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pH-Sensitive Quantum Dots

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We have designed organic ligands able to adsorb on the surface of CdSe−ZnS core−shell quantum dots and switch the luminescence of the inorganic nanoparticles in response to hydroxide anions. These compounds incorporate a [1,3]oxazine ring within their molecular skeleton, which reacts with the nucleophilic hydroxide anion to generate a 4-nitrophenylazophenolate chromophore. The chromogenic transformation activates an energy transfer pathway from the quantum dot to the adsorbed chromophores. As a result, the luminescence intensity of the coated nanoparticles decreases significantly in the presence of hydroxide anions. In fact, this mechanism can be exploited to probe the pH of aqueous solutions. Indeed, an increase in pH from 7.1 to 8.5 translates into a 35% decrease in the luminescence intensity of the sensitive quantum dots. Thus, our operating principles for luminescence switching can efficiently transduce a chemical stimulation into a change in the emissive response of semiconductor nanoparticles. In principle, this protocol can be extended from hydroxide anions to other target analytes with appropriate adjustments in the molecular design of the chromogenic ligands. It follows that luminescent chemosensors, based on the unique photophysical properties of semiconductor quantum dots, can eventually evolve from our design logic and choice of materials.

The photophysical properties of semiconductor quantum dots are markedly different from those of organic chromophores.[1−5] Indeed, the molar extinction coefficients, two-photon absorption cross sections, luminescence lifetimes, and photobleaching resistances of these inorganic nanoparticles are significantly greater than those of their organic counterparts. Furthermore, the broad absorption bands of quantum dots extend continuously from the ultraviolet to the visible region, offering a vast selection of possible excitation wavelengths. In addition, the narrow emission bands of these nanoparticles can precisely be positioned within the visible and near-infrared regions relying on careful adjustments of their elemental compositions and physical dimensions. In fact, the unique combination of these attractive features continues to stimulate the design of luminescent probes based on quantum dots for biomedical research.[6−12] It is now becoming apparent that these luminescent nanoparticles can complement conventional organic fluorophores in a diversity of imaging and sensing applications.

Decades of extensive investigations on the photochemical and photophysical properties of organic compounds have indicated a wealth of viable operating principles to signal target analytes with pronounced fluorescence changes.[13−16] These mechanisms generally transduce a recognition event into a detectable signal by coupling a receptor-substrate association with an electron or energy transfer process. The identification of strategies to extend these protocols from organic fluorophores to quantum dots can eventually lead to the development of luminescent chemosensors with superior properties. In fact, promising binding assays to sense large biomolecules and small organic compounds are starting to be designed around the properties of these luminescent nanoparticles.[17−29] In this context, we have devised a mechanism to transduce a chemical stimulation into a luminescence change on the basis of energy transfer from quantum dots to appropriate ligands adsorbed on their surface. Here, we illustrate our design and demonstrate with a representative example how changes in pH can efficiently switch the luminescence of our sensitive nanoparticles.

We have recently discovered that the [1,3]oxazine **1** (Figure 1) reacts with Bu_4NOH to form the hemiaminal **2**.[30] This quantitative transformation causes pronounced changes in the ultraviolet and visible regions of the absorption spectrum. Specifically, the spectrum of **1** (*a* in Figure 2) shows a band at 375 nm, which disappears after treatment with Bu_4NOH (*b*). Concomitantly, an intense band for the 4-nitrophenylazophenolate chromophore of **2** appears at 574 nm. The drastic increase in absorption wavelength with the transformation of **1** into **2** can, in principle, be exploited to activate an energy transfer process. For example, a luminescent partner with an emission band centered between 550 and 600 nm can donate excitation energy to **2**, but not to **1**. This design requirement happens to be satisfied by CdSe−ZnS core−shell quantum dots with a diameter of ca. 2.9 nm.[31] Indeed, their narrow emission at 555 nm (*c* in Figure 2) overlaps the absorption of **2** (*b*), but not that of **1** (*a*). Thus, the excitation energy of the quantum dots can efficiently be transferred to **2**, if donor and acceptor are constrained in close proximity.

