PHYSICAL REVIEW B VOLUME 42, NUMBER 17 15 DECEMBER 1990-I

Criterion of thermal denaturation for modified-self-consistent-phonon-theory mean-field calculations in DNA polymers

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(Received 7 June 1990)

More exact mean-field modified-self-consistent-phonon-theory calculations are shown that give self-consistent solutions at temperatures above those that led to the loss of solution in earlier calculations and above the actual melting temperatures of several DNA polymers. We show that these high-temperature solutions are unphysical and still indicate a softening of the helical system that can be associated with nonsolidlike behavior. The temperatures for the onset of unphysical behavior are very close to the critical temperatures of earlier calculations.

The modified self-consistent phonon approximation of lattice-dynamics theory (MSPA) has been developed as a mean-field theory of hydrogen-bond melting of DNA polymers.[1-3] This melting or denaturation involves the breakage of hydrogen bonds that hold together the double helix and the unstacking between neighboring bases on opposite strands, thus resulting in a separation of the two strands of the double helix accompanied by a loss of double helical conformation. The MSPA appears to be quite successful in predicting melting temperatures of various DNA polymers.[2-4] In the MSPA description, a real DNA polymer is treated as a system of mean-field, self-consistent, lattice harmonic oscillators with a soft hydrogen-bond vibration. Such a theory is expected to fully describe the thermal behavior of a real DNA polymer below its melting temperature. At the melting temperature the theory breaks down, as the base separation destroys the hydrogen bonding and no harmonic behavior is retained in the hydrogen bonds.

A real DNA polymer is a double helix of two strands each composed of nucleotides (bases and ribose phosphate groups). These two separate strands are linked together through hydrogen bonds between complementary bases. Compared with other bonds, the hydrogen bonds are much weaker and are broken at thermal denaturation. It is therefore a good approximation to assume, at the temperature range considered, all the internal bonds other than hydrogen bonds are harmonic. The hydrogen bonding, however, must be modeled by a nonlinear potential. Baird[5] has shown that a Morse potential can be used as an effective potential for a hydrogen-bonded system under certain circumstances. In the calculations referred to above we used a Morse potential as the true H-bond potentials in the MSPA scheme.

The Baird-Morse potential was an effective potential in that it was calculated as a function of only the distance between the heavy atoms on the ends of the hydrogen bond. The instantaneous position of the hydrogen atom was assumed to have relaxed to a position that minimized the energy of all the separate elements of the hydrogen-bonded system consisting of the two heavy atoms and the hydrogen nucleus. The Baird-Morse potential is then appropriate for a system in which the motion of the heavy atoms is very slow compared to the motion of the hydrogen. This seems appropriate to the DNA case as the principal H-bond stretch behavior of the helix is at ≈ 85 cm^{-1} whereas hydrogen atom motion is associated with modes at $\approx 3000\ \text{cm}^{-1}$.

In MSPA an effective harmonic force constant is determined by a suitable average over the second derivative of the true potential. This effective force constant is used in a lattice calculation to calculate normal modes of the system. The normal modes are then used with thermal weighting to determine the mean fluctuation in displacement across the hydrogen bonds. This mean displacement is used along with the true potential to recalculate an effective force constant, etc. The system of calculations is iterated until self-consistency.

In the MSPA calculations on perfect repeating polymers in earlier work[3,4] the changes in normal mode spectrum, for later iterations, were not determined by actual diagonalization. The new frequencies were found by a Green-function calculation, and the new eigenvectors were calculated by first-order perturbation theory. This considerably shortened the calculation time. In these calculations complete breakdown of the ability to find a self-consistent solution occurred for calculations above a critical temperature. A different approach was used in other papers that simulated melting from a nucleation site.[6-8]

The breakdown of self-consistent solution indicated that the double helix was not capable of being described in the usual way. One usually assumes that a system of bonded molecules can be treated as a solid, a system of masses and springs. The springs are represented by the effective force constants between atoms and are derived for displacements of atoms in the interatomic potential. This description breaks down when no self-consistent force constant can be found. This implied no simple linear restoring force for small displacements from equilibrium and the resulting state of the system would be such that it contains highly nonlinear solidlike molecules or possibly liquidlike molecules in some sense. The correlation of this calculated critical temperature with observed melting temperatures for a whole host of DNA polymers was taken to be an indication that this nonlinear nonsolidlike transition was associated with, or a precursor to, helix melting. The internal softening of the H-bond restoring forces could well have enhanced the ability of a water molecule to dynamically penetrate the helix and lead to altered H-bond behavior associated with the melted or hydrated state.

