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FULL PAPER

# An efficient method for the surface functionalization of luminescent quantum dots with lipoic acid-based ligands

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**Abstract:** We describe an operationally advantageous general methodology to efficiently activate lipoic acid-based compounds - a family of popular surface ligands for semiconductor nanocrystals - by the use of a borohydride exchange resin, and the use of the activated species to replace the native surface ligands of quantum dots. The procedure enables the phase transfer of the nanocrystals between polar and aqueous media and, if unsubstituted lipoic acid is used, a facile adjustment of their solubility in a wide range of solvents with varying polarity (from hexane to water). We show that the protocol is applicable to different types of nanocrystals and a variety of lipoic acid-based ligands, and that the resulting quantum dots maintain their optical properties - in particular, an intense luminescence - and long term colloidal stability.

## Introduction

Quantum dots (QDs) are crystals of semiconductor materials comprising from some hundreds to a few thousands of atoms, with a spherical shape and a diameter typically ranging between 1 and 15 nm. QDs are endowed with unique size-dependent optical and electronic properties, owing to quantum confinement.[1,2] If appropriate semiconducting materials are employed (e.g., CdS, CdSe, CdTe), such quantum dots (QDs) exhibit a very intense absorption and emission in the UV-visible-NIR region, and have thus emerged as substitutes for molecular fluorophores in a variety of applications.[3,4] The use of QDs for chemical and biochemical sensing,[5] medical diagnostics and therapy,[6] and as components of photodetectors,[7] light-emitting devices,[8] and solar cells[9] is well established and still actively investigated. Most fine chemical companies now offer QD samples in their catalogues, and flat screen televisions based on QD emission[10] have appeared on the consumer market.

Although high quality QDs can be prepared in aqueous media[11] or synthesized in biological/biomimetic systems,[12] the most reliable and popular synthetic methods exploit reactions of inorganic or organometallic precursors in organic solvents in the presence of appropriate surfactants.[13,14] The QDs afforded by such approaches are coated with a layer of highly hydrophobic molecular ligands[15] and are, therefore, (moderately) soluble only in non-polar organic solvents such as toluene, hexane or chloroform. In order to be used in bioimaging and medical therapy, however, the nanocrystals need to be compatible with and soluble in aqueous media[5,6].

In general, the application of these nanomaterials in diverse fields of technology implies their facile solution processing, which is in turn dictated by their solubility in common solvents. Various methods exist to engineer the affinity of semiconductor nanocrystals towards solvents. For example, QDs can be encapsulated within amphiphilic polymers or peptides, which provide a robust coating that preserves the photophysical properties of the nanoparticles and enhances their colloidal stability.[16] The increased diameter of the encapsulated nanoparticles, however, may be a problem for biomedical applications.[5,6] Alternatively, the ligands bound at the nanocrystals surface can be altered by chemical reactions.[17] The post-synthetic modification of the surface capping layer also enables the connection of functional molecular units to the QD, leading to the development of hybrid nanomaterials with emerging properties.[4–6,17]

A more straightforward methodology consists in covering the surface of the nanocrystals with functional ligands by replacement of the native ligands. Unfortunately the photophysical properties as well as the chemical and photochemical stability of the QDs are usually degraded upon exchange of the capping ligands.[18,19] Nevertheless, dihydrolipoic acid (DHLA) and related compounds, because of the presence of two thiol anchoring groups, are able to form robust monolayers on the surface of inorganic nanocrystals, and are frequently used as QD caps.[15,17,20,21,22]

DHLA is obtained from lipoic acid (LA) upon rupture of the disulfide bond of its 1,2-dithiolane moiety (Scheme 1).[23]

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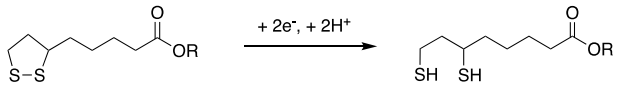



**Scheme 1.** Chemical reduction of lipoic acid-based compounds to the dihydrolipoic derivatives.

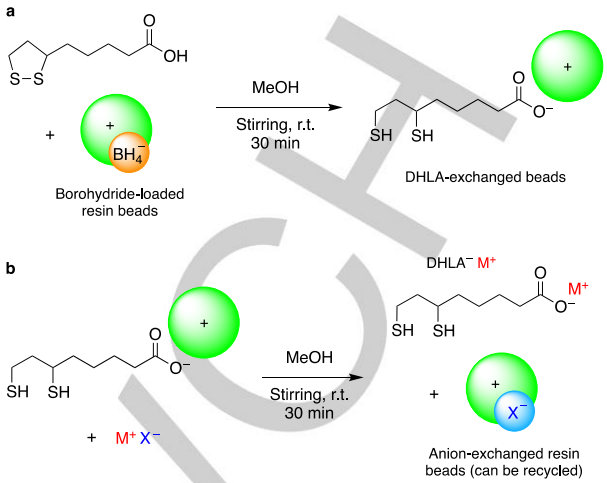
The conversion of LA to DHLA moieties is commonly carried out in solution using $NaBH_4$ as a reductant.[18-22,24] This route, though effective, requires careful preparation, storage, and handling of the DHLA-based ligands under inert atmosphere to prevent reoxidation of the bis-thiol to disulfide. Moreover, $NaBH_4$ cannot be used with functional ligands that contain moieties sensitive to $Na^+$ ions (e.g., receptors for metal ions). A method relying on UV irradiation to cleave the S–S bond of LA-type ligands was reported.[25] Although this route avoids the use of chemical reductants and enables ligand activation and QD functionalization to be performed in a single step, it requires a UV reactor and, more importantly, it cannot be employed for capping ligands bearing photosensitive units.

We recently devised[26] a procedure for efficiently converting lipoic acid into the active DHLA derivative, and subsequently using it to replace the native caps of QDs. Here we report a thorough description of this methodology, which involves the chemical reduction and ion exchange of LA compounds within a borohydride-loaded resin. In particular, we have tested the procedure on different types of ligands and nanocrystals, and we have investigated the changes in the photophysical properties and colloidal stability of the resulting quantum dots. We have also studied the effect of different reactants used to extract the reduced ligands from the resin on the solubility of the nanocrystals in solvents of varying polarity.

