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DNA Origami as a Tool to Design Asymmetric Gold Nanostructures

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Abstract

DNA origami technology provides a versatile approach for the chemical assembly of gold nanostructures. In this study the bottom-up approach of self-assembly using DNA in the origami process has been successfully applied to arrange five AuNPs asymmetrically. The DNA origami templates were modified to have binding sites that were extended with sticky ends to facilitate the attachment of the AuNPs. With the help of thiol chemistry, the AuNPs which were covered with DNA complementary to the sticky ends introduced on the DNA origami surfaces, we were able to attach the nanoparticles to the designed sites. It was realized that there were slight differences in the designed distances and the determined ones which were accounted for potentially by the deposition of the structures on the grids for imaging. The structures were characterized with gel electrophoresis and TEM. This asymmetric arrangement has the potential of exhibiting plasmonic behavior and circular dichroism when light is incident on the structure.

Keywords: DNA origami, folding, gelelectrophoresis, TEM, thiol chemistry, gold nanoparticles

1. Introduction

Since the advent of DNA origami in 2006 by Rothemund (2006), a lot of research has been ongoing to functionalize origami structures with nanomaterials to have specific properties in areas such as biology, materials science, physics and computer science. This was after a previous study had demonstrated the formation of programmable assembly of branched DNA junctionsand laid down the foundation for the pursuit and construction of nano-devices using DNA (Seeman, 1982). Some research groups (Mirkin, Letsinger, Mucic, & Storhoff, 1996; Alivisatos et al., 1996) have used DNA to assemble nanoparticles through hybridization as a bottom-up approach. The specific binding of the bases in DNA is responsible for its self-assembly giving a large amount of control in nanoscale devices assembly.

Rothemund's method (2006) is versatile, robust and significant, and can be used to construct both 2-D and 3-D structures. The DNA origami method uses shorter single-stranded staple DNA sequences to fold a long single-stranded scaffold DNA. For single-layered origami structures the mixture is heated for a few hours to fold while multi-layered structures can take up to days. The DNA origami method can produce both 2-D and 3-D structures of pre-arranged shapes (Rothemund, 2006; Douglas et al., 2009a; Douglas et al., 2009b; Amoako et al., 2013). The approximately 7200 base-scaffold and the numerous staples are mixed together in a suitable buffer during folding and then annealed over a certain temperature range (Rothemund, 2006; Douglas et al., 2009b; Castro et al., 2011). Individual staples can be extended with sticky ends (additional sequences) that protrude on the surfaceand allow the use of DNA origami as a template to assemble nanoparticles. Using the covalent bond between gold and sulfur, functionalized gold nanoparticles with complementary sequences can then hybridize with the sticky ends(Mirkin, Letsinger, Mucic & Storhoff, 1996; Nuzzo & Allara, 1983; Dubois & Nuzzo, 1992; Herne &Tarlov, 1997; Yang, Yau & Chan, 1998; Bain & Whitesides, 1989; Hickman et al., 1992; Mucic, Storhoff, Mirkin, & Letsinger, 1998; Storhoff et al., 2000; Storhoff, Elghanian, Mucic, Mirkin, & Letsinger, 1998; Jin, Wu, Li, Mirkin, & Schatz, 2003; Pearson et al., 2012). This process then attaches the gold nanoparticles onto the origami surface.

Well-structured metal nanoparticles could have potential electrical (Pearson et al., 2012), plasmonic (Kuzyk et al., 2012; Shen et al., 2012), and circular dichroism (CD)(Pearson et al., 2012; Shen et al., 2012) characteristics.

In this work, we demonstrate the use of DNA origami to arrange gold nanoparticles (AuNPs) asymmetrically. We believe this asymmetric arrangement of AuNPs has potential applications in plasmonics and circular dichroism.

2. Materials, Methods and Design

2.1 Materials

The experimental procedures following were adapted (Castro et al., 2011; Zhao, Jacovetty, Liu, & Yan, 2011; Tanton, 2002).

