# Direct Synthesis of Aqueous Quantum Dots through 4,4′-Bipyridine-Based Twin Ligand Strategy

Mausam Kalita, Sreeram Cingarapu, Santanu Roy, Seok Chan Park, Daniel Higgins, Ryszard Jankowiak, Viktor Chikan, Kenneth J. Klabunde, and Stefan H. Bossmann*

Department of Chemistry, Kansas State University, 213 CBC Building, Manhattan, Kansas 66506-0401, United States

S *Supporting Information*
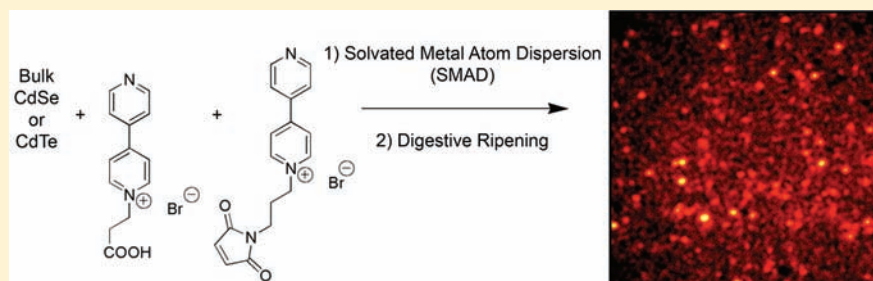
ABSTRACT: We report a new class of derivatized 4,4′-bipyridinium ligands for use in synthesizing highly fluorescent, extremely stable, water-soluble CdSe and CdTe quantum dots (QDs) for bioconjugation. We employed an evaporation–condensation technique, also known as solvated metal atom dispersion (SMAD), followed by a digestive ripening procedure. This method has been used to synthesize both metal nanoparticles and semiconductors in the gram scale with several stabilizing ligands in various solvents. The SMAD technique comprised evaporation condensation and stabilization of CdSe or CdTe in tetrahydrofuran. The as-prepared product was then digestively ripened in both water and dimethyl formamide, leading to narrowing of the particle size distributions. The ligands were synthesized by nucleophilic substitution (S_N2) reactions using 4,4′-bipyridine as a nucleophile. Confocal microscopy images revealed the orange color of the nanocrystalline QDs with diameters of ∼5 nm. The size has been confirmed by using transmission electron microscopy. As a part of our strategy, 85% of the 4,4′-bipyridinium salt was synthesized as propionic acid derivative and used to both stabilize the QDs in water and label basic amino acids and different biomarkers utilizing the carboxylic acid functional group. Fifteen percent of the 4,4′-bipyridinium salt was synthesized as *N*-propyl maleimide and used as a second ligand to label any protein containing the amino acid cysteine by means of a 1,4-Michael addition.

■ INTRODUCTION

The discovery of quantum dots (QDs) and their bright luminescence has inspired scientists to explore their application as bioimaging agents in medical diagnostics,[1,2] as photosensitizing agents in the photodynamic therapy of cancer,[3,4] and as components of solar cells[5,6] and light-emitting devices (LEDs).[7,8] QDs have size- and composition-tunable electronic and optical properties with sharp Gaussian emission spectra, in addition to large absorption coefficients across a wide spectral range.[9−11] These are definite advantages of QDs over traditional dyes as imaging agents in vivo and in vitro. Most reported syntheses of QDs are carried out by using hydrophobic ligand encapsulation.[12,13] However, the importance of synthesizing biocompatible, aqueous QDs is immense, especially for the purpose of labeling monoclonal antibody and biomarkers. Dubois et al. reported a synthesis of aqueous QDs by exchanging the initial hydrophobic ligand trioctylphosphine oxide (TOPO) with the hydrophilic ligand dithiocarbamate. This ligand exchange method required the presence of a ZnS shell around the CdSe core to prevent photoluminescence (PL) quenching.[14] Other synthesis procedures involved QD surface modification through imidazole-based random copoly-

mer ligands[15] and surfactant/lipid micelles,[16] resulting in large (diameter >10 nm) supramolecular assemblies. Chemical aerosol flow method also has been employed to synthesize CdTe/CdS//ZnS core/shell/shell QDs, which lack the freedom to choose ligands of interest.[17] These aqueous QDs can be monoconjugated through either carboxylate terminal or amine terminal groups. Direct synthesis of aqueous QDs from bulk CdSe or CdTe by "twin ligands" for bioconjugation was not known to date. Our synthesis comprises the environment friendly evaporation–condensation method known as solvated metal atom dispersion (SMAD) technique,[18,19] followed by digestive ripening to obtain stable, monodisperse, orange-colored QDs. The SMAD technique has already been used to synthesize hydrophobic QDs,[20] both aqueous and nonaqueous gold colloids,[20−23] and silver nanoparticles with biocidal activity.[23] The biggest advantages of this synthesis are the independence of the solvent and the ligand choice, no metal salt byproduct formation, and the possibility to scale up the reaction to gram scale for industrial applications. The choice of

