Simulation study of non-covalent hybridization of carbon nanotubes by single-stranded DNA in water

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Simulation study of non-covalent hybridization of carbon nanotubes by single-stranded DNA in water

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Master’s Thesis

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Abstract

Solubilization and separation is an important step in utilizing both the unique mechanical and electrical properties of carbon nanotubes (CNTs). Due to different possible chiralities of CNTs, which can have drastically different electrochemical properties, it is also necessary to have a method of separation that will distinguish between these different species. Recent discovery of single-stranded DNA (ssDNA) absorption onto CNTs have shown high affinity towards forming soluble hybrids in polar solvents. The interactions between the ssDNA and CNTs as well as the geometry of the hybrid structure are not well understood. In order to study these phenomena we have implemented multiple all-atom replica exchange simulations. Simulations are carried out in an aqueous environment and vary in single-stranded decamer composition as well as nanotube chirality. The oligonucleotides readily adsorb onto the carbon nanotube surface and immediately following begin a slow structural rearrangement. Dependent upon both oligonucleotide composition and nanotube chirality, the ssDNA is found to form several unique backbone geometries as defined by both local and global order parameters. In contrast to the multiple geometries the backbone may form to, the nucleotide bases are found to organize themselves into either parallel or anti-parallel conformation with a high degree of orientational order. Binding appears to be mainly driven by π-stacking interactions between DNA bases onto the carbon nanotube surface, equilibrium of the structures is also controlled by a complex mixture of forces including DNA conformational strain and solvent interactions. The
result of this is the free energy landscape is found to have multiple minima occupied at room
temperature which are separated by high energy barriers.

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providing support throughout this research.
1 Introduction

“Carbon nanotubes are molecular-scale tubes of graphitic carbon with outstanding properties. They are among the stiffest and strongest fibres known, and have remarkable electronic properties and many other unique characteristics. For these reasons they have attracted huge academic and industrial interest, with thousands of papers on nanotubes being published every year. Commercial applications have been rather slow to develop, however, primarily because of the high production costs of the best quality nanotubes.”

Peter Harris

1.1 Purpose

The main aim of my thesis has been to help understand non-covalent hybridization of CNTs and ssDNA. This research in hopes will assist in determining a method of selectively separating different nanotubes based on a select property. The main tool for this research has been molecular dynamic simulations while also utilizing replica exchange in order to maximize sampling. Experimentally, it is difficult to probe these CNT-DNA hybrid structures which in turn cause difficulties in determining any ways to make the binding selective. Experimental methods are also costly and time-consuming. With computational chemistry we do not have said limitations, and hope that some element of the CNT-DNA structure will provide a unique property that would allow for separation based on chirality, electrical properties, size, or any other unique characteristic of the nanotube.
My thesis is divided into three main sections. The first discusses nanotube properties with special attention paid to solubilization, electrical, and structural properties. The second discusses molecular mechanics and simulation techniques used in the study, including but not limited to molecular dynamics and replica exchange. The third discusses the simulations and results of simulations specific to the CNT-DNA system in an aqueous environment. These will focus around three ssDNA strands and two different nanotubes as discussed in said section.

1.2 Carbon Nanotube Properties

Single-walled carbon nanotubes\(^1\) (SWNTs) possess superb electronic and mechanical properties,\(^2\) offering numerous applications in materials,\(^3-7\) nanoelectronics\(^8-14\) and energy conversion.\(^15-20\) However, poor solubility of carbon nanotubes\(^21,22\) in aqueous and organic solvents due to their strong propensity to aggregate into stable bundles has impeded progress in many of these areas. Dispersion in a solvent is needed for separation of the nanotubes based on their electric and mechanical properties. Moreover, it enables their subsequent chemical manipulation, which is necessary for applications that require individual nanotube assembly.

This dispersion is especially important due to extremely different electronic properties of nanotubes based on their “chiral vector”. The chiral vector describes the two-dimensional direction in which a graphene honeycomb lattice can be wrapped in order to form a nanotube. This vector is defined by both \(n\) and \(m\) indices. Depending on these values, the nanotube can form one of three “chiralities”. These chiralities are described as “zigzag” \((m=0)\), “armchair” \((n=m)\), and “chiral” (all other combinations). Depending on the diameter and chirality of the carbon nanotube, small changes in the winding of the graphene lattice can change a metallic nanotube to become a large-gap semiconductor.\(^23\)
Recently, several groups have found that certain synthetic and natural polymers, including nucleic acids,\textsuperscript{24-26} polysaccharides\textsuperscript{27-29} and proteins\textsuperscript{30-32} bind to carbon nanotubes with high affinity to form soluble hybrids. Unlike earlier approaches, which relied on covalent functionalization of CNTs to generate soluble species, non-covalent decoration with polymers does not disrupt the structural and electric properties of pristine nanotubes. In particular, Zheng et al.\textsuperscript{24} have shown that ssDNA is especially effective in dispersing CNTs in water, with resulting CNT-DNA hybrid solutions stable for months at room temperature. The authors demonstrated that such DNA-coated tubes can be partially separated by their electrical properties and diameter using ion-exchange chromatography,\textsuperscript{33} as well as by length using size-exclusion chromatography,\textsuperscript{34} with the quality of separation apparently dependent on the DNA sequence.

### 1.3 Experimental Binding Modes

The binding modes and mechanism of formation of the hybrid structures is still not well understood. Surface binding of the ssDNA oligonucleotides was established through CNT band-gap fluorescence measurements by Strano et al.\textsuperscript{35} AFM images obtained by Gigliotti and coworkers show that long ssDNA strands bind tightly to CNTs to form regular structures in a sequence independent fashion.\textsuperscript{36} Using the same technique, Iijima et al. observed arch-like structures of DNA on multi-walled CNTs of different diameter, and found the morphology of bound DNA to be strongly influenced by the curvature of the nanotube surface.\textsuperscript{37} More recently, various wrapping morphologies of ssDNA were observed by TEM on single SWNTs and thin nanotube bundles.\textsuperscript{38}

While imaging and spectroscopy have been successful in confirming the binding of ssDNA to CNTs and establishing the rough picture of the surface morphology of bound oligonucleotides, there have been few attempts to probe the structure of the hybrids and pertinent
intermolecular interactions on the atomic level. Linear dichroism (LD) spectra of several ssDNA-CNT hybrids obtained by Rodger et al.\textsuperscript{39} suggest that DNA wraps the CNT at an oblique angle, with bases lying flat on the surface. Recently, Golovchenko et al.\textsuperscript{40} measured a large anisotropic hypochromicity in the UV absorption spectra of ssDNA homopolymers bound to CNTs, that is consistent with $\pi$-stacking of bases with the graphene lattice, and estimated the orientation of the nucleotides relative to the nanotube axis.

Still, experimental evidence presently available is incomplete and without sufficient detail to conclusively determine the mechanism of DNA-CNT interactions. Computer simulations can help fill the gaps and provide molecular level interpretation of the experimental data. In comparison with the substantial body of experimental work, only a few theoretical studies of ssDNA-CNT interactions have been reported. Initial molecular dynamics (MD) simulations of Gao et al.\textsuperscript{41,42} showed strong association of ssDNA octamers and short CNT fragments in water, with both surface adsorption and insertion into the nanotube possible. The latter encapsulation was subsequently observed experimentally by Okada et al.\textsuperscript{43} Yeh and Hummer used MD to study the electrophoretic transport of ssRNA through CNT membranes, and found that in the absence of an external electric field, RNA remains trapped in the nanotubes by hydrophobic forces.\textsuperscript{44} The translocation kinetics was found to be sequence dependant, which was attributed to variations in the interaction of different bases with the CNT. Lau et al. investigated the conformational stability of a double-sided DNA (dsDNA) octamer encapsulated in a hypothetical large diameter CNT, and found that the exclusion of counterions leads to significant structural deviations.\textsuperscript{45} Lu et al. used density functional theory calculations to study the interaction of an infinitely long (periodic) DNA molecule with an array of nanotubes, and showed that simultaneous charge flow through CNT and DNA is possible.\textsuperscript{46} The structure of the
DNA-CNT complex was optimized via short MD simulations in the absence of the solvent or counterions. Enyashin et al.\textsuperscript{47} characterized several complexes of infinite (periodic) ssDNA helically wrapped around a CNT using DFT tight-binding calculations and found that thymine and cytosine bind most efficiently, with significant DNA to CNT charge transfer possible in certain cases. Very recently, Johnson and Zhao reported an MD simulation of the binding of a Dickerson dodecamer dsDNA with an (8,8) CNT in water.\textsuperscript{48} Unlike ssDNA, dsDNA was found not to wrap around the tube, but rather attach to the surface via its hydrophobic end groups, without perturbing its solution structure, but affecting the A-DNA to B-DNA conversion kinetics. In a different study, Meng et al. investigated the interactions of individual nucleosides with CNT via TDFT and determined electronic features that can be used to identify individual bases,\textsuperscript{49} and their orientation to the nanotube axis.\textsuperscript{50} However, since these calculations are based on the structures of neutral isolated nucleoside-CNT complexes locally minimized in vacuum, it is uncertain how they may be related to a highly charged polynucleotide chain interacting with CNTs in solution.

