Ion-Tuned DNA/Ag Fluorescent Nanoclusters As Versatile Logic Device

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ABSTRACT A novel kind of versatile logic device has been constructed utilizing ion-tuned DNA/Ag fluorescent nanoclusters, with K^+ and H^+ as two inputs. A well-chosen hairpin DNA with a poly-C loop serves as the template for synthesizing two species of Ag nanoclusters. Several G-tracts and C-tracts on its two terminals enable the hairpin DNA to convert into the G-quadruplex and/or i-motif structures upon input of K^+ and H^+. Such a structural change remarkably influences the spectral behaviors of Ag nanoclusters. In particular, different species of Ag nanoclusters have distinct fluorescence responses to the input of K^+ and H^+. These unique features of DNA/Ag nanoclusters enable multiple logic operations *via* multichannel fluorescence output, indicating the versatility as a molecular logic device. By altering the specific sequence of the hairpin DNA, more logic gates can be constructed utilizing Ag nanoclusters.

KEYWORDS: DNA/Ag nanoclusters · logic gates · fluorescence spectrum · DNA structural change

Since molecular computing holds great promise for applications in computer and life sciences,[1,2] many efforts have been made to design and construct various logic gates utilizing different molecules or molecular-scale materials.[3−9] However, most previous logic gates usually perform only one operation. It is interesting and significant to design and construct versatile logic devices with the ability to perform multiple operations, which would meet the need of future development of DNA circuits. With this thought in mind, we endeavored to explore new utilization of DNA-related molecular candidates from the consideration of logic gate construction.

Several-atom noble metal (Au and Ag) nanoclusters exhibit molecule-like behavior with size-dependent, strong visible fluorescence.[10,11] Such molecular-scale metals have received considerable attention in the past few years, owing to their wide applications in bioimaging,[12−14] catalysis,[15,16] and chemical sensing.[17,18] To synthesize highly fluorescent metal nanoclusters, different kinds of molecules including polymers, proteins, or DNA are utilized as the stabilizers.[19−22] C-rich oligonucleotides have been found to be able to serve as ideal templates for the formation of highly fluorescent Ag nanoclusters,[12,22−29] owing to the specific C−Ag^+ interaction that can direct the growth of Ag nanoclusters. In some cases, two or more species of fluorescent emitters with different sizes can be formed in a DNA template, especially in a hairpin DNA structure with a poly-C loop.[24,27] Moreover, the fluorescence behaviors of Ag nanoclusters are largely dependent on the specific sequences and structures of DNA templates.[24,27,29] In particular, a previous study demonstrated that the color of Ag nanoclusters changes as the C-rich DNA template converts from single strand into the i-motif structure.[28] Accordingly, we hypothesize the formation of the G-quadruplex may also influence the fluorescent behaviors of Ag nanoclusters, albeit not reported before. Their unique features endow DNA/Ag nanoclusters with great potential for applications in some fields.

Herein, we utilize two cations, K^+ and H^+, to induce a hairpin DNA template (named HP26) to undergo structural changes, thereby modulating the fluorescence behaviors of HP26-stabilized Ag nanoclusters. The ion-tuned DNA/Ag fluorescent nanoclusters, in fact, behave as a novel kind of versatile logic device. HP26 consists of G-rich, poly-C, and C-rich regions, and first it is utilized as the stabilizer for synthesizing two species of Ag nanoclusters. Upon input of K^+ and H^+, HP26 is able to convert into the G-quadruplex (G4) and/or i-motif structures, and different species of Ag nanoclusters have distinct fluorescence responses to the inputs. This enables two or more logic operations to be performed together *via* multichannel fluorescence output.

RESULTS AND DISCUSSION

Figure 1 depicts the concept for the construction of a versatile logic device utilizing HP26-stabilized fluorescent Ag nanoclusters, with K^+ and H^+ as two inputs. With no input, HP26 forms a hairpin structure with a poly-C loop, where highly fluorescent Ag nanoclusters can be synthesized.[24,27]

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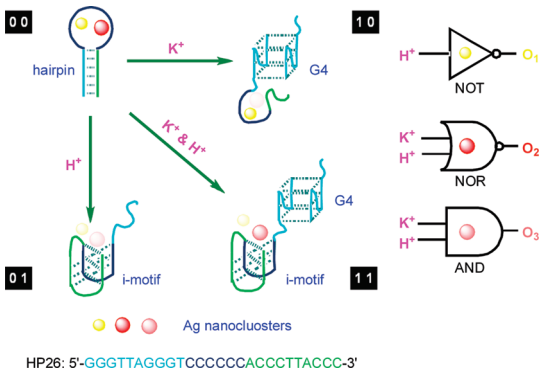


Figure 1. (Left) Schematic diagram of logic operations based on HP26-tuned fluorescent Ag nanoclusters. (Right) Corresponding symbols of logic gates. K^+ and H^+ serve as two inputs to trigger the allosterism of HP26 and modulate the fluorescence output.

