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Ultrathin Silica Coating of DNA Origami Nanostructures

Minh-Kha Nguyen,* Vu Hoang Nguyen, Ashwin Karthick Natarajan, Yike Huang, Joonas Ryssy, Boxuan Shen, and Anton Kuzyk*

ABSTRACT: The DNA origami technique has emerged as one of the most versatile bottom-up nanofabrication methods due to its ability to construct well-defined complex three-dimensional nanostructures and guide assembly of functional nanoscale objects with unprecedented precision, high yields, and controlled stoichiometry. Nonetheless, limited compatibility with biologically relevant fluids and typical solvents utilized in nanofabrication often restricts applications of DNA origami-based assemblies and devices. Here we present an approach for coating DNA origami structures with silica. By careful adjustment of experiment parameters, we achieved reproducible growth of ultrathin silica shell in solution without agglomeration or deformation of DNA origami structures. The silica-coated structures are stable in water and exhibit an increased resistivity to nuclease-mediated degradation. In addition, the coated structures preserve their structural integrity in polar organic solvents. We anticipate that our results will aid further advancement of DNA origami techniques as the nanofabrication method.

INTRODUCTION

Nucleic acids, proteins, carbohydrates, and lipids are four fundamental molecules of life and excellent building blocks for assembly of functional nanarchitectures.1,2 Among them, DNA has attracted substantial interest for fabrication of artificial molecular assemblies due to the simplicity, specificity, and programmability of Watson–Crick base-pairing and the ability to generate well-defined three-dimensional (3D) structures with tailored morphology and chemical addressability.3 In particular, the DNA origami technique3 provides an efficient strategy for engineering of complex nanostructures with arbitrarily prescribed shapes and rich types of hierarchical organizations.4 In addition, DNA origami structures have been widely used as templates for assembly of nanoparticles,5–11 proteins,12–15 fluorescent dyes,16–18 polymers19,20 and so on. Furthermore, applications of DNA origami constructs as molds21,22 and masks23,24 for nanofabrication have been proposed. Precise control over the nanoscale morphology and the ability to arrange multiple functional nanoscale components with high accuracy have enabled applications of the DNA origami technique in various fields, e.g., biomedical research,25,26 biophysics,27–29 biosensing30–33 nanophotonics,34–39 nanorobotics,40,41 and drug delivery.42,43 Despite the great promise of utility,44–46 the applicability of DNA origami-based assemblies and devices is often restricted by the limited compatibility with the biologically relevant fluids and common solvents employed in nanofabrication. For biomedical applications, enhanced stability of DNA origami structures against magnesium ion depletion and nuclease-mediated degradation have been achieved by using various approaches, including covalent cross-linking47 and stabilization through coating with positively charged species ranging from proteins48,49 to polymers50,51 and oligolysine conjugates.52,53 Reaching compatibility with nanofabrication relevant organic solvents remains a significant challenge. DNA origami constructs can preserve their structural integrity after exposure to common organic solvents after deposition on surfaces but not in solution.54–57

Silica coating has recently attracted significant interest as a protection strategy for the stability enhancement of DNA origami-based assemblies55 and as an approach for transferring unprecedented control over the nanoscale morphology offered by the DNA origami technique into inorganic materials.56,57 A modified Stöber method was applied for DNA origami-templated silica growth in a low-Mg2+ solution.55 Despite important advancements, the demonstrated approaches have serious limitations, e.g., an incomplete silica coating due to the substrate-based reactions56 or significant agglomeration and structural deformation of origami structures after silica coating.55 Achieving controlled silicification in solution with well-dispersed nondeformed silica-coated DNA origami structures has remained challenging. Here, we demonstrate an approach that enables fabrication of DNA origami@SiO2 nanostructures via well-established silica surface chemistry. Our method combines tailored response to environmental changes and precursor concentrations with

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the growth of silica on 3D DNA origami structures. Well-dispersed DNA origami@SiO$_2$ structures in solution were achieved with uniform coating and ultrathin silica shells. Furthermore, after the coating the DNA origami@SiO$_2$ structures were stable in DI water (for at least 10 months) and in pure IPA (for at least 3 days) and resisted nuclease-mediated degradation.

