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Phase transition of DNA compaction in confined space: Effects of macromolecular crowding are dominant*

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With a view of detecting the effects of macromolecular crowding on the phase transition of DNA compaction confined in spherical space, Monte Carlo simulations of DNA compaction in free space, in confined spherical space without crowders and in confined spherical space with crowders were performed separately. The simulation results indicate that macromolecular crowding effects on DNA compaction are dominant over the roles of multivalent counterions. In addition, effects of temperature on the phase transition of DNA compaction have been identified in confined spherical space with different radii. In confined spherical space without crowders, the temperature corresponding to phase transition depends on the radius of the confined spherical space linearly. In contrast, with the addition of crowders to the confined spherical space, effects of temperature on the phase transition of DNA compaction become insignificant, whereas the phase transition at different temperatures strongly depends on the size of crowder, and the critical volume fraction of crowders pertains to the diameter of crowder linearly.

Keywords: macromolecular crowding, Monte Carlo simulation, DNA compaction, phase transition

PACS: 87.15.Ak, 87.16.A–, 87.15.Cc, 87.14.G– **DOI:** 10.1088/1674-1056/ab5941

1. Introduction

DNA compaction, as for its biological importance[1,2] and the challenges to the current understanding of semi-flexible polymers,[3–5] has become the focus of many investigations,[6–11] in which a series of single molecule experiments concentrated on the dynamics of DNA compaction caused by multivalent counterions that the multivalent cation-dependent DNA toroid folded or unfolded step by step under tension,[6–11] the charge reversion in DNA compaction process[12,13] which has strong influences on the compaction by modulating the barrier for condensate nucleation, and the DNA compaction mediated by divalent counterions at different PH values.[14,15]

Concurrently, polyethylene glycol (PEG), bovine serum albumin (BSA) and dextran were used as crowders to mimic the macromolecular crowding in different confinement[16–18] and their effects on the complex phase transition of DNA compaction have been investigated thoroughly.[19–23] In a wider nanochannel, with increasing volume fraction of crowder, the conformation of DNA elongates and eventually condenses into a compact state; the corresponding threshold volume fraction of crowder is proportional to its size,[18,19] in contrast, when the cross-sectional diameter of the nanochannel was reduced to a relative narrow one, the compaction process was not observed.[19] The characterization of living cells that highly crowded macromolecules are encapsulated in micro-vesicles can be mimicked by the mixture of DNA and PEG within an aqueous micro-vesicle, which leads to phase segregation by depositing DNA near the vesicle surface and the phase separation process strongly depends on the vesicle size.[23]

All the reviews mentioned above highlight that effects of macromolecular crowding on the phase transition of DNA pertains to the colligative properties of the crowder and that DNA response to crowding is significantly dependent on the confinement. Nevertheless the dominant effects in the process of DNA compaction caused by multivalent counterions, confinement and macromolecular crowding have not been identified, to compare the effects between multivalent counterions and macromolecular crowding on the phase transition of DNA compaction in confined spherical space, the simulations about the phase transition of DNA compaction were carried out sequentially in free space, confined spherical space without crowders and confined spherical space with crowders.

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2. Model and simulation method

2.1. Simulation in free space

In free space, effects of space confinement and crowding effects were not considered and the condensed DNA was described by strong correlation model presented by Liu *et al.*,[24–27] in which the total energy can be summarized as

$$\xi_{\text{total}} = \sum_{i=1}^{N-1} \frac{\beta}{2}(\hat{t}_{i+1} - \hat{t}_i)^2 - \tilde{N}\Delta E, \tag{1}$$

where the first term on the right-hand side of Eq. (1) is the bending energy (ξ_{kp}), which is carried by the ensemble of segment orientations $\hat{t}_i$ of a given chain conformation. Here $\frac{\beta}{2}(\hat{t}_{i+1} - \hat{t}_i)^2$ with unit $k_{\text{B}}T$ indicates the bending energy for the ith vertex, where β, a dimensionless quantity, is the bending rigidity of the vertex and satisfies $\beta b = \alpha$, with $\alpha = 50.0$ nm and $b = 1.0$ nm being the persistence length of DNA and the segment length, respectively. The persistence length has been pointed out to be strongly dependent on temperature and its dependence is well approximated over temperature interval between 5 °C and 45 °C by the following function:[28]

$$\alpha = \left(\frac{2.31 \times 10^4}{T} - 30\right) \text{nm}, \tag{2}$$

which results in the temperature dependence of bending rigidity of DNA as $\beta = \frac{\alpha}{b} = (\frac{2.31\times10^4}{T} - 30)$ nm and will be used to detect temperature effects on the phases transition of condensed DNA in confined spherical space. Here T is the temperature in Kelvin.