4,4′-bipyridinium salts as ligands for QD stabilization and bioconjugation was inspired by the success of ligand exchange experiments in our lab, although the stability of QDs after ligand exchange was not sufficient for further application. We decided to use 4,4′-bipyridinium salts for direct surface passivation of CdSe and CdTe QDs through SMAD. The synthesis of aqueous CdSe and CdTe QDs was achieved by the following twin ligands: (1) 4,4′-bipyridinium carboxylic acid (**3**) used for water solubility through H-bonding with water and (2) 4,4′-bipyridinium maleimide (**7**) used for coupling with cysteine-SH through 1,4-conjugate addition or Michael addition reaction (Figure 1).
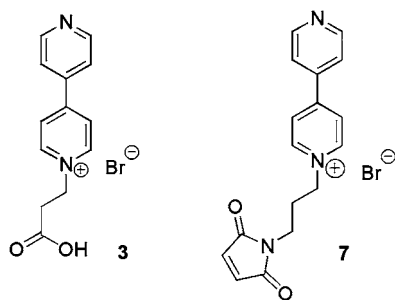

Figure 1. 4,4′-Bipyridinium salt-based twin ligands used to synthesize aqueous QDs.

QDs synthesized in gram quantities in a SMAD reactor in water had narrow size distributions from 4 to 4.5 nm. This is achieved by using the "digestive ripening" technique pioneered at Kansas State University.[24−26] This process involves refluxing of the as-prepared SMAD colloid in a solvent resulting in a remarkable narrowing of the size distribution observed in transmission electron microscopy (TEM) experiments.

■ EXPERIMENTAL SECTION

General Synthesis of a Water-Soluble CdSe/CdTe-Colloid Using 4,4′-Bipyridinium Ligands for Stabilization. A 39-boron nitride crucible (from Mathis) was assembled in the SMAD reactor, and 0.20 g of CdSe (1.04 mmol) was added to the crucible. Ligand **3** (9.71 g, 31.4 mmol) and ligand **7** (2.2 g, 5.2 mmol), dissolved in 40 mL of degassed nanopure water, were placed at the bottom of the reactor together with a stir bar. The reactor was attached to 100 mL of degassed tetrahydrofuran (THF) in a Schlenk tube. The reactor was then cooled down to 77 K by immersing it in a liquid nitrogen filled dewar, followed by the complete evacuation of the reactor until a vacuum or 0.53 Pa was reached. Fifteen milliliters of THF was evaporated in 30 min forming a layer of solvent on the walls of the reactor. Bulk CdSe on the crucible was heated slowly and cocondensed with THF (60 mL) over a period of 3 h. The frozen matrix had a brownish red color at the end of the vapor deposition process. Once the process was complete, the dewar was removed, and the reactor was filled with argon. The frozen matrix was melted by heating the exterior of the reaction vessel using a heat gun. The melted matrix was allowed to stir for 30 min. The brown red matrix was siphoned under argon into a Schlenk tube.

The Schlenk tube containing the freshly prepared CdSe-colloid, which was stabilized by the twin-4,4′-dipyridinium ligands in THF/ water and was connected to a vacuum line, and the THF was evaporated overnight. The total volume of the final colloid was 40 mL containing 0.20 g of CdSe.

A CdTe-colloid was also synthesized using the above procedure in which CdTe (0.2 g, 0.83 mmol) was added to the crucible while ligand **3** (7.73 g, 25 mmol) and ligand **7** (1.74 g, 4.15 mmol) were dissolved in degassed nanopure water (40 mL).

Digestive Ripening. The CdSe-colloid, stabilized by the twin-4,4′-dipyridinium ligands in water, was divided into two parts. Twenty milliliters of this suspension was filled in a 100 mL round-bottom flask with a glass window for UV/vis detection. The round-bottom flask was connected to an UV/vis spectrometer on-a-chip through an optical fiber for the recording of continuous UV/vis spectra. The colloid was refluxed under argon for 8 h.

