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Conformational transition of DNA induced by cationic lipid vesicle in acidic solution: spectroscopy investigation

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Abstract

The conformational transition of DNA induced by the interaction between DNA and a cationic lipid vesicle, didodecyldimethylammonium bromide (DDAB), had been investigated by circular dichroism (CD) and UV spectroscopy methods. We used singular value decomposition least squares method (SVDLS) to analyze the experimental CD spectra. Although pH value influenced the conformation of DNA in solution, the results showed that upon binding to double helical DNA, positively charged liposomes induced a conformational transition of DNA molecules from the native B-form to more compact conformations. At the same time, no obvious conformational changes occurred at single-strand DNA (ssDNA). While the cationic lipid vesicles and double-strand DNA (dsDNA) were mixed at a high molar ratio of DDAB vesicles to dsDNA, the conformation of dsDNA transformed from the B-form to the C-form resulting in an increase in duplex stability ($\Delta T_m = 8 \pm 0.4$ °C). An increasing in T_m was also observed while the cationic lipid vesicles interacted with ssDNA.

Keywords: Cationic lipid vesicle; Conformation; Spectroscopy; SVDLS

1. Introduction

Considerable interests in the DNA–cationic liposome complexes have been generated by the observation that certain aggregates between DNA and cationic lipid are efficient vehicles for delivery of foreign DNA or RNA into a wide variety of eukaryotic cells. While the mechanism of transfection with these agents is not well understood, the DNA–lipid complexes are thought to facilitate the transfer of DNA through cell membrane [1–6]. Thus, there are several fundamental interactions important in stabilization of cationic lipid-DNA complexes, in which electrostatic interaction between the cationic head groups and the negatively charged phosphate sites is thought to be the primary one [1]. Although the interaction between lipid and DNA has been investigated by enhanced resonance light scattering (RLS) [7], cryoelectron microscopy [8], atomic force microscopy (AFM) and DSC [9] etc., the physical characteristics, especially the conformations of DNA induced by lipid vesicles are poorly understood.

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There are two families of double-helical structures for DNA known as right-handed and left-handed. The familiar Watson–Crick B-form DNA is a right-handed double helix with 10 bp/turn. The C-form DNA also belongs to the B-form DNA family that has 9.33 bp per turn, and is rather like B-DNA in other respects [10]. The structures and their structural transitions between right-handed and left-handed and between different right-handed DNAs have been studied experimentally and theoretically [11,12].

Among several conformation measurements, circular dichroism (CD) is a powerful tool for solution samples. How to extract structure information from experimental CD data is a problem in the study. Singular value decomposition (SVD) is a powerful mathematical tool to decompose experimental CD spectra [13] and can also be considered as a basic step of the other CD analysis methods, which have been reviewed by several authors [13–15]. A combination of SVD with least squares, called singular value decomposition least square (SVDLS) analysis, is a new method for analysis of dynamic CD spectra. This method gives not only the number of components and their CD spectra, but also the fractional distribution of each component [16,17].

In this paper, we used dimethyldioctadecylammonium bromide (DDAB) lipid vesicles as a model biomembrane to study the conformational transitions of DNA induced by the interaction between DNA and small unilamellar vesicles (SUVs). The results showed DDAB vesicles induced a conformational transition of the DNA molecules.

2. Experimental and methods

2.1. Reagents

The double strand DNA (dsDNA), calf thymus DNA, was obtained from Sigma Chemical Co. (USA), single strand polynucleotides (ssDNA) 5′-d(CTGGGCTGCTTCCTAATGCAGGAGTCGC-AT)-3′ and 5′-d(ATATATATATATATATATATATAT-ATATATAT)-3′ were purchased from Sangon Co. (Shanghai, China). Didodecyldimethylammonium bromide (DDAB) was obtained from Aldich Co. (USA), and used without further purification. Stock solution of DNA were prepared by dissolving DNA in buffer solution and stored at 4 °C for more than 24 h with occasional gentle shaking to get homogeneity and used within 2 days. The concentrations of dsDNA were calculated according to the absorbance at 260 nm by using $\varepsilon_{\mathrm{dsDNA}} = 6600\ \mathrm{M}^{-1}\ \mathrm{cm}^{-1}$, and those of ssDNA were calculated by $\varepsilon_{\mathrm{ssDNA}} = 1 \times 10^4\ \mathrm{M}^{-1}\ \mathrm{cm}^{-1}$.