## Results and Discussion

***Reduction of the ligand.*** As discussed above, the dihydrolipoic moiety capable of binding the QD surface can be obtained by borohydride-promoted reduction of the corresponding lipoic acid compound. In our method the use of $NaBH_4$ is avoided and the reduction of the 1,2-dithiolane unit is achieved with a borohydride-loaded ion-exchange resin (BER),[27] as depicted in Scheme 2. BERs are commercially available or can be prepared by mixing an anion exchange resin, such as Amberlite® IRA-400, with an aqueous solution of $NaBH_4$ and stirring for a few hours.[28] In our case, acid titrations revealed that the resin contained typically 2.5 mmol of $BH_4^-$ per gram of polymer.

The conversion of LA to the DHLA anion was performed by adding the BER beads to a MeOH solution of lipoic acid, with a $BH_4^-$/LA molar ratio of about 2:1, and stirring for 30 minutes. The process could be conveniently monitored by absorption spectroscopy, by following the decrease of the disulfide absorption band of lipoic acid at 330 nm (Figure 1).[29] The absorbance in the 220-260 nm region – which is initially out of scale – also decreases. This observation indicates that DHLA, which exhibits a strong absorption feature in this spectral region,[29] is chemisorbed on the cationic resin (Scheme 2a).




**Scheme 2.** (a) Reaction between lipoic acid and borohydride exchanged resin beads, leading to the chemisorbed dihydrolipoic species ($DHLA^-$). (b) Extraction of $DHLA^-$ from the resin by anion displacement with a salt ($M^+X^-$).

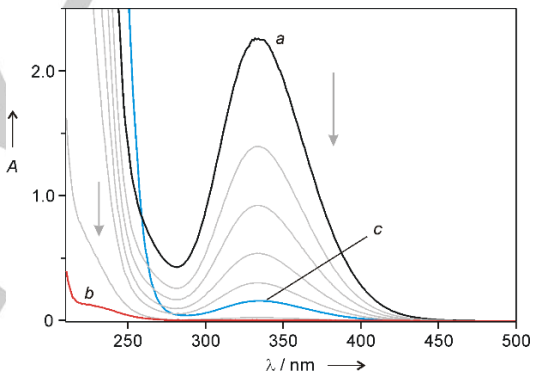



**Figure 1.** Absorption spectral changes measured for a $1.6\times10^{-2}$ M lipoic acid solution (*a*) upon addition of the BER (2 equiv of $BH_4^-$ with respect to LA) (grey curves). No more changes were detected after 30 min stirring and the spectrum (*b*) was obtained. Treating this solution with NaOH (2 equiv with respect to LA) and 30 min stirring afforded the spectrum (*c*). Conditions: MeOH, room temperature.

After removal of the solvent layer, the beads were washed with fresh methanol to remove unreacted LA and borohydride products. The DHLA species were extracted from the resin by treatment with a MeOH solution of a metal or ammonium salt: the $X^-$ anions displace $DHLA^-$ from the resin beads (which are successively recovered), and a methanol solution of the active ligand as its $M^+$ salt is obtained. We found that the role of $M^+X^-$ is conveniently played by hydroxides such as NaOH or TMAOH (TMA = tetramethylammonium).

Indeed, the addition of NaOH to the resin suspension (2 equiv with respect to the initial amount of LA) caused an immediate and significant absorption increase between 220 and 250 nm, whereas only a minor recovery of the band at 330 nm took place. The signal at 330 nm continued to increase upon stirring for ca. 20 min (Figure 1, curve *c*), however reaching a value much

smaller than the initial LA band (curve *a*). These observations indicate that the addition of NaOH causes the quick release of DHLA from the resin; on a longer time scale, a minor amount of unreacted lipoic acid was also released. Similar results were obtained when TMAOH was employed in the place of NaOH.

The increase of the absorption intensity at 330 nm was used to estimate the amount of unreacted lipoic acid, whereas the amount of DHLA released in the solution was determined with Ellman's reagent.[30] Under our experimental conditions (room temperature; 30 min stirring with BER, addition of 2 equiv of NaOH and 30 min stirring), the DHLA yield in the MeOH solution was 29%; 7% of unreacted LA was also extracted.

It is worthy to point out that the purification procedures usually carried out after the reduction of lipoic acid with $NaBH_4$ in homogeneous solution are not needed.[24] In fact the reactant in excess can be separated from the solution simply by decantation of the resin. Moreover, previous procedures[18–22,24] typically involved the preparation of stock quantities of reduced ligand, which would be stored under inert atmosphere at low temperature until used. With such a handy protocol, the amount of DHLA just necessary for a given QD batch can be prepared and readily utilized for the cap exchange.

***Ligand exchange and phase transfer of the QDs.*** A biphasic liquid system was prepared at room temperature by mixing a hexane solution containing the hydrophobic QDs (capped with long-chain phosphine, phosphine oxide, amine and/or carboxylic derivatives, see Experimental Section) and a methanol solution containing the DHLA ligand. Upon stirring the mixture, an efficient ligand exchange occurred and the QDs were transferred to the methanol solution, as indicated by the color change (Figure 2, left photographs).[18a,20–22] The phase transfer can be more clearly appreciated by looking at the QD luminescence upon near-UV illumination (Figure 2, right photographs). The weak bluish glow visible in the hexane layer after the cap exchange arises from the fluorescence of the hydrophobic ligands that remain in the less polar phase after the exchange.

In alternative, the hydrophobic QDs in solid form were added to the DHLA solution; a rapid dispersion of the nanocrystals in MeOH was observed, witnessing again the efficient replacement of the native hydrophobic ligands with DHLA.