In summary, large numbers of experiments clearly demonstrate the importance and broad utility of CNT-DNA complexes, however, due to lack of molecular level details, many aspects of the hybridization mechanism are not understood. While recent theoretical and spectroscopic studies provide valuable insight, a number of questions remain unanswered. In particular, the nature of ssDNA-CNT interactions is still uncertain. Various forces, including dispersion interactions and \(\pi\)-stacking appear to contribute to binding, but DNA conformational strain and solvation effects may also play an important role - how and to what extent has not been established. Moreover, the binding modes leading to thermodynamically stable hybrid conformations, which depend on the complex interplay of these factors, have not been
determined conclusively. Determining key interactions in this binding mechanism could allow for alterations to promote dominant interactions, leading to more stable and more selective binding of ssDNA-CNTs to allow for more efficient separation of the hybrid structures.
2 Computational Chemistry

"All these [chemical] rules were ultimately explained in principle by quantum mechanics, so that theoretical chemistry is in fact physics. On the other hand, it must be emphasized that this explanation is in principle. We have already discussed the difference between knowing the rules of the game of chess, and being able to play."

Richard Feynman

2.1 Introduction

The present chapter will introduce computational chemistry and the methods used in this study. Computational chemistry is best described as chemical modeling on an atomic, molecular, or regional level. Both the internal molecular forces and intermolecular forces can be studied depending upon the level of precision used in the simulation.

Various methods in computational chemistry can be thought of as puzzle pieces, and a combination of techniques is often used to complete the puzzle. For different problems, different methods will provide more information than others. In the present study, several different components of the CNT-DNA interactions were studied. Due to the immense size of the CNT-DNA system, quantum calculations would have been too cumbersome; therefore the main tool used in this study was replica exchange all atom molecular dynamics, which shall be discussed in detail further in this chapter.

This chapter will be divided into two major sections. First, a section on general molecular mechanics shall be presented. This section will follow the general outline presented by Grant and Richards (1995). Second, a general overview of replica exchange shall be provided. All materials in this chapter unless otherwise noted is obtained from Grant and Richards (1995).
2.2 Molecular Mechanics

2.2.1 Introduction

Due to the time-consuming nature of quantum mechanical simulations, simplified molecular representations are required for large systems over relatively long timeframes. Molecular mechanics simplify many dimensions of quantum mechanics to harmonic oscillators. As such, molecular mechanics can best be described as soft spheres attached by springs to represent bonds. The potential energy between two non-bonded atoms is expressed as the sum of Lennard-Jones and Coulomb potential functions:

\[ U = \sum_{i<j} 4\varepsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \sum_{i<j} \frac{q_i q_j}{r_{ij}} \]

where the sums are over all interaction pairs, \( \varepsilon \) and \( \sigma \) are the Lennard-Jones potential parameters, \( q_i \) is the partial charge of the \( i \)th interaction site, and \( r_{ij} \) is the distance between interaction sites \( i \) and \( j \). Interaction sites for the purpose of this research are atomic centers. This allows for all non-bonded potential energy calculations to be two-body calculations. This is a simplification since in real systems there are many-body components of non-bonded potential energy. To correct for this, parameters are set to implicitly account for these effects.

For bond lengths, a harmonic oscillator function is used in the following format:

\[ U_{\text{bond}} = k_r \sum_{\text{bonds}} (r_{ij} - r_0)^2 \]

where \( k_r \) is the spring constant, \( r_{ij} \) is the measured bond length, and \( r_0 \) is the equilibrium bond length. For the angular component, another harmonic oscillator is used:

\[ U_{\text{angle}} = k_\theta \sum_{\text{angles}} (\theta_{ijk} - \theta_0)^2 \]
where \( k_0 \) is the spring constant, \( \theta_{ijk} \) is the measured angle, and \( \theta_0 \) is the equilibrium bond angle. For the dihedral portion of potential energy, it is commonly given by a potential energy function of the following general form:

\[
U_{\text{dihedral}} = \sum_{\text{dihedrals}} K_{\text{torsion}}(\phi_{ijkl})
\]

where \( K_{\text{torsion}} \) is a constant and \( \phi_{ijkl} \) is the measured dihedral angle.

### 2.2.2 Force Field Parameterization

The quote by Richard Feynman to begin this chapter is especially prevalent in force field parameterization of molecular mechanic models. The parameters chosen for every atom in the system will affect the quality of results for the simulation. These parameters for atoms, molecules, or groups of molecules are known as force fields.

Much research has been devoted to force field parameterization and development. Depending upon the application, different force fields will produce different results. Common classical force fields include OPLS-AA\(^{51}\) (as used for the DNA in this simulation), AMBER, and CHARMM. Solvent models are also a common area of research. Water is one of the most studied solvents and many models exist\(^{52}\). Different water models are parameterized to match different observed qualities of water ranging from bond angle, partial charges, and hydrogen bonding lattices. For this simulation the water model chosen was the TIP3P model, which is a three-point model which closely replicates the experimental HOH angle of 104.5°.

Building these force fields is usually a product of smaller scale quantum mechanical calculations. By using small fragments, high quality calculations maybe used in order to determine properties such as charge and angle, which are held static at these values in subsequent molecular mechanics calculations.
2.2.3 Atomic Charges

Atomic charges are one of the most difficult as well as one of the most important aspects of a force field. Fixed charges are commonly located at the atom center. This is meant to be a sum of effects of all electrons and protons located within the atom. However, this may not always be an accurate representation due to induced dipole effects. These effects are very difficult to model with a static charge force field.

In order to account for these effects, charges in small molecules often have to be fitted to match experimentally observed properties. Larger molecules are more difficult due to the large number of charge sites and larger molecules are usually not as well studied. For these cases, most force fields are based on the charges from small molecules being transferable to similar pieces contained within larger molecules. The OPLS force field was built using this method. Another approach is to determine charges based on quantum mechanical calculations. The advantage to this method is that less experimental data is required in order to make a quality model.

The method of taking quantum mechanical calculations and transferring them into atomic charges is not a simple one. Electron clouds are difficult to change into a numerical charge and methods for doing this are not always absolute. Mullikan populations are often used in attempt to assign these charges. These have been described as unreliable. This is due to molecules that are contained within a molecule and their charges are known to display conformational dependency.

Another method for making atomic charges is to match an experimental quality while using quantum mechanical calculations to determine all else. This method is shown in research
by Li et. al that matches experimental dipole moments while using quantum calculations to determine atomic charge values\textsuperscript{54}.

While difficult to assign atomic charges for classical force fields, many force fields still produce quite similar results. In summation, force fields while uniquely created are usually in general agreement\textsuperscript{55}.

2.3 Simulations

2.3.1 Introduction

Two forms of simulations used in computational chemistry are molecular dynamics (MD) and Monte Carlo (MC). These calculations are used for molecular ensembles. The techniques used in these simulations are described in detail in “Computer Simulations of Liquids” (Allen and Tildesley 1987) and “Understanding Molecular Simulation” (Frenkel and Smit 2002).

MD utilizes Newton’s laws of motion to calculate the forces on molecules and atoms in a system and allow a system to evolve in time. The velocity and acceleration on all molecules are calculated from the forces, then moved in this manner over a small time-step, and recalculated for the subsequent time-step. For each step, depending on the ensemble used, either temperature (canonical ensemble) or energy (microcanonical ensemble) is maintained through an algorithm. Common algorithms include Nose-Hoover\textsuperscript{56} and Berendsen\textsuperscript{57}. The simulation is allowed to evolve for enough time-steps to obtain reliable averages.

Monte Carlo simulations are based on random alterations of the atomic and molecular coordinates. Energy change for each alteration is calculated, and each alteration can be accepted or rejected based on the energy change of the alteration. For Metropolis Monte Carlo simulations, the move is automatically accepted if it results in a lower energy state, and accepted or rejected based on a Boltzmann-weighted probability if the result is equal or higher energy.
The length of the simulation is determined by the number of attempted moves, and the system is allowed to change until adequate averages are obtained.

