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ORIGINAL PAPER

Influence of pH on aptamer-based gold nanoparticles colorimetric sensors

Jiye Li[1,2] · Xinyu Zuo[2,3,4] · Hao Liu[5] · Yuanyang Xie[1,2] · Yu Huang[1,2]

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Abstract

In recent years, aptamer-based gold nanoparticles (AuNPs) colorimetric sensors have received extensive attention, especially in discovery of disease markers and food safety. However, the detection sensitivity is not high enough and the detection results are prone to false positives. Therefore, it is urgently to improve the performance of sensors, ranging from the optimization of sensor detection conditions and establishment of new sensing methods. pH is an important parameter in the solution. In this article, pH was employed to adjust the aptamer charge to increase the sensitivity of lysozyme detection, and the detection limit can be approached as low as 0.05 nM. pH was also used to adjust the target charge to improve the performance of sensors. Chloramphenicol (CAP) and precursors of chloramphenicol (CAP-base) were used as targets to verify the charge effect introduced by pH adjustment. The experiment found that the neutral or electronegativity target would weaken the response of the sensor. To achieve the detection of CAP (electron neutral), a competitive colorimetric sensor had been successfully established to detect CAP. The Derjaguin–Landau–Verwey–Overbeck (DLVO) theory was used to explain the effect of pH on sensor performance. Therefore, by adjusting pH, the detection sensitivity can be improved significantly and a new sensing method can be established, which provide a broad application prospects for chemical, environmental and biological sensing.

Keywords Aptamer · Gold nanoparticles · Colorimetric · pH

Introduction

Compared with the traditional detection system, the colorimetric sensors is a simple and easy-to-use method to realize point-of-care test (POCT) with advantages of fast detection, high portablility, etc. [1]. At present, the development direction of colorimetric sensors is to reduce the limit of detection (sensitivity) and improve selectivity [2, 3]. Therefore, it is necessary to optimize the detection methodology and its sensing capability. pH is one of the most important parameters to influence sensing performance because it is associated with various chemical conditions, such as biological functions, microbialactivity, chemical behaviors in biochemistry, environmental science and chemistry [4]. In addition, pH plays an important role in the colorimetric sensors detection by affecting targets and probes. Qin et al. improved the selectivity of colorimetric sensors by adjusting pH and achieved selective detection of arginine [5]. Balamurugan Aet al. reduced the detection time by adjusting pH [6]. Nan Hao et al. made a pH-resolved colorimetric sensors for simultaneous multiple target detection [7]. Lu Li et al.

Jiye Li and Xinyu Zuo are contributed equally to this work.

✉ Yuanyang Xie
yuanyangxie@outlook.com

✉ Yu Huang
huangyu@cigit.ac.cn

Jiye Li
1426193454@qq.com

Xinyu Zuo
234122570@qq.com

Hao Liu
379337648@qq.com

[1] Chongqing Institute of Green and Intelligent Technology, Chinese Academy of Sciences, Chongqing 400714, China

[2] University of Chinese Academy of Science, Beijing 100049, China

[3] Chongqing University, Chongqing 400044, China

[4] Upper Changjiang River Bureau of Hydrological and Water Resources Survey, No.410 Haier Road, Jiangbei District, Chongqing 400021, China

[5] Chongqing Survey Institute, Yubei District, No.6 Dazhulin Eastern Road, Chongqing 401121, China

made label-free and pH-sensitive colorimetric materials for sensing urea [8]. The buffer solution, such as acetate, phosphate is usually employed to adjust pH. Therefore, pH adjustment is a significant method to improve sensing performance of colorimetric sensors.

Gold nanoparticles (AuNPs) are considered to be an ideal sensing platform in colorimetric sensors due to their unique physical, chemical and biological properties. The property of localized surface plasmon resonance (LSPR) provided by gold nanoparticle is strongly dependent on the interparticle distance as well as its size and shape [9]. Aptamers are single-stranded nucleic acid (ssDNA or RNA) and are well known for their high affinity to targets with high specificity [10, 11]. The aptamer-based AuNPs colorimetric sensors are one of the most frequently used sensors. It has shown good performance in detection of pesticides [7, 12], pathogenic bacteria [13, 14], and heavy metals [15, 16], etc. The aptamer is used as a probe to recognize target and carry a large amount of negative charge to make the system stable [9]. The aptamers specifically recognize and bind target, and then move away from the surface of AuNPs. The stability of gold nanoparticle is reduced and addition of salt induces aggregation of AuNPs. The degree of aggregation of gold nanoparticles triggered by addition of salt indicate signal of target [17].

