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Tunable and Reversible Aggregation of Poly(ethylene oxide-st-propylene oxide) Grafted Gold Nanoparticles

Céline Durand-Gasselin,[‡] Mathieu Capelot,[‡] Nicolas Sanson,^{*,‡} and Nicolas Lequeux[†]

[‡]Laboratoire de Physico-chimie des Polymères et Milieux Dispersés, UMR7615 UPMC-ESPCI-CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France, and [†]Laboratoire Physique et Etudes des Matériaux, UPR05, Ecole Supérieure de Physique et de Chimie Industrielles ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

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Two amino-terminated amphiphilic copolymers, M600 and M1000, with different ethylene oxide to propylene oxide EO/PO ratios, 1/9 and 19/3, respectively, were coupled by thioctic acid, which allows an excellent affinity with gold surface. Then, amphiphilic thermally responsive gold nanoparticles (AuNPs) were prepared either by ligands exchange on precursor gold nanoparticles or by direct reduction of gold source in presence of stabilizing copolymers. The as-obtained AuNPs are monodisperse with a size varying from 2 to 17 nm depending on the synthesis used. The main parameters controlling the AuNPs assemblies were identified: the ethylene oxide to propylene oxide ratio in the polymer corona, the ionic strength of the solution, and the curvature of AuNPs. An interesting result is the possibility to tune the aggregation temperature from 8 to 15 °C of AuNPs coated by the same polymer only by changing the curvature of the AuNPs from 17 to 2 nm. This temperature change versus the curvature of the nanoparticle is ascribed to the decrease in hydration volume per hydrophilic group in the corona due to the change of the polymer chain conformation with changing the particle size. Moreover, one unique aggregation temperature between 12 and 60 °C can be also obtained by mixing copolymers with different EO/PO ratios. Then, the corona, constituted by a mixture of polymers, behaves as a corona composed by an average statistic copolymer with the intermediate composition.

Introduction

Gold nanoparticles (AuNPs) and functionalized gold nanoparticles¹ have received considerable interest for applications in a diverse range of areas including biomedicine,² drug delivery,³ biodiagnostics,⁴ targeted therapies,⁵ and catalysis⁶ due to their unique physical and chemical properties. The synthesis of gold nanoparticles is now well described in the literature, but their selfassembly in 1D, 2D, or 3D remains a challenge.^{7,8} One of the promising ways to drive inorganic nanoparticles assemblies is the use of gold nanoparticles coated by stimuli-responsive polymers and especially thermoresponsive polymers.⁷

In the past decade, several authors have focused on the preparation of AuNPs coated with thermosensitive polymers that undergo structural changes in response to temperature stimulus.⁹ In this objective, thermosensitive gold nanoparticles were prepared with the most common polymer, poly(N-isopropylacrylamide) poly(NiP-

Am),^{10,11} which is a thermoresponsive polymer that undergoes a coil-to-globule transition in aqueous media at ~32 °C, i.e., at its "lower critical solution temperature" (LCST).¹² Poly(NiPAm) was generally synthesized by controlled radical polymerization, and polymer-protected gold nanoparticles were prepared by either "grafting from" or "grafting to" techniques. Reversible additionfragmentation transfer polymerization (RAFT) has the advantage to use di- or trithiobenzoate or carbonate as transfer agents which, after the polymerization, can be used as anchor groups (before or after reduction) for grafting thermosensitive polymers on the gold nanoparticle surface. The main problem of poly(NiPAm) is that its transition temperature is fixed in a broad range of concentration. Nevertheless, it is possible to adjust the transition temperature of poly(NiPAm) by copolymerization with hydrophilic or hydrophobic monomers.¹³ Tenhu et al. have reported the synthesis of NiPAm oligomers terminated with 2-hydroxyethyl acrylate (HEA).¹⁴ They mentioned that the transition temperature of these NiPAm oligomers can be tuned by adjusting either the length of the polymer chain or the concentration, but it is probably due to the fact that the transition temperature for very short polymer chains is very sensitive to the hydrophilic end group.

Recently, a new class of thermosensitive copolymers constituted by ethylene oxide oligomonomers of different lengths, i.e., di(ethylene oxide) (EO₂), oligo(ethylene oxide) (EO₈₋₉), analogue to the poly(ethylene oxide) (PEO), and presenting the same characteristics as linear polymer such as biocompatibility, antifouling behavior, and cell-repellent, tends to replace poly(*N*-isopropylacrylamide).^{15,16} These copolymers $poly((EO_2)_n - co - (EO_{8-9})_m)$ were

^{*}Corresponding author: e-mail nicolas.sanson@espci.fr; Tel 33 (0) 140 794 417; Fax 33 (0) 140 794 640.

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synthesized either by atom transfer radical polymerization (ATRP) in the case of methacrylate monomers¹⁵ or by RAFT for acrylate monomers.^{17,18} In both techniques, the temperature transition of these thermosensitive copolymers can be tuned from 15 to 90 °C by changing the ratio of ethylene oxide oligomonomers.^{15,17} Note that a slight difference of temperature transitions of these copolymers exists between the different authors probably due either to the monomer nature difference or to the fact that cloud point experiments were not measured at the same polymer concentration.