Chloroform was of analytical grade. Buffer solutions used in all experiments were prepared using analytical grade reagents: $Na_2HPO_4 \cdot 12H_2O$; $NaH_2PO_4 \cdot 2H_2O$; NaCl; and doubly purified water from Milli-Q system.

2.2. Sample preparation

For the preparation of DDAB vesicles, a dry film of 50 mg lipid was produced under rotary evaporation from a stock solution in chloroform, and then organic solvent was removed by purified nitrogen. The lipid film was hydrated to the desired concentration with 10 mM phosphate buffer, pH 6.8. The resulting multilamellar liposome suspension was sonicated for several hours (approx. 2 h in average) in a bath sonicator, until a clear suspension of SUVs was obtained [18]. The vesicle sizes of a few representative samples were determined by dynamic light scattering measurement on a DynaPro-MS/X dynamic light scattering instrument. The DDAB vesicles had diameters ranging from 40 to 70 nm. The final stock solution of DDAB vesicles was approximately 10.8 mmol l^{-1}.

Then DNA and lipid vesicles were gently mixed and incubated at room temperature for approximately 30 min to promote the formation of lipid vesicle-DNA complexes [19].

2.3. Spectroscopy methods

UV-Vis melting spectra were measured on a Carry 500 Scan UV-Vis-NIR Spectrophotometer (Varian, USA) using a 1.0 cm path length cell. The melting temperature was calculated by the software in the Carry WinUV software package (Varian, USA). CD spectra was measured using a 62A DS CD spectrometer (AVIV, USA) in a 1.0

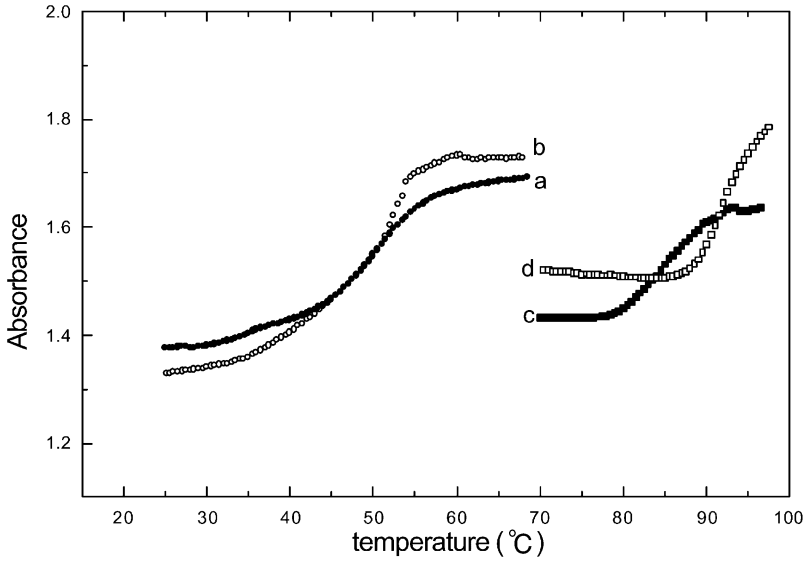

Fig. 1. UV melting of the thermal denaturation of: (a) ssDNA, 0.089 mmol l^{-1} 5′-d(ATATATATATATATATATATATATAT-ATAT)-3′; and (b) with DDAB vesicles at molar ratio 1.0; the thermal denaturation of (c) 0.073 mmol l^{-1} dsDNA; and (d) 0.092 mmol l^{-1} dsDNA with DDAB at molar ratio ([DDAB]/[DNA]) of five in pH 6.8, 5 mmol l^{-1} Na_2HPO_4–NaH_2PO_4 buffer, ionic strength = 0.1 mol l^{-1}.

cm path length of rectangular quartz cell at 25 °C, controlled by a thermoelectric cell holder (AVIV). Four scans were averaged per spectrum. Spectra of lipid–DNA complexes were subtracted from the background arising from the lipid vesicles alone every time. The spectra titration of DNA with DDAB vesicles was conducted by keeping the concentration of DNA constant, while varying the concentration of DDAB vesicles.

