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Tuning thermoresponsive behavior of diblock copolymers and their gold core hybrids. Part 2. How properties change depending on block attachment to gold nanoparticles

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ABSTRACT

Thermoresponsive diblock copolymers of di(ethylene glycol) methyl ether methacrylate (DEGMA) and oligo(ethylene glycol) methyl ether acrylate (OEGA) were synthesized by reversible addition–fragmentation chain transfer polymerization, allowing us to prepare diblocks with a thiol group at the desired chain end, and bond that block to a ~20 nm gold nanoparticle core. The cloud point and coil–globule transition window were measured by UV–*vis* spectroscopy. The gold core lowered the cloud point and narrowed the coil–globule transition window of all the diblock hybrids, but raised the cloud point of statistical copolymer hybrids that had similar cloud points. The extent of the change in the thermo-response properties of the hybrid diblock copolymers was more significant when the gold was bonded to the DEGMA block than the OEGA block. This block is less hydrophilic and sterically hindered than OEGA and may adsorb more effectively to the gold so that the hydration of the outer OEGA block is relatively unaffected by the Au core. This work indicates that diblock copolymers allow factors such as steric bulk and the effects on arrangement around a metal core to be effective tools for manipulating thermo-responsive properties that are not as significant with statistical copolymers.

1. Introduction

This paper reports the effects of bonding diblock copolymers to gold nanoparticles (AuNPs) of ~20 nm diameter. The study tested the effects of which block was bonded directly to the AuNP on the cloud point (CP) and the temperature range over which the coil-to-globule transition occurred. We also compared the effects to statistical copolymers with similar CPs and their hybrids. The diblock copolymers were made using DEGMA and OEGA and were prepared by reversible addition–fragmentation chain transfer (RAFT) copolymerization to yield well-defined block structures with a dithioester at one end (subsequently reduced to a thiol) and a carboxylic acid group at the other end. The colloidal gold nanoparticle (AuNP) cores were pre-synthesized by citrate reduction [1–5]. While there are some studies that have explored gold/polymer hybrid nanoparticles (AuHNPs) of homo- and co-polymers [6–13] this appears to be the first study of the effects of thermoresponsive AuHNPs prepared using diblock copolymers and evaluating the effects of which block is bonded to the AuNP on thermal response properties.

In prior work [14] we showed that the chain end placement of organic amphiphilic end groups (dithioester and carboxylic acid) on the DEGMA-OEGA diblock copolymers could alter the CP by as much as 28 °C and narrowed the coil-to-globule transition range by as much as 70% (from 13 °C to 4 °C) simply by reversing the end group placement on the diblock of an otherwise equivalent composition. In this work we performed a similar test using the AuNP as a "chain end". This was done by reduction of the dithioester chain end, and bonding the thiol to the AuNP, while maintaining the other chain end as a carboxylic acid.

The rationale for this design was threefold. Firstly, DEGMA and OEGA were selected for the diblock because they are both biocompatible and possess pendant ethylene glycol units. This will allow them to be used in the bloodstream and resist non-specific protein adsorption without "PEGylating" the surface as is typically done with nanoparticles intended for use in the body and delivery via the bloodstream [15–17].

Secondly, a diblock polymer matrix makes sense for a nanoparticle intended for use as a drug delivery device because one block can be designed to provide a suitable domain for the intended drug with an outer block designed to stabilize the nanoparticle in the bloodstream. In the prior work [14] we compared the relative effects of the length of the less hydrophilic DEGMA and more hydrophilic OEGA blocks, the placement of the amphiphilic chain ends, the "methyl effect" (acrylate vs. methacrylate backbone), and making one block a statistical OEGA/DEGMA block and the other a pure block, on CPs and the coil–globule transition temperature range.

