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Boolean-logic-based nano-platform for competitive detection of biomacromolecules, surfactants, and explosives

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ABSTRACT

We introduce a competitive strategy based on gold nanoparticles (AuNPs) to construct a nano-platform for sensing negatively charged analytes (NCA), including biomacromolecules, surfactants, and explosives. This approach is based on the competitive binding between NCA and AuNPs to positively charged coralyne. In the presence of NCA, the electrostatic attraction between NCA and coralyne is stronger than AuNPs binding to coralyne. The competitive interactions are programmable and can be utilized to regulate the absorbance and solution color of AuNPs via Boolean logic (such as YES, NOT, OR, INHIBIT, IMPLICATION logic gates). These integrated logic circuits are constructed based on dispersion-dominated AuNPs sensing progress, which avoids false results generated from the aggregation-dominated AuNPs sensor. The new concept of Boolean-logic-based nano-platform may find applications in a wide range of biological digital diagnosis and practical environmental applications and extend to further development of molecular computing circuits.

1. Introduction

Nanoscale materials have become one of the most exciting and fascinating research areas in the past decades [1,2]. Noble metal nanomaterials, in particular, gold nanoparticles (AuNPs) have received considerable interest in various areas of analytical chemistry because of the unique optical and physicochemical properties [3,4]. Colorimetric methods have been proven to be promising for the detection of small molecules or biological macromolecules because the results can be easily examined without the need for expensive instrumentation and time-consuming procedures [5,6]. Generally, colorimetric assay can be mainly categorized into two classes [7]. The first class utilizes functional nanoparticles, which are covalently modified with thiolated DNA aptamers. The AuNPs aggregation can be induced by a three-component sandwich assay format using interparticle cross-linking mechanism. The second broad approach relies on the electrostatic interaction between target and unmodified AuNPs. A notable benefit of the second strategy lies in the elimination of extra ligand preparation procedures needed in the three-component sandwich assay format. Therefore, the unmodified AuNPs have been extensively used to establish various optical biosensors for the detection of specific targets, including DNA sequences [8], small molecules [9,10], proteins [11], and ions [12], based on an interparticle crosslinking aggregation mechanism. However, a significant limitation for this kind of biosensors is that AuNPs are easy to be influenced by high ionic strength or the existence of other impurities [13]. As a result, undesirable aggregation of AuNPs may occur in complicated practical environments, which restricts their application in practical samples [14]. Thus, dispersion-dominated detection instead of aggregation-dominated detection may represent a more promising strategy in practical applications.

Although many colorimetric assays demonstrate that sensitive determination of specific analytes can be accomplished rapidly within a few minutes and simply without complex instrumentation, recognition of a single target is not sufficient to follow the practical need. A further issue in targets detection or analysis involves the parallel multiplexed analysis of several analytes. At present, as far as we know, very few detection sensors have

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been developed based on unmodified AuNPs [6,15–18]. It is highly desirable to develop a nanosensor that can detect a broad range of different molecular targets.

Molecular-based logic gates and computing hold great promise for applications in computer technologies and life sciences [19]. This has attracted wide-spread attentions and made great progresses focused on problems in Boolean logic at the molecular scale to seek ideal circuits that satisfy logic operations [20–22]. Toward this goal, various logic gates utilizing different molecules or molecular-scale materials, including DNA, enzymes, ions, and small molecules [23–27], have been designed and constructed. To accelerate further development, applications of molecular logic gates to solve practical problems are required. Because of the simple and rapid molecular recognition ability, colorimetric logic gates have been found great potential applications in biosensing and environmental monitoring [28–30]. To design and construct sensitive, selective, and colorimetric Boolean-logic-based nano-platform will be interesting and exciting.

Coralyne, applied as an anti-cancer drug, is a type of planar alkaloid with positive charges (Fig. S1a) [31]. It has been found that coralyne could be capable of binding polydeoxyadenosine with an apparent binding constant of $1.05 \times 10^5\ M^{-1}$ [32,33], and causing the aggregation of AuNPs due to the electrostatic attraction [34]. Recent researches are mainly focused on the detection of coralyne and investigation of its molecular interactions with nucleic acids through adenosine$_2$–coralyne–adenosine$_2$ coordination [35–37]. However, few sensing methods have concentrated on using coralyne as a recognition element to detect an analyte of interest [38,39]. We suspect that different affinities between positively charged coralyne and various categories of negatively charged analytes (NCA) might provide the possibility to design a colorimetric assay.

