Molecular imprinting ratiometric fluorescence sensor for highly selective and sensitive detection of phycocyanin

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ABSTRACT

A facile strategy was developed to prepare molecular imprinting ratiometric fluorescence sensor for highly selective and sensitive detection of phycocyanin (PC) based on fluorescence resonance energy transfer (FRET), via a sol-gel polymerization process using nitrobenzoxadiazole (NBD) as fluorescent signal source. The ratio of two fluorescence peak emission intensities of NBD and PC was utilized to determine the concentration of PC, which could effectively reduce the background interference and fluctuation of diverse conditions. As a result, this sensor obtained high sensitivity with a low detection limit of 0.14 nM within 6 min, and excellent recognition specificity for PC over its analogues with a high imprinting factor of 9.1. Furthermore, the sensor attained high recoveries in the range of 93.8–110.2% at three spiking levels of PC, with precisions below 4.7% in seawater and lake water samples. The developed sensor strategy demonstrated simplicity, reliability, rapidity, high selectivity and high sensitivity, proving to be a feasible way to develop high efficient fluorescence sensors and thus potentially applicable for ultratrace analysis of complicated matrices.

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1. Introduction

Eutrophication of inland lakes, reservoirs, estuaries, and coastal waters, is becoming a frequent phenomenon, which has received increasing attention due to its harmful impacts on the aquatic environment (Sun et al., 2015; Mishra and Mishra, 2014). Cyanobacterial blooms, as one of distinct types of eutrophication, have posed a serious threat to both the environment and humans, particularly under blooming conditions (Sun et al., 2015; Lyu et al., 2013). Phycocyanin (PC), an accessory cyanobacteria-specific pigment emitting red light with a maximum at about 650 nm, can provide effective indication to assess cyanobacterial blooms (Qi et al., 2014). Hence, identifying and quantifying PC by developing cost effective, rapid, facile and applicable methods is highly crucial.

Currently, fluorescent detection has become a powerful tool due to its high sensitivity, simplicity and low background signal. Thus, fluorescence materials have recently aroused wide concerns for detecting trace amounts of analytes (Yu et al., 2014). Up to now, most fluorescent materials employ a sole responsive signal for

detection, which can be readily perturbed by the change in fluorescence intensity and some external factors including environmental and instrumental efficiency (Koneswaran and Narayanawamy, 2012). Fortunately, ratiometric measurement has the advantages to eliminate environmental effects and to give more precise measurement by its self-referencing of two emission bands, since it uses the ratio of two fluorescent peaks instead of the absolute intensity of one peak (Liu et al., 2013). Owing to the improved sensitivity, ratiometric fluorescence technique has attracted increasing attention for trace level analysis. For example, Wang's group proposed several ratiometric probes for the visual observation of fluorescence color changes induced by analytes without the need of elaborate equipment (Yao et al., 2013; Zhang et al., 2014; Zhu et al., 2014). Zhang's group developed a nano-hybrid ratiometric fluorescence sensor for selective detection of mercuric ions. The sensor can effectively identify Hg²⁺ with the detection limit as low as 42 nM (Lan et al., 2014). However, as for most probes/sensors, selectivity is still very challenging especially for detection of trace analytes in complicated matrices.

Meanwhile, molecular imprinting technology (MIT) known as a technique for creation of tailor-made binding sites in a polymer matrix, i.e., molecularly imprinted polymers (MIPs), has attracted great concerns (Chen et al., 2011; Fu et al., 2015). The introduction

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of MIT into the design of fluorescence probes/sensors strategies will combine the advantages of high selectivity of MIPs with high sensitivity of fluorescence. So, it is naturally conceivable to develop molecular imprinting based fluorescence strategies with high selectivity and sensitivity for detection of low content target analytes from complex samples. However, as far as we know, there are few examples on molecular imprinting based ratiometric fluorescence probes/sensors. Recently, a kind of MIP coated quantum dot (MIP@QD) fluorescence sensor was reported, which combined with ratiometric fluorescence techniques to detect 2,4,6-trinitrotoluene (Xu and Lu, 2015). The assay platform exhibited excellent selectivity and sensitivity with a detection limit of 15 nM.

