Communication

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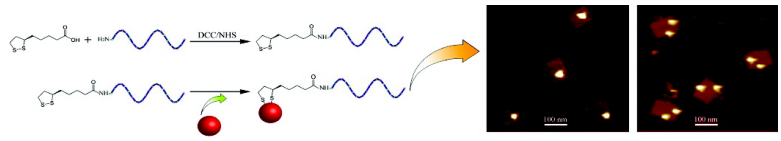

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Toward Reliable Gold Nanoparticle Patterning On Self-Assembled DNA Nanoscaffold

Jaswinder Sharma,[†] Rahul Chhabra,[†], Casper S. Andersen[‡] Kurt V. Gothelf,[‡] Hao Yan,*[,†] and Yan Liu*[,†]

Department of Chemistry and Biochemistry & The Biodesign Institute, Arizona State University, Tempe, Arizona 85287, Centre for DNA Nanotechnology at Department of Chemistry and iNANO, University of Aarhus, Denmark

Received April 17, 2008; E-mail: yan_liu@asu.edu; hao.yan@asu.edu

Organizing metallic nanoparticles in a well-controlled manner is of great interest for nanophotonics and nanoelectronics applications.[1] Toward this goal, DNA-directed assembly has shown great progress in constructing one-dimensional,[2] two-dimensional,[3] and discrete gold nanoparticle (AuNP) architectures.[4] One common strategy to obtain such structures was to first link a DNA molecule carrying a monothiol modification to AuNP (Figure 1a) and subsequently use the sequence information of DNA to control the positioning of the AuNP-DNA conjugates onto DNA scaffolds.[3,4] Very often the structure achieved suffered from low yield partly because of the limited strength of the linkage between the AuNP surface and the monothiol functionalized DNA molecules, and also because of competitive binding of other ligands during surface passivations.[3e] Recent reports have shown efforts of engineering polyvalent bindings toward strengthening the linkage between ligands and nanoparticle surfaces.[5] Nevertheless, it is desirable to develop robust strategies to obtain DNA templated discrete AuNP arrays with higher yield and reliability. Herein, we report the use of lipoic acid-modified DNA oligonucleotide to prepare a 1:1 ratio of AuNP−DNA conjugates with a bivalent thiolate−Au linkage (Figure 1b). The conjugates prepared here are further selectively mixed with other DNA strands and assembled into fixed sized DNA nanostructures carrying a discrete number of AuNPs at desired positions. Atomic force microscopy (AFM) imaging reveals a dramatically improved yield of the AuNP on DNA tile structure compared to the ensembles using monothiol AuNP-DNA conjugates.

To generate the dithiol-modified DNA, lipoic acid was first *N*-hydroxysuccimide (NHS) esterified using dicyclohexylcarbodiimide (DCC) in an organic media (see Supporting Information for detailed description and characterization). The activated lipoic ester was then reacted with amine modified DNA. HPLC purification of the reaction mixture indicates a ∼79% yield of the dithiol-modified DNA. The purified lipoic acid modified DNAs were mixed with 10 nm AuNPs (Ted Pella Inc.) in an 1:1 [DNA]:[AuNP] ratio. The resulting AuNP−DNA conjugates were then separated by agarose gel electrophoresis (Figure. 1d).[6] The 1:1 conjugates of AuNP−DNA were obtained from the second fastest migrating band. To render the AuNPs stable against high salt concentrations required for self-assembly of DNA, the nanoparticle surface was passivated with a layer of short oligonucleotide of 5 thymine residues modified with monothiol group (T_5-SH). As a control experiment, the same DNA sequence with monothiol group instead of an amine group was used (see Supporting Information for details). Similarly, following conjugation with AuNPs, agarose gel separation and surface passivation with T_5-SH, the AuNP−DNA conjugates with a monothiol linkage were obtained.