The discoloured hexane layer was removed if present, and traces of hydrophobic ligands and unreacted nanocrystals were washed away by treating the methanol suspension with fresh hexane. After evaporation of MeOH under vacuum, the QDs capped with $DHLA^-Na^+$ were dissolved in water. Large aggregates were separated from the aqueous suspension using a syringe filter, and unreacted DHLA was removed by means of 3 dilution/concentration cycles with a 30 kDa centrifugal filter.[31] Typically, a relatively concentrated (5-10 μM) solution of QDs in water could be eventually obtained.

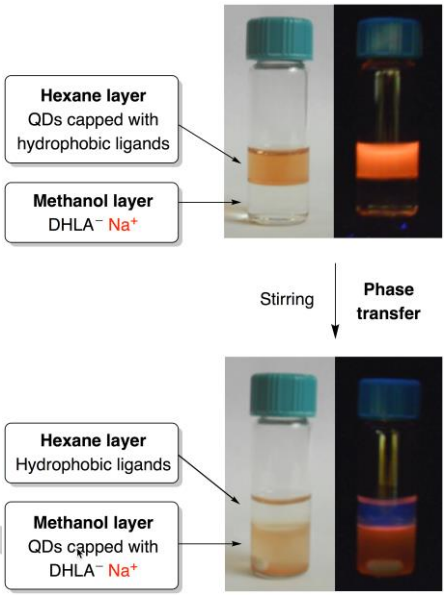



**Figure 2.** Phase transfer of the hydrophobic QDs in a polar solvent promoted by cap exchange with DHLA ligands. The photographs refer to an experiment in which CdSe-5ZnS core-shell nanocrystals ($d_{core}$ = 3.6 nm) were employed. The images on the left were taken under ambient light, while those on the right were obtained upon near-UV excitation.

**Table 1.** Spectroscopic properties ($H_2O$, r.t.) of different $DHLA^-Na^+$ capped QDs obtained by ligand exchange and phase transfer. Extracting agent: NaOH.

| | QD | *d* nm[c] | *s* nm[d] | $\lambda_{abs}$ ($\Delta\lambda_{abs}$) nm[e] | $\lambda_{em}$ ($\Delta\lambda_{em}$) nm[f] | $\Phi_{em,n}$ [h] | $\Phi_{em,w}$ [i] |
|---|---|---|---|---|---|---|---|
| 1 | CdS[a] | 2.8 | — | 381 (+9) | [g] | | |
| 2 | CdS[a] | 4.1 | — | 420 (+6) | [g] | | |
| 3 | CdSe[a] | 2.6 | — | 528 (+2) | [g] | | |
| 4 | CdSe[a] | 3.8 | — | 583 (0) | [g] | | |
| 5 | CdSe-5ZnS[b] | 2.7 | 1.6 | 545 (+3) | 562 (+2) | 0.14 | 0.044 |
| 6 | CdSe-3ZnS[b] | 3.4 | 0.9 | 562 (–2) | 585 (–1) | 0.34 | 0.18 |
| 7 | CdSe-5ZnS[b] | 3.6 | 1.6 | 572 (0) | 597 (–2) | 0.23 | 0.081 |
| 8 | CdSe-4ZnS[b] | 3.7 | 1.2 | 576 (–2) | 606 (–1) | 0.18 | 0.06 |
| 9 | CdSe-3ZnS[b] | 4.1 | 0.9 | 587 (–1) | 605 (0) | | |

[a] Core-only QDs. [b] CdSe-*n*ZnS Core-shell QDs; *n* denotes the number of ZnS monolayers present in the shell. [c] Core diameter. [d] Shell thickness. [e] $\lambda_{abs}$ = Wavelength of the lowest exciton absorption peak in $H_2O$; $\Delta\lambda_{abs} = \lambda_{abs}$ ($H_2O$) – $\lambda_{abs}$ ($CHCl_3$). [f] $\lambda_{em}$ = Wavelength of the emission band maximum in $H_2O$; $\Delta\lambda_{em} = \lambda_{em}$ ($H_2O$) – $\lambda_{em}$ ($CHCl_3$). [g] Not luminescent. [h] Emission quantum yield of QDs with native ligands in $CHCl_3$ or hexane. [i] Emission quantum yield of QDs capped with $DHLA^-Na^+$ in water.

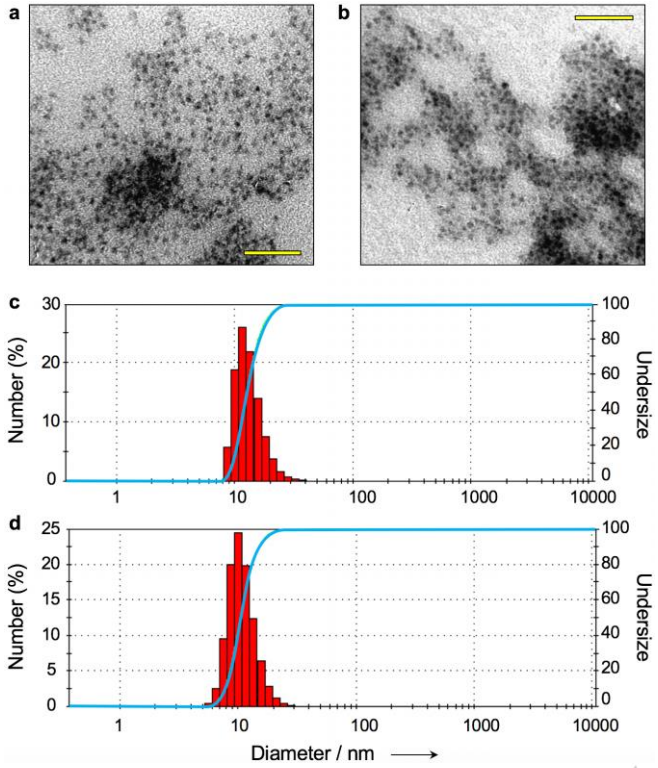



**Figure 3.** Effect of the cap exchange on the size and morphology of the QDs. Top: TEM Micrographs of CdSe-4ZnS QDs (entry 8 in Table 1) TOP/TOPO capped (a) and DHLA$^{-}$Na$^{+}$ capped (b) Scale bar, 50 nm. Bottom: Differential (red bars) and cumulative (blue lines) number distribution of particle size, obtained from DLS data, of CdSe QDs (entry 3 in Table 1) TOP/TOPO capped in chloroform (c) and DHLA$^{-}$Na$^{+}$ capped in water (d).

