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Interaction of Calf Thymus DNA with a Cationic Tetrandrine Derivative at the Air–Water Interface

Amparo Wong-Molina, Karen O. Lara, Mario Sánchez, María G. Burboa, Luis E. Gutiérrez-Millán, José L. Marín, and Miguel A. Valdez

1Departamento de Investigación en Polímeros y Materiales, 2Departamento de Investigaciones Científicas y Tecnológicas, 3Departamento de Investigación en Física, and 4Departamento de Física, Universidad de Sonora, Blvd. Luis Encinas y Rosales, Col. Centro, C.P. 83000, Hermosillo, Sonora, Mexico

The interaction of the semi-synthetic dicationic cyclophane-type macrocycle (TC) with calf thymus DNA was investigated at the air–water interface. The macrocycle has been prepared by chemical modification of 3,5-(+)-tetrandrine with acetylated groups. The macrocycle was mixed with arachidic acid in a chloroform solution (1:1, 1:3, 1:9, 9:1 arachidic acid:macrocycle weight proportions) and spread on a DNA buffer solution in a Langmuir Balance. Results indicate isotherms shifts and phase modification of the arachidic acid macrocycle mixture monolayers due to the DNA adsorption from the subphase after different times. The presence of the arachidic acid at the interface gives support to the macrocycle at the air–water interface, otherwise macrocycle molecules do not remain at the interface. Atomic force microscopy images of Langmuir-Blodgett monolayers obtained on mica demonstrate the DNA adhesion on the macrocycle domains. The DNA adsorption process was also monitored by Brewster Angle Microscopy images. Circular Dichroism spectra of different DNA:macrocyclic ratios were performed and show secondary structure changes of DNA. UV spectrometric measurements indicated a strong DNA-macrocycle interaction and molecular mechanics simulations corroborate that the macrocycle interaction with DNA occurs mainly in the major groove of the DNA molecule.

Keywords: DNA, Arachidic Acid, Tetrandrine, Langmuir-Blodgett Films, AFM, CO, BAM.

1. INTRODUCTION

The immobilization of DNA on different substrates has become a subject of great biological importance because of, among others, its relevance on the fabrication of biosensors and gene delivery. It is an emerging field with important medical and pharmaceutical applications. Different supports for the immobilization have been used and recently the investigations on Langmuir monolayers have achieved great relevance. Due to the importance of cationic lipids as vehicles for delivery of DNA, studies on DNA immobilization at the air-water interface have strongly concentrated on electrostatic interactions with cationic lipid monolayers. Other surfactants and lipids have also been used to support DNA at the air-water interface. Monolayers of binary phospholipids and/or cationic lipids mixtures at the air-water interface have also been considered to immobilize DNA from the subphase. These binary lipid mixtures play an important role in the DNA cell transfection. Some authors have found that immobilized polynucleotides on a thin film at the air-water interface preserve the geometry and integrity of DNA molecules as demonstrated by X-ray and neutron reflectometry techniques applied to liquid systems. The aggregation and kinetics of Immobilized DNA at the air-water interface have been visualized by fluorescence microscopy and by Brewster Angle Microscopy (BAM) and the corresponding Langmuir Blodgett films have been observed and measured by atomic force microscopy (AFM).

On the other hand, the interaction of different molecules with DNA produces important changes in the DNA secondary structure which can affect the functionality and the DNA helix structure.

In this paper, we are interested to investigate the interaction of DNA with a recently reported dicationic tetrandrine derivative bearing two acridine groups at the air–water interface.

Tetrandrine (TET) is a bis(benzyllisouquinoline) alkaloid isolated from the root of Stephania tetrandra S. Moore. This natural compound has several biochemical and
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pharmacological properties such as antipysetic, analgesic, antibacterial,ostatic and anti-tumoral. On the other hand, the chemical, physical and spectroscopic characteristics of TET are widely described in the literature. Its crystal structure was also elucidated and according to this, TET has the conformation of a triangle with a small cavity.

Moreno-Corral and Lara recently reported the synthesis of new dicatonic TET derivatives bearing anthraquinone and acridine groups and their complexation studies directed toward nucleotides in aqueous medium. In this work they demonstrated that quaternization of both nitrogen atoms of the alkaloid, with the apolar and planar units above mentioned, transform it into a dicatonic receptor with affinity for negative charges of anionic compounds, and with an extended cavity capable of significant hydrophobic and π-π stacking interactions with aromatic moieties of hydrophobic guests in aqueous medium.

