Long-range intermolecular interaction between broken DNA fragments

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We analyzed the long-range intermolecular interaction between fragments of broken DNA. We considered two constituents of long-range intermolecular interaction. The first is a net electrostatic Coulomb interaction between charges, involved in a structure of opposite nucleotides, which we evaluate using Debye-Huckel theory. The second one is the Van der Waals interaction between the nucleotides. The general Lifshitz theory of Van der Waals forces was used to evaluate this interaction. Numerical calculations showed that a repulsive force between broken DNA fragments can arise in specific cases. This repulsion can prevent DNA from repairing itself after a double-strand break. The height of the barrier decreases with an increase of the ionic strength of the intracellular milieu, or with a reduction of its viscosity.

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I. INTRODUCTION

The genetic macromolecule DNA is continually exposed to a wide variety of chemical and physical agents that can damage its structure. The most dangerous consequence of such exposure is a double-strand break of DNA. A sketch of a double-strand break is shown in Fig. 1(c). Structural damage interferes with DNA replication and transcription, and thus can lead to the loss and distortion of information stored in DNA [1]. Biological consequences of such damage include cell death and mutation, events that may cause cancer, mental retardation, and reduced growth and development [2]. The cell contains special enzymes which work to repair damaged DNA. The effectiveness of this enzymatic repair depends crucially on the long-range interaction between broken parts of the DNA double helix. In our previous work [3,4], we developed a model of the dispersion characteristics of interacting nucleotides, and showed the nonmonotonic character (including both repulsion and attraction) of the long-range interaction between broken DNA fragments. In some specific cases a repulsive potential barrier $V(R_0)>0$ arises inside the breakage area ($0<R_0<R$). The presence of such a barrier can sharply hinder the processes of DNA repair, and can even make this process impossible.

The total energy of the long-range interaction between end pairs of nucleotides situated in the area of DNA double-strand break involves two terms:

$$U=U^Q+U^{VDW}. \tag{1}$$

The first term U^Q (electrostatic energy) corresponds to the net Coulomb interaction of charges involved in the structure of opposite nucleotides. The second term U^{VDW} corresponds to the total Van der Waals interaction of the opposite nucleotides pairs, also called the dispersion interaction. In this work we present a detailed analysis of the total long-range intermolecular interaction of end pairs of nucleotides located in the area of DNA double-strand break.

II. ELECTROSTATIC INTERACTION OF WATSON-CRICK PAIRS NEAR A DOUBLE-STRAND BREAK

The electrostatic component of the long-range interaction [Eq. (1)] represents the total energy of pair Coulombic interactions $U^Q_{i,j}$ of the charges, facing each other across a double-strand break,

$$U^Q=\sum_{i=1}^{N_\alpha}\sum_{j=1}^{N_\beta} U^Q_{i,j}, \tag{2}$$

where N_α and N_β are the number of atoms in a Watson-Crick pair of nucleotides GC or AT ($N_\alpha=29$ for GC, $N_\beta=27$ for AT); $U^Q_{i,j}$ is the energy of a pair Coulombic interaction of charges Q_i and Q_j [see Fig. 1(d)]. We consider the charge distribution on the Watson-Crick nucleotide pairs GC or AT, taking into account the real geometry of the charge location [see Fig. 1(a)]. The distribution of the charge density on the surface of nucleotides was calculated for many nucleotides and their derivatives. The contribution of σ and π electrons was evaluated by Del Re and Huckel methods [5].

We used the Debye-Huckel theory [6] to evaluate the Coulombic interaction, which considers an ion solution of mobile light hydrated electrons e^- and heavy ions Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+}, Mn^+, H^+, OH^-, and others. According to this theory, the energy of the Coulombic interaction $U^Q_{i,j}$ between charges distributed on the surface of nucleotides is found by solving the Poisson-Boltzmann equation [6]

$$\nabla^2\tilde{\psi}=-\frac{4\pi e^2}{\varepsilon_w(0)k_bT}\sum_z n_z^0 e^{-z\tilde{\psi}}, \tag{3}$$