In contrast with the controlled radical polymerization techniques described above for the synthesis of thermosensitive polymers and polymer-protected AuNPs, we report a new versatile way to prepare gold nanoparticles protected by a thermoresponsive biocompatible polymer, which is a statistical polymer constituted by ethylene oxide (EO) and propylene oxide (PO) groups, $poly(EO_x-st-PO_y)$. These amino-terminated polymers were modified by dihydrolipoic acid (DHLA). This excellent anchor group provides a high stability of the polymer ligand on the gold nanoparticle surface compared to monothiol group.¹⁹ The transition temperature of these polymers can be tuned by adjusting the ratio between EO and PO groups. In the same time, monodisperse gold nanoparticles in the 2-17 nm size range were synthesized. Thermosensitive polymer-protected AuNPs were prepared by two ways: a "classic" ligands exchange or direct synthesis of gold nanoparticles in presence of the polymers. After transfer to aqueous solution, AuNPs coated by poly(EO_x-st- PO_{ν}) present a thermoreversible aggregation. Moreover, the aggregation temperature of the polymer-protected gold nanoparticles, i.e., the phase transition temperature of polymers located on the nanoparticle surface, can be adjusted by different ways. First, for a given polymer ligand, the aggregation temperature was modulated between 8 and 15 °C by changing the curvature of the AuNP surface, i.e., the gold nanoparticle size. Second, the grafting of a mix of polymers possessing different hydrophilicity on the nanoparticle surface allows us to tune the aggregation temperature in the 12-60 °C temperature range.

Experimental Section

Materials. Amino-terminated poly(ethylene oxide-*st*-propylene oxide), poly(EO_x-*st*-PO_y) Jeffamine M600 and M1000, with designed molar masses 600 and 1000 g/mol, respectively, were donated from Huntsman Performance Products. Didodecyldimethylammonium bromide (DDAB), sodium borohydride (NaBH₄), and gold(III) chloride (AuCl₃) were purchased from Alfa Aesar. Tetrabutylammonium borohydride (TBAB), hydrogen tetrachloroaurate(III) (HAuCl₄), decanoic acid, sodium citrate tribasic dehydrate, cetyltrimethylammonium bromide (CTAB), ascorbic acid, thioctic acid (TA), 4-(*N*,*N*-dimethylamino)-pyridine (DMAP), and *N*,*N'*-dicyclohexylcarbodiimide (DCC) were purchased from Sigma-Aldrich. All products were used as received. Ultrapure deionized water with a minimum resistivity of 18 MΩ·m (Milli-Q, Millipore, France) was used in the experiments.

Synthesis. *TA-M1000 and TA-M600.* Peptidide coupling of thioctic acid with Jeffamine polymers (M1000 and M600) was prepared following a procedure described in ref 20. Typically,

M1000 (20 g, 20 mmol, 1 equiv), DMAP (1.22 g, 10 mmol, 0.5 equiv), DCC (4.13 g, 20 mmol, 1 equiv), and CH₂Cl₂ (150 mL) were mixed in a 500 mL round-bottom flask. The content was stirred at 0 °C using an ice bath under a N2 atmosphere for 15 min. Thioctic acid (4.12 g, 20 mmol, 1 equiv), dissolved in CH₂Cl₂ (15 mL), was slowly dripped into the reaction using an addition funnel (30 min). The reaction mixture was left stirring for 2 h at 0 °C, then slowly warmed to room temperature, and left to stir overnight under N₂. Then, the mixture was filtered to remove urea. After evaporating the solvent (25 °C, 350 mbar), the reaction mixture was diluted with a saturated solution of NaHCO₃ (100 mL), and the crude product was extracted with CH₂Cl₂ (3 \times 100 mL). The combined extracted CH₂Cl₂ layers were dried over MgSO₄ and filtered, and the solvent was evaporated (60 °C, 350 mbar). The crude product was purified by chromatographic column on silica gel with first 90:10 (v/v)AcOEt:hexane to remove a fast-moving byproduct as shown by thin layer chromatography TLC and then 90:10 (v/v) CH_2Cl_2 : MeOH as the eluent to remove free M1000 as shown by TLC to obtain a yellow oil (~60% yield). TLC of the product using a 90:10 (v/v) CH₂Cl₂:MeOH eluent resulted in $R_f \sim 0.55$. ¹H NMR (400 MHz, CDCl₃): δ 3.66–3.40 (m), 3.35 (s, 3H), 3.18–3.05 (m, 2H), 2.48-2.32 (m, 3H), 1.92-1.84 (m, 1H), 1.75-1.59 (m, 4H), 1.50-1.42 (m, 2H), 1.24-1.05 (m). Same procedure was used to prepare TA-M600. ¹H NMR (400 MHz, CDCl₃): δ 3.68–3.38 (m), 3.35 (s, 3H), 3.21-3.09 (m, 2H), 2.50-2.27 (m, 3H), 1.95-1.90 (m, 1H), 1.75-1.67 (m, 4H), 1.51-1.46 (m, 2H), 1.22-1.16 (m).

DHLA-M1000. TA-M1000 (1 g, 0.83 mmol, 1 equiv) was dispersed in a mixture of MeOH (3 mL) and H₂O (6 mL) in a 50 mL round-bottom flask. The content was stirred under N₂ and cooled to 0 °C. Freshly prepared NaBH₄ solution (62.8 mg, 1.66 mmol, 2 equiv) dissolved in H₂O (6 mL) was slowly injected into the reaction mixture and was left under stirring for an additional 2 h at 0 °C. The reaction mixture was then warmed to room temperature and left to stir for 1 h. The content was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phase was dried over MgSO₄ and filtered, and the solvent evaporated to obtain a transparent oil (~81% yield). ¹H NMR (400 MHz, CDCl₃): δ 3.67–3.37 (m), 3.35 (s, 3H), 3.17–3.05 (m, 2H), 2.95–2.85 (m, 1H), 2.75–2.60 (m, 1H), 2.50–2.35 (m, 1H), 1.92–1.83 (m, 1H), 1.78–1.60 (m, 4H), 1.52–1.42 (m, 2H), 1.36–1.27 (m, 2H), 1.22–1.06 (m).

