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DNA adsorption and desorption on mica surface studied by atomic force microscopy

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ABSTRACT

The adsorption of DNA molecules on mica surface and the following desorption of DNA molecules at ethanol–mica interface were studied using atomic force microscopy. By changing DNA concentration, different morphologies on mica surface have been observed. A very uniform and orderly monolayer of DNA molecules was constructed on the mica surface with a DNA concentration of 30 ng/μL. When the samples were immersed into ethanol for about 15 min, various desorption degree of DNA from mica (0–99%) was achieved. It was found that with the increase of DNA concentration, the desorption degree of DNA from the mica at ethanol–mica interface decreased. And when the uniform and orderly DNA monolayers were formed on the mica surface, almost no DNA molecule desorbed from the mica surface in this process. The results indicated that the uniform and orderly DNA monolayer is one of the most stable DNA structures formed on the mica surface. In addition, we have studied the structure change of DNA molecules after desorbed from the mica surface with atomic force microscopy, and found that the desorption might be ascribed to the ethanol-induced DNA condensation.

1. Introduction

The interfacial behaviors of oligonucleotide and DNA have attracted much attention during the past few decades. This is because their adsorption and desorption properties at a liquid–solid interface are very important in the drug delivery [1–3], biosensor design [4–6], biomedical application [7–9], and basic separation theory [10–12].

The adsorption and motion of DNA at liquid–solid interface have been intensively investigated. Pastré et al. have developed a simple theory model to demonstrate the adsorption mechanism of DNA onto a mica surface [13]. In their study, the adsorption of DNA on the mica surface is due to the attraction force produced by divalent and trivalent cations that shared by two surfaces (DNA surface and mica surface). According to their model, attraction force produced by shared counterions and hydrophobic interactions of two surfaces governs the DNA adsorption on the mica surface. Cheng et al. have suggested a chemical band model, in which DNA adsorption is due to that the counterions were condensed along DNA molecules and reacted with the groups on the surface [14]. In addition, the structure of DNA adsorbed onto two-dimensional surface has been widely studied, and results indicated that the charge intensity and density of the surface could affect the structure of DNA after adsorbed onto two-dimensional surface [15]. Brett and Chiorcea studied the process of adsorption of DNA on a highly oriented pyrolytic graphite (HOPG) electrode surface using magnetic AC mode atomic force microscopy [16]. Some previous reports have also demonstrated the DNA motion at liquid–solid interface. Song et al. have studied the motion of DNA at the water–mica interface, and suggested that aggregation, dispersion, and rearrangement of DNA molecules took place at water–mica interface [17]. Zhao et al. investigated the effect of the immersion time in water on the morphological transitions of DNA molecules adsorbed on the mica surface, and found that DNA molecules underwent conformational transitions from network structure to rod-like structure, and to stretched wormlike coil with an increase of the immersion time [18]. Wu et al. have also studied the influence of ethanol/water on the formation of DNA film on mica surface, and they found that DNA molecules could move at the interface of ethanol/water and mica [19]. Although many studies about the DNA adsorption and movement on a liquid–solid interface have been reported, the desorption behavior of DNA molecules on this interface is to a large extent still unclear.

Atomic force microscopy (AFM) is a useful technique for imaging DNA and DNA–protein complexes on the flat surfaces [17,20–23]. This microscope generates a three-dimensional (3D) image by

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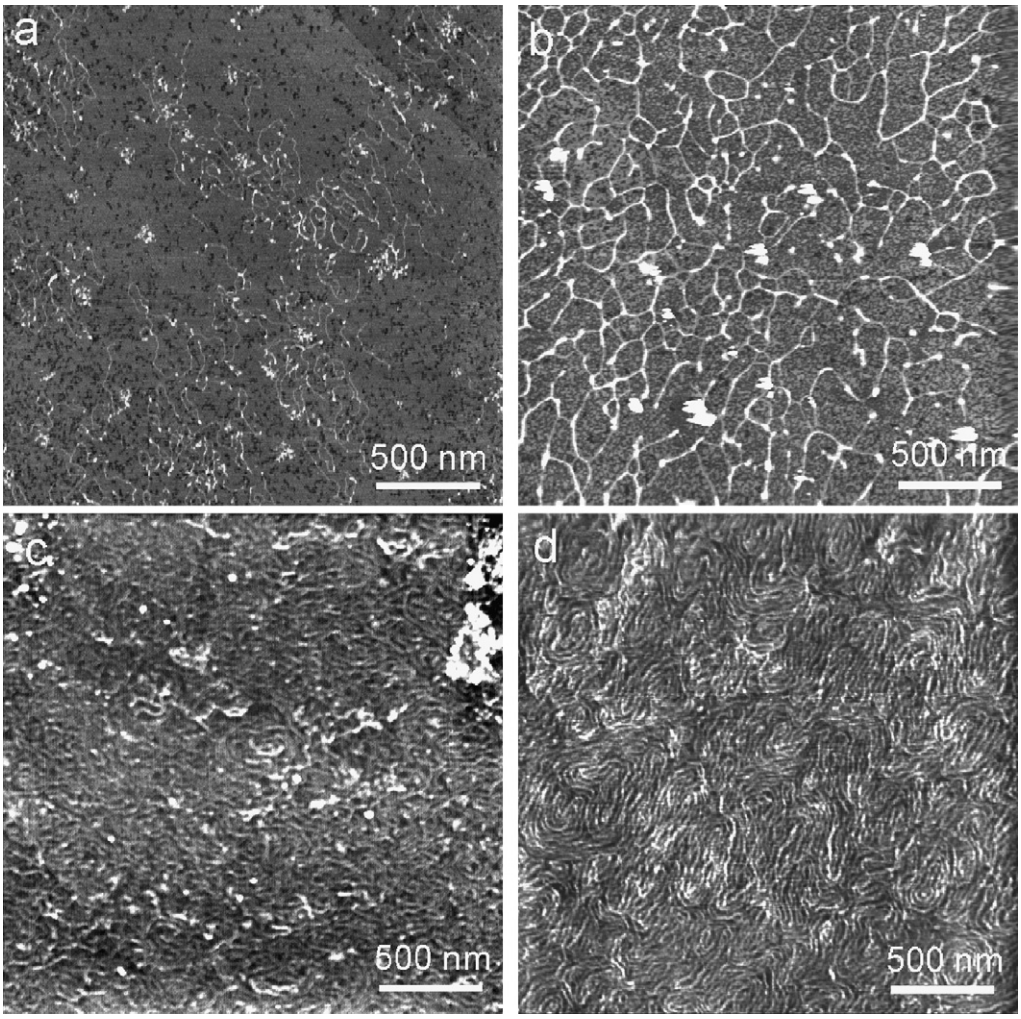