Another 20 mL of colloid was subjected to high vacuum to evaporate the water, thus forming the dry product. It was transferred to a 100 mL round-bottom flask and dissolved in 20 mL of dry dimethyl sulfoxide (DMF). Five milliliters of oleylamine was also added to increase the rate of monodisperse particle formation.[19] The reaction was refluxed for 3 h under argon (T = 154 °C). QDs in DMF were placed in an ultracentrifuge (8000 rpm) for 15 min, and the precipitate was dissolved in water. The synthesis of water-soluble CdSe- and CdTe-nanoparticles is summarized in Scheme 1. The overall yield of the synthesis of CdSe was 82 ± 2% and for CdTe was 80 ± 2%.

Scheme 1. Flow Diagram of Synthetic Steps of Water-Soluble QDs through Evaporation−Condensation (a) CdSe Ripened in DMF for 8 h and (b) CdTe QDs Ripened in DMF for 3 h
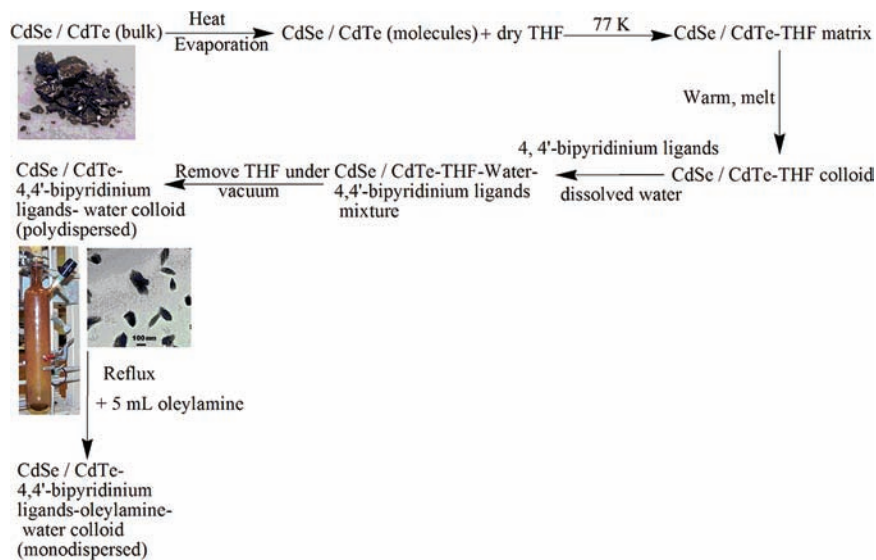
Toluene-soluble CdTe QDs were synthesized in SMAD using trioctylphosphine-hexadecylamine ligands followed by refluxing in toluene and *t*-butyltoluene as reported earlier.[20] The photostability of toluene-soluble QDs was to be compared with aqueous QDs to test the viability of aqueous QDs for biomedical imaging.

Nanoparticle Characterization. *TEM.* TEM images were taken on a Philips CM100 operating at 100 kV. The samples were prepared by a drop of 3 μL of CdSe and CdTe solution in water on a carbon-coated Formvar copper grid. The grids were allowed to dry overnight under vacuum in a desiccator.

X-ray Diffraction (XRD). Powder XRD (Scintag XDS 2000 spectrometer) was used to characterize the composition of the QDs. Cu Ka radiation was used with a curved crystal graphite monochromator. The operating range for the X-ray target was 45 kV and 45 mA. The X-ray scans were in range of 20 > 2*f* > 70°.

UV/vis Spectroscopy. UV/vis absorption spectra were measured by using a DH-2000 optical spectrophotometer (Ocean Optics Inc.)

Fluorescence Spectroscopy. Fluorescence spectra were obtained by using Fluoro Max-2 instrument from HORIBA Jobin Yvon Company. These samples were excited at 400 nm with slit width of 5 nm.

PL Spectroscopy. The PL quantum yield of CdSe and CdTe was calculated relative to Rhodamine 6G in methanol assuming its PL quantum yield as 95%.[27,28]

$$\Phi_{em} = \Phi_s \frac{I_{QD}}{I_s} \frac{A_s}{A_{QD}} \frac{n_{QD}^2}{n_s^2}$$

where I_{QD} and I_s (s, standard) are the integrated emission peak areas, A_{QD} and A_s are the optical absorptions (<0.1) at 480 nm, n_{QD} and n_s are the refractive indices of the solvents at 480 nm, and Φ_{em} and Φ_s are the PL quantum yield for the QD and standard, respectively.