Due to computational limitations, it is often difficult to simulate enough solvent around the modeled system to produce bulk solvent effects. Placing the system inside of a vacuum may produce results greatly varied from bulk solution results. In order to compensate for this problem, MD and MC simulations are commonly run with periodic boundary conditions. The experimental cell is surrounded by replicas of itself, where each atom or molecule reacts with only the closest partner in the neighboring replicas.

Lennard-Jones and Coulomb interactions are usually truncated in order to reduce computational time. Lennard-Jones interactions quickly extinguish as a function of distance, so this truncation usually has little effect on the results. Coulomb interactions on the other hand, are slow to decay, but for systems of balanced charge (usually accomplished by the addition of counter-ions), Ewald summations are adequate for handling the long-range electrostatics.

One of the most difficult problems with simulations is sampling all of phase space. Since molecular mechanics simulations are based on the ergotic hypothesis, it is important to be sure that during the simulation, all populated regions of the phase space have been visited. This is extremely difficult to confirm, therefore all simulations have some degree of uncertainty. If one views the potential energy phase space as a topographic map, it is easy to fall into a valley and become trapped. One possible way to reduce the uncertainty involved with this problem is to introduce a way to skip over the large energy barriers located along the topography. One such method to accomplish this is to introduce replica exchange.

2.3.2 Replica Exchange
In order to adequately sample phase space without running simulations for an unreasonable amount of time is often a difficult task. One such method for remedying this is to implement replica exchange. Replica exchange uses multiple simulations; each simulation begins with the same frame, but evolves at different temperatures. The higher temperature replicas easily move over higher energy barriers due to increased kinetic energy in the system. At a predetermined number of time-steps, an exchange is attempted between each adjacent replica simulation. This exchange usually follows the same rule as a Metropolis Monte Carlo move, namely the Metropolis-Hastings criteria. The Metropolis-Hastings criteria is defined:

\[
P(1 \leftrightarrow 2) = \min \left( 1, \exp \left( \frac{1}{k_b T_1} - \frac{1}{k_b T_2} \right) (U_1 - U_2) \right)
\]

where \( T_1 \) and \( T_2 \) are the reference temperatures, and \( U_1 \) and \( U_2 \) are the instantaneous potential energies of replica 1 and 2 respectively.

If the adjacent simulation at the time of the exchange has a lower energy state, or the state is accepted by the defined criteria, then the current frame in one simulation is replaced by the frame in the replica simulation. If it is rejected, then the original simulation continues as if no exchange were attempted. The difficulty in this technique is to choose the correct number of replicas in order to achieve improved enough sampling to compensate for the increased computational workload of having multiple simulations.
3 Modeling of Carbon Nanotubes

"No human investigation can be called real science if it cannot be demonstrated mathematically."

Leonardo da Vinci

3.1 Introduction

This chapter is intended to detail the model used for each of the molecular species in all simulations as well as analyze the results of said simulations. The chapter is divided into two main sections; the first describes all parameters used, the second analyzes and discusses results obtained from the simulations.

We use replica-exchange molecular dynamics (REMD) simulations\textsuperscript{58,59} to characterize the binding thermodynamics of several homonucleic and heteronucleic oligonucleotides to CNTs of different chirality in an aqueous environment. This approach allows us to efficiently sample the hybrid conformations, identify principle binding modes, and determine the effects of DNA sequence variation and nanotube geometry on hybrid structure and stability. We also explore the role of specific DNA-CNT interactions in the binding process, such as $\pi$-stacking of the aromatic bases with the nanotube lattice, relative to more global effects such as conformational strain and hydrophobic and hydrophilic desolvation. Understanding the interplay of these factors will provide important insight into the mechanism of non-covalent hybridization of CNTs by ssDNA. Since the physicochemical properties of the hybrids such as their solubility, electrostatic profiles, and optoelectronic activity are closely related to their molecular structure, characterization of the thermodynamic distribution of bound oligonucleotide conformations may provide guidance on designing improved CNT solubilization and separation techniques and bionanodevices.
3.2 Simulation Parameters

We used all-atom molecular dynamics simulations to study the binding of ssDNA to CNTs in an explicitly represented aqueous solvent environment. The DNA strands were chosen to be decamer oligonucleotides with three sequences: the homooligomers d(T) (TTTTTTTTTT) and d(G) (GGGGGGGGGG); and the heterooligomer d(TG) (TGTGTGTGTG). These sequences have been identified as particularly effective in dispersing and separating CNTs in water. We considered two chiral nanotubes, a (6,5) tube with diameter 7.46 Å and a (15,2) nanotube with a diameter of 12.6 Å, which were selected to investigate the effects of the graphene surface curvature on ssDNA binding. The nanotubes were modeled as infinitely long objects through the use of periodic boundary conditions.

All simulations were performed using the GROMACS simulation package. The potentials for the ssDNA and counterions were derived from the OPLSAA-2001 force field, and the TIP3P model was used for water. The CNTs were modeled using a pair wise additive potential developed by Koumoustakos et al., that was successfully used to study the solvation and self-aggregation of nanotubes in water. This forcefield is given by:

\[
U(r) = K_r \sum_{bonds} \left[ e^{-\gamma (r_{ij} - a)} \right] + \frac{1}{2} K_\theta \sum_{angles} \left( \cos \theta_{ijk} - \cos \theta_0 \right)^2 + \frac{1}{2} K_\phi \sum_{torsions} \left( 1 - \cos 2 \phi_{ijkl} \right) \\
+ \sum_{ij} 4 \epsilon_{CC} \left[ \left( \frac{\sigma_{CC}}{R_{ij}} \right)^{12} - \left( \frac{\sigma_{CC}}{R_{ij}} \right)^6 \right]
\]

where \(r_{ij}\) are the inter-carbon distances, and \(\theta_j\) and \(\phi_{ijkl}\) are all possible bond and torsional angles. The Morse stretch and cosine angle bending terms were derived to model the phonon structure of fullerene crystals. The 2-fold torsional term was introduced to account for strain due to the curvature of the graphene sheet, and parameterized to reproduce the strain energy of bent tetracene. The steric and dispersion interactions were modeled via a Lennard-Jones term with
parameters taken from the Universal Force Field. The specific parameters used in this study are summarized in Table 1.

Table 1. Single-wall carbon nanotube force-field parameters, adapted from Ref. 65.

<table>
<thead>
<tr>
<th>Bond Stretch</th>
<th>Angle Bend</th>
<th>Torsion</th>
<th>Lennard-Jones</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_r = 114.5$ kcal/mol</td>
<td>$K_\theta = 134.4$</td>
<td>$K_\phi = 6.0$ kcal/mol</td>
<td>$\varepsilon_{CC} = 0.1050$ kcal/mol</td>
</tr>
<tr>
<td>$r_0 = 1.418$ Å</td>
<td>$\theta_0 = 120.0^\circ$</td>
<td></td>
<td>$\sigma_{CC} = 3.851$ Å</td>
</tr>
<tr>
<td>$\gamma = 2.1867$ Å$^{-1}$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The CNT-DNA and CNT-water interactions were derived from the relevant force field parameters using the Lorentz-Berthelot combining rules. All bonds with hydrogen were constrained using the LINCS algorithm and the equations of motion were integrated using the Leapfrog integrator with a time step of 2 fs. Nose-Hoover thermostats were used to maintain constant temperature and periodic boundary conditions were applied in all directions. Electrostatic interactions were treated using the particle mesh Ewald (PME) method with a grid spacing of 0.8 Å and a real-space cutoff of 14 Å, while the Lennard-Jones interactions were smoothly truncated via potential shift at 14 Å.

The initial configurations of the CNTs were constructed using the TubeGen program. In order to avoid potential artifacts due to edge effects, the CNTs were treated as infinitely long periodic system along the nanotube axis, with the unit length and $L = 69.8$ Å (1036 atoms) and $L = 81.3$ Å (728 atoms) for the (15,2) and (6,5) CNT respectively. This approach is appropriate, given that the length of a typical CNT is several orders of magnitude larger than that of the ssDNA decamer. The latter oligonucleotides were built using the MAESTRO package (Schrödinger, Inc.) and the initial conformation was chosen to be the A-helix, the predominant form of ssDNA in an aqueous solution. The CNT axis was aligned with the $z$-axis of the simulation box, and the
ssDNA was placed next to the nanotube with its nearest atom 5.0 Å from the CNT surface. The system was then soaked in a pre-equilibrated box of solvent, and water molecules overlapping with the DNA and the nanotube were deleted. An appropriate number of Na\(^+\) counterions were added to maintain overall charge neutrality. The \(z\) dimension of the simulation box was chosen to coincide with the CNT unit length, and \(x\) and \(y\) dimensions were adjusted to allow a 10 Å buffer of solvent between the solutes and the cell boundary. This resulted in the in the simulation cell size of \(\sim50\times53\times81\) Å for the (6,5) CNT simulations and \(\sim55\times55\times70\) Å for the (15,2) CNT simulations, with the number of solvent molecules ranging from 6000 to 7000. The total system size, including the solvent, nanotube and DNA contained 21000-23000 atoms.