Fig. 1. Typical AFM images of DNA adsorbed on the mica surface with different DNA concentration: (a) 1 ng/μL, (b) 5 ng/μL, (c) 10 ng/μL and (d) 30 ng/μL. The scale bar for all images is 5 nm.

probing the sample surface with a sharp tip attached to the end of a flexible cantilever. Transmission electron microscopy is limited to thin electron translucent surfaces such as amorphous carbon, and can only be used to the samples in vacuum or embedded in ice. AFM, on the other hand, can be used to image DNA under biological conditions, making it possible to preserve the activity and integrity of specimen. The most popular substrate used in AFM imaging is muscovite mica, which supplies a highly negative-charged surface. The mica crystals exhibit a large degree of basal cleavage, allowing them to be split into atomically flat sheets. Weak electrostatic attachment of the DNA to the surface is obtained by using divalent cations as bridge ion (Mg^{2+} is generally preferred) [24].

In this work, we investigated the behavior of DNA molecules both on the mica surface and at the anhydrous ethanol–mica interface. It was found that the loosely dispersed DNA strands, networks and films could be created on the mica surface by controlling the concentration of DNA. The diameter of pores on the DNA films became smaller when the concentration of DNA was increased, and finally a flat-lying, densely packed DNA monolayer was formed. Various desorption degree of DNA on mica (0–99%) was achieved when transferring the samples to ethanol for 15 min. While flat-lying, densely packed DNA monolayer did not desorb at ethanol–mica interface. It was concluded that adsorption proceeded by physical and chemical (Mg^{2+} bridging) interaction between DNA and mica surfaces. The desorption of DNA on ethanol–mica interface was ascribed to the ethanol-induced condensation of DNA, which decreased upon the formation of DNA films.

2. Experimental

2.1. Materials

Lambda DNA (48,502 bp) was purchased from Sino-American Biotechnology Company (300 ng/μL, Branch Department of Peking, Beijing, PR China). Magnesium acetate ($Mg(OAc)_2$) and 3-aminopropyltriethoxy silane (APTES, 99%) were purchased from Aldrich. Ethanol (AR) was obtained from Beijing Chemical Reagent Factory (Beijing, PR China). Mica ($KAl_2(AlSi_3)O_{10}(OH)_2$, V-1 grade) was purchased from Linhe Street Commodity Marketplace (Changchun, China), and was cut into about 1 cm × 1 cm square pieces as substrates. Ultrapure water was used throughout the work.

2.2. Adsorption of DNA on mica surface

The DNA was diluted with ultrapure water to a concentration of 2–60 ng/μL. The diluted DNA solutions were mixed with 2 mM $Mg(OAc)_2$ solutions in equal volume as DNA forming solutions, and a droplet of the forming solution (20 μL) was dropped onto a freshly cleaved mica for about 10 min for DNA adsorption. Then