The calculation follows a different course if one does a full diagonalization of the harmonic secular equations at each iteration step. This procedure forces a solution with the appropriate number of modes for any size effective force constant. We find no critical temperature above which self-consistency completely breaks down, but rather a continuous nonlinear softening of effective force constant coupled to continuous nonlinear increase in the magnitude of fluctuation. The calculated system is forced to follow a superheated behavior at temperatures well above the melting temperature of the physical DNA helices. In this case other criteria of melting have to be searched for and we describe these criteria and compare the results to the earlier calculations. It should be pointed out that no full diagonalization is possible for the symmetry breaking case of defected calculations.[6-8]

In this paper we show that, for a homopolymer poly(dA)-poly(dT), although self-consistent solutions exist at temperatures equal to and above the previously determined melting tmeperature, these solutions are unphysical. These solutions provide a decreasing hydrogen-bond mean energy with increasing temperature. The situation is analogous to the early theory of van der Waals,[9] who found a multivalued solution for the pressure as a function of volume and an unphysical region where pressure increased with increasing volume. This unphysical behavior was associated with a gas-liquid transition.

We have also carried out a similar investigation for poly(dG)-poly(dC). We found a basically similar phenomenon as for poly(dA)-poly9dT), except the critical temperature is higher than that given previously by the earlier method.[3]

Due to the helical symmetry of the DNA molecule,[10] the dimensionality of the equation of motion can be reduced to the number of degrees of freedom of a single unit cell of the polymer. A single unit cell consists of a base pair (AT or GC) and the associated sections of the backbone. We assume that the hydrogen atoms are bound to their parent atoms so their masses are added to the masses of their parent atoms. In this limit the unit cell has 41 atoms, and its dimensionality is 123. We further assume, in the temperature range considered, all the internal motions other than hydrogen bonding to be purely harmonic, and we choose a Morse potential as the true hydrogen-bond potential:[5]

$$V=V_0(1-e^{-a(r-r_0)})^2-V_0\ . \tag{1}$$

The parameters V_0, a, and r_0 are determined by the following information: (1) x-ray data for the length of each hydrogen bond at room temperature, (2) the room-temperature hydrogen-bond force constants obtained by using the Lippincott-Schroeder model,[11] and (3) the room-temperature dissociation energy of the hydrogen bond, also obtained from the Lippincott-Schroeder model.

Such a periodic chain of DNA homopolymer with the repeat until labeled by an index n can be represented by an effective phonon Hamiltonian:[1]

$$H_0=\sum_{n\alpha}\tfrac{1}{2}M_\alpha\dot{\mathbf{u}}^2_{n\alpha}+\tfrac{1}{2}\sum_{n\alpha,m\beta}\tfrac{1}{2}\mathbf{u}_{n\alpha,m\beta}\phi_{n\alpha,m\beta}\mathbf{u}_{n\alpha,m\beta} \tag{2}$$

where $\mathbf{u}_{n\alpha,m\beta}\equiv\mathbf{u}_{n\alpha}-\mathbf{u}_{m\alpha}$ and $\mathbf{u}_{n\alpha}$ is the dynamic displacement vector of the αth atom in the nth unit cell. The force constant $\phi_{n\alpha,m\beta}$ is to be determined self-consistently at different temperatures for the hydrogen-bond degrees of freedom. We assume that only the force constants for hydrogen-bond stretch change significantly, while other force constants do not change over the temperature range considered. Thus all the self-consistent calculations are in the subspace of the hydrogen-bond stretch coordinates. The other force constants are the valence and nonbonded force constants. The valence force constants are refined based on the spectral data above 400 cm^{-1}.[12-14] The nonbonded force constants are fitted to experimental Brillouin observations.[15-17] Here the van der Waals interaction is assumed to be effective between nearest-neighbor unit cells and Coulomb forces are included over one turn of the helix,[18] and we choose the electric charges from Miller.[19]