In this paper, pH adjustment was employed to improve the performance of sensor on the basis of previous ones [18, 19]. A large amount of negative charge exhibited at the surface of aptamer enable aptamer-modified AuNPs to be stable at high salt concentration [9]. Aptamer-based AuNPs colorimetric sensors were used to detect lysozyme. The pH can affect the performance of sensor by affecting the charge of aptamer and improve the performance of sensor with detection of lysozyme. Furthermore, a pH optimized colorimetric strategy was introduced for the detection of CAP and its mechanism had been explained, which is beneficial to design aptamer-based AuNPs colorimetric sensors. The classic Derjaguin–Landau–Verwey–Overbeck (DLVO) theory was employed to explain the mechanism of pH effect on the aptamer-based AuNPs colorimetric sensors. pH adjustment to improve sensor performance provides a new strategy to meet the requirment of chemical and biological sensing in the near future.

Experimental section

Materials

Lysozyme, pepsin, choline oxidase (ChOx), glucose oxidase(GOx), and Chloroauric acid (HAuCl4·3H2O) were obtained from Sigma. Bovine serum albumin (BSA), human serum albumin (HSA), Chloramphenicol (CAP), Thiamphenicol (TAP), kanamycin sulfate (Kana), cephalexin monohydrate (CPX), ampicillin sodium salt (AMP), tetracycline hydrochloride (TC). The aptamer of lysozyme and CAP were purchased from Shanghai Biological Technology Development Co., Ltd and their sequences are listed in Table 1. Trisodium citrate anhydrous was procured from Alfa Aesar. Tris(2-carboxyethyl)phosphine hydrochloride (TCEP), acetate, and L-lysine (Lys) were purchased from Aladdin. Sodium acetate trihydrate and tris(hydroxymethyl) aminomethane (Tris) were purchased from BBI Life Sciences. HCl, NaH_2PO_4, Na_2HPO_4, and NaCl were procured from Chongqing Chuandong Chemical (Group) Co., Ltd. All reagents were of at least analytical grade. The ultrapure water used throughout the work had a resistivity higher than 18.00 MΩ cm^{-1}.

Apparatus

A custom-made absorption spectroscope was utilized to record the spectra. A tungsten halogen lamp (HL-2000-HP, Ocean Optics) was used as a light source to illuminate the sample, which was contained in a 1 cm path-length quartz cuvette in the dark. Then, quartz cuvette was used as the sample cell and the absorbance from the samples was recorded and analyzed by programs written in C++ and Matlab. Due to the properties of spectrometer (HR4000, Ocean Optics) and sample, the acquiring time to record a spectrum from 400 to 800 nm was set to be 1 ms. Transmission electron microscope (TEM) images were obtained by Zeiss LIBRA 200FEG TEM. The zeta potential was obtained by Malvern Zetasizer Nano ZS.

Preparation of aptamer-based AuNPs colorimetric sensor

The preparation of AuNPs was used as previously method [20]. $HAuCl_4·3H_2O$ (100 mL, 1 mM) was heated and boiled.

Table 1 Sequence of aptamer

Name	Sequence
Lysozyme aptamer	5′-SH-ATC AGG GCT AAA GAG TGC AGA GTT ACT TAG-3′
CAP aptamer	5′-A_5 CAA TAA GCG ATG CGC CCT CGC CTG GGG GCC TAG TCC TCT-3′

Then, trisodium lemon (15 mL, 1%) was added and heated. The mixed-solution was stirred continually for 15 min. Then, the prepared AuNPs were stored in the refrigerator at 4℃. The functionalized AuNPs were modified with HS-aptamers [20] and PloyA-aptamers [21].

Assay

Aptamer-based AuNPs colorimetric sensor for detection of lysozyme

Aptamers-based AuNPs (50 µL), NaCl (1.0 M, 300 µL), lysozyme (4.5 nM, 1550 µL) and acetate buffer (pH 4.0, 100 µL, 0.20 M) were incubated at room temperature for 1 h. The shift of resonance wavelength was used for quantitative analysis.