2.4. Singular value decomposition least squares analysis

To help ascertain the number of distinct forms of DNA present over a range of conditions, the CD spectral data were evaluated by singular value decomposition least squares analysis (SVDLS). In this analysis, several CD spectra were obtained over the same m wavelengths (m = total wavelengths). The spectra were grouped into series taken under identical conditions except for the changing of a single variable (the condition variables studied here are the molar ratios of DDAB vesicles to DNA). For SVDLS mathematical and computational details, see Zhu et al. [16,17].

3. Result and discussion

3.1. Stability of DNA–DDAB vesicles complexes

Fig. 1 displayed the plots of absorbance of nucleic acids at 260 nm (A_{260}) vs. temperature in the presence and absence of DDAB vesicles. 5′-d(ATATATATATATATATATATATATAT-ATATAT)-3′, can form double helix in buffer solution. In the absence of DDAB vesicles [curve (a) in Fig. 1], the thermal denaturation curve showed an obvious increase of A_{260} at approximately 50 °C that corresponded to the melting or helix-to-coil transition temperature (T_m). After adding DDAB vesicles to the solution at the molar ratio of DDAB vesicles to ssDNA 1.0, the T_m shifted to a higher temperature, giving ΔT_m (T_m of the complex $- T_m$ of the free DNA) of 3 ± 0.4 °C [curve (b) in Fig. 1]. The result showed that it made the thermodynamics stability of the helical form ssDNA increasing when interacted with the cationic lipid vesicles. The thermal denaturation curve of dsDNA [curve (c) in Fig. 1] showed T_m of 84 ± 0.2 °C. When DDAB vesicles were incor-

porated into dsDNA at the molar ratio of DDAB vesicles to dsDNA 5.0 [curve (d) in Fig. 1], the T_m shifted to a higher temperature, and the ΔT_m was 8 ± 0.4 °C. When DDAB vesicles were added to dsDNA solution, the cationic lipid vesicles also interacted with dsDNA by electrostatic attraction and tended to form complex [10–12,20,21,27]. As is known, if there is strong binding of ligand to the helical form of DNA, a very large increase in T_m should be observed [26]. This strong binding made the thermodynamics stability of DNA helix increasing [21–25]. The results all indicated that the cationic head groups of DDAB vesicles interacted with DNA strongly by electrostatic attraction when the DNA–DDAB vesicles complex was forming [6].

3.2. Circular dichroism study of nucleic acids–DDAB vesicles complexes

3.2.1. Circular dichroism of ssDNA–DDAB vesicles complexes

While the ssDNA, e.g. 5′-d(CTGGGCTGCTTCCTAATGCAGGAGTCGCAT)-3′, dissolved in buffer solution, it was in a random coil state. Its CD spectrum exhibited a strong positive Cotton effect at 278 nm corresponding to base stacking, and a weak negative Cotton effect at 248 nm corresponding to helicity [curve (a) in Fig. 2]. After adding DDAB vesicles to the solution, no obvious changes occurred on the spectra [curve (b)–(e) in Fig. 2]. But the ssDNA, 5′-d(ATATATATATATATATATATATATATATAT)-3′,can form double helix in buffer solution. Its CD spectrum showed strong negative Cotton effect at 247 nm and a weak positive Cotton effect at 265 nm [curve (a) in Fig. 3]. After adding DDAB vesicles to the solution, the negative Cotton effect at 247 nm corresponded to the helicity which was obviously increasing [Fig. 3, curve (b)–(d)]. The result showed that after interaction to DDAB vesicles, DNA double helix in solution was in a more helical state. It indicated that in the presence of DDAB vesicles the helix might become more compact.

