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Using DNA to Link Gold Nanoparticles, Polymers and Molecules: a Theoretical Perspective

One-Sun Lee, Tatiana R. Prytkova, and George C. Schatz*

Department of Chemistry, Northwestern University, Evanston IL 60208-3113

Abstract

This Perspective describes theoretical studies aimed at understanding the structural and thermal properties of materials in which DNA is used to link gold nanoparticles, or polymers or organic molecules. Particularly in the case of gold nanoparticles, the materials derived from this structural motif have proven to be important for biological sensing and other applications, however additional applications may arise as a result of recent advances in the preparation of crystalline materials based on DNA-linked particles. From a theory perspective these are challenging materials to describe due to the large number of atoms, and the polyelectrolyte character of DNA, however there has been important progress recently using all-atom and coarse-grained molecular dynamics, and with analytical theory. Among topics that we discuss are the structure and density of DNA when attached to gold particles, and the size and melting properties of DNA-linked nanoparticles in different environments.

Keywords

DNA; DNA-linked material; DNA melting; gold nanoparticle; functionalized nanoparticle; small molecule DNA hybrid; coarse-grained molecule dynamics

I. Introduction

Gel-like materials derived from DNA-linked nanoparticles, polymers, or molecules are a new class of materials that have emerged in the last 15 years¹ as a result of advances in synthetic methods including the ability to routinely synthesize oligonucleotides with specified base-pair sequences, and the ability to chemically tether oligonucleotides to metal (typically gold or silver) particles or to organic molecules.² Figure 1 shows a schematic of the structure of these materials, in which DNA hybridization is used to link together particles or polymers (or molecules). These materials have quickly demonstrated their usefulness for DNA and protein detection using optical^{3–5} and electrical^{6,7} methods, and there is increasing interest in using the functionalized nanoparticles for therapeutic applications, such as for siRNA delivery.^{8,9} Moreover a new generation of DNA-linked materials chemistry is starting to appear with the recent discovery that crystalline rather than amorphous (fractal¹⁰) structures can be produced when DNA links the particles together,

*Corresponding author: George C. Schatz, schatz@chem.northwestern.edu, Phone: (847) 491-5657, Fax: (847) 491-7713 .

and that the properties of these crystalline materials can be varied over a wide range by varying DNA length, base-pair sequence, and nanoparticle size and shape.¹¹⁻¹⁴ Fig. 2 shows a schematic of a crystal structure that has been synthesized, in this case with the gold nanoparticles forming fcc or bcc lattices that are linked by DNAs. The figure shows just one DNA linking each pair of nanoparticles, but in reality it is likely that several DNAs serve as linkers. However only a few percent of the DNAs that are attached to each particle are involved as linkers.¹⁵

The properties of these materials have been of great interest in theoretical modeling. When the first DNA-linked gold nanoparticle aggregates were synthesized by Mirkin and coworkers in the mid-1990s, it was quickly discovered that the thermal melting (dehybridization) transitions in these materials were quite different from the corresponding transitions for the same DNA structures in solution (hereafter called “free DNA”).^{3,16} Fig. 1 shows typical melting curves that are obtained by monitoring the absorption of light as a function of temperature, and we see that the aggregate material has much sharper melting than free DNA. This behavior also occurs for DNA-linked polymers¹⁷ and DNA-linked molecules,^{18,19} although not all DNA-linked structures show this effect.²⁰

A number of theoretical models have been proposed to explain the thermal melting behavior of the DNA-linked aggregate materials. These theories can roughly be grouped according to whether they consider the effect of many linked particles that undergo a bulk-like phase transition, or they consider melting of pairs of particles within an aggregate that are linked by several DNAs. Theories in the first group²¹⁻²³ involve statistical mechanical or mean-field methods in which the transition from a macroscopic aggregate into clusters and ultimately monomers is described. In these theories the dissociation of each pair of particles is assumed to be governed by the same melting curves as free DNA. In the second group, the coupling of closely packed DNA strands that link each pair of particles is considered, including cooperative effects that can arise from counterion release^{16,24} or entropic effects associated with the structural rigidity of the linked particles.¹⁸ The two theoretical approaches are not mutually exclusive, and indeed methods for combining these effects have been proposed.^{25,26}