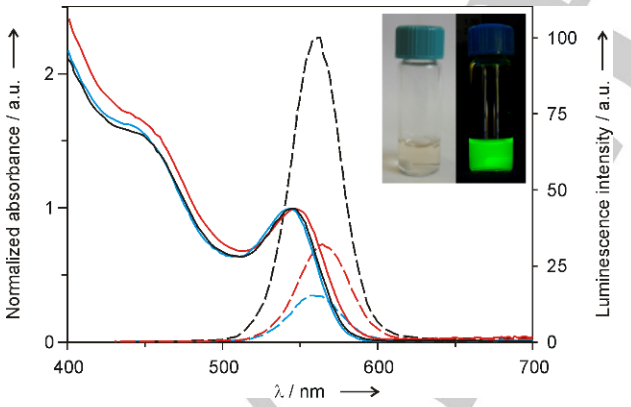



**Figure 4.** Absorption (full lines, left scale) and emission ($\lambda_{exc}$ = 420 nm; dashed lines, right scale) spectra of TOP/TOPO CdSe-5ZnS QDs (entry 5 in Table 1) in $CHCl_3$ (black), and of the same QDs in aqueous solution after cap exchange with DHLA$^{-}$Na$^{+}$ (red) or DHLA$^{-}$TMA$^{+}$ (blue). Inset: photograph of the DHLA$^{-}$Na$^{+}$ capped QDs in water under ambient light (left) and upon UV excitation (365 nm).

This method enabled us to produce water soluble DHLA$^{-}$Na$^{+}$ capped nanocrystals of different structure and size (Table 1). In all cases the phase transfer was complete within 1 min. In particular, CdSe-ZnS core-shell QDs yielded clear water solutions which were stable for at least 3 months. Transmission electron microscopy (TEM) and dynamic light scattering (DLS) measurements (Figure 3) showed that the cap exchange does not affect the size and morphology of the QDs and no aggregation takes place. Only a slight shift in the absorption and emission peak wavelengths was observed with respect to the starting QDs, indicating that the spectroscopic properties of the final products are preserved (Figures 4 and 5). The luminescence quantum yield of the final nanocrystals in aqueous solution was 30-50% of that of the native hydrophobic QDs, in line with literature reports.[18bd] As observed in earlier studies,[18b,32] CdS and CdSe nanocrystals devoid of a ZnS shell were not emissive after phase transfer.

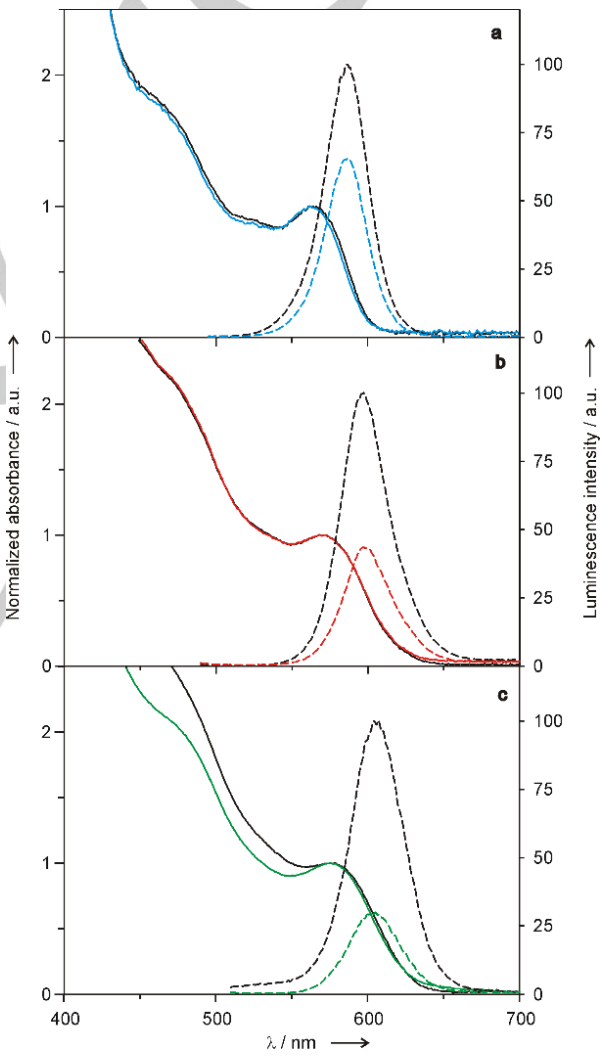
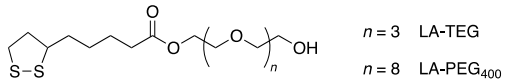



**Figure 5.** a) Absorption (full line, left scale) and emission ($\lambda_{exc}$ = 485 nm; dashed line, right scale) spectra of CdSe-3ZnS QDs (entry 6 in Table 1) TOP/TOPO capped in $CHCl_3$ (black) and DHLA$^{-}$Na$^{+}$ capped in $H_2O$ (blue). b) Absorption (full line) and emission ($\lambda_{exc}$ = 480 nm; dashed line) spectra of CdSe-5ZnS QDs (entry 7 in Table 1) TOP/TOPO capped in $CHCl_3$ (black) and DHLA$^{-}$Na$^{+}$ capped in $H_2O$ (red). c) Absorption (full line) and emission ($\lambda_{exc}$ = 450 nm; dashed line) spectra of CdSe-3ZnS QDs (entry 9 in Table 1) TOP/TOPO capped in $CHCl_3$ (black) and DHLA-$PEG_{400}$ capped in $H_2O$ (green). Adapted by permission of the Royal Society of Chemistry.[26a]

We found that the reduction with the borohydride-loaded resin is also effective for ligands consisting of a 1,2-dithiolane moiety attached to a oligo(ethylene glycol) hydrophilic domain,[20,21] such as LA-TEG and LA-PEG$_{400}$. As these compounds do not contain ionizable units, the reduced DHLA-based ligand does not stick to the resin; hence, the activated ligand can be collected without the extraction step described in Scheme 2b and used in the phase transfer step. Figure 5c shows the absorption and luminescence spectra of CdSe-ZnS QDs obtained by ligand exchange with DHLA-PEG$_{400}$.