In each case, the solvated system was first subjected to a 5000 step steepest-descent energy minimization to remove bad contacts. This was followed by six cycles of 10 ps MD simulation at constant NVT with the heavy atoms of the CNT and DNA restrained, during which the system was heated to room temperature (298 K) in 50 K intervals. The restraints were then removed and the system was relaxed for a further 10 ps. The resulting configurations were used as starting points for subsequent simulations.

Two simulation studies were conducted for each of the six ssDNA-CNT systems. First, a 5000 ps constant NVT simulation was performed to probe the overall dynamics of oligonucleotide-nanotube association. A replica exchange simulation was then initiated to efficiently sample the equilibrium ensemble of the hybrids, using 12 replicas with temperatures ranging from 298 K to 342 K evenly spaced in 4 K intervals. Each replica was evolved for 5000 ps, with replica exchanges attempted every 2 ps, for an aggregate 60 ns of sampling per system with an average exchange acceptance of 12%. In all simulations, the configurations were saved every 2 ps for subsequent analysis.
Finally, in order to establish the free ligand reference states for the study on hybridization energetics, an additional separate 5000 ps constant NVT simulation was performed for each of the three oligonucleotides and the two CNTs solvated in water, with counter ions added to the free DNA systems to maintain charge neutrality. The simulation parameters were the same as those used in the hybrid simulations.

3.3 **Structure of CNT-ssDNA hybrids**

3.3.1 Defining Geometry of CNT-ssDNA Structure

The nature of the binding modes, or the preferential geometry assumed by the ssDNA molecules upon binding to CNT are of particular interest as most physicochemical properties of the hybrids are closely related to their molecular structure. To identify the former, we first sought insight into the dynamics of the binding process. In Figure 1 we show the distance between the center of mass (COM) of the oligonucleotide and the nanotube axis as function of time, obtained from a 5000 ps constant NVT simulation at 298K.
Figure 1. The distance of the ssDNA backbone center-of-mass to the CNT axis as a function of time, obtained from the constant NVT simulation of the binding of the d(G) (black), d(T) (red) and d(TG) (blue) nucleotides to the (15,2) (upper panel) and (6,5) (lower panel) CNTs. In each of the six systems, a multi-stage process is clearly observable. The initial interaction of the oligonucleotide is established following a fast partial adsorption, evident in a rapid decrease in the COM distance within ~1000 ps. This is followed by a slow structural reorganization of the ssDNA to achieve a fully bound state. The step-like features in later stages of the distance profiles suggest that sections of the oligonucleotide chain adsorb sequentially. This is in part due to the fact that discrete self-stacking interactions between the DNA bases that are present in the native A-helix form must be broken before they can be replaced by favorable π-stacking interactions with the nanotube surface, which provides a first glimpse into the origin of the barriers governing the kinetics of hybridization. A detailed view of this process is available in the animated movies of the simulations provided as Supplementary Information. Comparison of the distance profiles for the (15,2) and (6,5) hybrids shows that the nanotube surface plays a
significant role in modulating the dynamics of non-covalent association. For example, the d(G) decamer binds rapidly to the surface of the (6,5) nanotube, with almost the entire chain adsorbing within 1000 ps, while the same takes almost 2500 ps and involves two distinct stages for the hybridization of the d(G) with the larger-diameter (15,2) tube. While in most cases the adsorption of oligonucleotide chains is largely complete within the 5000 ps of simulation time, in some cases, most notable for the heteronucleic d(TG) decamer associating with the (6,5) nanotube, only partial adsorption is achieved, demonstrating that the hybridization is a highly frustrated process involving large scale conformational changes in the DNA backbone during which significant barriers need to be overcome. Prompted by these findings, we performed replica-exchange MD simulations for each of the six systems in order to accelerate barrier crossings and improve the sampling of bound states. In Figure 2 we show the root-mean-square deviation (RMSD) of the oligonucleotide backbone atoms relative to the initial DNA configuration for room-temperature (298K) replicas. Following the initial adsorption, the RMSD are found to oscillate between several distinct values, suggesting that the bound state ensemble consists of a small number of structurally well-defined conformation families.

Figure 2. The RMSD of the ssDNA backbone from the initial structure as a function of time for the 298K trajectory of the replica exchange simulations of d(G) (left), d(T) (middle) and d(TG) (right) oligonucleotides with (15,2) (top) and (6,5) (bottom) CNTs.
Numerous transitions show that the barriers are crossed frequently and that stable states are visited multiple times, indicating that the bound state ensembles are well sampled in our simulations. In order to further characterize these ensembles, we analyzed the distribution of bound oligonucleotide conformations as a function of several order parameters. The RMSD plots in Figure 2 and visual inspection of the trajectories confirm that initial adsorption was largely complete within 1000 ps, following which the 298K REMD trajectory mostly samples bound hybrid states. Hence, the first 1000 ps were discarded and the subsequent analysis is based on conformations harvested over the last 4000 ps of the REMD simulation.

The principal features describing the conformation of the nucleic acid biopolymer are the backbone configuration and the orientation of the nucleoside side chains. The former is in principle completely described by a set of six dihedral angles ($\alpha, \beta, \gamma, \delta, \varepsilon, \zeta$) for each nucleotide in the chain. Apart from the inherent complexity of analyzing conformations in this six-dimensional order parameter space, changes in specific torsion angles are often compensated by changes in other torsional angles, resulting in multiple combinations of torsions that describe very similar structural motifs. Hence, we decided to use a simpler reduced representation of the backbone torsional space developed by Pyle and coworkers,\textsuperscript{71} which was shown to provide a good description of the backbone structure of flexible polynucleotides.\textsuperscript{72} In this approach, the local backbone conformation is described by a pair of pseudotorsional angles ($\eta, \theta$) which express the rotation around virtual pseudobonds connecting the C4' and P backbone atoms, such that $\eta \equiv \pi(C_{n-1}C_{n+1},P_{n},C_{n+2})$ and $\theta \equiv \pi(P_{n+1},C_{n+1},C_{n+2},P_{n+2})$, thus yielding four pairs of pseudotorsions per ssDNA decamer. These were computed for each of the sampled ssDNA conformations, and binned into $4^\circ \times 4^\circ$ bins. Kernel smoothing was then applied to the resulting two-dimensional
histograms to delineate high-density regions and identify statistically significant features. The latter was accomplished through the use of the Blackman window:

\[
W(\Delta, \omega) = \begin{cases} 
0.42 + 0.5 \cos\left(\frac{\Delta}{\omega}\right) + 0.08 \cos\left(2\pi \frac{\Delta}{\omega}\right) & |\Delta| < \omega \\
0 & \text{otherwise}
\end{cases}
\]

where \( \omega \) is the half-width of the window function and \( \Delta \) is the distance in parameter space. This window was chosen since it provides a good balance of computational efficiency and accuracy.

For pseudotorsion distributions, \( \Delta \) is defined as:

\[
\Delta_{ij} = \sqrt{\Delta\eta_{ij}^2 + \Delta\theta_{ij}^2}
\]

where

\[
\Delta\eta_{ij} = \min\left(\eta_i - \eta_j, 360 - |\eta_i - \eta_j|\right)
\]

\[
\Delta\theta_{ij} = \min\left(\theta_i - \theta_j, 360 - |\theta_i - \theta_j|\right)
\]