The affinity of the two sulfur atoms of lipoic acid derivatives for metals can be exploited to adsorb organic molecules on gold nanoparticles[32,33] and CdSe−ZnS core−shell quantum dots.[34] On the basis of these considerations, we have designed the [1,3]-oxazine **3** (Figure 1) and synthesized this compound in five steps

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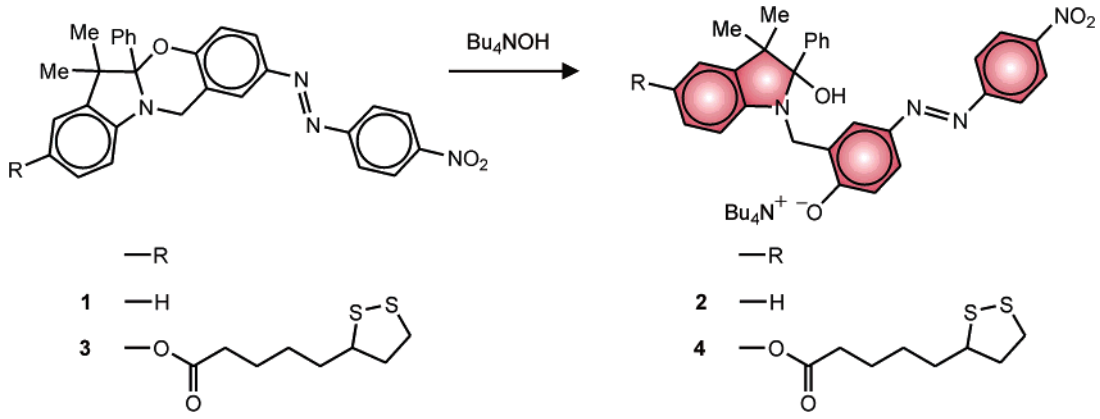

Figure 1. Transformation of the [1,3]oxazines **1** and **3** into the hemiaminals **2** and **4**, respectively, in the presence of Bu_4NOH.

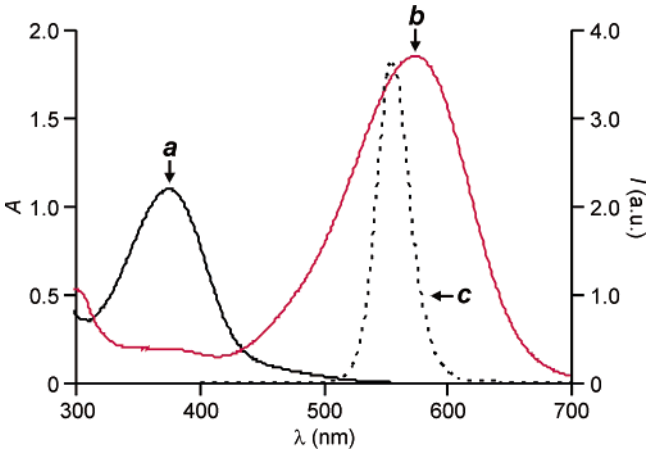

Figure 2. Absorption spectra of **1** (0.1 mM, MeCN, 20 °C) before (*a*) and after (*b*) the addition of Bu_4NOH (100 eq.). The emission spectrum (*c*) of CdSe−ZnS core−shell quantum dots (0.7 μM, $CHCl_3$, 20 °C, λ_{Ex} = 375 nm).