The stability of DHLA capped QDs prepared with the above described route on the long term was evaluated. For example, a dilute solution (130 nM) of the nanocrystals described in Figure 5b in deionized water was stored in a refrigerator at 5° C, and the absorption and luminescence spectra were monitored over 3 weeks (Figure 6). No precipitation was observed, although the emission quantum yield decreased from 0.081 to 0.05 during the first two weeks, in line with literature reports for DHLA-capped QDs.[33]

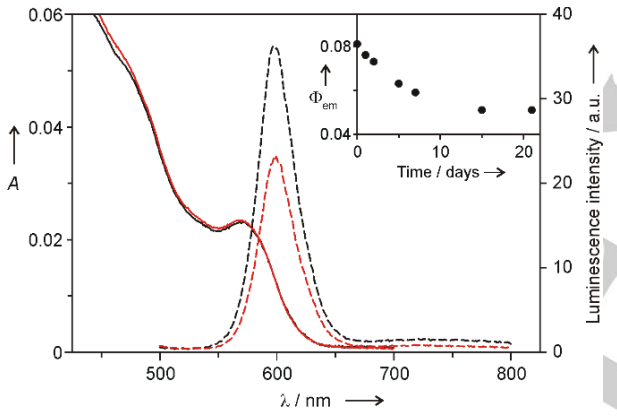



**Figure 6.** Absorption (full lines, left scale) and emission ($\lambda_{exc}$ = 480 nm; dashed lines, right scale) spectra of CdSe-5ZnS QDs (entry 7 in Table 1, 130 nM) capped with DHLA$^-$Na$^+$ in water, freshly prepared (black) and after 21 days of storage at 5 °C (red). The inset shows the evolution of the luminescence quantum yield over time. Adapted by permission of the Royal Society of Chemistry.[26a]

***Effect of the reactant employed to collect DHLA from the BER.*** To gain more insight about the role of the M$^+$X$^-$ species (Scheme 2b) in determining the properties of the final phase-transferred QDs, we carried out several cap exchange reactions employing different metal or ammonium salts or hydroxides to extract DHLA from the resin.

In a first instance, we explored the influence of the nature of the X$^-$ anion by using different sodium salts in the extraction step (Scheme 2b) and successively performing phase transfer on CdSe-ZnS core-shell nanocrystals. The results are summarized in Table 2. No phase transfer was observed with NaCl or NaBH$_4$, suggesting that chloride and borohydride anions are unable to displace DHLA$^-$ from the resin. Sodium carbonate and acetate afforded an incomplete extraction of the DHLA ligand and consequently a partial cap exchange occurred. Triflate and perchlorate salts allowed a complete extraction and consequently afforded cap-exchanged nanocrystals endowed with stability in water and photophysical properties similar to those prepared using sodium hydroxide. Sodium bromide also led to a complete cap exchange but a longer stirring time was required.

**Table 2.** Photophysical properties (H$_2$O, room temperature) of CdSe-5ZnS (entry 7 in Table 1) capped with DHLA$^-$Na$^+$ extracted from the BER using different sodium salts.

| Na$^+$X$^-$ | Phase transfer | Solubility in H$_2$O[a] | $\Delta\lambda_{abs}$ nm[b] | $\Delta\lambda_{em}$ nm[c] |
|---|---|---|---|---|
| NaCl | No | No | — | — |
| NaBH$_4$ | No | No | — | — |
| NaBr | Complete | Yes | –1 | –2 |
| Na$_2$CO$_3$ | Partial | Yes | –1 | –2 |
| NaCH$_3$COO | Partial | Yes | –2 | –2 |
| NaCF$_3$SO$_3$ | Complete | Yes | –2 | –1 |
| NaClO$_4$ | Complete | Yes | 0 | –1 |
| NaOH | Complete | Yes | 0 | –2 |

[a] The QDs are considered soluble if they form a homogeneous solution at the 0.5-1.0 μM concentration level. [b] $\Delta\lambda_{abs} = \lambda_{abs}$ (H$_2$O) – $\lambda_{abs}$ (CHCl$_3$); $\lambda_{abs}$ = 572 nm; wavelength of the lowest exciton absorption peak in H$_2$O; [c] $\lambda_{em}$ = 597 nm; wavelength of the emission band maximum in H$_2$O; $\Delta\lambda_{em} = \lambda_{em}$ (H$_2$O) – $\lambda_{em}$ (CHCl$_3$).

Successively, we investigated the effect of the M$^+$ cation by exchanging the ligand on CdSe-ZnS QDs using different alkali metal or ammonium hydroxides in the extraction step (Scheme 2b). The results are summarized in Table 3. In all cases the phase transfer was successful, the resulting QDs were soluble in water and their spectroscopic properties were preserved.