where $\tilde{\psi}=e\psi/k_bT$ is the normalized electrostatic potential, $\varepsilon_w(0)$ is the static (at $\omega=0$) value of the dielectric permittivity of intracellular liquid, and n_z^0 is the concentration of an ion species of valence z at a point in the salt solution where the potential is most conveniently taken to be zero. This nonlinear differential equation for the electrostatic potential is considerably simplified in case of $z\tilde{\psi}\ll 1$. Using the linear approximation $e^{-z\tilde{\psi}}\approx 1-z\tilde{\psi}$, the linearized Poisson-Boltzmann equation is

$$\nabla^2\tilde{\psi}=k^2\tilde{\psi}, \tag{4}$$

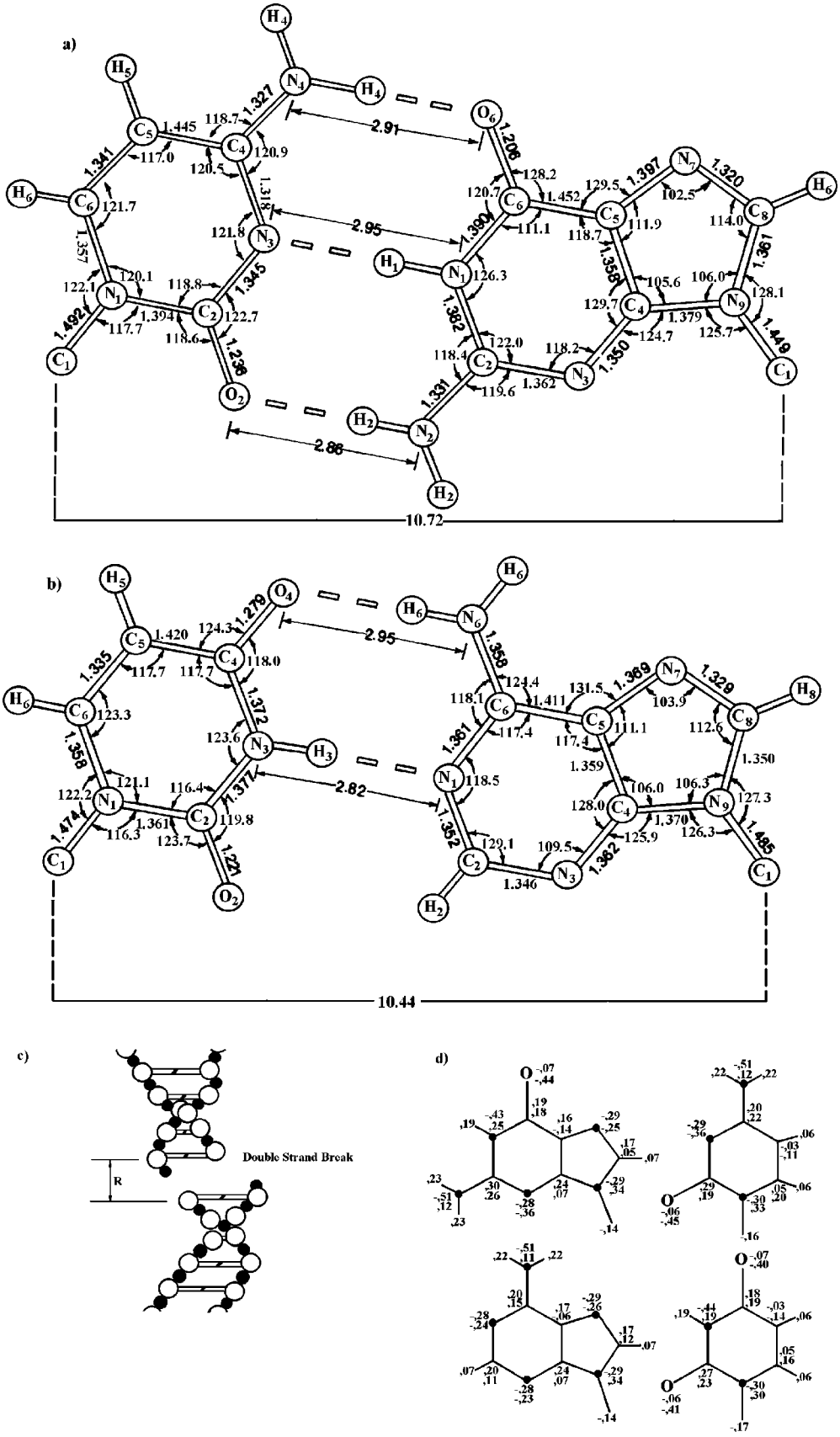

FIG. 1. (a) Coordinates of atoms for a *GC* nucleotide pair. (b) The coordinates of atoms for an *AT* nucleotide pair. (c) The sketch of the double strand break of DNA. (d) The charge density distribution for the nucleotides.

where $k^2=8\pi n/\varepsilon_w(0)k_bT$ is the Debye constant and $n=\frac{1}{2}\Sigma_z n_z^0 z^2$ is the ionic strength of the solution. The intracellular milieu is bulk neutral: $\Sigma_z n_z^0 z=0$.

The analytical solution of the linearized Poisson-Boltzmann equation (4) was found for the case of two charged spheres with radii a_1 and a_2 and the constant charges Q_i and Q_j. The total energy of the electrostatic interaction between two charges in the ionic solution has the form [6]

$$U_{ij}^{Q}=\frac{Q_iQ_j}{\varepsilon_w(0)r_{ij}}\exp^{-k(r_{ij}-a_i-a_j)}, \tag{5}$$

where r_{ij} is the distance between the two fractionally charged atoms. The corresponding radii of atoms a_i and a_j, involved in the structure of interacting nucleotides, were taken from the literature [5].

III. VAN DER WAALS INTERACTION OF NUCLEOTIDES NEAR A DOUBLE-STRAND BREAK

