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Mathematical modeling of DNA-mediated selective aggregation of CdS quantum dots

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ABSTRACT

We report a mathematical modeling of the DNA-mediated selective aggregation of CdS quantum dots. Addition of hybridized double-stranded DNAs into the suspensions of CdS quantum dots at the optimal salt concentration causes a selective aggregation and a fluorescence-quenching phenomenon depending on the target DNA sequence. We monitor the aggregation process with quasi-elastic light scattering (QELS), zeta potential, and conductivity measurements at different salt concentrations. To model the aggregation process, we use the constant-number Monte Carlo method with the aggregation kernel that accounts for the interparticle interaction from the classical DLVO model. We find that the calculated results are in good agreement with the experiments, and that the fractal dimension of the quantum dot aggregates is 2.3. Modeling also allows us to estimate that the total number of initial quantum dots in aggregates at the beginning of the fluorescence-quenching phenomenon is approximately 200. The insights gained in this study should be useful in the design of biosensors based on the fluorescence-quenching phenomenon caused by the quantum dot aggregation.

1. Introduction

Aggregation of nanoparticles has become increasingly important in many scientific and engineering fields due to the recent advances in nanotechnology. Especially, nanoparticles whose optical properties change with their size, morphology, and extent of aggregation find potential applications in numerous areas [1–6]. One of the most promising applications of nanoparticle aggregation is a DNA biosensor. Mirkin and co-workers [7], for instance, developed colorimetric sensors to detect DNA sequences using the aggregation of oligonucleotide-functionalized gold nanoparticles. DNA sensors based on the non-crosslinking aggregation of unmodified nanoparticles have also been reported by Rothberg and co-workers [8]. Based on a similar concept, we have recently developed a DNA biosensor using fluorescence-quenching phenomenon caused by the selective aggregation of water-soluble CdS quantum dots [9].

These sensors are mainly based on the selective aggregation phenomenon that depends on the target DNA sequence. Here, target DNA is the DNA of interest whose sequence is to be detected by the sensors. DNA sensors using selective aggregation of nanoparticles provide a rapid and easily discernible method for detecting specific mutation in DNA sequences. Most research, however, has been focused primarily on the detection of a mismatch in DNA sequences, not on the quantitative analysis of the DNA-mediated selective aggregation phenomenon that can be crucial in the control of detection time, reactor volume, etc.

For quantitative analysis of nanoparticle aggregation, we have recently rationalized aggregation of the gold nanoparticles by calculating the interparticle interaction energy and the stability ratio based on the classical Derjaguin–Landau–Verwey–Overbeek (DLVO) model [10]. We have also successfully performed a mathematical modeling of the gold nanoparticle aggregation using the constant-number Monte Carlo method [11].

In this paper, we attempt to mathematically model the DNA-mediated selective aggregation of water-soluble CdS quantum dots. First, we perform experiments to discern single-base mismatches in the DNA sequence using the selective aggregation of CdS quantum dots based on our previous report [9]. To model the aggregation process, one should solve the population balance equations (PBEs) that consist of a large set of integro-differential equations. Because the PBEs have no analytical solutions in most cases, one should resort to the numerical techniques. To solve the PBEs, we use the constant-number Monte Carlo method with the aggregation kernel that accounts for the interparticle interaction from the classical DLVO model. We then compare the calculated results with the experimental data to validate the assumptions made in the model. Note that this is, to the best of

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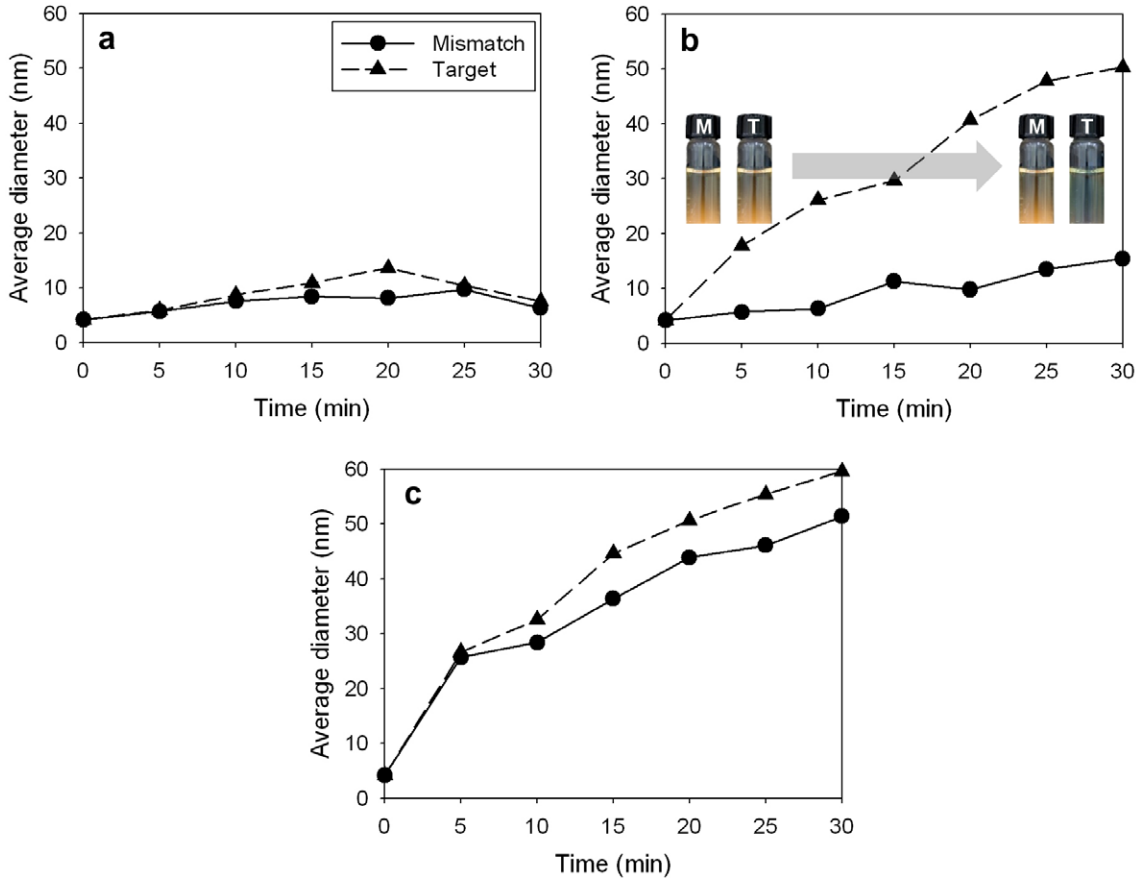