**EXPERIMENTAL SECTION**

**Materials.** Single-stranded circular DNA scaffold strands (p7560 and p7249) were purchased from tilibit nanosystems. DNA staple strands were purchased from biomers.net and Thermo Fisher Scientific. Buffers and other chemicals were purchased from either Sigma-Aldrich or Fisher Scientific. All reagents were commercially available and used without any further purification. Type I ultrapure deionized (DI) water, from a Milli-Q system, was used for all experiments.

**Assembly of DNA Origami.** The DNA origami templates were designed by using caDNano software.59 Two different 3D DNA origami nanostructures, i.e., 24 helix bundle (24HB) and 13 helix ring (13HR), were used (Scheme 1). The sequences of the staple strands and the designs are reported in the Supporting Information (Figures S1, S2 and Tables S1, S2). For the fabrication of the DNA origami structures, the scaffold (20 nM p7560 for 24HB and 10 nM p7249 for 13HR) was mixed with the relevant staples (10 times molar excess) in 1× TE buffer together with 15 and 10 mM MgCl$_2$ for 24HB and 13HR, respectively. The solution mixtures were ther- mally annealed at 66 °C for 10 min. The excess liquid was removed by centrifugal concentration by PEG precipitation.60 The samples in water and in IPA were kept at 4 °C and room temperature, respectively, for various durations and imaged by TEM.

**Stability Tests.** Stability of DNA Nanostructures in Water and Organic Solvent. After purification, the DNA origami and DNA@SiO$_2$ nanostructures were resuspended in DI water or IPA to a final concentration of ∼0.6 nM. The samples in water and in IPA were kept at 4 °C and room temperature, respectively, for various durations and imaged by TEM.

**Nuclease Degradation Assay.** DNA origami structures with and without silica coating were diluted to a final concentration of 1 nM in DNase reaction buffer containing different amounts of DNase I. The samples were incubated at 37 °C for 3 h and analyzed by using AGE and TEM.

**Characterization.** UV−Vis Spectroscopy. The concentration of the purified DNA origami structures was estimated by using UV−vis absorption spectroscopy and an extinction coefficient of $1.3 \times 10^4$ M$^{-1}$ cm$^{-1}$ at 260 nm.51

**TEM Imaging.** The DNA origami nanostructures were imaged by using either FEI Tecnai F12 or F20 electron microscopes operated at 120 or 200 kV, respectively. For imaging, the sample solutions (5 μL) were adsorbed onto a glow discharged carbon-film-coated copper grids for 5 min and then wiped away, followed by staining with a 0.5% uranyl formate solution containing 25 mM NaOH for 20 s.

**Atomic Force Microscopy (AFM) Imaging.** The height of DNA origami nanostructures (with and without silica) was obtained by using a Dimension Icon AFM (Bruker) equipped with a fluid cell and operated in ScanAsyst mode. ScanAsyst-Fluid+ probes (Bruker) were used for imaging. For AFM characterization, 5 μL of 100 mM NiCl$_2$ in 1× TE was deposited onto freshly cleaved mica (Ted Pella) for 1 min. The excess liquid was removed by filter paper. After that, 5 μL of sample was deposited for 4 min, followed by addition of 120 μL of 10 mM NiCl$_2$ in 1× TE. 40 μL of 10 mM NiCl$_2$ in 1× TE was added to the AFM probe.