The second term in the right-hand side of Eq. (1) is the attraction potential (ξ_{attr}) in the condensed configuration. In the buffer with multivalent counterions, to minimize the the electrostatic energy, condensed counterions arrange themselves in the ground state, verified by the results of optical tweezers and atomic force microscopy experiment,[10] such that a certain spacing exists between successive condensed counterions located on the DNA counter length. The conformation with condensed counterions can be expressed as $\cdots\ominus\cdots\oplus\cdots\ominus\cdots\oplus\cdots\ominus\cdots\oplus\cdots\ominus\cdots\oplus\cdots$, where $\oplus$ and $\ominus$ represent the condensed counterion and the negative part between the condensed counterions, respectively. The formation of the positive–negative complex can be identified by the range $\chi + \delta$ to $\chi - \delta$, where χ is the sum of the diameter of a DNA molecule and that of the multivalent counterions, while δ is the interduplex spacing fluctuation, which is approximately 10% of the interduplex spacing,[27] which originates from thermal fluctuation.[29]

Once DNA–DNA interduplex spacing between one condensed counterion and one nonadjacent negative part falls within this range, the attraction potential was reduced by ΔE, mainly determined by the valence and size of counterions.[27] In current simulation, the value of ΔE scaled by $k_{\text{B}}T$ was 10. $\tilde{N}$ was used to index the total number of the positive–negative complexes, so that the attraction potential (ξ_{attr}) in the condensed configuration can be expressed as $-\tilde{N}\Delta E$.

2.2. Simulation in confined spherical space without crowders

On the basis of the strong correlation model mentioned above, to detect the effects of confinement on the phase transition of condensed DNA, the DNA molecule incubated in buffer with multivalent counterions was confined within a spherical space as shown in Fig. 1(a). In current simulation, the spherical confinement was realized by an external potential $V_{\text{ext}}(r)$, that is,

$$\frac{V_{\text{ext}}(r)}{k_{\text{B}}T} = \begin{cases} 0, & (r \le R - 0.5d_i), \\ \infty, & (r > R - 0.5d_i), \end{cases} \tag{3}$$

which does not allow the DNA molecule to penetrate the spherical confinement space wall, where R is the radius of confined spherical space, r is the radial distance of the DNA molecule from the center of the spherical confinement space and d_i is the diameter of DNA molecule (d_{m}) which depends on the ion concentration in solution atmosphere.[30]

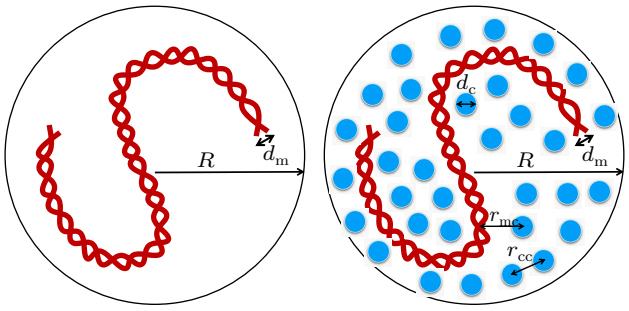


Fig. 1. Representation of condensed DNA in the confined spherical space without crowders (a) and that in the presence of crowders (b). R, d_{m}, d_{c}, r_{cc} and r_{mc} are the radius of confined spherical space, the diameter of DNA, the diameter of crowder, the distance between the center of crowders, the distance between the center of crowder and central line of DNA, respectively.

2.3. Simulation in confined spherical space in the presence of crowders

To further understand crowding effects on the phase transition of condensed DNA in confined spherical space, crowders with diameter d_{c} were added to the confined spherical space Fig. 1(b). The diameter of crowders generally used in experiments depends on the crowding agent, such as dextran, its diameter is related to its molecular weight (MW) as $d_{\text{c}} = 0.066 \times \text{MW}^{0.43}$ with MW in g/mol and d_{c} in nm.[31] The DNA molecule and crowders were still confined in a spherical space by the external potential $V_{\text{ext}}(r)$ in Eq. (3). Under these conditions, d_i indicates the diameter of DNA molecule (d_{m}) or that of crowder (d_{c}). The volume fraction of crowders in confinement is $\varphi = \frac{N_{\text{c}}(d_{\text{c}})^3}{8R^3}$, where N_{c} is the number of spherical crowders.

