

Water-Soluble Semiconductor Nanocrystals Cap Exchanged with Metalated Ligands

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ABSTRACT We report a novel method for cap exchange of emissive semiconductor nanocrystals (NCs) using thiol functional ligands metalated with zinc. Utilizing this method, the NCs can be several times brighter and much more resistant to precipitation compared to control samples. This method has been applied using a variety of caps such as dihydrolipoic acid and cysteine. Our data suggest that the improved properties of the metalated cap exchanged NCs are due to a ligand metathesis process occurring at the NC surface where the zinc complex reacts with NC surface bound ligands, gently removing them and replacing them with another cap. Overall, the use of metalated ligands helps resolve many long-standing issues concerning the application of small cap exchanged NCs for biological imaging.

KEYWORDS: nanocrystals · cap exchange · cadmium selenide nanocrystals · cadmium sulfide nanocrystals

Over the past decade, colloidal semiconductor nanocrystals (NCs) have emerged as promising fluorescent probes for biological applications.^{1,2} They have the advantages of good photochemical stability, continuous absorption spectra, and size- and composition-dependent optical properties.^{3,4} Much progress has been made in the synthesis of cadmium chalcogenide NCs with a high degree of monodispersity and crystallinity. The most widely used NCs for biological applications are made of CdSe cores overcoated with one or more layers of a wider band gap material like ZnS.^{5,6} The inorganic shell can efficiently passivate the core surface. With the excitation confined to the core, nonradiative recombination pathways can be suppressed, leading to enhanced photochemical stability and great improvement in the quantum yield (QY). More importantly, the shell can minimize cadmium leaching into biological environments, which significantly reduces cytotoxicity.⁷

High quality NCs are usually prepared in nonpolar organic solvents that make them insoluble in water. To obtain an aqueous dispersion, two strategies have been developed that are widely used to modify the

surfaces of NCs: (1) cap exchange where a large number of thiol or imidazole functional small molecules displace the original ligands in which the NCs are synthesized^{8–13} and (2) encapsulation of the NCs with their native ligands intact.^{14–17} Often encapsulation is performed with polymers such as amphiphilic poly(acrylic acid) or block copolymers. Although polymer encapsulated NCs can generally maintain their brightness and have good stability, their size increases substantially (>20 nm),¹⁶ resulting in poor intracellular mobility and no renal clearance in animal models, which limits their applications in biological studies.¹⁸ On the other hand, NCs cap exchanged with organic ligands can be smaller but do not have the same stability and brightness.¹¹ For example, NCs coated with dihydrolipoic acid (DHLA) are more stable than those coated with monomercapto ligands¹⁹ but will precipitate in some cases within days if stored on a benchtop.²⁰ The QY of cap exchanged NCs can decrease sharply depending on the quality of the inorganic surface passivation in the original sample.¹¹

We have developed a novel method for cap exchange of CdSe/ZnS core–shell NCs, which can significantly enhance the emission quantum yield and colloidal stability upon phase transfer into water. We found that if DHLA is metalated with zinc in the presence of base before mixing and cap exchanging CdSe/ZnS NCs in methanol, the NC aqueous dispersion is much brighter and is less prone to precipitation over time. We believe that these enhanced properties are the result of a direct chemical reaction of Zn(DHLA)₂ with the phosphonic acid species that initially coat hydrophobic nanocrystals, a process that prevents etching of the NC shell during cap exchange.

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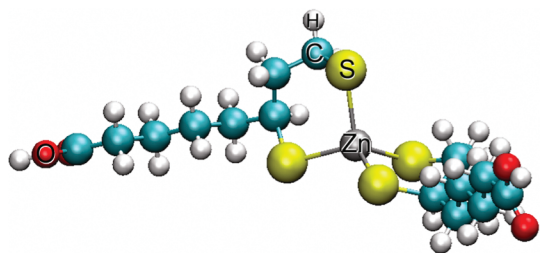


Figure 1. Optimized HF/LANL2DZ structure of a tetrahedral zinc complex with two DHLA ligands. There are a total of six conformers due to chirality of the DHLA and axial chirality of the ring systems; all these structures are stable, with significant interactions found between deprotonated DHLA and the coordinated zinc metal center.