Aptamer-based AuNPs sensor for detection of CAP or CAP-base

Aptamers-based AuNPs (50 µL), NaCl (2.0 M, 275 µL), CAP or CAP-base (0.19 mM, 1575 µL) and acetate buffer (pH 3.0, 100 µL, 0.20 M) were incubated 0.5 h at room temperature. The competitive colorimetric sensor for detection of chloramphenicol was established as follows. Aptamer-based AuNPs (50 µL), NaCl (2.0 M, 275 µL), CAP (475 µL), CAP-base (1.1 mL, 27.3 µM) and pH 3.0 acetate buffer (0.2 M, 100 µL) were incubated 0.5 h at room temperature. The ratio of absorbance at 620 nm and 520 nm (A620 nm/A520 nm) was used for quantitative analysis. Tap water and water collected from Jialing River was chosen as the real sample for measurement. They were filtered and purified by using a 0.22 µm PES membrane before use. All data were measured three times independently.

Results and discussion

Characterization and construction of Aptamer-based AuNPs colorimetric sensor

Figure 1a is the absorption spectra of AuNPs, HS-aptamer-based AuNPs and PloyA-aptamer-based AuNPs. AuNPs coated with citrate shows plasmon resonance absorption peak at 520 nm. After the anchor of PloyA-aptamer and HS-aptamer, the plasma resonance peak was moved from 520 to 528 nm and 524 nm, respectively. The inset shows the preparation of AuNPs with a red color and has a good dispersion. Figure 1b is the TEM image of AuNPs and the histogram of the inset is the dynamic light scattering (DLS) measuring the size of AuNPs, which shows about 10–20 nm. As shown in Fig. 1c, aptamers modified AuNPs have good salt resistance at low salt concentration. Once the concentration of NaCl approached 0.4 M, both HS-aptamer-based AuNPs and PloyA-aptamer-based AuNPs could be induced to aggregate and their plasmon resonance exhibit remarkable red-shift.

Influence of pH on sensing performance by affecting aptamer

To investigate the effect of pH on aptamer and sensor performance, HS-aptamer-based AuNPs colorimetric sensor was used to detect lysozyme. The aggregation of AuNPs is recognized as the type of non-crosslinking, so the detection speed is fast. Acetate buffer and phosphate buffer (0.01 M) were used to adjust the pH of mixture (150 mM NaCl, 50 µL aptamers-based AuNPs, and 3.8 nM lysozyme). The relative peak shift of aptamer-based AuNPs with different pH is shown in Fig. 3a. The mixed-solvent with different pH can shift the peak wavelength of AuNPs, indicating that pH is a key factor to affecte sensor performance.

It is known that the phosphate group of aptamer carries a large amount of negative charge [9], which makes the aptamer-modified AuNPs can be stable at high salt concentration. The stability of AuNPs system can be explained by Derjaguin–Landau–Verwey–Overbeck (DLVO) theory [22, 23]. DLVO describes that the relationship between the attraction (van der Waals forces) and repulsion (electrostatic interactions) of nanoparticles are contributed comprehensively to the stability of this system. When the electrostatic repulsion of the system is dominant, the system is stable and vice versa. According to the DLVO theory, the stability of the system is to be maintained at a certain point. Citrate and aptamers play an important role to make electrostatic repulsion dominant in the system during the process of preparation and preservation of gold nanoparticles. However, during the detection stage, it is necessary to reduce the electrostatic repulsion to make the gold nanoparticles aggregate. The reduction in aptamer charge can effectively promote the AuNPs to aggregate, thereby improve the detection sensitivity.

Adjustment of the pH is an effective method to adjust the charge of aptamer. At acidic conditions as shown in Fig. 2B, the zeta potential of aptamer-based AuNPs is negative while it is turned be to positive at alkaline condition. At the same time, the particle size of aptamer-based AuNPs increases with the decrease in pH (Fig. 2c). These phenomena are due to the reduction of electrostatic repulsion between the aptamer-based AuNPs under acidic conditions. Decrease in pH promotes the protonation of phosphate group, which reduces the negative charge of aptamer. Then the electrostatic repulsion between AuNPs is reduced and aggregation of AuNPs is promoted [24]. In other words, the sensitivity of sensor was able to be improved under acidic conditions. The isoelectric point of RNA is 2.5–2.9, while the isoelectric point of DNA (double-stranded) is approximately 4.0.

