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Facile synthesis of ionic liquid functionalized silica-capped CdTe quantum dots for selective recognition and detection of hemoproteins

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A facile and efficient approach for preparation of ionic liquid functionalized silica-capped CdTe QDs (CdTe/SiO_2/IL) was proposed in this work. The imidazolium-based ionic liquid N-3-(3-trimethoxysilylpropyl)-3-methyl imidazolium chloride was introduced and anchored on the surface of silica-capped CdTe QDs by the sol-gel technique, which played the role of recognition element due to the covalent coordination binding between the heme group of hemoprotein and the imidazolium cation in the ionic liquid. The synthetic CdTe/SiO_2/IL was further characterized by the elemental analysis, transmission electronic microscopy (TEM), X-ray photoelectron spectra (XPS) and fourier transform infrared spectroscopy (FT-IR). Combining the merits of the fluorescence property of the QDs and the covalent interaction of the ionic liquid with hemoproteins, the CdTe/SiO_2/IL exhibited high adsorption capacity and good specificity toward hemoproteins as well as was successfully applied in the fluorescence detection of hemoprotein in biological fluid. The strategy provided a promising way to fabricate functionalized fluorescence materials as biomedical/chemical sensors for the separation and detection of hemoproteins in proteomics research.

Introduction

As a group of novel green solvents, ionic liquids have attracted extensive attention due to their outstanding properties including negligible volatility, excellent thermal stability, remarkable solubility, low toxicity and favorable conductivity.[1] These attractive features of ionic liquids gained popularity in various applications including organic synthesis, electrochemical analysis, extraction- separation, catalysis and chemical sensors.[2-5] Especially, imidazolium-based ionic liquids aroused the interest of many researchers based on their unique properties that the imidazole ring is ubiquitous in nature and plays a critical role in many structures and functions within the human body due to that the imidazole ring is possible via its ability to bond to metals as a ligand and also to form hydrogen bonds with drugs and proteins.[6-8]

Recently, nanoparticles and biomaterials were reported to be integrated into a system, which was employed by the interactions between specific protein and ion exchange groups or affinity ligands in biological recognition and detection.[9-18] Particularly, QDs as unique nanoparticles have attracted extensive attention and gained popularity in various applications including protein assays, and can be attached the recognition element to the signal-generating transducer as desirable fluorescent label owning to their high luminescence efficiency, good photostability and size dependent emission wavelengths.[19-25] Meanwhile, protein assay has long been a crucial issue in bioscience as well as some of the related fields because protein is the most important biological macromolecule in life system, and is the main carrier of life activities as well as the main material basis of life phenomenon. For example, hemoproteins represent specific protein species and play important roles in numerous biological processes, particularly those involving transport of oxygen and electron transfer in life activities.[26] Several diseases, including anemia, erythrocytosis, and thalassemia are associated with significant variations in the hemoglobin concentration in the blood.[27] Myoglobin is the first cardiac biomarker found in the blood as an indicator of cardiac damage, which makes its detection in the first hours highly significant.[28] Thus, approaches allowing the rapid and accurate determination of the concentration of hemoprotein in the blood would assist clinical diagnosis and physiological research.[29] Recent studies show that the ferrous atom in the heme group of hemoproteins provides a vacant coordinating position, which offers possibilities for covalent coordination or interaction between the ferrous atom and the imidazolium cation in the ionic liquid.[26, 30] In this respect, the employment of ionic liquids as green solvents in separation, enrichment and detection of hemoproteins provides a promising alternative, which can be attributed to the fact that ionic liquids not only provide a novel and highly efficient reaction medium, but also serve as efficient participants in clinical diagnoses, biomedical and proteomics research.[1]

Herein, a new strategy for facile and efficient modification of ionic liquid (N-3-(3-trimethoxysilylpropyl)-3-methyl imidazolium chloride) on the silica-capped CdTe QDs was proposed in this work. The N-3-(3-trimethoxysilylpropyl)-3-methyl imidazolium chloride was chosen as the affinity ligand for specific recognition of hemoproteins. Combining the merits of

the fluorescence property of the QDs and the covalent interaction of the ionic liquid with hemoproteins, the as-prepared CdTe/SiO_2/IL exhibited high adsorption capacity and good specificity toward hemoproteins as well as was successfully applied in the fluorescence detection of hemoproteins in biological fluid.

