{min} \neq 0$ due to coupling. For any deformations according to the equations (4,5) minimum of the energy realized when strain in both components are proportional to each other $u(v) = -\gamma_{uv} v / C_u$, $v(u) = -\gamma_{uv} u / C_v$. Note, that the positive sign in one of the components is accompanied by a negative one in the other, in case $\gamma_{uv} > 0$. There is the same sign for both components in the case $\gamma_{uv} < 0$.

Let's consider coupling in the next general view $\gamma_{uv} = \gamma_0 \sqrt{C_u C_v}$ and $(-1 \leq \gamma_0 \leq 1)$. Deviation from the equilibrium state (or static strain) at one of the components, leads to a proportional deformation in the other component, and the energy of deformation (3) becomes:

$$\varepsilon(u, v_a) = \frac{1}{2} C_u (u - u_{min})^2 + \varepsilon_a, \quad (7)$$

where $u_{min} = -\gamma_0 \sqrt{C_v / C_u v}$, $\varepsilon_a = \varepsilon(u_{min}, v_a) = 1/2(1 - \gamma_0^2) C_v v_a^2$. The fig.2 shows the diagrams for two-components coupling in depends on value of $\gamma_0$ in the range $[-1; 1]$. The
diagrams show that modulus of coupling increasing leads to increasing of u-component minimum shift value with decreasing of the energy.

Since the DNA macromolecule is spiral and linear (generally pre-curved), a sign for additional positive or negative strain in u-component means the value of increase or decrease relatively equilibrium value. Thus, when $\gamma_0 > 0$ a positive strain in the v-component reduces the equilibrium deformation in the u component through coupling. In other words, the positive deformation in the u-component is complicated due to coupling with a positive strained v-component. And in case of $\gamma_0 < 0$, a positive strain in the v-component increases the equilibrium deformation in the u component. Or a negative coupling constant facilitates further positive straining the u-component.

Let us find the certain value $u = u_c$, for which deformation energy u-component is equal to deformation energy on the same value due to coupling with v-component. The value $u_c$ is found from the condition $\varepsilon_0(u_c, 0) = \varepsilon(u_c, v)$ ($\varepsilon_0(u_c, 0)$ is the deformation energy on value $u_c$ and $\varepsilon(u_c, v)$ is the deformation energy on value $v$). Then it has view $u_c = -C_vv/\gamma_{uv}$. There are 3 modes of behavior depending on the relative position $u_{min}$ and $u_c$. The first mode is implemented when $|u_{min}| > |u_c|$, that corresponds to value of coupling constant $|\gamma_0| > \sqrt{1/2}$. For the first mode elastic one-component deformation energy on value $u_{min}$ is higher then two-component deformation energy on the same value due to coupling with another deformed component on value $v$, and the inequality $\varepsilon_0(u_{min}, 0) > \varepsilon_a$ is true. The second mode corresponds to the condition $|u_{min}| = |u_c|$ or $\varepsilon_0(u_{min}, 0) = \varepsilon_a$ and value $|\gamma_0| = \sqrt{1/2}$. The third mode is in $|u_{min}| < |u_c|$, and meets the condition $|\gamma_0| < \sqrt{1/2}$. For the third mode the inequality $\varepsilon_0(u_{min}, 0) < \varepsilon_a$ is true (Fig.3). In this mode, two-component model with coupling probably realized only for deformations which are larger then value $u_c$.

The grey area shows the interval where coupling of component correspond to the third mode. For this mode the interrelation between components can lead to effective decrease one of components rigidity. Replacing v-component of the expression through u in energy (3), the energy have the form:

$$\varepsilon(u) = \frac{1}{2}(C_u - \frac{\gamma_{uv}^2}{C_v})u^2$$

Thus, the stiffness in one of the components can be effectively reduced because the interaction between components.

The effective reducing is small to do noticed impact to character of an elastic deformation. However, studying influence of conformational rearrangement on bend of the chain we have
concluded that conformational transition can be advantageous in deformed molecular chain of
a DNA type in the case of the strained fragment rigidity is lower then the average rigidity \[12\].
So coupling between components can provide more probable conformational transformations.
The latter is probably mechanism that couples elastic components.