Figures 3 and 4 show experiments that have been done with the intention of separating the two mechanisms. In Fig. 3,²⁷ DNA-linked polymers were examined in which the DNA is designed to allow two types of hybridization: (1) a “coded” region that enables the polymers to link together, and (2) a “noncoded” region that allows for hybridization to an oligonucleotide that is not involved in linking. By choosing the base-pair content appropriately, melting of the non-coded region can be chosen to occur at a lower temperature than the coded region. Fig. 3 therefore shows two melting transitions, however noteworthy is the fact that both melting transitions are sharp. This means that the melting can be sharp even when the aggregate remains intact, which is evidence for a cooperative model that doesn’t require a phase transition to occur. Fig. 4²⁸ shows the melting of aggregates in which PNA (peptide nucleic acid) rather than DNA is used to link the DNA-functionalized nanoparticles. In free DNA melting (Fig. 4a), as well as the melting of DNA-linked nanoparticles/polymers (Fig. 4c and 4e), the melting temperature increases with increasing salt concentration, due to stabilization of the duplex form that arises from screening of the phosphate repulsions. Free PNA-DNA duplexes, by contrast, show the opposite temperature dependence, as PNA is uncharged, and the screening better stabilizes the single stranded state. Fig. 4b and Fig. 4d show that the melting temperature of the PNA-linked DNA-functionalized nanoparticles or polymers increases with salt concentration, which is the opposite behavior of the free PNA-DNA duplexes. This indicates that counterion-mediated cooperative interactions in the aggregated state are important.

The structural properties of the DNA-functionalized and DNA-linked particles are also surprising. For example the maximum density of ss-DNA that can be attached to gold particles using thiol linkers is amazingly high²⁹ (compared to DNA-functionalized silica particles, or compared to DNA-functionalized flat gold surfaces), and has been found to depend on particle diameter, being largest for the smallest diameter particles.³⁰ In addition, the length of DNA, either that is attached to just one gold particle, or which through hybridization chemistry links two particles together is much shorter than in conventional Watson-Crick DNA, and it has been proposed that perhaps the DNA structure is A-form rather than B-form in these structures.^{31,32}

In this Perspective, we describe recent theoretical/computational work aimed at understanding these properties of DNA-functionalized nanoparticles and of DNA-linked nanoparticles/polymers/molecules. In Section II we consider the structural properties related to density and length of DNA while in section III we describe theory and related experiments that have provided insight concerning DNA-melting.

II. Structural properties

As noted above, the length of DNA attached to gold particles has attracted some interest, as it is considerably shorter than one expects based on the usual 3.4 Å per base pair separation in Watson-Crick B-form DNA. This shrinkage occurs for both ss-DNA and ds-DNA, but a challenge with modeling these structures is that the simplest models of DNA functionalized nanoparticles involve a lot of atoms, counterions and solvent. The simplest structure that has been studied experimentally involves 2 nm gold particles³³ that have a maximum of 4-5 ss-DNAs per nanoparticle. In this case, fully atomistic simulations can be done with explicit solvent, making it possible to provide a quantitative estimate of DNA-length. Fig. 5 shows the initial and equilibrated structures that result from these calculations, in this case with 4 ss-DNAs.³⁴ The Figure shows that the DNAs extend radially from the nanoparticle, with considerable curvature in each DNA strand. As a result, the calculated ss-DNA length corresponds to 2.2 Å/base, which is considerably shorter than Watson-Crick DNA. This value compares favorably with estimates from electrophoretic mobility measurements for larger gold nanoparticles functionalized with ss-DNA, where the estimated values are 1.9³⁵ and 2.2 Å/base.^{36,37}

Calculating the length of ds-DNA between gold particles is a serious challenge, but one estimate was provided recently by Lee and Schatz.³⁸ Fig. 6 shows the structure that was modeled, in this case consisting of a ds-DNA between two flat gold surfaces, with periodic boundary conditions applied so that the effective DNA-DNA separation is 55 Å. The DNA structure in this case was chosen to match recent experiments in the Mirkin group, and in this case there is a 4 bp coded linker region, an 18bp noncoded duplex region, and a 10 base poly-A segment. Fig. 6 shows three pictures of the overall structure. At the top the structure is taken to have 3.4 Å separations between each base, including the ss-DNA segments, while the middle shows the same structure after it is constrained to have the 2.55 Å/base pair length that is found experimentally.³¹ The bottom shows the result from MD simulations subject to the shorter length. We see that in order to accommodate this short length, the ss-DNA is partially collapsed onto the gold surface. The ds-DNA is still B-form, but bent. An intentionally inserted adenine at the boundary of the coded and noncoded regions makes this bent structure relatively stable. This provides a rationalization for why this extra adenine is found to aid in the formation of thermodynamic (as opposed to kinetic) structures. However we do not know the relative energetics of this structure compared to the corresponding structure that can be constructed with A-form DNA, so the question of which represents the correct DNA structure is not resolved.