Experimental

Materials

All reagents used were at least analytical grade. Tellurium powder, $CdCl_2$•$2.5H_2O$, $NaBH_4$, ammonium hydroxide (NH_3•H_2O), tetraethoxysilicane (TEOS), 3-chloropropyltrimethoxysilane, and N-methylimidazole were purchased from J&K Chemical Co. 3-Mercaptopropionic acid (MPA) was purchased from Alfa Aesar. Bovine hemoglobin (BHb, pI (point isoelectric) = 6.9, MW (molecular weight) = 64.5 kDa), equine myoglobin (Mb, pI = 7.0, MW = 16.7 kDa), bovine serum albumin (BSA, pI = 4.9, MW = 66.0 kDa), and lysozyme (Lyz, pI = 11.0, MW = 14.4 kDa) were purchased from Sigma-Aldrich Co. (St. Louis, MO). Bovine blood was kindly gifted by Xiaochuan Biotech. Co. Ltd. (Tianjin, China). Ultrapure water (18.2 MΩ cm) obtained from a Water Pro water purification system (Aquapro Corp., Delaware, USA) was used throughout this work.

Synthesis of ionic liquid N-3-(3-trimethoxysilylpropyl)-3-methyl imidazolium chloride (IL) [31, 32]

N-methylimidazole (10.12 g) and (3-chloropropyl) trimethoxysilane (24.23 g) were refluxed at 90 ℃ for 48 h in the absence of oxygen atmosphere. The obtained mixture was washed with ethyl acetate for several times, and dried under vacuum for 24 h. The resulting N-3- (3- trimethoxysilylpropyl)-3-methyl imidazolium chloride was a yellowish viscous liquid. 1H NMR (300MHz, $CDCl_3$): δ = 10.2 (s, 1H), 7.42 (dd, 1H), 7.26 (dd, 1H), 4.34 (t, 2H), 4.10 (s, 3H), 3.55 (s, 9H), 1.21 (t, 2H), 0.67 (t, 2H).

Synthesis of CdTe QDs

The CdTe QDs were synthesized according to previous reference with some modification.[20] Briefly, 12.5 mL of $CdCl_2$•2.5 H_2O solution and 180 mL of ultrapure water were added to a three-neck flask in the presence of 3-mercaptopropionic acid as a stabilizing agent, and then the mixture solution were adjusted to pH 10.0 with NaOH. Next, 1.5 mL of fleshly prepared NaHTe that were synthesized by tellurium powder and $NaBH_4$ under oxygen-free atmosphere was put into previous mixture. The resulting mixture was then refluxed at 100 ℃ under nitrogen environment for 2 h.

Fabrication of CdTe/SiO_2

CdTe QDs were encapsulated in silica spheres based on the stober method with some modifications.[33, 34] In brief, 8 mL of CdTe QDs solution, 40 mL of ethanol and 100 μL of TEOS were mixed into a 100 mL flask, and then 200 μL of NH_3•H_2O as the catalyst was added. The reaction was allowed to continue for 2 h with moderate stirring at room temperature. The obtained silica-capped CdTe QDs were centrifuged and washed with ethanol for three times to remove the excess reactants.

Preparation of CdTe/SiO_2/IL nanocomposite

The previous CdTe/SiO_2 was dispersed in 20 mL of 1:1 mixture of ethanol and ultrapure water. Next, 600 μL of previous N-3-(3-trimethoxysilylpropyl)-3-methyl imidazolium chloride and 200 μL of NH_3•H_2O were added to the above mixture under stirring constantly and the reaction was last for 12 h. The resultant nanoparticles were centrifuged and washed with ethanol and ultrapure water for three cycles.