2.1.1 Chemicals and supplies

All unmodified utrapage purified DNA oligonucleotides and Ethylenediaminetetraacetic acid (EDTA) were purchased from Sangon Biotech (Shanghai) Co. Ltd, suspended in ultrapure water and used without further purification. The 3'- and 5'- thiol-modified HPLC purified DNA strands were obtained from the same source while the Tris (hydroxymethyl) aminomethane (Tris), Agarose M, and magnesium acetate tetrahydrate ($(CH_3COO)_2Mg{\cdot}4H_2O$) were obtained from Bio Basic Inc (Markham, Canada). NA-red, and 6X loading buffer were obtained from Beyotime Institute of Biotechnology (Haimen, China) and the wide-range DNA marker from Takara Biotechnology (Dalian, China) Co. Ltd. The single-stranded viral genomic DNA M13mp18 used in the experiments was obtained from New England Biolabs (Ipswich, UK)and the boric acid (H_3BO_3), magnesium chloride ($MgCl_2$), and acetic acid ($C_2H_4O_2$) from Sinopharm Chemical Reagent (Shanghai, China) Co. Ltd. Freeze 'N' Squeeze DNA gel-extraction spin columns were acquired from Bio-Rad Laboratories Inc. (Hercules, USA)and Tris (carboxyethyl) phosphine hydrochloride (TCEP) and Bis (p-sulfonatophenyl) phenylphosphinedihydratedipotassium salt (BSPP) from Sigma-Aldrich, USA. 15 and 10nm AuNP colloids wereobtained from Ted Pella Incand other chemical reagents from Sinopharm Chemical Reagent Co. Ltd. Carbon copper grids and mica were bought from Beijing Zhongjingkeyi Technology Co. Ltd and finally uranyl acetate ($UO_2(CH_3COO)_2{\cdot}2H_2O$) from Structure Probe, Inc. (Beijing, China).

2.2 Methods

2.2.1 Phosphination and Concentration of AuNPs

We stabilized the 10 nm AuNPs with absorption of BSPP. BSPP (15 mg) was then added to the colloidal nanoparticle solution (50 mL) and the mixture shaken overnight with a constant temperature incubator at room temperature. Sodium chloride (solid) was slowly added to the mixture and stirred until the color changed from deep burgundy to light purple. The resulting mixture was centrifuged at 3000 rpm for 30 min and the supernatant carefully removed with a pipette. AuNPs were re-suspended in 1 mL solution of BSPP (0.5 mM). 500μL methanol was then added to precipitate the particles and the mixture again centrifuged at 3000 rpm for 30 min. The supernatant was carefully removed and the AuNPs re-suspended in 1mL of 0.5mM BSPP. The concentration of the AuNPs was estimated by the optical absorbance at 520 nm. Phosphine coating increases the negative charge on the particle surface and therefore stabilizes the AuNPs in high electrolyte concentrations at high particle density. The whole process was repeated to stabilize the 15nm AuNPs.

2.2.2 Preparation of AuNP-DNA conjugates

TCEP (20 mM, 1h) in water was used to reduce the disulfide bond in the thiol modified oligonucleotides to monothiol. Size exclusion columns (G-25, GE Healthcare) were used to purify the oligonucleotides and remove smaller molecules. Monothiol modified oligonucleotides and phosphinatedAuNPs were then combined (DNA to AuNP molar ratio of more than 200:1) in 0.5X TBE buffer (89 mMTris, 89 mM boric acid, 2 mM EDTA, pH 8.0) containing 50 mMNaCl for 40 hours at room temperature to ensure the AuNPs were fully covered by thiolated DNA. 0.5X TBE buffer in Microcon (100 KDa, Millipore, Billerica, MA) columns were used to wash AuNP-DNA conjugates to remove the excess oligonucleotides. The concentration of these AuNP-DNA conjugates was estimated from the optical absorbance at 520 nm. Freshly prepared AuNPs (10 nm and 15 nm), fully covered with DNA strands did not precipitate in buffer (5 mMTris, 1 mM EDTA, 12mM $MgCl_2$), which is preferred for the folding in DNA origami.