On the other hand, due to the well known ability of anthraquinonic and acridine of intercalating into base pairs in DNA and RNA, there are many reports in literature of molecules that have incorporated those units in an attempt to find systems capable of showing high affinity to DNA sequences at physiological pH, in order to develop new artificial nucleases, DNA sensors, and intercalating drugs.

Due to the acridine pKa of 5.6, its possibilities to be used as a catonic molecule are limited at low pHs. On the other hand, because both of the nitrogen atoms of the TET derivative (TC) are formally charged, this molecule is a dication at any pH. Considering the latter, only TC has a charge complementarity with anionic DNA at physiological pH. Besides, the incorporated unit of acridine in TC can help to form a more stable DNA-TC complex as a consequence of the intercalating ability of this polycyclic arene. Another advantage of TC over acridine is the presence of hydrophobic surface regions. In conclusion, TC has several structural advantages when compared with the simple acridine unit and as a consequence a more stable DNA complex is expected for this semi-synthetic molecule in aqueous medium at physiological pH.

In this paper we report the interaction of calf thymus DNA (DNA) with the TET derivative with two acridylmethyl groups (TC). Our interest is to get evidences of the DNA-TC interaction in solution and at the air-water interface. Due to the solubility of TC in water, we have achieved holding TC at the air water surface by using an arachidic acid/TC mixture. This mixture, spread on a DNA buffered solution, interact with DNA and is capable to attach it at the air-water interface. By using BAM and AFM we observed evidences of the DNA-TC interaction. Complimentary UV and CD spectroscopic measurements were performed to investigate the DNA/TC interaction in aqueous solution. Finally molecular simulations were performed in order to visualize the DNA-TC interaction.

2. EXPERIMENTAL DETAILS

Calf thymus deoxyribonucleic acid (DNA) was purchased from Life Technologies (Cat. No. 15633-019, Carlsbad, CA, USA). The average size obtained by gel electrophoresis, using a 1.2% agarose gel, was 150 bp. Arachidic acid (AA) (99%) was purchased from Aldrich (St. Louis, MO, USA). Chloroform (grade HPLC, 99.9%) and ethanol (reactive grade) were obtained from Sigma-Aldrich (México). TC was synthesized as described in a recent work. Deionized Milli-Q water (18.3 MΩ·cm) was used in all cases and it was obtained from an Easy pure/Barnstead instrument (E pure, Barnstead, Dubuque, IA, USA).

Langmuir balance (Nima Technologies, Ltd, Coventry, England, Langmuir Blodgett through, model type 611), whose surface tension precision is 0.1 mN/m, was used to obtain isotherms. The surface pressure π = γ - γ, i.e., the surface tension difference of the clean surface and the surface tension of the covered surface was measured by using a Wilhelmy plate made of a chromatography paper. The surface pressure and molecular area data were fed into a computer and recorded, using a barrier speed of 25 cm²/min.

AA and TC were dissolved in chloroform at different weight proportions 1:1, 3:2, 3:1 and 9:1, respectively. Different samples of 50 µl from a 1 mg/ml final concentration were deposited on a clean buffered solution (TRIS EDTA, pH 7.4) and on a DNA buffered solution (0.25 µg/ml) with a Hamilton microsyringe. This DNA concentration was chosen according the results obtained by some researchers and tested after several experiments performed in order to obtain smaller DNA aggregates in the AFM images. When the buffer solution was used as subphase, isotherms for AA and AA/TC mixtures were performed 15 min and 20 h after chloroform was evaporated. For the case of AA alone, isotherms showed differences in area smaller than 1%. On the other hand, differences of AA/TC isotherms were around 5% when they were compared at different times. For the case of DNA aqueous buffered subphase, isotherms were performed 4, 6 and 20 h after the AA/TC solution was spread. Temperature was kept at 20 C with the aid of a water circulator bath (Cole Palmer, model 1268-24, Chicago IL, USA). All experiments were carried out inside a dry free glass box.

In situ BAM images of AA/TC monolayers were obtained with and without a DNA solution subphase by using a MiniBAM Plus instrument (model 03027BMA045, Nanofilm, Menlo Park, CA, USA). Images were obtained at different pressures and for different AA/TC proportions. Langmuir-Blodgett monolayers were obtained on fresh cleaved mica from different AA/TC proportions at the air-water interface and at the surface pressure of 20 mN/m. Monolayers were dipped at speed 1 mm/min. These monolayers were analyzed by AFM.