In the confinement, the excluded volume interactions between crowders and that between crowders and DNA molecule take the general form of repulsive Lennard–Jones potential[32,33]

$$\frac{V_{ij}(r)}{k_{\mathrm{B}}T} = \begin{cases} \varepsilon\left(\frac{r_{ij}^{12}}{r^{12}} - 2\frac{r_{ij}^{6}}{r^{6}} + 1\right), & (r \le r_{ij}), \\ 0, & (r \ge r_{ij}), \end{cases} \tag{4}$$

where ε scaled by $k_{\mathrm{B}}T$ is the strength of the repulsive Lennard–Jones potential and its value scaled by $k_{\mathrm{B}}T$ is 5.0, i and j can be either one segment of DNA molecule or crowder, r is the distance between crowder i and j or the distance from crowder i to the central-line of the segment j of DNA molecule and r_{ij} is the cut-off distance of repulsive Lennard–Jones potential, for the interaction between spherical crowders, $r_{ij} = 2^{\frac{1}{6}} d_{\mathrm{c}}$, while for that between spherical crowder and DNA molecule, $r_{ij} = 2^{\frac{1}{6}} \frac{d_{\mathrm{c}}+d_{\mathrm{m}}}{2}$. The size of spherical crowder used in current simulation ranges from 2.0 nm to 4.0 nm and the diameter of DNA molecule is 2.0 nm.

2.4. Simulation method

In current Monte Carlo simulation, the sampling of the DNA chain conformations is based on the following protocols, namely, a sub-chain is rotated by a random angle around the straight line connecting two randomly chosen nonadjacent vertices, and the other parallel rotation is that the left (right) part of the chain was rotated with respect to a random axis that passed through the randomly chosen vertices.

Metropolis criterion is applied to determine whether the new conformation is accepted. The crowders in the confinement space undertook random walk and the step size was controlled by a random number, so that the acceptance ratio in the simulation was within a reasonable range. As qualified by the density distribution function per particle,[22] $\rho(r_j) = \frac{N_j}{N_{\mathrm{c}} \frac{4\pi}{3}[(r_j+\frac{\Delta r}{2})^3-(r_j-\frac{\Delta r}{2})^3]}$ (where N_{c} is the number of crowders in the confinement, N_j is the j-th bin of the histogram at the radial distance r_j and the bin size Δr), the distribution of crowders depends on the size of confined spherical space, in comparably small confined spherical space, the crowders tend to distribute near the inner surface of confinement space, by contrast, the distribution tends to be homogeneous with the increasing size of confinement space. Our simulations were carried out in a relatively large confined spherical space.

3. Results and discussions

As shown in Fig. 2(a), from top to bottom, the simulations of DNA compaction are carried out in free space, confined spherical space without crowders and confined spherical space with crowders, sequentially, with the temperature at 307.75 K and the radius of confined spherical space being 20.0 nm. The scaled gyration radius defined by the ratio of gyration radius of condensed DNA corresponding to different Monte Carlo steps (R_{g}) and gyration radius of initial conformation of condensed DNA (R_0) is used to describe the conformation transition and their corresponding scaled gyration radius changing with Monte Carlo steps was reduced sharply, indicating that the effects of macromolecular crowding in confined spherical space on the conformation transition of condensed DNA are dominant over those of multivalent counterions in free space or confined spherical space without crowders.