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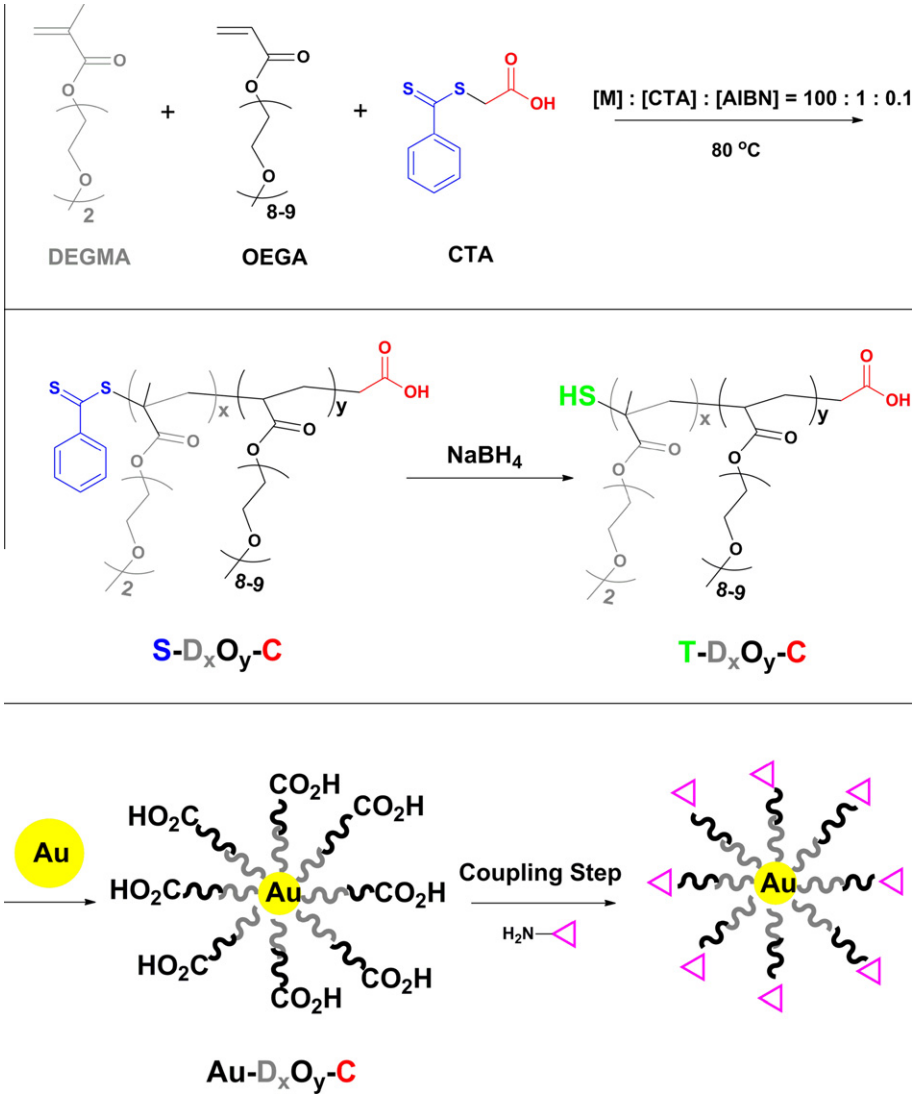
The large number of variables allowed one in principle to tune the "inner domain" polarity to make it suitable for a drug, and still control the final CP by adjusting the other variables while maintaining the outer OEGA block for stability in the bloodstream.

The rationale for coupling the diblock structure with an AuNP core was due to our ultimate objective, which was to design a thermo-responsive nanoparticle containing drug(s) for the treatment of cancer. For this purpose we wanted a nanoparticle that could travel safely through the bloodstream with minimal loss of the drug, target cancer cells by bearing a targeting device on the nanoparticle surface and deliver all or most of the therapeutic drug only once inside the cancer cells. The value of using an AuNP core in this design is that it absorbs 527 nm light (the absorption wavelength is tunable to the near IR region), which is safe for living tissue, but it causes the AuNP core to heat up. Therefore we can design the diblock copolymer in an AuHNP to possess a CP significantly higher than 37 °C (e.g. 44 ± 1 °C) to significantly reduce diffusion release of chemotherapy agents in the bloodstream (which is at ~37 °C), compared to thermo-responsive nanoparticles that are often designed with CPs closer to 37 °C. Therefore a patient would potentially experience fewer side effects because less chemotherapy drug is released outside the cancer cells, and potentially less drug is required to achieve the same positive effect.

Yet another advantage of using an AuHNP with an AuNP core is the potential to couple chemotherapy with hyperthermia. In this design, after allowing appropriate time for the chemotherapy drug(s) to work, an additional treatment with 527 nm light can be applied to heat the local area to even higher temperature to use hyperthermia [18] as a secondary treatment.

In this design then, an AuHNP containing chemotherapy drugs would be designed with an and AuNP inner core to convert 527 nm light to heat, an diblock copolymer shell with an inner block designed to be compatible with the desired drug(s), an outer OEG(M)A or DEG(M)A block for blood stability, and a final targeting device chemically bonded to the outer block for targeting cancer cells (Scheme 1). The CP itself would be controlled to a desired temperature (e.g. 44 ± 1 °C) by control of block lengths and block composition using either acrylate or methacrylates and balancing pure or statistical blocks as desired to get the best balance of CP and drug compatibility. Although our final AuHNP includes a targeting device that we did not include in this paper, the scope of this paper is focused on the study of the effect of the AuNP core on the



Scheme 1. Preparation of thiol-terminated diblock copolymer and AuHNP (Au–D_xO_y–C) core–shell nanoparticles bearing a cell-targeting device. Dark lines represent the OEGA block, lighter grey lines represent the DEGMA block, and red triangles represent the cell-targeting device. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)