Usually, there are mainly two methods used to synthesize fluorescence-based MIPs. One method is to synthesize functional monomers with fluorophore, such as pyrene derivative (Chen et al., 2014) and 1,8-naphthalimide dye (Rouhani and Nahavandifard, 2014), by monitoring the change of fluorescence spectrum from the combination of the analytes with fluorescent functional monomer. However, the method often needs complicated synthesis procedure for fluorescence functional monomer. The other method is embedding fluorescent signal into MIPs and detecting analytes by fluorescence spectroscopy (Liu et al., 2011). Among the optical materials investigated, QDs (Li et al., 2013; Tan et al., 2013; Zhou et al., 2014; Zhang et al., 2015) and organic fluorescent compounds (Descalzo et al., 2013) are the most widely used fluorescent signal sources. Similarly, the process is rather laborious and time-consuming. Therefore, to prepare fluorescence-based MIPs with a more labor-saving process and higher efficiency is of extreme significance and greatly desirable.

Herein, inspired by these studies, through a simple, time-saving and facile sol–gel polymerization process, we developed a novel molecular imprinting ratiometric fluorescence sensor for selective and sensitive detection of PC on the basis of fluorescence resonance energy transfer (FRET). Organic dye nitrobenzoxadiazole (NBD) was chosen as fluorescent donor, because of its three features: its emission spectrum partially overlapping with the absorption spectrum of PC for FRET, its high fluorescence efficiency for fluorescent detection, and its easy reaction with 3-aminopropyltriethoxysilane (APTES) for being easily attached onto the surface of silica particles. The obtained fluorescence sensor was well characterized and its analytical performances were investigated in detail. The potential application of the sensor to real samples including seawater and lake water was also explored.

2. Experimental

2.1. Reagents and materials

3-Aminopropyltriethoxysilane (APTES), bovine serum albumin (BSA), and 4-chloro-7-nitro-2,1,3-benzoxadiazole (NBD-Cl) were purchased from Sigma-Aldrich (Shanghai, China). Ammonium hydroxide (25%), absolute ethanol, methanol, acetic acid (HAc), tetraethoxysilane (TEOS) and phosphate buffered saline (PBS) were supplied by Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). Phycocyanin (PC), phycoerythrin (PE), and spirulina powder were kindly provided by Shandong Oriental Ocean Co. (Yantai, China). The PC obtained from spirulina has the molecular weight of 110 kDa containing two subunits, and its isoelectric point (pI) is 4.3, and its main functional groups are carboxyl and amino groups.

2.2. Characterization

Fluorescence measurements were performed on a Fluoromax-4 Spectrofluorometer (Horiba Scientific). UV–vis spectra were measured on a Thermo Scientific NanoDrop 2000/2000C

spectrophotometer (Thermo Fisher Scientific, Waltham, MA). The morphological evaluation was examined on a scanning electron microscope (SEM, Hitachi S-4800 FE-SEM, operating at 5 kV) and transmission electron microscopy (TEM, JEM-1230, operating at 100 kV). FT-IR analyses were carried out by a FT-IR spectrometer (Thermo Nicolet Corporation, USA).

2.3. Synthesis of APTES–NBD conjugates

The APTES–NBD conjugates were synthesized according to the reported method (Geng et al., 2010). 11.8 mg NBD-Cl was first dissolved in 10 mL anhydrous ethanol containing APTES (0.5 mL; molar ratio of NBD/APTS 1:40) with stirring in a dry nitrogen atmosphere. After 12 h of reaction in the dark, the APTES–NBD conjugates were formed in the mixture solution, which would be used as donor precursor.