2.2.3 Folding and purification of DNA origami cross-like structures

Our sample was prepared based on the procedures outlined in a previous study (Castro et al., 2011), but with some modifications to the annealing process. This modification involved combining 10nM scaffold (M13mp18), 100nM of each of the 178 staple oligonucleotides which were used without further purification, buffer and salts including 5 mMTris,1 mM EDTA (PH 7.9 at 20℃), and a magnesium screen covering 7 different concentrations from 12 mM at 2 mM intervals to 24 mM $MgCl_2$. Folding was carried out in a PCR tube by rapid heat denaturation followed by slow cooling from 65 °Cto 60 °C over a 50 minute interval, then 60 °C to 24 ℃ over 72 hours. We performed electrophoresis on samples using 2% Agarose gel (0.5X Tris/Borate/EDTA (TBE), 11 mM $MgCl_2$, 10 μL NA-red) at 70V for 3.5hours in an ice-water bath. Discrete bands were visualized with UV trans-illuminator (Peiqing JS-

680B). The desired bands were physically excised, crunched and filtered through a Freeze 'N' Squeeze spin column at 4 ℃ for 10minutes at 16000 ×g.

2.2.4 Preparation and purification of origami-AuNPs complexes

The purified DNA origami was mixed with AuNP-DNA conjugates in a ratio of 1:10 and annealed from 40 °C to room temperature. The annealed product of the DNA origami and AuNPs were loaded in a 1.0% Gel-red (Biotum) stained agarose gel (running buffer 0.5 X TBE containing 11 mM $MgCl_2$, loading buffer 50% glycerol, 70V constant Voltage). Selected bands were cut out and the DNA Origami-AuNPs complexes extracted from the gel with Freeze'N'Squeeze columns (Bio-Rad Laboratories Inc) at 4 °C.

2.2.5 TEM imaging

Transmission electron micrographs were obtained with a JEM-2100 (HR) TEM. The sample was negatively stained. A 3 μl sample solution was deposited onto the carbon-coated side of the TEM grid and allowed to adsorb for about 5 minutes. The grid sample-side was first immersed into a 2% uranyl acetate (Structure Probe, Inc) stain-solution droplet and incubated for 40 seconds. All excess liquid was dabbed off with the edge of a filter paper, and the grid allowed to dry completely. Images were taken at different accelerating voltages.

2.3 Design

2.3.1 Design of AuNPs Attachment Sites

The previously reported 12x24x38 DNA origami cross-like structure was used as the template to organize the AuNP structures (Amoako et al., 2015).The square lattice based caDNAno software was used to design the 3D cross-like structure. The 78 helix bundle multilayer was used to assemble the AuNPs after the following modifications were made to the staple strands at the attachment sites:

We designed a structure with the cross-like DNA origami as template using AuNPs. The idea was to make the nanoparticles structure have an asymmetric shape. We designed five nanoparticles attachment sites with one nanoparticle attachment site at each of the four ends of the cross-like structure and the last attachment site on top of the template. The attachment sites are shown as yellow and blue in Figure 1. Four attachment sites were designed at the bottom of the template with only one on the top surface. We designed the nanoparticles structure such that the separations between opposite sites were not equal. The separation between the attachment site at the top (yellow) and the one directly below (blue) was 16 nm (Figure 1). The separation between the attachment site on the left (yellow) and the one on the right (blue) was 26 nmwhile the separation between the AuNP on the surface of the template and those at the bottom was 12 nm. The surface nanoparticle was placed approximately at the center of the template.

To attach AuNPs to our cross-like structure, we made modifications to the staple strands at the designed attachment sitesby extending the DNA staples at the designed sites with specific sticky ends. The staples at the blue attachment sites (Figure 1) were extended at the 5' end with sequences ATATATATATATATAA (B) while the staples at the yellow attachment sites (Figure 1) were extended at the 5' end with sequences AAAAAAAAAAAAAAA (C) as shown in Table 1. Each site was designed with three staple sequences so that for the five AuNPs we extended 15 staple strands. The complementary sequences to B and C were N2 and N1 respectively. N1 and N2 were terminated on the 3' end with thiol (-SH) extensions as shown in Table 1 to covalently attach the phosphine stabilized AuNPs. Each of N1 and N2 were 15 ntlong. The two yellow sites were designed to attach two AuNPs and the three blue attachment sites designed to attach three AuNPs. The sticky ends were placed such that after hybridization of the cross-like structure they were displayed on the upper and bottom surfaces of the template.

When the sticky end extensions on the B-labeled sequences in Table 1 hybridize with the complementary sequences N2, the AuNPs stick out on the surface of the template. The sticky end extensions on the C-labeled sequences will also hybridize with the complementary sequences N1 and the AuNPs will stick out on the template surface.

