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Calculation of Melting Temperature and Transition Curve for Dickerson DNA Dodecamer on the Basis of Configurational Entropy, Hydrogen Bonding Energy, and Heat Capacity: A Molecular Dynamics Simulation Study

C. Izanloo[a], G.A. Parsafar[a,]*, H. Abroshan[a] and H. Akbarzade[a]
[a]*Department of Chemistry, Sharif University of Technology, Tehran, P.O. Box 11365-9516, Iran*

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A familiarity with denaturation process is highly significant in understanding the DNA replication, manipulation, and interactions involving DNA double helix stability. We have performed molecular dynamics simulation on B-DNA duplex (CGCGAATTGCGC) at different temperatures. At each temperature, configurational entropy was estimated using the covariance matrix of atom-positional fluctuations. By plotting the configuration entropy versus temperature, we calculated the melting temperature which was found to be 329.7 K. We also calculated the hydrogen bonding energy and heat capacity for the atoms participating in the hydrogen bonding between two strands of DNA. Moreover, their temperature dependencies were investigated to obtain the melting temperature which was found to be 330.9 K. Finally, by comparing the melting temperature and the shape of the transition curve obtained from different methods, it is concluded that the stacking interactions affect the shape of transition curve, while the hydrogen bonding and columbic interactions determine the position of the melting point temperature.

Keywords: DNA, Configurational entropy, Melting temperature, Molecular-dynamics

INTRODUCTION

For interacting particles, like atoms in an organic molecule, entropy is both a measure of disorder (spread of coordinates in the accessible phase-space) and of correlation between the atomic displacements. The conformations of macromolecules, such as proteins and nucleic acids, play an essential role in their biological functions. Since the configurational entropy is supposed to be quite crucial in many functions (*e.g.*, DNA denaturation, drug-DNA binding), considerable effort has been devoted to developing appropriate methods for its evaluation.

Molecular dynamics (MD) simulations are well suited to investigate the structural, dynamic, and thermodynamic properties of macromolecules [1-3]. MD simulations of nucleic acids have been reported by several groups, demonstrating results that reproduce the solution NMR data reasonably well [4-6]. During the past decades, the calculation of accurate free energy differences from molecular simulations has become possible in practice. In contrast, the reliable estimation of entropies and entropy differences from such simulations is still a difficult task [7-13]. The estimation of configurational entropy from molecular dynamics trajectories was first proposed by Karplus and Kushick using a quasiharmonic method [14]. The method was formulated in terms of internal (non-Cartesian) coordinates, which was not easily applicable. This approach was extended and applied to various biomolecular systems [15-17]. A decade later, Schlitter [18] introduced a heuristic formula, based on Cartesian coordinates, to compute an upper bound to the

*Corresponding author. E-mail: Parsafar@sharif.edu

absolute entropy of a molecule from a simulation trajectory. Calculation of the configurational entropy change of DNA is not currently feasible computationally due to the size of the double helix. Nonetheless, an assessment of the configurational entropy can be made from an MD trajectory based on the covariance matrix σ of the Cartesian atom-positional fluctuations. This method was successfully tested for biomolecular simulations of peptide folding [19,20] and applied to simulations of protein molten globule states [21].

Recently, Andricioaei and Karplus [22] revised the quasiharmonic approach to allow for the use of Cartesian coordinates. One advantage of the approaches based on the covariance matrix of atomic fluctuation, is the possibility to compute this quantity for different subsets of atoms or even some degrees of freedom. An analysis of the quasiharmonic assumption, corrections for the anharmonicity, and the second-order correlation effects have recently been reported [23]. Alternative formulations were proposed by Schlitter [18] and Andricioaei and Karplus [22], which resulted in very similar entropy estimations [23-26]. We have used the approach based on the covariance matrix of atomic mass-weighted fluctuations, because it allows not only the calculation of the configurational entropy of the entire chain but also the calculation of the configurational entropy for different subsets of atoms or degrees of freedom. For example, Jozˇica Dolenc *et al*. only considered the entropy change due to the change in ligand flexibility for calculation of configurational entropy change of Netropsin and Distamycin upon DNA minor-groove binding [27]. Shang-Te D. Hsu *et al*. calculated the configurational entropy changes of HIV-1 Env gp120, its receptor CD4, and their complex based on three different sets of atoms [28]. Presently, there is a growing interest in measuring [29-31], calculating [32-38] and ultimately controlling the changes in configurational entropy on binding.