2.4. Preparation of SiO₂@NBD/MIPs

The SiO₂@NBD/MIPs were prepared through a sol–gel process. SiO₂ nanoparticles were firstly synthesized according to the report (Gao et al., 2010). Subsequently, 160 µL of the above APTES–NBD conjugates solution and 20 mg of PC were added to 30 mL of ultrapure water containing 120 mg SiO₂ nanoparticles. After stirred for 30 min, 200 mL of NH₃·H₂O and 200 µL of TEOS were added and kept stirring overnight in the dark. Finally, the products were centrifuged and washed with methanol/HAc (9:1, v/v) for three times to remove PC, and then the resultant SiO₂@NBD/MIPs (MIPs, for simplicity) were dispersed in 10 mL ultrapure water for further use. As a control, their corresponding non-imprinted polymers SiO₂@NBD/NIPs, namely NIPs for simplicity, were synthesized under the identical conditions in the absence of the template PC.

2.5. Fluorescence measurement

All the fluorescence (FL) intensity detections were conducted under the same conditions: the excitation and emission slit widths were both 7 nm and the excitation wavelength was set at 468 nm with a recording emission range of 488–700 nm. SiO₂@NBD/MIPs or SiO₂@NBD/NIPs was added to the known concentration of analyte and the final concentration of MIPs or NIPs was 0.9 mg mL^{−1}.

2.6. Analysis of water samples

Samples including seawater and lake water were used to demonstrate the applicability of the SiO₂@NBD/MIPs for the detection of PC. Seawater samples were randomly collected from the surface seawater of Yellow Sea and lake water samples were collected from San Yuan Lake, located in the coastal zone of Yantai City. Before analysis, the water samples were filtered with 0.45 µm microfiltration membrane to remove the suspended particles. The spiked seawater and lake water samples diluted 100-fold with different concentrations of PC were used to validate the accuracy and practicality of the MIPs.

3. Results and discussion

3.1. Preparation and detection principle of SiO₂@NBD/MIPs

Scheme 1 illustrates the preparation process and possible detection principle of SiO₂@NBD/MIPs sensor. As seen, the donor precursor (APTES–NBD) was synthesized via the reaction of NBD-Cl with APTES by nucleophilic substitution. Then, SiO₂

Scheme 1. Schematic illustration for the preparation process and possible detection principle of $\text{SiO}_2\text{@NBD@MIPs}$.

nanoparticles were used as core materials, PC as the template molecule and TEOS as the cross linker, and the resultant APTES–NBD conjugates as donor precursor and APTES as functional monomers were spontaneously anchored onto the surface of the silica nanoparticles through a condensation reaction, which led to the formation of $\text{SiO}_2\text{@NBD@MIPs}$ after removing the embedded template PC. For this $\text{SiO}_2\text{@NBD@MIPs}$ sensor, upon light irradiation, there is only the emission spectrum of NBD in the absence of PC, however, in the presence of PC, the binding through hydrogen bond between the carboxyl group of PC and the amino group of APTES, will quench the NBD fluorescence and increase PC fluorescence emission through FRET, realizing ratiometric detection for PC.

Generally, FRET process requires the overlap of the donor emission spectrum of a fluorescent dye and the acceptor absorption spectrum of an analyte (or its derivatives) (Liu et al., 2013). In this study, APTES–NBD conjugates served as energy donor and PC as acceptor. As seen from Fig. S1A, the fluorescence emission spectrum of APTES–NBD conjugates overlapped the absorption spectrum of PC, which suggested that the resonance energy transfer from the APTES–NBD conjugates to PC may occur if they were spatially close to each other. The fluorescence emission of APTES–NBD conjugates can be strongly absorbed by PC, resulting in fluorescence quenching of the donor. Actually, the PC binding will quench the fluorescence of donor by two possible pathways: the resonance energy transfer and the common charge transfer between donor and PC. Fig. S1B demonstrates the quenching mechanism of donor fluorescence by the resonance energy transfer from donor to PC acceptor. When the excited-state electrons of the donor return to ground state through the pathway of a, b, and c, the ground-state electrons of the PC will transit to the excited states through the corresponding pathway of a', b', and c', respectively, due to the polar–polar resonance of donor and