From the effective Hamiltonian (2), one obtains a secular equation:

$$(\underline{\Phi}-\omega^2\underline{I})\mathbf{q}=0 \tag{3}$$

where $\underline{\Phi}$ is the force-constant matrix at temperature T, and ω and $\mathbf{q}$ are eigenfrequency and eigenfunction in mass-weighted Cartesian coordinates, respectively. As is well known, the helical symmetry factors this equation into block diagonal form, thus both ω and $\mathbf{q}$ are functions of a phase angle θ in the one-dimensional Brillouin zone, $-\pi<\theta<\pi$. By the usual procedure of the MSPA theory,[1,2] one obtains the mean square stretch of each of the hydrogen bonds:

$$D_i=\frac{1}{\pi}\sum_{\lambda}\int_0^{\pi}d\theta\frac{|s_i^{\lambda}(\theta)|^2}{2\omega_\lambda(\theta)}\coth\left[\frac{\omega_\lambda(\theta)}{2kT}\right] \tag{4}$$

and the effective force constant of each of the hydrogen bonds:

$$\phi_i=\frac{\int_{-h_i}^{\infty}du\,e^{-u^2/2D_i}(d^2/du^2)V_i(R_i+u)}{\int_{-h_i}^{\infty}du\,e^{-u^2/2D_i}} \tag{5}$$

where λ is the index of λth band and $s_i^{\lambda}(\theta)$ is the projection of the eigenfunction of band λ at phase angle θ onto the ith hydrogen-bond stretch. We also assume the effective hydrogen-bond stretch is centered at a mean position determined by the following condition:

$$V_i(R_i(T)+\mu_i(T))=V_i(R_i(T)-\mu_i(T)) \tag{6}$$

where $R_i(T)$ is the mean hydrogen-bond length and $\mu_{(T)}$ the effective hydrogen-bond stretch amplitude which is chosen as the full width at half maximum of the distribution function $\exp(-u^2/2D_i)$:

$$\mu_i(T)=2[2D_i(T)\ln 2]^{1/2} \ . \tag{7}$$

The lower limit of the integral in (5) is defined as $-h_i=R_m^i-R_i$, with $R_m^i=r_0^i-(1/a)\ln 2$ being the point where the hard core is struck.

Finally, from the effective Hamiltonian (2), we easily obtain the mean potential energy of each of the hydrogen bonds as

$$\langle V_i \rangle = \tfrac{1}{2}\phi_i D_i \ . \tag{8}$$

We now consider a B conformation poly(dA)-poly(dT). This DNA polymer has two hydrogen bonds in each unit cell, one is the bond adjacent to the major groove [N(6)—H—O(4)] and the other is the bond adjacent to the minor groove [N(1)—H—N(3)]. The Morse parameters and room-temperature force constants of these two bonds are displayed in Table I.

We evaluate the mean potential energy of these two hydrogen bonds by the following two approaches.

1. The secular equation is solved by first-order perturbation method. This is the method used before for those calculations on perfect homopolymers and copolymers.[3,4] One defines a $\underline{C}$ matrix which is the difference of the force-constant matrix: $\underline{C}=\underline{\Phi}-\underline{\Phi}_0$ caused by the change of hydrogen-bond force constants with changing temperature. The corresponding new eigenfrequencies are given by the equation $\det[1-\underline{g}(\omega^2)\underline{C}]=0$, where $\underline{g}$ is the Green function: $\underline{g}=[\omega^2-\underline{\Phi}_0]^{-1}$. The new hydrogen-bond eigenfunctions can be given as

$$\tilde{s}_i^{\lambda}(\theta)=s_i^{\lambda}(\theta)=\sum_{\gamma\neq\lambda}\sum_j \frac{s_j^{\gamma *}(\theta)c_j s_j^{\lambda}(\theta)}{\tilde{\omega}_{\lambda}^2(\theta)-\omega_{\lambda}^2(\theta)} s_i^{\gamma}(\theta) \ . \tag{9}$$

The critical temperature at which instability occurs is 329 K. We can extend the Green-function perturbation results to higher temperature by (1) using the second-order perturbation in calculating the new eigenfunctions and (2) using bisection methods to search for the zeros of $\det(1-\underline{g}\underline{C})$ within a given tolerance. In most of the previous calculations, the zeros of $\det(1-\underline{g}\underline{C})$ are computed based on a linear interpolation which may introduce certain errors in the new frequencies. The mean potential energy of the two hydrogen bonds calculated here is in the temperature range of 293–363 K.

2. The secular equation is solved exactly. This is done by directly diagonalizing the secular equation to obtain new eigenfrequencies and eigenfunctions at any iteration and a given temperature. Unlike the situation in the first-order perturbation calculation, the solutions of the secular equation are stable at least up to a temperature as high as 513 K. Comparing the results of these two approaches, one finds that they agree very well at temperatures below 329 K. Starting from 329 K the mean square stretch obtained by the first-order perturbation calculation deviates from that of the exact calculation; the former becomes larger and larger than the latter. The mean potential energy of the two hydrogen bonds calculated here is in the temperature range of 293–403 K.