The structure and dynamics of DNA are the key to understanding the biological effects of DNA and have been subjected to extensive theoretical studies for a long time. One feature of DNA that has attracted noticeable attention is its thermal denaturation, *i.e.*, the transition from the native double-helix B-DNA to its melted form, in which the two strands spontaneously separate upon heating [39], because it provides an example of a one-dimensional phase transition. Experiments have shown that this transition is very sharp, which suggests that it could be first order [40]. The simplest strategy for the characterization of DNA denaturation is that of the melting temperature, T_m, the temperature at which half of the melting has taken place.

It is well known that because of polyionic nature of DNA, solvent counterions are required for its stability. We performed DNA dynamics simulation in water medium in the absence of any counterions. Surprisingly, at zero concentration of counterions, a dodecamer DNA duplex appears to be in a metastable state. MacKerell has reported a no-salt DNA simulation with periodical boundaries and a 13 Å cut-off for the treatment of long range electrostatic interactions [41]. MacKerell indicated that stable structures can be achieved using atom-based truncation schemes for the treatment of the electrostatic interactions. Therefore, a significant portion of phosphate charge was neutralized with water molecules hydrating the DNA. Mazur performed DNA dynamics in a water drop without any counterions and cutoffs applying periodical boundary conditions [42]. He concluded that DNA dynamics virtually do not change and the fine DNA structure remains similar to that observed in other calculations and experiments.

The aim of this study is to investigate the configurational entropy, hydrogen bonding (hb) energy, and heat capacity of a 12 base-pairs (bp) segment of DNA at different temperatures to obtain T_m. Simulations were carried out on a B-form sequence d(CGCGAATTCGCG), known as Drew-Dickerson oligomer, which has been extensively studied both structurally and theoretically [43], because of containing the underlined EcoRI binding sit (CGCGAATTCGCG) and the central AATT sequence which constitutes a feature -- spine of hydration -- stabilizing B-form DNA. We have used an approach which is based on the covariance matrix of atomic mass-weighted fluctuations, because it allows for the calculation of the configurational entropy for different subsets of atoms or degrees of freedom. We have computed the H-bond energies (angle and distance dependencies) according to the explicit hydrogen-bond term previously used in some versions of CHARMM force field. Finally, we shall compare the T_m and shape of transition curves obtained from the configurational entropy, hydrogen bonding energy, and heat capacity, to scrutinize the impact of different interactions on the denaturation process.

COMPUTATIONAL PROCEDURES

MD simulations were carried out in hexagonal cell with the periodic boundary conditions imposed on the xy-plane and z-direction. Simulations were run on a B-form sequence d(CGCGAATTCGCG) employing Protein Data Bank (PDB) crystal structures (1bna.pdb) [44]. This DNA was solvated with 3626 TIP3P water molecules which allowed for a 10 Å-shell of water around the solute. The MD simulation was carried out at seven different temperatures, within the range of 280-400 K with 20 K intervals, in the *NPT* ensemble. For each system, 7 ns of MD simulation were run. An integration time step of 2 fs was used. Each MD simulation was carried out at a constant temperature and pressure (1 atm) using the Langevin dynamics. Long range electrostatic interactions were started using the PME (particle mesh Ewald) approach and the cut-off distance for van der Waals interaction was 12 Å. All simulations were carried out using version 27 of the CHARMM force field [45,46] and the molecular dynamics program NAMD 2.6 [47]. The cell dimensions were 42.5 × 46.9 × 63.9 $Å^3$. Each system contained 11636 atoms.