Another surprising structural property of the DNA-functionalized gold nanoparticles is that the maximum density of ss-DNA attached to gold nanoparticles is higher for particles with a smaller radius of curvature than for a larger radius of curvature. This density corresponds to a mean separation between DNAs of 27 Å for 10 nm diameter nanoparticles, increasing to 39 Å for 200 nm nanoparticles. The latter number is the same as one finds for flat gold surfaces. Hurst et al.³⁹ have proposed that a driving force for this is “splaying” of the DNAs that occurs for small particles as this reduces repulsions between the phosphates on the DNAs. Fig. 7 shows atomistic molecular dynamics calculations that we have performed to study this result, in this case by tethering seven DNAs to a flat gold surface. The distance between ss-DNAs is initially taken to be 27 Å, but it increases to 37 Å upon equilibration. The simulations show that this occurs because counterion-mediated osmotic effects cause the DNAs to move apart and splay outward, thus providing a rationalization for the observed DNA separations.

III. Thermal melting properties

The unusual melting properties of the DNA-linked gold particles and polymers were described in the Introduction, including attempts to untangle the two mechanisms either by studying systems that could melt without disaggregating, or by studying the effect of changing the charge state of the aggregate. Recently an alternative approach to establishing the melting mechanism has appeared, in which DNA is used to link molecules rather than nanoparticles or polymers, and the hybridization produces a dimer of two molecules rather than an extended aggregate. This immediately removes the aggregate phase transition mechanism from consideration, leaving us with cooperative melting as the only remaining mechanism. The experiments demonstrate sharp melting for these Small-Molecule-DNA-Hybrid (SMDH) structures.

Figure 8 shows the structure of the SMDH complex. Here three DNA strands are attached to a 1,3,5 tris (phenyl ethynyl) benzene core. By varying the concentration of the SMDH's, it is possible to produce SMDH dimers (Fig. 8a) with a relatively rigid barrel-like structure. The measured melting curves are presented in Fig. 9a and it is clear that the SMDH dimer has much sharper melting than free DNA.

To interpret these results, we have considered both an analytical model and molecular dynamics simulations.¹⁸ The analytical model examined the entropy change associated with melting the first, second or third DNA in the SMDH complex. A key factor is that after one DNA melts the two remaining duplex strands still hold the SMDH structure intact, and this makes the effective concentration of the ss-DNAs larger than it would if these ss-DNAs had been free. This leads to a reduction in melting entropy for the first and second DNA melting events, but the third DNA melting releases this entropy, resulting in a cooperative effect. Counterion release also sharpens the melting transition.

The molecular dynamics studies of DNA melting are based on a coarse-grained model of DNA that is depicted in Fig. 8b. We used this model, as opposed to an atomistic model, due to the long timescale of the simulations needed to describe an equilibrium melting event. In this model each nucleobase is represented by a bead, as are the sugar and phosphate groups and the counterions. The organic molecule anchor is represented as a bead that can form three bonds, each being attached to a DNA strand. Molecular dynamics simulations are then done for a SMDH dimer that is inside a small box with reflecting boundary conditions, with enough time included in the simulation so that the SMDH can melt and rehybridize several times during the simulation. The fraction melted is then determined by counting the fraction of hybridized base-pairs at each temperature. The resulting melting curves are presented in Fig. 9. Although the calculated melting curves are broader than their experimental

counterparts for both the free DNA and SMDH complexes (compare Figs. 9a and 9b), the sharpening of the melting behavior in going from free DNA to the SMDH complex is apparent. We have used a quasi-harmonic analysis to calculate the entropy changes associated with melting of the first, second and third DNAs, and the results are consistent with the analytical model described above.

IV. Future perspectives

The results that we have summarized here show that DNA-linked nanoparticles, polymers and molecules lead to a new class of nanomaterials with a number of unusual properties that provide both challenges and opportunities for theory and computation. Some of the properties can be understood with standard atomistic molecular dynamics simulations, but in other cases coarse-grain models or even simple analytical models can play an important role, particularly if the key degrees of freedom that are responsible for the unusual properties can be identified. The results we have obtained demonstrate the richness of effects that is possible with DNA, as factors such as base-pair hybridization and the polyelectrolyte properties of DNA can be used in a variety of ways that determine the structural, mechanical and thermal properties of the DNA-linked aggregate materials.

The materials generated so-far are only the beginning of what in principle can be fabricated. With respect to the nanoparticle crystal materials that were mentioned in the Introduction, one can imagine that many different kinds of particles/polymers/molecules, and many different lengths and sequences of DNA or other linkers can be brought together to build structures that could have functionality on many different length scales. There have been problems in the past with kinetic structures dominating the fabrication, so the choice of DNA-linker will have to be carefully controlled to avoid this. In addition, many of the most interesting properties of the DNA-linked materials have required a high density of DNA so there might be important constraints to making useful materials.

The new DNA materials described here have provided important challenges for theory which in some cases have resulted in new methods or models. The coarse-grained DNA model described in Section III was an adaptation of a previously developed model which had the advantage of describing the melting transition in free-DNA correctly. This model is a tremendous simplification on the atomistic models, but at the same time it is too complex for many purposes. Simpler models of DNA have been developed, but not for describing melting transitions. The model described in Section III is sophisticated enough to describe melting, but it also has limitations with respect to precise values of the melting temperature, or issues related to the structure of single-stranded DNA. Thus there is room for new MD and mean-field models.