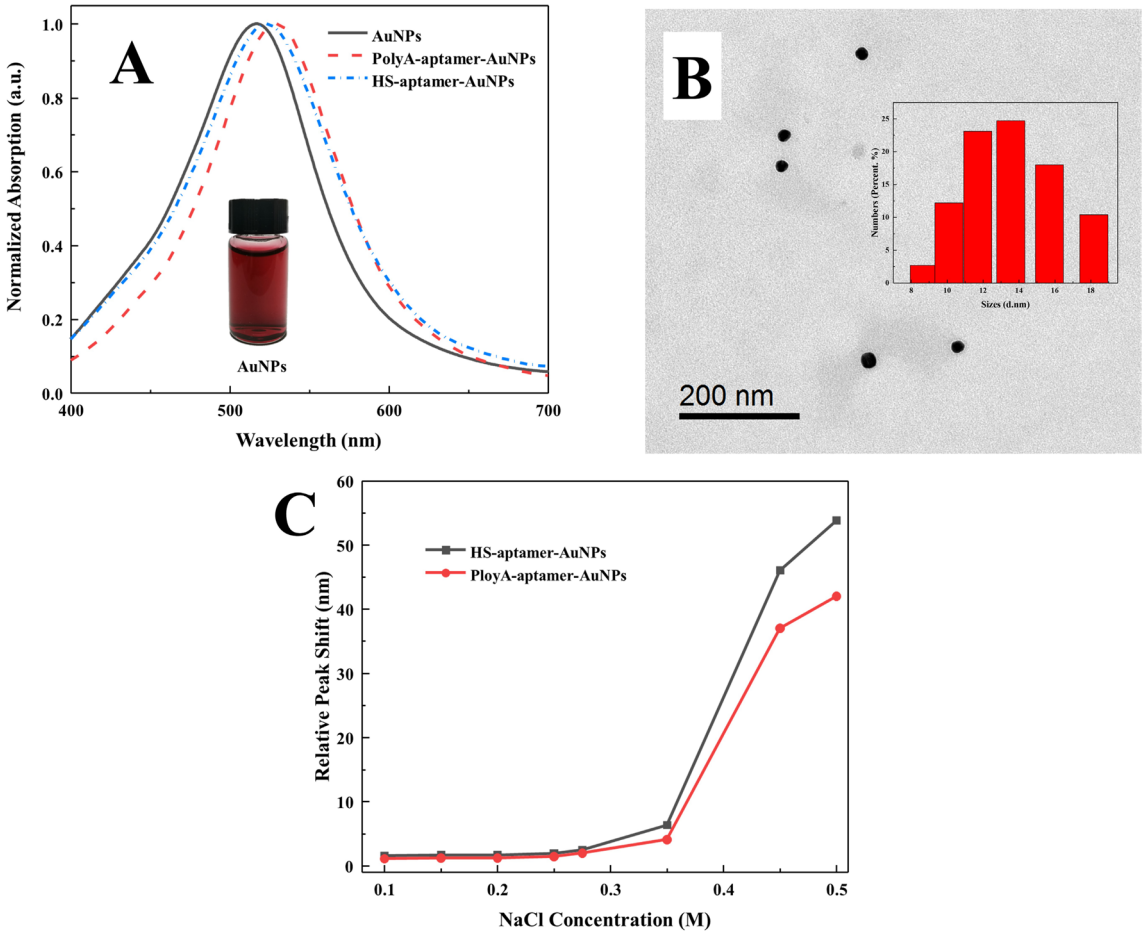


Fig. 1 **a** The normalized absorption spectra of AuNPs, HS-aptamer-AuNPs, and PolyA-aptamer-AuNPs (the inset is a photograph of prepared AuNPs); **b** TEM image of AuNPs (the inset is the DLS measurement about the size of AuNPs); **c** The concentration effect of NaCl solution on the aptamer-based AuNPs colorimetric sensors

The isoelectric point of single-stranded DNA (aptamer) is comparable to that of RNA due to the similar structure. When the pH of buffer was set to below 3.0, the aptamer had almost no negative charge. The reduced electrostatic repulsion produces an unstable AuNPs system. It was found that the influence of buffer with different pH tends to be consistent. When the pH was above 7.0 (phosphate buffer, 100 μL, 0.20 M), the hydroxide will further increase the electrostatic repulsion, making AuNPs to be more difficult to aggregate.

On the other hand, Yuan et al. showed that AuNPs modified with amphoteric-ligands can form hydrogen bonds with ligands on the adjacent AuNPs through protonation of the sulfonic acid group of ligand, thereby triggering aggregation [25]. Similarly, protonated phosphate groups can also form hydrogen bonds with adjacent phosphate groups, further promotes the aggregation of AuNPs. To ensure the sensitivity and stability of sensor, the experimental conditions were optimized and test pH was set to be 4.0. The final detection limit of lysozyme is 0.05 nM. Scheme 1a describes the effect of pH on this sensor performance. To our knowledge, this is currently the lowest detection limit of aptamer-based AuNPs colorimetric sensor (Table 2).