3.2.2. Circular dichroism of dsDNA–DDAB vesicles complex

The CD spectra in the UV range can be used to monitor the conformational transition of DNA [28,29]. In the absence of the DDAB vesicles, the CD spectrum of dsDNA was of typical B-form, which exhibited a positive Cotton effect at 277 nm and a negative Cotton effect at 245 nm as shown in Fig. 4a. After adding DDAB vesicles to the dsDNA solution, the positive Cotton effect of B-DNA at 277 nm and the negative Cotton effect at 245 nm, all shifted to longer wavelengths, at the same time, with the increase of the concentration of DDAB vesicles, the $\Delta\varepsilon$ value was decreased gradually [curve (b)–(j) in Fig. 4]. When the molar ratio of DDAB vesicles to dsDNA reached approximately 1.79, the induced CD spectrum showed weak positive Cotton effect at 285 nm and negative Cotton effect at 251 nm.

The CD spectra suggested that the relative amounts of at least two conformations contribute to the changing shape of the spectra in the presence of the DDAB vesicles. For this reason, the CD spectra were subjected to analysis by SVDLS. The result showed that two principal conformations occurred in the solution (Fig. 5). The first principal conformation showed a strong negative Cotton effect at 250 nm and a weak positive Cotton effect at 285 nm [curve (a) in Fig. 5] belonging to C-form DNA [11,12], the other one showed a positive Cotton effect at 271 nm and a negative Cotton effect at 241 nm [curve (b) in Fig. 5] belonging to B-form DNA. It can be seen that after adding DDAB vesicles to the dsDNA solution, it was a mixture of B-form DNA and C-form DNA in the solution.

The fractional distribution of each component with the molar ratios of DDAB vesicles to DNA was also obtained from the SVDLS analysis in Fig. 5. The two conformations, i.e. B-form and C-form DNA coexisted in the solution with fractions of 0.64, 0.36 without DDAB vesicles. When the molar ratio of DDAB vesicles to dsDNA shifted to 1.50, the fraction of B-form DNA decreased rapidly whereas the C-form DNA fraction increased rapidly. And then C-form was the only conformation in the solution. This result clearly

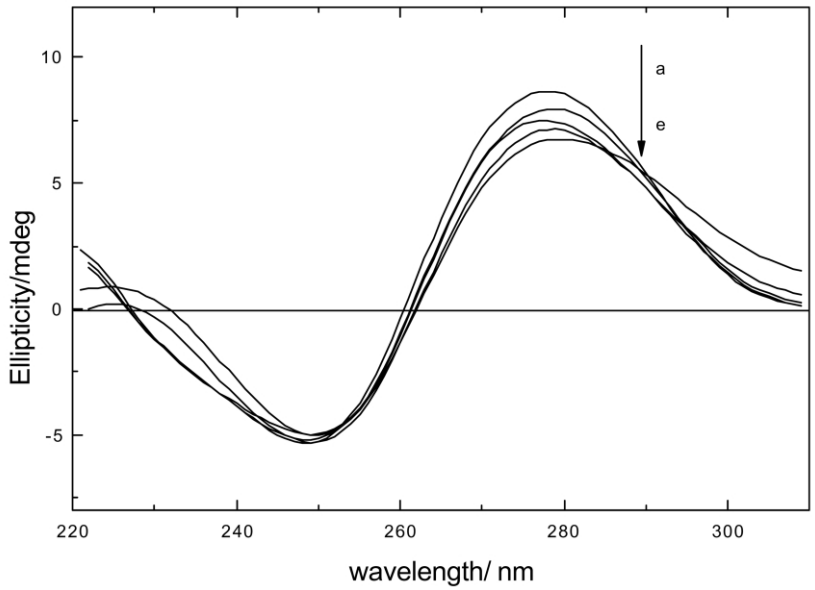

Fig. 2. CD spectra of ssDNA, 0.045 mmol l^{-1} 5′-d(CTGGGCTGCTTCCTAATGCAGGAGT CGCAT)-3′, with different concentrations of DDAB vesicles, the molar ratios of DDAB vesicles to ssDNA are: (a) 0; (b) 0.12; (c) 0.24; (d) 0.48; and (e) 1.2 in pH 6.8, 5 mmol l^{-1} Na_2HPO_4–NaH_2PO_4 buffer solution, ionic strength = 0.1 mol l^{-1}.

