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Theoretical treatment of helix–coil transition of complexes DNA with two different ligands having different binding parameters

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The melting transition of DNA–ligand complexes, allowing for two binding mechanisms to different DNA conformations is treated theoretically. The obtained results express the behavior of the experimentally measurable quantities, degree of denaturation, and concentrations of bound ligands on the temperature. The range of binding parameters is obtained, where denaturation curves become multiphasic. The possible application to the nanocomposites crystallization is discussed.

Keywords: DNA; binding parameters; degree of denaturation; DNA–ligand complexes; helix–coil transition

Introduction

The phenomenon of the helix–coil transition in biopolymers has been known since 1960s (Poland & Scheraga, 1970; Vedenov, Dykhne, & Frank-Kamenetskii, 1971) and it is still vigorously discussed (Barbi, Lepri, Peyrard, & Theodorakopoulos, 2003; Chalikian, 2003; Cule & Hwa, 1997; Garel, Monthus, & Orland, 2001; Munoz & Serrano, 1997; Takano, Nagayama, & Suyama, 2001). There are two main reasons for such continuous interest. From the biological point of view, the helix–coil transition is connected with such important genetic processes as transcription and translation. On the other hand, from the physical point of view, the interest is caused by the fact that double-stranded DNA is an example of one-dimensional cooperative system with large-scale correlations (Vedenov et al., 1971).

Over the past century considerable attention has been paid to the theory of helix–coil transition in biopolymers, particularly in DNA (Frank-Kamenetskii, 1997; Poland & Scheraga, 1966; Wartell & Benight, 1985). In the investigation of DNA molecular structure and function it is ultimately important to reveal the role of DNA interaction with water and different low-molecular compounds (ligands) dissolved in water. The influence of water, ions, and ligands on the structure and functions of DNA was intensively investigated (Garbett, Ragazzon, & Chaires, 2007; Zimmer & Wahnert, 1986). The interaction of ligands with double-stranded DNA is a fundamental feature for many intracellular processes. Ligands with reduced or no sequence specificity are often able to impact on the regulation, transcription, and translation processes (Nelson, Ferguson, & Denny, 2007). Because of the sophisticated double-helical structure of DNA, different binding specific or unspecific non-covalent modes become possible: intercalation (Reha et al., 2002), bis-intercalation (Krishnamoorthy, Duportail, & Mely, 2002), minor groove binding (Reddy, Sharma, & Lown, 2001), major groove binding (Niidome et al., 1996), a combination of those (Larsson, Carlsson, Jonsson, & Albinsson, 1994), and binding via non-classical modes (Lipscomb et al., 1996).

Current research is focused on the theoretical model of the helix–coil transition of DNA–ligand complexes allowing for two types of the ligand to the double-stranded DNA (ds-DNA) and two types of binding to single-stranded (ss-DNA). The suggested model is useful to analyze the experimentally obtained results for simultaneous binding of two different ligands having different binding parameters with ss- and ds-DNA (Karapetian et al., 1996). While our previous work (Karapetian et al., 1996) was focused mainly on the effect of ligands on the DNA stability and cooperativity of melting, the present study is devoted to the cold denaturation phenomena, experimentally observed e.g. by Dubins, Lee, Macgregor, and Chalikian (2001).

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Theory

We have implemented the standard model of DNA–ligand melting (Karapetian et al., 1996; Vedenov et al., 1971). The molecule consists of N base pairs. In the area of helix–coil transition each base pair can adopt one of the two conformational states: helix and coil. The macromolecule is divided into n regions consisting of N_1 coil base pairs and N_2 helical base pairs. The total number of base pairs remains constant during the melting process