Influence of pH on performance by affecting target

The response speed is another criteria to evalute sensor and the speed of ployA modified AuNPs colorimetric sensor is faster than thiol bonds counterpart [21]. Therefore, a competitive colorimetric strategy by using gold nanoparticles modified with ployA was established to distinguish chloramphenicol (CAP) and chloramphenicol precursors (CAP-base), although they have similiar strucutres as shown in Fig. 3. The experimental condition was set to be pH 3.0 and high salt concentration (0.275 M NaCl). The aptamer-based AuNPs colorimetric sensor showed different responses to the presence of CAP and CAP-base (Fig. 4a). The response of

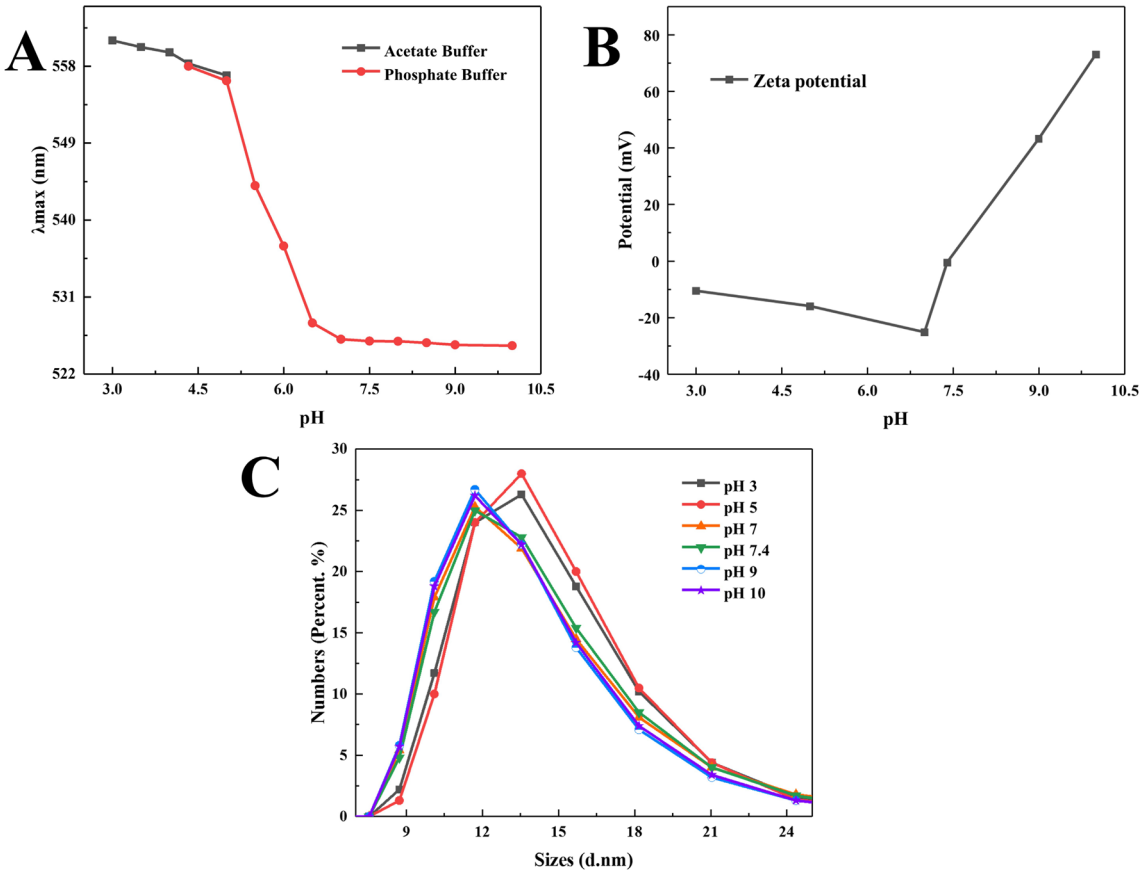
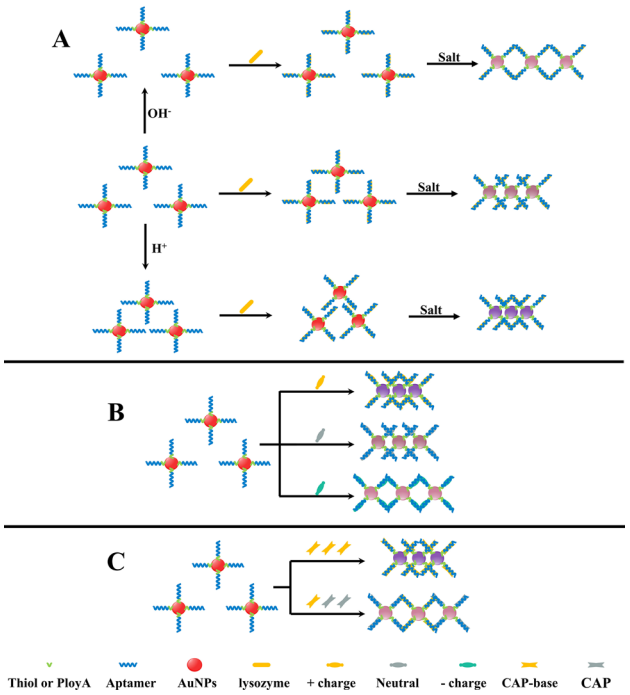