DHLA-M600. TA-M600 (1 g, 1.25 mmol, 1 equiv) was dispersed in MeOH (10 mL) in a 50 mL round-bottom flask. The content was stirred under N₂ and cooled to 0 °C. NaBH₄ (141.9 mg, 1.36 mmol, 3 equiv) dissolved in H₂O (7.5 mL) was slowly injected into the reaction mixture, and the solution was left under stirring for an additional 2 h at 0 °C and then 1 h at room temperature. The content was extracted with CH₂Cl₂ (~93% yield). ¹H NMR (400 MHz, CDCl₃): δ 3.68–3.47 (m), 3.43 (s, 3H), 3.25–3.1 (m, 2H), 2.9–2.7 (m, 1H), 2.55–2.45 (m, 1H), 2.35–2.25 (m, 1H), 2.0–1.9 (m, 1H), 1.77–1.65 (m, 4H), 1.52–1.48 (m, 2H), 1.40–1.30 (m, 2H), 1.28–1.11 (m).

Gold Nanoparticles (AuNPs). AuNPs coated with DHLA-M600 or/and DHLA-M1000 were prepared directly by precipitation or by cap exchange of gold nanoparticles stabilized by decanoic acid, by CTAB, and by citrate ions (see Supporting Information for as-prepared AuNPs syntheses). In the following, polymer-stabilized gold nanoparticles will be labeled AuNPx@ DHLA-M1000 and AuNPx@DHLA-M600, where x is the mean core size measured by TEM.

AuNP2@DHLA-M1000 and AuNP2@DHLA-M600. AuNPs with a core diameter of ~2 nm were synthesized via direct reduction of gold chloride in the presence of DHLA-M1000 or DHLA-M600. Typically, AuCl₃ (7.5 mg, 0.025 mmol, 1 equiv) was dissolved in DDAB solution (2.5 mL, 100 mM in toluene) by sonication. Then, TA-M1000 (90 μ L, 0.075 mmol, 3 equiv) or TA-M600 (60 μ L, 0.075 mmol, 3 equiv), dissolved into toluene (2.5 mL) by sonication, was mixed to the gold salt solution. Finally, TBAB (25 mg, 0.097 mmol, 4 equiv), dissolved in DDAB solution (1 mL, 100 mM in toluene), was injected to the gold salt solution

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Table 1. Summary of the Characteristics of Jeffamine Polymers, M1000 and M600, Used in This Study

Jeffamine	ratio EO/PO^a	HLB value ^a	$M_{n,\mathrm{NMR}}^{b}$ (g/mol)	$M_{n,MALDI-TOF}^{c}$ (g/mol)	$M_{\mathrm{n,GPC}}^{d}$ (g/mol)	$M_{\rm w}/M_{ m n,GPC}^{d}$	LCST ^e (°C)
M600 M1000	1/9 19/3	2.0 17.0	580 990	580 960	1020	1.03	28 > 80

^{*a*} Given by Huntsman. ^{*b*} Determined from ¹H NMR studies. ^{*c*} Determined using MALDI-TOF studies (see Figure S1 in Supporting Information). ^{*d*} Determined using LiNO₃ GPC (Shodex silica gel columns, poly(ethylene oxide) calibration). ^{*e*} Determined by turbidity measurements using UV-vis spectroscopy.

during vigorous stirring. A dark brown color appears immediately. After 30 min of stirring, AuNPs were dried by evaporation of toluene, redispersed in EtOH (500 μ L), and purified three times by ultrafiltration for 30 min using a Vivaspin disposable system (cutoff 5000 MW). EtOH was removed, and purified particles were finally redispersed in 10 mM KCl solution cooled to 0 °C using an ice bath and stored at 4 °C.

AuNP6@DHLA-M1000, AuNP6@DHLA-M600, and AuNP6@DHLA-M600/M1000. 6 nm size gold nanoparticles capped by decanoic acid were synthesized by the procedure described in ref 21 (see Supporting Information). Ligands exchange was carried out by mixing 20 μ L of DHLA-M1000 (16 μ mol, 3 equiv) or 13 μ L of DHLA-M600 (16 μ mol, 3 equiv) to AuNP6 solution in toluene (1 mL, 5.5 μ mol Au, 1 equiv). After 30 min of stirring, the AuNPs were concentrated, redispersed in EtOH, and purified three times by ultracentrifugation at 280000g for 30 min at 15 °C. The purified AuNPs were finally redispersed in 10 mM KCl solution cooled to 0 °C using an ice bath. AuNP6 were also cap-exchanged with mixtures of DHLA-M600 and DHLA-M1000 ligands in a 75/25 and 50/50 molar ratio using the same procedure as described above.

AuNP7@DHLA-M1000 and AuNP7@DHLA-M600. CTAB-protected AuNPs of diameters ~7 nm were prepared by a seeding growth approach²² (see Supporting Information). 20 μ L of DHLA-M1000 (17 μ mol, 6 equiv) or 20 μ L of DHLA-M600 (25 μ mol, 8 equiv) was mixed with 5 mL of AuNP7 aqueous solution (3 μ mol, 1 equiv). After 90 min of stirring at room temperature, the AuNPs were redispersed in EtOH and purified by ultrafiltration for 30 min using Vivaspin (cutoff 10 000 MW). The purified particles were finally redispersed in 10 mM KCl solution.

AuNP13@DHLA-M1000, AuNP13@DHLA-M600, AuNP17@DHLA-M1000, and AuNP17@DHLA-M600. Citrate-stabilized AuNPs of diameters 13 and 17 nm were synthesized using the standard citrate reduction method²³ (see Supporting Information). $15 \,\mu$ L of DHLA-M1000 ($12.5 \,\mu$ mol, 5 equiv) or $10 \,\mu$ L of DHLA-M600 ($12.5 \,\mu$ mol, 5 equiv) was mixed with 10 mL of AuNP13 or AuNP17 solution ($2.5 \,\mu$ mol, 1 equiv). After 2 h of stirring, the AuNPs were purified three times by centrifugation for 20 min. The purified particles were finally redispersed in 10 mM KCl solution. In the case of DHLA-M600, the temperature during exchange reaction and purification was maintained between 0 and 4 °C.

Characterization. UV-vis Spectroscopy. Absorbance measurements were carried out at different temperatures with a UV-vis Hewlett-Packard 8453 spectrophotometer using a quartz cell, in a wavelength ranging from 200 to 1100 nm, and equipped with a temperature controller (± 0.1 °C).