AFM images were obtained from AA/TC monolayers obtained directly from the air water interface. Adsorbed DNA on AA/TC monolayers were also investigated. The DNA adsorption was analyzed by submerging AA/TC monolayers (deposited on mica) in a DNA buffered solution of 10 μg/ml. After 30 min, samples were gently washed with milli-Q water and analyzed. The measurements were performed in a JEOL instrument (model JSM-450, Akishima, Tokyo, Japan) in the non-contact mode, using silicon nitride cantilevers NSC15 from MicroMasch (Wilsonville, Oregon, USA).

Circular dichroism (CD) measurements were performed in a Jasco J-810 spectropolarimeter (Easton, MD, USA) at room temperature (around 23 °C). DNA concentration was kept fixed at 0.1 mg/ml and was mixed with different TC aqueous solutions (0.01, 0.025, 0.05, 0.1, 0.2, and 0.3 mg/ml) in the same buffer and pH as the DNA solutions. Both sample and reference were run three times and averaged. The wavelength range used was 180–300 nm and the cell path length was 0.1 cm.

UV spectrometric measurements were performed in a spectrophotometer Lambda 2 (Waltham, Massachusetts, USA). A one centimetre quartz cuvette cell holder was used. Spectrophotometric titrations were performed on 1.75 x 10^{-5} M TC solution in a phosphate buffer (0.052 M and 0.05 M NaCl). Typically aliquots of fresh DNA standard solutions were added to TC solutions. The pH was checked at the beginning and at the end of the titration and was found constant in all cases. The TC concentration was kept constant and the DNA concentration varied in the range 1.25 x 10^{-6}–5.0 x 10^{-5} M. The absorbance measurements were taken at the 368 nm wavelength. The association constant, K_{a}, was obtained fitting the experimental data to the Eq. (1), using a nonlinear least-squares regression:

\[ A_{ab} = (A_0 + A_m K[G]_T)/(1 + K[G]_T) \]  

Where \( A_{ab} \) is the observed absorbance of the complex, \( A_0 \) is the absorbance of free TC alone, \( A_m \) is the maximum absorbance of TC induced by the presence of DNA and \( [G]_T \) is the total DNA concentration. The Origin 7.5 software was used to get the better fit with the experimental data.

Molecular modeling. Hypercube's hyperchem 7.52 package was used to perform molecular mechanics simulations. The MM+ force field was employed as implemented in the 6.03 version and the likely structure of TC was found following the method explained by Moreno Corral and Lara. Various TC-DNA complexes were explored electronically using the MM+ force field with the purpose of establishing the factors that govern the molecular recognition of the TC with the double-stranded DNA fragment (GTAAAGATGATTC), obtained from the salmon DNA sequence. The procedure was the following: the double-stranded DNA fragment was constructed from the nucleic acid databases implemented in Hyperchem 7.52. The TC molecule was positioned manually to the DNA minor and major grooves. All complexes were optimized using the MM+ force field followed by molecular mechanics simulations and finally re-optimized with the MM+ method.

3. RESULTS AND DISCUSSION

In Figure 1 we show the isotherms of AA and the mixture AA/TC in the weight proportion 1:1 spread on buffer solution. We also show the effect of the DNA adsorption on the mixture monolayer 4 and 20 h after the AA/TC was spread on the DNA solution. It can be observed an isotherm shift due to the DNA adsorption at the air water interface, similar to the one observed by several researchers. After 20 h DNA molecules have penetrated the AA/TC monolayer and the isotherm reaches a limiting area around 77 Å^2, in comparison with the limiting area of the AA/TC mixture spread on the buffer solution (around 57 Å^2). On the other hand, in the condensed zone, the extrapolated area at zero pressure gives 36 Å^2 for the isotherm, 20 h after the AA/TC spreading on the DNA solution, in comparison with the extrapolated area of the pure AA/TC mixture (22 Å^2). This last value is almost the same value obtained for pure AA. This would mean that for this AA/TC weight proportion, corresponding to 3 AA molecules per one TC molecule in the monolayer, both species occupy the same average molecular area as AA alone. This is could be an evidence of an AA-TC interaction at the air-water interface. Other interesting feature is that the kink produced in the AA isotherm at 27 mN/m is changed by a smoother curve, indicating

Fig. 1. Isotherms of arachidic acid (AA) (1) and the mixture 1:1 w/w AA: tetrandrine derivative (TC) on buffer TRIS EDTA (2) (3) and (4) represent isotherms of the 1:1 AA/TC monolayer 4 h and 20 h after the mixture AA/TC was spread on a DNA buffered sulphate, respectively. DNA concentration used in the sulphate was 0.05 μg/ml buffer TRIS EDTA and pH 7.4. Temperature was kept at 20 ± 0.1 °C.
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![Graph showing interaction of Cali Thymus DNA with a cationic tetrandrine derivative at the air-water interface.]