RESULTS AND DISCUSSION

We have prepared zinc-metalated ligands by mixing NaOH, DHLA, and zinc nitrate; these samples were characterized with NMR, mass spectroscopy, and theoretical modeling. First, *ab initio* simulations at the HF/LANL2DZ level of theory supports the formation of a tetrahedral coordinated $(\text{DHLA})_2\text{Zn}^{2-}$ complex, as shown in Figure 1. Although there is some evidence of ring strain, the very strong counterpoise corrected calculated interactions (-135.0 ± 1.7 kcal/mol) of a bidentate single ligand with the zinc metal center strongly indicates that zinc complexes are stable (see Supporting Information for details). Carbon and proton NMR investigations demonstrate zinc complexation; mass spectrometry also confirms an interaction of DHLA ligands with zinc metal atoms, also shown in the Supporting Information. We next examined whether cap exchange of CdSe/ZnS NCs in methanol with these zinc-metalated ligands would render water-soluble emissive semiconductor NCs with enhanced properties. To this end, a methanolic dispersion of zinc coordinated DHLA was intermixed with a dry powder of CdSe/ZnS NCs at room temperature overnight. After precipitation with the addition of excess hexane and drying, the NCs were efficiently solubilized in an aqueous 0.1 M NaOH solution and then purified with buffer or D.I. water. Control samples of NCs cap exchanged without zinc, and another without zinc or base, were also prepared. Analysis of the aqueous CdSe/ZnS sample demonstrates that the metalated ligand exchanged samples are many times brighter and less prone to precipitation compared to these controls.

Figure 2 shows the absorption and emission spectra of well passivated CdSe/ZnS NCs cap exchanged by different methods. All the samples preserved their optical absorption and emission profiles, although the emission QY of the zinc-metalated sample is $\sim 2\times$ greater than either the DHLA or base-treated DHLA cap exchanged samples. Time-dependent quantum yield measurements show that the zinc-metalated cap exchanged CdSe/ZnS NCs are much more stable than others as demonstrated in Figure 3. It is interesting to note that the quantum yields of the DHLA and base-treated DHLA samples was found to

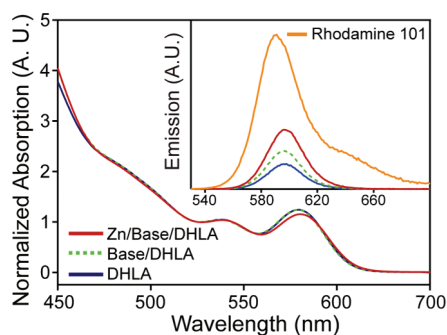


Figure 2. Normalized absorption spectra of 598 nm emitting CdSe-ZnS NCs after cap exchange by different methods. Inset: Photoluminescence spectra of the same NCs samples and rhodamine 101 dye, corrected with the same optical density at the excitation wavelength of 525 nm.

converge after a few days, which might suggest that the surfaces of NCs have been passivated to similar extent. However, both samples precipitated completely after four days, while the metalated sample is stable for over a week. We also found that the enhancement in quantum yield is dependent on the initial surface passivation; in a less robustly overcoated sample of CdSe/ZnS NCs, a nearly 5-fold enhancement in the QY of the aqueous dispersion was observed through the use of zinc-metalated DHLA. To demonstrate the versatility of our method, several thiol functional ligands, such as 11-mercaptoundecanoic acid and cysteine, were zinc-metalated and used to cap exchange CdSe/ZnS NCs; we have also cap exchanged blue emitting CdS/ZnS NCs with metalated DHLA. All these samples were much brighter and more stable in water compared to appropriate controls; these results indicated that the enhanced brightness and stability of metalated ligand cap exchanged NCs is a general phenomenon. In fact, Zn-cysteine cap exchanged NCs were stable for ~ 3 months when stored in a refrigerator; this sample fared much better than the control that precipitated in a single day.