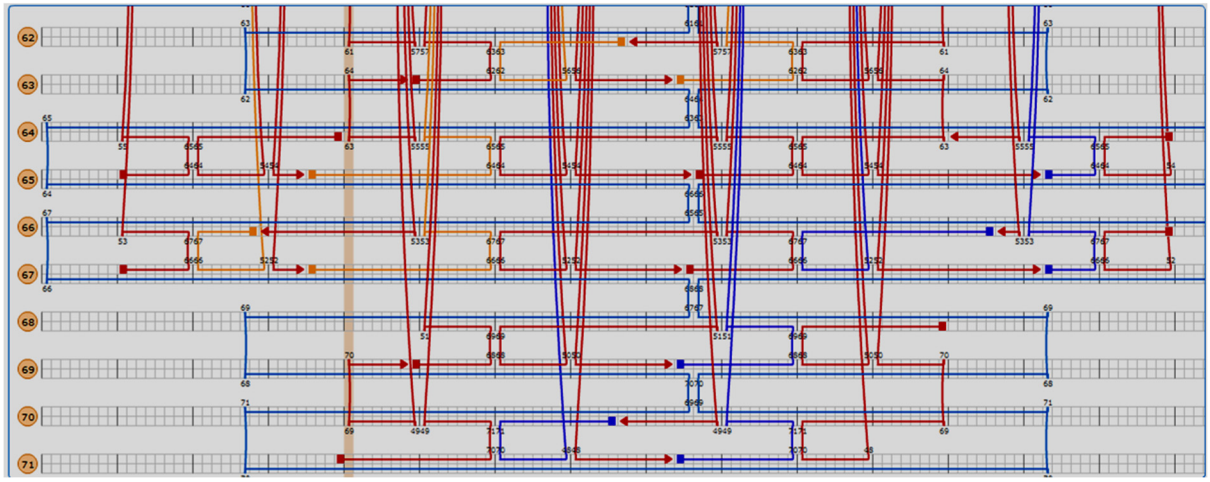

Figure 1. Gold nanoparticles attachment sites. Yellow and blue indicate the designed attachment sites for AuNPs. Red indicates the DNA staple single strands used to fold the scaffold strand (light blue)

Table 1. Staple DNA sequences with the extended sticky ends. B1 to B6 are indicated as yellow in Figure 1while C1 to C9 are indicated as blue in Figure 1

B1	ATATATATATATATAACAACGAGGGTAGTAAACGGGTAAAATGTAGCGCGTTTT	54
B2	ATATATATATATATAGCCTCCCTCAGAGCAACCACCACTTG	41
B3	ATATATATATATATAGCCGGTCGCTGAGGACAGCATAGCGATTACTAA	48
B4	ATATATATATATATAGAATTTACCGTTCCAGTAAGGCAGGTCAATTCATTAATTTG	56
B5	ATATATATATATATAAGTAACAATTTCGGAACGTA	35
B6	ATATATATATATATAATTATTCTGAAACATGAAAGAAGTTTTACACGG	48
C1	AAAAAAAAAAAAAAAACGAAAATCCCAGGGTGGTTATCGGGAGAAACACCGGA	52
C2	AAAAAAAAAAAAAAAATCTTTTCACCAGTGAGACGTCCAC	39
C3	AAAAAAAAAAAAAAAATTGGGCGGCTAACTCTGTGTTTGG	40
C4	AAAAAAAAAAAAAAAAGGTGACCGACAATGCGCAGA	36
C5	AAAAAAAAAAAAAAAGTTGAAAATCTCCAAAAAAAAACAACTTTGGCTT	49
C6	AAAAAAAAAAAAAAAGAGAATAATTTTTTACCGGATACTGACCAATTAAGA	51
C7	AAAAAAAAAAAAAAAATACAGCCCTCATTTTCTGTAAGTAAATTCTGA	48
C8	AAAAAAAAAAAAAAATCAGGAGGTTTAGCCTCATTTCCAATAATAAGAGCAATAATA	57
C9	AAAAAAAAAAAAAAAAAGCCCAATAGGAGCATTCCACTCATTATACCTTATGGAGCAA	58
N1	TTTTTTTTTTTTTT-SH	15
N2	TATATATATATATAT-SH	15

3. Results and Discussion

To minimize nonspecific binding between the negatively charged DNA strands and the metal surface, and also to increase the stability of the colloids, we prepared the AuNPs using a negatively charged phosphine shell. This reactive phosphine shell is easily displaced by thiolated DNA strands in the presence of $NaCl_2$. In solution, Brownian motion brings the functionalized AuNPs and the sticky ends on the DNA origami surfaces into close proximity. Since these DNA single strands are complementary they hybridize.

