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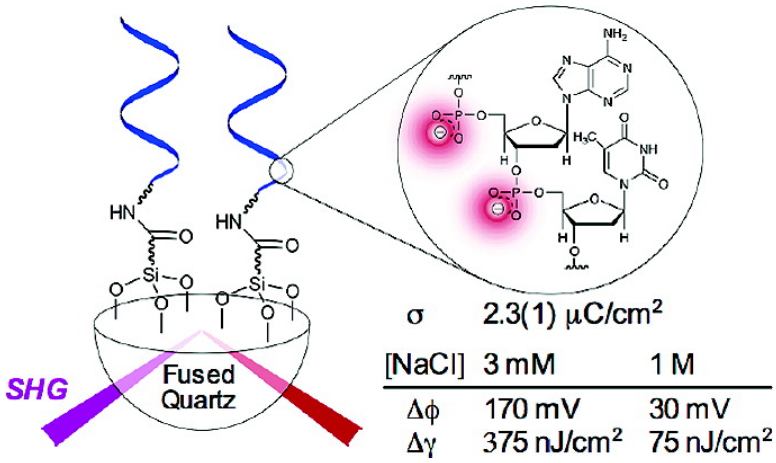

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DNA Single Strands Tethered to Fused Quartz/Water Interfaces Studied by Second Harmonic Generation

Faith C. Boman, Michael J. Musorrafiti, Julianne M. Gibbs, Brian R. Stepp, Anne M. Salazar, SonBinh T. Nguyen, and Franz M. Geiger*

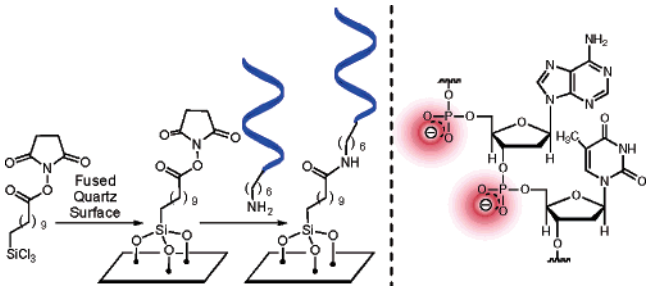
Department of Chemistry and Nanoscale Science and Engineering Center, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208

Received August 10, 2005; E-mail: geigerf@chem.northwestern.edu

DNA forms the basis of all life processes[1] and has received significant attention in many areas of science.[2−9] While intense research has focused on characterizing DNA at interfaces for the purpose of biodiagnostics, many of these studies require the synthesis of oligonucleotides labeled with fluorescent,[10,11] electrochemical,[12,13] radioactive,[14,15] or nanoparticle[2,16] tags to afford detection. Label-free techniques for DNA detection, such as surface plasmon resonance spectroscopy,[17,18] atomic force microscopy,[19,20] X-ray spectroscopies,[21,22] and Fourier transform infrared (FTIR) spectroscopy,[22,23] eliminate the synthetic steps necessary for labeling oligonucleotides but often require surfaces with high dielectric constants.

Here, we are taking the first step toward circumventing these issues by applying nonlinear optical methods to study DNA single strands that are chemically attached to fused quartz/water interfaces. This work has important implications for predicting and controlling macromolecular interactions, improving biodiagnostics, and understanding life processes. Specifically, we use second harmonic generation (SHG) to obtain—without the use of labels—the full thermodynamic state information for surface-bound DNA as a function of the ionic strength in the surrounding aqueous solution. The nonlinear optical response, that is, the SHG *E*-field, is proportional to the electrostatic potential at the interface.[24,25] This method, pioneered by Eisenthal and co-workers,[25−27] is called the "$\chi^{(3)}$ technique" and is applied here to track the interfacial potential set up by the phosphate charges along the backbone of the oligonucleotides. These phosphate groups thus act as intrinsic labels, which do not require any DNA modification (Scheme 1).

Scheme 1. Succinimide Siloxane Linker and Oligonucleotide Attachment via Amide Bond Formation (left). Negative Charges on the Phosphate Groups Lining the DNA Backbone (right) Act as an Intrinsic Label in the Nonlinear Optical Measurements



Our experiments were carried out on fused quartz lenses functionalized with a succinimide-terminated silane that was then reacted with a 3′-amine-terminated 5′-AAA AAA AAA AAA TTT-3′ oligonucleotide strand. The functionalized surface was placed under milipore water maintained at pH 7 using HCl and NaOH, and the ionic strength was adjusted using NaCl. Using a 120 fs optical parametric amplifier,[28] second harmonic generation (SHG) signals from the functionalized aqueous/solid interface were obtained at 325 nm near total internal reflection, off two-photon resonance, and at room temperature.

