Nanoparticle Assembly

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Triggered In situ Disruption and Inversion of Nanoparticle-Stabilized Droplets**

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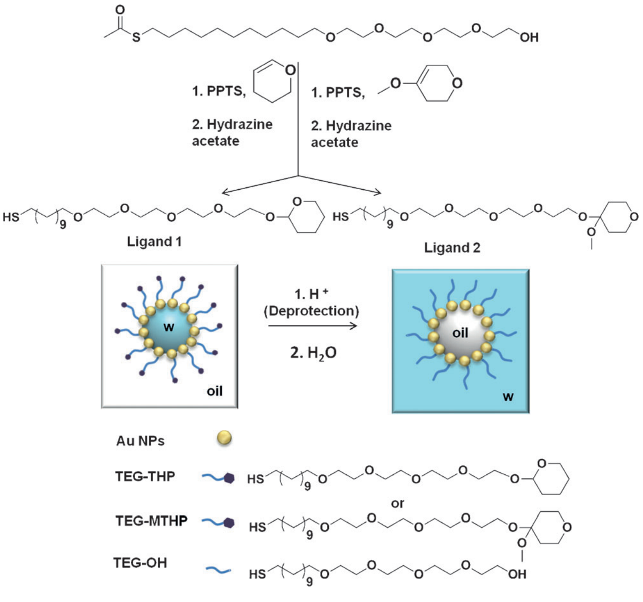
Described in the early 1900s, particle-stabilized droplets, or "Pickering" emulsions, have established renewed interest due to the rapid recent developments in nanoparticle synthesis and surface functionalization.[1–3] Particle stabilization of fluid–fluid interfaces results from a reduction in interfacial energy that scales with particle size, and depends on particle wettability.[4] For microparticles, the free-energy gain associated with interfacial segregation of particles is much larger than thermal energy, while for nanoparticles such stabilization is less profound, especially for particles under 10 nm diameter. Nonetheless, several examples of stable emulsion droplets formed by the presence of nanoparticles in immiscible fluids have been reported.[5–9]

Particle wettability, described by the contact angle θ between the solid and the oil–water interface, dictates the type of emulsion formed. In general, hydrophilic particles ($\theta < 90°$) produce oil-in-water (o/w) emulsions, while hydrophobic particles ($\theta > 90°$) give water-in-oil (w/o) emulsions. Phase inversion of particle-stabilized emulsions has been reported by variation of the oil/water ratio, particle hydrophilicity, pH and salt concentration.[10–13] Phase inversion from water-in-air (w/a) powders to air-in-water (a/w) foams was accomplished by changing the air/water volume ratio, using fumed silica agglomerates to stabilize the interface.[10] In the same study, inversion was observed over a series of different samples using particles of varying wettability. With increasing hydrophobicity, the system evolved from aqueous dispersions, to a/w foams, to w/a powders.

Möhwald and co-workers described 2-bromopropionate functionalized Au NPs as stabilizers for o/w droplets, and examined the effect of surface charge on the assembly of NPs at a w/o interface using carboxylate-terminated ligands. This produced large (millimeter diameter) droplets of hexane in water prior to droplet coalescence.[14,15] We previously studied Au NPs covered with a mixed hydrophobic/hydrophilic monolayer, giving stable μm-sized o/w droplets.[5] In this system, only a narrow ratio of hydrophobic to hydrophilic ligands (ca. 1:1) led to stable droplets, while PEGylated Au NPs (PEG = poly(ethylene glycol)) proved effective for oil–water interfacial stabilization with a wide variety of organic solvents.[6,16]

Here we describe the preparation of Au NPs decorated with ligands having acid-labile tetrahydropyranyl (THP) ether chain-ends, and their use in stabilizing w/o emulsions in which pH or light serves as a trigger for "in situ emulsion inversion". The advantage of this process is found in its simplicity, while the ability to perform the inversion in situ through a ligand transformation is novel and distinct from the preparation of a range of NP samples that exhibit variable wettabilities. The change in wettability of the NPs upon ligand deprotection enables the inversion to occur, and the chemistry of the protecting group proved crucial for achieving a rapid inversion.