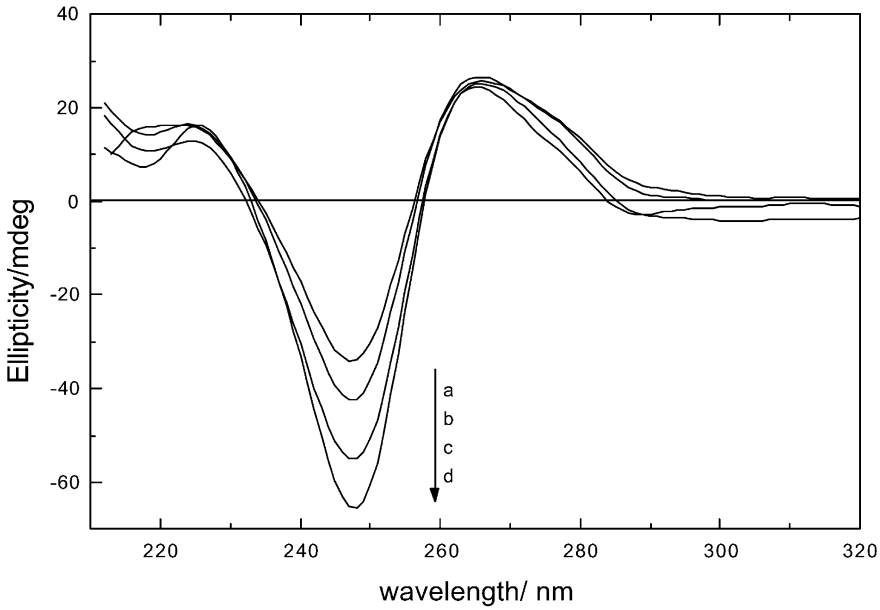

Fig. 3. CD spectra of ssDNA (5′-d(ATATATATATATATATATATATATATAT)-3′) 0.089 mmol l^{-1} with different concentrations of DDAB vesicles, the molar ratios of DDAB vesicles to ssDNA are: (a) 0; (b) 0.24; (c) 0.61; and (d) 1.0 in pH 6.8, 5 mmol l^{-1} Na_2HPO_4–NaH_2PO_4 buffer solution, ionic strength = 0.1 mol l^{-1}.