Microscopy. Transmission electron microscopy (TEM) images were acquired on a JEOL 100CX microscope operating at an acceleration voltage of 80 kV. High-resolution TEM (HRTEM) images were performed with a JEOL 2010 field electron gun microscope operating at an acceleration voltage of 200 kV. Samples were prepared by spreading a drop of sample on an ultrathin 300 mesh Formvar/carbon-coated copper grid and dried in air. The particle size distributions were determined using ImageJ software.

Thermogravimetric Analysis. Thermogravimetric analysis (TGA) was performed using an SDT 2960 analyzer from TA Instruments equipped with a flow gas system. The materials were treated under nitrogen (N_2) flow with a heating rate of 10 °C/min up to 600 °C.

Dynamic Light Scattering. Dynamic light scattering (DLS) was carried out on a CGS-3 goniometer system equipped with HeNe laser illumination at 633 nm and an ALV/LSE-5003 correlator. All samples were filtered through 0.2 μ m Millipore syringe filters. The samples were kept in the apparatus at different temperatures for 10 min prior to measurements. The data were collected by monitoring the scattered light intensity at a scattering angle of 90°. The hydrodynamic size distribution was obtained using CONTIN algorithm and represented in percentage of the diffused intensity.

Results and Discussion

Synthesis and Characterization of Ligands. In this study, two commercial amino-terminated $poly(EO_x-st-PO_y)$ Jeffamine, M1000 and M600, were used as starting polymers. These polymers were characterized by ¹H NMR, IR spectroscopy, MALDI-TOF, and GPC (Figures S1, S2, and S3 in the Supporting Information), and their main characteristics are reported in Table 1. M1000 is mainly composed of ethylene oxide groups and does not exhibit phase transition at temperature lower than 80 °C in water analogue to linear poly(ethylene oxide) chains.²⁴ The second polymer, M600, contains a large fraction of propylene oxide groups and presents a lower critical solution temperature (LCST) in water at ~ 28 °C determined by UV-vis spectroscopy using the "cloud point" method.²⁵ M600 and M1000 were modified into the corresponding dithiolane-terminated ligands, TA-M600 and TA-M1000, respectively, in two reaction steps (Scheme 1): thioctic acid (TA) was coupled to amino-terminated M600 or M1000 in dichloromethane via a peptide group according to a procedure described in the literature.²⁰ After purification, the reduction of terminal 1,2-dithiolane to dithiol (DHLA-M600 and DHLA-M1000) was achieved either prior AuNPs cap exchange using NaBH₄ in alcohol/water mixture or simultaneously during growth of the AuNPs from gold(III) chloride, using tetrabutylammonium borohydride as coreducing agent. The forming amide bond and the ring-opening of the dithiolane group are confirmed by IR spectroscopy and ¹H NMR (Figures S2 and S3 in the Supporting Information).

Synthesis and Characterization of Polymer-Protected AuNPs. Highly monodisperse gold nanoparticles (AuNPs) stabilized with modified Jeffamine ligands were prepared using two distinct methods as shown in Scheme 2: (i) AuNP2@DHLA-M600 and AuNP2@DHLA-M1000 were directly synthesized by reducing simultaneously gold salt and end-capped Jeffamine polymer with dithiolane group in organic solvent (Scheme 2A).

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⁽²⁵⁾ UV-vis spectroscopy allows us to build the phase diagram of the M600 Jeffamine in the range of concentration from 0.2 to 48 wt %. For this, we collect the transmitted intensity as a function of the temperature. For a given concentration (g/mL), we decide to determine the cloud point, i.e., the phase transition temperature T_c , as the temperature where the transmitted intensity reaches 50% of the incident intensity. The lower critical solution temperature corresponds to the minimum of the function $T_c = f(\text{concentration})$.

Scheme 1. Schematic Representation of the Synthetic Strategy for Modification of the Jeffamine M600 (x = 1, y = 9) and M1000 (x = 19, y = 3) into Corresponding TA-Jeffamine and Then DHLA-Jeffamine



Scheme 2. Synthetic Route for the AuNPs Synthesis: (a) One-Pot Synthesis in Toluene for AuNP2@DHLA-Jeffamine; (b) Ligands Exchange in Toluene for AuNP6@DHLA-Jeffamine and in Water for AuNP7@DHLA-Jeffamine, AuNP13@DHLA-Jeffamine and AuNP17@DHLA-Jeffamine



A high ligand/Au molar ratio of 3:1 was fixed to ensure a large excess of free ligands and guarantees complete passivation of gold nanoparticles surface. Independently of this study, Mattoussi and coauthors have very recently proposed a similar method to ours to prepare AuNPs stabilized by poly(ethylene glycol) (PEG) by reduction of thioctic acid grafted PEG (molecular weight of 550 or 750 g/mol) and HAuCl₄ in water using NaBH₄.²⁶ They found that the nanoparticle size can be controlled by varying the TA-PEG ligand to gold ratio. As ligand/Au ratio decreases from 10:1 to 1:4000, the diameter of AuNPs increases from 1.5 to 18 nm. In the present study, no effort was conducted to control the AuNPs size by changing the ligand to Au ratio. (ii) AuNPs capped with DHLA-Jeffamine were also obtained by a ligands exchange procedure (Scheme 2B). AuNPs functionalized by decanoic acid (AuNP6) were synthesized following reduction of gold salt in toluene by TBAB.²¹ CTAB-stabilized AuNPs (AuNP7) were prepared following seed growth approach.²² Citrate-stabilized AuNPs (AuNP13 and AuNP17) were also prepared following the well-known Turkevich method.²³ Decanoic acid, CTAB, and citrate ions are weak ligands for gold and are easily exchanged by dithiol-terminated Jeffamine ligands. The exchange procedure for CTAB and citrate-capped AuNPs was directly conducted in aqueous suspension of as-synthesized gold nanoparticles. Exchange temperature

