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Number-controlled spatial arrangement of gold nanoparticles with DNA dendrimers†

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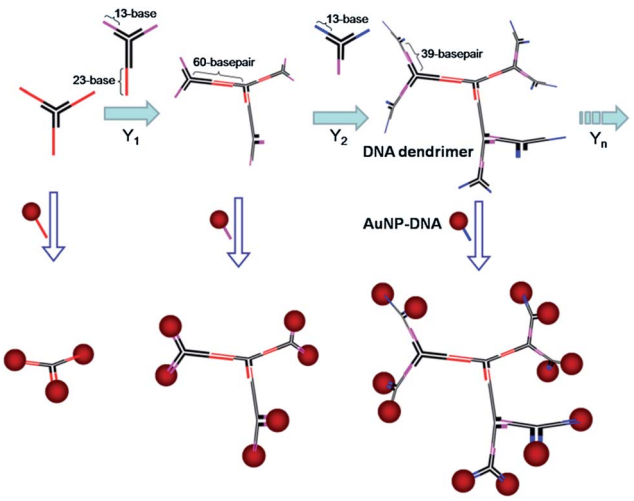
In this study we described a controlled self-assembly of gold nanoparticles mediated by DNA dendrimers. Stepwise titration of three-arm Y-shaped DNA monomers through a divergent route can assemble different generations of DNA dendrimers with discrete DNA sticky ends on the surface. Hybridizing gold nanoparticles bearing one single-stranded DNA to different generations of DNA dendrimers thereby results in assembly of number-controlled discrete gold nanoparticle groupings. The conjugation strategy used herein provides a novel model for spatial positioning of functionalized nanoparticles and precise construction of multivalent nanomaterials.

Gold nanoparticles (AuNPs) are being actively developed as building blocks for nanophotonic and nanoelectronic materials.[1,2] Many of their properties, such as surface plasmon resonance, depend critically on the interaction to their neighbouring particles.[3,4] Bottom-up self-assembly provides a decent way to organize nanoparticles over different distances and geometries precisely.[5] Among various self-assembly methods, DNA is now widely employed as a template for nanoparticle assembly[6–17] because of its remarkable molecular recognition properties and structural features.[18] However, number-controlled spatial arrangement of nanoparticles groupings still remains as a challenging goal. Meanwhile, dendrimers,[19] a class of highly branched macromolecules with uniform size, receive increasing attention for their multivalent and nanosized structures providing great potential to program nanoparticle assemblies. But most of dendrimers involve multi-step synthesis and purification processes, as well as complex procedures to incorporate more branches. In contrast to conventional wisdom, DNA dendrimers based solely on DNA self-assembly could be obtained in high yields without any purification owing to the precise recognition of DNA hybridization.[20–22] Herein we report a straightforward method to control the assembly of discrete structures of AuNPs using DNA dendrimers. The outermost sticky ends of the DNA dendrimers could be evenly distributed in three dimensions as their globular structures, which make them extremely suitable for being used as scaffolds to place nanoparticles in precise spatial positions.

Our strategy is described in Scheme 1. DNA dendrimers were prepared using step-by-step assembly of Y-shaped DNA (Y-DNA). As the structure of Y-DNA is approximately planar,[23] a three-dimensional scaffold can be accessed by choosing the lengths of DNA duplex between each layer to be approximately 3.75 turns (39 basepairs). In particular, to eliminate the possible



Scheme 1 Strategies employed in controlled spatial arrangement of gold nanoparticles using DNA dendrimers as scaffolds.

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steric issues caused by multiple branched sides, 60 basepairs (~5.75 turns) spacer were introduced between the first layer and the core. This design can not only delay the saturation occurring at a certain layer, but also improve assembly efficiency of the sticky ends. As each Y-DNA bearing three arms, the number of outermost branches could be controlled to certain value. DNA mono-modified AuNPs were then assembled *via* hybridization to the sticky ends on DNA dendrimers surface, which were used as scaffolds to control programmed spatial arrangement of nanoparticles.