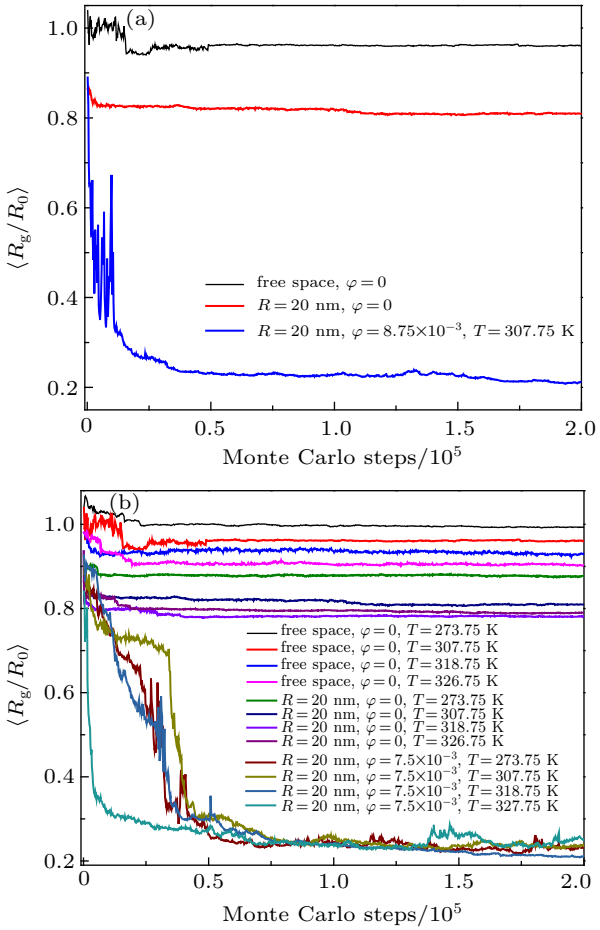


Fig. 2. Scaled gyration radius of condensed DNA changes with Monte carlo steps. (a) From top to bottom, the scaled gyration radii correspond to the simulations carried out sequentially in free space, confined spherical space without crowders and confined spherical space with crowders; the radius of the confined spherical space is 20.0 nm, the contour length of the condensed DNA is 299.0 nm, and the temperature is 307.75 K. (b) Effects of temperature on the scaled gyration with the temperature ranging from 273.75 K to 326.75 K. The radius of confined spherical space and the diameter of crowder are 20.0 nm and 1.0 nm, respectively.

Electric field was applied to introduce DNA molecule into the confined space,[17,19] and it is inevitable that its thermal effects will increase the temperature in the confined space; as tested by previous experiments and theoretical work,[28,34,35] the increase in temperature not only leads to the softness of DNA, but also promotes the DNA compaction process.[34,35] Effects of temperature on the phase transition of condensed DNA were determined and indicated in Fig. 2(b), where the four lines in the top, middle and bottom of Fig. 2(b) indicate

effects of temperature on the conformation transition of condensed DNA in free space, confined spherical space without crowders and confined spherical space with crowders. As temperature increases from 273.75 K to 326.75 K, the scaled gyration radii corresponding to the top four lines or the middle four lines in Fig. 2(b) were not reduced noticeably. By contrast, the scaled gyration radii of the bottom four lines in Fig. 2(b) reduce sharply and overlap each other, which further proves that macromolecular crowding has dominant effects on the conformation transition of condensed DNA over confinement, multivalent counterions and thermal effects from the electric field.

When the temperature increases from 273.75 K to 307.75 K, the reduction of the scaled gyration radius indicated by the middle four lines in Fig. 2(b) is obviously sharp compared to that of the top four lines, so it is reasonable to think that the conformation transition in confined spherical space without crowders within this temperature range is subjected to a more complex process than that in free space. Further investigation on the conformation transition of condensed DNA changing with temperature in the confined spherical space without crowders is carried out and the results are plotted in Fig. 3, in which the scaled gyration radius changing with temperature in different confined spherical space undergo a sharp transition, which is strongly dependent on the the radius of the confined spherical space and disappears when the radius is larger than 57.0 nm. The relation between the radius of confined spherical space and the temperature corresponding to the sharp transition is indicated in the inset that the temperature corresponding to the sharp transition linearly pertains to the radius of its confined spherical space.

The autocorrelation of the segment orientation is defined as $\langle \hat{t}(s) \cdot \hat{t}(s') \rangle = \exp(-\frac{|s-s'|}{\alpha})$, $|s-s'|$ represents the contour length between any two different points along the DNA molecule. As a powerful tool, it is often used to detect the structure of condensed DNA conformation. For a toroid structure, the autocorrelation of the segment orientation oscillates periodically and every period indicates one loop structure in the condensed conformation. Here the autocorrelation of the segment orientation is applied to identify the sharp transition in different confined spherical spaces. The autocorrelation of segment orientation in the confined spherical space with radius 20.0 nm was indicated in Fig. 3(b), where the autocorrelations of segment orientation corresponding to the temperature ranges from 303.75 K to 306.75 K and from 312.75 K to 315.75 K, respectively, indicate the ones before and after the sharp transition. Obviously, the autocorrelations of segment orientation in either temperature ranges overlap, but the ones after the sharp transition shift left in comparison with the ones before the sharp transition. This implies that the conformations of condensed DNA became more compact after the sharp transition, which is justified by the fact that the number of segment contained in every period of the autocorrelation after the sharp transition becomes less than the ones contained in every period of the autocorrelation before the sharp transition.