was maintained near 0 °C to prevent precipitation of highly hydrophobic DHLA-M600 ligands in the case of citrate-capped gold nanoparticles. For CTAB-stabilized AuNPs, the large excess of CTAB allows solubilization of DHLA-Jeffamine, and the exchange reaction has been successfully conducted at room temperature. For decanoic acid-stabilized AuNPs, ligands exchange was achieved in toluene, which is a good solvent for DHLA-Jeffamine. All gold nanoparticles dispersions were carefully purified from free ungrafted copolymer chains by repeated washing/centrifugation cycles and finally redispersed in 10 mM KCl solution cooled to 0 °C. These suspensions stored at 4 °C were found to be very stable for several months and do not show any sign of agglomeration, except for AuNP17@DHLA-M600 which tends to precipitate in a few days (see below for discussion). All polymer- stabilized AuNPs were characterized by TEM, DLS, and UV–vis spectroscopy.

Figure 1 shows TEM images acquired for gold nanoparticles coated with DHLA-M600 prepared by either one-pot synthesis (Figure 1A) or ligands exchange (Figure 1B–E). TEM images allow us to estimate average size and polydispersity of the prepared AuNPs@DHLA-M600. In all cases, nanoparticles have largely a spherical shape and present a narrow size distribution (see Figure S4 in Supporting Information). The size and shape of as-prepared polymer-protected gold nanoparticles do not evolve during the exchange reaction. TEM data are reported in Table 2.

The surface density, i.e., the number of polymer chains (chains/ nm²) attached to a nanoparticle surface, was calculated from the thermogravimetric analysis. TGA measurements on prepared nanoparticles indicated the decomposition of modified poly(EO_x-st- PO_{ν}) in the temperature range 350–400 °C, values consistent with published work.²⁷ The density grafting of polymer chains on gold nanoparticles surface estimated to be 4.0 ± 0.5 chains/nm² was nearly constant and independent of both the gold nanoparticles size and the Jeffamine nature. These high values of surface density were consistent with the small size of the ligand and the strong affinity of the dithiol function with gold surface. Because of the large excess ligands used for cap exchange or for direct synthesis, we anticipate that all AuNPs have their surface totally passivated with dithiol ligands in agreement with the independence of the ligand surface density with (i) the method used to prepare AuNPs, (ii) the surface curvature of the nanoparticle cores, and (iii) the short length of the $poly(EO_x-st-PO_y)$ polymers. The measured grafting density is compatible with that reported with monothiol ligands. Tenhu et al.¹⁰ reported poly(NiPAm)-SH coated AuNPs with polymer grafting density ranged from 1.8 to 3.6 chains/nm². Corbierre et al.²⁸ also reported AuNPs coated with very short polymers, PEO₄₅-SH, PS₁₉-SH, and C₁₄-SH, with grafting densities were 2.0, 4.2, and 5.5 chains/nm², respectively.

UV-vis spectroscopy is the technique of choice for the study of aqueous solution of gold nanoparticle suspensions due to the characteristic surface plasmon band (SPR) which is very sensitive to the size, the shape, and the local environment of gold nanoparticles. Figure 2 shows typical UV-vis absorption spectra for gold nanoparticles suspensions in 10 mM KCl aqueous solution measured at temperature below the temperature transition of the grafted polymer to ensure a sufficiently hydrated state of the polymer and a good dipersion of nanoparticles. The temperature of experiments was fixed at 4 °C for all AuNPs grafted with DHLA-M600. For AuNPs@DHLAM-M1000, there is no or little effect of the temperature on the plasmon resonance absorption, so measurements were performed at room temperature.

⁽²⁶⁾ Oh, E.; Susumu, K.; Goswami, R.; Mattoussi, H. Langmuir 2010, 26, 7604–7613.

⁽²⁷⁾ Madorsky, S. L.; Straus, S. J. Polym. Sci. 1959, 36, 183-194.

⁽²⁸⁾ Corbierre, M. K.; Cameron, N. S.; Lennox, R. B. Langmuir 2004, 20, 2867–2873.



Figure 1. TEM images of AuNPs prepared by the two methods: (A) one pot synthesis, (B–E) ligands exchange. (A) AuNP2@DHLA-M600, (B) AuNP6@DHLA-M600, (C) AuNP7@DHLA-M600, (D) AuNP13@DHLA-M600, (E) AuNP17@DHLA-M600. Corresponding size distributions are reported in the Supporting Information.

Table 2. Sun	mary of Averag	e Sizes of Polymer	-Protected AuNPs	Extracted from	TEM and DLS
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	DHLA-M600			DHLA-M1000		
	$D_{\rm c} ({\rm nm})^a$	$D_{\rm h} ({\rm nm})^b$	$h (\mathrm{nm})^d$	$D_{\rm c} ({\rm nm})^a$	$D_{\rm h}({\rm nm})^c$	$h (\mathrm{nm})^d$
AuNP2	2.0 ± 0.3	6.3 ± 0.1	2.2 ± 0.2	2.0 ± 0.5	8.1 ± 0.3	3.1 ± 0.4
AuNP6	5.6 ± 0.7	12.1 ± 0.2	3.3 ± 0.5	6.0 ± 0.7	15.6 ± 0.3	4.8 ± 0.5
AuNP7	7.3 ± 0.6	14.9 ± 1.2	3.8 ± 0.9	7.3 ± 0.5	15.6 ± 0.1	4.2 ± 0.3
AuNP13	12.8 ± 1.2	24.8 ± 1.9	6.0 ± 1.6	13.4 ± 0.9	24.4 ± 0.2	5.5 ± 0.6
AuNP17	17.2 ± 1.9	42.2 ± 3.0		16.7 ± 1.7	29.7 ± 0.6	6.5 ± 1.2
<i>a a a</i>		. h				

^{*a*} Core diameters determined by TEM. ^{*b*} Hydrodynamic diameters determined by DLS at 4 °C. ^{*c*} Hydrodynamic diameters determined by DLS at 25 °C. ^{*d*} $h = (D_h - D_c)/2$.