Protein adsorption

The capacity of CdTe/SiO_2/IL toward hemoproteins and non-hemoproteins was carried out by incubating CdTe/SiO_2/IL (2 mg) in a solution of protein samples with different concentrations (0.2 mg/mL to 1.0 mg/mL) in 0.1 mol/L Tris-HCl buffer (pH 7.0) at room temperature. Then the supernatant was separated by centrifugation and detected by the UV-vis spectrophotometer. The adsorption capacity (Q) is calculated using the equation below:

$$Q = (C_0 - C_t)\, V/\, W \ (mg/g) \qquad (1)$$

where C_0 (mg/mL) and C_t (mg/mL) are the initial and equilibrium concentrations of the protein, respectively, V (mL) is the volume of the initial solution, W (g) is the weight of CdTe/SiO_2/IL.

Protein analysis

2 mg of the CdTe/SiO_2/IL was immersed in 1.5 mL of the binary protein mixture (0.4 mg/mL BHb and BSA; 0.4 mg/mL Mb and Lyz). After incubation at room temperature under gentle shaking, the mixtures were centrifuged and the supernatant was obtained. The elution of hemoprotein after adsorption was performed by using Na_2CO_3-$NaHCO_3$ buffer (pH 10.0) after washed by 0.1 mol/L phosphate buffer, as well as 0.5% SDS aqueous solution. Finally, the supernatant was collected and analyzed by SDS-PAGE.

Characterization

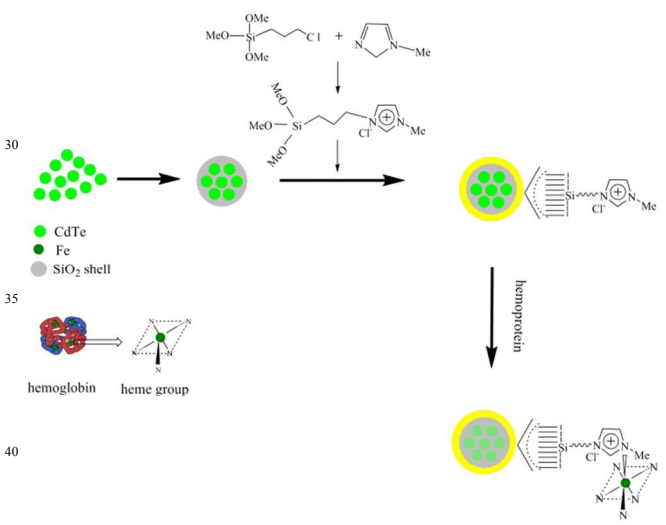
High-resolution transmission electron microscopy (HRTEM) imaging was performed on a Tecnai G2 F20 transmission electron microscope with the voltage of 200 kV (FEI, Holland). Elemental analysis was performed on an elemental analyzer elementar (Vario EL cube, Germany). The X-ray photo-electron spectroscopy (XPS) measurements were performed on a Kratos Axis Ultra DLD spectrometer employing a monochromated Al-Kα X-ray source (hv=1486.6 eV) (Krato, UK). The source X-rays were not filtered and the instrument was calibrated against the C1s band at 285.0 eV. Fourier-transform infrared (FT-IR) spectra (4000–400 cm^{-1}) in KBr were recorded by using a Vector 22 FT-IR spectrophotometer (Bruker, Germany). UV-vis spectra (200-

800 nm) were recorded on a UV-2450 spectrophotometer (Shimadzu, Japan). Fluorescence (FL) measurements were performed on an F-4500 fluorospectrophotometer (Hitachi, Japan). Gel electrophoresis was carried out by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) with 15% separating gel and 6% stacking gel (Bio-Rad).

Results and discussion

Preparation and characterization of CdTe/SiO_2/IL

The CdTe/SiO_2/IL was synthesized as illustrated in Scheme 1. In the first step, CdTe QDs were encapsulated into silica to form CdTe/SiO_2 nanoparticles. Silica is one of the proper inert materials for coating QDs due to its biocompatibility for impeding the leakage of heavy metal ions into the environment and reducing the toxicity of CdTe QDs, stability against degradation, as well as the well-developed silica surface functionalization chemistry for providing further modification. Subsequently, the synthetic N-3-(3-trimethoxysilylpropyl)-3-methyl imidazolium chloride was immobilized on the surface of CdTe/SiO_2 for selective capture and detection of hemoproteins, according to coordination effect between the hemoprotein and the imidazolium cation in the ionic liquid.[26]



Scheme 1 Schematic representation of the preparation procedure for CdTe/SiO_2/IL and its affinity interaction with the hemoglobin.