$$N = N_1 + N_2 \tag{1}$$

Solution also contains two types of ligands with different binding parameters. Let us suppose we have ligands bound with single-stranded regions with binding constants K_1' and K_1'' and with double-stranded regions with binding constants K_2' and K_2''. The total number of ligands is equal to k, the number of molecules bound with single-stranded regions by the first mechanism is equal to k_1', by the second mechanism is equal to k_1'', the number of molecules bound with double-stranded regions by the first mechanism is equal to k_2', by the second mechanism is equal to k_2''. Let F_1 and F_2 be the free energies per base pair at the coil and helical states, correspondingly, F_0 is the free energy of helix initialization, Ψ_i^α is the free energy of binding ($i = 1, 2$ and $\alpha = \prime, \prime\prime$), and W is the number of microstates of macromolecule, corresponding to the given energy. Thus, the total free energy can be computed by the following equation (Grigoryan, Mamasakhlisov, & Karapetian, 2014; Karapetian et al., 1996)

$$F = F_1 N_1 + F_2 N_2 + nF_0 + \sum_{i=1,2}\sum_{\alpha=\prime,\prime\prime} k_i^\alpha \Psi_i^\alpha - T \ln W \tag{2}$$

Using the most probable distribution approach, we obtain the following system of equations for the concentrations $c_i^\alpha = \frac{k_i^\alpha}{N_i}$

$$\begin{aligned}
\frac{c_1' r_1' / 2}{1 - c_1' r_1' / 2} &= \frac{PK_1'}{2}\left[\frac{2D}{P} - 2(1-\vartheta)c_1' - 2(1-\vartheta)c_1'' - \vartheta c_2' - \vartheta c_2''\right] \\
\frac{c_1'' r_1'' / 2}{1 - c_1'' r_1'' / 2} &= \frac{PK_1''}{2}\left[\frac{2D}{P} - 2(1-\vartheta)c_1' - 2(1-\vartheta)c_1'' - \vartheta c_2' - \vartheta c_2''\right] \\
\frac{c_2' r_2'}{1 - c_2' r_2'} &= \frac{PK_2'}{2}\left[\frac{2D}{P} - 2(1-\vartheta)c_1' - 2(1-\vartheta)c_1'' - \vartheta c_2' - \vartheta c_2''\right] \\
\frac{c_2'' r_2''}{1 - c_2'' r_2''} &= \frac{PK_2''}{2}\left[\frac{2D}{P} - 2(1-\vartheta)c_1' - 2(1-\vartheta)c_1'' - \vartheta c_2' - \vartheta c_2''\right]
\end{aligned} \tag{3}$$

where K_i^α are the binding constants, D is the total concentration of ligands, r_i^α is the number of binding sites per ligand, P is the total concentration of phosphate groups, and ϑ is the helicity degree. Equation for the effective parameter of the helix growth yields

$$S* = S\frac{\left(1 - c_1' r_1'/2\right)^{\frac{2}{r_1'}}\left(1 - c_1'' r_1''2\right)^{\frac{2}{r_1''}}}{\left(1 - c_2' r_2'\right)^{\frac{1}{r_2'}}\left(1 - c_2'' r_2''\right)^{\frac{1}{r_2''}}}, \tag{4}$$

where $S = \exp\left(\frac{F_1 - F_2}{T}\right) = \exp\left(-\frac{\Delta H}{RT} + \Delta S\right)$ is the helix growth parameter for the pure DNA, where ΔH is the change of enthalpy and ΔS is the change of entropy of one base pair formation. The order parameter, describing the helix–coil transition is the helicity degree, defined as

$$\theta = \frac{1}{N}\langle N_2 \rangle, \tag{5}$$

where $\langle ... \rangle$ means the thermodynamic average.

Results and discussion

To address the effect of the ligands, described above, the helicity degree has been calculated using the Equations ((3–5)). In this paper, we focused our attention on the ligands with higher affinity to native DNA. Solution of the Equation (3) has been obtained numerically.