**RESULTS AND DISCUSSION**

**Primary Silica Growth in MgAc Solution.** The silica growth on DNA origami nanostructures proceeds in two steps. First, an alkylalkoxysilane with a positively charged group is used as a coupling agent that electrostatically associates with the negatively charged phosphate backbone of DNA. Then, the silanol groups of the coupling agent serve as a co-condensation site for TEOS to form silica shell around the DNA structures (Scheme 1). We systematically investigated the effects of different conditions, e.g., type of coupling agent, pH, silica precursors ratios to phosphate groups on DNA structures, silica growth time, and MgAc and DNA origami concentration, on the silica growth process. We optimized the experimental conditions, e.g., type of coupling agent, pH, silica precursors ratios to phosphate groups on DNA structures, silica growth time, and MgAc and DNA origami concentration, on the silica growth process. We optimized the experimental conditions, e.g., type of coupling agent, pH, silica precursors ratios to phosphate groups on DNA structures, silica growth time, and MgAc and DNA origami concentration, on the silica growth process.
conditions on 24HB (Scheme 1, Figures S1 and S3a) to obtain a well-dispersed DNA nanostructures with uniform silica coating.

First, we characterized the influence of the coupling agents and the initial pH. TMAPS has been widely employed as an initiator species for the silica growth on dsDNA or DNA structures in most of the previous works. Less attention has been given to the effects of different coupling agents with respect to controlling a uniform silica coating on DNA origami. Besides TMAPS, we tested APTES, i.e., a significantly less hazardous coupling agent, as an alternative. The interaction of the coupling agent with the DNA backbone and the subsequent condensation of TEOS can be strongly influenced by pH. In general, the condensation reaction of silanol groups occurs before the silane hydrolysis is completed, and the pH strongly affects the polymerization rate of SiO₂. On the other hand, the DNA origami structures are stable in the pH range between 5.5 and 9.5. To eliminate the possible negative effects of buffers’ components on the silica coating process, we dispersed the DNA origami structures in buffer-free aqueous solution of 15 mM MgAc (pH ∼ 6) and adjusted the pH if necessary. The effects of different coupling agents and pH on achieving well-dispersed DNA origami@SiO₂ core–shell nanostructures are shown in Figure 1.

Interestingly, after a 5 day silicification at pH 6, some of 24HB structures were stacked tip-to-tip in APTES surfaces at a solution pH is determined by their surface pKᵢ. Previous studies using contact angle titration and fluorescent nanoparticle adhesion assay have revealed that amino groups from the APTEs surfaces have pKᵢ ≈ 7.3. Solving the Henderson–Hasselbalch equation using this pKᵢ value

\[
f_{NH₃⁺} = \frac{1}{1 + 10^{pH-pKᵢ}}
\]

where \(f_{NH₃⁺}\) is the fraction of the –NH₃⁺ groups in APTES, indicates that the degree of ionization of amino groups in APTEs surfaces changes rapidly in the pH range from 6 to 9. The amino group of APTEs on a surface is fully protonated below pH 6 and nearly neutral above pH 9 (see the Supporting Information for additional discussion on the ionization states of APTEs). Typically, silica gels condensed from silanol groups with the presence of aminosilanes exhibit a surface amine-attaching functionality. In addition, the edges of DNA origami structures are commonly modified with single-stranded DNA (ssDNA) loops or extensions to prevent double-helical blunt-end interactions. Because of the short persistence length of ssDNA, this results in a high density of negative charges at the certain edges of DNA origami structures. At pH 6, the strong interaction of positively charged APTEs with ssDNA on the short edges of 24HB structures leads to enhanced tip-to-tip stacking interactions. While the –N′(CH₃)₃ groups of TMAPS are also positively charged, the interaction between –N’ and the negative charges of ssDNA could be reduced by the presence of –CH₂ groups. Therefore, the stacking of 24HB in TMAPS–TEOS is lower than in APTEs–TEOS. Guided by the results presented in Figure 1, we chose pH 9 and deposition time of 5 days for further experiments.

Next, we investigated the influence of the molar ratio of the coupling silane agent/phosphate group on DNA origami (C/P). After the coating, the structures were well dispersed at C/P ratios of 2:1 and 3:1 and aggregated at C/P ratios larger than 3:1 (Figure 2). To evaluate the role of the coupling agents on the silica deposition process, we also performed coating using TEOS only (Figure S4). Although the silica deposition from TEOS is apparent, the 24HB formed disordered aggregates not by tip-to-tip stacking but also by side-to-side binding. It is known that intermediate silica species (from the hydrolysis of TEOS) and DNA origami carry negative charges. The positively charged groups of the coupling agents considerably reduce the repulsion between silanol and phosphate groups and promote uniform growth of the silica network by first assembling around individual DNA strands and subsequently encompassing the entire origami nanostructures. Guided by the results presented in Figure 2, we chose the 3:1 C/P ratio to grow thin silica shell on DNA origami.