Upon addition of K^+, the G-tracts of HP26 fold into a bimolecular G4 structure stabilized by K^+. This will induce the hairpin structure to unwind; namely, HP26 is subject to a hairpin-to-G4 structure conversion. Upon addition of H^+ (pH → 5.0), the C-tracts of HP26 fold into the i-motif structure,[30] suggesting that HP26 will undergo a conformational change from the hairpin to i-motif structure. In the presence of K^+ and H^+, the G4 and i-motif structures will be formed together. These structural changes are expected to remarkably influence the specific interaction between C residues and Ag nanoclusters, thereby modulating the fluorescence behaviors of Ag nanoclusters.

As a precondition for logic operations, the fluorescent Ag nanoclusters were prepared as described previously,[27,28] with the hairpin structure of HP26 as the synthesis template. In this case, yellow and red fluorescent emitters are formed together (Figure 2a,b). Interestingly, after the as-prepared Ag nanoclusters are incubated with K^+ and H^+, a new fluorescent emitter emerges (see Figure 2c), accompanied by the disappearance of the yellow and red species. The as-prepared DNA/Ag nanoclusters are found able to remain stable enough for 1−2 weeks under the synthesis conditions, which enables their subsequent utilization for logic operations.

To further confirm the formation of Ag nanoclusters, we utilize transmission electron microscope (TEM) to characterize the as-prepared Ag colloid (Figure 2d). It is found that different sizes (Ø 1−2 nm) of Ag particles are formed in a one-pot synthesis. These nanoclusters consist of several Ag atoms, which correspond to the yellow and red fluorescent emitters (Figure 2a,b).

To clearly demonstrate what happens to HP26-stabilized Ag nanoclusters upon addition of K^+ and H^+, circular dichroism (CD) is utilized to characterize the secondary structure of the DNA stabilizer (Figure 3a). In the original state, there is a positive band near 265 nm with a shoulder around 280 nm in the CD spectrum of HP26, indicating the formation of a B-form

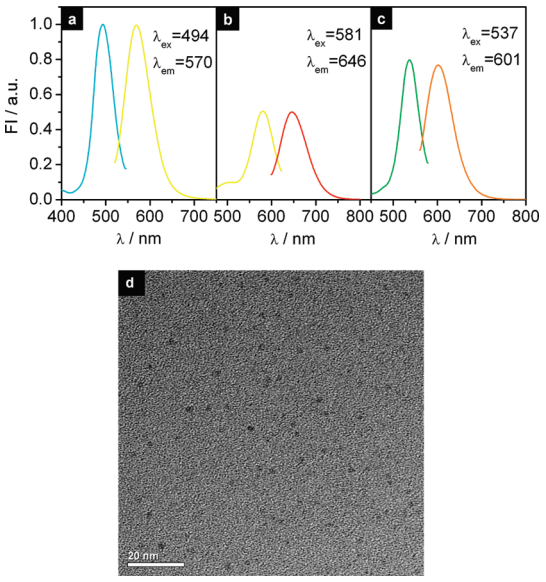


Figure 2. Fluorescence behaviors and TEM image of HP26-stabilized Ag nanoclusters. Yellow (a) and red (b) fluorescent emitters in 10 mM Tris-Ac buffer (pH 8.0). (c) Orange fluorescent emitter in 10 mM Tris-Ac buffer (pH 5.0, 100 mM K^+). In each panel: left, excitation spectrum; right, emission spectrum. (d) TEM image of as-prepared HP26-stabilized Ag nanoclusters.

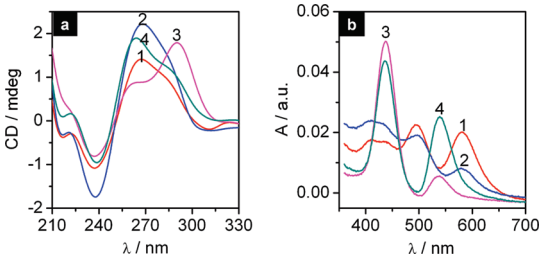


Figure 3. CD spectra (a) and UV−vis absorption spectra (b) of HP26-stabilized Ag nanoclusters in 10 mM Tris-Ac buffer (pH 8.0): 1, no cation; 2, 100 mM K^+; 3, H^+ (pH → 5.0); 4, K^+ and H^+.