Fig. 2. Isotherms of the mixture 3:1 w/w AA:TC on buffer TRIS EDTA (1) and isotherms of the 3:1 AA:TC monolayer (2) and (3) after the mixture AA:TC was spread on a DNA buffered subphase, respectively. DNA concentration used in the subphase was 0.25 μg/ml buffer TRIS EDTA and pH 7.4. Temperature was kept at 29±0.1°C.

A longer Liquid Expanded phase as a consequence of the AA-TC interaction. This change of phase disappears with the DNA adsorption, producing a more flexible and expanded monolayer.

In Figure 2 we show the isotherms of the AA/TC mixture in the weight proportion 3:1, which corresponds to 10 AA molecules per one TC molecule at the interface. The isotherms obtained 4 and 20 h after the AA/TC spreading on the DNA aqueous subphase are also shown. For the isotherm obtained 20 h after the AA/TC spreading, the limiting and the extrapolated areas were smaller (48 and 25 A², respectively) in comparison to the ones obtained for the 1:1 AA:TC monolayer, probably due to the decreasing number of TC molecules at the air-water interface. In this case, the kink observed in the AA isotherm at 27 mN/m is also observed for this AA:TC proportion, probably due to the higher AA proportion. We also see that the solid like region characteristic of the AA isotherm does not completely disappear. On the contrary, after 20 h the isotherm shows two solid-like structures at higher pressures. Notice the plateau observed around 47 mN/m as a consequence of the equilibrium between the two solid-like phases. For the case of the isotherms obtained with the 9:1 AA:TC weight proportion (not shown), the limiting area, obtained 20 h after the AA:TC spreading, was around 39 A², larger also in comparison with the corresponding area of the AA:TC mixture deposited in buffer solution (32 A²). Therefore, we can observe a clear correlation between the TC proportion in the monolayer and the area increase of isotherm shift produced by the DNA-TC interaction.

It is difficult to explain in detail the mechanism of DNA adsorption at the interfacial film. However, considering the chemical structural characteristics of TC (and the previously reported studies of TC directed toward nucleotides), we can expect that the major forces stabilizing its DNA complex result from ion pairing between the charged groups of DNA and TC and from stacking or hydrophobic interactions. As we will see later, both results of the molecular modeling and the complexity studies in solution of this work prove, in several ways, participation of electrostatic interactions. On the other hand, a possible experimental evidence of the π-stacking interaction in the complex, also provided by the complexation studies in solution, is the hypochromic effect induced in the DNA UV-vis absorption spectra in the presence of TC.

The compressibility of monolayers, defined as $C_v = (1/A)(dA/d\ln \sigma)$, where $A$ and $\sigma$ are the area and the surface pressure of the monolayer, respectively, is a more precise tool to analyze the equilibrium phases and the flexibility of monolayers along isotherms.

In Figure 3 we show the behavior of the compressibility at different pressures of three different AA:TC complexes, when DNA is adsorbed after 20 h at the monolayer in the air-water interface. As a reference we show also the compressibility behavior of the AA monolayer. For AA is easy to observe the Liquid Condensed-Solid (LCS) equilibrium phases represented by the peak at 26.1 mN/m with a $C_v$ value of 0.014 mN/m. Another peak is shown at 51.2 mN/m with a $C_v$ value of 0.0049 mN/m, corresponding to the solid-solvent equilibrium. The presence of TC mixed with AA causes significant changes in the monolayer rigidity. When the AA:TC 3:1 proportion is used only on buffer solution, the transition between the liquid condensed and liquid expanded phases is observed at 28 mN/m. For the proportion 1:1 this equilibrium appears at 27 mN/m (not shown). This phase equilibrium can be noticed also in Figures 1 and 2. As long as DNA is being

![Graph showing compressibility of AA/TC mixtures with different AA:TC w/w proportions, 20 h after mixture was spread on a DNA buffered solution. DNA concentration used in the subphase was 0.25 μg/ml buffer TRIS EDTA, pH 7.4. Temperature was kept at 29±0.1°C. The compressibility of anodic acid (AA) is plot as reference (solid line).]

adsorbed, this phase equilibrium is shifted to higher pressures as can be observed in Figure 3.

