PEGylation of gold-decorated silica nanoparticles in the aerosol phase

This article has been downloaded from IOPscience. Please scroll down to see the full text article.

2013 Nanotechnology 24 335602

(http://iopscience.iop.org/0957-4484/24/33/335602)

View the table of contents for this issue, or go to the journal homepage for more

Download details:
IP Address: 216.243.176.222
The article was downloaded on 25/07/2013 at 02:41

Please note that terms and conditions apply.
PEGylation of gold-decorated silica nanoparticles in the aerosol phase

Pingyan Lei and Steven L Girshick

Department of Mechanical Engineering, University of Minnesota, 111 Church Street SE, Minneapolis, MN 55455, USA

E-mail: slg@umn.edu

Received 10 April 2013, in final form 26 June 2013
Published 23 July 2013
Online at stacks.iop.org/Nano/24/335602

Abstract

Coating of gold-decorated silica nanoparticles with polyethylene glycol (PEG) was carried out in the aerosol phase. The process involves first functionalizing the nanoparticles at \( \sim 225 ^\circ C \) with a bifunctional reactant, 2-mercaptoethanol (ME), for which one end is a thiol that attaches to the gold surface and the other end is a terminal hydroxyl group, and then introducing ethylene oxide (EO), which reacts at \( \sim 440 ^\circ C \) with the hydroxyl group via a ring-opening polymerization to grow PEG. The morphology, elemental composition and surface chemistry of the PEGylated nanoparticles were characterized by means of transmission electron microscopy, energy dispersive x-ray spectroscopy in scanning transmission electron microscopy, x-ray photoelectron microscopy and Fourier transform infrared spectroscopy. The increase in mobility diameter of the nanoparticles due to PEG growth was measured on-line by tandem differential mobility analysis. The PEG coating thickness was found to increase with increases in gold decoration density, flow rate of ME, and flow rate of EO. Coating thicknesses up to \( \sim 4.5 \) nm were measured on nanoparticles whose initial mobility diameter equaled 39 nm.

(Some figures may appear in colour only in the online journal)

1. Introduction

Gold nanostructures are currently the subject of intense interest. The surface plasmon resonance of gold nanoparticles and nanoshells enables laser-based imaging and heating for biomedical applications [1–3]. Additionally, gold nanoparticles with diameters below about 5 nm have been shown to be effective catalysts. Combined with their absorption in the visible, this makes gold nanoparticles a promising material for solar-driven photocatalysis [4–8].

Among materials that have been used as substrates for gold nanoparticles or nanoshells, silica (SiO\(_2\)) has probably been the most utilized, as its dielectric properties and high chemical and thermal stability make it an excellent choice for many applications. Synthesis of SiO\(_2\)@Au nanostructures is usually accomplished by means of wet chemistry [9–11]. Recently, Boies \textit{et al} reported an aerosol method for producing gold-decorated silica nanoparticles [12]. Aerosol methods for multilayer nanoparticle synthesis have several potential advantages over liquid-phase methods, for example they are less prone to contamination from impurity residues, do not require the use of surfactants (which typically must then be removed before addition of the next layer), involve continuous flows with residence times of seconds rather than multi-step batch processes with residence times of many hours or even days, and are scalable to high production rates. However, for biomedical and many other potential applications, the final desired product remains nanoparticles in stable liquid (often aqueous) dispersion. Therefore, an important challenge for nanoparticle aerosol technology is to develop methods for transferring nanoparticles from the aerosol to the hydrosol phase.

One method for transferring nanoparticles from the aerosol phase to aqueous dispersion is to coat them with a hydrophilic substance such as polyethylene glycol (PEG). PEG is widely used to coat nanoparticles for biomedical applications, as it is biocompatible and hydrophilic, thus improving solubility, suppressing nanoparticle aggregation, reducing uptake by the reticuloendothelial system and increasing blood circulation time for drug delivery [13, 14].
If a robust method for PEGylation of nanoparticles in the aerosol phase were available, then the particles could readily be transferred into stable aqueous dispersion before they experienced the aggregation that often accompanies particle collection as a dry powder. Thus the advantages of aerosol processing could be realized, while still producing a liquid dispersion as end product.