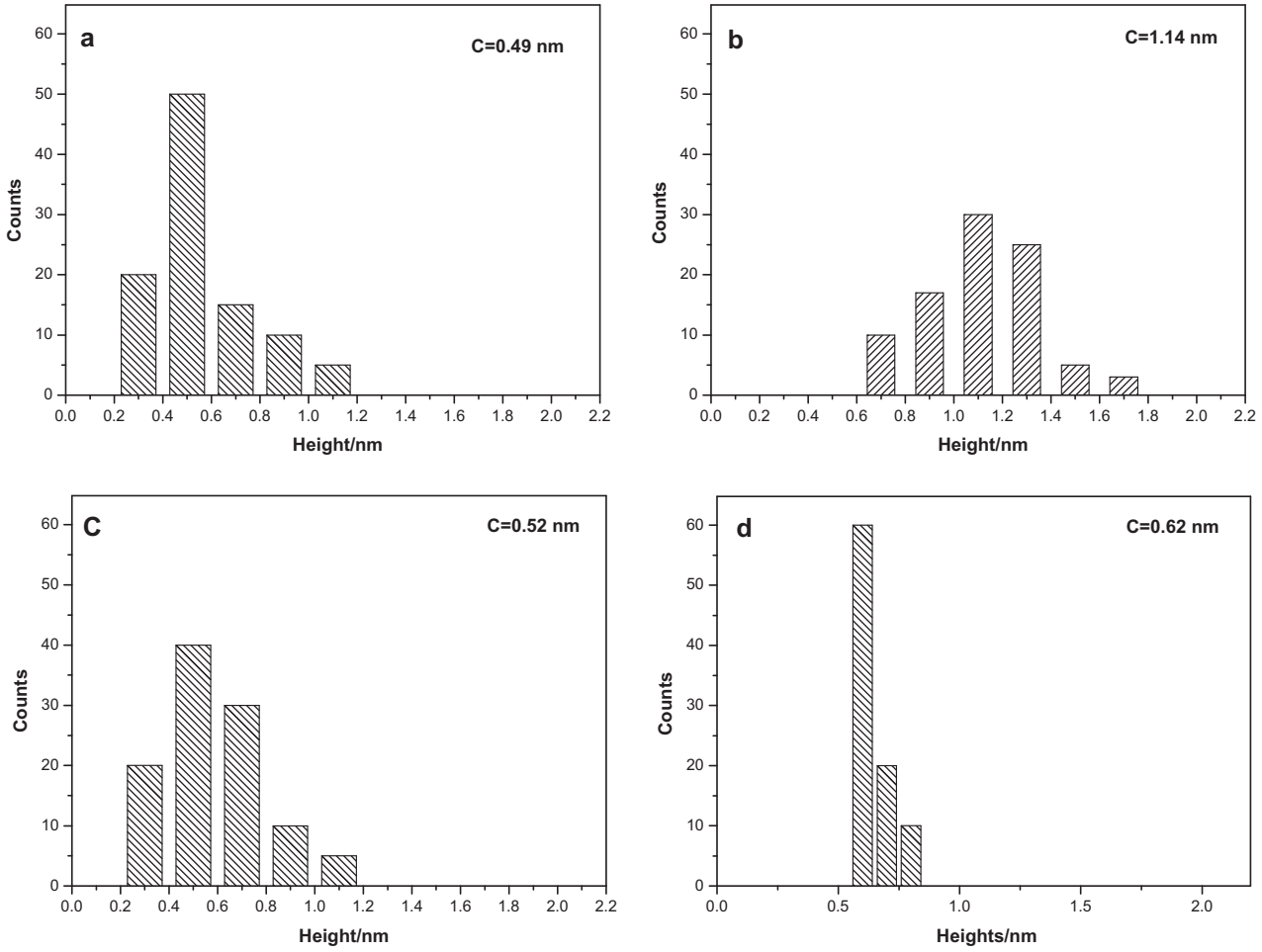

Fig. 2. Histograms of the height distribution for the DNA adsorbed on the mica surface with different DNA concentration: (a) 1 ng/μL, (b) 5 ng/μL, (c) 10 ng/μL and (d) 30 ng/μL.

the sample was rinsed with ultrapure water for about 30 s and dried under air.

2.3. Desorption of DNA on ethanol–mica interface

In a desorption experiment, the sample was immersed into anhydrous ethanol for about 15 min. Then the sample was taken out of ethanol, and was rinsed with ultrapure water for about 30 s and dried under air.

In a control experiment, to confirm the effect of ethanol on the desorption of DNA, 10 μL λ-DNA solution containing 1 mM $Mg(OAc)_2$ were mixed with 190 μL ethanol. A droplet of the forming solution (20 μL) was dropped onto a freshly cleaved mica surface and was dried under air and prepared for AFM imaging.

2.4. Atomic force microscopy measurements

All AFM experiments were accomplished by using a Digital Instruments Nanoscope IIIa (Santa Barbara, CA) in tapping mode. Standard silicon (Si) cantilevers (spring constant, 20–100 N/m) were used under its resonance frequency (typically, 200–400 kHz). All AFM images were acquired at room temperature under the ambient conditions, and images are presented as raw data except for flattening. The scan rate was 1–1.5 Hz. The height of fibers was measured by section analysis. All average values were measured at least from five different AFM images.

3. Results and discussion

3.1. Adsorption of DNA with different concentrations on the mica surface

In our experiments, the final concentration of Mg^{2+} was 1 mM, which is the optimal Mg^{2+} concentration for DNA adsorption on mica [17]. Here Mg^{2+} was used as the bridge between DNA and mica surface. Because both the DNA phosphate backbone and mica surface are negatively charged, once DNA solution are dropped onto a mica surface without bridge cations, DNA cannot be immobilized on the mica surface.