Fig. 2 **a** The relative peak shift of aptamer-based AuNPs with different pH solution; **b** The zeta potential of aptamer-based AuNPs with different pH solution; **c** The DLS measuring the size of AuNPs with different pH solution

sensor to CAP-base was more obvious, and the response to CAP was worse. Although CAP-base and CAP have a similar structure, the target charge is inconsistent under acidic conditions. The CAP-base has an amino group so it exhibits positively charged under acidic conditions. However, CAP has a secondary amino group and is difficult to be protonated under acidic conditions. Therefore, it exhibited electrically neutral. According to the DLVO theory, a positively charged CAP-base acts as a counter ion, which reduces the electrostatic repulsion and contributes to the aggregation of AuNPs. Since the CAP is electrically neutral, the aptamer cannot reduce the electrostatic repulsion of the system after the capture of CAP. Then the aggregation of gold nanoparticle is difficult to be initiated. This further confirms that the DLVO theory is able to be applied to explain the effect of target charging on the sensor.

A sophisticated experiment was designed to verify the effect of target charging on sensor performance. When the buffer of pH was10.0, the response of sensor to CAP base was significantly weakened, and the peak position of AuNPs with CAP appeared merely blueshift (Fig. 4b). High pH inhibited the protonation of primary ammonia but promoted deprotonation of hydroxyl groups. Therefore, negatively charged CAP produced blue-shift spectra of gold nanoparticle. On the other hand, CAP-based is not charged, which resulted in weak aggregation of AuNPs (Fig. 4c). The charge effect of target on AuNPs is described in Scheme 1b.

Furthermore, to detect CAP, a competitive colorimetric sensing strategy was established as shown in Scheme 1c. When CAP and CAP-base were introduced in the solvent simultaneously, CAP competed with CAP-base to attract aptamers. Since the CAP is electrically neutral, the surface charge of gold nanoparticles did not change after its capture of CAP. The large amount of negative charge carried by aptamer still prohibited the aggregation of AuNPs. In contrast, the capture of CAP carried out by aptamer prohibited the captures of CAP-base. Then the CAP-base can no longer enter the electric double layer of AuNPs and perform as counterion. Therefore, due to the competitive aptamers of CAP and CAP base, disaggregation of gold nanoparticles



Scheme 1 **a** Influence of different pH on sensor performance; **b** the influence of targets with different charges on colorimetric sensors; **c** The principle of competitive colorimetric sensor detecting CAP

was achieved. The degree of disaggregation is related to the amount of CAP. Figure 5 describes the responses and TEM images of aptamer-based AuNPs for 0 μM and 32 μM CAP with 15 μM CAP-base, which further proves the feasibility of this method. By optimizing experimental parameters, including the concentration of probe, sample pH, the final detection limit of CAP was 22 nM. Furthermore, to verify the potential applications of this method, the real samples were detected by the known quantity of CAP spiked in tap and river water (Table 3). The high recoveries indicate the