The thicknesses of silica shells have been well controlled by adjusting the amount of TEOS and the molar ratio of H₂O/TEOS for inorganic nanoparticles@SiO₂ (NPs@SiO₂). However, less attention has been given to the effects of molar ratio of the TEOS/phosphate group (T/P), which is a convenient control parameter for the silica coating of DNA structures. To investigate the effect of T/P ratio on the silica growth on origami structures, different TEOS concentrations were used in the growth mixture (Figure 3). As the ratio of T/P increased from 10:1 to 40:1, the thickness of the silica shell
increased accordingly. The core-free silica particles appeared at the T/P ratio of 40:1. It is interesting to note that at the T/P ratio of 30:1 rather specific tip-to-tip stacking is observed for both TMAPS−TEOS and APTES−TEOS (Figure 3c,g). At higher T/P ratio, the 24HB formed agglomerates not only through tip-to-tip stacking but also through side-to-side binding. Guided by the results presented in Figure 3, we chose the T/P ratio of 20:1 for further experiments.

Next, we tested the influence of DNA origami concentration on the silica growth process. The concentration of 24HB was varied between 2 and 20 nM, keeping the C/P and T/P ratios fixed at 3:1 and 20:1, respectively. The results in Figure S6 indicate that the concentration of DNA origami template strongly affects the growth rate of silica layers. Although constant ratios of C/P and T/P were used, the concentrations of coupling agents and TEOS changed according to the concentration of origami. Higher concentrations of 24HB, coupling agents, and TEOS resulted in fast condensation and aggregation (Figure S6f,f'). At low concentrations of 24HB, coupling agents, and TEOS, the effective interaction between the origami structure and the silica precursors was reduced, leading to the formation of free silica gel (Figure S6a,a'). Interestingly, the APTES−TEOS silica coating was more sensitive to concentration of origami than TMAPS−TEOS.

With the investigated ratios of C/P, T/P, and pH, the suitable concentrations of DNA origami which results in well-dispersed structures are 12−14 and 6−16 nM for APTES−TEOS and TMAPS−TEOS, respectively. It has been reported that screening of negative charges on DNA origami by Mg2+ ions in buffers prevents efficient interaction of coupling agent with DNA.55−58 We tested whether reduced Mg2+ concentration (0.2 mM) would lead to better results in comparison to 15 mM Mg2+ used throughout the study (Figures S7 and S8). After a 5 day coating with APTES−TEOS in aqueous solution of 0.2 mM MgAc, the 24HB structures expanded, especially at the tips. Most of the TMAPS−TEOS-coated 24HB structures were broken. The internal structure of DNA origami was more disturbed by TMAPS than by APTES due to the stronger interaction of TMAPS with the phosphate groups of DNA backbone. The increased repulsion between DNA helices at a low Mg2+ concentration led to structural damage and deformation of DNA origami under the silicification process with TMAPS−TEOS and with APTES−TEOS, respectively.