The second part of expression (1) characterizes the Van der Waals interaction $U^{VDW}=\Sigma_{k=1}^{2}\Sigma_{l=1}^{2}U_{k,l}^{VDW}$ between the nucleotide pairs on opposite sides of a DNA double-strand break. Here $U_{k,l}^{VDW}$ is the energy of the Van der Waals interaction between individual nucleotides k and l.

A. General electrodynamic interaction of nucleotide pairs

The energy of the dispersion interaction of two nucleotides in the intracellular milieu is best described by Lifshitz's general theory of Van der Waals forces [7]. Here we apply this theory to the specific geometry of interacting nucleotides.

The dispersive interaction between two spherical particles in the intracellular milieu a distance R apart can be written [7]

$$U_{k,l}^{VDW}(R)=-\frac{27\hbar}{16\pi^3}\frac{V_kV_l}{R^6}\times\int_0^{\infty}\frac{[\varepsilon_l(i\xi)-\varepsilon_w(i\xi)][\varepsilon_k(i\xi)-\varepsilon_w(i\xi)]}{[\varepsilon_l(i\xi)+2\varepsilon_w(i\xi)][\varepsilon_k(i\xi)+2\varepsilon_w(i\xi)]}d\xi, \tag{6}$$

where $\varepsilon_l(i\xi)$ and $\varepsilon_k(i\xi)$ are the dielectric permittivities of the interacting particles as functions of the imaginary frequency $\omega=i\xi$; $\varepsilon_w(i\xi)$ is the dielectric permittivity of the intracellular milieu, and V_k and V_l are the volumes of the particles.

Expression (6) holds for short distances $R\ll\lambda_0$, where λ_0 is the characteristic absorption wavelength of the particles. This expression directly determines the energy of the dispersive interaction between two nucleotides on opposite sides of a DNA double-strand break of large width R, provided that $\overline{R}_{k,l}<R\ll\lambda_0$. Here $\overline{R}_{k,l}\equiv\sqrt{S_{k,l}}\approx 7$ Å is the typical linear size of nucleotides and $S_k, S_l\approx 50$ Å^2 the area of nucleotide surfaces.