ENTROPY CALCULATIONS

Configurational entropy calculations were done following the formulation by Schlitter [18], which provides an approximate [23] upper bound to the absolute entropy *S*:

$$S < S_{\text{Schlitter}} = \frac{1}{2} k_{\text{B}} \ln \det \left[\underline{\mathbf{1}} + \frac{k_{\text{B}} T e^2}{\hbar^2} \underline{\mathbf{M}}\,\underline{\boldsymbol{\sigma}} \right] \tag{1}$$

where k_B is Boltzmann factor, *T* is the absolute temperature, e is Euler's number, $\hbar$ is Planck's constant divided by 2π, $\underline{\mathbf{M}}$ is a 3*N*-dimensional diagonal matrix containing the *N* atomic masses of the solute atoms for which the entropy is calculated, and $\underline{\boldsymbol{\sigma}}$ is the covariance matrix of atom-positional fluctuations with the elements:

$$\sigma_{ij} = \langle (x_i - \langle x_i \rangle)(x_j - \langle x_j \rangle) \rangle \tag{2}$$

where x_i is the Cartesian coordinate of atom i, considered in the entropy calculation. Entropy calculations were made on trajectory structures save every 1 ps. Since the rigid body motion would not remove automatically during the calculation, fitting procedures are usually adopted [19]. In this work, however, we did not apply a least-squares fitting to exclude overall translational and rotational motions in the calculation of the configurational entropy [19], because we would rather calculate the transition curve from entropy data, so that, if all the rigid body (translation and overall rotation) were kept in one data, it would be repeated in the others, as well.

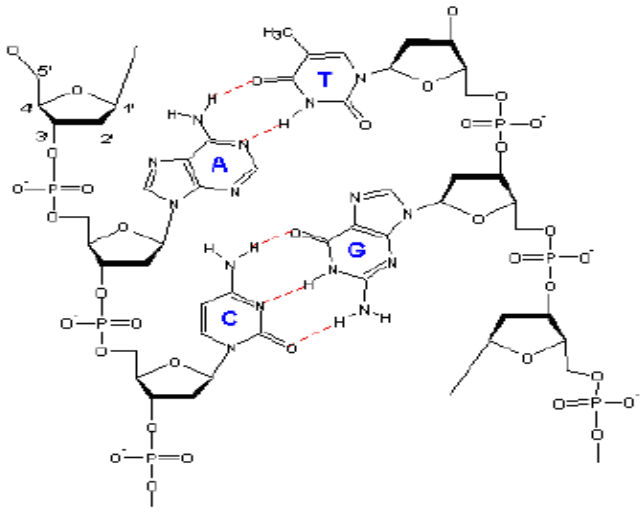

Fig. 1. A portion of primary structure of DNA, only with two base pairs. Hydrogen bondings (red line) between the pairs of Adenine, Thymine, Guanine, and Cytosine are shown.

Figure 1 depicts a portion of the primary structure of DNA, only with two base pairs. Four different bases in DNA are shown in this figure. A stands for adenine, G for guanine, C for cytosine, and T for thymine. Subsets of atoms that were used in the calculation of the configurational entropy were those that participated directly in hydrogen bonding in 5′-GCGTTAACGC-3′ sequence. For example, O, N and N atoms in guanine. Hydrogen atoms were not included in this calculation because of their high fluctuation and being poorly approximated by the harmonic oscillator. The backbone and the terminal base pairs exhibited big movements, partially as a result of their extensive contact with the surrounding solvent molecules, hence, their exclusion from the calculation.