Secondary Silica Coating in a Mutual Solvent. In a modified Stöber method, a mutual solvent of alcohol, e.g., isopropanol (IPA), and water is commonly used for the preparation of NPs’ silica shells for two main reasons.78 The first is increased homogenization of precursors. The second is
the ability to control the rate of the hydrolysis-condensation reactions and an inorganic polymerization process with silica layers. DNA origami structures are not stable in IPA; hence, this solvent is not suitable for direct silica coating of origami constructs. However, the stability of DNA was improved by the presence of silica shell after the primary coating in 15 mM MgAc solution, and the mixture of IPA and water can be used as solvent in the secondary silica coating on DNA@SiO2-1. Our previous works demonstrated that a solution of 80% v/v IPA in water was an optimum solvent for a silica coating on metallic NPs.79,80 To increase the hydrolysis of TEOS and fabricate smooth silica shells, an initial pH range of 10.8–11.4 has been applied in many studies.81–85 Herein, we investigated various percentages of IPA for the secondary coating process at pH 10.8 for 24 h (Figure S9). Calculated amounts of IPA, TEOS, and NH4OH were added directly into the solution after a 5 day reaction of the primary coating process. Without IPA, silica gel cloud formed around DNA@SiO2 structures (Figure S9a). After the addition of TEOS and IPA (from 20% to 40% v/v), the formation of silica shells was clearly visible despite agglomeration (Figure S9b,c). With 80% v/v IPA, large silica networks were formed (Figure S9d). Furthermore, addition of 40% v/v IPA without TEOS into the solution after a 5 day reaction of the primary coating also resulted in agglomeration of silica-coated 24HB (Figure S10a). The agglomeration is due to the IPA-induced complete hydrolysis of silica precursors and condensation of free silica clusters formed in the primary coating process. Interestingly, shaking at 300 rpm during the silicification produced better results than the same rate stirring, which resulted in significant deformation of origami structures (Figure S10b). To gain better control of silica deposition during the secondary coating, we performed additional purification of DNA@SiO2-1 after the primary coating (see the Supporting Information for purification of DNA@SiO2). To achieve ultrathin silica shells and monodisperse DNA@SiO2, a solvent of 20% v/v IPA at pH 10.8 and a T/P molar ratio of 5:1 were experimented for the secondary silica coating with various concentrations of purified 24HB DNA@SiO2-1 (Figure 4). Strong agglomeration was observed in samples with 24HB DNA@SiO2-1 concentrations above 80 pM due to the increased polymerization rate of silanol at high concentrations in a less polar IPA solution. The agglomeration was reduced by decreasing the concentration of DNA origami, and a well-dispersed structure secondary silica coating (named DNA@SiO2-2) was obtained at 25 pM (Figure 4d). Silica layers after the coating were denser than after the primary coating (Figure S11), providing direct evidence that DNA origami structures are completely encapsulated with silica shells.

Application of the Silica Coating Protocols to 13HR DNA Origami. To validate our method, the protocols for the primary and secondary silica coatings were applied to ring-shaped DNA origami structures consisting of 13 DNA helices (13HR) with the outer diameter of 66 nm and the inner diameter of 46 nm (Figure 5). In contrast to the 24HB, the 13HR structures did not form agglomerates even after the 9 day primary silica coating process and were well dispersed in solution (Figure S12). This observation strongly confirms that the tip-to-tip stacking of 24HB is related to the flexibility and charge density of ssDNA at the short edges of origami constructs.

AFM Characterization of Silica Shell Thickness. The thickness of the silica shells after the primary and the secondary silica coatings was characterized by using AFM (Figure 6 and Figure S13). The height of both 24HB and 13HR increased after the coatings. The average heights (N = 50) of the monodisperse nanostructures of 24HB, 24HB DNA@SiO2-1, and DNA 24HB @SiO2-2 were 10.1 ± 0.6, 12.6 ± 0.6, and 13.7 ± 0.7 nm, respectively (Figure 6d). The average heights (N = 50) of the 13HR, 13HR DNA@SiO2-1 and 13HR DNA @SiO2-2 were 5.2 ± 0.5, 7.5 ± 0.4, and 8.1 ± 0.4 nm, respectively (Figure 6h). The AFM imaging confirmed the formation of silica shells and their nanoscale thickness.