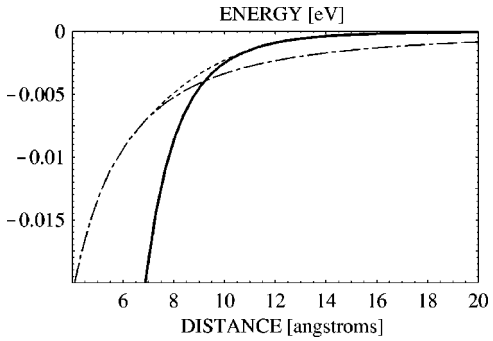

FIG. 2. The calculated Van der Waals energy of interaction between *CG-CG* nucleotide pairs. (a) Calculation according to Eq. (7)—solid curve. (b) Calculation according to Eq. (9)—dashed curve. (c) Interpolation—dotted curve.

We emphasize that the total energy of the dispersive interaction U^{VDW} includes the energy of the interaction of every nucleotide with both of the nucleotides of the pair on the opposite side of the DNA double-strand break. It is very important that calculation of the dispersive energy of DNA fragments can be done considering only the final nucleotide pairs (i.e., without considering of the pairs, more removed from the DNA double-strand break). This arises from the rapid [proportional to $(R+n\Lambda)^{-6}$] decrease of the contribution to the energy of far removed ($n>0$) nucleotide pairs. Here $\Lambda=3.4$ Å is the nucleotide spacing along DNA.

In the limiting case of small distances between nucleotides $R<\overline{R}_{l,k}$ and $R\ll\lambda_0$, their dispersive interaction can be approximated by the interaction between two parallel planes [7]. In this approximation the dispersive interaction is described by the pressure of the fluctuating electromagnetic field on the surface of the planes:

$$P_{k,l}(R)=\frac{\hbar}{8\pi^2R^3}\int_0^{\infty}\frac{[\varepsilon_l(i\xi)-\varepsilon_w(i\xi)][\varepsilon_k(i\xi)-\varepsilon_w(i\xi)]}{[\varepsilon_l(i\xi)+\varepsilon_w(i\xi)][\varepsilon_k(i\xi)+\varepsilon_w(i\xi)]}d\xi. \tag{7}$$

For planes with area S_l or S_k the corresponding energy of the interaction is described by the expression

$$U_{k,l}^{VDW}(R)=-\frac{\hbar}{16\pi^2}\frac{\tilde{S}_N}{R^2}\times\int_0^{\infty}\frac{[\varepsilon_l(i\xi)-\varepsilon_w(i\xi)][\varepsilon_k(i\xi)-\varepsilon_w(i\xi)]}{[\varepsilon_l(i\xi)+\varepsilon_w(i\xi)][\varepsilon_k(i\xi)+\varepsilon_w(i\xi)]}d\xi, \tag{8}$$

where $\tilde{S}_N$ is the effective area of the smaller (S_l or S_k) of the two interacting nucleotides l and k, lying on opposite sides of the double-strand break. For this planelike geometry the energy of the dispersive interaction $U^{VDW}=\Sigma_{i=1}^{2}U_{i,i}^{VDW}$ accounts for the interaction of each of the nucleotides only with the nucleotide directly on the opposite side of the double-strand break.

TABLE I. Water spectral parameters [6].

Microwave range: Debay relaxation		
$d=74.8,\ 1/\tau=1.05\times10^{11}$ rad/s$=6.5\times10^{-5}$ eV		
IR range: damped oscillator form		
ω_n, eV	f_n, eV^2	g_n, eV
2.07×10^{-2}	6.25×10^{-4}	1.5×10^{-2}
6.9×10^{-2}	3.5×10^{-3}	3.8×10^{-2}
9.2×10^{-2}	1.28×10^{-3}	2.8×10^{-2}
2.0×10^{-1}	5.69×10^{-3}	2.5×10^{-2}
4.2×10^{-1}	1.35×10^{-2}	5.6×10^{-2}
UV range: damped oscillator form		
ω_j, eV	f_j, eV^2	g_j, eV
8.25	2.68	0.51
10.0	5.67	0.88
11.4	12.0	1.54
13.0	26.3	2.05
14.9	33.8	2.96
18.5	92.8	6.25

The most interesting range of distances is near the critical value $R\approx\overline{R}_{k,l}$, which divides the regions where expressions (6) and (8) apply. For such a range of R neither relation (6) nor (8) is valid.