Several studies have reported PEGylation of silica–gold nanostructures by means of wet chemistry [15–19]. To the best of our knowledge, the only previous report of aerosol-phase PEGylation of nanoparticles of any substance appeared in the PhD thesis of Calder [20], who developed a two-step chemical vapor deposition approach. In the first step, the nanoparticle is functionalized with a bifunctional reactant that attaches at one end to the nanoparticle surface while the other end has a terminal hydroxyl group. In the second step, ethylene oxide (EO) is introduced into the aerosol stream, which is then sent through a tube furnace. The EO reacts with the terminal hydroxyl group via a ring-opening insertion polymerization to grow PEG. Calder demonstrated this approach by PEGylating silicon nanoparticles, functionalized with ethylene glycol, and gold nanoparticles, functionalized with 2-mercaptoethanol (ME).

In this paper we report an aerosol method for PEGylation gold-decorated silica nanoparticles. Silica nanoparticle synthesis, gold nanoparticle synthesis, gold decoration on the silica surfaces, and PEG coating are all accomplished in a continuous gas stream. Our PEGylation reaction scheme, which extends Calder’s approach to PEGylating isolated gold nanoparticles, is illustrated in figure 1.

First, the gold-decorated silica nanoparticles are surface modified with hydroxyl groups by reacting with ME. Thiols are well known to attach to the gold surface by a Au–S covalent bond [21]. At temperatures of around 225°C the thiols form disulphides [20], which adsorb to the gold surface, providing a monolayer of thiolated roots for PEG growth. Then EO vapor is injected into the aerosol stream and exposed to elevated temperature, thereby opening the ring structure of the thiolated monolayer and facilitating PEG growth by polymerization.

2. Experimental procedure

The experimental setup used to produce SiO$_2$@Au@PEG nanoparticles is shown schematically in figure 2. The method used to produce an aerosol of gold-decorated silica nanoparticles is described by Boies et al [22]. Silica nanoparticles are synthesized by thermal decomposition of tetraethyloxysilicate (TEOS) in a nitrogen atmosphere. In the experiments reported here, TEOS vapor, at a flowrate of ~0.018 sccm, is generated by a bubbler, and is carried by 10 sccm of nitrogen into a decomposition furnace, where it mixes with 2.5 slm of nitrogen at a temperature of 900°C. This temperature is sufficiently high to decompose the TEOS, leading to generation of SiO$_2$ nanoparticles by gas-phase nucleation. An additional 2 slm of nitrogen is
added, providing some dilution so as to reduce agglomeration, before the flow enters a second-stage furnace, referred to as the ‘sintering furnace’, which operates at 1200 °C, high enough to spheroidize any agglomerates.

Following the sintering furnace, the silica aerosol passes through a hot-wire chamber where gold nanoparticles are generated. The heated wire consists of gold-coated platinum. As platinum has a higher melting temperature than gold, the wire temperature can somewhat exceed the melting temperature of gold while still maintaining electrical resistive heating. The gold vapor generated from the wire, diffusing to colder regions, undergoes homogeneous nucleation, producing gold nanoparticles. The size distribution of the gold nanoparticles can be controlled by adjusting the wire power and the flow rate of nitrogen that passes over the wire [12]. In this work, with the nitrogen flow rate set by the upstream conditions discussed above, the wire power was set to 19.2 W. The hot-wire chamber is followed by a gold decoration chamber, which controls the residence time for scavenging of the gold nanoparticles by the larger silica nanoparticles.

PEGylation of the gold-decorated silica nanoparticles is accomplished by means of the reaction scheme outlined in figure 1. The gold-decorated silica nanoparticles are functionalized with hydroxyl groups in a first tube furnace, set to 225 ± 5 °C, where ME vapor, generated by a bubbler, is introduced with 100 sccm of nitrogen carrier gas. The surface-modified nanoparticles together with EO vapor then flow through a second tube furnace, where PEGylation occurs. The final product is collected on stainless steel mesh and silver filters (Sterlitech Corp.) as well as on transmission electron microscopy (TEM) grids (Ted Pella 01890). The collected samples were characterized by TEM (Tecnai G² F30), Fourier transform infrared spectroscopy (FTIR, Nicolet Magna 550), and x-ray photoelectron spectroscopy (XPS, Surface Science SSX-100).