Let us consider the two following most interesting cases. If the total concentration of ligands in solution is very low $\frac{2D}{P} <$, the melting curve obtained for the certain values of binding constants K_i^α is presented in Figure 1. In Figure 1 we compare denaturation curve for the pure DNA (curve 1) with those for the DNA–ligand complex (curve 2). Because of higher affinity of ligands to the helical regions of DNA, the denaturation curve is shifted to the low values of the parameter S i.e. to the high temperatures. Thus, the low concentrations of ligands led to the stabilization of ds-DNA helical structure.

At the same time, if the total concentration of ligands in solution is comparable with those for the phosphate groups $\frac{2D}{P} \sim 1$ and $PK_1' >> 1$, $PK_2' >> 1$, $PK_2'' >> 1$, $PK_2' >> 1$ DNA–ligand complexes exhibit both high-temperature and low-temperature denaturation with the wide "window" of stable double helix in the area of helix–coil transition of the pure DNA (see Figure 2, curve 1). In this case, the key point is the higher affinity to native DNA in comparison with denaturated one. The

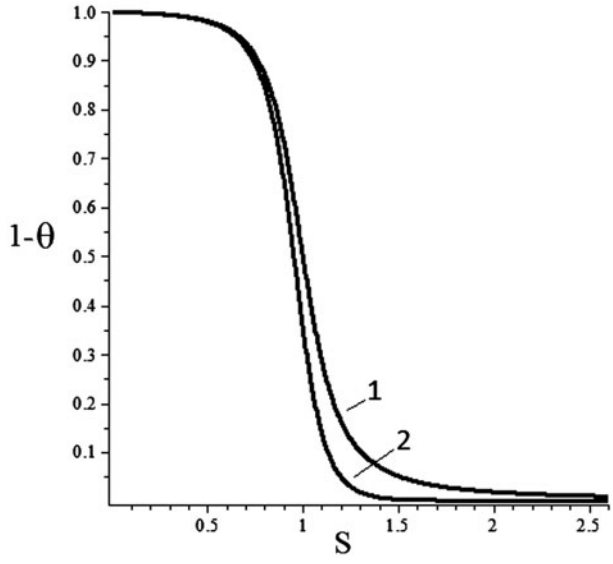

Figure 1. Dependence of the degree of denaturation $1-\theta$ on the parameter of the helix growth S. Line 1 is the denaturation curve for the pure DNA. Line 2 is the denaturation curve for $\frac{2D}{P} = 1.4 \times 10^{-2}$, $r_1' = 2$, $r_1'' = 2$, $r_2' = 4$, $r_2'' = 4$, $K_1' = 2.9 \times 10^4$ M^{-1}, $K_1'' = 10^2$ M^{-1}, $K_2' = 9.6 \times 10^5$ M^{-1}, and $K_2'' = 10^7$ M^{-1}.

high-temperature denaturation of the DNA–ligand complex is substantially shifted to the high-temperatures area in comparison with the pure DNA ("hot" denaturation). At the same time, at high-temperature conditions at which the pure DNA still remain denaturated, DNA–ligand complex exhibits native state. Within the decrease of temperature DNA–ligand complex undergoes "cold" denaturation, while the pure DNA becomes helical (Figure 2, curve 3).

"Cold" denaturation phenomenon was observed experimentally for proteins and nucleic acids (Dubins et al., 2001; Mikulecky & Feig, 2002; Privalov, 1990). The mechanism of "cold" denaturation was addressed in a huge amount of publications (Badasyan et al., 2014; Hayrapetyan et al., 2014; Mikulecky & Feig, 2004; Privalov, 1990). The "cold" denaturation of DNA–ligand complex is accompanied by redistribution of ligands, bound with molten regions of DNA (see Figure 3, curve 3). While the concentrations of ligands bound with native regions, c_2^{α} remains constant during the "cold" and "hot" denaturation, the concentrations of ligands bound with molten regions are abruptly increase in the area of "cold" denaturation. Thus, the stabilization of the molten phase occurs because of ligands are bound with denaturated DNA. To understand the mechanism of cold denaturation the simplest case of DNA–ligand interaction has been considered, where low-molecular compounds are bound with single-stranded regions with binding constant K_1' and with double-stranded regions with binding constant K_2', where $K_2' \gg K_1'$. In this case, the system of Equation (3) will be transformed as