The population of each histogram bin \( P_i \) was then replaced by

\[
P_i^* = \sum_j W(\Delta_{ij}, \omega) P_j
\]

reflecting the local population density in the neighborhood of bin \( i \). The smoothing width \( \omega = 20^\circ \) was found to provide good resolution the principal features of the \((\eta, \theta)\) landscape. The resulting smoothed population distribution maps for the six hybrid systems are shown in Figure 3. In all cases, the maps reveal multiple well-defined and relatively narrow high-density regions spanning discrete sections of the \((\eta, \theta)\) space, indicating that the hybrid ensemble consists of a number of distinct DNA backbone conformations separated by high barriers. A significant variation in population distributions is observed both among different DNA sequences and between the two nanotubes.
While the d(G) and d(T) hybrid distributions show a single dominant peak, the d(TG) hybrids exhibit a more complex landscape comprising multiple peaks of comparable height, suggesting a significant degree of structural heterogeneity of the complexes. We next examine how the variation in nanotube diameter affects the conformational distribution of bound hybrids. This is of particular interest, since non-covalent complexation with ssDNA has been proposed as a means of separating mixtures of industrially produced CNTs according to their diameter. Since most physicochemical properties of such hybrids are closely linked to their molecular structure, the effectiveness of separation would largely depend on the degree to which their equilibrium structures differ. For example, the ion-exchange chromatography approach used by Zheng et al.\textsuperscript{33} to achieve partial diameter based separation of ssDNA-CNT hybrids relies on the difference in electrostatic profiles of the charged complexes, which in turn strongly depends on the
distribution of the DNA backbone charge, and hence ultimately on the conformations of bound oligonucleotides. The pseudotorsional population distributions of the d(G) decamers bound to (15,2) and (6,5) are quite similar, the only significant difference being the principal peak shifting slightly from $\eta \approx 180^\circ$, consistent with the primarily helical conformations, to $\eta \approx 140^\circ$ suggesting an increased degree of zigzag bending in the backbone. This is accompanied by a shift in population from the minor peak at $(240^\circ,90^\circ)$ to that at $(270^\circ,245^\circ)$. In contrast, the d(T) hybrids show a much more pronounced variation in $(\eta, \theta)$ distributions, with significant population shift from the region at $(240^\circ,140^\circ)$ of the (15,2) hybrid to the new peak centered at $(40^\circ,180^\circ)$ of the (6,5) hybrid. The differences in the relatively complex topologies of the d(TG) maps were more subtle, although population from several backbone states significantly populated in the (15,2) hybrids appears to shift to a single peak region at $(280^\circ,145^\circ)$ in the (6,5) complexes. In summary, the variation in the pseudotorsional distributions of the ssDNA bound to CNTs of different diameter is primarily in the $\eta$ direction and appears most pronounced for the d(T) oligonucleotide.

The orientation of nucleotide side chains is adequately represented by two parameters: the pseudorotation ($P$) describing the pucker of the furanose sugar ring, and the dihedral angle $\chi$ (describing the relative orientation of the base with respect to the sugar. In this study, we adapt the Alton/Sundarlingan\textsuperscript{73} definition, where $P$ is expressed in terms of the furanose dihedrals ($\nu_1-\nu_5$) as:

$$P = \tan^{-1}\left(\frac{(\nu_2 + \nu_4) - (\nu_1 + \nu_3)}{2\nu_0(\sin 36^\circ + \sin 72^\circ)}\right)$$

and $\chi = \pi(O4'-C1'-N1-C2)$ or $\chi = \pi(O4'-C1'-N9-C4)$ for thymine or guanine bases respectively. The $(P, \chi)$ values were computed for the ten bases in each of the sampled bound DNA
conformations, and the kernel smoothing procedure identical to the one described in the previous section was then used to construct the \((P, \chi)\) population distribution maps for each of the six hybrids, which are shown in Figure 4. In contrast with the \((\eta, \theta)\) maps, the \((P, \chi)\) distributions show little variation with either DNA sequence or CNT diameter. The d(T) and d(G) complexes with both (15,2) and (6,5) nanotubes exhibit a single broad high-density region with \(P \sim 100^\circ - 180^\circ\) (corresponding to the C2'-endo pucker) and \(\chi \sim 170^\circ - 250^\circ\).

Figure 4. The contour plots of the smoothed bound nucleotide conformational distribution (arbitrary units) as a function of the ribose pseudorotation (\(P\)) and the base torsion angle (\(\chi\)), for the d(G) (left), d(T) (middle) and d(TG) (right) oligonucleotides hybridized with the (15,2) (upper panels) and (6,5) (lower panels) CNT.

The heteronuclear d(TG) hybrids show a more diverse landscape, further reflecting the rich morphology indicated by the backbone distributions, with additional peaks present at \((240^\circ, 100^\circ)\) and \((340^\circ, 150^\circ)\), consistent with the C4'-endo and C2'-exo puckers respectively. Interestingly, the former is the most populated state for the (15,2) hybrid, while the latter is preferred in the (6,5) hybrid.
While the two sets of order parameters discussed thus far give an excellent description of the local DNA structure, in order to fully characterize the surface morphology of adsorbed oligonucleotides it is useful to investigate the distribution of additional order parameters describing the global structure of the chains. End-to-end distance \((d_{e2e})\) and radius of gyration \((R_g)\) are two parameters frequently used to characterize the overall fold of polymer chains. Here, we define the former as the distance between the terminal P at the 3' end of the oligonucleotide, and the O3' at the 5' end. 

\(R_g\) is defined with respect to the backbone atoms as:

\[
R_g = \sqrt{\frac{1}{N} \sum_i (r_i - r_{CM})^2}
\]

where the summation runs over \(N\) backbone atoms, and \(r_{CM}\) is the backbone center of mass. The population density maps, shown in Figure 5, were constructed using the procedure described previously, with \((d_{e2e}, R_g)\) pairs for each sampled configuration histogramed into bins of width \(\Delta R_g = 0.2 \text{ Å} \) and \(\Delta d_{e2e} = 1.0 \text{ Å}\), followed by kernel smoothing with \(\omega = 3.0 \text{ Å}\).
Figure 5. The contour plots of the smoothed DNA conformational distribution (arbitrary units) as a function of the backbone end-to-end distance ($d_{e2e}$) [Å], and the backbone radius of gyration ($R_g$) [Å], for the d(G) (left), d(T) (middle) and d(TG) (right) oligonucleotides hybridized with the (15,2) (upper panels) and (6,5) (lower panels) CNTs.

In all cases, the distributions exhibit several narrow peaks, frequently separated by wide unpopulated regions, once again demonstrating that the hybrid ensembles comprise of a small number of structurally distinct binding modes. The d(G) hybrids favor more compact conformations, with majority of population clustered within $d_{e2e} = 15-25$ Å and $R_g = 10-13$ Å, although slight preference for more extended conformation is observed for the (6,5) complexes.

On the other hand, the d(T) hybrids clearly favor extended conformations, with most populated states found between $d_{e2e} = 40-50$ Å and $R_g = 15-17$ Å. As in the case of d(G) complexes, the high-density regions for the d(T)–(6,5) hybrids show a discernable shift towards more extended conformations in comparison with their (15,2) counterparts. In contrast, the d(TG) hybrids show the opposite behavior. While most populated regions lie in $d_{e2e} = 25-45$ Å and $R_g = 12-15$ Å range, therefore in between high density areas observed for d(T) and d(G) complexes, the (6,5)
bound d(TG) DNA strands favor significantly more compact forms [maximum at 
\((d_{e2e}, R_g) = (25, 13)\)] versus the \((15,2)\) hybrids [maximum at \((d_{e2e}, R_g) = (44,14)\)].

In summary, the differences in equilibrium conformational distributions of 
oligonucleotides bound to \((15,2)\) and \((6,5)\) hybrids appear to be largest for d(TG), followed 
closely by d(T), while d(G) exhibits less variation. This can explain why the former two were 
found to be more effective in separating the nanotubes via the ion-exchange chromatography 
experiments of Zheng et al.\textsuperscript{33}

Since the above findings suggest that the equilibrium ensembles consist of a small 
number of distinct states, we next attempted to qualify these individual binding modes. This was 
accomplished through cluster analysis of the full set of sampled configurations for each of the six 
hybrids. First, a similarity matrix was generated by computing the RMSD deviation of DNA 
backbone atoms between all pairs of conformations. Non-overlapping clusters of similar 
structures were then identified according to the algorithm by Daura et al.,\textsuperscript{74} such that the DNA 
backbone RMSD between all members of a given cluster was within 2.0 Å. The results for the 
six simulations are shown in Figure 6 as matrices representing all pairs of sampled 
conformations. The upper left half of each matrix shows the computed RMSD values with 
grayscale intensity indicating the degree of similarity, white being the most similar (RMSD 
zero). The lower right half portion shows pairs of structures belonging to the top five clusters, 
with red being the largest cluster, followed by yellow, blue, green and magenta. Each cluster was 
then assigned to a single binding mode. It is immediately apparent that these five most populated 
modes comprise more than half of the total conformations in each simulation, confirming that the 
rich hybrid morphology consists of a few structural families. While the top (red) binding mode of
d(T) and d(TG) hybrids is significantly more populated than the rest, this is not the case for d(G) hybrids where the top two clusters are of comparable size.

Figure 6. Cluster analysis of the conformations of d(G) (left) d(T) (middle) and d(TG) (right) complexes with the (15,2) (upper panels) and (6,5) (lower panels) CNT. The upper left half of each matrix shows the backbone RMSD of each pair of sampled structures (darker areas-hi-}

Figure 6. Cluster analysis of the conformations of d(G) (left) d(T) (middle) and d(TG) (right) complexes with the (15,2) (upper panels) and (6,5) (lower panels) CNT. The upper left half of each matrix shows the backbone RMSD of each pair of sampled structures (darker areas-higher RMSD). The lower right portion indicates structure pairs belonging to the top five clusters, color coded red (largest), blue, yellow, green and magenta (smallest).