Gel-filtration chromatography (GFC) was used to determine the hydrodynamic diameters (HD) of the NC samples after cap exchange, as shown in Figure 4. The NC sample cap exchanged under basic conditions showed the largest retention volume corresponding to the lowest HD (8.5 ± 0.3 nm), which was reduced by more

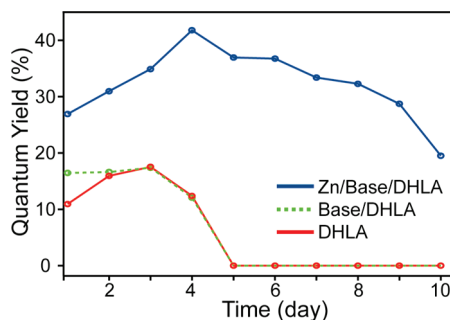


Figure 3. Quantum yield of CdSe-ZnS NCs cap exchanged by different methods over time. The samples in pH 7 phosphate buffer were kept in the dark at room temperature. Precipitation of the samples is indicated by a quantum yield of 0%.

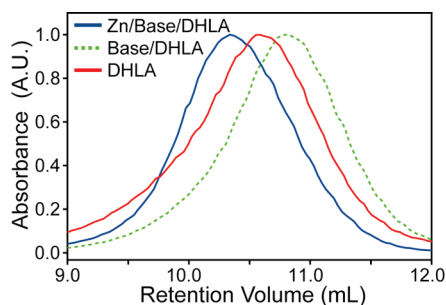


Figure 4. GFC analysis of DHLA-coated NCs ligand-exchanged by metalated and nonmetalated organic.

than 10% compared to the sample cap exchanged with DHLA under the neutral condition (9.4 ± 0.2 nm). Such a reduction in size under basic conditions might be due to the etching of the ZnS shell surface by high concentration of thiolate anion during the cap exchange. On the other hand, by using a Zn/Base/DHLA complex as the ligand source, the HD of the NC sample was found to have the largest HD of 10.5 ± 0.3 nm, as shown in Figure 4. The use of smaller, green emitting NCs can lower the HD further.¹¹

The sum of these observations suggests that a fundamental difference exists in the surface repassivation mechanism of NCs with metalated ligands vs the organic substrate alone. We can demonstrate that this is due to the interaction of the metalated ligands with the NC caps during the exchange process. It was recently established that phosphonate species (such as phosphonic acids) present as impurities in commonly used solvents coat as prepared CdSe NCs;^{21,22} furthermore, Weiss's group has shown that only these caps remain bound to the NC surface after processing.²³ We have confirmed the same is true with our core/shell CdSe/ZnS NCs, as seen in the ³¹P spectrum of precipitated CdSe/ZnS NCs in Figure 5 (inset). This result is sensible as our core NCs are overcoated with cadmium and zinc sulfide in the presence of tetradecyl-

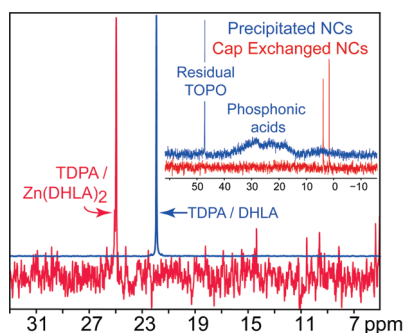


Figure 5. ³¹P NMR spectra of tetradecylphosphonic acid after exposure to DHLA (blue) and to Zn(DHLA)₂ (red) under basic conditions. Inset shows the ³¹P NMR spectra of precipitated CdSe/ZnS NCs in CDCl₃ (blue) and Zn(DHLA)₂ cap exchanged NCs (red) in D₂O. The residual TOPO peak at $\delta = 47.2$ ppm is not bound to the NCs, as evident from the sharpness of the resonance. The broad peaks from $\delta = 0-40$ ppm are likely due to phosphonic acids, phosphonates, and phosphates coating the NCs according to refs 21–23. After cap exchange, these features are absent, while two sharp resonances appear from $\delta = 0-5$ ppm (most likely phosphate species).