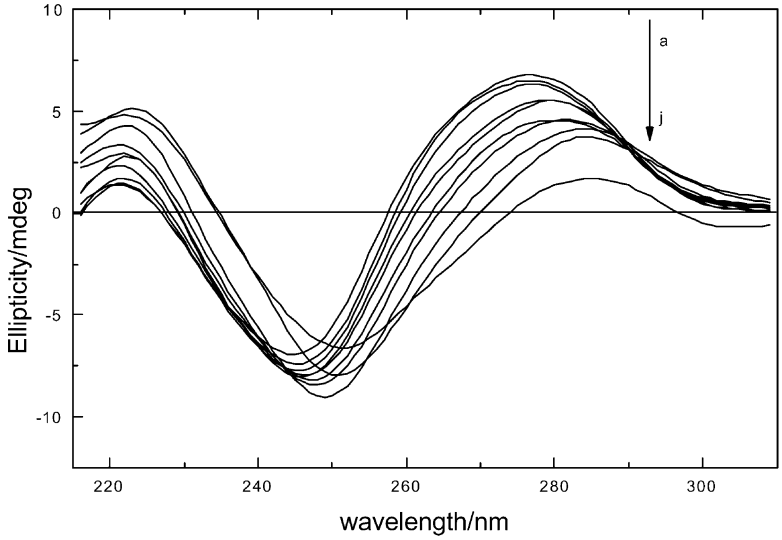

Fig. 4. CD spectra of 0.061 mmol l^{-1} dsDNA with different concentrations of DDAB vesicles, from a to j, the molar ratios of DDAB vesicles to dsDNA are: 0; 0.15; 0.28; 0.50; 0.59; 0.73; 0.89; 1.19; 1.49; and 1.79 in pH 6.8, 5 mmol l^{-1} Na_2HPO_4–NaH_2PO_4 buffer solution, ionic strength = 0.1 mol l^{-1}.

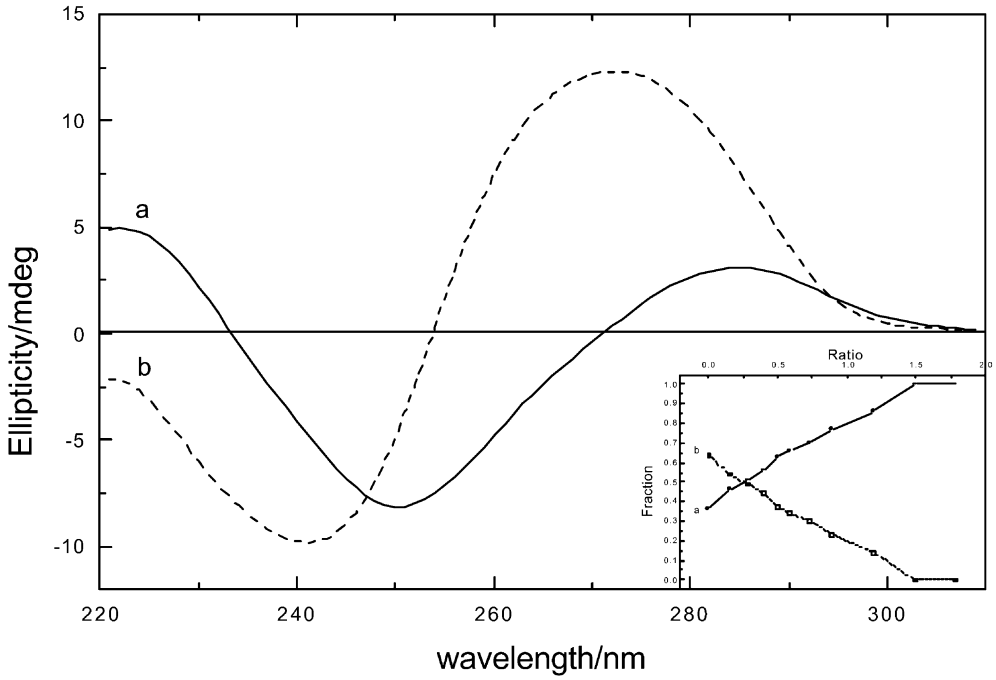

Fig. 5. Principal CD spectra of different conformations of dsDNA calculated from SVDLS: (a) C-form; (b) B-form. Insert: fraction distribution of each component of DNA with different molar ratios of DDAB vesicles to dsDNA. (a) The fraction of C-form; and (b) the fraction of B-form in pH 6.8, 5 mmol l^{-1} Na_2HPO_4 –NaH_2PO_4 buffer solution, ionic strength = 0.1 mol l^{-1}.