To analyze the contribution of individual modes to the overall hybrid ensemble, in Figure 7 we plot the \((\eta, \theta)\) and \((d_{c2c}, R_g)\) values for the conformations comprising the top five binding modes the d(G)-(15,2) complex. Comparison with Figures 3 and 5 shows that while several modes contribute to the high density region of the \((\eta, \theta)\) map, each of the peaks seen in the \((d_{c2c}, R_g)\) map is built of conformations belonging to a single cluster, indicating that these global
order parameters are better descriptors of different bound states. The morphological diversity of the hybrid structures is evident from the images of representative hybrid conformations for each binding mode shown alongside the plots. In all cases, the primary interaction of the DNA with CNTs is through stacking of the DNA bases onto the graphene. The diversity of the binding modes stems from the multitude of possible stacking orientations, coupled with solvation effects, backbone and sugar ring strain induced by the nanotube surface curvature, and the self-stacking propensity of nucleotides. For example, the principal (red) binding mode shows the oligonucleotide chain helically wrapped around the tube for about ¾ of its length, following which it exhibits a sharp turn. The origin of this kink can be understood by examining the orientation of the nucleotide bases. While the bases are aligned roughly parallel to each other on the same side of the backbone throughout the initial helical segment, the turn coincides with the flipping of base to the opposite side. This is a well-known feature of nucleic acid structure known as the switch-turn. Two such turns can be observed in the

Figure 7. ($\eta, \theta$) (left) and ($d_{z2z}, R_g$) (right) distribution maps for the conformation clusters belonging to five most populated binding modes of the (15,2)-d(G) complex. The clusters are color coded from the largest (red), followed by yellow, blue, green, to the smallest (magenta). The color-coded representative structures from each binding mode are shown. The pie chart shows the population of each binding mode as a fraction of the total sampled conformations.
second (yellow), more extended binding mode, which thus comprises of three helical segments interrupted by turns. The third mode (blue) introduces self-stacking between the bases in the middle of the chain (known as the stack-turn), resulting in a hairpin conformation of the polynucleotide chain straddling the nanotube. Combinations of these motifs lead to more complex structural features of the last two less significant binding modes, with DNA chains exhibiting progressively more disorder, and poorer interactions with the nanotube surface. For comparison, in Figure 8 we show the binding modes and the respective $(\eta, \theta)$ and $(d_{e2e}, R_g)$ maps for the d(T)-(6,5) complex.

![Figure 8](image)

Figure 8. $(\eta, \theta)$ (left) and $(d_{e2e}, R_g)$ (right) distribution maps for the conformation clusters belonging to five most populated binding modes of the (6,5)-d(T) complex. The clusters are color coded from the largest (red), followed by yellow, blue, green, to the smallest (magenta). The color-coded representative structures from each binding mode are shown. The pie chart shows the population of each binding mode as a fraction of the total sampled conformations.

Similar to the d(G) complex, significant overlap is observed in the $(\eta, \theta)$, since different hybrid configurations often contain similar local structural features, while the $(d_{e2e}, R_g)$ show good discrimination between the different modes. The top two conformations (red and yellow), which together contain half of the overall population, feature largely extended nucleotide chains consisting of a number of helical segments interrupted by switch-turns, with most bases in good
contact with the nanotube surface. Interestingly, the two minor binding modes (blue and green) show highly compact, almost cyclic helical wrapping around the small-diameter (6,5) CNT, that still affords good stacking of the bases to the nanotube surface. Notably absent from the ensemble are the stack-turn motifs, which is not unusual, since the poly d(T) sequences are known to exhibit poor self-stacking properties due to interference of methyl substituents with the alignment of pyrimidine rings. Similar findings were observed for the remaining four hybrids, and the figures are provided as Supporting Information.

Finally, to complete the picture of hybrid geometry, we consider the structure of the ssDNA-nanotube interface formed by the nucleotide bases stacking onto the graphene surface. It is clear that the alignment of base planes parallel to the nanotube surface is strongly preferred. This arrangement maximizes favorable $\pi$-stacking interactions and was prevalent in all of the identified binding modes. However, since the nanotubes provide a cylindrical binding surface of anisotropic curvature it is of interest to explore whether the $\pi$-stacked bases display orientational preference with respect to the longitudinal and lateral directions along the surface. To check this, we specify the orientation of the surface-stacked bases via the angle between the nucleic acid base ground state transition dipole-moment vector and the direction of the nanotube axis. The dipole moment vectors are defined as

$$\mathbf{\mu} = \sum_i q_i (\mathbf{r}_i - \mathbf{r}^*)$$

where $q_i$ are the partial charges at atomic sites $\mathbf{r}_i$, $\mathbf{r}^*$ is the center of mass of the DNA base, and the summation runs over all base atoms. The directions of the dipole moments for thymine and guanine bases are illustrated in Figure 9. In Figure 10 we plot the distribution of $\cos \theta = \mathbf{\mu} \cdot \mathbf{\hat{z}}$, with the nanotube axis aligned with the $z$-axis for the six systems. $P(\cos \theta)$ was obtained by
histograming the values of $\cos \theta$ for bases stacked with the nanotube surface over the entire simulation.

A given base is considered stacked if more than half of the pyrimidine or purine ring atoms are in Van der Waals contact with the nanotube. In all cases, the distributions are strongly peaked around $\cos \theta = \pm 1$, indicating the surface bound bases strongly prefer orientations which align their dipole moment with the nanotube axis. Interestingly, while the d(G) sequences favor parallel alignment, the d(T) chains align their dipole moments in anti parallel fashion. This opposing preference is reflected in the bimodal distribution of the heteronuclear d(TG) strands, which show both anti-parallel and parallel preference. While the d(G) distributions show little variation between the (15,2) and (6,5) hybrids, the d(T) distribution is more strongly peaked for the latter. These findings are consistent with the hypochromicity measurements of Golovchenko,\textsuperscript{40} as well as linear dichroism measurements of Rodger\textsuperscript{39} and the calculations of Kaxiras,\textsuperscript{50} all of which predict parallel alignment of the guanine dipole moments. Their data was less conclusive for thymine sequences, possibly due to larger variations among different CNT type hybrids, since the spectroscopic measurements were performed on samples containing mixtures of CNTs.

3.3.2 Hybrid Thermodynamics

Non-covalent association of the polyelectric DNA strands with CNTs is a complex process controlled by numerous competing intramolecular and intermolecular forces. It is therefore of interest to explore how and to what extent each of these contribute to the thermodynamics of hybridization and the relative stability of hybrid conformations. Broadly, the binding energetics can be divided into contributions from solvation, the DNA-nanotube
interactions and DNA conformational strain. Since the CNT does not undergo structural change upon complexation, the contribution from the CNT internal energy is negligible.

As the complexation with ssDNA was found solubilize highly hydrophobic CNTs, solvent interactions are expected to play an important role in the thermodynamics of DNA-CNT association. In principle, interaction of the solute with a polar solvent such as water can be divided into contributions from electrostatic screening due to long-range solvent polarization and specific short-range interactions (such as hydrogen bonds), as well as the non-polar contributions. Since the CNT in our model is uncharged, the long-range electrostatic profile of the hybrids should not differ significantly from that of free ssDNA strands, and hence the contribution of long-range solvent polarization to binding thermodynamics is expected to be minor. Hence, we focus on the two solvation components most affected by the binding process: the hydrophilic interactions expressed in terms DNA-water hydrogen bonding and the hydrophobic component, which includes contributions from the non-polar dispersion interactions and free energy cost due to solute cavity formation. The hydrophobic contribution to the binding free energy is generally proportional to the change in the solvent-exposed surface area (SASA) of the solute, \( \Delta G_{np} = \gamma \Delta (\text{SASA}) \), with \( \gamma \) being the empirical surface tension coefficient. In Tables 2 and 3 we report, for the (15,2) and (6,5) hybrids respectively, the ensemble average changes in the total number of DNA-water hydrogen bonds and the SASA upon complexation, relative to the average values obtained from free solvated DNA and CNT simulations. In all cases, the binding is accompanied by loss of favorable solute-solvent hydrogen bonds, compensated by the reduction of SASA due to burial of large portions of nanotube surface through stacking of DNA bases. The desolvation penalty is the largest for d(G), with a loss of \(~10-12\) hydrogen bonds, and the smallest for d(T), where 5-6 hydrogen bonds are lost. There is
little variation between the two nanotubes. The decrease in SASA is slightly larger at ~1000 Å² for the (15,2) hybrids, compared to ~750-950 Å² for the (6,5) complexes, with more variation among the DNA types.