■ RESULTS AND DISCUSSION

The SMAD technique was first reported in 1986. It has been successfully used to synthesize metal nanoparticles and

Scheme 2. Synthesis of Carboxylic Acid Derivative of 4,4′-Bipyridine (3)
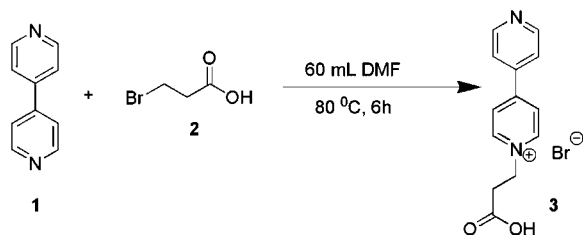
semiconductor nanocrystals.[20,25,29] We have performed the facile synthesis of two 4,4′-bipyridinium ligands with high yields affording grams of the products, which were required for stabilizing CdSe and CdTe semiconductor nanocryctals synthesized by SMAD.
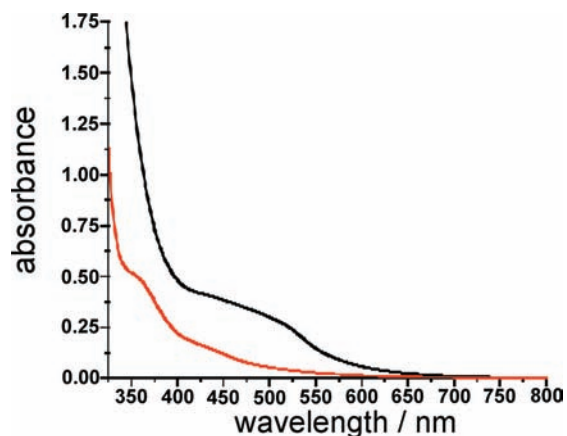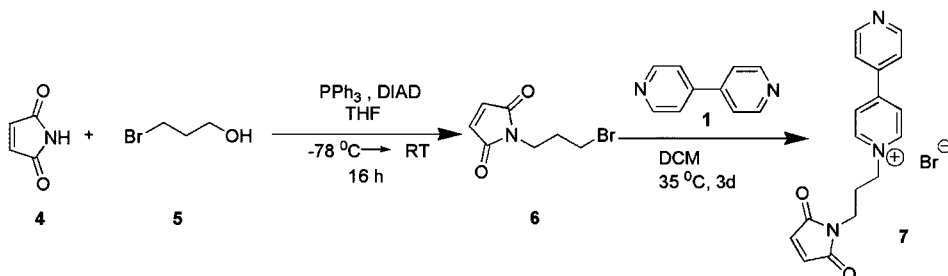
Figure 2. UV−vis spectra of CdSe ripened in water and in DMF: black line, reflux in DMF (8 h); red line, reflux in water (8 h).

Synthesis of the 4,4′-Bipyridine-Based "Twin Ligands". The choice of the ligand was inspired by our preliminary work in ligand exchange between 4,4′-bipyridine and TOPO, although the QDs resulted after the ligand exchange had broad size distribution making them less useful for bioconjugation. The two 4,4′-bipyridine-based "twin ligands" were chosen, because they feature very similar shapes [the dihedral angles between the pyridine and the pyridinium rings are 33.4° (3) and 34.1° (7) according to AM1 calculations] and charge densities at N_6 [−0.084 (3) and −0.087 (7); see Figure S17 in the Supporting Information], the nitrogen center for coordination to CdSe and CdTe. It is our working hypothesis that we can vary the ratio of the twin ligands (3 and 7) at the QDs' surfaces without significantly changing the properties of the organic layer around the QDs. The logic behind the use of 85% carboxylic acid terminal derivative of 4,4′-bipyridine (3) was to solubilize the QDs in water. The one step synthesis of (3) consisted of a nucleophilic substitution reaction by a S_N2 mechanism in DMF affording 80.2% yield (Scheme 2).

Our initial attempt to use a terminal maleimide derivative of 4,4′-bipyridine (7) as ligand for QD stabilization was not successful, as the ligand was water-soluble only before binding with the QDs, resulting in their rapid aggregation after QD synthesis. Compound 7 was prepared in a two-step chemical synthesis. The maleimide (4) served as a nucleophile in a Mitsunobu reaction, leading to compound 6 in 70% yield.[30] In the second step, 4,4′-bipyridine acted as a nucleophile to displace the bromide in the C−Br bond of 6. It is important to permit this reaction to run for 3 days at 35 °C to form the monosubstituted product (Scheme 3).
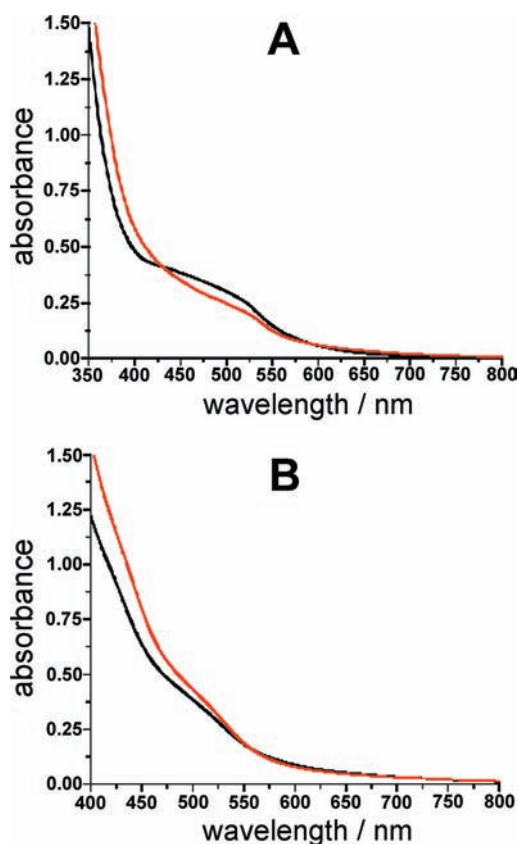
Scheme 3. Synthesis of Maleimide Derivative of 4,4′-Bipyridine (7)

