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Controlled functionalization of gold nanoparticles through a solid phase synthesis approach†

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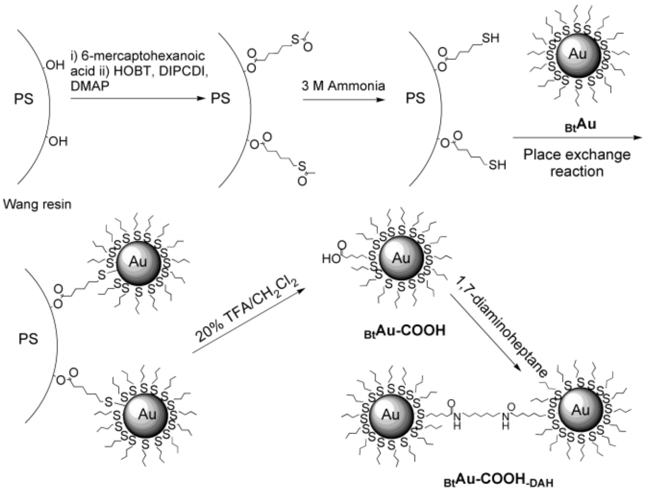
A novel solid phase synthetic strategy was developed in this work for controlled functionalization of gold nanoparticles.

The synthesis and study of gold nanoparticles is a major area of current nanoparticle and nanomaterial research.[1–6] Gold nanoclusters have potential applications for nanoelectronics, nanodevices, bio- and chemosensor development. However, controlling the number of functional groups on the nanoparticle surface remains a significant challenge. So far only two examples have been reported on nanoclusters with discrete numbers of surface functional groups. The first example is based on triphenylphosphine-protected gold nanoclusters reported by Hainfeld *et al*.[7] This method is limited to gold nanoclusters with a diameter smaller than or around 1.4 nm and have poor environmental and thermal stability. In a second example, Alivisatos *et al*. reported the separation of gold nanoparticle–DNA conjugates with discrete numbers of DNA molecules by electrophoresis.[8] However, this approach is not a general synthetic approach to prepare gold nanoparticles with different organic functional groups in large quantities.

For the first time, we report the use of a novel solid phase synthesis technique to control the place exchange reaction and to prepare monolayer-protected gold nanoparticles with a single surface functional group, or an anisotropic distribution of functional groups. Solid phase synthesis is a synthetic strategy in which chemical reactions are conducted on a solid support such as a polymer resin. While this technique has been used extensively in peptide and combinatorial library synthesis,[9,10] it has never been applied in nanoparticle research.

The synthetic strategy used in our study is outlined in Scheme 1. A difunctional 6-mercaptohexanoic acid, with thiol group protected by an acetyl group,[11] was attached to polystyrene Wang Resin through ester bond formation.[12,13] After the deprotection of the acetyl group, the thiol groups were allowed to undergo a place exchange reaction with butanethiolate-protected gold nanoparticles ($_{Bt}$Au), which were prepared according to the Shiffrin reaction with an average diameter of 2.8 nm.[4] The effective place exchange reaction between resin-bound thiol ligands and $_{Bt}$Au nanoparticles was clearly observed from the darkening of the resin beads after 12–24 hours of incubation of nanoparticles with resin beads in solution. After washing off any unexchanged nanoparticles, the resin-bound nanoparticles were cleaved from the resin using 20% TFA in CH_2Cl_2. After washing and purification, pure nanoparticle product $_{Bt}$Au–COOH was obtained with a yield around 50%. The obtained nanoparticles can be precipitated out and re-dissolved in organic solvents such as dichloromethane. TEM and XRD analysis show that the $_{Bt}$Au–COOH sample has the same average diameter of 2.8 nm as the $_{Bt}$Au nanoparticles, indicating that the structure of the nanoparticles remain intact during the solid phase synthesis.



Scheme 1 HOBT, 1-hydroxybenzotriazole; DIPCDI, 1,3-diisopropylcarbodiimide; DMAP, 4-(dimethylamino)pyridine.