**Table 3.** Photophysical properties (H$_2$O, room temperature) of CdSe-5ZnS (entry 7 in Table 1) capped with DHLA$^-$Na$^+$ extracted from the BER using different metal or ammonium hydroxides.

| M$^+$OH$^-$ | Phase transfer | Solubility in H$_2$O[a] | $\Delta\lambda_{abs}$ nm[b] | $\Delta\lambda_{em}$ nm[c] |
|---|---|---|---|---|
| LiOH | Complete | Yes | 0 | –1 |
| NaOH | Complete | Yes | 0 | –2 |
| KOH | Complete | Yes | –4 | –3 |
| TMAOH[d] | Complete | Yes | 0 | 0 |
| TBAOH[e] | Complete | Yes | 0 | –5 |

[a] The QDs are considered soluble if they form a homogeneous solution at the 0.5-1.0 μM concentration level. [b] $\Delta\lambda_{abs} = \lambda_{abs}$ (H$_2$O) – $\lambda_{abs}$ (CHCl$_3$); $\lambda_{abs}$ = 572 nm; wavelength of the lowest exciton absorption peak in H$_2$O; [c] $\lambda_{em}$ = 597 nm; wavelength of the emission band maximum in H$_2$O; $\Delta\lambda_{em} = \lambda_{em}$ (H$_2$O) – $\lambda_{em}$ (CHCl$_3$); [d] TMA = tetramethylammonium; [e] TBA = tetra(*n*-butyl)ammonium.

Extraction with salts of transition metal ($Cu^{II}$ triflate) and lanthanide ($La^{III}$ triflate) ions was also attempted; phase transfer in methanol was observed but the QDs could not be dissolved in water. As the hydration of $Cu^{2+}$ and $Ln^{3+}$ ions is strongly exothermic, it can be hypothesized that the lack of solubility of the QDs in water is due to a very strong binding of copper and, in particular, lanthanum ions to the carboxylate residues on the QD surface. Moreover, the QDs suspended in methanol exhibited no luminescence, most likely because these ions can enable electron-transfer quenching pathways.[34] The same result was observed when $[Ru^{II}(bpy)_3](ClO_4)_2$ (bpy = 2,2′-bipyridine) was used in the extraction step.[35]

***Modulation of the QDs solubility.*** During the experiments performed to investigate the influence of the extraction step (Scheme 2b) in the ligand exchange process (Figure 2), we realized that the nature of the $M^+X^-$ species can significantly affect the solubility pattern of the final QDs in different solvents. We thus monitored the solubility of different phase-transferred QDs in a range of solvents of varying polarity, from hexane to water.

The results of these tests, summarized in Table 4, show that using the same cap exchange procedure and the same capping agent (lipoic acid) it is possible to tune the solubility of the QDs in different solvents simply by changing the type of salt used in the resin extraction step. DHLA-capped QDs possess a negatively charged surface wherein carboxylate residues are paired with $M^+$ counterions; evidently, the nature of such cations affects the ability of the QDs to be dispersed in different solvents. Although counterion effects in nanocrystals capped with ionic ligands have been described,[36] reports on the role of counterions for tuning the solubility of charged QDs in polar solvents are unprecedented.

**Table 4.** Solubility chart in various solvents at room temperature of CdSe-3ZnS QDs (entry 9 in Table 1) capped with DHLA and different $M^+$ countercations.[a]

| | Solvent (ε[b]) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| $M^+$ | Hexane (1.89) | Toluene (2.38) | Chloroform (4.81) | THF (7.58) | Acetone (20.7) | Methanol (32.7) | Acetonitrile (35.9) | DMSO (46.5) | Water (80.2) |
| $Li^+$ [c] | | ● | ● | | | | | | ● |
| $Na^+$ [c] | | | ● | ● | | | | | ● |
| $K^+$ [c] | | | | | | ● | | | ● |
| $Mg^{2+}$ [c] | | | | | | | | | |
| $Ca^{2+}$ [c] | | | | | | | | | |
| $NH_4^+$ [c] | | | ● | | | | | | |
| $TMA^+$ [c] | | | | | | ● | | ● | ● |
| $TEA^+$ [c] | | | | | | ● | ● | | ● |
| $TBA^+$ [c] | | | ● | ● | ● | ● | ● | ● | ● |
| $TOA^+$ [c] | | | | | | ● | | | |
| $CTA^+$ [d] | ● | ● | ● | ● | | | | | |
| nQDs[e] | ● | ● | ● | ● | | | | | |

[a] Circles indicate that the QDs form a homogeneous solution at the 0.5-1.0 μM concentration level. TMA = tetramethylammonium; TEA = tetraethylammonium; TBA = tetra(*n*-butyl)ammonium; TOA = tetra(*n*-octyl)ammonium; CTA = cetyltrimethylammonium. [b] Relative dielectric constant. [c] Hydroxide, nitrate, perchlorate or triflate salts. [d] bromide salt. [e] Native QDs TOP/TOPO capped.

In all the dispersions listed in Table 4 the nanocrystals maintained their spectroscopic properties; the shifts of the absorption and emission peaks with respect to the native QDs did not exceed 5 nm (see, e.g., Figure 7).

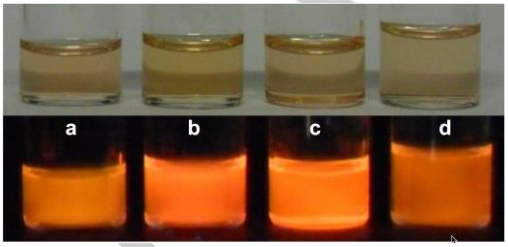



**Figure 7.** Photographs of 0.5 μM CdSe-5ZnS QDs (entry 7 in Table1) capped with $DHLA^-TBA^+$ in methanol (a), acetonitrile (b), DMSO (c) and water (d) under ambient light (top) and UV light (365 nm, bottom). Adapted by permission of the Royal Society of Chemistry.[26a]

A rationalization of the solubility pattern shown in Table 4 can be attempted considering that dissolution thermodynamics is determined by the combination of endothermic (breaking of the interactions between QDs in the solid phase and between solvent molecules) and exothermic (solvation of the polyanionic QDs and their counter-cations) processes. The large solvation enthalpies of alkali cations and quaternary ammonium ions with short alkyl groups (e.g. $TMA^+$) in polar solvents may explain why the corresponding $DHLA^-M^+$ QDs are soluble in methanol and/or water. Although it may be anticipated that tetraalkylammonium ions with longer chains could render the QDs compatible with less polar organic solvents, a clear trend was not observed. Specific effects may be significant in particular cases: for example, cation-π interactions of the lithium ions with the aromatic solvent molecules could explain the solubility of $DHLA^-Li^+$ QDs in toluene. It is worth to note that QDs capped with $DHLA^-$ and $TBA^+$ ions are soluble in a large variety of solvents, ranging from chloroform to water (Table 4, Figure 7). This finding indicates that such bulky cations afford a good balance, in terms of solid phase and solvation energies, in solvents as different as water and chloroform.