The morphologies of DNA with different concentrations on the mica surface were first investigated by AFM. Fig. 1a shows the AFM image of DNA molecules (1 ng/μL) adsorbed on the mica surface. The DNA chains were loosely and randomly dispersed on the mica surface, and the distance between the chains was disordered. Because the DNA concentration is very low, DNA molecules cannot cover the entire surface, and also cannot overlap or cross each other to form a DNA network. Fig. 1b is the AFM image of DNA adsorbed on the mica surface at a concentration of 5 ng/μL. The mica surface was covered by a two-dimensional large-scale DNA network, in which DNA chains aggregated by crossing or overlapping each other. The DNA networks had many big meshes that appeared as the dark regions in the image, and exposed a large part of mica surface. The formation of networks might be affected by three kinds of effects: the electrostatic attraction between the

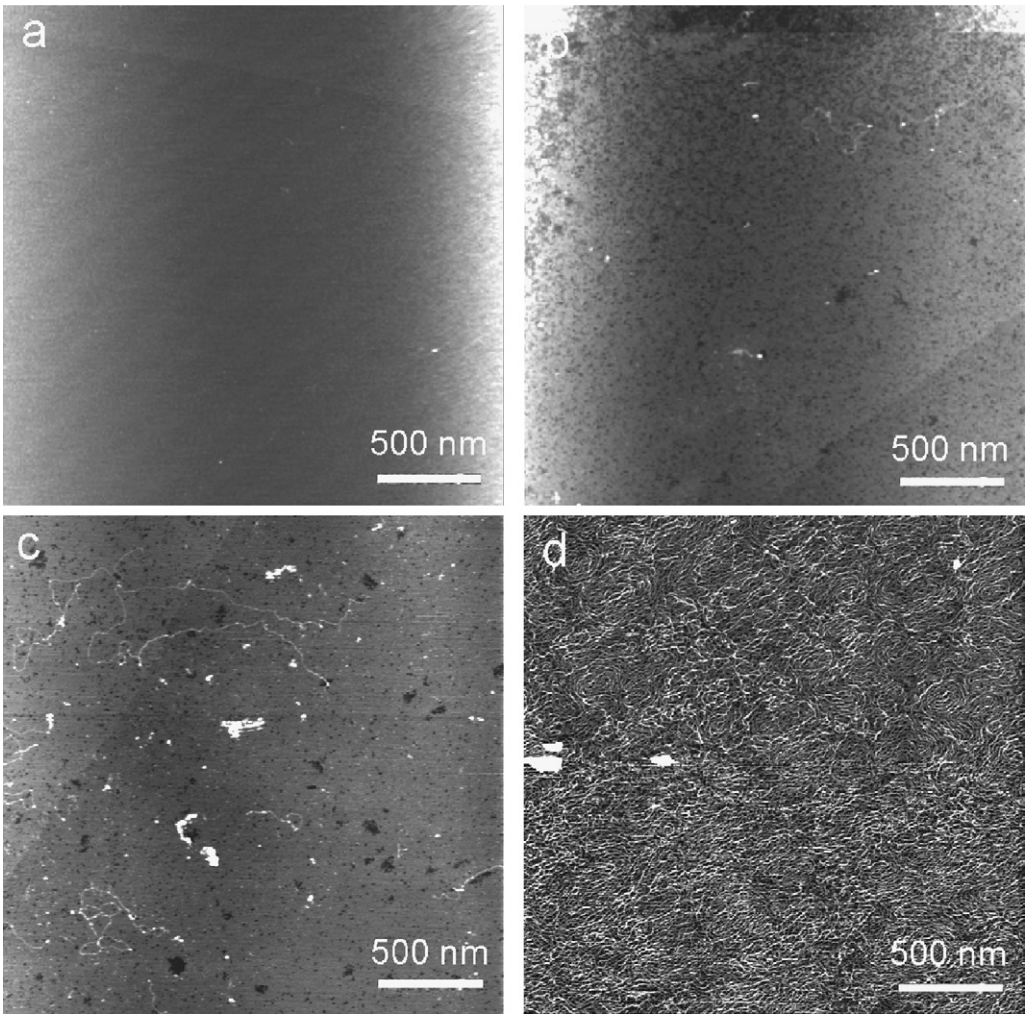

Fig. 3. Typical AFM images of DNA molecules on the mica surface after immersing in ethanol for about 15 min with different DNA concentration: (a) 1 ng/μL, (b) 5 ng/μL, (c) 10 ng/μL and (d) 30 ng/μL. The scale bar for all images is 5 nm.

phosphate groups of DNA and mica surface with Mg^{2+} as a bridge ion [25]; the hydrophilic force between DNA and mica surface [26]; some sticky ends created by breaking the DNA chains also induce the aggregation of DNA chains on the mica surface [19]. As the three effects randomly existed on DNA molecules and the mica surfaces, the DNA chains in DNA networks were highly disordered. When the DNA concentration was increased to 10 ng/μL, the DNA films were constructed on the mica surface (as shown in Fig. 1c). The bare mica surface area was obviously lower compared to the DNA networks shown in Fig. 1b. The interchain distances decreased and tended to be uniform. When DNA concentration was further increased to 30 ng/μL, the bare mica surface area was further decreased, and the interchain distances were very uniform (Fig. 1d). These AFM results indicate the formation of a very uniform and ordered DNA film on the mica surface. It is obvious that the uniformity of the interchain distances is strongly dependent on the DNA concentrations, since the compactness of the DNA films increased as DNA concentrations increased.

It should be pointed out that the rinsing and drying process can affect the morphology of DNA, which causes some differences between the structures that we have observed and that of the actual DNA morphology. However, a lot of information on DNA morphology can still be revealed by ex situ AFM studies [27]. In addition, the reproducibility is very good in our experiment. The morphologies of DNA with different concentrations on the mica surface are reproducible by imaging more than five DNA samples and 10 different points on each DNA sample.