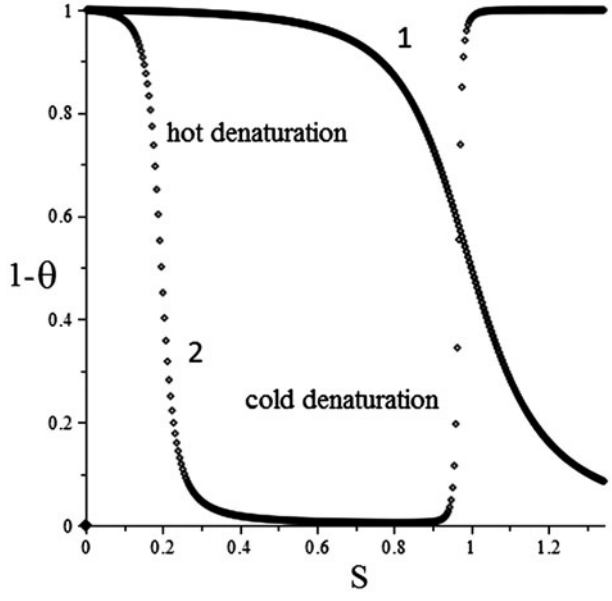

Figure 2. Dependence of the degree of denaturation $1-\theta$ on the helix growth parameter S. Line 1 is the denaturation curve for the pure DNA. Line 2 is the denaturation curve for $r_1' = 2$, $r_1'' = 2$, $r_2' = 4$, $r_2'' = 4$, $K_1' = 2.9 \times 10^4$ M^{-1}, $K_1'' = 10^2$ M^{-1}, $K_2' = 9.6 \times 10^5$ M^{-1}, and $K_2'' = 10^7$ M^{-1}.

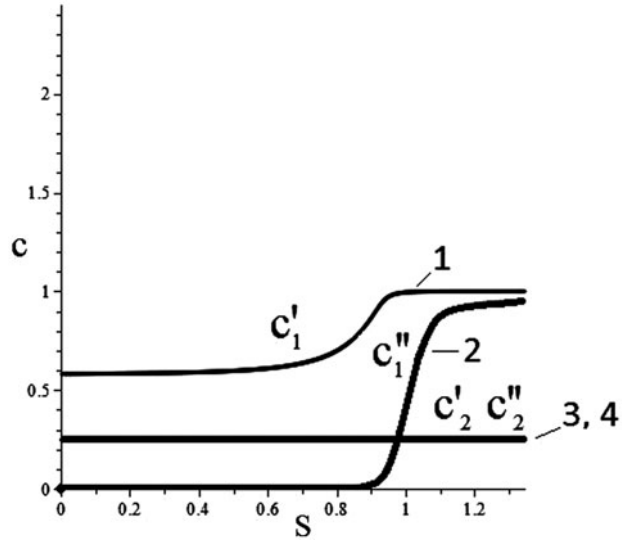

Figure 3. Dependence of the ligand concentrations c_i^{α} on the helix growth parameter S. The 1, 2, 3, and 4 lines describe ligand concentration dependence of the helix growth parameter S for c_1', c_1'', c_2' and c_2'', respectively. Results are obtained for the values of parameters: $r_1' = 2$, $r_1'' = 2$, $r_2' = 4$, $r_2'' = 4$, $K_1' = 2.9 \times 10^4$ M^{-1}, $K_1'' = 10^2$ M^{-1}, $K_2' = 9.6 \times 10^5$ M^{-1}, and $K_2'' = 10^7$ M^{-1}.