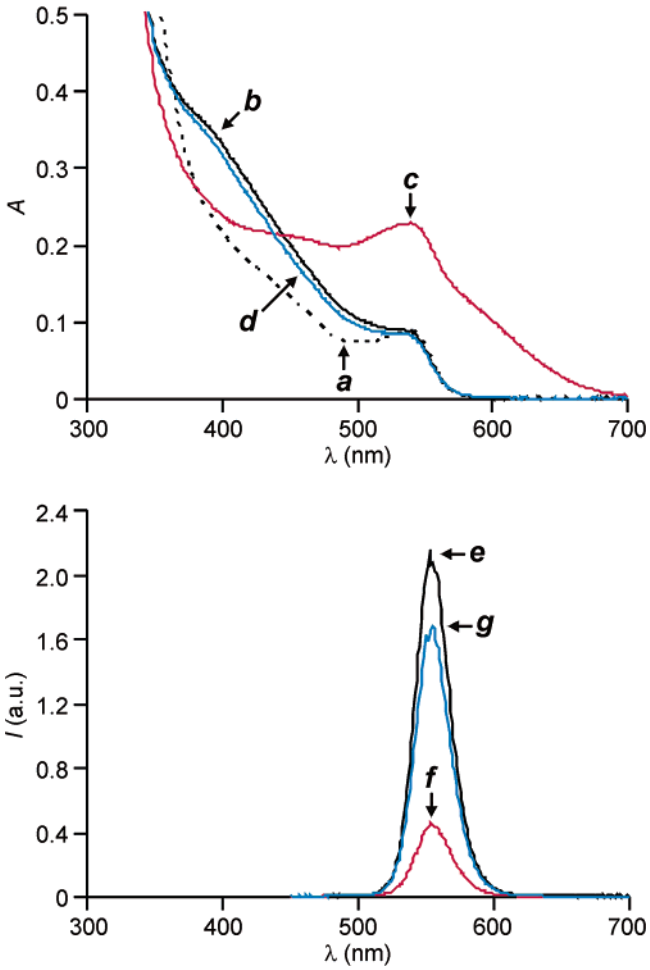

Figure 3. Absorption spectra of CdSe−ZnS core−shell quantum dots (1.8 μM, $CHCl_3$, 20 °C) before (*a*) and after (*b*) the attachment of **3** to their surface and after the consecutive addition of Bu_4NOH (*c*, 4.8 mM) and CF_3CO_2H (*d*, 6.9 mM) to the coated nanoparticles. The emission spectra of CdSe−ZnS core−shell quantum dots (0.9 μM, $CHCl_3$, 20 °C, λ_{Ex} = 423 nm) coated with **3** before (*e*) and after the consecutive addition of Bu_4NOH (*f*, 2.4 mM) and CF_3CO_2H (*g*, 2.3 mM).

(Figures S1 and S2) starting from commercial precursors. The treatment of preformed CdSe−ZnS core−shell quantum dots with **3** in $CHCl_3$ encourages the attachment of this particular organic ligand on the inorganic nanoparticles. Consistently, the absorption spectra, recorded before (*a* in Figure 3) and after (*b*) exposing the quantum dots to **3**, show the appearance of a band at 398 nm. This band resembles that of **1** (*a* in Figure 2) and its absorbance, relative to the one for the quantum dots at 539 nm, indicates that each nanoparticle is coated by an average of six [1,3]oxazine molecules.[35]

The addition of Bu_4NOH to a solution of the modified quantum dots encourages the transformation of **3** into **4** (Figure 1) on the surface of the nanoparticles. Concomitantly, the absorption spectrum (*c* in Figure 3) reveals the appearance of the characteristic band at 553 nm for the 4-nitrophenylazophenolate chromophore of **4**. This band resembles that of **2** (*b* in Figure 2) and overlaps the emission of the quantum dots (*c*). In fact, the pronounced absorbance increase in this range of wavelengths translates into a luminescence decrease of ca. 80% (*e* and *f* in Figure 3). The significant overlap between the emission of the quantum dots and the absorption of the 4-nitrophenylazophenolate ligands suggests that energy transfer form the inorganic to the organic components is mainly responsible for luminescence quenching. At this stage, however, the participation of electron-transfer processes in the regulation of the emissive behavior of the modified quantum dots cannot be excluded. In principle, the chromogenic transformation of **3** into **4** might also alter the ability of the organic ligands to exchange electrons, in addition to energy, with the quantum dots upon excitation. In any case, the changes in the absorption and emission spectra of the coated nanoparticles caused by the addition of Bu_4NOH are both reversible. After the subsequent addition of CF_3CO_2H, the absorption of the 4-nitrophenylazophenolate chromophore in the visible region fades (*d* in Figure 3) with a concomitant enhancement in the luminescence of the associated quantum dots (*g*).

The chromogenic transformation of the organic ligands on the surface of the quantum dots transduces effectively the