ylphosphonic acid (TDPA). The fact that phosphonic acids and similar species cover our core/shell NCs is key to understanding why our method creates much more robust water-soluble nanocrystals. It is known that thiol-coordinated zinc metal centers are reactive with phosphate esters.^{24,25} Considering that a phosphonic acid is less sterically hindered than an ester, we examined the reactivity of DHLA and Zn(DHLA)₂ with TDPA using ³¹P NMR spectroscopy. TDPA and DHLA were mixed overnight in methanol under cap exchange conditions; the material was dried and studied with ³¹P NMR in D₂O, which shows that the TDPA phosphorus resonance at $\delta = 21.9$ ppm is unaltered compared to the neat ligand. This demonstrates that there is little to no interaction with DHLA and TPDA. However, Zn(DHLA)₂ is reactive with TDPA under the conditions of cap exchange; the addition of TDPA to Zn(DHLA)₂ in basic methanol results in the immediate formation of a precipitate that is only weakly soluble in D₂O. The precipitated product has a downfield shifted ³¹P resonance at $\delta = 25.0$ ppm (compared to the $\delta = 21.9$ ppm resonance of TDPA), which is consistent with the formation of an electron withdrawing zinc adduct. The ³¹P spectrum of cap exchanged CdSe/ZnS NCs are shown in the inset of Figure 5; in this sample, the broad resonances in the $\delta = 0-40$ ppm region are now absent. While two resonances are observed ($\delta = 1.7, 3.9$ ppm, most likely phosphate species), a $\delta = 25.0$ ppm peak is absent. We attribute this to the low solubility of the TDPA-Zn adduct in D₂O and the fact that several possible phosphorus species are coating our NCs.

These results support a mechanism where a metalated ligand reacts with a surface bound cap and “gently” removes it without etching the NC. In the process of complexation, the zinc must shed one of its DHLA ligands^{24,25} that binds to the NC surface. Essentially, in the presence of zinc–thiol complexes, a metathesis reaction occurs at the NC surface that helps preserve the qualities of the original material; this mechanism is also consistent with previous results that demonstrated direct chemical reactions of trimethoxysilane-functional caps with phosphonate ligands on CdSe NC surfaces.²² Such a mechanism also explains the hydrodynamic diameter results that change depending on the method of cap exchange as shown in the GFC data; at the same time, the zeta potentials of the as-prepared samples are identical from electrophoresis results shown in the Supporting Information. We believe this is the origin of the significant improvement in the optical properties and enhanced stability of metalated cap exchanged NCs in water. The well-known loss of quantum yield using neat mercapto-acid surfactants for cap exchange is likely due to etching of the inorganic NC surface, allowing the thiol ligands to coordinate to a free metal center and react to remove the native organic caps by our proposed mechanism; however, this process occurs at the expense of the inorganic shell passivation.

CONCLUSION

We have demonstrated a method to create small metalated ligand exchanged NCs with enhanced optical properties. This method seems general across a variety of ligands and NC substrates; further, the

cap exchange process appears to occur by a metathesis reaction occurring at the surface of the core/shell NC. We hope that this research will lead to the development of smaller and brighter NC biological imaging agents.

EXPERIMENTAL SECTION

Materials. All chemicals were obtained from commercial sources and were used as received unless indicated.