acceptor. The coupled transitions will lead to the highly efficient quenching of donor fluorescence (Gao et al., 2008). On the other hand, it has to be noted that the fluorescence of donor may also be quenched by the charge transfer, as illustrated in Fig. S1C. PC has many amino groups and the amino group has a nitrogen lone-pair electron, while NBD has an electron-deficient aromatic ring with a nitro. When the absorption band of PC (at 620 nm) overlaps with the emission band of APTES–NBD conjugates (at 535 nm), a charge transfer interaction may occur between electron-rich amino group of PC and the electron-deficient aromatic ring of NBD. However, in the case of PC, the resonance energy transfer is a predominant quenching process. Hence, in the presence of PC, the excited-state energy of the donor APTES–NBD conjugates could be transferred to PC (Fig. S1B), leading to the reduction of donor fluorescence and the increase of acceptor fluorescence. Therefore, the as-prepared $\text{SiO}_2\text{@NBD@MIPs}$ sensor could realize ratiometric fluorescence detection of PC based on FRET.

3.2. Characterization of $\text{SiO}_2\text{@NBD@MIPs}$

The morphological structures of SiO_2 , $\text{SiO}_2\text{@NBD@MIPs}$ and $\text{SiO}_2\text{@NBD@NIPs}$ were characterized by TEM and SEM, as shown in Fig. 1. It was observed from Fig. 1A that SiO_2 nanoparticles had good dispersion with the average diameter about 70–90 nm. As seen from Fig. 1B, MIPs also exhibited good dispersion and the imprinting shell thickness was about 5–10 nm calculated from the TEM image. Noticeably, the MIPs displayed a highly rough outside polymeric surface (Fig. 1C), and in contrast, the surface of NIP particles was still smooth (Fig. 1D), which indicated that there are a large number of exposed complementary imprinted cavities on the surface of MIPs while no recognition sites on the surface of NIPs.

The UV absorption and fluorescence spectra were employed for

Fig. 1. (A) TEM image of SiO_2 (inset: SEM image), (B) TEM images of $\text{SiO}_2\text{@NBD@MIPs}$, (C) SEM images of $\text{SiO}_2\text{@NBD@MIPs}$, and (D) TEM image of $\text{SiO}_2\text{@NBD@NIPs}$ (inset: SEM image).

characterization of APTES–NBD conjugates. As known, the NBD–Cl, as an amine reactive reagent, is not fluorescent until it is covalently linked (Carlson et al., 2006). As seen from Fig. S2, the NBD–Cl has no absorption spectrum at 468 nm (a), however, after it reacted with APTES, new absorption spectrum at 468 nm emerged (b) as well as the fluorescence spectrum at 535 nm (d), indicating the APTES–NBD conjugates were successfully obtained. Moreover, the absorption spectrum of the $\text{SiO}_2\text{@NBD@MIPs}$ at 468 nm (c) and its fluorescence spectra at 535 nm (e) further confirmed the successful modification of the APTES–NBD conjugates onto the surface of the silica nanoparticles through sol–gel process.

The infrared spectra of SiO_2 (a) and MIPs (b) were displayed in Fig. S3. As can be seen, the characteristic peaks around 466 and 802 cm^{-1} could be ascribed to Si–O stretching vibration, and the wide and strong absorption band around 1095 cm^{-1} belonged to stretching vibrations of Si–O–Si, illustrating the presence of SiO_2 matrices in the two materials. The characteristic peak of amino groups at around 1388 cm^{-1} , verified the successful introduction of amine ligands at the surface of silica nanoparticles, and we can judge the successful preparation of $\text{SiO}_2\text{@APTES-NBD@MIPs}$ instead of $\text{SiO}_2\text{@APTES}$, since the APTES–NBD conjugates had been evidenced as above UV and fluorescence spectra.

3.3. Fluorescence properties of the $\text{SiO}_2\text{@NBD@MIPs}$

Fluorescence performances of the $\text{SiO}_2\text{@NBD@MIPs}$ sensor for PC strongly depended on the variables including pH, response time and the fluorescence stability. And the relevant variables were studied systematically as follows. The effect of solution acidity on the $\text{SiO}_2\text{@NBD@MIPs}$ response to PC has been discussed, since pH played an important influence on the charge of PC and

the fluorescence intensity of MIPs. Experimental results showed that the I_{657}/I_{535} ratio of MIPs performed well in the pH range from 4 to 8.5 (Fig. 2A). Under strong acidic conditions ($\text{pH} < 4$), the amino groups on the surface of MIPs may be partially protonated, which decreased the electrostatic interaction of MIPs and PC. When pH was higher than 8.5, PC may be slightly denatured, which may decrease the interaction between the PC and the imprinted cavities. It can be clearly seen that the I_{657}/I_{535} ratio of MIPs increased with the increase of pH from 4 to 6 and then decreased when pH values were higher. This revealed that pH 6 was the most suitable condition for detection of PC, which was selected for further experiments.