Biochemical Stability Tests. To expand the utility of the DNA origami technique as the nanofabrication method, DNA-origami-based assemblies need to be stable under various conditions relevant to the fabrication and/or application procedures. Limited compatibility of DNA origami-based assemblies with solvents and biologically relevant fluids often restricts applications of the DNA origami technique. The stability of DNA origami structures in low magnesium buffers and resistance to degradation by nucleases are often prerequisites for biomedical applications.51–53 Encouraged by our results on stability at low Mg2+ concentration (Figure S6a), the exposure to DI water was tested on both 24HB, i.e., bare...
DNA origami, and 24HB DNA@SiO$_2$-1, i.e., encapsulated structures. The 24HB were completely damaged after 1 week in DI water (Figure S14a). Because of the absence of Mg$^{2+}$ ions, the repulsive electrostatic interactions between neighboring helices induced disintegration of origami structures. In contrast, after the primary coating, the 24HB DNA@SiO$_2$-1 were stable in DI water for at least 10 months (Figure S14b). To evaluate the resistance to the nuclease-mediated degradation, we performed a DNase I titration assay, where uncoated 24HB and 13HR structures (1 nM) were incubated with increasing amounts of enzyme in DNase I buffer for 3 h at 37 °C. As observed by AGE and TEM (Figure 7a,e), bare 24HB structures were completely degraded at 4 U/mL of DNase I, and bare 13HR structures were significantly damaged in 0.5 U/mL (Figure 7b,f). In contrast, the degradation of DNA@SiO$_2$-1 structures was considerably reduced (Figure 7c,g). Remarkably, DNA@SiO$_2$-2 structures resisted the degradation and maintained their structural integrity (Figure 7d,h). The increased stability after the secondary silica coating originates from both the increased thickness and the reduced porosity of silica shells.

We also evaluated stability of origami structures in a polar organic solvent, i.e., IPA, before and after the silica coating (Figure S14c,d). DNA origami constructs deposited on surfaces can preserve their structural integrity after exposure to certain organic solvents.54,84 However, applications of DNA
origami technique in solution have almost exclusively relied on aqueous buffers, with a few exceptions. As expected, we did not observe any bare DNA origami structures in TEM after 1 day exposure to IPA. However, after the primary silica coating, the 24HB DNA@SiO$_2$-1 structures were stable in pure IPA for at least 3 days.

**CONCLUSIONS**

Through systematic screening of reaction conditions, we developed a method for coating of DNA origami structures with ultrathin silica shells in solution. Well-dispersed silica-coated structures were obtained by using APTES and TMAPS coupling agents that facilitated deposition of silica from TEOS. The TMAPS–TEOS coating was demonstrated to be successful with the wide range of pH and DNA origami concentration. On the other hand, the APTES–TEOS produced better results at low Mg$^{2+}$ concentrations. In addition, we demonstrated that the density of silica shells can be improved with a secondary coating in a solution of 20% v/v IPA. Silica-coated DNA origami structures were stable against exposure to DI water and DNA nuclease. Furthermore, the structures were stable in pure IPA for several days, at least. The presented method can be easily adopted to origami constructs of various morphology, further advancing the utility of the DNA origami technique in nanofabrication and biomedical applications.

**ASSOCIATED CONTENT**

1. Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.chemmater.0c02111.

Staple sequences, strand routing diagrams, and TEM images of 24HB and 13HR; thermal annealing of DNA origamis; ionization states of APTES at a given solution pH; influences of the coupling agents, origami, and MgAc concentrations on the silica coating on 24HB; primary silica coating under static condition; secondary silica growth on 24HB DNA@SiO$_2$-1 under different IPA concentrations and mixing methods; TEM images of DNA@SiO$_2$ structures at the optimum conditions; histogram of the heights of 24HB and 13HR structures (with and without silica); stability of 24HB structures (with and without silica) in various solvents; purification of 24HB DNA@SiO$_2$-1 structures (PDF)

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**Author Contributions**

K.N. and A.K. conceived the research and designed the experiments. V.N. and A.N. designed the DNA origami nanostructures. K.N. performed silica deposition experiments as well as TEM and AFM characterizations. B.S. and J.R. assisted with AFM imaging. Y.H. performed the gel electrophoresis experiments. A.K. and K.N. wrote the manuscript. All authors have given approval to the final version of the manuscript.

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**Notes**

The authors declare no competing financial interest.

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