The size and morphology of the resulting CdTe/SiO_2/IL were investigated by HRTEM. As shown in Figure 1a, the size of the CdTe QDs was about 3 nm. After the sol-gel reaction, CdTe QDs were encapsulated in silica and the average diameter of CdTe/SiO_2 was about 78 nm (Figure 1b). The subsequent obtained CdTe/SiO_2/IL was displayed in Figure 1c and 1d and the diameter of the nanocomposite increases to approximately 84 nm, corresponding to a 3 nm thick layer on the surface of CdTe/SiO_2.

The successful synthesis of CdTe/SiO_2/IL was confirmed by elemental analysis (Table 1). Comparing to the CdTe/SiO_2, the resultant CdTe/SiO_2/IL has higher content for nitrogen element, which indicated the successful polymerization of N-3-(3-trimethoxysilylpropyl)-3-methyl imidazolium chloride on the surface of CdTe/SiO_2. In order to further confirm the surface composition of the CdTe/SiO_2/IL, XPS of nanoparticles were performed. As shown in Figure 2, the XPS survey showed the characteristic Cd $3d_{5/2}$ at 403.2 eV and Cd $3d_{3/2}$ at 410.0 eV, which confirmed the existence of CdTe QDs in the nanocomposite. The appearance of the signals of N 1s at 398.4 eV, C 1s at 285.0 eV, O 1s at 531.8 eV and Cl 2p at 196.7 eV indicated that the ionic liquid was successfully modified in the CdTe/SiO_2/IL. FT-IR spectra of CdTe QDs and as-prepared nanoparticles were shown in Figure 3. For MPA stabilized CdTe QDs, asymmetric and symmetric stretching bands of -COO- were observed at 1552 cm^{-1} and 1400 cm^{-1}, respectively (Figure 3a). The characteristic signals of the stretching vibration of Si-O-Si at 1087 cm^{-1} and Si-O vibration at 794 cm^{-1} were observed in the spectrum of CdTe/SiO_2 (Figure 3b), which proved the CdTe QDs was successfully loaded inside silica. The out-of-plane C-H bending of imidazole at 740 cm^{-1}, in-plane imidazole ring bending at 950 cm^{-1} and imidazole H-C-C and H-C-N bending at 1165 cm^{-1} were also observed in Figure 3c, suggesting the existence of ionic liquid in the resultant composite.

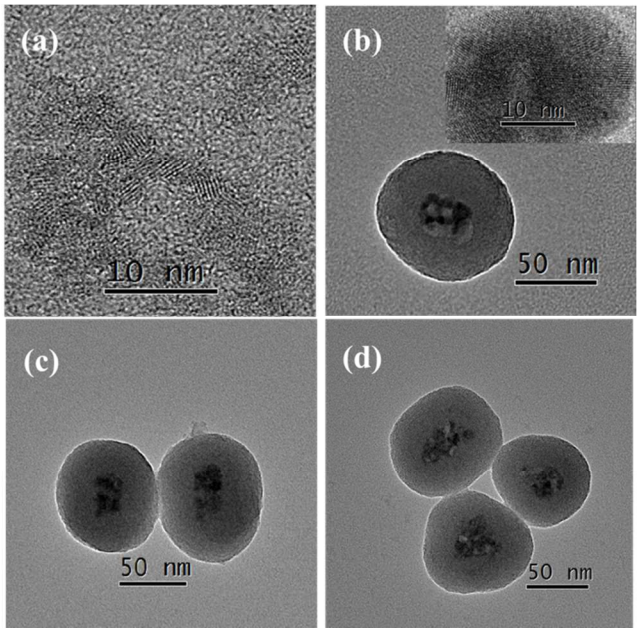


Figure 1 HRTEM images of CdTe QDs (a), CdTe/SiO_2 (b) (inset: high magnification HRTEM image of CdTe/SiO_2), and CdTe/SiO_2/IL (c, d).