Tandem differential mobility analysis (TDMA) [23] was used to obtain on-line measurements of the increase in particle mobility diameter that occurred due to coating with PEG. The TDMA system consisted of two differential mobility analyzers (DMA, TSI model 3085), one upstream and the other downstream of the second tube furnace. Particles are charged to a known bipolar charge distribution before entering each DMA, using a neutralizer with a Po-210 radiation source. The first DMA passes only particles of specified mobility diameter. The second DMA, in series with a condensation particle counter (TSI model 3025A), measures the size distribution of particles exiting the second furnace.

Experiments were conducted with variation of several operating parameters, including total aerosol flow rate through the hot-wire and decoration chambers, ME flow rate, EO flow rate, and temperature of the second tube furnace.

3. Results and discussion
The hot-wire power was fixed at 19.2 W while different flow rates of the silica aerosol were sampled from the exit of the sintering furnace and passed through the hot-wire chamber. Figure 3 shows high resolution TEM (HRTEM) images of gold-decorated silica nanoparticles obtained with flow rates of 1.7 slm, 3.2 slm and 4.5 slm, for which the corresponding residence times in the decoration chamber equal 92, 49, and 35 s, respectively. The images clearly show the gold decoration, with gold nanoparticles appearing darker than silica due to their higher mass contrast. As the aerosol flow rate increases, the residence time correspondingly decreases, and the size of the gold nanoparticles is seen to decrease. In the 1.7 slm case, shown in figure 3(a), the residence time in the decoration chamber is relatively long, and the size distribution of the gold nanoparticles is broad, including some relatively large gold nanoparticles of 5–8 nm in diameter. In this case there is evidently some pile up of gold nanoparticles on the silica surface. For the two cases of higher flow rate the gold nanoparticles are isolated on the silica surface and appear more monodisperse. Their mean diameter, as determined by image analysis (ImageJ software), equals approximately 3 nm in the 3.2 slm case, figure 3(b), and 1.5 nm in the 4.5 slm case, figure 3(c).

Spatially resolved elemental analysis of the nanoparticles was obtained with the TEM operating in scanning TEM (STEM) mode, using energy dispersive x-ray analysis (EDS). Figure 4(a) shows a bright-field STEM image of a nanoparticle produced using a flow rate of 1.7 slm, with four points on the particle surface labeled for EDS analysis. Figure 4(b) shows the corresponding EDS energy spectra. Point 1 is located on a small darker particle, and is located...
Figure 4. Gold-decorated silica nanoparticle: (a) bright-field STEM image; (b) EDS position scans at points 1–4 labeled on the image.

Figure 5. TDMA measurements of normalized particle size distributions of PEGylated gold-decorated silica nanoparticles: (a) repeated scans at 189 sccm of EO, compared to a case without introduction of EO; (b) with various EO flow rates.

off the edge of the large lighter-color particle; point 2 is a bare portion of the surface of the large lighter-color particle; and both points 3 and 4 are on small darker particles that lie on the surface of the large lighter-color particle. As the TEM grid was composed of copper and carbon, signals attributed to both Cu and C were detected at all locations. At point 1, other than the Cu and C background, only Au is detected; at point 2, only Si and O are detected; and at both points 3 and 4 all of Au, Si and O are detected. These results are consistent with the expectation that the particle in figure 4(a) consists of a silica nanoparticle decorated with smaller gold nanoparticles. While this particle was chosen for EDS analysis because the relatively large gold nanoparticles make it possible to focus with EDS on the four different points highlighted, thus making the conclusions unambiguous, it is reasonable to assume that the results apply as well to the cases with smaller and more monodisperse particles, as in figures 3(b) and (c), which may be more suitable for applications.