RESULTS

The structural stability in molecular dynamics simulations is often characterized by the RMSD of atomic positions from a suitable reference structure. The calculated RMSDs at some temperatures are presented in Fig. 2. On the basis of this figure, we consider the initial time of 2000 ps (pico second) needed to reach the equilibrium state. As shown in Fig. 2, it is obvious that the RMSD values increase with temperature.

We have calculated the entropy on the basis of the approach described in the previous section. Figure 3 shows the configurational entropy for the DNA segment at different temperatures. The fluctuations in entropy are indicative of the exploration of phase space by the DNA; each jump opens up a new region of phase space. Amino acids are flexible, so fluctuations in the configurational entropy are large. The entropy increases within the temperature range of 280-400 K, but the increase within the range of 320-340 K is significantly bigger than that for the other ranges.

The convergence of entropy can be easily seen in Fig. 3 after some period of time. We have shown the equilibrium entropy for each temperature with a point in Fig. 4, but the line, which is fitted them with a mathematical method (Spline estimation and cubic constrained algorithm with the coefficient of determination $R^2 = 1$), is simply drawn to guide the eye. This is a transition curve which resembles a first order phase transition curve. Inflection point of this curve turned out to be 329.7 K which was the melting temperature for the DNA

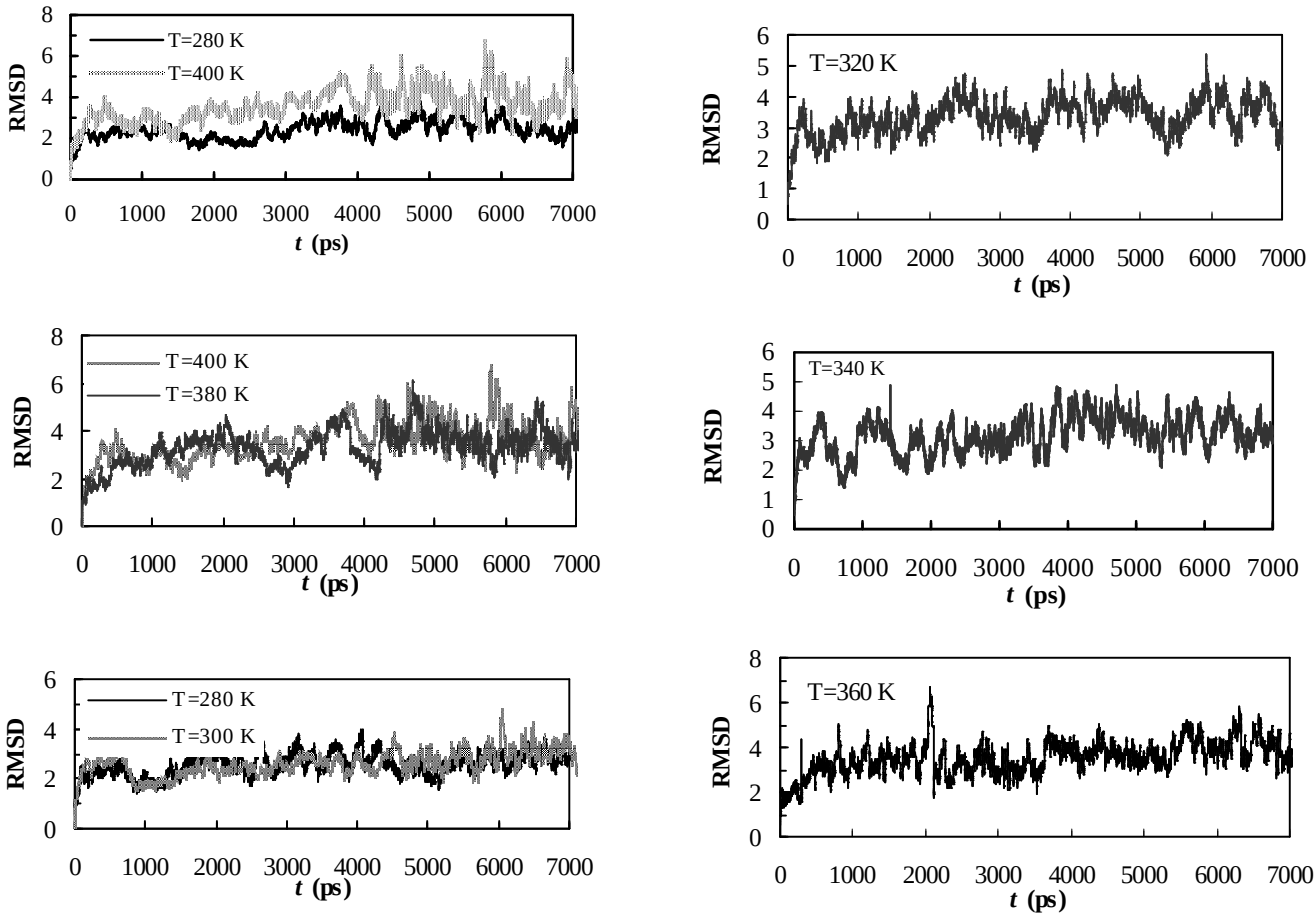

Fig. 2. Atom-positional RMSD of trajectory structures from the initial structures within 7-ns simulations at given temperatures.