The height of the DNA molecules adsorbed on the mica surface was measured using cross-section analysis, and the histogram of their distribution was shown in Fig. 2. When the DNA concentration was 1 ng/μL, the average height was about 0.49 nm (Fig. 2a). This height is in accordance with that of single double-stranded DNA that is reported to be 0.5 nm by AFM in air [28,29]. Thus at a low concentration, DNA chains cannot overlap or cross each other. When the DNA concentration was increased to 5 ng/μL, the average height was about 1.14 nm (Fig. 2b). This value is about twice of the single double-stranded DNA chain, indicating the overlapping of DNA bundles with about two chains. When the DNA concentration was increased to 10 ng/μL, the average height was about 0.52 nm (Fig. 2c). But the height distribution of the fibers was broad, and the height scaled from 0.3 nm to 1.1 nm. It is clear that the DNA film was not very flat and uniform. Contrarily, when the DNA concentration was 30 ng/μL, the height distribution of the fibers became narrower. Most of the height was located at around 0.62 nm (Fig. 2d), which indicated the formation of flat and uniform DNA monolayer. The average height is higher than the reported height of single double-stranded DNA. The reason might be that some sticky ends bound other chains and formed triple-stranded DNA [30,31].

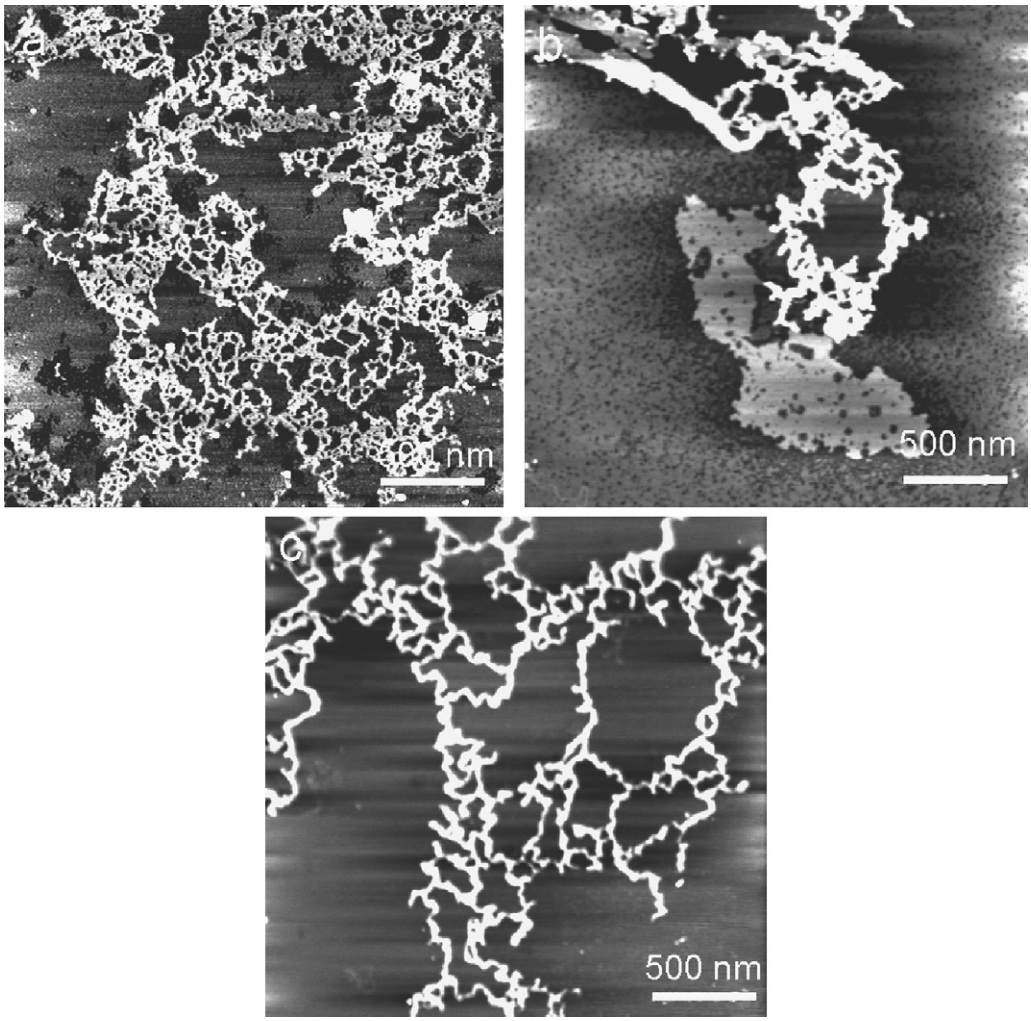

Fig. 4. Typical AFM images of the DNA structures induced by highly concentrated ethanol under different DNA concentration: (a) 1 ng/μL, (b) 5 ng/μL and (c) 10 ng/μL. The scale bar for all images is 5 nm.

The sticky ends might be created by breaking the DNA chains during sample preparation. Thus the average height is a little higher than that of single double-stranded DNA.