TABLE I. Morse parameters and room-temperature hydrogen-bond force constants of poly(dA)·poly(dT).

Bond	a (Å $^{-1}$)	V_0 (mdyn Å)	r_0 (Å)	ϕ (mdyn Å $^{-1}$)
N(6)—H—O(4)	2.713	0.019 59	2.698	0.1166
N(1)—H—N(3)	2.402	0.017 02	2.782	0.1147

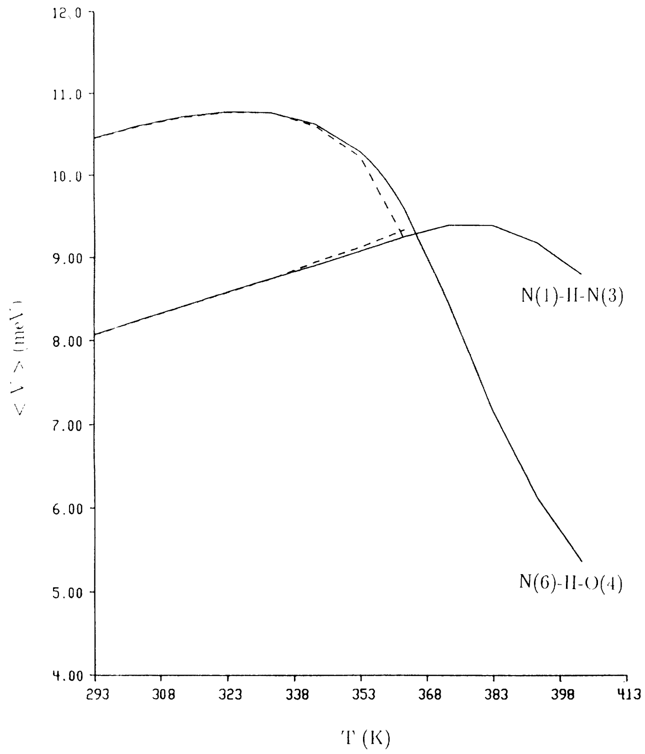

FIG. 1. Plot of the mean potential energy of the two hydrogen bonds of poly(dA)·poly(dT) vs temperature. The solid lines are from the exact calculation, and the dashed lines are from the first-order perturbation calculation.

The results of the two approaches are displayed in Fig. 1. As expected, the two approaches give the same results at temperatures below 329 K, and even at higher temperatures they do not differ too much, indicating the mean potential energy is a less sensitive quantity than other parameters. However, the most prominent feature is the existence of an anomalous region where the mean potential energy decreases with temperature. The anomaly first occurs at 329 K, where the potential energy of the major groove begins to drop from its peak at 328 K. The solutions of the secular equation at temperatures equal to and higher than 329 K are unphysical, as physically the mean potential energy of a harmonic system should be a monotonically increasing function of temperature. This implies the MSPA theory for poly(dA)-poly(dT) fails in some sense at temperatures equal to and above 329 K.

The anomalous behavior of the mean potential energy of the hydrogen bonds at temperatures equal to and higher than 329 K is actually a direct result of a more rapidly decreasing hydrogen-bond force constant than the increasing rate of the corresponding mean square stretch over the temperature range. Since the hydrogen-bond force constants are consistently adjusted to the true effective potential of the hydrogen bonds, namely, the Morse potential, the unphysical result of the mean potential energy of the hydrogen bonds means this adjustment physically breaks down at 329 K. Hence the MSPA theory fails at temperatures equal to and higher than this critical temperature, even though self-consistent solutions exist mathematically at higher temperatures. The Morse potential can be used in simulations for both solid and liquid systems. Since it is bounded, i.e., approaches zero at large distances, it can lead to melted or liquidlike behavior. The harmonic or effective harmonic potential is unbounded, i.e., approaches infinity for large displacements regardless of the size of the effective force constant. This is a potential that can only be associated with bound systems that cannot wander away from each other. The breakdown in the ability of a MSPA theory to sensibly represent a bound system is again an indication of an essential thermal-induced softening of the system that can be a necessary precondition to melting of the system. The agreement in the temperature of this breakdown with that of the earlier work would argue those MSPA calculations can give indication of a softening of the system that correlates with observed melting of the physical system.

This work is supported by ONR Grant No. N00014-89-K-0115 and National Institutes of Health (NIH) Grant No. GM 24443.

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