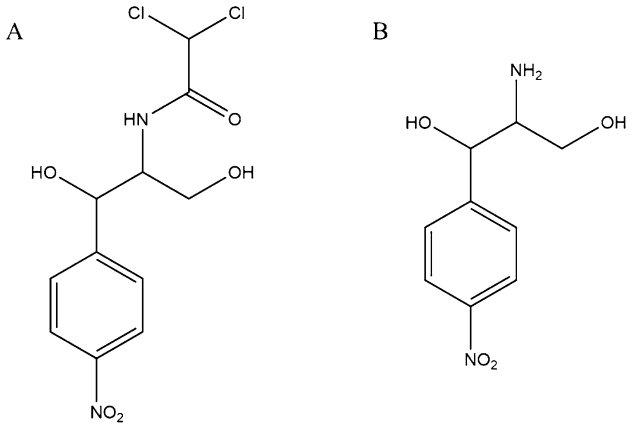


Fig. 3 **a** Chemical structures of CAP; **b** Chemical structures of CAP-base

feasibility of this method and prove the potential applications of this method in environmental monitoring.

Conclusions

The effect of pH on AuNPs colorimetric sensor is presented in this paper. The parameter of pH has the capability to determine the surface charge of aptamer and target. Therefore, it was employed to adjust the charge ability of probe to promote the aggregation of AuNPs. In addition, the effect of target charge on the sensor performance is experimentally demonstrated as well. The adjustment of pH was implemented to improve the sensitivity of sensor. The experimental results are universal for aptamer-based AuNPs colorimetric sensor and could provide a guideline for the design of aptamer-based AuNPs colorimetric sensor and its performance.

Table 2 Sensitivity of colorimetric detection lysozyme

Materials	Probe	Assay	Method	LOD	Reference
AuNPs	Human serum albumin (HSA)	Colorimetric	Interionic interaction	50 nM	[26]
AuNPs	Aptamer	Colorimetric	Silver reduction	0.1 ng/mL	[27]
AuNPs	Cys-Ala-Leu-Asn-Asn (CALNN)	Colorimetric	Interionic interaction	80 pg/mL	[28]
AuNPs	Aptamer	Colorimetric	Catalytic properties of the AuNPs	16 nM	[29]
AuNPs	Aptamer	Colorimetric	PDDA induced aggregation	4.4 nM	[30]
MBs	Aptamer	Colorimetric	Competition colorimetric	10 nM	[31]
Cu@Au NPs	Aptamer	Colorimetric	Iodide-based colorimetric detection	60 nM	[32]
AuNPs	Aptamer	Colorimetric	pH adjustment	0.05 nM	This work