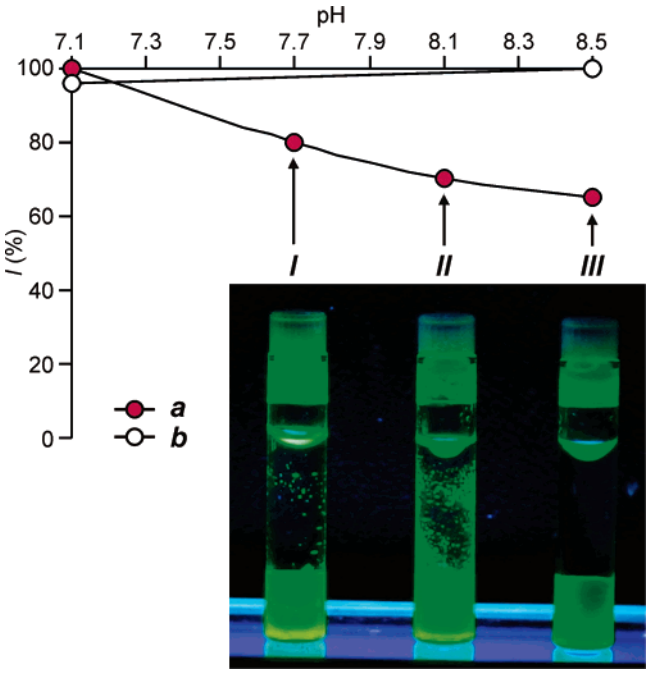

Figure 4. Emission intensity of a solution of CdSe−ZnS core−shell quantum dots (0.8 μM, 300 μL, $CHCl_3$, 20 °C, λ_{Ex} = 430 nm, λ_{Em} = 555 nm) with (*a*) and without (*b*) **3** on their surface and Bu_4NCl (1 M, 50 μL, dichloroethane) after treatment with sodium phosphate buffer (500 μL) and dilution with $CHCl_3$ (4.3 mL). Photographs of solutions of CdSe−ZnS core−shell quantum dots (0.8 μM, 300 μL, $CHCl_3$) coated with **3** and Bu_4NCl (1 M, 50 μL, dichloroethane) under ultraviolet illumination after treatment with sodium phosphate buffer (500 μL) at the pH values (*I*−*III*) indicated in the plot.

presence of hydroxide anions into a detectable change in luminescence intensity. The very same process can be exploited to probe the pH of aqueous solutions in two-phase systems. Specifically, aliquots of sodium phosphate buffer at fixed pH can be added to a $CHCl_3$ solution of the modified quantum dots. After vigorous mixing, the sensitive nanoparticles in the organic phase adjust their luminescence intensity to the pH of the aqueous phase. In fact, the intensity at 555 nm decreases by ca. 35% with an increase in pH from 7.1 to 8.5 (*a* in Figure 4). The fading in luminescence with the gradual pH increase is also evident in the corresponding photographs (*I*−*III* in Figure 4). By contrast, quantum dots lacking the chromogenic ligand **3** on their surface are insensitive to the pH of the aqueous phase (*b* in Figure 4) under otherwise identical conditions. Thus, the chromogenic and pH-sensitive organic ligands are, indeed, responsible for the regulation of the emissive behavior of the inorganic nanoparticles.