For studies of the PEGylation process, the total aerosol flow passing through the hot-wire chamber, the decoration chamber and the first tube furnace was maintained at 4.5 slm. At the exit of the first tube furnace, with the nanoparticles now surface functionalized with ME, 1.0 slm of flow was sampled into the neutralizer and first DMA. The mobility-diameter-filtered output from the first DMA was then passed through the second tube furnace. Figure 5 shows TDMA results for several cases where gold-decorated nanoparticles with a mobility diameter of 39 nm were passed to the second tube furnace, the temperature of which equaled 440°C ± 10°C. In figure 5(a), three scans are repeated for the same condition, with the EO vapor flow rate equaling 189 sccm, and are compared to the case without introduction of EO. The shift in the particle size distribution with the introduction of EO is seen to be quite reproducible. The magnitude of the shift is characterized by fitting each of the main peaks to a Gaussian curve and then determining the shift in the peak of the Gaussian. (The small satellite peaks in the mobility distribution measurements are due to particles that are doubly charged by the neutralizer.) From this, introduction of 189 sccm of EO causes the particle mobility diameter
Figure 6. TDMA measurements of PEG coating thickness versus EO flow rate: (a) with varying PEGylation temperature; (b) with varying ME carrier gas flow rate; (c) with/without inclusion of the decoration chamber.

to increase by approximately 9 nm. Assuming that the particles are spherical and that the diameter increase is due to PEGylation, this corresponds to a PEG coating thickness of ~4.5 nm, i.e., half the increase in diameter. Note that this figure represents the increase in particle mobility radius which does not necessarily equal the actual PEG chain size. As the EO flow rate increases, the particle size distribution shifts to the right, as seen in figure 5(b), indicating that the PEG coating thickness increases with increasing EO flow rate.

In addition to the EO flow rate, several other operating parameters affect the PEG coating thickness. Figure 6 shows the results of TDMA measurements of coating thickness, obtained in experiments in which the conditions varied included the temperature of the second tube furnace (figure 6(a)), the ME flow rate (figure 6(b)), and the inclusion or not of the gold decoration chamber (figure 6(c)). In all cases shown the mobility diameter selected by the first DMA (i.e., of the un-PEGylated particle) equaled 39 nm, as in figure 5. In each case, the PEG thickness increases with EO flow rate, consistent with figure 5(b).

For the experiments for which results are shown in figure 6(a), the temperature of the second tube furnace (i.e., the PEGylation temperature) was set to either 250, 340 or 440°C, while keeping other conditions the same (with the decoration chamber, and with 100 sccm of nitrogen carrier gas for the ME). The results indicate that the PEGylation temperature is a critical parameter for PEG growth, with the PEG growing much faster at 440°C than at 250 or 340°C.

The ME flow rate is proportional to the flow rate of the nitrogen in which the ME is carried. In figure 6(b), results of experiments are compared in which two different flow rates of N₂ carrier gas were used for delivering the ME vapor, with inclusion of the decoration chamber and with the PEGylation temperature at 440°C. Doubling the ME flow rate is seen to double (or slightly more) the coating thickness. Presumably, increasing the ME flow rate results in the creation of more Au–S bonds, providing a greater density of terminal hydroxyl groups for initiation of PEGylation, and evidently this in turn causes the coating thickness to increase. As discussed in [14], conditions of relatively low PEG grafting density lead to a ‘mushroom’ conformation in which the PEG chains spread over the nanoparticle surface, while conditions of high grafting density produce a ‘brush-type’ arrangement in which the PEG chains stick straight out from the particle surface. Thus, for the same PEG chain length (which is presumably related to the EO flow rate), a higher density of terminal hydroxyl groups that serve as PEGylation sites leads to a larger particle mobility diameter (hence, coating thickness), which is what is measured by TDMA.

Figure 6(c) shows the effect of including the decoration chamber, with experiments conducted using 100 sccm of nitrogen carrier gas for the ME and the PEGylation temperature at 440°C. The decoration chamber provides a longer residence time for the silica nanoparticles to scavenge the gold nanoparticles that are generated in the hot-wire chamber. While some degree of decoration is achieved by simply mixing the silica and gold nanoparticles within the hot-wire chamber, adding the decoration chamber increases the gold nanoparticle decoration density [22]. Thus, similarly to the case of increasing the ME flow rate, the density of available sites for initiation of PEGylation is increased by adding the decoration chamber. Consistent with this interpretation, figure 6(c) shows that the coating thickness is increased by adding the decoration chamber, for the same EO flow rate.