Figure 2 shows the 0.6% agarose gel electrophoresis of the conjugated DNA origami/AuNP structures. The M13mp18 scaffold DNA strand was used as marker and shown in lane 1. Lane 2 contained the DNA origami cross-like structure and the AuNPs. The AuNP arrangement on the origami structure shown in the Figure indicates the nanoparticles arrangement below the origami structure. The band containing the origami/AuNP complex is as indicated (Figure 2). This lane also contained the excess AuNPs that were not involved in binding, and the band is indicated (Figure 2).

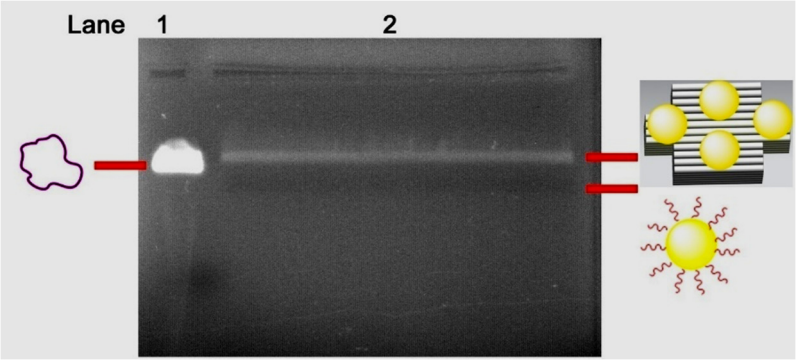

Figure 2. Gel red stained 0.6% agarose gel electrophoresis of assembled cross-like origami/AuNP products. Lane 1 contains M13mp18 scaffold marker with the band indicated. Lane 2 contains metalized origami structures and the well-formed structure is indicated with the clear band. Excess AuNPs migrate faster and are indicated in the not-clear band

We arranged two types of AuNPs shapes. One type used only the four attachment sites under the DNA origami cross-like structure while the other used all the five designed attachment sites. We used the two types of sticky ends to attach four 15 nm AuNPs under the cross-like structure as shown in Figure 3. The separation between the AuNPs in Figure 3a match the caDNAno designed separation distances. All the separation distances were determined from the centers of the AuNPs. The separation from the centers of the AuNPs between the left AuNP labeled as 4 (top attachment site in caDNAno in Figure 1) and the right AuNP labeled as 3 (down attachment site in caDNAno in Figure 1) in the TEM image in Figure 3a is ~24 nm. The separation between the top AuNP labeled as 1 (right attachment site in caDNAno in Figure 1) and the down AuNP labeled as 2 (left attachment site in caDNAno in Figure 1) in Figure 3a is ~40 nm. These two separation distances (that is 1→2 and 3→4) were designed to be 26 nm and 16 nm respectively. Figure 3b shows that the separation distances are ~30 nm and ~18 nm respectively for 1→2 and 3→4. In Figure 3c, the separation distances are ~40 nm and ~20 nm for 1→2 and 3→4 respectively.

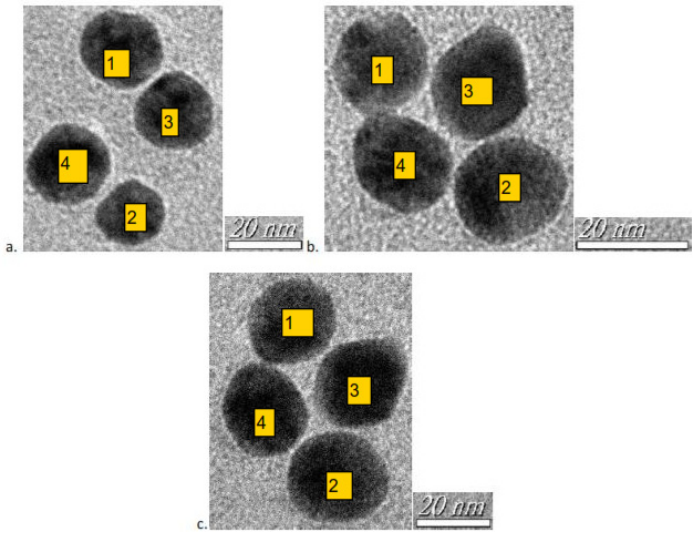

Figure 3. TEM images of 15 nm AuNP assemblies at the bottom of theDNA origamicross-like structure. (a-c) are cross sections of the four 15 nm AuNPs structures formed. The scale bars are indicated besides the images