In summary, we have identified a mechanism to signal changes in pH with luminescent quantum dots. Our strategy is based on the pH-induced transformation of chromogenic ligands adsorbed on the surface of quantum dots. This process activates an energy transfer pathway from the quantum dots to the adsorbed ligands, causing a marked decrease in luminescence intensity. Thus, this mechanism can efficiently transduce a chemical stimulation into a luminescence change. In principle, our design can be adapted to signal a diversity of target analytes and, therefore, it can lead to the development of luminescent chemosensors based on the unique properties of quantum dots.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Bawendi, M. G.; Steigerwald, M. L.; Brus, L. E. *Annu. Rev. Phys. Chem.* **1990**, *41*, 477−496.
(2) Alivisatos, A. P. *Science* **1996**, *271*, 933−937.
(3) Efros, Al. L.; Rosen, M. *Annu. Rev. Mater. Sci.* **2000**, *30*, 475−521.
(4) Yoffe, A. D. *Adv. Phys.* **2001**, *50*, 1−208.
(5) Burda, C.; Chen, X. B.; Narayana, R.; El-Sayed, M. A. *Chem. Rev.* **2005**, *105*, 1025−1102.
(6) Niemeyer, C. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5796−5800.
(7) Willner, I.; Katz, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6042−6108.
(8) Alivisatos, A. P. *Nature Biotechnol.* **2004**, *22*, 47−52.
(9) Rosi, N. L.; Mirkin, C. A. *Chem. Rev.* **2005**, *105*, 1547−1562.
(10) Gao, X.; Yang, L.; Petros, J. A.; Marshall, F. F.; Simons, J. W.; Nie, S. *Curr. Opin. Biotechnol.* **2005**, *16*, 63−72.
(11) Medintz, I. G.; Uyeda, H. T.; Goldam, E. R.; Mattoussi, H. *Nature Mater.* **2005**, *4*, 435−446.
(12) Michalet, X.; Pinaud, F. F.; Bentolila, L. A.; Tsay, J. M.; Doose, S.; Li, J. J.; Sundaresan, G.; Wu, A. M.; Gambhir, S. S.; Weiss, S. *Science* **2005**, *307*, 538−544.
(13) Ricco, A. J., Crooks, R. M., Eds. *Acc. Chem. Res.* **1998**, *31*, 199−324.
(14) Ellis, A. B.; Walt, D. R., Eds. *Chem. Rev.* **2000**, *100*, 2477−2738.
(15) Fabbrizzi, L., Ed. *Coord. Chem. Rev.* **2000**, *205*, 1−232.
(16) de Silva, A. P., Tecilla, P., Eds. *J. Mater. Chem.* **2005**, *15*, 2617−2976.
(17) Willard, D. M.; Carillo, L. L.; Jung, J.; Van Orden, A. *Nano Lett.* **2001**, *1*, 469−474.
(18) Wang, S.; Mamedova, N.; Kotov, N. A.; Chen, W.; Studer, J. *Nano Lett.* **2002**, *2*, 817−822.
(19) (a) Tran, P. T.; Goldman, E. R.; Anderson, G. P.; Mauro, J. M.; Mattoussi, H. *Phys. Status Solidi B* **2002**, *229*, 427−432. (b) Medintz, I. L.; Clapp, A. R.; Mattoussi, H.; Goldman, E. R.; Fisher, B.; Mauro, J. M. *Nature Mater.* **2003**, *2*, 630−638. (c) Medintz, I. L.; Clapp, A. R.; Melinger, J. S.; Deschamps, J. R.; Mattoussi, H. *Adv. Mater.* **2005**, *17*, 2450−2455. (d) Goldman, E. R.; Medintz, I. L.; Whitley, J. L.; Hayhurst, A.; Clapp, A. R.; Uyeda, H. T.; Deschamps, J. R.; Lassman, M. E.; Mattoussi, H. *J. Am. Chem. Soc.* **2005**, *127*, 6744−6751.
(20) Patolsky, F.; Gill, R.; Weizmann, Y.; Mokari, T.; Banin, U.; Willner, I. *J. Am. Chem. Soc.* **2003**, *125*, 13918−13919.
(21) Nagasaki, N.; Ishii, T.; Sunaga, Y.; Watanabe, Y.; Otsuka, H.; Kataoka, K. *Langmuir* **2004**, *20*, 6396−6400.
(22) Hildebrandt, N.; Charbonnière, L. J.; Beck, M.; Ziessel, R. F.; Löhmannsröben, H.-G. *Angew. Chem., Int. Ed.* **2005**, *44*, 1−5.
(23) Geissbuehler, I.; Hovius, R.; Martinez, K. L.; Adrian, M.; Thampi, K. R.; Vögel, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1388−1392.
(24) Dyadyusha, L.; Yin, H.; Jaiswal, S.; Brown, T.; Baumberg, J. J.; Booy, F. P.; Melvin, T. *Chem. Commun.* **2005**, 3201−3203.
(25) Hohng, S.; Ha, T. *ChemPhysChem* **2005**, *6*, 956−960.
(26) Oh, E.; Hong, M.-Y.; Lee, D.; Nam, S.-H.; Yoon, H. C.; Kim, H.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3270−3271.
(27) Bakalova, R.; Zhelev, Z.; Ohba, H.; Baba, Y. *J. Am. Chem. Soc.* **2005**, *127*, 11328−11335.
(28) Sandros, M. G.; Gao, D.; Benson, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 12198−12199.
(29) Zhang, C.-Y.; Yeh, H.-C.; Kuroki, M. T.; Wang, T.-H. *Nature Mater.* **2005**, *4*, 826−831.
(30) (a) Tomasulo, M.; Raymo, F. M. *Org. Lett.* **2005**, *7*, 4633−4636. (b) Tomasulo, M.; Sortino, S.; White, A. J. P.; Raymo, F. M. *J. Org. Chem.* **2006**, *71*, 744−753.
(31) The diameter of the quantum dots was estimated from the wavelength (539 nm) of their band-gap absorption, according to a literature protocol (Yu, W.; Qu L.; Guo W.; Peng, X. *Chem. Mater.* **2003**, *15*, 2854−2860).
(32) Mangeney, C.; Ferrage, F.; Aujard, I.; Marchi-Artzner, V.; Jullien, L.; Ouari, O.; Rekaie, E. D.; Laschewsky, A.; Vikholm, I.; Sadowski, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 5811−5821.
(33) Abad, J. M.; Mertens, S. F. L.; Pita, M.; Fernandez, V. M.; Schiffrin, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 5689−5694.
(34) Uyeda, H. T.; Medintz, I. L.; Jaiswal, J. K.; Simon, S. M.; Mattoussi, H. *J. Am. Chem. Soc.* **2005**, *127*, 3870−3878.
(35) The molar extinction coefficient of **3** is ca. 20.7 mM^{-1} cm^{-1} at 342 nm in $CHCl_3$. That of the quantum dots can be estimated to be ca. 97.5 mM^{-1} cm^{-1} at 539 nm in the same solvent, relying on a literature protocol (ref 31).