The chemical composition of the SiO₂@Au@PEG nanoparticles was characterized by means of EDS, XPS and FTIR spectroscopy. The results shown are all for cases in which the decoration chamber was used, the flow rate of nitrogen carrier gas for the ME equaled 100 sccm, and the PEGylation temperature equaled 440°C.

Figure 7 shows a dark-field STEM image together with an EDS position scan of a PEGylated gold-decorated silica nanoparticle, obtained with an EO flow rate of 189 sccm. In dark-field STEM, the gold nanoparticles appear as bright dots. The EDS scan shown was carried out on one such bright dot, indicated by the red circle in the image. The results clearly show signals of Si, O, and Au, as expected for a gold-decorated silica nanoparticle. A PEG coating is expected to produce signals from C and O, but, as carbon is present in the TEM grid and oxygen in the silica, EDS in itself cannot confirm the presence of PEG. Moreover, the signal from sulfur, expected from the thiol attachment to the gold, was too weak to be detected in the EDS scan, and therefore requires additional diagnostics to confirm.

XPS elemental analyses were conducted of particles collected on silver membrane filters. Figure 8 shows results for EO flow rates of 0, 56 and 189 sccm. Each scan is normalized by the Au 4f signal. As the EO flow rate increases from 56 to 189 sccm, the Si (2s and 2p) and S (2s and 2p)
signal intensities are relatively unaffected, while the C 1s and O 1s signal intensities increase. This result is consistent with the TDMA results showing that increasing the EO flow rate causes the coating thickness to increase. It should be noted that for the case of zero EO flow rate, where a thiolated monolayer is expected, some damage of the sample filters was observed after XPS analysis. The weakness of the sulfur signal in this case may have been at least partially caused by desorption of the monolayer thiol groups under x-ray radiation during XPS analysis.

The surface chemistry of the PEGylated particles was characterized by FTIR, as shown in figure 9. The signal associated with the O–Si–O asymmetric stretching mode (∼1110 cm$^{-1}$) shows for the case of pure silica as well as for all of the PEGylated gold-decorated nanoparticle samples. As the EO flow rate increases, the signal intensities of the C–H stretching mode (2800–3000 cm$^{-1}$) and the C–O stretching mode (∼1040 cm$^{-1}$) increase, again consistent with the observation that the PEG coating thickness increases with increasing EO flow rate.

4. Summary and conclusions

In summary, gold-decorated silica nanoparticles have been PEGylated using a two-step aerosol process. In the first step, gold nanoparticles decorating the silica surface serve as sites for functionalization with a bifunctional reactant, 2-mercaptoethanol, at a temperature of around 225 °C, with a thiol group attaching to the gold nanoparticle and a terminal hydroxyl group at the other end. Ethylene oxide vapor is then introduced into the aerosol stream, and, at a temperature around 440 °C, reacts with the hydroxyl group via a ring-opening polymerization to grow PEG. Increase of the ethylene oxide flow rate causes the PEG coating thickness to increase. For a given ethylene oxide flow rate, conditions that increase the surface density of sites available for PEGylation also cause the coating thickness to increase, apparently because they lead to a more brush-type as opposed to mushroom configuration.

This work has demonstrated the feasibility of PEGylating gold-decorated silica nanoparticles in an aerosol stream, but has not explored what production rates might be possible, nor has enough material been produced to conduct studies of the stability of the PEGylated nanoparticles in aqueous dispersion. Such studies are the subject of ongoing research.

Acknowledgments

This work builds on the PhD research of Steven A Calder at the University of Minnesota. His contributions, as well as those of Jeffrey T Roberts, now at Purdue University,
are gratefully acknowledged. This research was partially supported by the US National Science Foundation under award number CBET-1066343. Parts of the characterization work were carried out at the Characterization Facility, University of Minnesota, which receives partial support from the US National Science Foundation through the Materials Research Science and Engineering Centers (MRSEC) program.

References

[16] Xing H Y et al 2012 Biomaterials 33 1079–89