Fig. 1. Average diameter as a function of time after addition of the perfectly matched (target) and single-base mismatched (mismatch) dsDNA at different NaCl concentrations: (a) 0.8 mM; (b) 1.2 mM; (c) 1.6 mM. Pictures in panel b show the suspensions under UV-lamp (at the excitation wavelength of 365 nm) at 0 (left) and 30 (right) min after addition of dsDNAs; the labels "M" and "T" indicate the mismatch and target, respectively.

our knowledge, the first study that reports a mathematical modeling of the selective aggregation of CdS quantum dots depending on the target DNA sequence. We expect that these results should provide a quantitative understanding of the DNA-mediated aggregation and the fluorescence quenching of CdS quantum dots, and hence help in the design of a molecular sensing system based on the selective aggregation of CdS quantum dots.

2. Experimental procedure

The experimental procedures are based on our previous report [9]. First, mercaptoacetic acid-stabilized CdS quantum dot suspensions were prepared as follows. We added 8.0 μL of mercaptoacetic acid to 100 mL of 1.12×10^{-4} M $CdCl_2$ in water. The pH was adjusted to 11 by dropwise addition of 0.5 M NaOH solution. Then 50 mL of 7.5×10^{-5} M Na_2S in water was slowly added to the resulting alkaline solution with vigorous stirring under nitrogen atmosphere. The reaction mixture was stirred overnight at room temperature.

We designed the single-stranded oligonucleotide probe (5′-AAT CAG AAG CCC TTT-3′), the target oligonucleotide with its perfectly complementary sequence (5′-AAA GGG CTT CTG ATT-3′), and the sequence with a single mismatched base (5′-AAA GGG CTT CTG ATG-3′) based on the BRCA2 sequence (GenBank Number: NM_000059) from Bioneer Inc. (Daejeon, Korea). Note that the single-stranded DNA (ssDNA) of the 5′ → 3′ direction hybridizes with the complementary ssDNA of the 3′ → 5′ direction.

We hybridized 2 μL of 0.2 mM oligonucleotide probes in 0.15 M NaCl/0.1 M phosphate buffer solution at pH 7 with 2 μL of their complementary (target) or single-base mismatched oligonucleotide at the same concentration. Note that the double-stranded DNA (dsDNA) with the target and probe DNAs would have a perfectly matched sequence whereas that with the single-base mismatched one and probe would have a mismatch. We added 4 μL of 0.1 mM DNA solution to 1.3 mL CdS quantum dot suspension, and then added 0.59 mL of distilled water and 0.1 mL of the same buffer to prevent abrupt aggregation. Finally, 0.2 M NaCl stock solutions were added so that the final NaCl concentrations were 0.8, 1.2, and 1.6 mM. The final DNA concentration was 200 nM.

Quasi-elastic light scattering (QELS) and zeta potential measurements were used to monitor the average diameter and surface potential of the particles with a Malvern Nano-ZS instrument. Ionic strength of CdS quantum dot suspensions was monitored from electrical conductivity measurement: conductivity was calibrated with the known ion concentration, and was used to estimate the ionic strength in suspension.

3. Constant-number Monte Carlo method with interparticle interaction

In the case of single-component irreversible aggregation, the case we consider here, a population balance equation can be written as

$$\frac{\partial n(m,t)}{\partial t} = \frac{1}{2}\int_0^m K(m-m',m')n(m-m',t)n(m',t)dm' - \int_0^\infty K(m,m')n(m,t)n(m',t)dm', \quad (1)$$