Table 1 Elemental compositions measured by elemental analysis

% (m)	C	H	N
CdTe/SiO_2	4.05	3.06	0
CdTe/SiO_2/IL	7.34	3.45	2.10

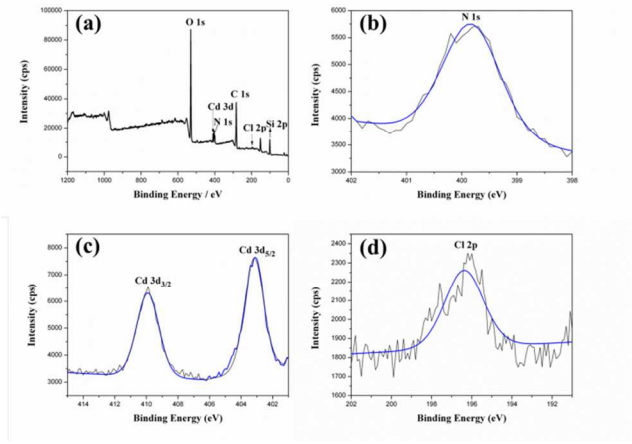


Figure 2 XPS spectra of the as-prepared CdTe/SiO_2/IL. (a) XPS survey spectrum; (b) binding energy spectrum of N 1s; (c) binding energy spectrum of Cd $3d_{3/2}$ and $3d_{5/2}$; (d) binding energy spectrum of Cl 2p.

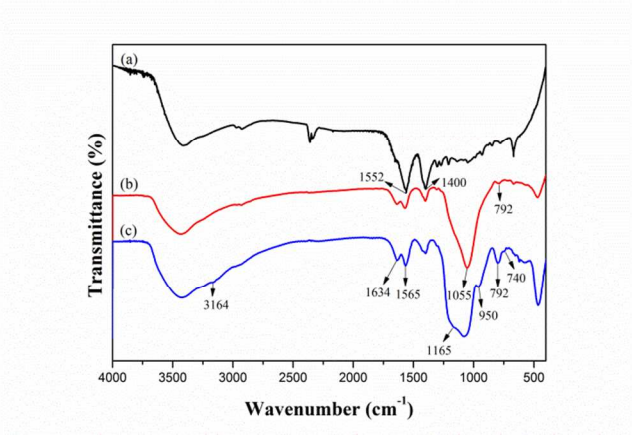


Figure 3 FT-IR spectra of CdTe QDs (a), CdTe/SiO_2 (b) and the as-prepared CdTe/SiO_2/IL (c).

Protein adsorption with CdTe/SiO_2/IL

In order to investigate the interaction of the CdTe/SiO_2/IL with hemoproteins，the non-hemoproteins BSA and Lyz which had similar molecular weight with BHb and Mb were chosen as the contrasted proteins, respectively. The adsorption capacity of four proteins is shown in Figure 4. The maximum adsorption capacity of hemoproteins BHb and Mb was 790.7 and 377.8 mg/g, respectively, and the adsorption of BSA and Lyz were 37.8 and 14.1 mg/g, respectively. The binding behavior was determined by the special coordination effect between the CdTe/SiO_2/IL and the proteins with heme group. For non-hemoproteins, BSA and Lyz showed much less adsorbing capacity, suggesting the physical binding was the primacy factor between the CdTe/SiO_2/IL and them. The results illustrated the ionic liquid functionalized silica-capped CdTe QDs owned higher adsorption capacity due to the covalent coordination between hemoproteins and the N-3-(3-trimethoxysilylpropyl)-3-methyl imidazolium chloride.