To obtain different generations of DNA dendrimers, equal moles of oligonucleotides (for example, Y_{na}, Y_{nb} and Y_{nc}) were mixed together to form dendrimer monomers (Y_n, the n^{th}-generation Y-DNA). The 13-base or 23-base sticky ends on the Y-DNA arms (Scheme 1) construct stable self-assembled structures at room temperature.[24] The n^{th}-generation DNA dendrimer was named G_n, and stepwise titration of Y_n to G_{n-1} ($n \geq 1$), DNA dendrimers of different generations can be synthesized *via* the hybridization of sticky ends (Fig. 1a). Here every new layers of Y_n that were added on G_{n-1} are different and we assemble the G series dendrimer in a manner of A-B-C-D-E. As we had found in the previous report,[21] such assembly strategy yielded the best quality of DNA dendrimers. Therefore the sticky ends on surface of each generation G_n are different, either 13 or 23 bases in our experiments, which can avoid crosstalk between the different layers. The self-assembled DNA dendrimers were then characterized by agarose gel electrophoresis and dynamic light scattering (DLS). As shown in Fig. 1b, DNA dendrimers of different generations appeared in agarose gel as a single band with a high yield in the absence of purification. DNA dendrimers of higher generations exhibited reduced mobility since the larger sizes, the slower the migrations. Here the size effect (but not the charges) dominates in the gel electrophoresis. Thus the mobility of G_{n+1} was slower than that of G_n as shown in the gel. DLS measurement (Fig. 1c) showed, hydrodynamic radius increased from ~12 nm for G_1 to ~28 nm for G_4, which is consistent to the gel electrophoresis result. The structure of DNA dendrimer (G_4) was further confirmed by atomic force microscopy (AFM). The G_4 samples were deposited on mica and imaged by tapping mode under buffer, which revealed highly branched dendritic nanostructure (Fig. 1d).

Such nanoscale, size-controllable DNA dendritic structures with known surface sticky ends can be used as scaffolds for nanoparticles arrangement. Here we assemble AuNPs which bear only one single-stranded DNA (in terms of DNA mono-functionalized AuNPs), because such monovalent AuNPs can preclude crosstalk during assembly and significantly improve the assembly accuracy. The synthesis of DNA mono-functionalized AuNPs was carried out by incubation 1 : 1 molar ratio of BSPP (bis(*p*-sulfonatophenyl)phenylphosphine dehydrate dipotassium salt) capped Au particles with lipoic acid modified DNA (lipoic-DNA) and purification of the desired adducts from agarose gels (Fig. 2) (the detailed protocol can also be found in the ref. 25). Since agarose gel electrophoresis-based separation of monofunctionalized AuNPs to two-, three- or even more DNA functionalized AuNPs requires a significantly long single-stranded DNA (usually >50 bases for 5 nm AuNPs) for a better resolution, lipoic-DNA (13 bases or 23 bases) used to hybridize on DNA dendrimers surface were obviously too short. To solve this problem, we hybridized a longer strand (EXT-Y_n) as a helper to 'extend' the lipoic-DNA strand (LA-cY_n).[9] The resulting AuNP–DNA conjugates were then separated by gel electrophoresis as shown in Fig. 2a. After extracting DNA

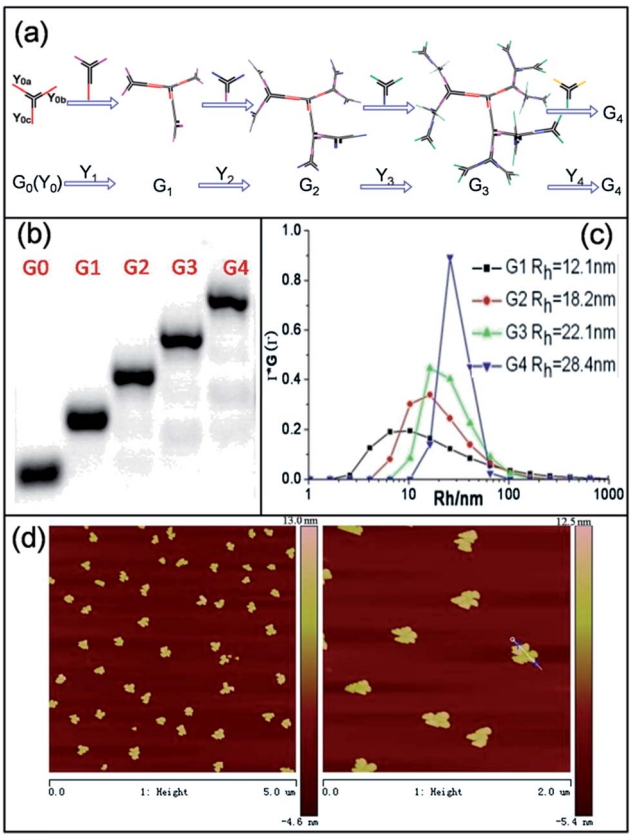

Fig. 1 (a) The assembly strategies to construct DNA dendrimers; (b) agarose gel electrophoresis of G_0–G_4; (c) size distribution by DLS of G_1–G_4; (d) AFM images of G_4.