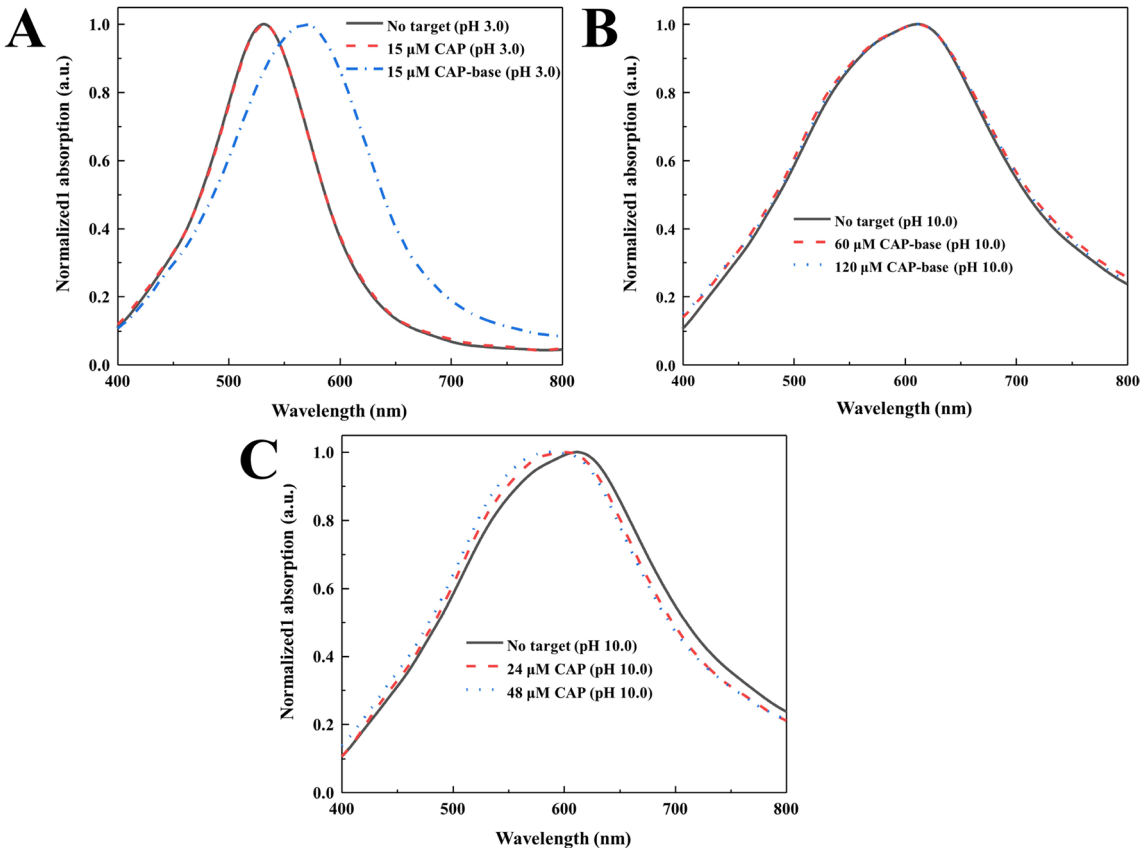


Fig. 4 **a** The normalized absorption spectra of Aptamer-based AuNPs detection CAP and CAP-base at pH 3.0 (0.275 M NaCl); **b** The normalized absorption spectra of the aptamer-based AuNPs detecting CAP directly in high pH (0.90 M NaCl); **c** The normalized absorption spectra of the aptamer-based AuNPs detecting CAP-based directly in high pH (0.90 M NaCl)

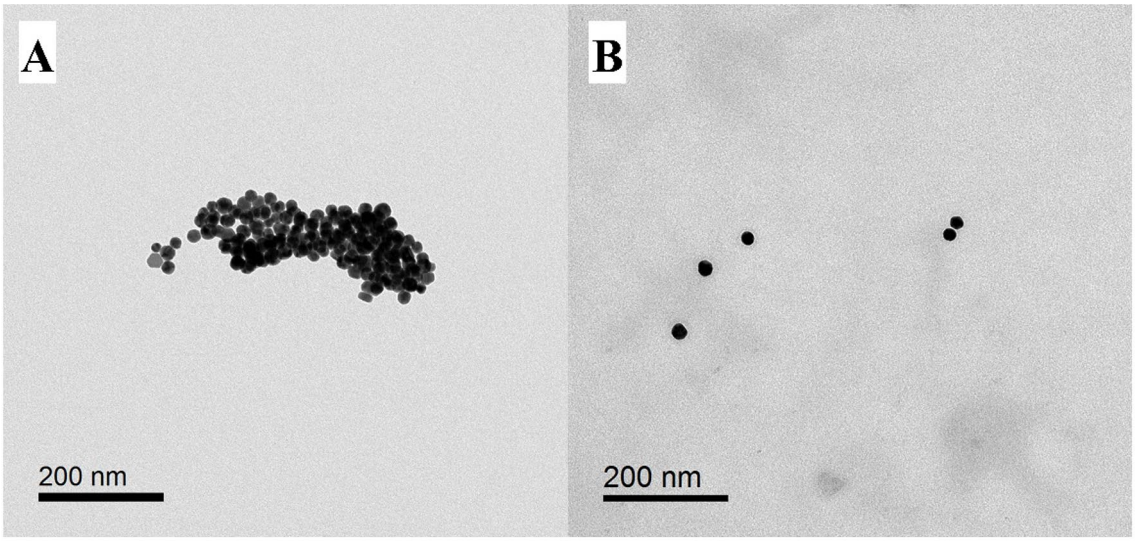


Fig. 5 **a** TEM images of aptamer-based AuNPs added CAP-base (15 μM) at pH 3.0; **b** TEM images of aptamer-based AuNPs added CAP (32 μM) and CAP-base (15 μM) at pH 3.0

Table 3 Performance of colorimetric assay for CAP determination in real water sample

Sample number	Sample	Added concentration (μM)	Detected concentration (μM)	Recovery (%)
1	Tap water	0.4	0.319	79.8
2	Tap water	0.8	0.658	82.3
3	Tap water	1.6	1.382	86.4
4	Tap water	2.4	2.210	92.1
5	River water	0.4	0.300	75.0
6	River water	0.8	0.642	80.3
7	River water	1.6	1.336	83.5
8	River water	2.4	2.170	90.4

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