3.2. Desorption of DNA with different concentrations at ethanol–mica interface

Fig. 3 is a series of typical AFM images of DNA molecules on the mica surface after immersing into ethanol for about 15 min. Fig. 3a shows the AFM image of a sample with the DNA concentration of 1 ng/μL, indicating that almost all of the DNA molecules have desorbed from the mica surface. The mica surface was very clean, and only a few light spots existed on it. We suggest that the light spots on the mica surface might be the aggregates of salts. From the AFM results, it can be deduced that ethanol breaks the bridge function of Mg^{2+} ions between DNA and mica surface, which promotes the desorption of DNA molecules form mica. It was reported that ethanol can induce DNA condensation under properly controlled conditions, and high concentrations of ethanol were commonly used to precipitate DNA [32,33]. It was thought here that the DNA molecules adsorbed on the mica surface were destructed by ethanol and left from the mica surface. When the concentration of DNA was increased to 5 ng/μL, most of DNA molecules also desorbed from the mica surface after immersing into ethanol (Fig. 3b), but only a few single DNA molecules existed on the mica surface. When the DNA concentration was further increased to 10 ng/μL, more single DNA molecules existed on the mica surface (as shown in Fig. 3c). And some rod-like nanostructures existed on the mica surface, which might result from the condensation of DNA caused by ethanol [34]. Under this concentration (10 ng/μL), a disorderly DNA film has been constructed on mica surface, while most of DNA molecules have desorbed from the mica surface when immersing in ethanol. Fig. 3d shows that DNA films were remained when the DNA samples (30 ng/μL) were immersed in ethanol for desorption. Before immersion in ethanol, DNA molecules of 30 ng/μL adsorbed on the mica surface can form a very uniform and orderly monolayer. And after immersion, it is interesting to find that the DNA film still existed on the mica surface but not desorb from the mica surface. These desorption results indicate that the degree of desorption decreased with the increase of the DNA concentration. It reveals that the structure of DNA molecules adsorbed on the mica surface determines the ability of resist-desorption. Only when very uniform and orderly DNA monolayer are formed on the mica surface, the desorption of DNA molecules from the mica surface does not occur. That is also one of the reasons that constructing a uniform DNA monolayer has attracted much attention, which is that the uniform DNA monolayer is very stable and suitable for studying the DNA properties.

The above AFM results show that DNA molecules adsorbed on the mica surface could desorb when immersing into ethanol under