Table 2. Important contributions to the binding thermodynamics of the ssDNA complexes with the (15,2) CNT

<table>
<thead>
<tr>
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<th>d(G)</th>
<th>d(T)</th>
<th>d(TG)</th>
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<tr>
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<td>-1084 (51)</td>
<td>-1007 (76)</td>
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</tr>
<tr>
<td>1</td>
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<td>14.4 [0.26]</td>
<td>44.7 [0.17]</td>
</tr>
<tr>
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<td>-25.7 [0.12]</td>
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\(^a\) The Δ are the changes relative to the average values of obtained from the simulation of free DNA and CNT in water. \(^b\) The total number of hydrogen bonds between DNA and water. \(^c\) The total solvent-accessible surface area of ssDNA and CNT. \(^d\) The average values for the conformational population clusters identified in Section III, in decreasing size. \(^e\) The fraction of the total population in a given cluster is in square brackets. \(^f\) The standard error (parenthesis) was calculated using a double-exponential autocorrelation model of Hess. The large spreads reflect structural heterogeneity of the equilibrium ensemble.

observed for the latter, possibly due to higher curvature of the CNT surface. Taking an average energy of DNA-water hydrogen bond of 5.0 kcal/mol and a typical value of \(\gamma = 0.005\) kcal/mol/Å², solvation effects are found to disfavor hybridization, with a penalty ranging from...
~20 kcal/mol for (15,2)-d(T) to ~50 kcal/mol for (15,2)-d(G) complex. These findings are consistent with the observation that d(G) oligonucleotides are less efficient in solubilizing nanotubes than their d(T) counterparts, and suggest that the origin of hybrid stability lies elsewhere.

The rearrangement of the backbone and base configuration from the A-helix form favored by free ssDNA in solution to a variety of bound hybrid conformations leads to a change in the internal energy of the oligonucleotide. To evaluate the contribution of this strain energy to the hybridization energetics we computed the difference in average DNA conformational energy \( (U_{\text{conf}}) \) obtained from the hybrid and corresponding free DNA simulations,\

\[
\Delta U_{\text{strain}} = \langle U_{\text{conf}} \rangle_{\text{hybrid}} - \langle U_{\text{conf}} \rangle_{\text{free}}
\]

Table 3. Important contributions to the binding thermodynamics of the ssDNA complexes with the (6,5) CNT

<table>
<thead>
<tr>
<th></th>
<th>d(G)</th>
<th>d(T)</th>
<th>d(TG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta H)-bonds(^a,b)</td>
<td>-10.5 (0.6)</td>
<td>-6.3 (0.8)</td>
<td>-6.5 (0.8)</td>
</tr>
<tr>
<td>( \Delta \text{SASA} (\text{Å}^2))^a,c</td>
<td>-961 (28)</td>
<td>-885 (24)</td>
<td>-744 (36)</td>
</tr>
<tr>
<td>( \Delta U_{\text{strain}} ) (kcal/mol)(^a)</td>
<td>-63.2 (10)</td>
<td>43.4 (9)</td>
<td>57.6 (12)</td>
</tr>
<tr>
<td>Cluster(^d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-90.1 [0.23]</td>
<td>11.2 [0.33]</td>
<td>60.5 [0.31]</td>
</tr>
<tr>
<td>2</td>
<td>-89.5 [0.19]</td>
<td>32.2 [0.19]</td>
<td>60.6 [0.14]</td>
</tr>
<tr>
<td>3</td>
<td>-99.3 [0.16]</td>
<td>95.9 [0.09]</td>
<td>25.7 [0.12]</td>
</tr>
<tr>
<td>4</td>
<td>6.1 [0.13]</td>
<td>71.5 [0.09]</td>
<td>26.3 [0.10]</td>
</tr>
<tr>
<td>5</td>
<td>-0.1 [0.09]</td>
<td>61.2 [0.08]</td>
<td>60.5 [0.07]</td>
</tr>
<tr>
<td>( U_{\text{int}} ) (kcal/mol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster(^d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-205.4</td>
<td>-175.1</td>
<td>-169.4</td>
</tr>
<tr>
<td>2</td>
<td>-184.6</td>
<td>-168.3</td>
<td>-179.3</td>
</tr>
<tr>
<td>3</td>
<td>-199.9</td>
<td>-162.7</td>
<td>-174.7</td>
</tr>
<tr>
<td>4</td>
<td>-180.6</td>
<td>-164.8</td>
<td>-174.5</td>
</tr>
<tr>
<td>5</td>
<td>-167.9</td>
<td>-164.5</td>
<td>-128.1</td>
</tr>
<tr>
<td>( \pi)-stack contacts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster(^d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.5 (0.2)</td>
<td>8.2 (0.3)</td>
<td>7.8 (0.5)</td>
</tr>
<tr>
<td>2</td>
<td>9.7</td>
<td>9.3</td>
<td>8.8</td>
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<tr>
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<td>7.9</td>
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<td>8.0</td>
<td>8.9</td>
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<tr>
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<td>-----</td>
</tr>
<tr>
<td>5</td>
<td>8.5</td>
<td>8.3</td>
<td>6.3</td>
</tr>
</tbody>
</table>

The ∆ are the changes relative to the average values of obtained from the simulation of free DNA and CNT in water. The total number of hydrogen bonds between DNA and water. The total solvent-accessible surface area of ssDNA and CNT. The average values for the conformational population clusters identified in Section III in decreasing size. The fraction of the total population in a given cluster is in square brackets. The standard error (parenthesis) was calculated using a double-exponential autocorrelation model of Hess.

The $U_{\text{conf}}$ is taken to be the sum of all bonded and non-bonded interactions between DNA atoms computed without cut-offs. The ensemble average strain energies for the (15,2) and (6,5) hybrids are given Tables 2 and 3, respectively, along with the averages computed for each of the five largest population clusters identified in Section III. The former display considerable variation, with the d(T) and d(TG) complexes showing an increase in conformational strain of ~20-80 kcal/mol upon hybridization, while the d(G) hybrids show a decrease of ~15-60 kcal/mol. The relatively large uncertainty reflects large variations in strain energy with even modest conformational changes due to strong intramolecular repulsion of the polyelectric. In general, the most populated clusters in a given hybrid tend to have the lowest strain, although this is not always the case [for example (15,2)-d(T) and (6,5)-d(TG)]. This correlation can clearly be seen in the free energy maps of $\Delta U_{\text{strain}}$ vs. number of $\pi$-contacts given in Supporting Information.

Finally, an important contribution to hybridization energetics comes from direct interactions of ssDNA with the CNT, in particular, the $\pi$-stacking of DNA bases with the nanotube surface. In Tables 2 and 3 we report the ensemble averages of the DNA-CNT interaction energies for the (15,2) and (6,5) hybrids, along with the corresponding values for the five principal population clusters. In all cases, the interactions strongly favor hybridization, stabilizing the complexes by 150-190 kcal/mol. In general, the more populated clusters exhibit more favorable interactions, however this is not always the case, indicating that although DNA-CNT interactions contribute strongly to hybridization, equilibrium bound state distribution is controlled by a complex interplay of factors. Since the primary interaction mechanism is
believed to be through $\pi$-stacking of DNA bases with the CNT graphene lattice, it is of interest to explore how the latter correlate with the interaction energy. As in Sec. III, we define a base to be in a $\pi$-stacking contact with the nanotube if half or more of the heterocycle atoms are in Van der Walls contact of the CNT surface. Hence, the ssDNA decamer can form up to 10 contacts provided all the bases were stacked with the CNT. The number of $\pi$-contacts averaged over all bound states, as well as the corresponding values for individual clusters for all six hybrids are shown in Tables 2 and 3. Comparison with the interaction energy data shows the two are strongly correlated, with decrease in interaction energy generally paralleling an increase in the number of $\pi$-contacts, confirming that $\pi$-stacking is the principal mechanism of DNA-CNT interaction and a major source of hybrid stability.