The presence of DNA in the monolayer, 20 h after the AA/TC spreading, modifies the compressibility for the three AA/TC mixtures analyzed as can be observed in Figure 3. We observe that the values of \( C_s \), corresponding to a LC-S equilibrium, are higher in comparison with the values without the presence of DNA for the three mixtures analyzed: 0.030, 0.020 and 0.016 mN/m, respectively for the 9:1, 3:1 and 1:1 AA/TC monolayers adsorbed by DNA molecules 20 h after spreading. This indicates that the DNA adsorbed at the AA/TC monolayer produces a more flexible film. Notice in Figure 1 that the pressure for this transition is shifted to around 42 mN/m for the 1:1 proportion as a consequence of the DNA adsorption and the higher TC concentration in the monolayer. The calculation of \( C_s \) for the monolayer corresponding to the 3:1 AA/TC proportion, performed after 20 h DNA was adsorbed, shows two peaks corresponding to the equilibrium of two solid phases, occurring at 43.8 and 50 mN/m approximately. These transition points, showing the transition, can better be observed in Figure 2.

In Figure 4 we show the BAM images obtained at low pressure (around 4 mN/m) for the different AA/TC monolayers and also the images obtained 4 h after the same AA/TC proportions were spread on the DNA subphase. We notice that images of the AA/TC monolayers on pure water show bright aggregates probably rich in TC surrounded by a dark zone which corresponds to the Liquid Expanded (LE) phase of AA. These aggregates become more dense and interconnected when the TC concentration in the monolayer is higher. The presence of DNA in the subphase produces aggregates even brighter and more dense at the interface. Specially interesting is the Figure 4(d) for the 1:1 AA:TC proportion. In this case we notice a more fibrillated structure due to the DNA-TC interaction at the interface. We also notice the holed areas, probably corresponding to the AA in the LE phase.

The appearance of the condensed domains with the surface pressure increasing, confirms the existence of different

Fig. 4. BAM images of different AA/TC monolayers obtained at a pressure around 4 mN/m: (a) and (c) were obtained from 3:1 and 1:1 AA/TC w/w proportions, respectively, spread directly on water; (b) and (d) were obtained from 3:1 and 1:1 AA/TC w/w proportions, respectively, spread on a DNA buffered solution. Images were obtained 4 h after the AA/TC mixtures were spread on the DNA subphase. DNA concentration used in the subphase was 0.25 µg/ml Pacific TRIS EDTA, pH 7.4. Temperature was kept at 20 ± 0.1 °C.

The domains grow larger and stack up to form a tightly aggregated morphology at high surface pressure.

Results of the CD spectroscopic measurements of different DNA/TC proportions are shown in Figure 5. The structure of DNA solution corresponds to a B form, similar to the structure reported by other researchers at low salt concentration. The absence of a negative band around 295 nm, as demonstrated by Cowman and Fasman, is due to the long size of DNA molecules. The influence of the TC interaction on the DNA structure produces changes similar to the ones due to a C form in the DNA structure, similar to the C DNA structure observed by Hanlon et al. due to a high salt concentration and to the influence of some solvents on the shift to longer wavelengths and to the decreasing of the ellipticity values.

A similar decrease of the intensity was observed by Prokop et al. around the positive band of 280 nm due to the DNA-anti-tumor platinum complexes. Notice that the peak around 278 nm is shifted to shorter wavelengths when the TC proportion is increased, probably caused by the low solubility of the DNA/TC complex.

In order to study the TC-DNA complex formation, we performed titration experiments by the UV-Vis spectrophotometric technique. Studies were carried out in aqueous solution and pH and ionic force were also controlled to guarantee having predominantly the DNA in its fully ionized form. A DNA stock buffered solution was added step by step to the TC dissolved in the same solvent. During the titration, the UV spectra of TC showed a significant hypochromism at its maximum absorption as an indication of the TC-DNA interaction. This hypochromic effect is frequently observed with similar complexes and can be attributed to the intercalation of the azaaromatic units into base pairs in DNA helices driven by π-stacking interaction.