Desorption and regeneration is an important indicator for the application of materials. The adsorbed hemoproteins could be

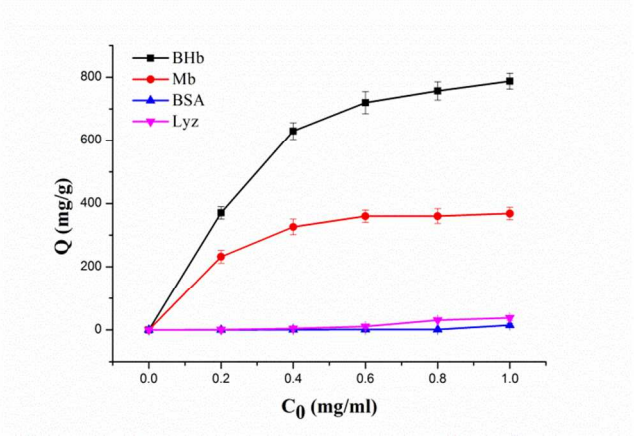


Figure 4 Adsorption isotherm of four proteins (BHb, Mb, BSA and Lyz) on CdTe/SiO_2/IL.

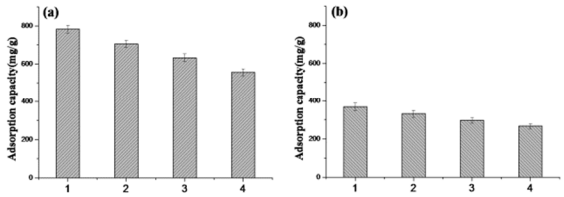


Figure 5 Adsorption-desorption ability of the CdTe/SiO_2/IL to BHb (a) and Mb (b).

eluted by using Na_2CO_3-$NaHCO_3$ buffer and phosphate buffer, as well as SDS aqueous solution. SDS provided anionic moiety to replace the heme-group and form ion-pair with cationic ionic liquid, and hemoproteins were thus released and CdTe/SiO_2/IL material could be regenerated.[26] The adsorption-desorption cycles were repeated four times using the same batch of the CdTe/SiO_2/IL material to study the reversible binding and release behaviour. As shown in Figure 5, there are about 30% and 27% loss observed for the binding capacity of CdTe/SiO_2/IL to BHb and Mb respectively after four adsorption-regeneration cycles. The results indicated that CdTe/SiO_2/IL retained its recovery efficiency, which was a clear superiority over disposable materials and could be used repeatedly at least within four cycles.

Specific capture of hemoprotein from protein mixtures

The specificity of the CdTe/SiO_2/IL was demonstrated by the capturing of model hemoprotein (BHb or Mb) from the mixtures, and the SDS-PAGE was used to visualize protein samples. As presented in Figure 6, the bands of BHb and BSA appeared in the mixture of BHb and BSA without treatment (lane 1). After treatment with the CdTe/SiO_2/IL as described in the experimental section, the supernatant was detected. It was found from lane 2 that hardly any BHb was left. Namely, almost all of the BHb was captured by the CdTe/SiO_2/IL. However, the band of BSA had hardly changed, indicating that BHb was effectively isolated from the coexisting protein species in the mixture. The result demonstrated the high specificity of CdTe/SiO_2/IL toward BHb. At the same time, the pre-concentration of the eluted BHb was

achieved in lane 3. Likewise, Mb was also effectively isolated from the coexisting protein species and the eluted Mb was obtained. The observation illustrated the applicability of the approach for the effective isolation and enrichment of hemoprotein from mixture samples.