Figure 3. Evolution of absorbance spectra for CdSe (A) and CdTe (B) during digestive ripening in DMF. (A) Red line, after 4 h of reflux; black line, after 8 h of reflux. (B) Black line, after 1 h of reflux; red line, after 3 h of reflux.

The 85:15/3:7 ligand ratio approach solved not only the water solubility problem but also introduced two sites for potential double bioconjugation. The double bioconjugation schemes through −COOH and maleimide termini will be reported in an upcoming paper.

UV/vis Data Analysis. It is noteworthy that the positions of the UV/vis absorption maxima/shoulders of the CdTe QDs that have been prepared in DMF and in water differ by 50 nm. In accordance with the literature, the observed red shift can be attributed to a larger particle size when ripened in DMF, as compared to in water[31,32] (Figure 2). The CdTe QDs growth was expedited by addition of 5 mL of oleylamine, which acted as a weak amine stabilizer, thereby helping with growth kinetics.[27]

The evolution of the particle size during digestive ripening of QDs was monitored through dynamic UV/vis spectra. It was observed that there was change in the particle size distribution as well as enhanced absorbance as the particles were ripened for extended period of time (Figure 3). It must be noted that the successful digestive ripening procedure had to be performed in DMF in the presence of oleylamine to be efficient.

The fluorescence spectra of CdSe and CdTe QDs complimented the UV/vis data, as there was a red shift by about 50 nm in CdTe spectrum, emphasizing larger sized CdTe QDs (Figure 4).

The (quantum yield) QY of the aqueous QDs was found to be 12%, which is comparable to QY of 16−28% for QDs in organic solvents, when QDs are excited at 390 nm with slit width of 5 nm[18,25] (Table 1). Quantum yields in the range from
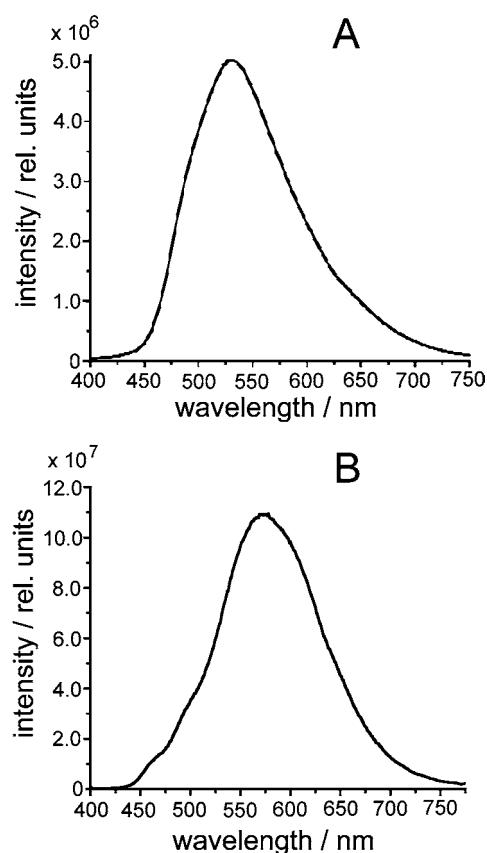

Figure 4. Fluorescence spectra of CdSe and CdTe QDs synthesized by twin ligand strategy. (A) Water-soluble CdSe synthesis, λ_{EM}(max) = 530 nm. (B) Water-soluble CdTe synthesis, λ_{EM}(max) = 572 nm; concentration, 5.0 mM (CdSe).