$$\begin{aligned}\frac{c_1' r_1' / 2}{1 - c_1' r_1' / 2} &= \frac{PK_1'}{2}\left[\frac{2D}{P} - 2(1-\vartheta)c_1' - \vartheta c_2'\right] \\ \frac{c_2' r_2'}{1 - c_2' r_2'} &= \frac{PK_2'}{2}\left[\frac{2D}{P} - 2(1-\vartheta)c_1' - \vartheta c_2'\right]\end{aligned} \quad (6)$$

If the total concentration of ligands in the solution is comparable with those for the phosphate groups $\frac{2D}{P} \sim 1$ and $PK_1' >> 1$, $PK_2' >> 1$, DNA–ligand complexes also exhibit both high-temperature and low-temperature denaturation (see Figure 4). At the same time, if binding of ligand to ss-DNA is suppressed, $K_1' = 0$ we have only heat denaturation with the substantial stabilization of helical DNA (see Figure 5). The higher binding affinity to double-stranded regions results the almost constant concentration of ligands bound with native DNA (see Figure 3). Simultaneously, at low temperatures the system seeks for the state with lower internal energy. In case of saturation for the ligands that are bound with ds-DNA the only option is to increase the number of ligands bound with ss-DNA (see Figure 3). Thus, the main reason of cold denaturation is the ligands ability to bind with single-stranded regions of DNA with the binding constants lower than those for the double-stranded regions.

Thus, the appropriate choice of the binding constants permits to fix the order parameter of the ds-DNA in the wide enough range of temperature conditions. This mechanism should be especially important for the control of polymer's nanocomposites crystallization (Grigoryan et al., 2014), where we need to cool the sample, but at the same time to keep the DNA molecules at the ordered state.

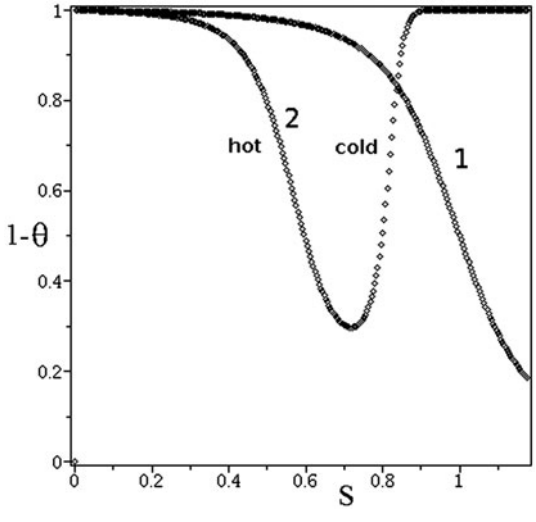

Figure 4. Dependence of the degree of denaturation $1-\theta$ on the helix growth parameter S. Line 1 is the denaturation curve for the pure DNA. Line 2 is the denaturation curve for $r_1' = 2$, $r_2' = 4$, $K_1' = 2.9 \times 10^4$ M^{-1}, and $K_2' = 11.7 \times 10^7$ M^{-1}.

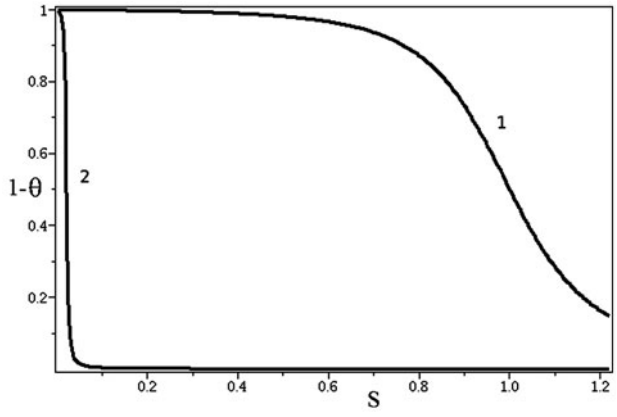

Figure 5. Dependence of the degree of denaturation $1-\theta$ on the helix growth parameter S. Line 1 is the denaturation curve for the pure DNA. Line 2 is the denaturation curve for $r_1' = 2$, $r_2' = 4$, $K_1' = 0$ M^{-1}, and $K_2' = 1.7 \times 10^7$ M^{-1}.

