



Facile fabrication of luminescent hyaluronic acid with aggregation-induced emission through formation of dynamic bonds and their theranostic applications

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ABSTRACT

Aggregation-induced emission (AIE) is an abnormal phenomenon, which has been extensively explored for various applications. Taken advantage of the unique AIE feature, a number of luminescent nanoprobes with strong fluorescence intensity could thus be fabricated through different strategies; however, the fabrication of AIE-active carbohydrate polymers is still challenge owing to the poor solubility of carbohydrate polymers in most of organic solvents. In this work, a rather facile strategy has been developed for fabricating AIE-active sodium hyaluronate (Sh) through the formation of dynamic phenyl borate between the phenylboronic acid groups of AIE dye (An-B(OH)₂) and Sh in a “one-pot” route. This reaction could occur under low temperature, air atmosphere and in the present water. The physicochemical properties, biocompatibility, biological imaging and drug delivery performance of the final An-Sh fluorescent organic nanoparticles (FNPs) were confirmed by different characterization techniques. Results suggested that An-Sh FNPs possess high water dispersibility, strong fluorescence, and good biocompatibility. These excellent properties make An-Sh FNPs great potential for biological imaging and controlled drug delivery applications. In conclusion, we have developed a facile one-pot strategy for the preparation of AIE-active FNPs through the formation of dynamic bonds in rather mild experimental conditions. The outstanding properties and performance of An-Sh FNPs make them promising candidates for biological imaging and controlled drug delivery applications.

1. Introduction

A recently proposed concept—theranostic that is aiming at real-time monitoring and personalized medicine of the therapeutic process, has attracted considerable research interest, because of its vast application prospect in cancer therapy [1,2]. In past, traditional molecular contrast agents, therapy drugs or nanomedicine agents have got great progresses respectively in therapeutics and diagnostics. Nevertheless, integrating therapeutics and diagnostics in a single system has become current research focus, which accorded with theranostics [3–5]. As selection of drug to cure cancer, platinum drug is one of the most effective therapeutic agents against many cancers [6–8]. As we all know that cisplatin (CDDP) could bind to DNA, inhibiting DNA replication and furthermore inducing cancer cell apoptosis [9–11]. However, CDDP also cause toxic effects, like myelosuppression, anaphylactic reaction,

gastrointestinal reaction and nephrotoxicity [12,13]. As the consequence, in theranostic except personalized medicine, real-time monitoring of drug delivery/release was also the crucial object, because the therapeutic efficiency is dependent on the concentrations of the effective drugs in the cancer tissues [14].

In the past, utilizing multifunctional fluorescent organic nanoparticles (FNPs) to monitor drug was the most common strategies [15]. Furthermore, the FNPs with excellent properties possessed the potential application of cell imaging [16]. Nevertheless, most of traditional fluorescence has inherent disadvantages, especially organic dyes are confronted with notorious aggregation-caused quenching (ACQ) effect, which will result in obvious fluorescence quenching when the organic dyes were encapsulated in FNPs [17–19]. In sharp contrast with the ACQ effect, some organic dyes showed the much efficient fluorescence emission in their aggregation state as compared with their well

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dissolution state [20–22]. This phenomenon was first proposed by Tang et al. in 2001 and named as aggregation-induced emission (AIE) [19,23–25]. Since then, it has been extensively exploited for their potential application in various fields. Especially, the fabrication of AIE-active FPNs has raised considerable research attention over the past few years. A larger number of AIE-active FPNs have been fabricated through different strategies [26,27]. For example, Zhang et al. have reported the fabrication of AIE-active FPNs through the self-assembly of hydrophobic AIE-active dyes and synthetic amphiphilic polymers in the mixture of water and organic solvents [16,28–31]. Tang et al. have reported the preparation of AIE-active silica nanoparticles through the linkage of AIE dyes with silylated derivatives [32,33]. We have recently developed a variety of simple and efficient strategies for fabrication AIE-active FPNs with different functions, which include the ring-opening reaction, emulsion polymerization, addition fragmentation chain transfer (RAFT) polymerization, supramolecular interactions and formation of Schiff base [26,34–37]. However, to the best of our knowledge, there is still lack of efficient strategies for fabrication of AIE-active carbohydrate polymers owing to the poor solubility of carbohydrate polymers in organic solvents [27,38–40]. Sodium hyaluronate (Sh) is composed of glucuronic acid, which could be prepared by lactic acid bacteria fermentation [41–43]. Due to Sh existing in physiological components of human widely, it has been recognized as a safe substance with good biocompatibility and biodegradability [44–46]. Except good biocompatibility, Sh could even accelerate the wound healing and moisturize [47,48]. In view of these excellent properties, Sh has been widely applied to various fields, including eye surgery, the production of cosmetics, treatment of arthritis and accelerating the wound healing and moisturize [43,45,49]. More importantly, the carboxyl groups of Sh could be utilized to coordinate with anticancer agent CDDP. Therefore, the AIE-active Sh could be potentially applied for biological imaging and cancer therapy simultaneously [15,50,51].