Table 1. Quantum Yield of Water-Soluble QDs

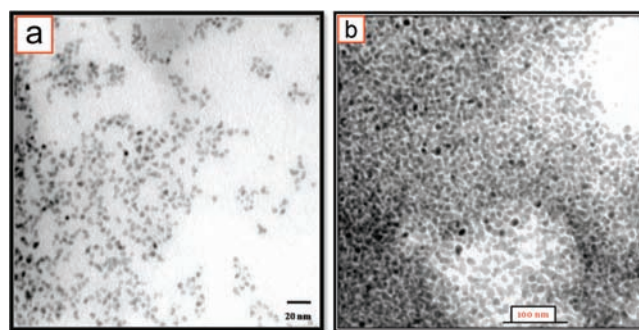| QDs	absorbances	$\lambda_{max,fluorescence}$ (nm)	QY (%)
CdTe	0.09	572	12 ± 1
CdSe	0.09	530	25 ± 2

Figure 5. TEM images of (a) CdSe ripened in DMF for 8 h and (b) CdTe QDs ripened in DMF for 3 h.

Table 2. Comparison of Lifetime of Aqueous QDs with Organic QDs

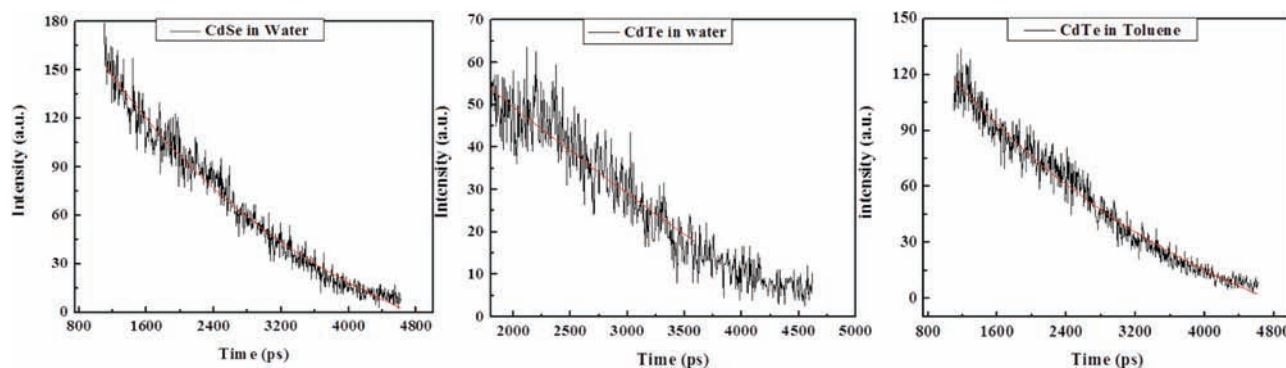| QDs	lifetime (ns)
CdTe in water	13.5 ± 1.0
CdSe in water	3.0 ± 0.5
CdTe in toluene	3.5 ± 0.5

Figure 6. Fluorescence decay of CdSe in water, CdTe in water, and CdTe in toluene after exciting with Ti:sapphire laser (λ_{EX} = 390 nm).

0.5 to 0.9 for QDs that have been prepared in nonaqueous systems have been reported.[31] The significantly lower QY of QDs from aqueous preparations may be attributed to the presence of water in the organic ligand sphere. We did not find evidence from XRD spectroscopy for chemical reactions occurring at or within the QDs (Figure S5 in the SI).

The TEM images showed the average particle size of both CdSe and CdTe QDs to be 4.0 and 4.5 nm, respectively (Figure 5). The histogram of the QDs size distribution, as obtained by using IMAGE/NIH, is shown in Figure S4 in the SI. The orange color of these QDs was confirmed with confocal microscopy.

Time-Resolved Decay Study of QDs. The photostability of aqueous QDs was compared with QDs synthesized in toluene through SMAD technique-digestive ripening[20,21] (Table 2). The lifetime of the samples was measured in a time-domain spectrometer, which used cavity-dumped output of a mode-locked Ti:sapphire laser (λ_{max} = 780 nm, repetition rate = 2 MHz, average power = ~80 mW) passing through a nonlinear crystal to double the frequency (λ_{max} = 390 nm), which was used to excite CdSe in water, CdTe in water, and CdTe in toluene and collected by 520, 570, and 610 nm filters, respectively. The Ti:sapphire laser produced 20 fs pulse, and the time resolution of our measurement is 70 ps. Suitable band-pass filters collected the emitting light. The fluorescence was collected to the perpendicular direction of the incident light to avoid any laser light going to the detector. A sensitive photodiode was used to collect the emitted photons. The collected data were then fit with exponential functions, and the best fit was obtained by either single or multiple exponential functions. Then, the fluorescence decay time was obtained from the fitted data (Figure 6).