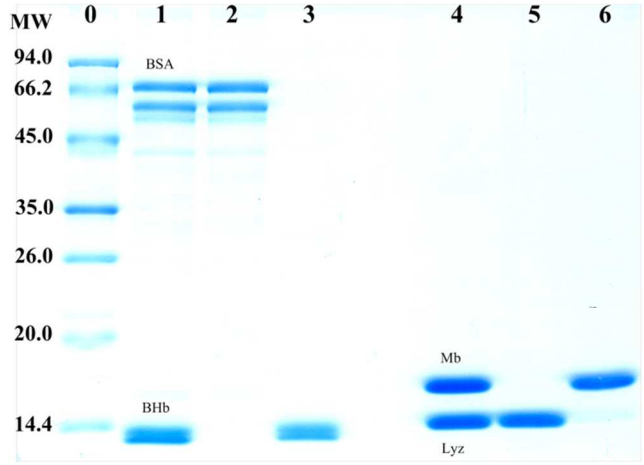


Figure 6 Analysis of hemoprotein before and after treatment with CdTe/SiO_2/IL by SDS-PAGE. Lane 0, protein marker; lane 1, 0.4 mg/mL of protein mixture (BHb + BSA) before treatment; lane 2, 0.4 mg/mL of protein mixture (BHb + BSA) after treatment; lane 3, BHb isolated and enriched from the protein mixture (BHb + BSA) with the present procedure; lane 4, 0.4 mg/mL of protein mixture (Mb + Lyz) before treatment; lane 5, 0.4 mg/mL of protein mixture (Mb + Lyz) after treatment; lane 6, Mb isolated and enriched from the protein mixture (Mb + Lyz) with the present procedure.

Optosensing of hemoproteins by CdTe/SiO_2/IL

The recognition behavior was studied by the change of the fluorescence intensity of the CdTe/SiO_2/IL. The quenching amount, defined as (F_0/F)-1, was used as the index of the quenching capacity. As shown in Figure 7, the FL intensity of the CdTe/SiO_2/IL was quenched by the increase of the hemoproteins. However, as for the non-hemoproteins, the fluorescence signal had no obvious change because nonspecifically physical binding was the primary factor and the affinity was weak. An interesting phenomenon was that the degrees of quenching of different hemoproteins (BHb or Mb) were different. Why the quenching amounts of CdTe/SiO_2/IL toward BHb or Mb were different? The reason is that although BHb and Mb are structurally similar, Mb contains one heme prosthetic group; BHb consists of four Mb-like subunits ($2\alpha+2\beta$), each containing one heme prosthetic group.[35] The fluorescence quenching effect of CdTe/SiO_2/IL is based on the interaction of the heme group and the N-3-(3-trimethoxysilylpropyl)-3-methyl imidazolium chloride, so the fluorescence quenching degree of CdTe/SiO_2/IL toward BHb is much stronger than Mb, almost 4.8 times as much. The fluorescence quenching followed the Stern-Volmer equation.

$$F_0/F=1+K[Q] \quad (2)$$

F_0 and F were the FL intensity of CdTe/SiO_2/IL in the absence and presence of the protein, respectively, K was the Stern-Volmer constant, [Q] was the concentration of the protein.

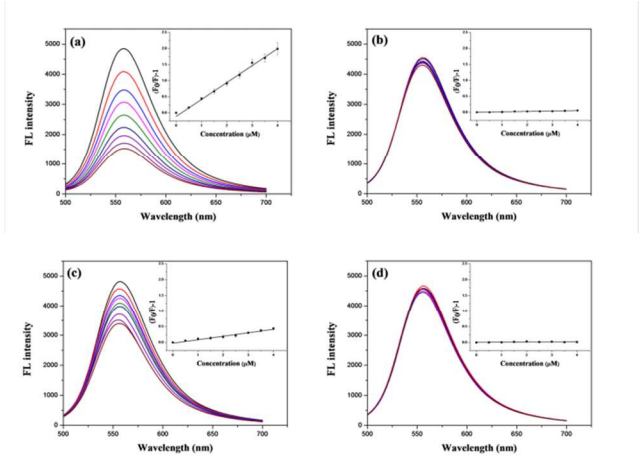


Figure 7 Fluorescence emission spectra of CdTe/SiO_2/IL with addition of indicated concentration of hemoproteins (a: BHb; c: Mb) or non-hemoproteins (b: BSA; d: Lyz) solution. Insets were the corresponding plots of (F_0/F)-1 against the concentration of the corresponding proteins.

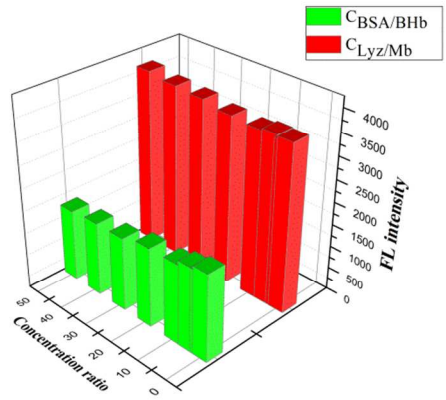


Figure 8 Effect of the competitive non-hemoproteins on the binding of hemoproteins on the CdTe/SiO_2/IL. Binding was done by increasing the concentration of non-hemoproteins (BSA, Lyz) and fixing the concentration of hemoproteins (BHb or Mb, 3 μM), respectively.