Instrumentation. ^1H , ^{13}C , and ^{31}P NMR spectra were recorded on Bruker Avance 400 and 500 NMR spectrometers; methanol- d^4 was used as the NMR solvent. Chemical shifts were reported in the scale relative to methanol- d^4 as an internal reference (the quintet was calibrated to be 3.31 ppm). UV-vis absorbance spectra were taken using a Varian Cary 300 Bio spectrophotometer. Fluorescence emission spectra were taken using a customized Fluorolog (HORIBA Jobin Yvon) spectrofluorometer. The absorbance of all solutions was kept near or below 0.1 OD at the excited wavelength to avoid inner-filter effects. GFC analysis was performed on an ÄKTA prime system with a Superose 10/300 GL column (Tricorn). Phosphate buffer (pH 8) was used as the mobile phase with a flow rate of 0.5 mL/min; absorption at 280 nm was used to observe materials in the column. Gel electrophoresis was performed on a Minigel electrophoresis system (FisherBiotech) with 0.3 wt % Agar in phosphate buffer (pH 8) at 3.8 V/cm. NCs were diluted to about 300 nM before loading onto the gel. Gels were visualized under the UV light with a fixed digital camera. ESI-MS was performed on a Finnigan LCQ Classic mass spectrometer at the UIC Research Resource Center.

NC Synthesis. Core CdSe^{26,27} and core shell CdSe/ZnS NCs²⁸ were synthesized according to the cited references. A single sample with an as-prepared quantum yield of 94% was used for the majority of the work in this study. Samples were processed by addition of a small amount of isopropanol followed by methanol to precipitate the samples. The supernatant is discarded, leaving behind a gel most likely composed of a decylamine-tetradecylphosphonic acid adduct used in the ZnS overcoating procedure. The CdSe/ZnS NCs were extracted from this gel by several washings of hexane; the washings were collected from which the NCs were precipitated again through the addition of a few drops of isopropanol and sufficient methanol. The precipitate was collected by centrifugation and dried under reduced pressure. In a typical preparation, 1.0 g of a 3.58×10^{-8} mol NC/g growth solution is prepared in this manner; the material was then divided into three equal portions to cap exchange with DHLA, base/DHLA, and Zn/base/DHLA, as described below. When water solubilizing these NCs with amphiphilic 40% octylamine modified poly(acrylic acid), the quantum yield (QY) is 73%; however, these NCs have a hydrodynamic diameter of over 20 nm.

CdS/ZnS NCs were also synthesized using established methods.^{29,30} These materials are precipitated from growth solution using pure isopropanol; the sample is centrifuged and the supernatant is discarded. The remaining solid is washed with methanol and dried under reduced pressure.

Cap Exchange with Dihydrolypoic Acid (DHLA). DHLA was prepared using an established protocol.³¹ Approximately 100 mg of DHLA (0.5 mmol) in 2 mL of methanol was added to dry NC precipitates. The mixture was stirred at room temperature for ~24 h. Over time, the sample becomes a homogeneous, clear solution; the overcoated sample was then precipitated with a small quantity of isopropanol followed by excess hexane. After centrifugation, the precipitate was dispersed in a 0.1 M NaOH aqueous solution. The sample was further purified by four cycles of dialysis through a centrifugal filter (100 kDa MW cutoff regenerated cellulose membrane, Millipore) using pH = 7 phosphate buffer. Finally, the sample was purged through a 0.2 μm filter and diluted to a proper concentration for analysis.

Cap Exchange with Base/DHLA. DHLA (~100 mg, 0.5 mmol) was dissolved in 2 mL of methanol solution containing 60–80 mg of NaOH. This solution was added to the precipitated NCs and then the cap exchange was performed with the same procedure

as above. In this procedure, the cap exchanged NCs do not form a clear homogeneous solution in methanol.