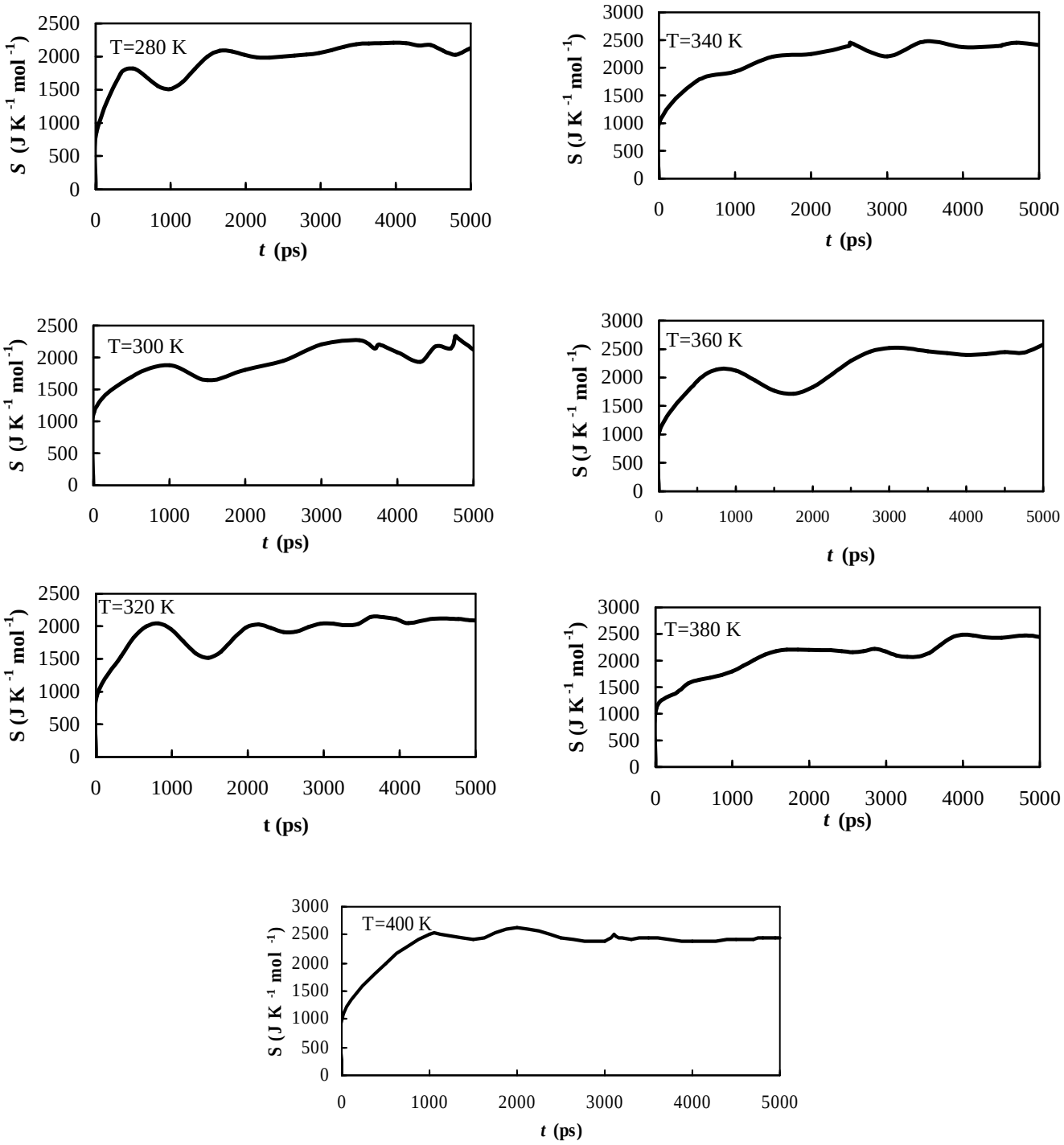

Fig. 3. Calculated configurational entropy for those atoms participating in the H-bonding between two strands for Dickerson DNA in water medium.

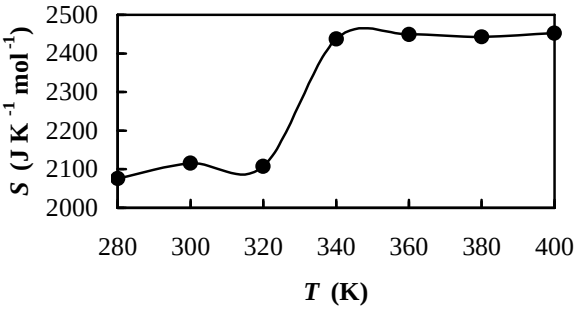

Fig. 4. The calculated configurational entropy *vs*. *T* to estimate the melting temperature obtained from simulation. The simulation data are fitted by a cubic constrained spline with $R^2 = 1$.

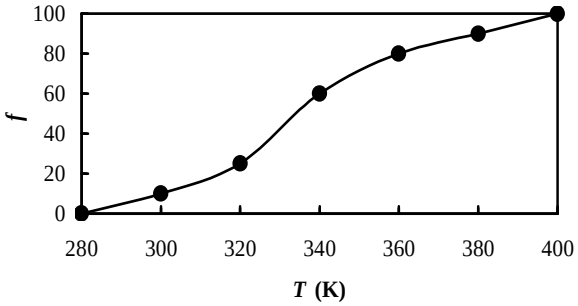

Fig. 5. Fraction of denatured bases (*f*) *vs*. temperature. The points are connected to each other by spline estimation method and cubic constrained algorithm with $R^2 = 1$.

segment used in the simulations. We put the segment in water medium without adding any cations. Therefore, Coulomb forces among phosphate groups were present. The melting temperature experimentally measured for Dickerson DNA was 341 K [48] in the presence of 1 M NaCl. Hence, the significance of Columbic interactions is obvious and the counterions stabilize it by neutralizing the negative charges of DNA, so, the 11 K difference in T_m between the experimental and simulation data may be attributed to the segment stabilization by counterions.

The entropy jump shown in Fig. 4 is related to the disruption of interactions (H-bond and stacking interactions) between base pairs. Therefore, two strands of DNA separated out from each other at high temperatures. As the two strands become further apart, water molecules can penetrate into the interbase gaps and it may become energetically favorable to form H-bond with water molecules rather than between the strands [49], which leads to an increase in entropy.