To quantitatively compare the yield of AuNP assemblies using these two strategies, we used the scaffolded DNA origami method developed by Rothemund[7] to organize the AuNPs into discrete nanostructures. We have previously shown that via nucleated self-assembly the rectangular shaped origami DNA nanostructure can be quantitatively

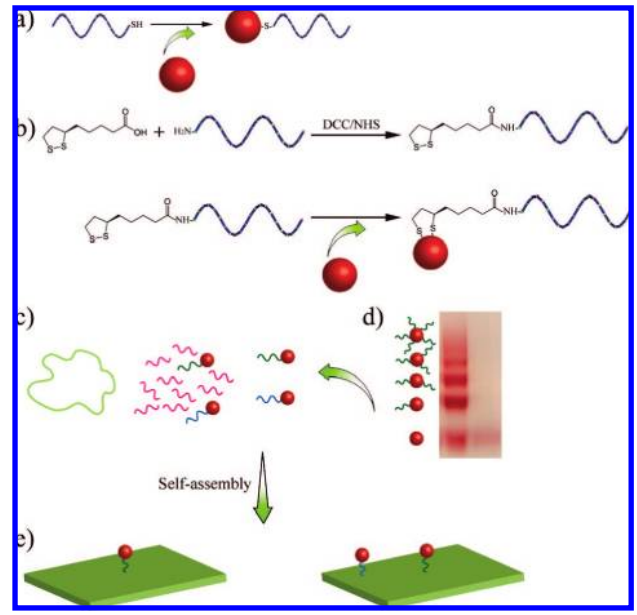

Figure 1. Conjugation strategies employed in the preparation of AuNP−DNA conjugates and ultimately their utilization in the self-assembly of DNA origami nanoarrays: (a) strategy showing monothiol-modified DNA in the preparation of AuNP−DNA conjugates; (b) lipoic acid-mediated AuNP−DNA conjugates and their preparation scheme; (c) general outline of the nucleated self-assembly process which requires long, circular viral genome (green colored loop) along with unmodified "helper strands" (purple colored strands) and discrete AuNP-DNA conjugates (blue and green colored strands). Red colored ball represents AuNPs; (d) agarose gel showing the separation of AuNP-DNA conjugates into discrete structures; (e) cartoons showing DNA origami nanoarrays each carrying one and two AuNPs.

generated and purified with nearly 100% yield.[8] For the origami tile assembly, a single stranded viral M13 DNA is folded by a set of ∼200 short helper strands, whose sequences are deliberately designed to guide the folding of the long viral DNA following a specific folding path. In the first demonstration, DNA origami tiles carrying a single AuNP per tile were assembled by taking out two neighboring helper strands at a desired position (32 nt each) and replacing those strands by a a longer DNA with combined sequence (69 nt, with extra 5Ts at the 5′ end) that is attached to a AuNP at 1:1 ratio, by the two methods outlined above. The longer length of the DNA strand on the AuNP is required to have a good band separation in the gel electrophoresis.[6] Following AFM imaging (Figure 2), the number of DNA tiles carrying one or none AuNP are counted. The table in Figure 2c lists the result of the statistical analysis. The yield of the desired final structure (one AuNP per origami tile) was significantly improved from 45% (monothiol approach) to 91% (dithiol approach), showing the improved bond strength by the lipoic acid mediated AuNP–DNA conjugates over the monothiol conjugate. This demonstrates the reliability of our new strategy.

We further increased the complexity to obtain discrete AuNP nanostructures by organizing two AuNPs in deliberately designed

[†] Arizona State University.
[‡] University of Aarhus.

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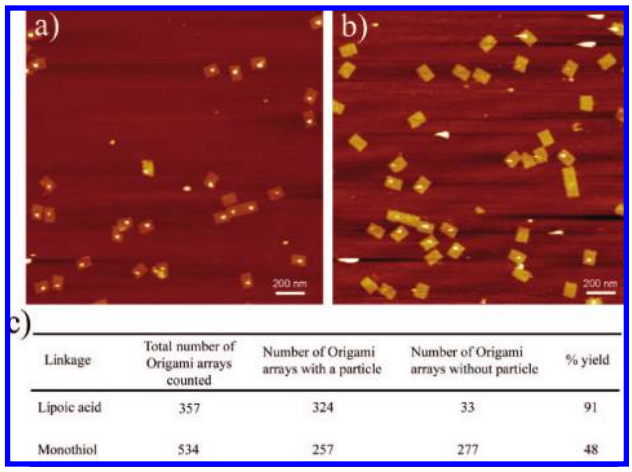
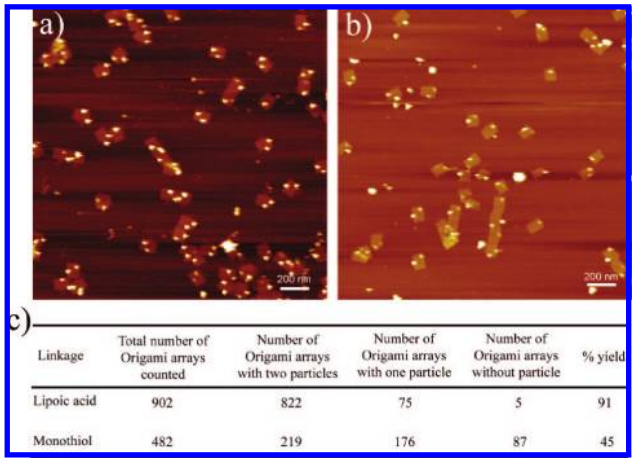


c)