Cap Exchange with Zn/Base/DHLA. DHLA (~100 mg; 0.5 mmol) was dissolved in 2 mL of methanol solution containing 60–80 mg of NaOH. To the solution ~70 mg of $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (~0.24 mmol) was added; the light scattering mixture was stirred vigorously with heating until becoming clear. This solution was then added to a dry powder of NCs, which were subsequently processed as above. In this procedure, the cap exchanged NCs do not form a clear homogeneous solution in methanol. We found that the NCs cap exchanged with metalated DHLA have an initial QY of 54.1%, which drops to 26% after dialysis with pH 7 buffer. Likewise, the initial QY of the sample shown in Figure S6 is 33.4% before dialysis, which drops to 13% after dialysis. Another sample was processed by dissolution into D_2O for ^{31}P spectroscopy.

Cap Exchange with Base/Cysteine. This procedure is adapted from ref 11. L-Cysteine (~60 mg; 0.5 mmol) was dissolved in 2 mL of a 0.1 M NaOH solution. This solution was added to 1 mL of a ~1 μM chloroform dispersion of NCs. The mixture was stirred for 0.5 h. The organic phase was removed by pipet; the liquid phase was treated for 0.5 h under reduced pressure. The sample was then passed through a 0.2 μm filter and diluted to a proper concentration for optical characterization with D.I. water.

Cap Exchange with Zn/Base/Cysteine. This procedure is adapted from ref 11. L-Cysteine (~60 mg; 0.5 mmol) was dissolved in 2 mL of a 0.1 M $\text{Zn}(\text{NO}_3)_2$ solution followed by addition of 0.8 g NaOH. This mixture was added to 1 mL of an ~1 μM chloroform dispersion of NCs. The mixture was stirred for 0.5 h. The organic phase was removed by pipet, while the liquid phase was treated for 0.5 h under reduced pressure. The sample was then passed through a 0.2 μm filter and diluted to a proper concentration for optical characterization with D.I. water.

Tetradecylphosphonic Acid (TDPA) Reaction with Zn/Base/Cysteine. First, a DHLA-metalated zinc adduct is prepared as above. Next, 1 equiv of TDPA to zinc is added to the methanolic dispersion and stirred overnight. It was noticed that upon addition to TDPA a white precipitate forms immediately. After drying, the solution is mixed with D_2O and analyzed with ^{31}P NMR spectroscopy. Due to the very low solubility, the NMR signal was averaged overnight. A control sample was prepared as above without the addition of $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$; instead, the H_2O equivalent was added to the DHLA and TDPA in methanol and stirred overnight. No precipitation is formed in this sample; further, after drying, the sample is very soluble in D_2O .

Theoretical Modeling. *Ab initio* calculations on various DHLA/Zn adducts were performed at the Hartree-Fock level of theory using the LANL2DZ basis set.^{32–34} This level of theory was employed as some calculations involved over 100 atoms which preclude the use of more sophisticated model chemistries. The Gaussian '03 software package implemented on the UIC Argo cluster was used to perform these calculations;³⁵ visualizations were rendered using VMD for Windows.³⁶ Geometries were optimized to stationary points which was verified with frequency calculations. The smallest, most stable form of a DHLA/Zn complex was found to be an anionic (due to the presence of two thiolate groups) $(\text{DHAl})_2\text{Zn}$ tetrahedral coordinated complex; the overall charge was set to -2 with a singlet spin state. Higher spin states were examined; however, the singlet was found to be the ground electronic state. Interaction energies of a single DHLA with the remaining Zn(DHLA) fragment was calculated taking into account basis set superposition errors using the counterpoise method.³⁷ The interaction of thiol-functional (nondeprotonated) DHLA was examined as well as linear clusters of terminal and bridging DHLA/Zn fragments were also examined.

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Supporting Information Available: Proton and carbon NMR, mass spectrograms of base-treated and zinc-metalated DHLA ligands, theoretical structures of large zinc–DHLA clusters, as well as spectroscopic characterization of other samples. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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