3 The deformation related with internal conformation
change under the force

Let us consider the deformations of the double helix, which are accompanied by conformational
changes in the structure of monomer links. The potential energy of monomer links may be
presented as a non-linear function, \( \Phi(r_n) \) of relative displacement of their structural elements,
\( r_n \) \[11\]-\[13\]. The variable \( r_n \) is different from elastic components, because the elastic components
describe relative motion of monomer links as whole (external components). In the same time
relative displacement of structural elements inside a monomer link is described by internal com-
ponent \( r_n \). The potential energy of the conformational transformation according to trajectory
determined by \( \Phi(r_n) \) in the case when one external component is coupled with the internal component may be presented as:

\[
E_{pot} = \frac{1}{2} \sum_{n=1}^{N} \left\{ C_v (v_{n+1} - v_n)^2 + C_r (r_{n+1} - r_n)^2 +
\chi (v_{n+1} - v_{n-1}) F(r_n) + \Phi(r_n) \right\},
\]

where \( C_v \), \( C_r \) are rigidity of external and internal component along molecule correspondingly.
\( \chi F(r_n) \) describes coordinated mobility of the external and internal components. In the state of
homogeneous conformation (all monomers have equal \( r_n = r \) density of potential energy can be written like (4):

\[
\varepsilon(v, r) = \frac{C_v v^2}{2} + \chi v F(r) + \frac{\Phi(r)}{2},
\]

where \( v_{n+1} - v_n = v \) is a change in one component of the elastic rod, \( r_{n+1} - r_n = 0 \). In the minimum of conformational energy \( F(r) \sim -r, \Phi(r) = 0 \) or \( const \), the energy (9) takes the form similar to (3). However, in case of a local conformational change (e.g. under the force action,
in the presence of proteins, intercalations with small molecules or site specific conformational shift), the change of the elastic component associated with conformational component is also
localized and proportionate to \( F(r) \):

\[
v = -\frac{\chi F(r)}{C_v}.
\]

To include in our consideration the mechanism allowing one of the component changes,
applied to one of the components force is considered. But it can’t explain why sign of coupling
parameter changes under applied force about 35pN \[2\]-\[9\]. Based on our previous research, we
can conclude that adding of conformational component was missing link in those approaches.
Lets consider chain of two coupled components. One of them is deformed by applied force and
another coupled with generalized conformational component. To isolate the role of component
coupling regards the case of small conformational changes \( r \to 0 \). In this case,\( \Phi(r) \to 0, \chi F(r) \to -\chi_r \), the energy gets a view:

\[
\varepsilon(u, v) = \frac{C_u u^2}{2} + \frac{C_v v^2}{2} + \gamma_{uv} uv - ufh - \chi_r v.
\]
To determine the ground state of the macromolecular chains, with interrelation of components, we find the minimum of energy (4):

$$\frac{\partial \varepsilon(u, v)}{\partial u} = C_u u + \gamma_{uv} v - f h = 0;$$  \hspace{1cm} (13)

$$\frac{\partial \varepsilon(u, v)}{\partial v} = C_v v + \gamma_{uv} u - \chi_r = 0.$$  \hspace{1cm} (14)

Putting $u$ from the first equation into the second find expressions for both components in the view:

$$v = \frac{\chi_r C_u - \gamma_{uv} f h}{C_u C_v - \gamma_{uv}^2};$$ \hspace{1cm} (15)

$$u = \frac{f h C_v - \gamma_{uv} \chi_r}{C_u C_v - \gamma_{uv}^2}.$$  \hspace{1cm} (16)

Both components have the same denominator, so the signs of the components is determined by the numerators. The same sign of both components, that corresponds effectively negative sign of coupling component:

$$\begin{cases} 
\chi_r C_u - \gamma_{uv} f h > 0, \\
 f h C_v - \gamma_{uv} \chi_r > 0.
\end{cases}$$

And different sing of components, that corresponds effectively positive sign of coupling component:

$$\begin{cases} 
\chi_r C_u - \gamma_{uv} f h > 0, \\
 f h C_v - \gamma_{uv} \chi_r < 0.
\end{cases}$$

Solving the systems of inequalities we find the circumstances, which determine the signs of coupled components:

$$\frac{\gamma_{uv}}{C_u} < \frac{\chi_r}{f h} < \frac{C_v}{\gamma_{uv}},$$  \hspace{1cm} (17)

if components have the same sign.