These results suggest that the aqueous CdTe QDs are of similar photostability as their toluene soluble analogues. This is an important finding, because it indicates that these water-soluble materials can be used as cellular probes. However, the stability of the QDs in aqueous solution is achieved at the expense of their fluorescence quantum yields. It should be noted that our data prove that the QDs are not aggregating/oxidizing in water, as this could have been expected from CdTe in water. Therefore, the photostable aqueous QDs have potential applications in both in vitro and in vivo imaging.

CONCLUSIONS

We have achieved the direct synthesis of aqueous CdSe and CdTe QDs by SMAD, followed by digestive ripening. The synthesis of QDs from aqueous precursors in the presence of two chemically closely related ligands ("twin ligands") leads to water-soluble QDs with tunable ligand spheres. The results revealed that water-based QDs are equally photostable as conventionally prepared QDs. Although the fluorescence quantum yields of water-based QDs are lower than of conventional QDs, they are sufficient for biological applications. We will report the use of these QDs as imaging "tools" in detecting DNA−estrogen adducts, potential biomarkers for breast and prostate cancer.[33−35] In vivo tumor imaging with these QDs conjugated with tumor homing peptide iRGD[36] is currently carried out. Beside the water solubility, another advantage of these QDs is the possibility of double bioconjugation through both −COOH and maleimide termini. We believe that aqueous QDs will open a window of opportunity for biomedical application in future.

ASSOCIATED CONTENT

ⓢ Supporting Information

Chemical synthesis of 4,4′-bipyridinium salt-based ligand, confocal microscopy images. photostability experiment, the laser experiment parameters, data processing, ζ-potential of water-soluble QDs, ^{1}H and ^{13}C NMR spectra, net atomic charges and dipole contributions, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Tel: 785-532-6817. Fax: 785-532-6666. E-mail: sbossman@ksu.edu.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Bruchez, M. Jr.; Moronne, M.; Gin, P.; Weiss, S.; Alivisatos, A. P. *Science* **1998**, *281*, 2013−2105.

(2) Dubertret, B; Skourides, P.; Norris, D. J.; Noireaux, V.; Brivanlou, A. H.; Libchaber, A. *Science* **2002**, *38*, 2759−1762.

(3) Rakovich, A.; Savateeva, D.; Rakovich, T.; Donegan, J. F.; Rakovich, Y. P.; Kelly, V.; Lesnyak, V.; Eychmuller, A. *Nanoscale Res. Lett.* **2010**, *5* (4), 753−760.

(4) Chen, J. Y.; Lee, Y. M.; Zhao, D.; Mak, N. K.; Wong, R. N. S.; Chan, W. H.; Cheung, N. H. *Photochem. Photobiol.* **2010**, *86* (2), 431−437.

(5) Huynh, W. U.; Peng, X. G.; Alivasatos, A. P. *Adv. Mater.* **1999**, *11*, 923−927.

(6) Huynh, W. U.; Dittmer, J. J.; Alivasatos, A. P. *Science* **2002**, *295*, 2425−2427.

(7) Caruge, J.-M.; Halpert, J. E.; Bawendi, M. G. *Nano Lett.* **2006**, *6*, 2991−2994.

(8) Achermann, M.; Petruska, M. A.; Koleske, D. D.; Crawford, M. H.; Klimov, V. I. *Nano Lett.* **2006**, *6*, 1396−1400.

(9) Dabbousi, B. O.; Rodriguez-Viejo, J.; Mikulec, F. V.; Heine, J. R.; Mattoussi, H.; Ober, R.; Jensen, K. F.; Bawendi, M. G. *J. Phys. Chem. B* **1997**, *101*, 9463−9475.

(10) Zimmer, J. P.; Kim, S.-W.; Ohnishi, S.; Tanaka, E.; Frangioni, J. V.; Bawendi, M. G. *J. Am. Chem. Soc.* **2006**, *128*, 226−2527.

(11) Peng, Z. A.; Peng, X. *J. Am. Chem. Soc.* **2001**, *123*, 183−184.

(12) Murray, C. B.; Norris, D. J.; Bawendi, M. G. *J. Am. Chem. Soc.* **1993**, *115*, 8706−8715.

(13) Talapin, D. V.; Rogach, A. L.; Kornowski, A.; Haase, M.; Weller, H. *Nano Lett.* **2001**, *1*, 207−211.

(14) Dubois, F.; Mahler, B.; Dubertret, B.; Doris, R.; Mioskowski, C. *J. Am. Chem. Soc.* **2002**, *129*, 482−483.