The number of functional groups attached to gold nanoparticles is controlled by the functional group density of the solid support. If the density of the free thiol groups attached to the Wang Resin is low enough that two adjacent thiol groups are relatively far away from each other as shown in Scheme 1, only one resin-bound thiol group will be attached to a gold nanoparticle by place exchange reaction. When the resin-bound nanoparticles are cleaved from the solid resin, nanoparticles with a single carboxylic group should be obtained as the major product. In our study, we chose Wang Resin with a functionality of 1.4–3.2 mmol g^{-1} as the solid support. According to calculation, there would be less than one –SH per 20 nm^3 (see ESI†). Through solid phase synthesis gold nanoparticles with a single surface functional group should be obtained as the major product.

It is assumed that if there is only one carboxylic group present on the nanoparticle surface, when an aliphatic diamine is added to couple with the nanoparticles, one should see, by TEM analysis, the formation of nanoparticle pairs instead of trimers, tetramers, and larger aggregates formed from nanoparticles with more than one functional group. The coupling reaction was conducted according to the following conditions. Approximately 5 mg of dried $_{Bt}$Au–COOH was dissolved in 400 μL dichloromethane and 100 μL DMF. To this solution, approximately 500 times equivalent *N*-hydroxysuccinimide (NHS) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) in 100μL DMF was added. The reaction mixture was heated at 40 °C for four hours followed by purification through a column of Sephadex LH-20 gel. To the activated nanoparticles about 100 times equivalent 1,7-diaminoheptane in a minimum of DMF was added to form the coupled nanoparticle product $_{Bt}$Au–COOH-$_{DAH}$ for TEM analysis.

Fig. 1a and b are the TEM images of $_{Bt}$Au–COOH nanoparticles, and the diamine-coupled $_{Bt}$Au–COOH-$_{DAH}$nanoparticles. From these images, one can clearly see that the nanoparticles from the $_{Bt}$Au–COOH sample are randomly distributed while a large number of pairs appeared in the $_{Bt}$Au–COOH-$_{DAH}$ sample. The distance between the two nanoparticle cores in the pairs is around 1.0–1.5 nm, which corresponds to the length of the organic ligand bridge between the two nanoparticles. By counting the number of nanoparticle pairs that appeared in several TEM images of this sample, it was estimated that about 60–70% of the solid phase synthesis product is single functional group-modified nano-

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† Electronic supplementary information (ESI) available: experimental section and analytical data. See http://www.rsc.org/suppdata/cc/b3/b312819a/

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particles. Analysis of some very diluted samples of $_{\text{Bt}}$Au–COOH-$_{\text{DAH}}$ indicates that the nanoparticle pairs observed in Fig. 1b are not due to a coincidental aggregation effect. At a closer look, a very small fraction (less than 5%) of nanoparticle trimers and aggregates are also present along with some individual nanoparticles (25%). The individual nanoparticles are likely non-functionalized nanoparticles or nanoparticles not coupled with diaminoheptane. The nanoparticle trimers and aggregates correspond to nanoparticles with more than one functional group. Additionally, UV-visible absorbance measurements show a 20 nm redshift of the SPR band of the $_{\text{Bt}}$Au–COOH$_{\text{DAH}}$ nanoparticles relative to the SPR band of the $_{\text{Bt}}$Au gold nanoparticles. A similar shift has been observed by Feldheim with molecularly bridged silver nanoparticle pairs.[14]

Theoretically one could also prepare gold nanoparticles with single or other controlled numbers of functional groups through place exchange reaction in solution by using a very small ratio of the incoming thiol ligands *versus* the replaced thiol ligand.[6] However, no in-depth study has ever been reported on the effectiveness of such an approach. To compare these two different approaches, we have prepared two place exchange reaction products using 11-mercaptoundecanoic acid as the incoming ligand: one was targeting less than 5% exchange ratio ($_{\text{Bt}}$Au–COOH$_{5\%}$) and another sample was aimed for 40% exchange ratio ($_{\text{Bt}}$Au–COOH$_{40\%}$). The two place exchange reaction products were also coupled with 1,7-diaminoheptane for TEM analysis. It was noticed that while the coupling product of $_{\text{Bt}}$Au–COOH$_{5\%}$ remains soluble in dichloromethane, the coupling product of $_{\text{Bt}}$Au–COOH$_{40\%}$ is insoluble in most organic solvents, indicating the formation of large aggregates due to multiple functional groups. For this reason, the TEM analysis of the 40% place exchange product was not obtained.