THP ethers are commonly employed acid-labile alcohol protecting groups in organic and polymer chemistry. In this study, THP ether protected tetraethyleneglycol (TEG) compounds **1** and **2** with chain-end thiols were synthesized and used as ligands to afford NPs that change wettability upon introducing acid (Scheme 1). These TEG-THP functionalized Au NPs are dispersible in organic solvents, and stabilize w/o emulsions. Treatment with acid destabilizes the emulsion, and addition of water leads to phase inversion and production of stable o/w droplets. Ligand **1** was prepared as shown in



Scheme 1. Ligand synthesis and schematic representation of a TEG-THP Au NP stabilized w/o emulsion and emulsion inversion.

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Scheme 1, by the reaction of the thioacetate-terminated TEG with 3,4-dihydro-2*H*-pyran and catalytic pyridinium-*p*-toluene sulfonate. Reduction of the thioacetate using hydrazine acetate gave ligand **1** in 90 % yield. Ligand **2** was synthesized similarly, from 5,6-dihydro-4-methoxy-2*H*-pyran.

Au NPs were prepared following the report of Stucky and co-workers, using [$AuPPh_3Cl$] and borane *tert*-butylamine complex (*t*Bu-$NH_2 \cdot BH_3$) as the reducing agent.[17] Interestingly, Au NPs functionalized entirely with TEG-THP did not stabilize droplets. Instead, a 9:1 TEG-THP:TEG ligand ratio proved most suitable, and w/o emulsions were formed by adding 0.1 mL of water to 0.9 mL of a 5 $mg\,mL^{-1}$ 1,2,4-trichlorobenzene (TCB) solution of Au NPs, followed by vigorous shaking. The surfactant character of these mixed monolayer-functionalized Au NPs is appreciable: the interfacial tension of TCB/water, measured by pendant drop tensiometry, was reduced by the Au NPs from 45 $mN\,m^{-1}$ for the pure liquids to 18 $mN\,m^{-1}$ in the presence of the Au NPs.

Figure 1 a shows optical micrographs of stable w/o droplets formed using TEG-THP Au NPs (ligand **1**). Emulsion disruption was achieved by introducing *p*-toluene sulfonic acid (PTSA) or pyridinium *p*-toluene sulfonate (PPTS) into the water phase prior to droplet formation. In a typical procedure, 0.1 mL water containing one of the acids was added to a 0.9 mL of a 5 $mg\,mL^{-1}$ Au NP solution in TCB, followed by vigorous shaking to give a w/o emulsion. Figure 1 b and c show confocal micrographs of w/o emulsions that are destabilized with 20 $mg\,mL^{-1}$ PPTS or 5 $mg\,mL^{-1}$ PTSA, respectively. Figure 1 d shows the change in droplet size over time, until complete disruption was achieved, and the droplets grew as they merged. The droplets in the sample with no added acid did not increase in size over time, and such acid-free emulsions were stable for weeks or longer. In the presence of acid, a significant increase in droplet size was observed due to coalescence (Figure 1 b and c).

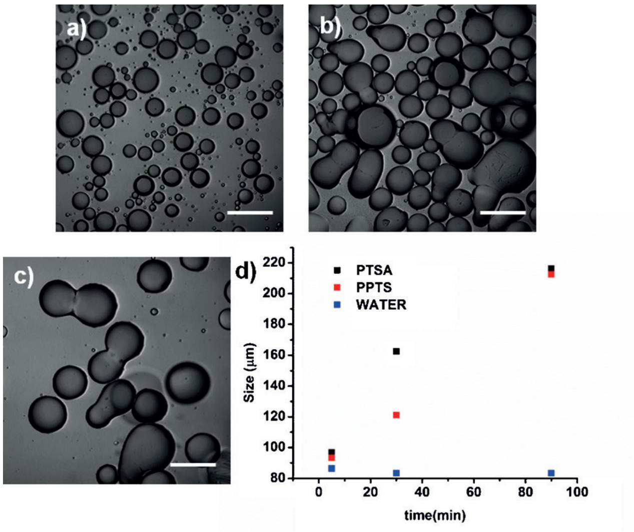

Figure 1. Water-in-oil droplets stabilized by TEG-THP functionalized Au NPs: a) 90 min after their formation in the absence of acid; b) with PPTS; c) with PTSA (scale bars 300 μm); d) change in average droplet diameter over time.