AuNPs present an intense surface plasmon band with a maximum at ~524 nm, which is characteristic of individually dispersed gold nanoparticles. Only two spectra do not exhibit a surface plasmon band, i.e., AuNP2@DHLA-M600 and AuNP2@DHLA-M1000, confirming that the size of gold nanoparticles is smaller than 3 nm. The plasmon bandwidth increases and the plasmon intensity decreases with decreasing the size of the nanoparticle in agreement with reported data.²⁹ This variation of the plasmon absorption is responsible of a color change from dark-brown to red as the size of nanoparticles increases from 2 to 17 nm (see inset in Figure 2). As said above, we confirm that the nature of the grafted modified Jeffamine has no noticeable effect on UV-vis absorption spectra, which guarantee that, at 4 °C, DHLA-M600-coated nanoparticles are well dispersed in solution.

In complement to UV-vis experiments, average hydrodynamic diameters, D_h, of gold nanoparticles were determined by DLS at 4 °C for AuNPs@DHLA-M600 and 25 °C for AuNPs@DHLA-M1000. The results are listed in Table 2 side-by-side with core diameters, $D_{\rm c}$, obtained by TEM. Obviously, $D_{\rm h}$ are larger than homologous TEM diameters because light scattering is sensitive not only to inorganic core but also to hydrated polymeric chains bounded on the surface. The similar values of $D_{\rm h}$ measured for AuNPs of different size grafted with DHLA-M600 and DHLA-M1000 confirms the absence of aggregates in solution. However, for the largest AuNPs ($D_c = 17 \text{ nm}$) stabilized with DHLA-M600, the value of D_h is inconsistent with that obtained with DHLA-M1000 ($D_{\rm h} = 42 \, \rm nm$ versus $D_{\rm h} = 30$ nm, respectively). This unexpected value is probably due to the presence of a few small aggregates. Indeed, because the intensity of scattered light depends on the sixth power of the size, DLS signal is very sensitive to the presence of large objects, even in small fraction. However, we think that the fraction of aggregates

^{(29) (}a) Mie, G. Ann. Phys. 1908, 25, 377–445. (b) Mulvaney, P. Langmuir 1996, 12, 788–800. (c) Link, S.; El-Sayed, M. A. J. Phys. Chem. B 1999, 103, 4212–4217.
(c) Heinglein, A. Langmuir 1999, 15, 6738–6744.



Figure 2. UV-vis absorption spectra of AuNPs in 10 mM KCl solution of (a) AuNPs@DHLA-M600 measured at 4 °C and (b) AuNPs@DHLA-M1000 measured at 25 °C. Inset: pictures of AuNP2@DHLA-M1000 (left) and AuNP6@DHLA-M1000 (right) suspensions.

is marginal in regard to dispersed particles because the red shift of the plasmon band, which is expected in case of the presence of agglomerates, is not observed in this particular sample.

Combining DLS and TEM investigations allows us to estimate the thickness of hydrated polymers located around the nanoparticle (Table 2). We observe that the thickness of the polymer layer increases when increasing the gold nanoparticle size. From the smallest to largest nanoparticles, the polymer layer increases from ~2 to 6 nm (~3 to 6 nm) for AuNPs@DHLA-M600 (AuNPs@ DHLA-M1000). This behavior is consistent with a conformation change of the polymer grafted on the AuNPs surface when the size of the nanoparticle increases. This important point will be discussed after the description of the thermal properties of polymer-protected gold nanoparticles.

In preliminary conclusion, we have demonstrated that different and versatile methods can be used to prepare highly spherical monodisperse AuNPs stabilized with $poly(EO_x-st-PO_y)$ polymers over the size range between 2 and 17 nm, well dispersed and presenting an excellent stability with time (more than 6 months).

Thermosensitive Gold Nanoparticles. The thermoresponsive character of gold nanoparticles induced by polymers grafted on the gold surface was established by UV–vis spectroscopy and light scattering experiments. Here, we specify that the aggregation temperature of gold nanoparticles, T_{agg} , corresponds to the phase transition temperature of the polymers. Indeed, when the temperature increases above the phase temperature transition of the polymers, water becomes a poor solvent for the grafted polymer chains inducing collapse of the dehydrated polymers on the particle surface. Then, hydrophobic interactions appeared and lead to the formation of large aggregates (Scheme 3),¹¹ which can be easily redispersed by cooling the agglomerated suspension below T_{agg} with gentle shaking.

DLS and UV-vis absorption do not show evidence of agglomeration for AuNPs grafted with DHLA-M1000 when the temperature increases up to 70 °C. Because Jeffamine M1000 contains only three propylene oxide monomer units, this polymer is highly similar to pure poly(ethylene oxide), which is well-known to be swelled in a large range of temperature. This situation is very different in the case of suspensions of nanoparticles grafted with DHLA-M600, for which an increase of the temperature induces the aggregates formation. Indeed, the gold nanoparticles agglomeration results in a color change from red to purple. This is due to a shift of the resonance toward longer wavelengths, induced by a dipole-dipole

Scheme 3. Schematic Representation of the Formation of Aggregates Induced by Thermoresponsive Polymers^a



 a Inset: AuNP6@DHLA-M600 in 10 mM KCl solution dispersed at 5 $^\circ C$ (left) and aggregated at 20 $^\circ C$ (right).