## Conclusions

In this work we have described a general methodology for the chemical activation of lipoic acid-type ligands and their successive utilization for phase transfer of semiconductor quantum dots in polar and aqueous solvents. Our results show that the protocol is applicable to different types of nanocrystals and a variety of dithiolane-based ligands, and that the resulting QDs maintain their optical properties (in particular, an intense luminescence) and long-term colloidal stability.

The procedure is handy and has several practical advantages:

(i) the resin-supported reactant can be separated from the reaction product simply by decantation or filtration;
(ii) the reduction can be performed at room temperature and in aerated conditions;
(iii) the reaction time is much shorter (ca. 1 h) than that required when $NaBH_4$ is used (ca. 5 h);
(iv) the ligand can be quickly reduced, just in the amount necessary for the successive cap exchange, thus avoiding the preparation of DHLA stock solutions and their storage at low temperature under inert atmosphere.

Moreover, in the case of ligand exchange with lipoic acid, our method enables the precise modulation of the QD solubility in a wide variety of organic solvents through the choice of the countercations associated with the carboxylate moieties of the surface-attached DHLA species. The fact that QDs capped with the same organic ligand exhibit significantly different solubility properties is indeed a remarkable finding.

Engineering the surface capping layer of QDs constitutes a versatile approach to modulate their properties or to implement new functions. Thus, the development of simple and efficient routes for the chemical modification of the nanocrystals surface is desirable. In particular, the ability to predetermine the solubility of QDs in common solvents without affecting their photophysical behaviour is a necessary step forward toward the application of these nanomaterials.

## Experimental Section

***Reagents and Solvents.*** Lipoic acid (LA, (±)-α-Lipoic acid, ≥98%), sodium borohydride ($NaBH_4$, ≥98%), anion exchange resin $Cl^-$ loaded (Amberlite® IRA-400 chloride form), cadmium oxide (99.99%), selenium powder (99.5%, 100 mesh), sulphur powder (99.98%), tris(*n*-octyl)phosphine oxide (TOPO, 90%), tris(n-octyl)phosphine (TOP, 97%), *n*-hexadecylamine (HDA, 98%), *n*-octadecylamine (ODA, 97%), oleic acid (OA, ≥99%), diethyl zinc (1 M solution in *n*-heptane), sodium hydroxide (NaOH, ≥98%), lithium hydroxide monohydrate (LiOH, >99.0%), potassium hydroxide (KOH, ≥98%), tetramethylammonium hydroxide (TMAOH, ~97%), tetraethylammonium perchlorate ($TEAClO_4$, 99%), tetraethylammonium nitrate ($TEANO_3$, >99%), tetra(*n*-octyl)ammonium hydroxide (TOAOH, 20% in methanol), cetyltrimethylammonium bromide (CTABr, ≥99.0%), and 5,5′-dithiol-bis(2-nitrobenzoic acid) (DTNB, ≥98%) were purchased from Sigma Aldrich and Fluka, and were used without further purification. Tetra(*n*-butyl)ammonium hydroxide (TBAOH, 25% in methanol) was purchased from J. T. Baker Chemical Co. Synthetic grade hexane, toluene, $CHCl_3$, acetone and methanol were purchased from Sigma-Aldrich. Spectroscopic grade tetrahydrofuran, acetonitrile and dimethyl sulfoxide were purchased from Merk-Uvasol. A Milli-Q Millipore system was used for the purification of water (resistivity ≥ 18 MΩ·cm). Millipore Amicon Ultra-0.5 mL centrifugal filters (30000 Da cut off) were purchased from Sigma-Aldrich.

***Instrumental measurements.*** TEM experiments were carried out with a Philips CM 100 transmission electron microscope operating at 80 kV. A drop of QD solution was deposited on a Formvar resin film supported on conventional copper microgrids and the sample was dried under vacuum. DLS measurements were performed with a Malvern Nano ZS instrument equipped with a 633 nm laser diode. The measurements were carried out at room temperature in air-equilibrated solutions placed in 1 cm quartz cuvettes. Electronic absorption spectra were measured at room temperature on air-equilibrated solutions of the samples contained in quartz cuvettes (1-cm optical path length). The concentration of the solutions was typically $10^{-7}$ M. Absorption spectra in the 190-1100 nm range were recorded with a Perkin Elmer λ45 spectrophotometer. The precision on the wavelength values was ± 1 nm. Luminescence spectra in the 250-900 nm range were recorded with a Perkin Elmer LS50 or an Edinburgh Instruments FLS920 spectrofluorimeter equipped with a Hamamatsu R928 photomultiplier. Luminescence spectra were recorded at room temperature (ca. 295 K) on solutions of samples contained in quartz cuvettes (1-cm optical path length). Luminescence quantum yields were determined with the optically dilute method using Rhodamine 6G (Φ = 0.94 in EtOH) as a standard.[37]

***Synthesis of the Quantum Dots.*** Hydrophobic core CdS and CdSe semiconductor nanocrystal quantum dots were prepared following the procedures published by Peng and coworkers[14cd] with minor modifications. Core-shell CdSe-ZnS QDs were prepared by overcoating a CdSe core with a ZnS shell using either SILAR[14e] or one-time-precursors-injection[14b,38] approaches. The core diameter and the QD concentration were estimated according to published methods.[39] The shell thickness was estimated as reported in each synthetic protocol.[14be,38] The resulting nanocrystals were covered with TOPO (*tris*-[*n*-octylphosphine]oxide), TOP (*tris*-[*n*-octyl]phosphine), OA (oleic acid), ODA (*n*-octadecylamine) and/or HDA (*n*-hexadecylamine) as passivating surface ligands to prevent particle aggregation.