DNA duplex.[31] Upon addition of K^+, the positive band near 265 nm and negative one at 245 nm become more dominant, while the shoulder around 280 nm almost disappears. It is the typical characteristics of a parallel G4 structure.[31] Upon addition of H^+, there is a strong positive band near 290 nm in the CD spectrum, which is characteristic of an i-motif structure.[31] Undoubtedly, both G4 and i-motif structures are formed in the presence of K^+ and H^+. These CD data confirm our design for DNA structure changes induced by K^+ and/or H^+.

As DNA-stabilized Ag nanoclusters have specific absorption bands,[22,23,26] UV−vis absorption spectroscopy is also utilized to characterize the HP26-stabilized Ag nanoclusters under different conditions (Figure 3b). When HP26 adopts the hairpin structure, there are two obvious peaks near 493 and 580 nm in the absorption spectrum (curve 1), corresponding to yellow and red fluorescent emitters (see Figure 2a,b). Upon addition of

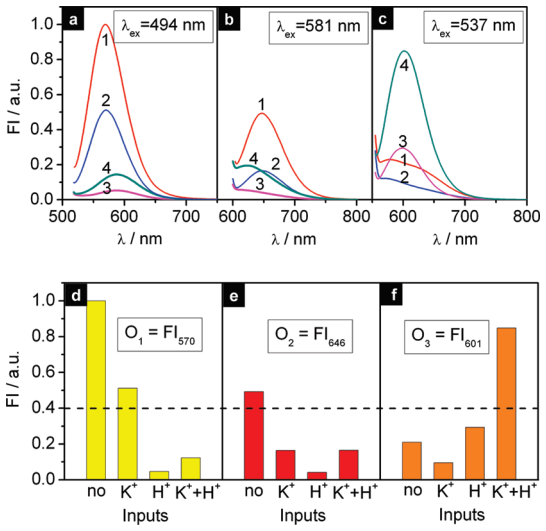


Figure 4. HP26-stabilized Ag nanoclusters for multiple logic operations. (a–c) Fluorescence emission spectra of Ag nanoclusters at different excitation wavelength in 10 mM Tris-Ac buffer (pH 8.0) at four input modes: 1, no input; 2, 100 mM K^+; 3, H^+ (pH → 5.0); 4, K^+ and H^+. (d–f) Bar representations of the fluorescence intensity at 570 nm (FI_{570}), 646 nm (FI_{646}), and 601 nm (FI_{601}). The same threshold value (0.4) for output 1 or 0 is set at all fluorescence channels.

TABLE 1. Truth Tables for NOT, NOR, and AND Logic Gates

INPUTS		OUTPUTS		
K^+	H^+	FI_{570}	FI_{646}	FI_{601}
0	0	1	1	0
1	0	1	0	0
0	1	0	0	0
1	1	0	0	1

K^+, HP26 converts into the G4 structure. In this case, the absorption bands of yellow and red species become unobvious (curve 2), which should be attributed to a sharp alteration of the DNA–Ag nanoclusters interaction during DNA structural change. When H^+ is added, HP26 converts into the i-motif structure, and the absorption bands of yellow and red species disappear completely (curve 3). Nevertheless, a very strong band and a small peak appear near 437 and 539 nm. This unusual phenomenon should be attributed to the change of external conditions (pH value) and DNA–Ag interaction. Upon addition of both K^+ and H^+, the absorption band near 539 nm becomes quite remarkable (curve 4), corresponding to the orange fluorescent emitter (see Figure 2c). These spectral changes mainly originate from the alternation of DNA–Ag nanoclusters interaction upon addition of K^+ and H^+. In the original state, the poly-C loop of hairpin DNA encapsulates the Ag particle *via* the C–Ag interaction and provides it perfect protection. When the DNA template converts into the G4 structure in the