interaction between plasmons of neighboring nanoparticles.³⁰ Figure 3A shows the UV-vis absorption spectra of AuNP6@DHLA-M600 suspensions taken at different temperatures. The spectra superimpose until 12 °C, and then a red shift of about 25 nm (from 524 to 550 nm) appears when the temperature reaches 14 °C. This shift is more and more pronounced as temperature increases, indicating the aggregation of gold nanoparticles. The aggregation mechanism of nanoparticles as a function of the temperature was confirmed by light scattering experiments (see Figure 3B). Below 12 °C, the intensity profiles versus the average diameter (intensity distribution) are similar. At 12 °C, the small shift of the size distribution toward larger size corresponds to the beginning of aggregates formation. Above 14 °C, the size distribution profile is shifted of more than 1 decade. Similar behaviors were reported for all AuNPs@DHLA-M600. In the case of AuNP2@DHLA-M600 suspension, the aggregation temperature can only be determined by DLS because of the weak SPR. Maintaining AuNPs@DHLA-M600 suspensions above the aggregation temperature for several hours results in a macroscopic precipitation. However, as said above, the AuNPs can be easily redispersed by cooling the suspensions. By the excellent correlation between these two techniques, we can determine precisely T_{agg} for each thermosensitive AuNPs. In the following part, the reversibility of the aggregation and the different parameters which affect T_{agg} , are examined.

The reversible process of thermo-driven aggregation for polymerprotected gold nanoparticles was confirmed through a complete heating–cooling cycle in UV–vis spectroscopy. Starting from a AuNP6@DHLA-M600 dispersion at 4 °C (with a surface plasmon band at 524 nm), the maximum of the surface plasmon band, λ_{SPR} , shifts to around 550 nm at 14 °C and returns exactly at 524 nm with decreasing the temperature (Figure 4). The dissociation temperature was found to be sligthly lower (hysteresis of 1–2 °C) than the temperature observed for their aggregation as already

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Figure 3. (a) UV–vis spectra of AuNP6@DHLA-M600 in 10 mM KCl solution vs temperature from 6 to 18 °C (ramp 0.4 °C/min). (b) Intensity distribution versus size determined by DLS for the same particles as a function of the temperature (ramp 0.1 °C/min).



Figure 4. Evolution of maximum wavelength (λ_{SPR}) as a function of the temperature for AuNP6@DHLA-M600 in 10 mM KCl solutions for one heating—cooling cycle (ramp 0.4 °C/min). Inset: variation of maximum wavelength for different cooling/heating cycles of AuNP6@DHLA-M600 in 10 mM KCl solution (ramp 0.5 °C/min).

observed in published work.³¹ The phenomenon of aggregation– dissociation can be repeated many times over heating–cooling cycles without evidence of irreversible agglomeration (see inset of Figure 4). The thermal reversibility is also observed by DLS experiments (see Figure S5 in the Supporting Information).

It is known that the transition temperature of a polymer depends on the total polymer concentration in solution. Indeed, for a polymer having a LCST phase diagram, when the polymer concentration increases or decreases, the phase transition temperature increases on the both sides of the LCST. The effect of the total polymer concentration on the phase transition temperature and therefore on T_{agg} was indirectly studied by varying the concentration of AuNP6@ DHLA-M600 (see Figure S6 in the Supporting Information). In 1 decade of concentration, T_{agg} remains constant at 12 °C, independent of the total polymer concentration in solution. Then, T_{agg} does not depend on the total polymer concentration but only of the local polymer concentration around the nanoparticle core, which remains constant with decreasing the AuNPs concentration.

Before going into details in the influence of the core size on T_{agg} , we would like to present the effect of salt on the thermoresponse of AuNPs grafted with DHLA-M600. Yusa et al.¹¹ reported that poly(NiPAM) ($M_n \sim 10^4$ g/mol) coated gold nanoparticles do not agglomerate at temperature above the LCST of poly(NiPAM) in pure water, whereas a reversible association is observed in 50 mM



Figure 5. Variation of hydrodynamic diameter (D_h) with temperature of AuNP2@DHLA-M600, AuNP6@DHLA-M600, and Au-NP13@DHLA-M600 in 10 mM KCl solutions (ramp 0.1 °C/min).

NaCl solution. It was argued that in water above LCST dehydrated poly(NiPAM) polymer chains may be prevented from aggregation by electrostatic repulsion of surface charges of bare gold. In presence of salt, charges are screened and flocculation occurs. In our case, the difference of thermal association behavior with or without salt (10 mM KCl) was sometimes observed according to the batch of ligand synthesis. In addition, reversible aggregation was established in pure water at the same aggregation temperature than in 10 mM KCl. We agree with the justification of Yusa et al., but we think that charges come from the ligands rather than from the core bare. In particular, we do not exclude the presence of residual noncoupled DHLA grafted on the surface of AuNPs. Beyond a critical threshold, the number of DHLA end carboxylic groups may be sufficient to prevent aggregation. To support this assumption, we checked that decreasing the pH to 4 with HCl (protonated acid groups) had the same effect as the addition of salt (screening charges) on flocculation. On the other hand, we studied the effect of salt concentration on T_{agg} . When the salt concentration increases from 10 to 500 mM, T_{agg} of AuNP6@DHLA-M600 shifts toward low temperatures from 12 to 8 °C (see Figure S7 in the Supporting Information). In 1 M KCl solution at 4 °C, the color of the AuNPs dispersion is already purple, indicating that T_{agg} is below 4 °C. This effect of salt concentration on transition temperature is well-known for linear polymer chains such as poly-(ethylene oxide), for which the interaction between electrolyte and water induces a quick dehydration of the polymer chains.³²

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⁽³²⁾ Bailey, F.; Callard, R. J. Appl. Polym. Sci. 1959, 1, 56-62.



Figure 6. Dependence of the aggregation temperature (T_{agg}) as a function of the core diameter (D_c) estimated by TEM. Inset: schematic representations of the grafted polymer chains on AuNPs surface.