Hydrogen Bonding Potential

For the stability of H-bond, two factors are important: the distance between donor-acceptor must be less than 3 Å and the angle of donor-H-acceptor must be approximately 160° [51]. At each temperature, we calculated the average distance of donor-acceptor and the average angle of donor-H-acceptor. Then, by taking into account the factors mentioned above, the fraction of denatured base-pairs, *f*, was calculated. Such calculations were done at seven different temperatures; the results are depicted in Fig. 5. This curve was somewhat broader than its experimental counterpart, particularly in the shoulder regions of the curve, because in simulation there is some arbitrariness in the molecular level for the definition of base pairing which influences only the shape of the curve, but not the melting temperature [50]. Based on the *f* curve, the melting temperature obtained was 330.9 K which was insignificantly different from the value 329.7 K, calculated from the configurational entropy (see Fig. 4).

We may calculate the hydrogen bonding energy for base pairs between two strands of DNA, that is, for the same selected atoms used to calculate the configurational entropy. We may use the functional form of the hydrogen bond potential energy as follows [51]:

$$E_{hb} = \left(\frac{A}{r_{AD}^{6}} - \frac{B}{r_{AD}^{4}} \right) \cos^4(\theta_{A-H-D}) \cos^2(\theta_{AA-A-D}) SW(r_{AD}, \theta_{AHD}) \quad (3)$$

where atoms AA, A, H, D denote acceptor antecedent, acceptor, hydrogen, and donor heavy atom, respectively, while $-B^2/4A$ and $\sqrt[6]{2A/B}$ are the well depth and optimal distance, respectively. Table 1 represents values of the parameters for the hydrogen bonding in nucleic acids [51]. Switching function SW, is applied to steadily decreasing E_{hb} (hydrogen bonding energy) to zero beyond a cut-off distance (>3 Å) and angle ($\theta_{AHD} > 160°$). We may measure the average distances and angles and then calculate E_{hb} from Eq. (3).

Figure 6 shows E_{hb} as a function of temperature. This curve

Table 1. The Values of Parameters for Hydrogen Bonding in Nucleic Acids, Taken from Reference [44]

Donor	Acceptor	E_{min} (kcal mol^{-1})	R (E_{min}) (Å)
N	N	-5.00	3.0
N	O	-4.90	2.9

Table 2. The Equilibrium Entropy and Hydrogen Bonding Energy Only for Atoms Involving in the Hydrogen Bonding Between two Strands, at Different Temperatures

T (K)	S (J K^{-1} mol^{-1})	E_{hb} (kcal mol^{-1})
280	2075.773	15938.43
300	2115.486	13307.68
320	2107.030	11129.59
340	2437.143	6881.945
360	2448.938	3612.439
380	2443.025	1735.651
400	2452.650	0

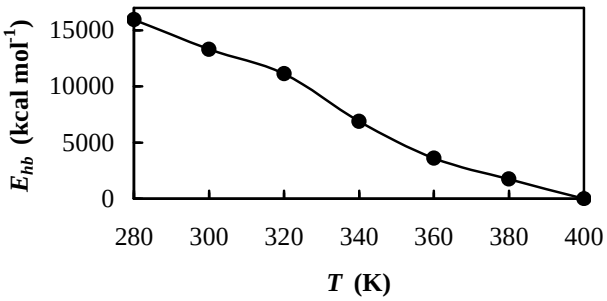

Fig. 6. Hydrogen bonding energy *vs*. temperature.

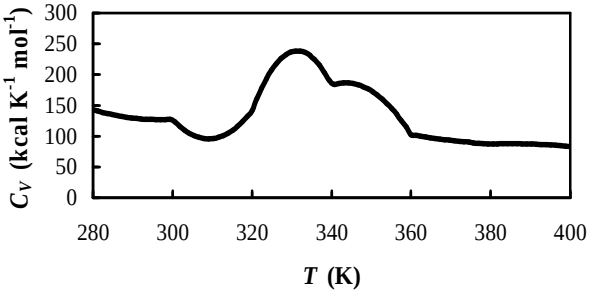

Fig. 7. The calculated isochoric heat capacity *vs*. temperature for the thermal denaturation of DNA molecule, the melting temperature is roughly at 330.9 K.

is somehow similar to a first order phase transition curve, except for its smooth change around T_m. It is probably due to the hydrogen bonding criteria.