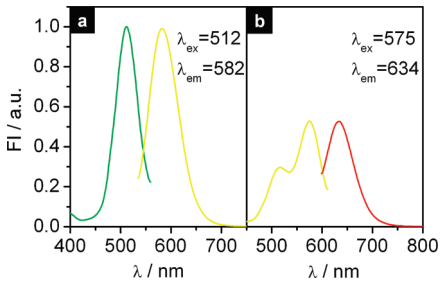
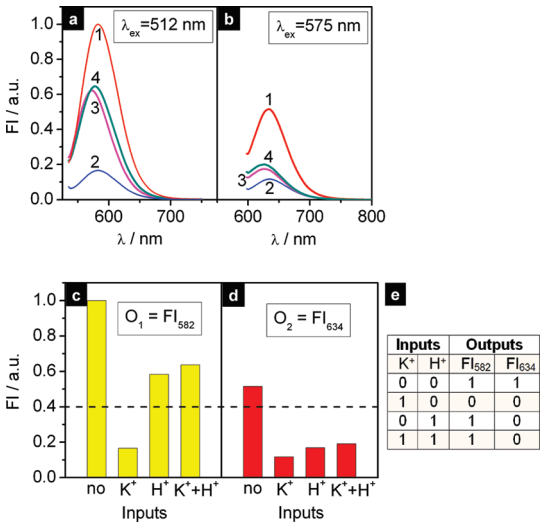


Figure 5. Fluorescence behaviors of HP22-stabilized Ag nanoclusters in 10 mM Tris-Ac buffer (pH 8.0): (a) yellow species; (b) red species. In each panel: left, excitation spectrum; right, emission spectrum.

presence of K^+, the hairpin loop no longer exists, and what stabilizes Ag nanoclusters is a C-rich single strand tethered to the G4 structure, which can wrap on the Ag surface. This change will weaken the DNA–Ag interaction, owing to the flexibility of the random coil. After the DNA template converts into the i-motif structure upon addition of H^+, most of the C nucleotides exist in the form of $C–C^+$ base pairs, and so encapsulating or wrapping Ag nanoclusters is no longer allowed. This will alter the nature of the DNA–Ag nanoclusters interaction.

The above observations well demonstrate that the ion-induced structure changes of the DNA stabilizer have a great influence on the spectral behaviors of Ag nanoclusters. This provides a rationale for the construction of fluorescent logic gates *via* cation-tuned DNA/Ag nanoclusters. Figure 4 depicts three logic operations based on HP26/Ag nanoclusters at different excitation wavelengths. When excited at 494 nm (Figure 4a), the yellow fluorescent emitter is active. Its fluorescence is strong (output 1) in the absence of H^+, while the signal is relatively low (output 0) upon input of H^+. This is in accordance with a NOT logic gate behavior,[32] which is expressed more clearly by a bar presentation of the fluorescence output (Figure 4d). Changing the excitation wavelength to 581 nm (Figure 4b), the red emitter becomes active. Its fluorescence emission is observed without any input, whereas addition of K^+ and/or H^+ sharply weakens the fluorescence signal. The corresponding bar presentation is given in Figure 4e, consistent with a two-input NOR gate behavior.[33] If the excitation wavelength is changed to 537 nm (Figure 4c), a strong orange emission is observed in the presence of both K^+ and H^+; otherwise the output signal is relatively low (Figure 4f). This is coincident with a two-input AND gate behavior.[33] The corresponding truth tables of three logic gates are listed in Table 1.

Previous studies have demonstrated that the sequences of DNA stabilizers have a notable influence on the fluorescence behaviors of Ag nanoclusters.[25,27] Therefore, more logic gates can be constructed just by altering the DNA sequence of HP26. Typically, the



Inputs		Outputs	
K^+	H^+	FI_{582}	FI_{634}
0	0	1	1
1	0	0	0
0	1	1	0
1	1	1	0

Figure 6. HP22-stabilized Ag nanoclusters for logic operations. (a, b) Fluorescence emission spectra excited with different wavelengths at four input modes: (1) no input; (2) 100 mM K^+; (3) H^+; (4) K^+ and H^+. (c, d) Bar representations of the fluorescence intensity at 582 nm (FI_{582}) and 634 nm (FI_{634}). The same threshold value (0.4) for output 1 or 0 is set at all fluorescence channels. (e) Truth tables for IMPLICATION and NOR logic gates.

spacers between G-tracts or C-tracts are shortened to a single residue. The resulting sequence d($G_3TG_3TC_6$-AC_3AC_3), herein referred to as HP22, is also utilized as the template for synthesizing Ag nanoclusters. Like HP26, HP22 is able to form a hairpin structure with a poly-C loop where highly fluorescent Ag nanoclusters are formed. Figure 5 shows the as-prepared nanoclusters stabilized by HP22, of which two fluorescence emissions (yellow and red) are observed. Similarly, this kind of nanocluster is also utilized for logic operations.