Figure 4 shows the arrangement of 5 AuNPs using all the designed attachment sites on the cross-like structure. Two different diameters of AuNPs were used, and were made up of three 15 nm and two 10 nm diameter nanoparticles. The 15 nm diameter AuNPs are labeled as 2, 4 and 5 in Figure 4 while the 10 nm diameter AuNPs are labeled as 1 and 3. The TEM image of AuNPs reveals that their shape is not all spherical as was assumed. Some even showed triangular shapes. Figure 3 shows the symmetric nature of the AuNP arrangement. The

introduction of the fifth AuNP on the surface of the Origami structure breaks this symmetric frame, introduces asymmetry into the arrangement and makes the arrangement three dimensional. The potential coupling of the bottom layer AuNPs to the single AuNP in the upper layer makes the AuNPs structure truly 3-D and possibly chiral. TEM images are used to characterize DNA origami template self-assembly of AuNPs, where the interparticle distance can be used to deduce the designed separation distance. However, increased forces that act on the larger nanoparticles as the sample dries on the TEM grid could be sufficient in distorting the arranged AuNPs shape. Slight deviations from the designed structures could be seen in Figure 4. In Figure 4aand 4b, we see clearly that the number 5 AuNP is placed above number 1 AuNP as designed, but the bottom placed AuNPs are displaced from their designed positions if compared to Figure 3. Figure 4c shows that the top placed AuNP slightly displaces the number 1 labeled AuNP. The displacement by the number 5 AuNP is complete in Figure 4d and therefore moving the number 1 AuNP further away. This displacement renders the AuNP structure in Figure 4d two dimensional.

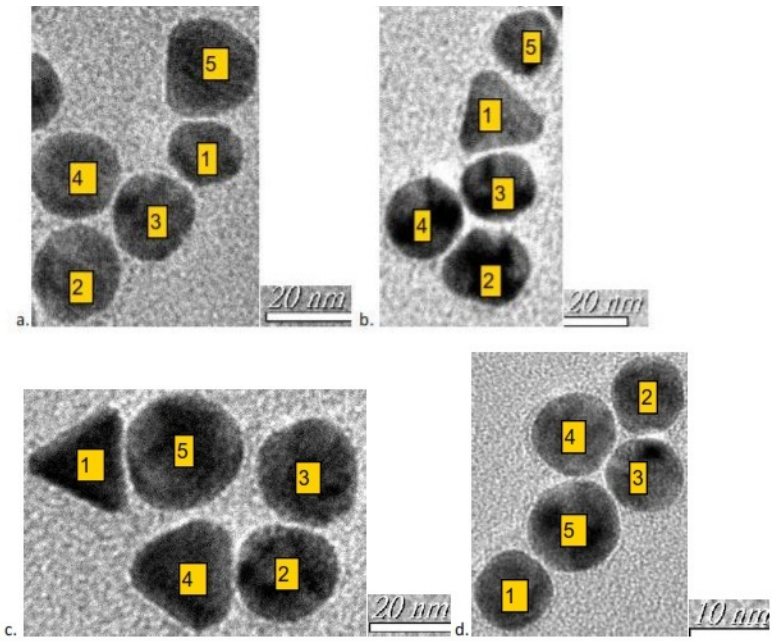

Figure 4. TEM images of 15 nm and 10 nm AuNP assemblies using the DNA origami cross-like structure. The scale bars are indicated besides the images

4. Conclusion

In conclusion, we have been able to use DNA origami to arrange an asymmetric AuNPs structure with the potential to exhibit plasmonic behavior and circular dichroism. We have also completely characterized our AuNPs structure and determined their inter-particle distances. There were slight differences in the designed distances and the determined distances. These differences were possibly due to the deposition of samples onto the TEM grids for Tem imaging.

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