Conclusions

The biphasic behavior obtained above theoretically was observed experimentally (Guan, Shi, Li, Zhao, & Li, 2007) for the binding of dicationic Hoechst 33,258 and intercalator EtBr (Karapetian et al., 1996).

- The existence of both hot and cold denaturation transition is common for the ligands that bind with multiple binding modes at the certain relations between the binding constants.
- DNA complexes with two types of ligands having different binding parameters with ss- and ds-DNA exhibit both "hot" and "cold" denaturation.
- The range of high temperature exists, where the DNA–ligand complex occurs in the native state.
- The temperature of hot denaturation of DNA–ligand complex is substantially less than those for the pure DNA.

References

Badasyan, A., Tonoyan, Sh. A., Giacometti, A., Podgornik, R., Parsegian, V. A., Mamasakhlisov, Y. Sh., & Morozov, V. F. (2014). Unified description of solvent effects in the helix–coil transition. *Physical Review E, 89*, 022723–1–022723-10.

Barbi, M., Lepri, S., Peyrard, M., & Theodorakopoulos, N. (2003). Thermal denaturation of a helicoidal DNA model. *Physical Review E, 68*, 061909-1–061909-14.

Chalikian, T. (2003). Hydrophobic tendencies of polar groups as a major force in molecular recognition. *Biopolymers, 70*, 492–496.

Cule, D., & Hwa, T. (1997). Denaturation of heterogeneous DNA. *Physical Review Letters, 79*, 2375–2378.

Dubins, D. N., Lee, A., Macgregor, R. B. Jr., & Chalikian, T. V. (2001). On the stability of double stranded nucleic acids. *Journal of the American Chemical Society, 123*, 9254–9259.

Frank-Kamenetskii, M. D. (1997). Biophysics of the DNA molecule. *Physics Reports, 288*, 13–60.

Garbett, N. C., Ragazzon, P. A., & Chaires, J. B. (2007). Circular dichroism to determine binding mode and affinity of ligand–DNA interactions. *Nature Protocols, 2*, 3166–3172.

Garel, T., Monthus, C., & Orland, H. (2001). A simple model for DNA denaturation. *Europhysics Letters, 55*, 138–140.

Grigoryan, Z. A., Mamasakhlisov, Y. Sh., & Karapetian, A. T. (2014). Orientation order in DNA-containg polymer composites: The melting effect. *National Academy of Sciences of Armenia Reports, 114*, 123–129.

Guan, Y., Shi, R., Li, X., Zhao, M., & Li, Y. (2007). Multiple binding modes for dicationic hoechst 33258 to DNA. *Journal of Physical Chemistry B, 111*, 7336–7344.

Hayrapetyan, G. N., Iannelli, F., Lekscha, J., Morozov, V. F., Netz, R. R., & Mamasakhlisov, Y. Sh. (2014). Reentrant melting of RNA with quenched sequence randomness. *Physical Review Letters, 113*, 068101–1–068101-5.

Karapetian, A. T., Mehrabian, N. M., Terzikian, G. A., Vardevanian, P. O., Antonian, A. P., Borisova, O. F., & Frank-Kamenetskii, M. (1996). Theoretical treatment of melting of complexes of DNA with ligands having several types of binding sites on helical and single-stranded DNA. *Journal of Biomolecular Structure & Dynamics, 14*, 275–283.