***Preparation of the Borohydride-Exchanged Resin.*** The synthesis of the $BH_4$-resin was carried out according to a published procedure.[28] Briefly, 4 g of Amberlite® IRA-400 (chloride form) resin were placed in a 100 mL one-neck round-bottom flask equipped with a stirring bar. A water solution of $NaBH_4$ (920 mg in 40 mL) was added and the neck was sealed with a rubber seal. The mixture was gently stirred for at least 3 hours in order to allow the complete exchange of the chloride anions with borohydride. The resin was filtered and washed with water to remove the excess of sodium borohydride and sodium chloride released during the exchange reaction. The resin beads were then dried under reduced pressure. The amount of $BH_4^-$ per g of resin was estimated via acid titration.

***Ligand Reduction.*** In a 4-mL glass vial a solution of lipoic acid ($2.66\times10^{-5}$ mol in 500 μL of MeOH) was mixed with 19 mg of $BH_4^-$ resin (2.5 mmol $BH_4^-$ per g). The mixture was stirred at 400 rpm for at least 30 min. The methanol layer was removed and the beads were washed 3 times with 500 μL of methanol to remove unreacted lipoic acid and hydrolyzed borohydride products. Methanol (500 μL) and $M^+X^-$ (from 1.2 to 4 eq with respect to the $BH_4^-$ content) were then added to the beads. The mixture was stirred for at least 30 min in order to extract the reduced lipoic acid from the resin. In the case of hydroxide salts, 1.2 eq of $M^+OH^-$ and 30 min of stirring were enough to extract the reduced ligand

from the resin; perchlorate, nitrate and bromide salts required a larger amount (up to 4 eq) and a longer stirring time (up to 3 hours). The beads were washed two times with 200 μL of fresh methanol to recover as much reduced ligand as possible. The methanol fractions were combined and the residual solid was discarded. In the case of ligands consisting of a lipoic acid moiety attached to a hydrophilic poly(ethylene glycol) chain (LA-TEG, LA-$PEG_{400}$),[18] the reaction was slower than for parent LA, and no base was required to extract the reduced ligand from the resin.

***QD Cap exchange and phase transfer.*** The desired amount of QDs (from 1/20000 to 1/30000 QD/lipoic ligand ratio, depending on QD size) was dissolved in 1 mL of hexane. The solution was added to the vial containing the reduced ligand (see above) in methanol, thus forming a biphasic mixture. The transfer of QDs from the hexane to the methanol layer was immediately observed. To ensure a complete cap exchange, the biphasic system was stirred for 2-3 hours or, in the case of larger QDs, overnight. The methanol layer appeared clear or turbid, depending on the counter-cation employed in the previous step (see Table 2). The hexane layer (turned colorless) was removed and the methanol suspension was washed five times with hexane (2 mL) in order to remove unreacted nanocrystals and native hydrophobic ligands. The methanol was evaporated under reduced pressure and resulting dried QDs were dissolved in proper solvents for further studies. In the case of water solutions, the mixture was first passed through a syringe filter (0.46 μm pore size) to remove possible large aggregates and was successively purified with 3 cycles of dilution/concentration with a centrifugal filter (Amicon Ultra-0.5 mL, 30 kDa, 7000 rpm, 12 minutes) to eliminate the excess of free ligand. Alternatively, hydrophobic QDs were added as solid/paste to the solution of reduced ligand in methanol, thus obtaining a suspension. All the successive isolation and purification steps were performed as described above.

***Determination of the DHLA yield.*** The amount of DHLA in solution after extraction from the BER was determined by measuring the concentration of its thiol groups using Ellman's reagent (5,5′-dithiol-bis(2-nitrobenzoic acid), DTNB).[30] 10 μL of a MeOH solution containing a $DHLA^{-}M^{+}$/LA mixture after extraction from the resin (initial LA concentration, $1.6\times10^{-2}$ M) were mixed with 2 mL of Ellman's reagent solution ($2.1\times10^{-4}$ M in 5 mM phosphate buffer at pH 7.5).[29] The formation of the reaction product, the 5-thio-2-nitrobenzoate ($TNB^{2-}$), was monitored recording the absorbance at 412 nm, and the concentration of the SH groups was determined using a molar absorption coefficient of 14150 $M^{-1}$ $cm^{-1}$ for $TNB^{2-}$ at 412 nm.[40] The DHLA concentration was calculated as [SH]/2.

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**Keywords:** CdSe • nanoparticle • phase transfer • semiconductor nanocrystal • solubility

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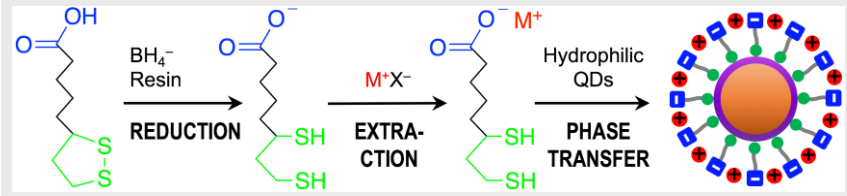


The exchange with ligands comprising the 1,2-dithiolane moiety, activated by means of a borohydride-loaded resin, enables the transfer of hydrophobic quantum dots in polar solvents while preserving their spectroscopic properties. If lipoic acid is used as the capping ligand, the solubility of the dots in solvents from hexane to water can be finely tuned by the choice of the countercations associated with carboxylate residues present on the nanocrystal surface.

**Photoactive semiconductor nanocrystals**

*Marcello La Rosa, Tommaso Avellini, Christophe Lincheneau, Serena Silvi, Iain A. Wright, Edwin C. Constable and Alberto Credi**

***Page No. – Page No.***

**An efficient method for the surface functionalization of luminescent quantum dots with lipoic acid-based ligands**