The response time of the MIPs was also investigated to assess the accessibility to binding sites. As seen from Fig. 2B, the fluorescence intensity at 535 nm decreased fast within 6 min when the concentration of PC was 100 nM, after which the curve became flat. Therefore, 6 min was chosen as the response time for further experiments. The response time of the MIPs is short, which can be attributed to the thin imprinting layer. As can be seen from the TEM image of $\text{SiO}_2\text{@NBD@MIPs}$, after sol–gel polymerization process, the imprinting layer on the surface of SiO_2 is only several nanometres, which provides low mass transfer resistance, high site accessibility toward the template PC, resulting in the rapid response of the MIPs for PC. As is well known that, reducing the imprinting-shell layer thickness is an effective way to shorten the response time of MIPs for template. Moreover, the fluorescence stability of $\text{SiO}_2\text{@NBD@MIPs}$ was also investigated during the storage by repeatedly detecting the fluorescence intensity every day. The intensity retained 98% of its initial response when the MIPs were stored for 10 days (Fig. 2B, inset), which implied that the resultant MIPs displayed good physical stability and chemical

Fig. 2. (A) Effect of pH on the I_{657}/I_{535} ratio of $\text{SiO}_2\text{@NBD@MIPs}$ in the presence of 100 nM PC at room temperature, (B) fluorescence response time of $\text{SiO}_2\text{@NBD@MIPs}$ for PC (inset was fluorescence intensity change of $\text{SiO}_2\text{@NBD@MIPs}$ within 10 days).

inertness.

3.4. Sensitivity and selectivity of the sensor

To evaluate the sensitivity of the $\text{SiO}_2\text{@NBD@MIPs}$ sensor, fluorescence responses were measured upon addition of different amounts of PC in water dispersion and a working curve was established by plotting the ratio of the emission intensities at 535 nm and 657 nm (I_{657}/I_{535}) versus PC concentration (Fig. 3A). It can be seen that in the absence of PC, excitation of the MIPs at 468 nm could only result in the emission of the donor APTES–NBD conjugates at 535 nm, and no characteristic emission of PC acceptor was observed. With the addition of PC, the APTES–NBD emission at 535 nm gradually decreased, and the emission band at 657 nm appeared and increased remarkably, which corresponded to the fluorescence emission of PC, indicating that the energy of the donor APTES–NBD conjugates could be transferred to PC. By plotting the emission intensity ratio versus PC concentration, the calibration curve for the MIPs was obtained (inset of Fig. 3A). As seen from the figure, the ratio of the intensities at 657 nm to that at 535 nm (I_{657}/I_{535}) increased steadily with PC concentration increasing and the linear range was 1–250 nM with the detection limit (LOD, $S/N=3$) of 0.14 nM, owing to the two well-resolved

Fig. 3. The fluorescence spectra of the ratiometric sensor with addition of the different concentrations of PC for the MIPs (A) and for the NIPs (B). Concentrations of PC from left to right are 0, 20, 30, 60, 85, 100, 120, 150, 200 and 250 nM. Concentration of MIPs or NIPs was 0.9 mg mL^{-1} ; excited light, 468 nm; slit widths of excitation and emission, 7 nm. Inset shows the linear relations between I_{657}/I_{535} and the concentrations of PC from 0 to 250 nM.