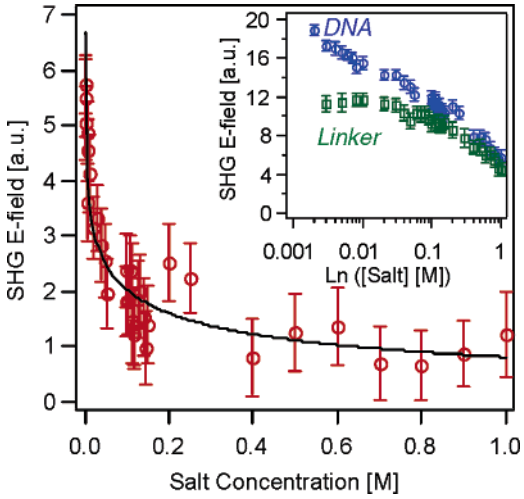


Figure 1. SHG *E*-field (p-in/p-out) versus salt concentration at pH 7 and room temperature for 5′-AAA AAA AAA AAA TTT-3′ oligonucleotides anchored to a fused quartz/water interface after subtracting the SHG *E*-field contribution from the succinimide linker. The SHG *E*-field depends linearly on the static electric field generated by the interfacial potential, Φ_o, via the third-order nonlinear susceptibility, $\chi^{(3)}$. The interfacial potential is calculated using the Gouy−Chapman model (solid black line)[25−27] and results in the SHG *E*-field decay with increasing salt concentration. Inset: SHG *E*-field for the DNA (circles) and for the succinimide linker (squares) as a function of salt concentration.

In our typical $\chi^{(3)}$ experiment, the negative charges of the oligonucleotide strand are screened out by increasing the salt concentration. This, in turn, lowers the electrostatic potential at the interface. One would thus expect a lower SHG *E*-field as the salt concentration is increased. In contrast, the SHG response from the uncharged linker should remain constant until a much higher salt concentration is reached, at which point processes other than simple charge screening may come into play.

This is indeed what is observed in our experiment (Figure 1). The SHG *E*-field can be described by the Gouy−Chapman model,[29,30] which results in an interfacial charge density of 2.3(1) μC/cm^2 for our single-stranded oligonucleotide. If all 14 negative charges along the backbone are sampled by the $\chi^{(3)}$ experiment, this charge density would correspond to a surface coverage of around 1×10^{12} strands/cm^2. This agrees well with other measured oligonucleotide surface coverages on gold and silica that range between 1×10^{11} and 2×10^{13} strands/cm^2.[31−33] Between 3 mM and 1 M salt concentration, the interfacial potential decreases from 170 to 30 mV in absolute value (Figure 2), which is in good

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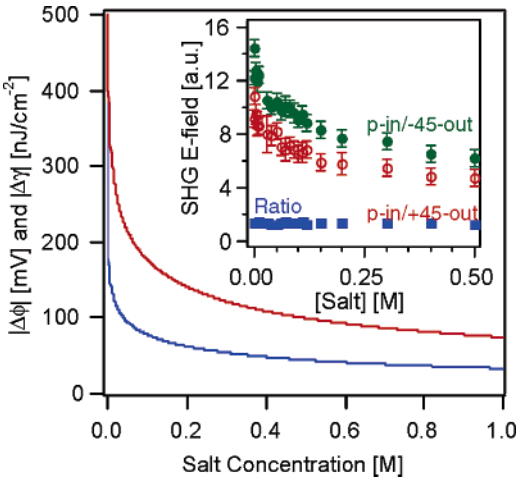

Figure 2. Interfacial potential (top line) and interfacial energy density (bottom line) for the DNA single strand as a function of salt concentration calculated from the Gouy−Chapman model and the Lippmann equation. Inset: SHG *E*-field for the DNA single strand as a function of salt concentration for the polarization combination p-in/−45-out (filled circles), p-in/+45-out (empty circles), and the ratio of (p-in/−45-out)/(p-in/+45-out) (filled squares).

agreement with theoretical predictions by Pettitt and co-workers.[34] Likewise, the change in the interfacial energy density, which is calculated from the interfacial charge density and the interfacial potential through the Lippmann equation,[29] decreases from 375 to 75 nJ/cm^2 over the same salt concentration range.

Over the range of salt concentrations investigated in our work, polarization-resolved measurements show an approximately 150% stronger SHG response polarized at −45° away from the plane of incidence as compared to +45° (Figure 2 inset) when probing the DNA-functionalized interface with p-polarized light. Within experimental noise, the ratio of these two SHG measurements appears to be independent of salt concentration. This is consistent with SHG optical rotatory dispersion (SHG−ORD) angles (∼ −20°) that remain constant for both high and low salt concentrations. To the extent that these measurements report on chirality,[35,36] they would suggest a chiral contribution to the $\chi^{(3)}$ effect. Detailed investigations regarding the microscopic origin of this effect, including SHG−CD measurements,[35,36] are forthcoming.

In conclusion, we have shown that the interfacial charge density, interfacial potential, and the change in the interfacial energy density for single-stranded DNA at fused quartz/water interfaces can be determined via nonlinear optical measurements. Our approach circumvents experimental challenges associated with preparing labeled oligonucleotides and does not require surfaces with high dielectric constants. The results from our measurement can aid in improving the design of new biomaterials[4] and highly sensitive sensors for biodiagnostics.[6] The thermodynamic state information obtained from our $\chi^{(3)}$ experiments has important implications for predicting and controlling macromolecular behavior and can be used to test and advance theoretical frameworks for understanding biomolecular interactions. Future work will address the polarization response of chiral conformations of single-stranded DNAs, its $\chi^{(3)}$ response, and DNA duplex formation and melting.

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Supporting Information Available: Succinimide linker synthesis and characterization, SHG spectra, and SHG power response. This material is available free of charge via the Internet at http://pubs.acs.org.

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