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Original article

Redox-responsive supramolecular nanoparticles based on amphiphilic sulfonatocalixarene and selenocystamine dihydrochloride

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ABSTRACT

A supramolecular nanoparticle was fabricated based on the aggregation of amphiphilic *p*-sulfonatocalixarene induced by selenocystamine dihydrochloride (Se-Cys). The application of Se-Cys remarkably decreases the critical aggregation concentration of sulfonatocalixarene, and the resultant spherical nanoparticle was investigated by fluorescence spectroscopy, dynamic laser scattering, and transmission electron microscopy. Owing to the property of Se-Cys, the nanoparticles showed the redox-responsive disassembly behaviors with the addition of H_2O_2 and GSH.

1. Introduction

Stimuli-responsive nanoparticles show good potential in the fields of controllable drug and gene delivery [1–3]. Among various smart nanoparticles employing the responsiveness toward external stimuli such as pH [4,5], light [6,7], temperature [8], enzymes [9,10] and redox [11], redox-responsive nanoparticles have drawn wide attention owing to their controllable encapsulation and delivery of biological/medicinal substrates in physiological environments. Selenium is a semimetallic chemical element [12] and can be incorporated in proteins to make selenoproteins, which prevent cellular damage from free radicals [13]. Besides its biological functions, selenium also possesses unique chemical properties such as the weaker electronegativity of selenium and the bigger radius than sulfur [14], which makes the selenium compounds easier to be oxidized or reduced. In addition, with a lower bond energy (Se–Se 172 kJ/mol) than the disulfide (S–S 240 kJ/mol), the diselenide is regarded as a good candidate to build the redox-responsive system [15]. Xu, Zhang and co-workers constructed several diselenide-containing polymers by condensing organic diselenocyanates or diselenosulfates with an acid or base initiator and investigated their self-assembly behavior as well as applications as physiological condition-responsive drug delivery vehicles [16–20]. However, selenium-containing nanoparticles are rarely reported due to the relatively difficult preparation [16]. Recently, we developed an easy way to fabricate nanoparticles based on the complexation of *p*-sulfonatocalixarenes [21–24], which could decrease the critical aggregation concentration (CAC), enhance the aggregate stability, and regulate the degree of order in the aggregates. Using the similar strategy, a number of supramolecular assemblies were successfully constructed through the induced aggregation of different macrocycles including cyclodextrin [25,26], pillararene [27–29] and cucurbituril [30,31], *etc.* Herein, we wish to report another type of induced aggregation, *i.e.*, the guest-induced aggregation of amphiphilic calixarene, where *p*-sulfonatocalix[4]arene tetrahexyl ether (SC4A-H) and selenocystamine dihydrochloride (Se-Cys) (Scheme 1) were selected as host and guest, respectively. It is our special interest to investigate the possibility of guest Se-Cys to induce the aggregation of SC4A-H and the responsiveness of the resultant assembly to redox stimuli.

2. Experimental

Selenocystamine dihydrochloride (Se-Cys) was purchased from Sigma. Nile Red was purchased from J&K Scientific. GSH was purchased from Aladdin. All of chemicals were used without further purification. SC4A-H was synthesized according to the reported procedure [32]. A thermostated and fully computer-operated isothermal calorimetry (VP-ITC) instrument, purchased from Microcal Inc., Northampton, MA, was used for all microcalorimetric experiments. All microcalorimetric titrations were

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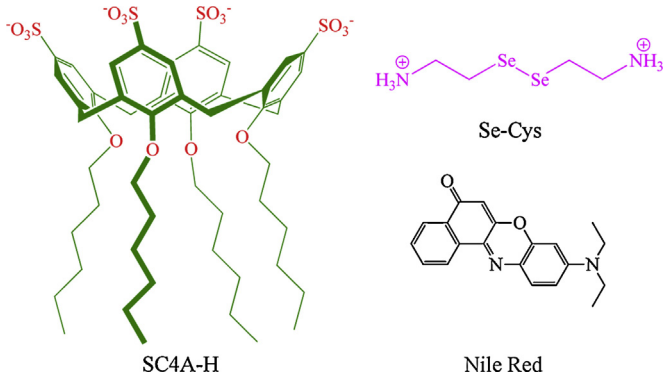

Scheme 1. Structures of SC4A-H, Se-Cys and Nile Red.

performed in aqueous solution at atmospheric pressure and 298.15 K. Each solution was de-gassed and thermostated by a ThermoVac accessory before the titration experiment. Twenty-eight successive injections were made for the titration experiment. A constant volume (10 μL/injection) of SC4A-H solution in a 0.250 mL syringe was injected into the reaction cell (1.4227 mL) charged with redistilled water. High-resolution TEM images were acquired using a high-resolution TEM (Tecnai G2 F20 microscope, FEI) equipped with a CCD camera (Orius 832, Gatan) operating at an accelerating voltage of 200 kV. The sample for TEM measurements was prepared by dropping the solution onto a copper grid. The grid was then air-dried. The sample solution for DLS measurements was prepared by filtering the solution through a 450 nm Millipore filter into a clean scintillation vial. The samples were examined on a laser light scattering spectrometer (BI-200SM) equipped with a digital correlator (TurboCorr) at 636 nm at a scattering angle of 90°. Steady-state fluorescence spectra were recorded in a conventional quartz cell (light path 10 mm) on a Varian Cary Eclipse equipped with a Varian Cary single-cell peltier accessory to control temperature. λ_{ex} = 550 nm; bandwidth (ex), 10 nm; bandwidth (em), 5 nm.