Linkage	Total number of Origami arrays counted	Number of Origami arrays with a particle	Number of Origami arrays without particle	% yield
Lipoic acid	357	324	33	91
Monothiol	534	257	277	48

Figure 2. Typical AFM images of DNA origami nanoarrays with a single AuNP−DNA conjugates prepared using (a) lipoic acid and (b) monothiol-modified DNA oligonucleotides, respectively. (c) Table of statistical analysis of the origami nanoarrays by counting the AFM images covering completely different areas (see Supporting Information for more images).



c)

Linkage	Total number of Origami arrays counted	Number of Origami arrays with two particles	Number of Origami arrays with one particle	Number of Origami arrays without particle	% yield
Lipoic acid	902	822	75	5	91
Monothiol	482	219	176	87	45

Figure 3. Typical AFM images of DNA origami nanoarrays with two AuNP-DNA conjugates prepared using (a) lipoic acid and (b) monothiol-modified DNA oligonucleotides. (c) Table of statistical analysis of the origami nanoarrays by counting the AFM images covering completely different areas (see Supporting Information for more images).

patterns with controlled interparticle spacing. In this case, we followed the same procedure and chose to use two helper strands in the origami nanoarray to conjugate to the 10 nm AuNP with both dithiolate and monthiolate linkages. The sites of the modified helper strands are ~47 nm distant from each other (Figures 3 and 4). Again, statistical analysis unambiguously revealed the improved conjugation with lipoic acid-mediated conjugates (Figure 3c). The yield of the desired structure (two AuNPs per origami tile) improved from 45% to 91%, demonstrating the fidelity of the new approach.

In summary, the new AuNP-DNA conjugation strategy used herein has led to self-assembling of DNA tile-templated AuNP nanoarrays with significantly improved yield with reduced errors. Error reduction in self-assembling structures of increased complexity is of great importance for practical applications of any self-assembling system. In the case of DNA self-assembly and directed self-assembly, there has been great efforts in designing error correction DNA tiles[9a] and proof-reading schemes for DNA directed nanoparticle assembly.[9b] Our way of error reduction is to tackle the problem in the first step or before the assembly happens and try to make the bioconjugation chemistry more robust. Here we showed that the yield of origami tile-templated AuNP structures can be higher than 90%, we believe there is still room

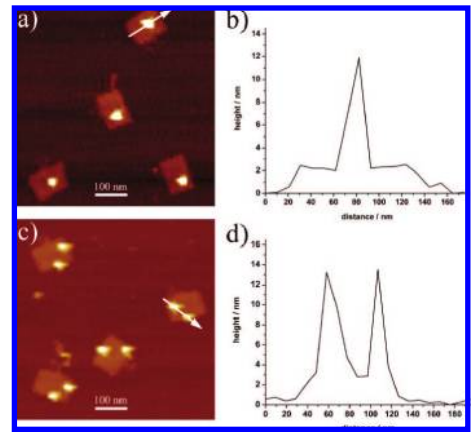


Figure 4. Zoom-in AFM images (a and c) and corresponding height profiles of DNA origami tile-directed AuNP−DNA assemblies prepared using the new strategy. Note the measured height matches the size of 10 nm AuNP.

for further improvement by introducing even stronger AuNP−DNA conjugation strategies, as polyvalency has been shown to play a significant role in improving ligand−receptor binding affinities.[10] Moreover, by combining robust bioconjugaton chemistry with other error reduction/correction strategies, it is possible to construct highly reliable multicomponent nanoparticle architectures with great potential for both fundamental understanding of proximity/spatial configuration dependent particle−particle interactions and nanodevice applications.

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Supporting Information Available: DNA sequences, experimental methods, additional AFM images. This material is available free of charge via the Internet at http://pubs.acs.org.

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