The initial average droplet size of ca. 90 μm increased to 200 μm within 90 min, a result of deprotecting the acid-labile hydrophobic chain-ends, making the NPs hydrophilic and dispersable in the aqueous phase. Complete oil–water phase separation occurred after several hours for droplets stabilized by TEG-THP ligand **1** were subjected to acid. This observation is consistent with literature reports for the time-scale typical of THP deprotection.[18] In control experiments, o/w emulsions stabilized only with TEG Au NPs (i.e., a hydroxy periphery) were not affected by the presence of acid, and no coalescence was observed.

To accelerate emulsion destabilization, we chose methoxy tetrahydropyran (MTHP, Scheme 1) as an alternative protecting group, since deprotection of MTHP-ethers occurs much faster than that of THP ethers.[19] Au NPs stabilized by TEG-MTHP were synthesized similarly to the TEG-THP NPs, and once again the incorporation of the TEG-OH ligand in a mixed monolayer proved necessary for emulsion stabilization, and a 9:1 TEG-MTHP:TEG-OH ligand ratio was most useful. W/o droplets stabilized by TEG-MTHP ligands were disrupted quickly by acid: the green fluorescence seen in Figure 2 is a result of FITC-dextran dye encapsulated in the aqueous phase. In the presence of PTSA, emulsion disruption is initiated as the droplets are formed, and complete phase separation occurs in 15 min. These MTHP-AuNP emulsions are stable for long time periods in the absence of acid, and the interfacial tension of TCB/water (measured by pendant drop tensiometry) was measured as 24 $mN\,m^{-1}$ in the presence of TEG-MTHP Au NPs.

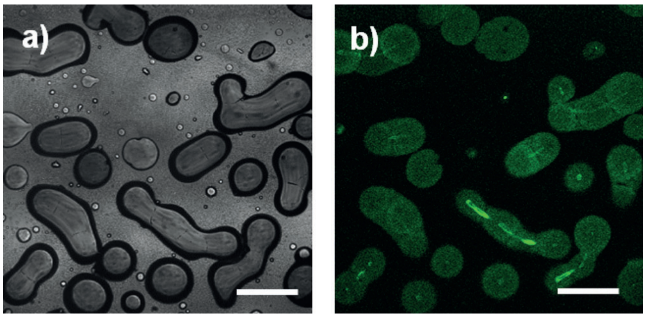

Figure 2. Fluorescence confocal microscopy images of emulsions stabilized with TEG-MTHP Au NPs in the presence 5 $mg\,mL^{-1}$ PTSA after 5 min (scale bars 300 μm).

Acid-triggered processes can be translated to light-activated processes when performed in the presence of photoacid generators (PAGs), as exploited extensively in microelectronics fabrication.[20,21] We found that disruption of the Au NP stabilized emulsion droplets was triggered upon exposure to light when a PAG was used. We chose 2-(4-methoxystyryl)-4,6-bis(trichloromethyl)-1,3,5-triazine as an oil-soluble PAG. Emulsions were formed by shaking 0.1 mL of water with a solution of Au NPs in an excess of TCB containing the PAG (0.05 $mg\,mL^{-1}$). Figure 3 a is an optical image of the droplets, which were stable for long periods of time before UV irradiation. Shortly after irradiation (5 min exposure at 365 nm), the droplets began to coalesce, leading

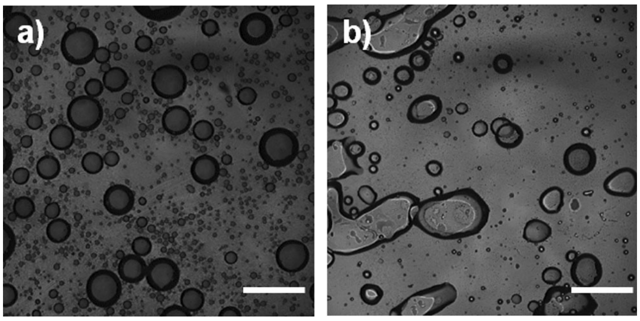

Figure 3. Microscopy images of droplets stabilized with TEG-MTHP functionalized Au NPs in the presence of PAG a) before and b) after UV irradiation (scale bar 300 μm).

to complete emulsion disruption in less than 30 min. In control experiments, emulsions without the PAG subjected to the same UV conditions showed neither coalescence nor emulsion disruption, confirming that the functional ligands are critically important to this process.