Krishnamoorthy, G., Duportail, G., & Mely, Y. (2002). Structure and dynamics of condensed DNA probed by 1,1′-(4,4,8,-8-Tetramethyl-4,8-diazaundecamethylene)bis[4-[[3- methylbenz-1,3-oxazol-2-yl]methylidine]-1,4-dihydroquinolinium] tetraiodide fluorescence. *Biochemistry, 41*, 15277–15287.

Larsson, A., Carlsson, C., Jonsson, M., & Albinsson, B. (1994). Characterization of the binding of the fluorescent dyes YO and YOYO to DNA by polarized light spectroscopy. *Journal of the American Chemical Society, 116*, 8459–8465.

Lipscomb, L. A., Zhou, F. X., Presnell, S. R., Woo, R. J., Peek, M. E., Plaskon, R. R., & Williams, L. D. (1996). Structure of DNA-porphyrin complex. *Biochemistry, 35*, 2818–2823.

Mikulecky, P. J., & Feig, A. L. (2002). Cold denaturation of the hammerhead ribozyme. *Journal of the American Chemical Society, 124*, 890–891.

Mikulecky, P. J., & Feig, A. L. (2004). Heat capacity changes in RNA folding: Application of perturbation theory to hammerhead ribozyme cold denaturation. *Nucleic Acids Research, 32*, 3967–3976.

Munoz, V., & Serrano, L. (1997). Development of the multiple sequence approximation within the AGADIR model of alpha–helix formation: Comparison with Zimm–Bragg and Lifson-Roig formalisms. *Biopolymers, 41*, 495–509.

Nelson, S. M., Ferguson, L. R., & Denny, W. A. (2007). Non-covalent ligand/DNA interactions: Minor groove binding agents. *Mutation Research, 623*, 24–40.

Niidome, T., Ohmori, N., Ichinose, A., Wada, A., Mihara, H., Hirayama, T., & Aoyagi, H. (1996). Binding of cationic a-helical peptides to plasmid DNA and their gene transfer abilities into cells. *Journal of Biological Chemistry, 272*, 15307–15312.

Poland, D., & Scheraga, H. A. (1966). Phase transition in one dimension and the helix–coil transition in polyamino acids. *Journal of Chemical Physics, 45*, 1456–1464.

Poland, D. C., & Scheraga, H. A. (1970). *The theory of helix–coil transition*. New York, NY: Academic Press.

Privalov, P. L. (1990). Cold denaturation of protein. *Critical Reviews in Biochemistry and Molecular Biology, 25*, 281–306.

Reddy, B. S., Sharma, S. K., & Lown, J. W. (2001). Recent developments in sequence selective minor groove DNA effectors. *Current Medicinal Chemistry, 8*, 475–508.

Reha, D., Kabelac, M., Ryjacek, F., Sponer, J., Sponer, J. E., Elstner, M., … Hobza, P. (2002). Intercalators. 1. Nature of stacking interactions between intercalators (ethidium, daunomycin, ellipticine, and 4′,6-diaminide-2-phenylindole) and DNA base pairs. Ab initio quantum chemical, density functional theory, and empirical potential study. *Journal of the American Chemical Society, 124*, 3366–3376.

Takano, M., Nagayama, K., & Suyama, A. (2001). Investigating a link between all-atom model simulation and the Ising-based theory on the helix–coil transition: Equilibrium statistical mechanics. *Journal of Chemical Physics, 116*, 2219–2228.

Vedenov, A. A., Dykhne, A. M., & Frank-Kamenetskii, M. D. (1971). The helix–coil transition in DNA. *Uspekhi Fizicheskikh Nauk, 105*, 479–519.

Wartell, R. M., & Benight, A. S. (1985). Thermal denaturation of DNA molecules: A comparison of theory with experiment. *Physics Reports, 126*, 67–107.

Zimmer, Ch., & Wahnert, U. (1986). Nonintercalating DNA-binding ligands: Specificity of the interaction and their use as tools in biophysical, biochemical and biological investigations of the genetic material. *Progress in Biophysics and Molecular Biology, 47*, 31–112.