To find the dependence $U_{k,l}^{VDW}$ in the whole range of distances R (including the area $R\approx\overline{R}_{k,l}$), we interpolated expressions (6) and (8) from the regions $R\leqslant 2\overline{R}_{k,l}$ and $R\geqslant 2\overline{R}_{i,j}$ (where these expressions are valid) into the region $\overline{R}_{k,l}/2\leqslant R\leqslant 2\overline{R}_{k,l}$. The dependence of the Van der Waals energy of the nucleotide pairs *CG-CG* is shown in Fig. 2. Our approach allows us to calculate with high precision the energy of the Van der Waals interaction (and accordingly the total energy of interaction) of the opposite nucleotide pairs for all distances.

B. Dispersion characteristics of nucleotides and intracellular liquid

In general, the sign and character of the Van der Waals interaction are defined by the dependence of the dispersion characteristics of the interacting nucleotides and the intracellular liquid in the entire spectral range (from $\omega_{min}=0$ up to x-ray frequencies $\omega_{max}\approx c/R$). The total interaction, its sign and the dependence on the distance R, are determined by a balance of a number of separate components with different signs and values in the different spatial and spectral regions [Eqs. (1), (2), (6), and (8)]. This is true for both the electrostatic and electrodynamic interactions. Expressions (6) and (8) show that the sign of the dispersion interaction can change depending on the dispersion of the dielectric permittivity of nucleotides and intracellular liquid in different frequency ranges. For this reason small errors in the values of parameters can lead to large errors in the final value of the interaction, and even to an uncertainty in the interaction. The use of purely modeled values [4] for the dielectric permittivities does not provide sufficient precision. In this work the dependences $\varepsilon_k(\omega)$, $\varepsilon_l(\omega)$, and $\varepsilon_w(\omega)$ were obtained from experimental UV and IR spectra of the nucleotides and the intracellular liquid. The dispersion characteristics of the interacting nucleotides were found from a Kramers-Kronig analysis of the absorption spectra [8]. The dielectric permittivity of the intracellular aqueous solution was divided into Debye dipolar and damped resonance terms. The Debye relaxation depends on the temperature and the viscosity of water (relaxation time τ). Furthermore, water shows strong absorption (and charge fluctuations) at infrared and ultraviolet frequencies. In the x-ray range the dielectric permittivity of water has the form [6]

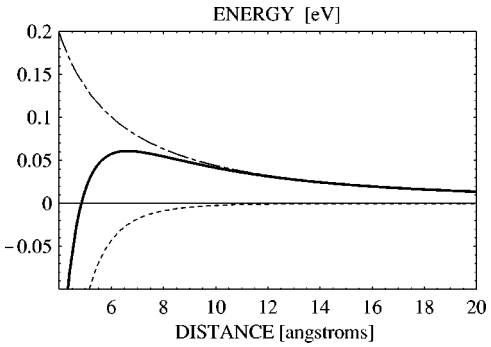

FIG. 3. The calculated energy of interaction between oriented *CG-CG* nucleotide pairs. (a) Electrostatic energy—dashed curve. (b) electrodynamic energy—dotted curve. (c) Total energy—solid curve.

$$\epsilon_w(\omega)=1-\frac{\omega_p^2}{\omega^2}, \tag{9}$$

where $\hbar\omega_p=45$ eV is the plasma frequency energy for water.

Quasifree hydrated electrons in the intracellular milieu also influence the interaction between the nucleotides. The additional term in the dielectric permittivity of water, due to the availability of quasifree hydrated electrons, is given by

$$\epsilon_g(\omega)=-\frac{4\pi n_g e^2}{m\left(\omega^2+i\dfrac{\omega}{\tau_g}\right)}, \tag{10}$$

where n_g is the concentration of hydrated electrons, $\tau_g\approx 7.8\times10^{-4}c$ is the relaxation time of hydrated electrons [4], and e and m are the charge and mass of the hydrated electrons. We note that the effect of the heavy ions in the liquid intracellular milieu on the permittivity is negligible due to their large mass.