Heat capacity can be computed on the basis of $C_v = (\partial E_{hb}/\partial_T)$. We have calculated S and E_{hb} merely for the atoms which contribute to the hydrogen bonding between two strands. The computed values for S and E_{hb} at different temperatures are summarized in Table 2. Figure 7 shows the heat capacity *vs*. temperature -- the data at each temperature are specified with a point. It is almost like a first order phase transition curve and its maximum point was found to be 330.9 K.

DISCUSSION

Molecular Dynamics simulation was carried out on the Drew-Dickerson oligomer with d(CGCGAATTCGCG) sequence and B-form structure. The simulations were run in *NPT* ensemble for 7ns at seven different temperatures within 280-400 K with the 20 K intervals. Then, for each temperature, the configurational entropy was calculated by Schlitter formula (see Fig. 3). The transition curve was computed on the basis of configuratinal entropy, (see Fig. 4). This curve shows a sharp slope at the transition temperature (at which 50 percent of interstrand hydrogen bonds break apart) and, in this regard, is similar to a first order phase transition. Schlitter formula is merely used for the atoms participating in the interstrand hydrogen bondings. We have used the distance A-D < 3 Å and the angle A-H-D < 160° criteria for hydrogen bonding to obtain the fraction of denatured base pairs (*f*), (see Fig. 5). The *f* curve had a jump at transition temperature which was relatively broader than that of entropy curve. The transition temperature that was obtained from the *f* curve and the entropy curve was found to be 330.9 K and 329.7 K, respectively. Dickerson DNA was set in pure water medium, so its high melting point temperature was a criterion for stability of Dickerson DNA. We may conclude that the spine of hydration phenomena stabilizes Dickerson DNA. We have excluded the counter ions from simulation box which leads to a difference between experimental and simulation melting points 341 K and 329.7 K, respectively. The presence of counterions in neutralizing the negative charges of the DNA is of significance in the DNA stabilization, because their presence increases the T_m by about 11 K.

We have calculated the average distance for A-D and average angle for A-H-D and AA-A-D, to obtain the hydrogen bond energy, E_{hb} (see Fig. 6 and Table 2) at different temperatures. The E_{hb} also shows a jump at the transition temperature but with a slightly broader and steady behavior. Finally, the hydrogen bonding energy was used to calculate the isochoric heat capacity, for which the results are shown in Fig. 7 and the melting temperature was found to be 330.9 K.

The interstrand interactions are distrupted by the melting [47]. Both nonbonding stacking and hydrogen bonding take part in the helix stability. Therefore, both interactions are weakened by the melting. In the calculation of the configurational entropy, shown in Fig. 4, both nonbonded stacking and hydrogen bonding interactions were taken into account. For this reason, the temperature-jump at the transition was sharp, and very much similar to the experiment. On the contrary, in the calculation of hydrogen bonding energy, and its contribution to C_v, shown in Figs. 6 and 7, respectively, the former interactions were excluded. For this reason, the sharpness in E_{hb} and the maximum C_v at the transition temperature were much smoother than those observed experimentally.

In summary, we may conclude that the columbic interactions displace the melting point, whereas, the no bonded stacking interactions affect the sharpness of energy and heat capacity at the transition temperature of the DNA.

We have performed DNA dynamics simulations in water medium in the absence of any counter ions. DNA stability under these conditions indicates that a significant portion of phosphate charge neutralization is performed by the water molecules hydrating the DNA. The stabilization of DNA due to counter ions awaits investigation.

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