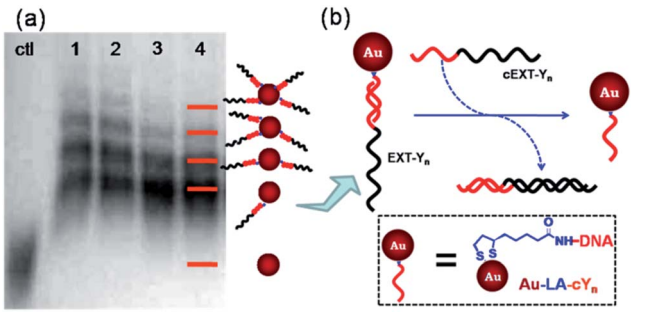

Fig. 2 The preparation of monofunctionalized gold nanoparticles with lipoic acid modified DNA. (a) The separation of AuNP–DNA conjugates into discrete structures characterized using agarose gel electrophoresis: lane ctl, AuNP; lane 1, AuNP + LA-cY_0/EXT-Y_0; lane 2, AuNP + LA-cY_1/EXT-Y_1; lane 3, AuNP + LA-cY_2/EXT-Y_2; lane 4, AuNP + LA-cY_3/EXT-Y_3. (b) Schematic methods to get desired a short oligonucleotide strand monofunctionalized AuNPs.

monofunctionalized nanoparticles from the corresponding band, EXT-Y_n was removed upon hybridization to a fully complementary DNA strand (cEXT-Y_n) (Fig. 2b) and the desired short lipoic-DNA modified AuNPs were obtained.

With DNA dendrimer scaffolds and DNA mono-modified AuNPs in hand, we proceeded to test the ability of these scaffolds to yield nanoparticle groupings with spatial control. When G_0, which has three branched sticky ends, was incubated with certain amount of corresponding complementary DNA monofunctionalized AuNPs, Au trimers were obtained as transmission electron microscopy (TEM) images showed in Fig. 3a. Due to the conformational freedom of Y-DNA, triangles of gold nanoparticles have angular flexibility and not showed as perfect triangle-like arrangements. Likewise, well-defined gold particle hexamers could be obtained by the hybridization of G_1 with six complementary gold monoconjugates (Fig. 3b), and hybridization of G_2 and nanoparticle–DNA conjugates results in the synthesis of complexes containing 12-nanoparticle (Fig. 3c). To our knowledge, the precise control over the spatial arrangement of 12 discrete nanoparticles in such a straightforward manner has not been reported, although this strategy becomes less feasible as the generations of the dendrimers increase. As we found that, the desired assemblies were not formed by incubation of G_3 and G_4 with corresponding AuNP monoconjugates, respectively. TEM images revealed that 22 or less nanoparticles groupings were yielded (Fig. 3d, S6 and S7†). The most likely explanation is that the higher generation dendrimers, the more floppy the DNA structures are, and the more crowded sticky ends on surface. Steric effect and electrostatic repulsion may cause serious obstacle for site-specific assembly.

To sum up, we reported the use of DNA dendrimers as scaffolds to direct the assembly of discrete gold nanoparticle groupings. DNA dendrimers can be constructed in a straightforward way with high yields. Different numbers of AuNPs clusters were formed according to TEM images. The capability of using DNA dendrimer-based assembly allowed one to use several components at same time and only the right component with right sequence can assemble at the specific position. The arrangement of nanoparticles on DNA dendrimers provides a new strategy for multiple components such as sliver nanoparticles,[26] quantum dots,[27] nanodiamonds[28] *etc.* for nanophotonic and sensoring applications.

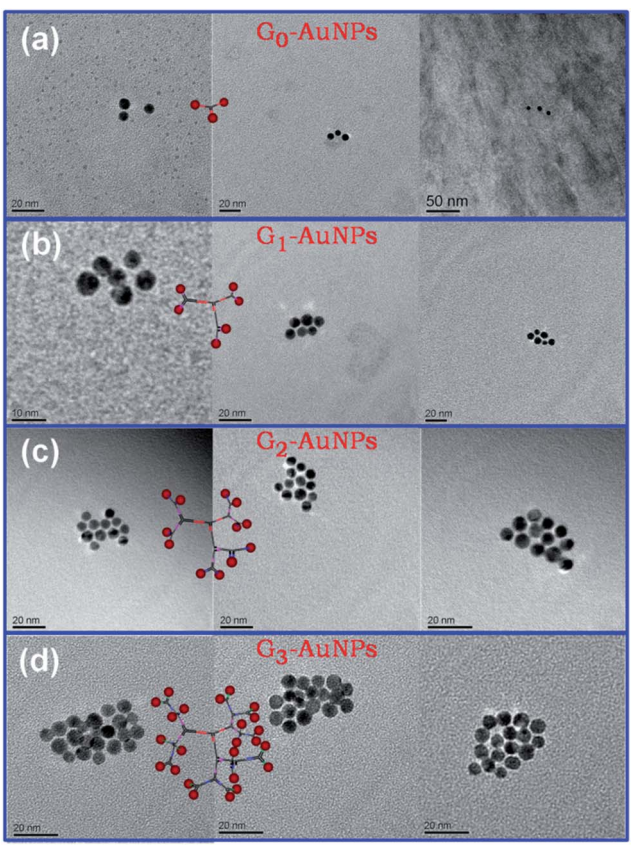

Fig. 3 TEM images of DNA monofunctionalized AuNPs incubated with (a) G_0, (b) G_1, (c) G_2 and (d) G_3, respectively.

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