3. Results and discussion

Before studying the aggregation of SC4A-H induced by Se-Cys, we investigated the self-aggregation behavior of SC4A-H by means of isothermal titration microcalorimetry (ITC) experiment and fluorescence spectroscopy (using Nile Red as a probe) [33]. As seen in Fig. 1, the fluorescence intensity of Nile Red gradually enhanced with the addition of SC4A-H. Generally, the hydrophobic Nile Red tends to fluorescence in the hydrophobic microenvironment, such as the interior of SC4A-H micelles. The significantly enhanced fluorescence of Nile Red above 0.33 mmol/L may indicate the formation of SC4A-H micelles in aqueous solution. The critical aggregation concentration (CAC) of SC4A-H obtained from the

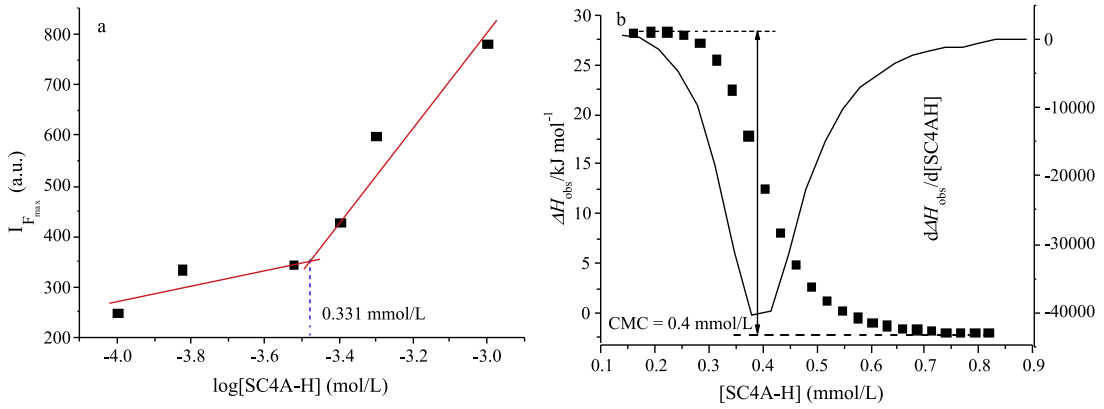

Fig. 1. (a) Dependence of the fluorescence intensity of Nile Red at 650 nm in aqueous solution of SC4A-H on SC4A-H concentration (25 °C, pH 7.0). (b) Titration of 25 aliquots (10 μL) of 4.92 × 10^3 μmol/L solution of SC4A-H into pure water at 25 °C. Observed reaction enthalpy (ΔH_{obs}) *versus* the total SC4A-H concentration in the reaction cell. The red line represents the first derivative of ΔH_{obs} against the concentration of SC4A-H.

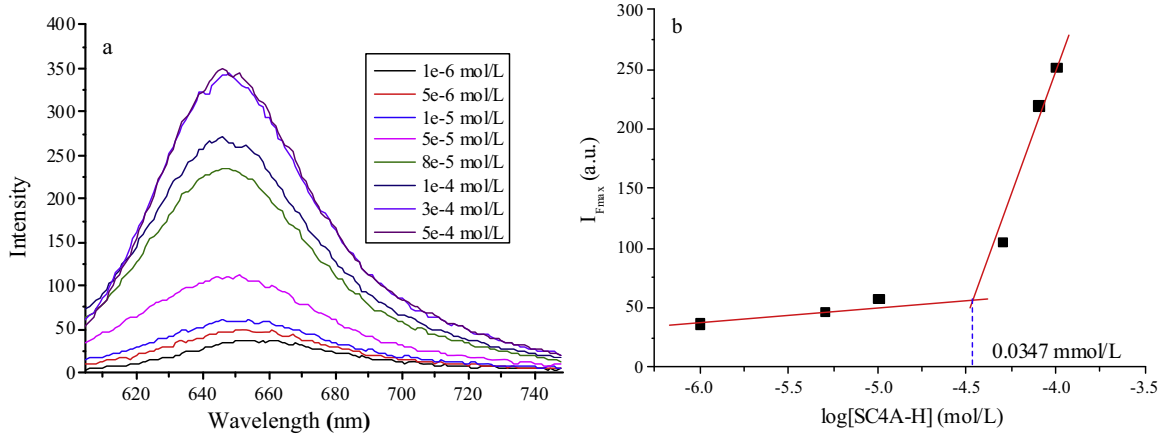

Fig. 2. (a) Fluorescence spectra of Nile Red at different SC4A-H concentrations in the presence of Se-Cys (50 μmol/L) and (b) dependence of the fluorescence intensity of Nile Red at 652 nm on SC4A-H concentration (25 °C, pH 7.0).