Herein, the Boolean-logic-based nano-platform utilizing the ratio of UV–vis absorption at 644 and 521 nm (A_{644}/A_{521}) and solution color as outputs is constructed for rapid, colorimetric, and digital sensing a broad range of NCA, including biomacromolecules, surfactants, and explosives for the first time. To examine the flexibility of our colorimetric assay, we chose heparin (Hep), sodium dodecyl sulfate (SDS), and picric acid (PA) as model molecules. To the best of our knowledge, utilizing coralyne for the detection of SDS and PA has not been reported to date. The structures of Hep, SDS, and PA are shown in Fig. S1b–d in the Supporting Information. This colorimetric "readout" offers exceptional merits such as rapidness (less than 5 min), simple operation process (it can be easily employed by an operator with minimum scientific training), and low-cost portable instrument (the analyte can be readily detected with the naked eye). By taking advantages of the competitive detection, the dispersion-dominated method could effectively reduce inaccuracy and false results caused by undesirable aggregation of AuNPs.

2. Material and methods

2.1. Materials

Coralyne was purchased from Acros (NJ, USA). Chloroauric acid ($HAuCl_4$) was purchased from Sigma–Aldrich Co. Ltd. Other chemicals employed were obtained from Aladdin Reagent Co. Ltd. All chemicals were used without further purification. Picric acid was prepared with concentration of 1.0×10^{-2} M in NaOH. Other solutions were prepared by ultrapure water with a resistivity of 18.2 MΩ cm.

2.2. Instrumentation

Absorption spectra were recorded using a UV–vis 2450 spectrophotometer (Shimadzu, Japan). TEM images were acquired on a JEM-2100 scanning at 200 kV (JEOL, Japan). Samples were prepared by dropping 2 μL of a colloidal solution for five times onto a carbon-coated copper grid. The photographs in this assay were taken with a Cannon 600D digital camera after 10 min incubation. All experiments were conducted at room temperature.

2.3. Synthesis of gold nanoparticles

Gold nanoparticles were prepared by citrate reduction of $HAuCl_4$ [40]. A stirred solution of $HAuCl_4$ (2 mL of 1% $HAuCl_4$, 47 mL of H_2O) was heated to boiling, and then 1 mL of 5% sodium citrate was quickly added under stirring, resulting in a color change from pale yellow to wine red. Then, the mixed solution was heated under stirring for another 30 min and cooled to room temperature. The AuNPs were stored in 4 °C before use.

3. Results and discussion

Scheme 1 outlines the proposed strategy for the sensing of a wide spectrum of NCA. The 13 nm AuNPs used in our assay have been synthesized and stabilized with citrate via the electrostatic repulsion against van der Waals attraction. In the presence of NCA, coralyne added to the solution containing AuNPs could firstly combine with NCA due to their strong electrostatic attraction. As a result, the AuNPs would be prevented from aggregation, displaying an intense absorption at 521 nm and a red colloid solution. On the contrary, in the absence of the analytes, coralyne could lead to AuNPs aggregation, resulting in a concomitant red-to-blue color variation due to a bathochromic shifting and dampening of the nanoparticle surface plasmon resonance. It should be noted that NCA hardly bind with AuNPs because of the electrostatic repulsion, and the AuNPs solution remains dispersed. Therefore, the competitive reaction between NCA and AuNPs with coralyne can be expected to provide a quantitative readout for a panel of NCA.

The 13 nm AuNPs were prepared using a literature method [40]. The typical morphology of AuNPs is shown in a transmission electron microscopy (TEM) image (Fig. S2a), indicating that the AuNPs are roughly spherical in shape around 13 nm and the monodispersed AuNPs present a typical red color. In addition, the AuNPs have been characterized by UV–vis absorption spectroscopy as well. The maximum absorption peak at 521 nm can be observed (Fig. S2b), which further confirms that ~13 nm AuNPs have been prepared successfully [41]. The concentration of AuNPs (~3.3 nM) was calculated based on the previous report [42].

Based on the fact that the aggregation of AuNPs can be induced by coralyne, we first designed the NOT and YES logic gates (Fig. 1A). Coralyne is the only input, A_{644}/A_{521} and solution color serve as two outputs here. The absence and presence of coralyne is defined as "0" and "1", respectively. The output signals are considered as "0" if the solution color is blue and "1" when it is red. Threshold value is set at 0.8 to judge the positive and negative output signals for A_{644}/A_{521}. In this system, in the presence of coralyne (input = 1), the aggregation of AuNPs was triggered, leading to the color turned to blue (output = 0) and A_{644}/A_{521} value increased (output = 1). In contrast, no aggregation was observed in the absence of coralyne. The corresponding truth table and UV–vis absorption responses are shown in Fig. 1B and C.

To further investigate coralyne-induced AuNPs aggregation, we compared the color changes and UV–vis absorption responses after the addition of various concentrations of coralyne. As shown in Fig. 1D, photographs displayed the color changes clearly from red to blue with increasing concentrations of coralyne. When the final concentration of coralyne was below 1.0 μM, the aggregation of AuNPs occurred inconspicuously. The AuNPs began to undergo aggregation when the coralyne concentration was greater than