An "in situ" emulsion inversion was achieved by adjusting the oil/water ratio following the acid-triggered phase separation, by addition of water and agitation of the resulting mixture. Figure 4 illustrates the process, and FITC-dextran was used to distinguish the aqueous phase in the fluorescence images (Figure 4d–f). Initial w/o droplets containing FITC-dextran and acid in the water phase (Figure 4a and d) resulted in coalescence (Figure 4b and e) and ultimately complete phase separation of the oil and water phases (Figure 4g). As the Au NPs became water soluble, they were expelled into the aqueous phase (left tube, Figure 4g). Following phase separation, 2 mL of water was introduced, and the solution shaken to form new o/w emulsions. As seen in the optical and fluorescence images in Figure 4c and f, stable o/w emulsions form. This in situ inversion is tracked easily by the fluorescent aqueous phase, which is the inner phase in the case of w/o emulsions, and the outer phase for o/w emulsions. The photograph in Figure 4h shows stable w/o emulsions in the absence of acid, and stable o/w emulsions that form upon acid-triggered disruption and inversion.

Insight into the deprotection process was gained from pendant drop tensiometry measurements. A drop of TEG-MTHP Au NPs in TCB was introduced into water; after stabilization of the droplet, PTSA (5 $\mathrm{mg\,mL^{-1}}$) was added to aqueous phase. A sudden drop in interfacial tension was observed, and this decline continued at a rate greater than that prior to adding acid. A final interfacial tension value of 16 $\mathrm{mN\,m^{-1}}$ was obtained, attributed to efficient deprotection and the presence of TEG-OH functionality on the Au NPs (Supporting Information).

CdSe quantum dots (QDs) coated with TEG-THP and TEG-MTHP ligands were also prepared and tested in this emulsion inversion process. Ligand exchange was performed on CdSe/ZnS core–shell QDs functionalized initially with their native alkyl ligands, using methanol as the solvent, for 3 h at 70 °C. CdSe QDs functionalized with TEG-THP and TEG-MTHP form w/o droplets, using toluene or TCB as the oil phase, that are stable for days (Figure 5a). Unlike the Au NPs, the use of a mixed monolayer with TEG ligand was not necessary for droplet stabilization. Emulsion disruption was