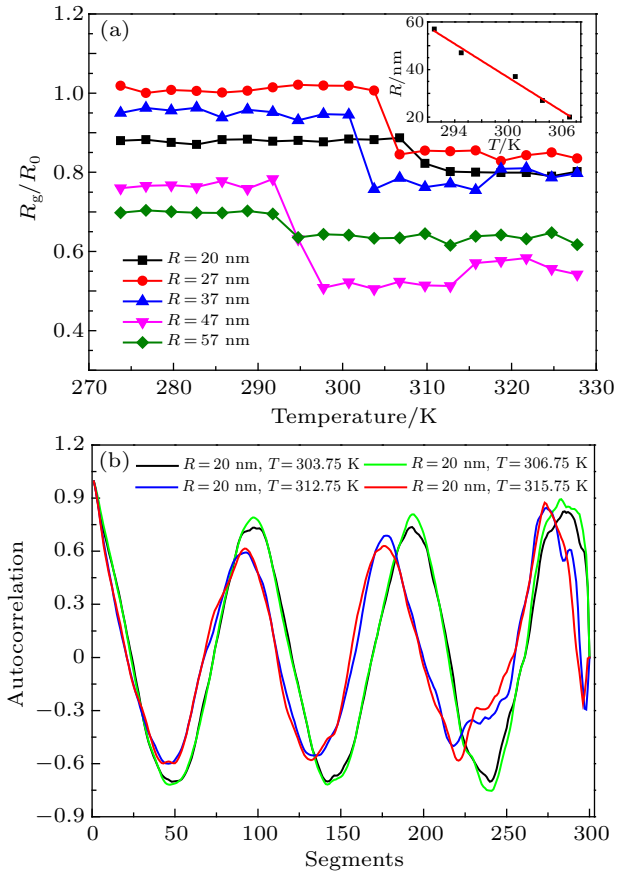


Fig. 3. Effects of temperature on the phase transition of condensed DNA in confined spherical space without crowders. (a) The phase transition of condensed DNA with contour length 299.0 nm in confined spherical space with radius ranging from 20.0 nm to 57.0 nm and the relation between the radius of confined spherical space and the temperature corresponding to the phase transition is indicated in the inset. (b) The autocorrelation of the conformation of condensed DNA with contour length 299.0 nm in confined spherical space with radius 20.0 nm before and after phase transition, the autocorrelation after phase transition shifts left as compared with the one before.

Effects of macromolecular crowding on the conformation transition of condensed DNA in confined spherical space is dominant over the effects of temperature and leads to the overlapping of scaled gyration radius of condensed DNA shown in the four lines in the bottom of Fig. 2(b). Further investigation of the macromolecular crowding effects on the transition of condensed DNA in confined spherical space at different temperatures are shown in Figs. 4(a)–4(c), with the scaled gyration radius of condensed DNA as a function of the volume fraction (φ) of crowders in confined spherical space and effects of the size of crowders on the transition of the condensed DNA conformation were first detected at different temperatures. The volume fraction corresponding to the starting point of the totally condensed state was defined as critical volume fraction (φ^*) and has been indicated by empty symbols in Figs. 4(a)–4(c). The condensed conformations with different-size crowders underwent phase transition and the critical volume fraction (φ^*) was dependent on the size of crowders linearly as

indicated by their corresponding inset. Then the linear dependence of critical volume fraction (φ^*) on the size of crowders at different temperature was reorganized in Fig. 4(d), no obvious difference was observed from their comparisons, which not only highlights the dominant effects of macromolecular crowding over other factors further, such as temperature, but also indicates that the thermal effects caused by electric field can be overlooked safely for the negligible effects of temperature on the phase transition in confined spherical space with crowders.