The absorptions recorded at 368 nm were plotted versus the DNA concentration. A typical hyperbolic behavior was found corresponding for a complex of 1:1 stoichiometry and therefore data could be fitted by Eq. (1) (see experimental section). Figure 6 shows the UV titration plot. A binding constant of $1.6 \times 10^6$ M$^{-1}$ was obtained which indicates formation of a very high stable TC-DNA complex in solution. It is important to mention that the order of the association constant found by this study is in agreement with those reported in literature for similar systems.

On the other hand, in Figure 7 we show the AFM images of monolayers using two different AA/TC proportions. Figures 7(a) and (b) show the images for monolayers of 9:1 and 1:1 AA/TC proportions, respectively. We notice that both images show separated regions by a thin strip, probably rich in TC molecules. For the 9:1 AA/TC monolayer, the large areas have an average height of 1.5 nm, probably constituted mainly of AA molecules in a liquid condensed phase and the thin darker strips have an average height of 0.5 nm. In the case of 1:1 AA/TC monolayers, the large areas have an average height of 1.0 nm. This different average height is probably caused by a higher TC proportion in these regions, interacting with AA molecules. The dark strips are wider in comparison with the ones observed for the 9:1 monolayer and have the same average height.

The effect of DNA on AA/TC monolayers observed after they were submerged on a DNA solution and gently washed, as described in the experimental part, can be observed in Figures 7(c) and (d), where a 9:1 and 1:1 AA/TC proportions, respectively were used. In Figure 7(c) we can observe two different domains, as observed in Figure 7(a). We observe that DNA aggregates are attached at zones where TC molecules are found probably without AA molecules. These aggregates have an average height
higher than 12 nm and an average diameter of 400 nm. Similar sizes of DNA aggregates were found by Mitra and Imae.25

In the case of monolayers with a larger TC proportion, we should observe a higher DNA concentration attached to the monolayer. In Figure 7(d), where a 1:1 AA:TC proportion was used, in fact we notice at the bottom of the picture the AA domains surrounding TC molecules (small dark zones). It seems that DNA aggregates are attached to planar zones constituted mostly by TC molecules. The average diameter of the DNA strips are 50 nm and the average height is 1.8 nm, similar to the one found by Mitra and Imae.25 We notice in this case that DNA aggregates are longer than the ones observed on the monolayer built with 9:1 AA:TC proportion. It is possible that as long as many TC molecules are present, more DNA molecules can remain more elongated, interacting with TC along the DNA chains and showing a more fibrillated structure.

Finally in Figure 8 we show the image of the DNA-TC interaction resulted with the lowest energy found by molecular dynamics. The force field, MM+e, suggests that interactions between TC and DNA are mainly into the major groove. These electrostatic interactions are formed between quaternary nitrogen atoms of the TC charged positively and oxygen atoms charged negatively of the phosphate groups of the DNA fragment. Figure 8(a) shows the TC molecule localized in the major groove of the DNA fragment. In Figure 8(b), atoms participating in these interactions are labeled with their respective symbols. As we can see, there are two main interactions. One of these interactions is between O1 and N1 and separated by a distance of 4.30 Å. The second electrostatic interaction has a distance of 4.44 Å between O2 and N2.

The TC prefers the phosphate groups of the DNA fragment GTAAAGATGATTC. This is due to the steric hindrance generated by the acridine groups. These bulky
We found that both of the oxygen atoms of the COO⁻ group in the AA molecule interact electrostatically with the hydrogen atoms on the carbon atom adjacent to the quaternary nitrogen atoms of the TC molecule shown in Figure 8(b) (results not shown).

In addition to the possible hydrophobic interactions between the tail of the AA and the hydrophobic region of the TC molecule, the previously mentioned interactions could explain the stability of the AA/TC monolayers. It is also possible to conclude from the results, that one TC molecule remaining at the air-water interface could be supported by one AA molecule and simultaneously interacting with a DNA chain.

4. CONCLUSIONS

The overall results of the present study corroborate the DNA adhesion on the TC domains. It seems to be possible that, as long as many TC molecules are present, more DNA molecules can become enlarged, interacting with TC along the DNA chains, showing a more fibrillated structure. The latter feature would constitute a peculiar behavior of this system and make it an attractive candidate for the direct detection of DNA. Work is in progress along this line and will be published elsewhere.

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