The selectivity factor (SF) is defined as the ratio of the K_{heme} and $K_{non\text{-}heme}$, which illustrated the selectively of the fluorescence nanocomposite. The $SF_{BHb/BSA}$ and $SF_{Mb/Lyz}$ were 41.9 and 27.3, respectively, which indicate the CdTe/SiO_2/IL had higher selectively and special recognition for hemoproteins. And then, the competitive experiments were performed by changing the ratio of different concentrations of non-hemoproteins and the fixed concentration of hemoprotein. As shown in Figure 8, the FL intensity of CdTe/SiO_2/IL had little change with the increase of the ratio of $C_{BSA/BHb}$ or $C_{Lyz/Mb}$. The result can be explained that although BSA (Lyz) has the molecular weight similar to BHb (Mb), BHb and Mb own the heme groups and have the specific recognition ability due to the covalent coordination binding with

the imidazolium-based ionic liquid. Through the competitive experiments, it was further confirmed that the CdTe/SiO_2/IL had the specific recognition and higher selectivity for hemoproteins.

Practical application in biological fluid

Specific and sensitive detection of proteins in biological samples is also one of the most important goals. To confirm the ability of the approach to sensitively detect the hemoprotein from real complex biological fluid, bovine blood was chosen and detected by the standard addition method. The recoveries of these measurements were 95.0-114.0% (Table 2), which indicated the accuracy and reliability of the as-prepared fluorescence material for the determination of hemoprotein in complexity real sample.

Table 2 Results for the determination of the BHb in 2000-fold dilution of bovine blood

	BHb concentration (10^{-7} M)		
sample	spiked	measured[a]	%[b]
bovine blood	0	5.2 ± 0.3	
	5.0	10.9 ± 0.1	114.0 ± 2.0
	10.0	14.7 ± 0.4	95.0 ± 4.0
	20.0	24.2 ± 1.2	95.0 ± 6.0
	30.0	36.1 ± 0.9	103.0 ± 3.0

[a]mean ± std, n=3; [b]mean ± std recovery %, n=3.

Conclusions

A novel and facile approach for fabrication of fluorescent material was proposed for selective recognition and detection of hemoproteins due to the coordination effect between the hemoprotein and the imidazolium cation in the synthetic ionic liquid. The resulting CdTe/SiO_2/IL exhibited high adsorption capacity and higher selectivity as well as specific capture of hemoproteins from mixture samples. Besides, the CdTe/SiO_2/IL satisfied the determination of hemoprotein by the change of fluorescent signal, and was successfully applied in biological fluid. The approach for the synthesis of CdTe/SiO_2/IL provides a facile strategy to fabricate functionalized fluorescent material and the CdTe/SiO_2/IL is expected to be a good biochemical sensor in selective isolation and detection of hemoproteins in proteomics.

Acknowledgments

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Notes and references

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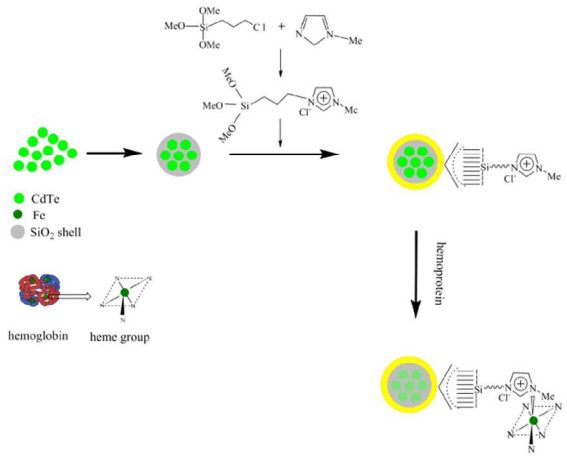
TOC graphic



A novel ionic liquid functionalized silica-capped CdTe quantum dots was fabricated and used for selective recognition and detection of hemoproteins.