To further investigate the role $\pi$-stacking in hybrid thermodynamics, we computed the free energy profiles as a function of end-to-end distance ($d_{e2e}$) and the number of $\pi$-stacked bases ($n$). The former was found to be a good descriptor of morphological diversity of hybrids, while the latter captures the interaction energetics. The free energy profile along any set of order parameters ($X,Y$) is determined by first calculating the probability distribution $P(X,Y)$ through histogram analysis of the bound state population. The relative free energy of any two states is then given by

$$\Delta G = -k_B T \ln \frac{P(X_2,Y_2)}{P(X_1,Y_1)}$$
Figure 11 shows the relative free energy profiles for each of the six hybrids. All profiles exhibit a rugged landscape with multiple well-defined minima separated by high barriers. Comparison with Figures 7 and 8 and data in Tables 2 and 3 shows that individual minima can be associated with the previously identified major population clusters, confirming that the latter constitute distinct stable states of the hybrid systems. The overall features of the profiles are not unlike those of other orderly self-associating macromolecular structures, such as folded proteins, although there are important differences. While proteins generally exhibit a 'funneled' free energy landscape, with the principal basin of attraction around the native state global minimum significantly lower than other nearby minima, the hybrid profiles often have several low lying minima of comparable stability, with $\Delta G$ within 0.5 kcal/mol of each, suggestive of a frustrated system. This latter is particularly true of d(G) and d(TG) hybrids, while the d(T) hybrid profiles do show a somewhat funneled landscape, with minimum free energy basin ~1.5 kcal/mol lower.
than other local minima. Another difference between d(T) hybrids and their guanine containing counterparts is that the lowest lying minimum of the former coincides with the maximum number of \( \pi \)-contacts, while the latter have a global minimum at an intermediate number of surface stacked bases. The origin of these differences is likely in the increased propensity of guanine bases to self-stack, which provides an alternative stabilization mechanism to surface-stacking. Such self-stacking is clearly visible in Figure 7 (blue structure) corresponding to the minimum at \((n,d_{z2e})\sim(4,20)\) of the d(G)-(15,2) profile, and is observable in other structures provided in Supporting Information. In contrast, self-stacking in polythymine strands is suppressed due to interference of methyl substituents with proper ring alignment.

Further insight into the thermodynamics of ssDNA-CNT hybridization can be obtained by exploring the stability of the complexes as a function of temperature. Such studies are often used to probe the energetics of DNA strand self-association and protein folding. In Figure 12 we show the average number of \( \pi \)-stacking contacts \((n)\) between DNA bases and the CNT surface as a function of temperature, for each of the six hybrids, which were obtained from the corresponding high-temperature REMD trajectories. In all cases, a steady decline in \((n)\) can be observed with increasing temperature, indicating that complex degradation occurs through a gradual loss of \( \pi \)-interactions. A qualitative
Figure 12. The average number of $\pi$-stacking contacts as a function of temperature, obtained from high temperature REMD trajectories for d(G) (black), d(T) (red) and d(TG) (green) complexes with (15,2) (top) and (6,5) (bottom) CNTs. Thermal decomposition data points to higher stability of d(T) hybrids compared to d(G), and also higher stability of (15,2) CNT complexes compared to (6,5) CNT hybrids.

An estimate of relative stability of the hybrids can be obtained by considering $T_m$, or the temperature at which one-half of the original contacts have been lost. Comparison of the curves for d(T) and d(G) clearly point to a higher stability of the d(T) hybrids, consistent with the analysis of free energy profiles in the previous section. For example, (15,2)-d(G) complexes exhibit $T_m \sim 340$ K, at which point less than 25% of the (15,2)-d(T) contacts have been lost, and a similar ratio can be observed for the (6,5) hybrids. d(TG) complexes, on the other hand show an intermediate stability. These results are consistent with the observation by Zheng et al.\textsuperscript{24} that d(T) sequences
are more efficient in solubilizing CNTs than their d(G) counterparts, as well as the results of DFT calculations of Enyashin et al.\textsuperscript{47} Contrasting the thermal decomposition curves for (15,2) and (6,5) CNT hybrids, the latter complexes show a lower stability, with all nucleotides having $T_m < 340$ K, whereas this is the case only for the least stable (15,2)-d(G) complexes with the larger-diameter CNT.
4 Summary

While a number of experimental studies have shown that single stranded DNA readily bind to single-walled carbon nanotubes to form water soluble hybrids, relatively little is known about the details of this process on an atomic level. To address this issue, we have carried out all-atom replica-exchange molecular dynamics simulations of the three ssDNA oligonucleotides of different sequences associating with two types of chiral nanotubes in water. In all six systems, stable complexes were found to form through non-covalent adsorption of DNA onto the nanotube surface, with aromatic bases stacking onto the graphene lattice, leaving the charged backbone exposed to the solvent. However, in contrast to simple models which predict a regular helical wrapping of the nanotube by the polynucleotide chain, we find that the hybrids exhibit a complex morphology, where several bound states with distinct DNA backbone geometries are populated at thermal equilibrium. The conformational population distribution of surface bound oligonucleotides was found to depend on the nucleotide sequence, and to a lesser extent, on nanotube diameter. Interestingly, we observed considerably less variation in the distribution of the nucleotide conformations among different hybrids than in backbone geometry. This is not unusual however, since the parallel stacking with the relatively rigid nanotube surface limits the range of possible sugar puckering conformations and base rotamers. More strikingly, in addition to favoring surface stacked conformations, the nucleotide bases were found to exhibit strong orientational preference along the surface, such that the ground-state dipole moments align with the nanotube axis. This behavior was observed spectroscopically through hypochromicity measurements\(^40\) and via linear dichroism,\(^39\) and was also predicted by quantum chemical calculations of nucleotide-nanotube interactions.\(^{46,49,50}\) Curiously, either a parallel or anti-parallel orientation is observed for a given nucleotide type, but not both. While this could be the result of
kinetic trapping due to high barrier for transition from an all-parallel to all-anti-parallel state, another possibility is that the directionality is due to the chiral nature of the (15,2) and (6,5) nanotubes. The chirality imparts a definite handedness to the tubes (both of which are right-handed) thus breaking the symmetry, and resulting in different orientation of the graphene lattice with respect to the parallel and anti-parallel nucleotides.

Our analysis of binding thermodynamics has shown that the hybridization is driven by the attractive non-covalent interactions, primarily through stacking of the DNA bases with the nanotube surface. These are sufficiently strong to overcome the desolvation penalty arising from the net loss of hydrogen bonding with the solvent that is not full compensated by the reduction of SASA, and in most cases, the accompanying increase in DNA conformational strain. Nonetheless, the equilibrium distribution of hybrid conformations is controlled by a complex interplay of competing effects leading to a room temperature ensemble consisting of a number of significantly populated bound states. This complex morphology is reflected in the rugged free energy landscapes featuring multiple minima separated by relatively high barriers (~3 kcal/mol or more) which would be crossed infrequently at 298K, resulting in a number of metastable conformational states. In addition, qualitative differences were observed between free energy profiles corresponding to d(G) and d(TG), and those of d(T) complexes. While the latter display some funnel like features with most populated state significantly lower than other metastable minima, the former consist of two or more low lying minima of similar energy, indicative of a frustrated (i.e. glassy) system. Moreover, whereas the global minimum of both d(T) complexes corresponds to conformations with all bases fully stacked onto the nanotube surface, this is not the case for the guanine containing complexes. We believe this is due to a known propensity of purine bases towards self-stacking, which provides additional stabilization to states with
fewer stacking contacts with the CNT, leading to a richer morphology of surface bound structures. Conversely, polypyrimidines exhibit negligible self stacking, leading to increased flexibility of the polythymine strands. This allows the oligonucleotide to adapt conformations which permit more effective stacking interactions with the nanotube surface, resulting in more stable complexes. The increased stability of d(T) complexes is also reflected in the thermal decomposition curves. These findings could explain the high efficiency of poly d(T) oligonucleotides in solubilizing nanotubes in comparison with other sequences observed by Zheng et al. 

Non-covalent hybridization of CNTs by ssDNA has also been proposed as an approach for sorting CNTs based on their diameter and conductivity. Since most physicochemical properties of the hybrids are related to their molecular structure, efficient separation could be achieved provided the hybrid structural distributions are sufficiently different. Our results show that even though conformational distributions of different diameter CNTs complexed with a given oligonucleotide are not identical, they still retain a high degree of overlap. Among the three sequences considered, the d(TG) hybrids exhibit the largest shift in conformational population between the two types of CNTs. It is thus not surprising that Zheng et al. found the latter sequence to be most efficient in facilitating diameter based CNT separation. 

Likewise, the observed differences in thermal stability of ssDNA-CNT complexes with CNTs of different diameter suggest than an alternative approach to diameter based sorting based on selective thermal precipitation may be viable. Nevertheless, full separation of hybrids may very well be difficult to achieve.

In summary, we have obtained a comprehensive characterization of the equilibrium morphology and thermodynamics of non-covalent complexes of single-walled carbon nanotubes.
and ssDNA decamers. While this study provides an important step to understanding these complex systems, there is still much more to be learned. For example, at higher salt strength, the conformational equilibrium may be altered due to strong interactions of the ions with the charged DNA backbone. Similarly, it is possible that longer polynucleotide chains would prefer to adopt more regular helical structures which afford optimal $\pi$-stacking of the bases to the CNT surface.
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