Thus the dielectric permittivity of water is given by

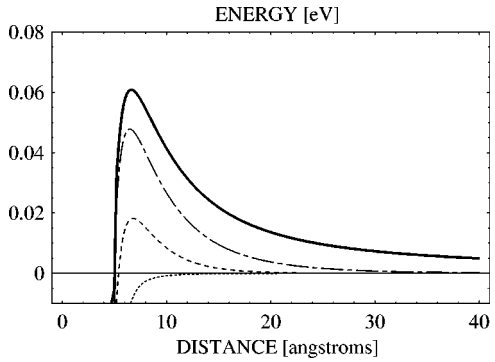

FIG. 4. The total energy of interaction between oriented *CG-CG* nucleotide pairs as a function of the distance between them and the Debye constant of the intracellular milieu. (a) $k=0$—solid curve. (b) $k=10^7$—dashed curve. (c) $k=2.5\times10^7$—dotted curve. (e) $k=5\times10^7$—small dotted curve. The viscosity of the intracellular liquid is $\nu=\nu_0$.

$$\epsilon(\omega)=1+\frac{d}{1-i\dfrac{\omega}{\tau}}+\sum_{n=1}^{11}\frac{f_n}{\omega_n^2-\omega^2-ig_n\omega}-\frac{4\pi n_g e^2}{m\left(\omega^2+i\dfrac{\omega}{\tau_g}\right)}. \tag{11}$$

The spectral parameters d, f_n, and g_n, which characterize the dielectric permittivity of water, are given in Table I.

IV. NUMERICAL CALCULATIONS AND DISCUSSION

We calculated the total energy between the ends of a double-strand break based on the expressions for the Coulomb [Eq. (5)] and Van der Waals [Eqs. (6)–(8)] interaction between the end pairs of nucleotides. We show the dependence of the electrostatic energy of the oriented pairs of nucleotides *CG-CG* in Fig. 3 (dashed curve). The electrodynamic component of the energy (dotted curve) and the total energy (solid curve) for the same nucleotide pairs are also shown in Fig. 3.

The electrostatic and electrodynamic energies are monotonic: the Coulomb interaction is repulsive and the Van der Waals interaction is attractive. The total energy of the interaction is nonmonotonic. Thus, as a result of the long range interaction, a potential barrier $U\approx3k_bT$ appears in a range of R. This potential barrier can prevent the DNA from repairing after a double-strand break. Our numerical calculations of the total energy have shown that the ion composition of the intracellular milieu and its viscosity affect the height of this repulsive barrier. The calculated dependence of the total energy for the pairs *CG-CG* as a function of the distance R between them and of the ionic strength of the intracellular solution are presented in Fig. 4. As shown in Fig. 4, the height of the barrier decreases to $V\approx0.9k_bT$ with an increasing Debye constant up to $k=2.5\times10^7$ (dotted curve), at which the influence of this barrier on the repair process considerably decreases. An increase in the viscosity of the intracellular aqueous solution up to $\nu=10\nu_0$ leads to a decrease in the height of the repairing barrier down to $V\approx2k_bT$ for the pair *CG-CG* (Fig. 5). The calculated dependence of the total energy between the nucleotide pairs *CG-CG* with the viscosity of intracellular liquid, $\nu=100\nu_0$ is presented in Fig. 6. In this figure the height of the barrier decreases down to $V\approx0.6k_bT$.

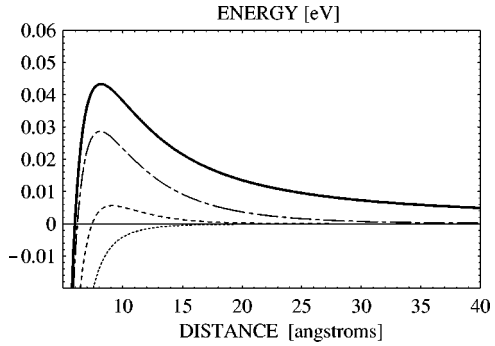

FIG. 5. The total energy of interaction between oriented *CG-CG* nucleotide pairs as a function of the distance between them and the Debye constant of the intracellular milieu. (a) $k=0$—solid curve. (b) $k=10^7$—dashed curve. (c) $k=2.5\times10^7$—dotted curve. (e) $k=5\times10^7$—small dotted curve. The viscosity of the intracellular liquid is $\nu=10\nu_0$.