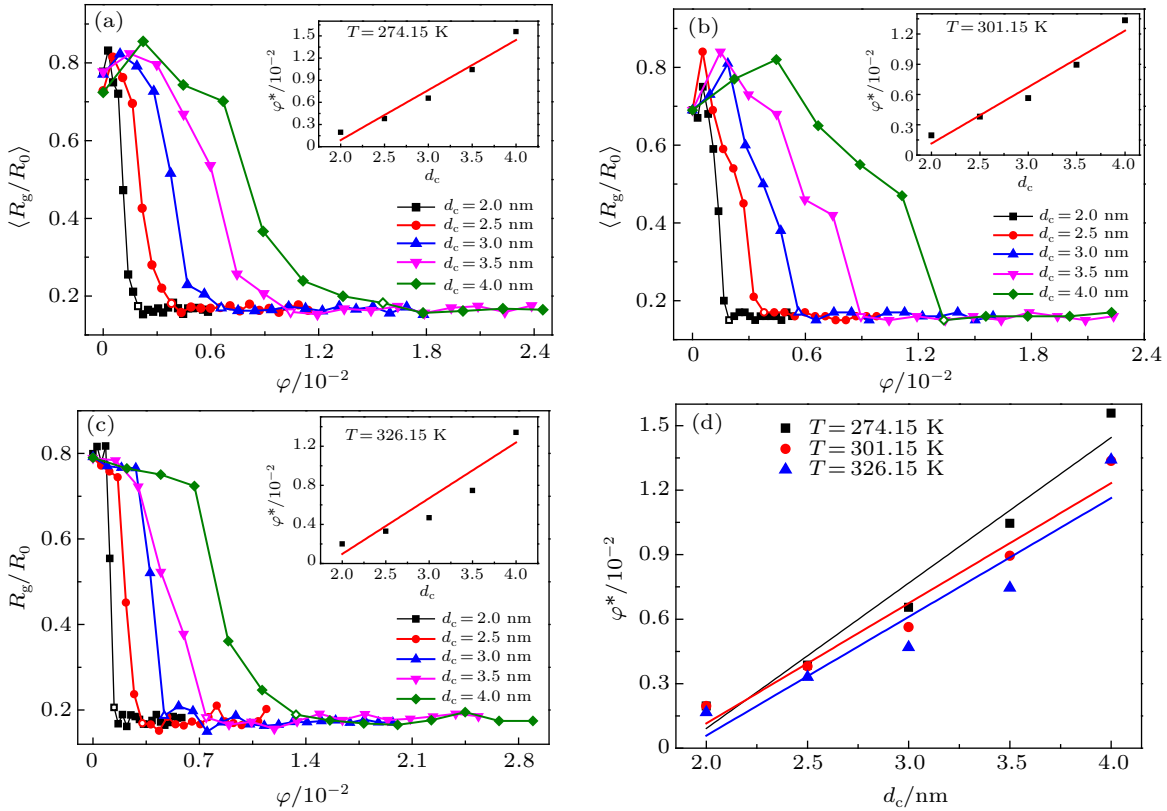


Fig. 4. Scaled gyration radius at different temperatures changes with the volume fraction φ of the crowders in the confined spherical space ((a)–(c)), the radius of confined spherical space is $R = 33.0$ nm, the size of crowders (d_c) ranges 2.0–4.0 nm, and the critical volume fraction φ^* corresponding to the different-size crowders is indicated by an open symbol. Their insets demonstrate that the critical volume fraction φ^* pertains to the crowder size proportionally. (d) The relations between the critical volume fraction φ^* and the crowder size at different temperatures are drawn together, which indicates that effects of temperature on phase transition are insignificant.

4. Conclusions

In current work, effects of macromolecular crowding on phase transition in confined space have been identified by Monte Carlo simulations performed in free space, confined spherical space without crowders and confined spherical space with crowders, respectively. The simulation results indicate that effects of macromolecular crowding on the conformation transition are dominant over those of multivalent counterion and confined space. In the confined spherical space with radius 20.0 nm, the macromolecular crowding is caused the scaled gyration radius to reduce by about 59% compared that in the same confined spherical space without crowders.

Effects of macromolecular crowding on the phase transition in confined space are dominant over effects of temperature. The condensed DNA with contour length 299.0 nm is confined in free-crowder spherical space with radius ranging from 20.0 nm to 57.0 nm, its corresponding scaled gyration radius changing with temperature undergoes a sharp transition and the temperature corresponding to every sharp transition pertains to the radius of spherical space linearly. When crowders are added to the spherical space, macromolecular crowding leads to obvious phase transition of condensed DNA with respect to volume fraction of crowders, whereby the phase transition depends on the size of crowder and its corresponding critical volume fraction is proportional to diameter of crowder linearly. In contrast, their reorganization of linear relations between the size of crowder and its corresponding critical volume fraction further indicates that temperature has no significant effects on the phase transition in the confined spherical space with crowders.

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