(15) Liu, W.; Greytak, A. B.; Lee, J.; Wong, C. R.; Park, J.; Marshall, L. F.; Jiang, W.; Curtin, P. N.; Ting, A. Y.; Nocera, D. G.; Fukumura, D.; Jain, R. K.; Bawendi, M. G. *J. Am. Chem. Soc.* **2010**, *132*, 472−483.

(16) Fan, H.; Leve, E. W.; Scullin, C.; Gabaldon, J.; Tallant, D.; Bunge, S.; Boyle, T.; Wilson, M. C.; Brinker, C. J. *Nano Lett.* **2005**, *5*, 645−648.

(17) Yan, C.; Tang, F.; Li, L.; Li, H.; Huang, X.; Chen, D.; Meng, X.; Ren, J. *Nanoscale Res. Lett.* **2010**, *5*, 189−194.

(18) Klabunde, K. J.; Timms, P. L.; Skell, P. S.; Ittel, S. *Inorg. Synth.* **1979**, *19*, 59−86.

(19) Cingarapu, S.; Yang, Z.; Sorensen, C. M.; Klabunde, K. J. *Inorg. Chem.* **2011**, *50*, 5000−5005.

(20) Cingarapu, S.; Yang, Z.; Sorensen, C. M.; Klabunde, K. J. *Chem. Mater.* **2009**, *21*, 1248−1252.

(21) Stoeva, S.; Klabunde, K. J.; Sorensen, C. M.; Dragieva, I. *J. Am. Chem. Soc.* **2002**, *124*, 2305−2311.

(22) Lin, S.; Franklin, M. T.; Klabunde, K. J. *Langmuir* **1986**, *2*, 259−260.

(23) Smetana, A. B.; Klabunde, K. J.; Marchin, G. R.; Sorensen, C. M. *Langmuir* **2008**, *24*, 7457−7464.

(24) Franklin, M.; Klabunde, K. J. In *High-Energy Processes in Organometallic Chemistry*; Suslick, K. S., Ed.; ACS Symposium Series; American Chemical Society: Washington, DC, 1987; pp 246−259.

(25) Lin, S.; Franklin, M. T.; Klabunde, K. J. *Langmuir* **1986**, *2*, 259−260.

(26) Klabunde, K. J. Method of Coating Substrates with Solvated Clusters of Metal Particles. U.S. Patent 4,877,647, 1989.

(27) Zhu, C.-Q.; Peng, W.; Xin, W.; Li, Y. *Nanoscale Res. Lett.* **2008**, *3*, 213−220.

(28) Cumberhand, S. L.; Hanif, K. M.; Javier, A.; Khitrov, G. A.; Strouse, G. F.; Woessner, S. M.; Yun, C. S. *Chem. Mater.* **2002**, *14*, 1576−1584.

(29) Trivino, G.; Klabunde, K. J.; Dale, E. *Langmuir* **1987**, *3* (6), 986−992.

(30) Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352−5355.

(31) Krauss, T. D.; Peterson, J. J. *Nat. Mater.* **2012**, *11*, 14−6 and references therein.

(32) Chan, W.; Maxwell, D. J.; Gao, X.; Bailey, R. E.; Han, M.; Nie, S. *Anal. Biotechnol.* **2002**, *13*, 40−46.

(33) Cavalieri, E.; Stack, D. E.; Devanesan, P. D.; Todorovic, R.; Dwivendy, I.; Higginbotham, S.; Johansson, S. L.; Patil, K. D.; Gross, M. L.; Gooden, J. K.; Ramanathan, R.; Cerny, R. L. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 10937−10942.

(34) Li, K. M.; Todorovic, R.; Devanesan, P. D.; Higginbotham, S.; Kofeler, H.; Ramanathan, R.; Gross, M. L.; Rogan, E. G.; Cavalieri, E. L. *Carcinogenesis* **2004**, *25*, 289−297.

(35) Cavalieri, E.; Chakravarti, D.; Guttenplan, J.; Hart, E.; Ingle, J.; Jankowiak, R.; Muti, P.; Rogan, E.; Russo, J.; Santen, R.; Sutter, T. *Biochim. Biophys. Acta* **2006**, *1766* (1), 63−78.

(36) Sugahara, K. N.; Teesalu, T.; Karmali, P. P.; Kotamraju, V. R.; Agemy, L.; Girard, O. M.; Hanahan, D.; Mattrey, R. F.; Ruoslahti, E. *Cancer Cell* **2009**, *16*, 510−520.

4526

dx.doi.org/10.1021/ic202252m | *Inorg. Chem.* 2012, 51, 4521−4526