emission peaks with comparable fluorescence intensities. Meanwhile, the fluorescence property of the non-imprinted $\text{SiO}_2\text{@NBD@NIPs}$ to PC was also examined. From Fig. 3B, we can see that fluorescence intensity of NIPs was slightly decreased with the addition of PC, and hence, the sensitivity was much lower and the linear range was narrower (inset of Fig. 3B). As observed from Fig. 3, MIPs and NIPs offered different linear relationships, and the decrease of fluorescence intensity of MIPs was much larger than that of the NIPs at the same PC concentration. So, a high imprinting factor could be obtained of 9.1. For the MIPs, most of the recognition sites were located on the surface of silica matrix, so PC has more chance to enter the recognition sites, quenching the fluorescence intensity of the donor APTES–NBD conjugate obviously and increasing the fluorescence intensity of PC. As for NIPs, there are no recognition sites on the surface of silica matrix, so PC cannot enter into the inner of the NIPs, resulting in slight variation of the fluorescence intensity. And the fluorescence intensity of the donor can only be quenched by non-specific adsorption of PC. The results further demonstrated that the MIPs based fluorescence sensor could sensitively detect PC.

The selectivity of MIPs sensor was further evaluated by a competitive binding test using PE, spirulina powder and BSA. PE is

Fig. 4. The selectivity of MIPs and NIPs for PC over other analogues including spirulina, PE and BSA at concentration of 11 mg L^{-1} . Concentration of MIPs or NIPs was 0.9 mg mL^{-1} ; excited light, 468 nm ; slit widths of excitation and emission, 7 nm .

Table 1
Results for the determination of the PC in seawater and lake water samples.

Sample	Added (nM)	Found (nM)	Recovery ^a ± RSD (%)
Seawater	0	0	–
	20.00	19.78	98.9 ± 3.4
	50.00	53.70	107.4 ± 3.8
	100.00	109.54	109.5 ± 4.1
Lake water	0	0	–
	20.00	18.76	93.8 ± 3.5
	50.00	52.03	104.1 ± 4.2
	100.00	110.20	110.2 ± 4.7

^a Average value from three individual experiments.

the analogue to PC and spirulina powder contains amounts of PC and PE. In order to contrast, we also used BSA with different shapes and molecular weights from PC as a competitive protein. It can be seen from Fig. 4 that PC induced a prominent fluorescence ratio (I_{657}/I_{535}) increment compared to the blank sample (no protein was added). In contrast, addition of other proteins led to smaller or no fluorescence ratio change, because the recognition sites of PC imprinted cavities were not complementary to them, resulting in less chance to enter the recognition sites. And it can also be seen that the fluorescence ratio of the spirulina is higher than that of PE, since spirulina powder contains certain amounts of PC. The results implied that the MIPs had a high selectivity for PC over other competitive proteins.

3.5. Practical application of the sensor to environmental water samples

To further evaluate its applicability in real water samples, the MIPs ratiometric fluorescence sensor was applied to detect PC in real water samples diluted 100-fold spiked with different amounts of PC, including seawater and lake water. Studies were carried out with three concentrations (25, 50 and 100 nM) spiked in each sample. Each concentration was done in triplicate, and the averages were presented with relative standard deviation (RSD). As listed in Table 1, satisfactory recoveries were attained of 98.9–109.5% with RSDs of 3.4–4.1% for the spiked seawater samples and

93.8–110.2% with RSDs of 3.5–4.7% for the spiked lake water samples, respectively. The results indicated that the MIPs ratiometric fluorescence sensor was practically feasible for accurate determination of trace PC in complicated environmental water samples, and consequently algae blooms monitoring and removal/remediation could be successfully performed.

4. Conclusions

In summary, we have successfully constructed a novel PC imprinted ratiometric fluorescence sensor via facile sol-gel polymerization for the recognition and detection of PC based on FRET. By taking advantages of the high selectivity of MIPs and the high sensitivity of ratiometric fluorescence, the sensor demonstrated highly selective and sensitive recognition and determination of PC. The simple, rapid, reliable, time-saving and cost-effective strategy provided an excellent fluorescent analysis platform for PC monitoring. Moreover, this strategy may provide an alternative approach for constructing FRET-based detection systems for sensitively and selectively recognizing and detecting a variety of analytes for potential utilizations.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.bios.2015.10.019>.

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