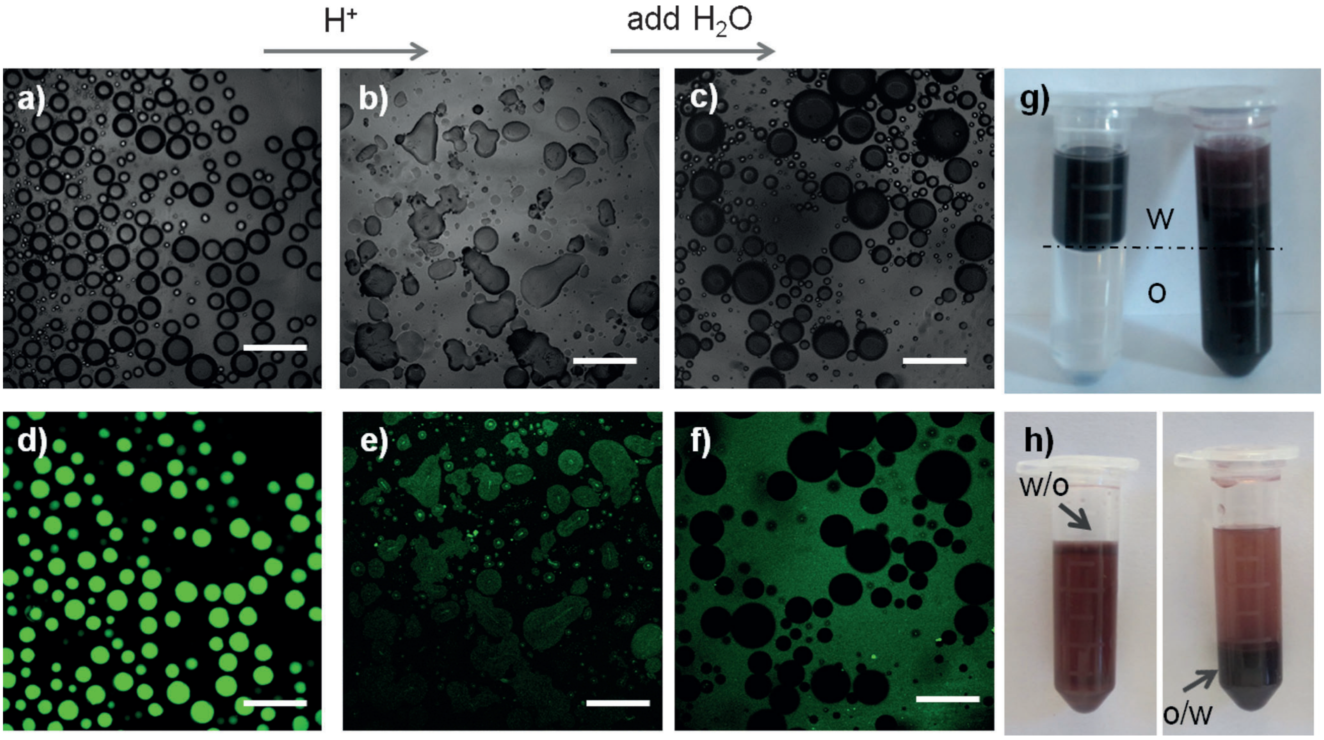

Figure 4. Confocal microscopy images of: a,d) w/o emulsion; b,e) disrupted w/o emulsions; and c,f) o/w emulsions. The fluorescence in (d), (e), and (f) is from the presence of FITC-dextran in the water phase. Images of g) phase-separated NP solution (left vial); stable w/o emulsions (right vial) and h) w/o emulsions (left vial); inverted o/w emulsions (right vial). TEG-MTHP Au NPs were used in the experiments. Scale bar 300 μm.

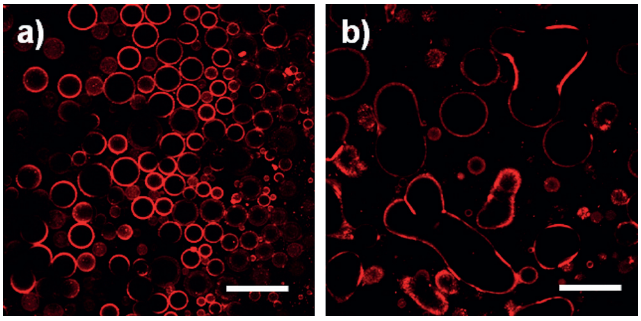

Figure 5. Fluorescence confocal microscope images of a) o/w emulsions of CdSe NPs coated with TEG-MTHP and b) disrupted w/o emulsions in the presence of PTSA. Scale bar 300 μm.

observed in the presence of 5 mg mL^{-1} PTSA, as shown in Figure 5b for MTHP-TEG covered CdSe NPs. However, even after phase separation, the QDs did not transfer into water phase, and emulsion inversion did not occur, possibly attributable to retention of a portion of the native ligands on the QDs.

In summary, NPs were prepared with responsive ligands in the form of THP and MTHP protected alcohols, affording a new route to acid- and photo-induced in situ phase inversion of NP-stabilized emulsion droplets. Ligand-functionalized Au NPs were converted from oil-dispersible to water-dispersible, by cleaving the labile chain-end in the presence of acid, thus giving the desired ability to invert the NP-stabilized emulsion system. The choice of protecting group was shown to dictate the time-frame of emulsion disruption, which will be useful in extending this work to applications in site-isolated delivery and/or repair.

Experimental Section

Au NP synthesis: Au NPs were synthesized following a literature procedure.[16] In a typical experiment, 61.8 mg (0.125 mmol) of [$AuPPh_3Cl$] was mixed with ligand **1** (108 mg, 0.232 mmol) and TEG-OH (9.8 mg, 0.025 mmol) in THF (10 mL). *t*Bu-$NH_2 \cdot BH_3$ (108 mg, 1.24 mmol) was added, and the mixture was stirred at room temperature for 2 h, then at 55 °C for 30 min. The mixture was allowed to cool to room temperature, and the Au NPs were precipitated in hexanes, then centrifuged and washed three times with hexane/methanol mixtures. The isolated Au NPs (ca. 5 nm as measured by TEM) were soluble in common organic solvents. Confocal microscopy*:* a Leica TCS SP2 LCSM laser scanning confocal microscope under Ar-laser excitation was used to image the emulsions. Samples were prepared by adding droplets and a small amount of solvent into a single-well glass microscope slide and covering the glass slide with a cover-slip. Pendant drop tensiometry: a Dataphysics OCA-15 tensiometer was used in pendant drop mode to measure the interfacial tension between water and TCB in the presence of NPs. Based on the shape of the pendant drop, the interfacial tension between the liquids was calculated using the instrument software and the Young–Laplace equation.

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