Effect of the Nanoparticle Size on the AuNPs Aggregation. Figure 6 shows the dependence of T_{agg} with the gold nanoparticles core diameter, D_c , determined by TEM. The dependence of the aggregation temperature decreases from 15 to 8 °C for small AuNPs (2, 6, and 7 nm) and reaches a plateau at 8 °C for large gold nanoparticles (13 and 17 nm). This unexpected result is explained by a conformation change of the polymer chains on the gold nanoparticles surface. For small gold nanoparticles possessing a high curvature radius, the polymer chains that are end-attached to the surface are swollen by the solvent with a "cone" conformation. At constant grafting density, when the nanoparticle size increases, the curvature becomes larger, inducing a compression and a stretching of the polymer chains located side-by-side on the gold surface (see schemes in Figure 6). This stretching is confirmed by an increase of the thickness of the polymer layer, h, on AuNPs surface, estimated using DLS and TEM experiments (Table 2). The compression of the polymer chains leads to a decrease of the hydration state of the monomer units along the polymer chains, which induces a decrease of the phase transition temperature of the polymer and consequently of the aggregation temperature of the AuNPs. The formation of a dense polymer brush on AuNPs surface when the nanoparticle size increases can be also observed by calculating the polymer concentration at the outer shell of the polymer brush as a function of the size of the AuNPs using the Daoud-Cotton star polymer model $\varphi(r) \sim 1/r$, where *r* is the distance from the core surface (Figure 7).³³ The polymer concentration at the outer surface (*r* = $D_{\rm h}/2$) related to the polymer concentration on the core surface $(r = R_c), \varphi/\varphi_0$, was evaluated assuming φ_0 is constant for all particles. φ/φ_0 increases with the AuNPs size for both polymers, i.e., AuNPs@DHLA-M600 and AuNPs@DHLA-M1000. According to the theory, the Flory-Huggins interaction parameter, χ , increases monolithically with φ . Moreover, χ is conversely proportional to the transition temperature of the polymer, $\chi \sim 1/$ $T.^{34}$ Therefore, T_{agg} decreases with φ and R_{core} in agreement with our experimental data (Figure 6). To support the model, we can note that as core particle size increases, φ/φ_0 tends to reach an asymptotic value (stretch mode), in agreement with the saturation of the aggregation temperature.

Polymer Corona Composition Effect. The aggregation temperature can be modulated by changing the nature (EO/PO ratios) of polymer ligands. Because of the limited number of



Figure 7. Calculated polymer concentration at external surface $\varphi(r)$ ($r = D_h/2$) related to concentration at the core surface (φ_0) vs core diameter. φ_0 is proportional to grafting density and is constant for all samples. The lines are for guide eyes.



Figure 8. Evolution of maximum wavelength (determined by UV–vis spectroscopy) as a function of the temperature for AuNP6@DHLA-M600/M1000 in 10 mM KCl solution with different molar ratios DHLA-M600/DHLA-M1000: 100/0, 75/25, and 50/50 (ramp 0.4 °C/min).

available commercial Jeffamine copolymers, we tried to tune T_{agg} by grafting a mixture of two different modified Jeffamine ligands, having different LCST behavior (M600 close to 28 °C and M1000 higher than 80 °C) as recently described in the literature.³⁵ These two modified copolymers, DHLA-M600 and DHLA-M1000, were mixed together, in different molar ratios (100/0, 75/25, and 50/50), and then grafted to AuNP6. Figure 8 shows the evolution of λ_{SPR} as a function of the temperature of these gold nanoparticles solutions, named AuNPs@DHLA-M600/M1000. The aggregation temperature of mixed polymer-coated AuNPs shifts toward high temperature when the proportion of DHLA-M1000, quite similar to pure poly(ethylene oxide), increases in the polymer mixture. The AuNP6@DHLA-M600/M1000 aggregate at 12, 25, and 50 °C for DHLA-M600/DHLA-M1000 molar ratios of 100/0, 75/25, and 50/50, respectively, with relative sharp transitions. Davis et al.,¹⁷ who prepared AuNPs with dual temperature responsive polymers, observed two different transition temperatures corresponding to those of each different thermosensible grafted polymers. The aggregation temperature is mainly controlled by the more hydrophilic grafted polymer, which is able to stabilize the colloids even after the collapse of the more hydrophobic one on the core surface. In contrast to Davis's

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⁽³⁴⁾ Xu, R.; Winnik, M. A.; Riess, G.; Chu, B.; Croucher, M. V. Macromolecules 1992, 25, 644-652.

⁽³⁵⁾ Zhao, B.; Zhu, L. Macromolecules 2009, 42, 9369-9383.

works, our AuNPs coated with a mix of copolymers showed an intermediate T_{agg} between the LCST of both DHLA-Jeffamine. The mixed polymer corona seems to behave as a corona constituted by a statistical copolymer, poly(EO_x-st-PO_y), with an intermediate composition and with an unique transition. These two contradictory results required complementary investigations. The composition of the polymer corona provides another variable allowing for the precise tuning of the aggregation temperature of those AuNPs in a broad range of temperature.

Conclusions

Dithiol-functionalized statistical copolymers, poly(ethylene oxide-*st*-propylene oxide), were grafted on gold nanoparticle surface of different sizes. Highly monodisperse, thermosensitive, and stable AuNPs were obtained in aqueous solution and present well-controlled reversible thermosensitive aggregation behavior. The aggregation temperature, T_{agg} , is sensitive to the nature of the grafted copolymer, to the salt concentration, and to the AuNPs size. First, we have demonstrated that the grafting of the same thermosensitive polymer on gold nanoparticles of different size

(from 2 to 17 nm) can be used to modulate the T_{agg} of gold nanoparticles in a temperature range from 8 to 15 °C. This thermal response is due to the conformation change of the grafted polymer on the gold surface which is directly correlated to the hydration state of the polymer chain. The composition of the polymer corona also provides another variable allowing tuning the aggregation temperature of those AuNPs in broad range of temperature from 12 to 50 °C.

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Supporting Information Available: MALDI-TOF, ¹H NMR, and IR spectra, synthesis protocols of AuNPs precursors, size distributions of TEM images, evolution of λ_{SPR} vs concentration and ionic strength. This material is available free of charge via the Internet at http://pubs.acs.org.