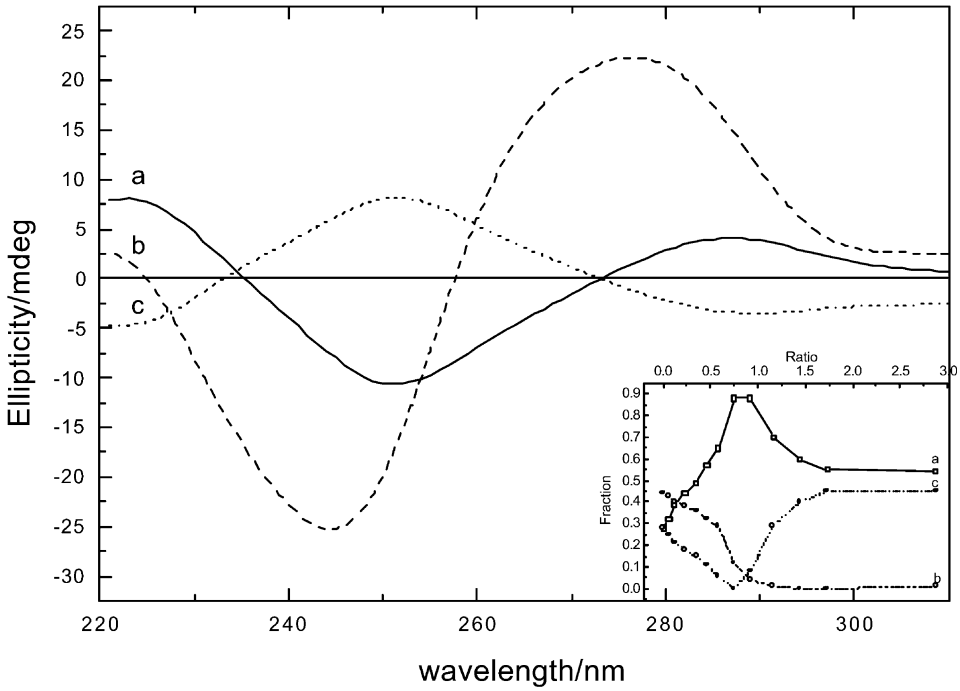

Fig. 6. Principal CD spectra of different conformations of dsDNA calculated from SVDLS: (a) C-form; (b) B-form; and (c) left handed C-form. Insert: fraction distribution of each component of DNA with different molar ratios of DDAB vesicles to dsDNA. (a) The fraction of right-handed C-form; (b) the fraction of B-form; and (c) the fraction of left handed C-form in pH 4.5, 5 mmol l^{-1} Na_2HPO_4–NaH_2PO_4 buffer solution, ionic strength = 0.1 mol l^{-1}.

supported the suggestion that dsDNA existed in C-form after interacting with DDAB vesicles.

3.3. The influence of pH to the dsDNA–DDAB vesicles complex

The pH value of solution can influence the conformations of DNA, and even the molar ratio beyond which the DNA–DDAB vesicles complex was forming. The CD spectra all suggested that the relative amounts of at least two conformations contributed to the changing shape of the spectra in the presence of the DDAB vesicles at different pH values (figure not shown). So the CD spectra were also subjected to analysis by SVDLS.

From the analysis results we can see that in an acidic environment (pH 4.5), the first three singular value and autocorrelations were calculated by SVDLS dominating over the remaining values. The first principal conformation showed a typical CD spectrum of B-form DNA [curve (b) in Fig. 6], but the other two principal conformations had CD spectra with a very good mirror–image relationship. Curve (a) in Fig. 6 had a strong negative Cotton effect at 251 nm and a weak positive Cotton effect at 285 nm, while curve (c) had a strong positive Cotton effect at 251 nm and a weak negative Cotton effect at 285 nm. Since the strong negative Cotton effect at 251 nm and the weak positive Cotton effect at 285 nm were characteristic of C-form DNA [11,12], curve (c) in Fig. 6 may be considered as right-handed C-form DNA. The fractional distribution of each component with the different molar ratios of DDAB vesicles to dsDNA was also obtained from the SVDLS analysis as shown in Fig. 6. The three conformations, i.e. B-form, C-form and left-handed C-form DNA coexisted in the solution with the fractions of 0.44, 0.28 and 0.28 without DDAB vesicles. When the molar ratio of DDAB vesicles

Table 1
SVDLS analysis results in different pH buffer solutions

pH	Fraction		Molar ratio
	B-form	C-form	
4.5	0.44	0.56	1.73
5.5	0.60	0.40	1.50
6.6	0.63	0.37	1.50
6.8	0.64	0.36	1.49

to dsDNA shifted to 0.75, the fraction of B-form and left-handed C-form DNA decreased rapidly, whereas the right-handed C-form DNA fraction increased rapidly. And then right-handed C-form and B-form DNA decreased while the left-handed C-form DNA increased in the solution until the molar ratio of DDAB vesicles to dsDNA reached 1.73. At this time, the fraction of left-handed C-form and right-handed C-form were 0.55 and 0.45.