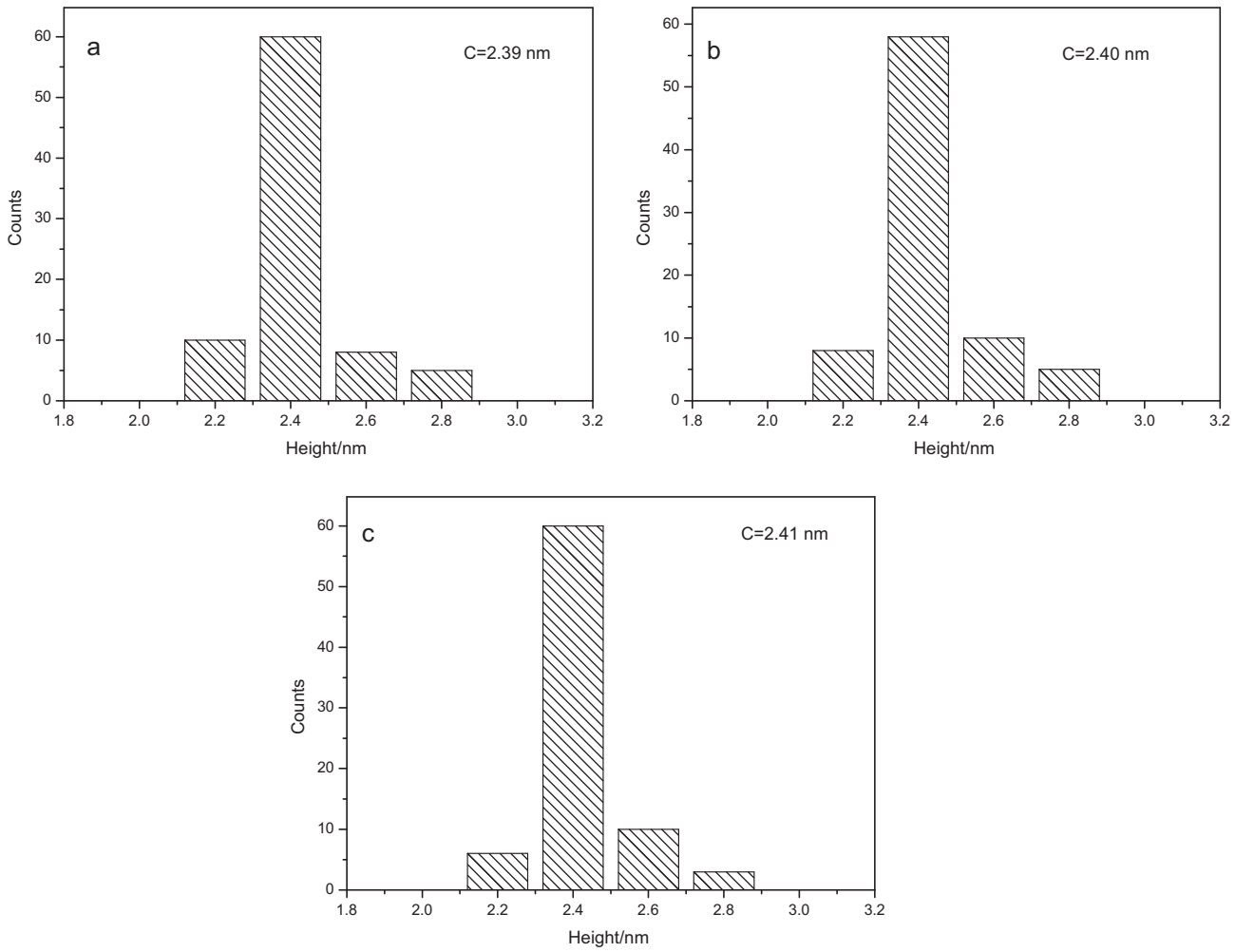

Fig. 5. Histograms of the height distribution for DNA structures caused by ethanol under different DNA concentrations: (a) 1 ng/μL, (b) 5 ng/μL and (c) 10 ng/μL.

relatively low DNA concentration. Then it is very important to understand how ethanol can induce the desorption of DNA from the mica surface. To achieve this aim, AFM was used here to monitor the DNA in the immersing ethanol solution, and DNA analogs were detected, as shown in Fig. 4. The DNA chains obviously aggregated and formed networks at various DNA concentrations (1, 5 and 10 ng/μL). The fibers of the network became wider than that of DNA networks shown in Fig. 1b. The formation of similar DNA analogs after immersing in ethanol with different DNA concentration indicates that these structures are likely to be DNA products condensed by ethanol. The compact DNA networks are similar to those previously reported by Lang in the DNA condensation by ethanol solutions [35], in which they reported that at high DNA concentration and 10–95% ethanol, DNA formed fibrous networks of predominantly polygonal meshes. In our present work, the heights of the fibers in these DNA networks were measured from cross-section analysis of AFM images, and the main height was about 2.4 nm (Fig. 5).

To understand the effect of ethanol on the desorption of DNA, a control experiment was performed. Fig. 6a shows the AFM image of a control experiment in which ethanol was added into aqueous solution of DNA containing 1 mM Mg^{2+}. DNA molecules exist as small compact particles, i.e., globules, rods and toroids, which are observed on the mica surface. A magnified AFM image of the refined structures of the compact particles was shown in Fig. 6b. Ethanol-induced DNA structural transitions have been reported by Fang et al. and Lang et al. [32,35,36]. Lang et al. found that at the situation of low DNA concentration and 95% ethanol, DNA formed rod-like particles. Fang et al. found that at a concentrations of ethanol (>20%), DNA formed flower shaped condensates and toroids. We suggest that the obtained small compact particles are resulted from the ethanol-induced DNA condensation. Fig. 6c shows the height histogram of the condensed DNA and a statistical analysis shows the main height was about 2.39 nm, which agreed well with the height of compact DNA networks obtained after adsorptions, as shown in Fig. 5. It reveals that the height of DNA condensates caused by highly concentrated ethanol is independent of the DNA concentration. On the other hand, the morphology of the condensates induced by ethanol is contrarily dependent on the DNA concentration.

3.3. Possible explanation of DNA adsorption and desorption on mica

To summarize the observations so far for DNA adsorption and desorption, we conclude that DNA forms different structures bonded on the mica surface by Mg^{2+} bridging, and also desorbs from the mica surface as condensed DNA molecules. The desorption degree of DNA at ethanol–mica interface decreases with the increase of DNA concentration, and almost no desorption occurs on the uniform and orderly DNA monolayers. According to the obtained results, we suggest that the condensation of DNA by ethanol is the main factor of desorption. In aqueous solution, DNA and counterions (Mg^{2+}) are more or less in the free ion form rather

