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Self-assembly of two ferrocence- and α-cyclodextrin-derived unconventional amphiphiles with redox responsiveness

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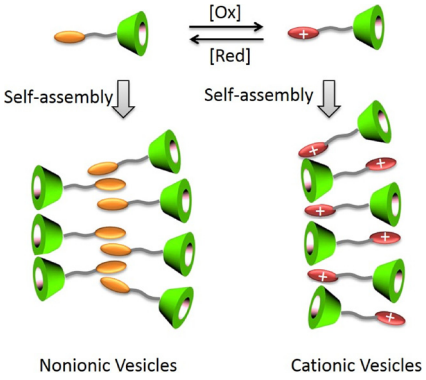
GRAPHICAL ABSTRACT



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ABSTRACT

We report the self-assembly of two α-cyclodextrin-derived unconventional amphiphiles containing a ferrocence and a ferrocenium terminal group (Fc-EG-αCD and Fc^+-EG-αCD), respectively. Fc-EG-αCD was synthesized and then oxidized giving the oxidized state molecule Fc^+-EG-αCD. The self-assembly behaviors of the molecules were investigated by several complementary techniques including TEM observations, DLS and other spectral measurements. Vesicles were formed in both systems. However, they adopted different molecular arrangements due to the varied electric properties of Fc and Fc^+. Moreover, the reversibility of the redox-responsive self-assembly was successfully achieved. Our results enriches the self-assembly systems based on CD derivatives and provides a new route for the fabrication of more stimuli-responsive amphiphilic self-assemblies.

1. Introduction

Stimuli-responsive amphiphilic self-assembly has attracted a lot of attention in recent years due to its wide potential applications in various fields, such as drug delivery and smart materials [1–3]. The utilization of numerous external stimuli, such as light [4], redox [5], pH [6], and heat [7], have been broadly employed in the construction of stimuli-responsive self-assembles. Modulation of these stimuli usually changes the responsive groups' polarity or steric structures, leading to a change in the hydrophobic-hydrophilic balance and further in the aggregation behavior.

One of the most commonly used stimuli, redox, is used for fabricating self-assemblies that are sensitive to oxidizing and reducing

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agents, such as GSH, which is a target substance of drug delivery during cancer therapy [8–11]. Redox-active systems bear important potential applications, hence redox-sensitive amphiphilic self-assemblies have been extensively developed [12]. When the redox-responsive group encounters an oxidant or reductant, it will undergo a transformation between the oxidized and reduced state, leading to a redox-sensitive self-assembly behavior [13]. The general strategy is to introduce a redox-switching group by employing synthetic approaches or non-covalent interactions. Ferrocence (Fc) is one of the most frequently employed redox-responsive units because of its good modifiability [1].

Cyclodextrins (CDs) are one of the most famous host molecules, with a hydrophilic outer surface and hydrophobic cavity [14], and have been found to be very versatile in self-assembly chemistry [15]. By including hydrophobic chains in the cavities surfactant aggregates can be destroyed. Furthermore, CDs can also provide multiple hydrogen bonding sites and play a key role as a building unit in self-assembly systems by either the host-guest approach or by covalent modification [15]. Modifying natural CDs can extremely expand the number of CD derivatives, providing a greater selection for building self-assembly systems [16–18]. A number of CD-derived amphiphiles have been designed with CDs as the hydrophilic group [19–23]. In general, these molecules contain one or more CD guest moieties, along with the inter- or intra-molecular inclusion complexation when they self-assemble. For example, Fc, as a “star” guest of β-CD, is a star chemical modification moiety of β-CD in the fabrication of redox-active self-assembly systems [21,24,25].

However, redox-responsive self-assemblies based on Fc- and CD-derived amphiphiles, in the absence of host-guest complexation, have rarely been reported. The donut-like CDs act as a hydrophilic group, and the special steric structure may offer some unconventional assistance in the self-assembly process [26]. Therefore, we focused on the development of redox-responsive self-assemblies based on the Fc- and CD-derived amphiphiles without host-guest complexation. α-CD was selected as they are incapable of forming stable 1:1 inclusion complexes with one another due to the size mismatching [27]. A α-CD derivative bearing a Fc terminal group has yet to be reported. Development of such amphiphiles and investigating their self-assembly behaviors and molecular arrangements is important to their fundamental research and potential applications.

Herein, an amphiphilic Fc-EG-αCD was designed and synthesized, as well as its oxidized state Fc^+-EG-αCD was obtained upon oxidization, which performed as an unconventional bola-type amphiphile. Vesicles outer surface, formed in an aqueous solution, were composed of α-CD groups for Fc-EG-αCD vesicles, whereas Fc^+-EG-αCD molecules adopted a more antiparallel manner forming a monolayer. Upon the addition of an oxidant and reductant, the reversible redox-responsive self-assembly behaviors of the aggregates was verified. This work provides a new route for the design of more stimuli-responsive amphiphilic self-assemblies.