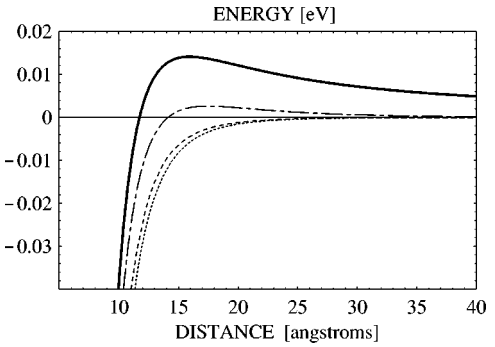

FIG. 6. The total energy of interaction between oriented *CG-CG* nucleotide pairs as a function of the distance between them and the Debye constant of the intracellular milieu. (a) $k=0$—solid curve. (b) $k=10^7$—dashed curve. (c) $k=2.5\times10^7$—dotted curve. (e) $k=5\times10^7$—small dotted curve. The viscosity of the intracellular liquid is $\nu=100\nu_0$.

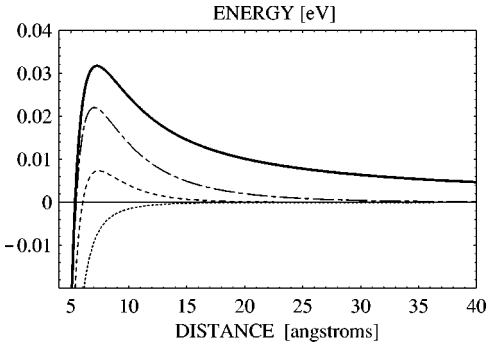

FIG. 7. The total energy of interaction between oriented *TA-TA* nucleotide pairs as a function of the distance between them and the ionic strength of the intracellular milieu. (a) $k=0$—solid curve. (b) $k=10^7$—dashed curve. (c) $k=2.5\times10^7$—dotted curve. (d) $k=5\times10^7$—small dotted curve. The viscosity of the intracellular liquid is $\nu=\nu_0$.

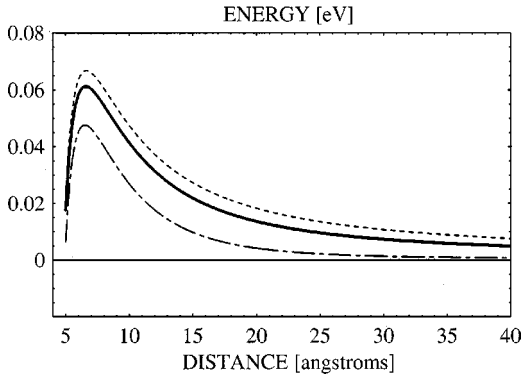

FIG. 8. The effect of the electrostatic interaction between phosphate groups on the total long-range interaction. (a) The interaction between *CG-CG* bases without accounting for electrostatic interactions between phosphates (solid curve). (b) Accounting for fractionally charged phosphate groups on different sides of the double-strand break (dashed curve). (c) The same as (b), except that an oxygen atom in phosphate group is neutral (dotted curve).