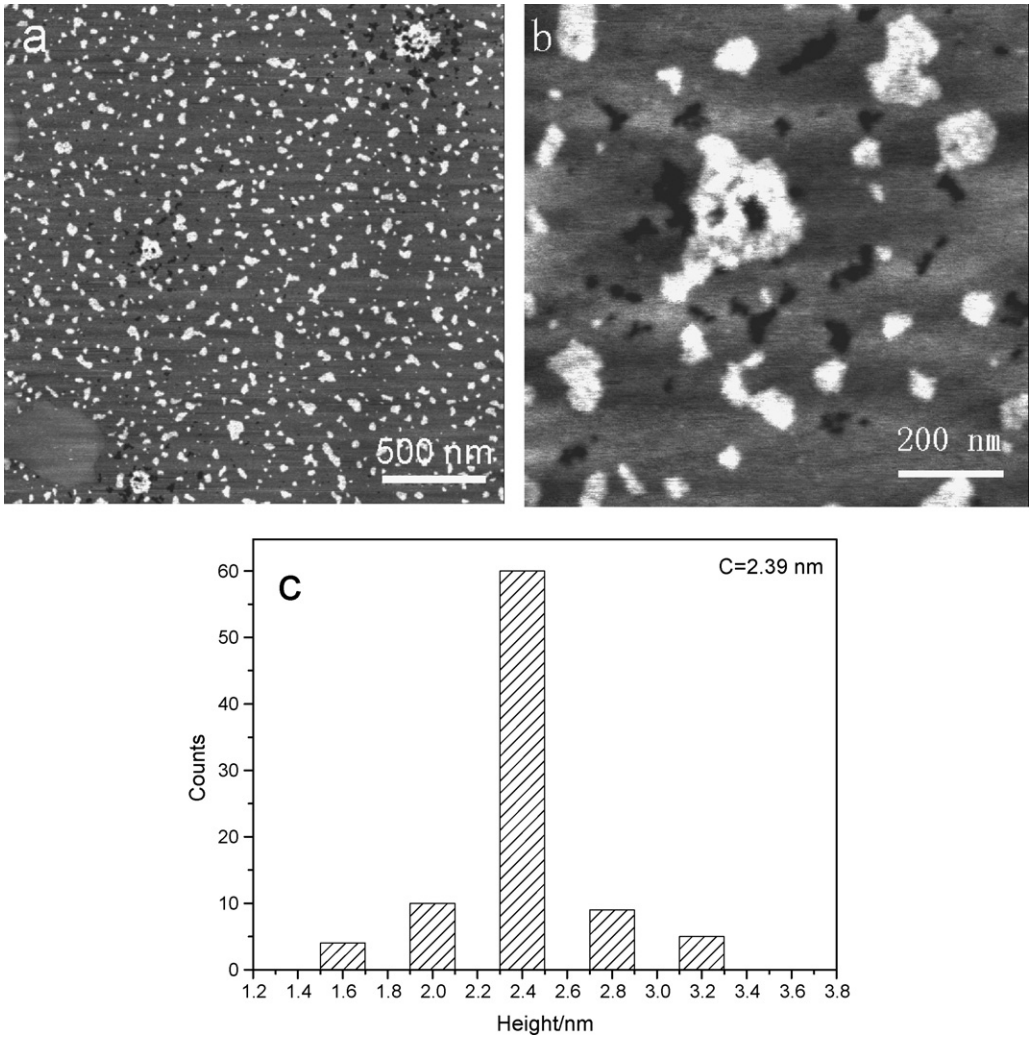

Fig. 6. (a) Typical AFM image of condensed DNA at 98% ethanol, (b) the magnified AFM image of (a) and (c) histogram of the height distribution for the condensed DNA. The scale bar for all images is 5 nm.

than the ion pair form (that is, they are surrounded by one or more layers of water molecules). Water has a high dielectric constant (e), which from Coulomb's law indicates that the electrostatic force (F) between two ions of opposite charge is very weak in water:

$$F = \frac{Q_1 \times Q_2}{e \times r_2}$$

where Q is the charge on each ion, e is the dielectric constant and r is the distance between them. Adding ethanol decreases the dielectric constant of the DNA aqueous solution. As e decreases, F increases and finally anion and cation form an ion pair and results in the condensation of DNA, and which prevents the adsorption of DNA on the mica surface. However, when DNA forms uniform and orderly DNA monolayers, DNA does not desorb from the mica surface. The possible reason is that DNA strands can be uniformly adsorbed on the mica surface by electrostatic attachment by Mg^{2+}. DNA and Mg^{2+} have been fixed on the mica surface, and DNA and Mg^{2+} ion are in pair form rather than free ion form, so adding ethanol can not lead anion and cation to reform an ion pair and result in the condensation of DNA.

From above results, it can be found that uniform and orderly DNA monolayer is the most stable structure, which may be one of the reasons that DNA monolayer is always pursued by scientists. It should be noted that in the previous studies on DNA imaging, DNA solution mixed with a cation was firstly dropped onto freshly cleaved mica, and several minutes later it was treated with ultrapure water or ethanol for 20 s [37]. The use of ethanol is to move the free DNA but not the DNA adsorbed on the mica surface. In our desorption experiment, ethanol-induced DNA condensation inhibited the adsorption of DNA onto the mica surface under low DNA concentration. The different action of ethanol suggests that ethanol-induced condensation of DNA is not a rapid process. In previous studies, DNA adsorbed on the mica surface was washed with ethanol for only 20 s, where DNA condensation could not occur in such a short time. While in our work, DNA dropped on the mica surface was immersed in ethanol for 15 min, and during this time ethanol could condense DNA into rigid structures and inhibit the adsorption of DNA on the mica surface. Once the DNA strands have been uniformly adsorbed on the mica surface by electrostatic attachment by Mg^{2+}, the DNA condensation cannot occur during the immersion process in ethanol, which allows the uniform DNA films to retain on the mica surface without desorption.

4. Conclusion

In this paper, we investigated the adsorption of DNA on mica surface, and further studied the desorption of DNA molecules at the ethanol–mica interface. By studying with AFM, we demonstrated that the affinity of DNA on mica surface increased with the increase of DNA concentration. DNA molecules form uniform monolayer

on mica surface at high concentration, and DNA does not desorb from the mica at the ethanol–mica interface. In contrast, at relatively low concentration of DNA, loosely and randomly dispersed DNA chains, disordered networks, and irregular films of DNA are formed on the mica surface, and desorption of DNA from the mica occurs at the ethanol–mica interface. Therefore, we can conclude that uniform monolayer of DNA is relatively stable comparing with the other DNA structures we obtained on the mica surface. The experimental results reveal that desorption of DNA from the mica at ethanol–mica interface is caused by the ethanol-induced condensation of DNA.

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