Quotes to highlight

“The structural and thermal properties of the DNA-functionalized and DNA-linked particles are surprising, involving an interplay of polyelectrolyte and base-pair hybridization effects”.

“The new DNA materials described here have provided important challenges for theory, where both atomistic and coarse-grained descriptions provide useful information.”

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Biographies

One-Sun Lee is a post-doctoral researcher in the Schatz group at Northwestern University. He obtained his Ph.D in chemistry from Seoul National University and he has worked in the Saven group at University of Pennsylvania. His research interest is the design and modeling of nanoscale materials including DNA-functionalized metal particles and artificial membranes.

Tatiana Prytkova is a postdoctoral research fellow in the group of Professor Schatz. Her research involves developing methodology to study the thermodynamic and structural properties of self-assembled structures made from DNA. She obtained her Ph.D. in theoretical chemistry at Duke University with David Beratan where she worked on electron-transfer reactions in proteins, molecular recognition in protein-ligand interactions and UV-damaged repair mechanisms.

George C. Schatz is Morrison Professor of Chemistry and of Chemical and Biological Engineering at Northwestern University. His degrees are from Clarkson (B.S.) and Caltech (Ph.D.). He works broadly in theory/computation related to nanoscience, interfaces, gas phase, and soft materials.

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Figure 1. Schematic illustration of DNA-functionalized gold nanoparticles or polymers linked together with complementary linker DNA or PNA. Bottom shows typical melting curves, comparing free DNA with a DNA linked structure. Schematic adapted from Ref. ²⁸, with melting data taken from Ref. ¹⁹.

Figure 2.

DNA-functionalized gold nanoparticles that are assembled into different crystallographic arrangements by changing the linker sequence. (a) Face centered cubic arrangement induced by a self-complementary sequence, and (b) body centered cubic arrangement is induced by an asymmetric linker sequence. See Ref. ¹¹.

Figure 3.

(a) Composite structure in which A_{10} strands initially melt from the fully aggregated system as the temperature is increased, and then the aggregate dissociates at a higher temperature.

(b) Fraction of ss-DNA for the system shown in (a) versus temperature. The theoretically fitted curve agrees well with the measured melting profile (adapted from Ref.²⁷.)

Figure 4.

(a) Melting temperature versus salt concentration for DNA:DNA (red) and PNA:DNA (blue) duplexes (18 bp) in solution. Temperature melting profile of (b) PNA-linked AuNP, (c) DNA-linked AuNP, (d) PNA-linked polymer and (e) DNA-linked polymer. See Figure 1 for the structures (adapted from Ref. ²⁸).

Figure 5.

Starting ($t = 0$) and equilibrated ($t = 8$ ns) structure of ss-DNA functionalized gold nanoparticle (diameter of gold particle is ~ 2 nm) obtained from an atomistic molecular dynamics simulation. Even though the expected radius would be ~ 49 Å for a Watson-Crick *B*-DNA structure, the simulation with 0.5 M salt shows a radius of 29 Å, which is consistent with recent experiments. Adapted from Ref.³⁴.

Figure 6.

The conformation of DNA between gold surfaces based on molecular dynamics simulations at the atomistic level. (a) The initial conformation of DNA is based on the Watson-Crick *B*-DNA structure. (b) Initial structure when the distance between gold surfaces is reduced to 163 Å through the application of a force *F* as indicated by the arrows in (a). This distance is consistent with observations for a face centered cubic structure. (c) Structure after a 10 ns molecular dynamics simulation, where the ds-DNA is found to maintain a *B*-DNA structure with 30° bending of the linker ds-DNA. (d) Sequence of DNA used in the simulation. Results are adapted from Ref. ³⁸.

Figure 7.

(a) Starting and (b) equilibrated structures of seven DNAs on a flat gold surface based on molecular dynamics simulations. Here the distance between ss-DNAs is initially taken to be 27 Å based on experiments for small particles, but the distance between DNAs in the equilibrated structure is found to be 37 Å, similar to experiment for large particles. This arises because counterion-mediated osmotic effects cause the DNAs to move apart and splay outward. (c) DNA sequence used in the simulations. Results are adapted from Ref. ⁴⁰.

Figure 8.

(a) Structure of small molecule DNA hybrid (SMDH) and the DNA sequence that was used in this work. A Tris(phenyl-ethynyl)benzene core is used as an anchor for the three DNAs. (b) Coarse grained model of the SMDH that was used for the molecular dynamics simulation. Adapted from Ref. ¹⁸.

Figure 9. Melting curves obtained from (a) experiment and (b) molecular dynamics simulations for free DNA and the SMDH complex. Results are adapted from Ref. ¹⁸.