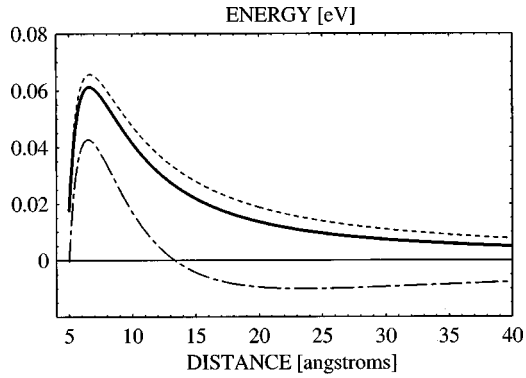

FIG. 9. The effect of the electrostatic interaction between phosphate groups on the total long-range interaction. (a) The interaction between *CG-CG* bases without accounting for electrostatic interactions between phosphates (solid curve). (b) Accounting for fractionally charged phosphate groups on same side of the double-strand break (dashed curve). (c) The same as (b), except that an oxygen atom in phosphate group is neutral (dotted curve).

The repulsive barrier $V \approx 0.5 k_b T$ appears between *TA-TA* nucleotide pairs at the physiological viscosity $\nu = \nu_0$ and the same distance R. Increasing the viscosity of the intracellular solution decreases this barrier (Fig. 7). All other configurations of oriented pairs of nucleotides have no such barrier $[V(R) < 0]$ in the region of the double-strand break, and the total energy of interaction is always attractive.

Our calculation the electrostatic interaction between fractionally charged bases neglected the electrostatic interaction between phosphate groups. To check the influence of these groups, we calculated the total energy of *CG-CG* pairs on opposite sides of a double-strand break, taking into account the electrostatic interaction between the fractionally charged bases and phosphate groups. We considered two situations—when the phosphate groups are on the same side of the double strand break, and when they are on opposite sides [1]. The fractional charges on the phosphate groups were taken from Ref. [5], but we believe that due to the much faster relaxation of electrons in fractionally charged atoms of the phosphate group, the oxygen atom facing the break will be quickly changed (due to the rupture of the 3- or 5-in. bond between the phosphate and the sugar ring). We consider two extreme situations: when the oxygen atom facing the break area has the same fractional charge as the nonbroken strand, and when this oxygen atom is neutralized. Note that the actual interaction energy will be between these two extremes. As seen in Fig. 8, the barrier to repair is decreased for fractional charged phosphates, and is increased if the oxygen facing the break is neutralized. As mentioned above, the actual total energy will be between these two extremes. The same situation occurs when the phosphate groups are on opposite sides of the break (Fig. 9). Thus the influence of the charged phosphate groups can be neglected in this problem.

This study is a continuation of previous work [3,4], where only the dispersive interaction between separate nucleotides in solution was studied. Including the Coulomb interaction between nucleotides can lead to a barrier to DNA repair.

Thus in this work a detailed analysis of the net intermolecular interaction of end pairs of nucleotides on opposite sides of a DNA double-strand break was performed. We showed that a repulsive barrier $V(R) > 0$ with an amplitude of several $k_b T$ can arise between oriented pairs of nucleotides *CG-CG* and *TA-TA*. The height of this barrier is reduced with an increase of the ionic strength force or viscosity of the intracellular milieu. An understanding of the formation and repair of single- and double-strand DNA breaks is an important step in resolving the many health problems associated with exposure to DNA-damaging agents.

ACKNOWLEDGMENT

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[1] R. Meyer, *Molecular Biology and Biotechnology* (VCH, New York, 1995).

[2] H. Dertinger and H. Jung, *Molecular Radiation Biology* (Springer-Verlag, New York, 1970).

[3] A. O. Pinchuk and V. I. Vysotskii, Bioelectrochem. Bioenerg. **48**, 329 (1999).

[4] V. I. Vysotskii, A. A. Kornilova, and I. I. Samoylenko, Radiat. Biol. Radioecology (Moscow) **37**, 404 (1997).

[5] W. Saenger, *Principles of Nucleic Acid Structure* (Springer-Verlag, New York, 1987).

[6] A. Parsegian, *Physical Chemistry: Enriching Topics From Colloidal and Surface Science* (THEOREX, La Jolla, California, 1975).

[7] Yu. S. Barash, *Van-der-Vaals Forces* (Nauka, Moscow, 1988).

[8] A. O. Pinchuk, V. I. Vysotskii, and A. A. Zhmudskii, *Spectroscopy of Biological Molecules: New Directions* (Kluwer, Dordecht, 1999), pp. 403 and 404.