Some other spectra of dsDNA-DDAB vesicles complexes in different pH conditions were also analyzed. The results in different pH solutions were summed up in Table 1. The molar ratio listed in Table 1 was the one beyond that the C-form DNA was the major conformation in solution. The fraction of B-form increased with the increasing of pH value. And the molar ratio was the same to that of forming DNA–DDAB vesicles complex. It was similar to the results reported before [10–12,20,21,27].

4. Discussions

The main conformations of DNA have been ascertained, such as A-form, B-form family and Z-form. But the most principal conformation is B-form that has 10 bp per turn. The major groove is 'coated' by a unimolecular layer of water molecules which interact with the exposed C=O, N and NH functions and also extensively solvate the phosphate backbone of DNA. At the same time, the minor grooves contain well ordered, zig-zag chains of two water molecules per base-pair. Another conformation belonging to B-form family, C-form DNA, has 28 bp in three full turns of the helix, and is rather like B-DNA in other respects (for details, see Table 2). It has been obtained at rather low humidity [10].

Double helix form DNA is not really a rigid molecule, especially in solution. Therefore, it is possible that several conformations co-exist in one system. But B-form is the most familiar conformation and the other conformations exist in very low contents in bioenvironment. So it is B-form that has the highest thermodynamics stability. For transforming to other conformations, some exogenous conditions are required. An acidic environment made possible conformational transition. While dsDNA dissolved in buffer solution, the fractions of B-form in buffer solutions of pH 4.5, 5.5, 6.6 and 6.8 were 0.44, 0.60, 0.62 and 0.64, respectively (Table 1). Right-handed C-form and left-handed C-form were also observed in the pH 4.5 buffer solution (Fig. 6).

But the emphasis is that water molecules are important to the conformations of DNA. Water molecules interact with the exposed C=O, N and NH functions of ribose and also extensively solvate the phosphate backbone of either dsDNA or ss-DNA [10,20]. While the DNA–DDAB vesicles complex was forming, the cationic head groups of DDAB vesicles also interacted with the ribose and phosphate by electrostatic attraction [6]. There existed a competition between water molecules and DDAB vesicles. At the high molar ratio of the DDAB vesicles to DNA, water contents in the micro surrounding around the DNA can be

Table 2
Average helix parameters for the two DNA conformations

Structure type	Residues per turn	Twist per bp (t/°)	Rise per bp (Å)	Groove width (Å)		Groove depth (Å)	
				Minor	Major	Minor	Major
B-form	10	36	3.3-3.4	5.7	11.7	7.5	8.8
C-form	9.33	38.5	3.31	4.8	10.5	7.9	7.5

decreased. DNA coil is in an out-of-order state that cannot be influenced by the water content. But when double helix DNA interacted with the cationic lipid vesicles, the water molecules were hard to touch the interaction sites. This would make the helicity stronger. Then the liposome-mediated conformational transition could be anticipated. Thus, the conformation of DNA was changed from the B-form to a more compact one.

5. Conclusion

By means of CD spectroscopy together with the analysis method of SVDLS, the conformational transitions of double helix DNA (both dsDNA and ssDNA) from B-form to C-form in solution were studied. Although there were different contents of B-form and other conformations in different acidic buffer solutions, there was a conformational transition of DNA induced by the interaction between DNA and cationic lipid vesicles. The interactions of DNA and cationic lipid vesicles can make the B-form transforming to more compact conformations.

Acknowledgments

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