2. Experimental section

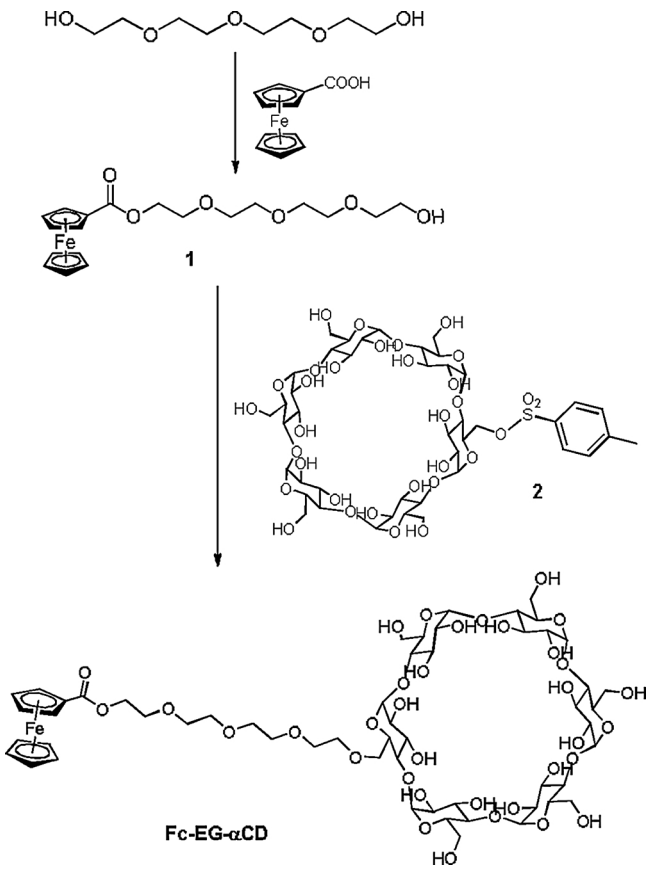
2.1. Materials

Ferrocenecarboxylic acid, oxalyl chloride, 4-dimethylaminopyridine (DMAP), triethylene glycol, glutathione (GSH), $FeCl_3$, α-cyclodextrin and triethylamine (TEA) were purchased from J&K Chemical Ltd. Other reagents are of analytical purity. All solvents and reagents were used without any further purification.

2.2. Synthesis of Fc-EG-αCD

Fc-EG-αCD was designed and synthesized as demonstrated in Scheme 1. Compound **1** was synthesized by the following procedure, while compound **2** was synthesized according to literature [28].

Ferrocenecarboxylic acid (2.06 g, 8.95 mmol) was dissolved in CH_2Cl_2 (100 mL), and then oxalyl chloride (2.3 mL, 26.9 mmol) was added slowly. The mixture was stirred at RT for 3 h to obtain a dark red solution. The solution was evaporated under vacuum giving a red oil (chlorocarbonyl ferrocene). The red oil was dissolved in THF (100 mL) and added dropwise to a solution containing triethylene glycol (8.75 g, 45.0 mmol), DMAP (0.12 g, 1.0 mmol), TEA (6.24 mL, 44.7 mmol) and THF (400 mL) at 0 °C under N_2. After the addition, the mixture was stirred at RT overnight. After the reaction reached completion, THF was removed by rotary evaporation. The obtained oil was purified by column chromatography (EA/PE = 1/3) giving compound **1** as a red oil. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 4.75, 4.49, 4.29-4.25 (m, 9H, protons of Fc moiety), 4.56 (t, 2H, Fc-COO-**CH_2**-CH_2-), 3.70, 3.61-3.47, 3.40 (m, 15H, protons of EG chain).



Scheme 1. Synthesis of Fc-EG-αCD.

Fc-EG-αCD was synthesized by the reaction of compound **1** and **2** [29]. Compound **1** (0.66 g, 1.62 mmol), compound **2** (1.85 g, 1.64 mmol) and TEA (2.29 mL, 16.5 mmol) were dissolved in DMF (300 mL). The mixture was heated at 80 °C for 4 days under N_2. After the reaction reached completion, the solvent was removed by vacuum distillation giving a brown oil. The oil was recrystallized three times using DMF/acetone to offer Fc-EG-αCD as a brown solid. ^{1}H NMR (D_2O, 500 MHz, ppm): δ 5.32, 5.10, 4.87 (m, 9H, protons of Fc moiety), 4.98 (s, 6H, H_1 of α-CD), 4.44 (t, 2H, Fc-COO**CH_2**-), 3.93-3.72, 3.58-3.45 (m, 67H, protons of EG chain and $H_{2\text{-}6}$ of α-CD). MALDI-TOF: 1361.41([M + H]$^+$).

2.3. Sample preparation

A 1 mmol/L aqueous solution of Fc-EG-αCD was first prepared. A 0.1 mol/L solution of the oxidant $FeCl_3$ was prepared in CH_3CN. 100 μL of the $FeCl_3$ solution was mixed with 1 mL of the Fc-EG-αCD solution giving the Fc^+-EG-αCD solution. The reductant GSH was dissolved in water (10 mmol/L), and 50 μL was injected Fc^+-EG-αCD solution. All