$$\frac{\chi_r}{f h} < \frac{\gamma_{uv}}{C_u} < \frac{C_v}{\gamma_{uv}},$$  \hspace{1cm} (18)

if the components have different signs. So we have found the circumstances between conformational parameter and force. The circumstances determines signs of coupled components. In the first case the system has solution the same sing that can be interpreted as negative sign of coupling. In the second case, the solution correspond to positive of coupling without conformational component. This circumstance is in agreements with experiment which demonstrate that under external force the signs of twist and stretching are the same, if the force value is lower then a critical value. But for the force beyond the critical value, the signs of twist and stretching are opposite.

### 4 Discussion and Conclusions

In the order to estimate the effect of conformational component on twist-stretching coupling consider rigidity parameters in accordance to experimental data [3]. In the framework of our model twist rigidity $C_v = 197 \text{ kcal/mol}$, stretching rigidity $C_u = 55 \text{ kcal/mol}$, the twist-stretch...
Table 1: Values of shift and energy minimum for stretching coupled with twist

| $\gamma_0$ | $|u_{min}|$ | $\varepsilon(u_{min}, v_0)$ |
|------------|-----------|------------------|
| $v_0 = 0.013$ |
| 0.13       | 0.003     | 0.016            |
| 0.3        | 0.007     | 0.015            |
| 0.7        | 0.017     | 0.008            |
| 0.9        | 0.022     | 0.003            |
| $v_0 = 0.08$ |
| 0.13       | 0.02      | 0.62             |
| 0.3        | 0.045     | 0.574            |
| 0.7        | 0.106     | 0.322            |
| 0.9        | 0.136     | 0.12             |

Coupling $|\gamma_{uv}| = 13.5 \text{ kcal/mol}$, it correspond to the value of $\gamma_0 = 0.13$. Component of stretching is extension deviation, twist is rewriting as $\Delta T_w/T_{uw} \approx \frac{v}{36v/180^\circ}$. In the table we present values of deformations and energy for different meanings of $\gamma_0$. The values coincide with experimental data [3] for $\gamma_0 = 0.13$. Increasing of $\gamma_0$ leads to increasing deformation [3] and decreasing of energy.

Note the special case, when $\gamma_{uv} = \pm \sqrt{C_u C_v}$. The density of energy may be written in the form:

$$\varepsilon(u, v_0) = \frac{1}{2} C_u (u - u_{min})^2,$$

where $u_{min}(v) = \mp \sqrt{C_v/C_u} v_0$. In this case deformation in u-component induced by coupling with v-component realized without additional energy.

In the case of force induced deformation with interrelation between components of deformation and conformational changes we estimate range of force where both coupled elastic components are the same sign.

$$\frac{\chi_r \gamma_{uv}}{C_v} < fh < \frac{\chi_r C_u}{\gamma_{uv}}; \quad (20)$$

Substituting the values of the parameters in the relation (19), the estimation for coupling function between conformational component and twist is derived. The range of force of the same sing of twist and stretch is:

$$0.07 \chi_r < fh < 4 \chi_r. \quad (21)$$

Since the maximum value of the force for such a regime is $f_c = 35pN$ then last equation gives upper bound for conformation - twist coupling $\chi_r/h < 8.8pN$. As force is more then $2pN$ rotation translates into twist changing [2], that determine low bound for conformation - twist coupling $\chi_r/h > 2.9pN$. Hence while the double helix conformation resists to force influence, the deformation occurs in the specific way. As ever double helix undergoes conformational changes under the force the deformation goes in the other way. Parameter $\chi_r$ is a barrier which is formed by conformational stability of $v$-component in the range of minima of pseudorotation angle.

Thus, the paper presents a model of DNA deformation that takes into account the internal conformational component to describe coupled elastic deformations. Due to the coupling of the elastic component with the conformational component, additional term arises in the coupled elastic components solutions. This term competes with the contribution associated with the
directed action of the applied force and provides possibility of change of character of deformation. Thus, the model not only allows one to describe the unusual relationship between twisting and stretching of a macromolecule under the action of an applied force, but also to clarify its nature contained in the features of the internal structure of the double helix.

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