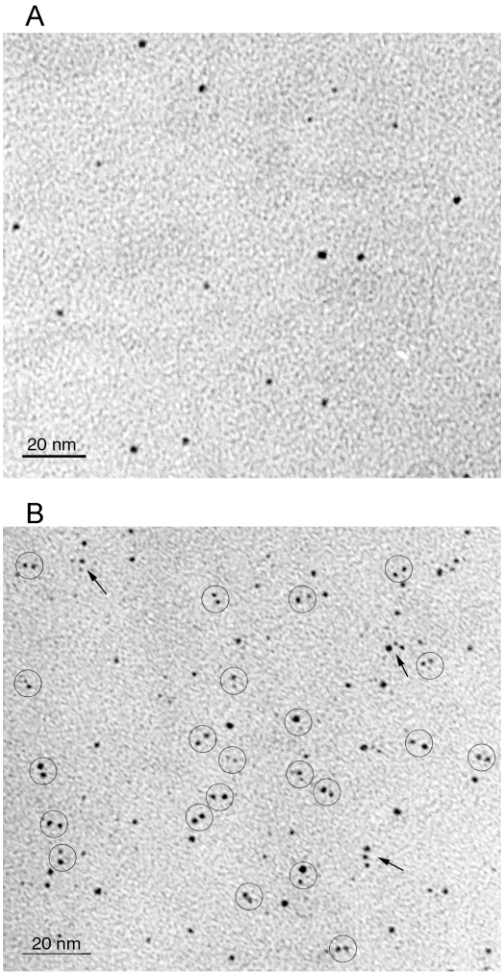

Fig. 1 TEM images of $_{\text{Bt}}$Au–COOH (a) and $_{\text{Bt}}$Au–COOH$_{\text{DAH}}$(b) nanoparticles. Circles: dimers, arrows: possible trimers. Samples were prepared by adding approximately 1μL of sample in appropriate solvent onto a 300 mesh formvar grid and immediately wicked off using filter paper. Images were obtained using a JEOL 100CX TEM at 80 KeV.

A TEM image of the 5% exchange product coupled by diaminoheptane shows the presence of mainly individual nanoparticles along with less than 6% nanoparticle dimers and trimers (see ESI†). This result indicates that the solid phase modification is a much better approach in preparing nanoparticles with controlled functionality. In order to limit the number of functional groups attached to the nanoparticles during the place exchange reaction, the concentration of the incoming ligand has to be very low. As a result, the chance for the incoming ligands to collide with nanoparticles is extremely low, which inevitably leads to a low efficiency of ligand exchange. In contrast, in solid phase synthesis, the incoming ligands are immobilized on the polymer bead and by increasing the reaction temperature, nanoparticles have a much better chance of collision with the ligands to allow place exchange reaction to occur. More importantly, once the nanoparticle is attached to the beads, this nanoparticle will not react further with other ligands to allow attachment of multiple surface functional groups. It should be pointed out here that the number of functional groups attached to nanoparticle surface through solid phase synthesis has not been determined unambiguously. It is possible that there is more than one carboxylic group attached anisotropically to one side of the nanoparticle. Due to the steric hindrance, coupling of the nanoparticles by alkyl diamine could also lead to dimers rather than trimers, tetramers and large aggregates. Further characterization is being conducted to distinguish these two possibilities.

Through this exploratory study, we demonstrate the feasibility of solid phase synthesis as a potential technique for controlling the surface functionality of nanoparticle materials. This technique is not only limited to gold nanoparticles, but can be adapted to any other types of nanoparticles with appropriate solid phase reactions. Gold nanoparticles with controlled functionality can be treated as real "molecules" and traditional synthetic chemistry, supramolecular chemistry, and polymer chemistry may be conducted on them to make higher order nanoparticle macrostructures and assemblies. Further investigations along these lines will likely result in a completely new direction in the nanoparticle field.

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