Figure 6 depicts two logic operations based on HP22/Ag fluorescent nanoclusters. Herein, K^+ and H^+ also serve as two inputs to induce the structural change of the DNA stabilizer HP22. Excited at 512 nm (Figure 6a), the yellow emitter exhibits a strong emission (output 1) in most cases, except input of only K^+ (output 0). Figure 6c shows a bar representation of the fluorescence output, which is in accordance with a two-input IMPLICATION logic gate.[32] While the excitation wavelength is changed to 575 nm (Figure 6b), the red fluorescent emitter becomes active and behaves as a NOR logic gate,[33] the bar representation of which is given in Figure 6d. The truth tables of the above two logic gates are showed in Figure 6e.

For the present logic system, the output of one gate cannot be used as an input of another gate, so these logic gates are unlikely to be incorporated within a network. Nevertheless, the construction of a logic network may be achieved utilizing the DNA/Ag nanoclusters system in which some replacement DNA strands serve as the inputs. It has been reported that the fluorescence behaviors of Ag nanoclusters can be modulated *via* DNA stabilizer replacement.[13] This provides another rationale for the construction of other logic gates based on the DNA/Ag system. In particular, for such a logic system, the input of a replacement strand will release the original DNA stabilizer, and then the DNA output can serve as one input of another appropriate logic gate. This will enable the utilization of a DNA/Ag nanoclusters system for the development of DNA circuits.

CONCLUSIONS

We have devised a new kind of molecular logic device utilizing ion-tuned DNA/Ag fluorescent nanoclusters. In contrast to previous counterparts performing only one logic operation,[3−8] our designed logic gates show their versatility: (1) By changing the excitation wavelength, the DNA-tuned Ag nanoclusters are able to perform multiple logic operations together *via* multichannel fluorescence output; (2) simply altering the specific sequence of the DNA stabilizer, more logic gates can be constructed utilizing Ag nanoclusters. The developed versatile logic device may find applications in further development of DNA circuits.

METHODS

Oligonucleotides. Purified oligonucleotides were obtained from Sangon Biotechnology Co., Ltd. (Shanghai, China). The stock solutions of oligonucleotides were prepared in 10 mM Tris-Ac buffer (pH 8.0) and quantified using UV−vis absorption spectroscopy with the following extinction coefficients ($\varepsilon_{260\ nm}$, $M^{-1}\ cm^{-1}$) for each nucleotide: A = 15 400, G = 11 500, C = 7400, T = 8700. After diluted to required concentrations with the Tris-Ac buffer, the DNA solutions were heated at 88 °C for 10 min to dissociate any intermolecular interaction and slowly cooled to 4 °C, to form the desired secondary structures.

Synthesis of DNA/Ag Fluorescent Nanoclusters. A 30 μM solution of $AgNO_3$ was added into 5 μM solutions of oligonuleotides in 10 mM Tris-Ac buffer (pH 8.0). After 2 h at 4 °C, 30 μM $NaBH_4$ was added into the mixture, allowing for overnight reaction in the dark at 4 °C to form highly fluorescent Ag nanoclusters. The as-prepared colloid was kept in the dark at 4 °C for further use.

Transmission Electron Microscopy. The TEM image of as-prepared HP26/Ag nanoclusters was obtained at room temperature with a TECNAI G2 high-resolution transmission electron microscope operating at 200 kV.

CD Measurements. A JASCO J-820 spectropolarimeter (Tokyo, Japan) was utilized to collect the CD spectra of oligonucleotides (3 μM) at four input modes at room temperature. Three scans from 210 to 330 at 0.1 nm intervals were accumulated in an optical chamber (2 mm optical path length) with a scan rate of 100 nm min^{-1} and automatically averaged by the software. The background of the buffer solution was subtracted from the CD data. Throughout the experiments, the lamp of the spectropolarimeter was always kept under a stable flow of dry purified nitrogen (99.99%), to avoid ozone production.

UV−Vis Absorption Spectroscopy. The absorption bands of DNA/Ag nanoclusters in 10 mM Tris-Ac buffer at different input modes were recorded with a Cary 500 Scan UV−vis−NIR spectrophotometer (Varian, USA) in the wavelength range from

360 to 700 nm, to indicate the change in spectral behaviors of nanoclusters induced by external stimuli.

Logic Operations Based on DNA/Ag Nanoclusters. After addition of K^+ (100 mM) and H^+ (pH is adjusted from pH 8.0 to pH 5.0) in 10 mM Tris-Ac buffer, the as-prepared Ag nanoclusters were incubated at 4 °C to achieve the structure conversion of oligonucleotides. Then, the fluorescence emissions of DNA/Ag nanoclusters were read out at multiple wavelengths using a LS 55 fluorescence spectrometer (PerkinElmer, USA).

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