In this report, we develop a novel and efficient method to fabricate multifunctional AIE-active FPNs relied on the formation of dynamic phenyl borate between the phenylboronic acid terminating AIE dye (An-B(OH)₂) and sodium hyaluronate (Sh) for the first time. The experimental procedures were described in Scheme 1 in detailed. Firstly, the AIE dye An-B(OH)₂ terminated with phenylboronic acid group was directly synthesized through three step organic reactions [28]. Then An-B(OH)₂ can be facily conjugated with Sh through the formation of dynamic phenyl borate between the phenylboronic acid groups and the

diol group of glucose units. To evaluate the potential biomedical applications of the final An-Sh FPNs, the physicochemical properties, biocompatibility, cell uptake behavior as well as drug delivery performance were investigated. Our results demonstrated that multifunctional AIE-active carbohydrate polymers could be simply fabricated through a rather efficient one-pot strategy. The final FPNs showed great potential for various biomedical applications.

2. Experimental sections

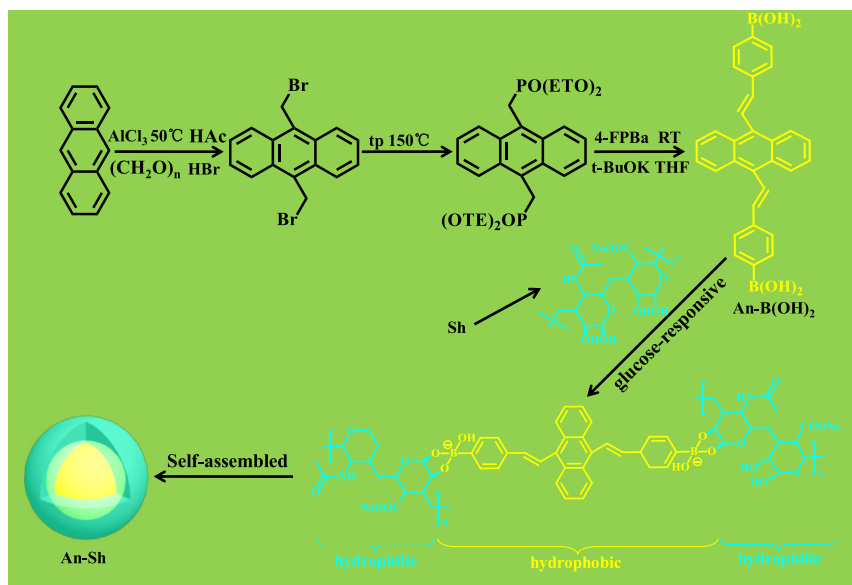
2.1. Materials and characterization

All chemical agents were of analytical grade and used as received without any further purification. The chemicals such as 4-Formylphenylboronic acid (*Mw*: 149.9 Da, 98%), Anthracene (*Mw*: 178.3 Da, 98%), Triethyl phosphite (*Mw*: 166.2 Da, 98%), CDDP (*Mw*: 300.0 Da, 98%), Sodium hyaluronate (98%) and Aluminum chloride hexahydrate (*Mw*: 241.4 Da, 97%) were purchased from Sinopharm Chemical reagents Co., Ltd. (Shanghai, China).

The synthetic polymers and materials were characterized by Fourier transform infrared (FT-IR) spectroscopy using KBr pellets. The FT-IR spectra were supplied from Nicolet5700 (Thermo Nicolet corporation). Transmission electron microscopy (TEM) images were recorded on a Hitachi 7650B microscope operated at 80 kV, the TEM specimens were got by putting a drop of the nanoparticle ethanol suspension on a carbon-coated copper grid. The X-ray photoelectron spectra (XPS) were performed on a VEGESCALAB220-IXL spectrometer using an Al Kα X-ray source (1486.6 eV). ¹H nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance-400 spectrometer with D₂O, DMSO and CDCl₃ as the solvents. The fluorescence spectra were obtained from the Fluorescence spectrophotometer (FSP, model: C11367-11), which purchased from Hamamatsu (Japan).

2.2. Synthesis of 9, 10-Bis (bromomethyl) anthracene

The anthracene (5.7 g, 32 mmol), (CH₂O)_n (3.6 g), and a catalytic amount of AlCl₃ dissolved in acetic acid (60 mL) with 33% HBr and stirred for 6 h at 50 °C. The resulting solid was washed with water and dried in vacuum one night. The residue product was recrystallized in toluene three times to obtained flaxen solid. Yield 6.7 g (64%). ¹H NMR (300 MHz, CDCl₃): δ 8.38 (m, 4H), δ 7.65 (m, 4H), δ 5.54 ppm (m, 4H)



Scheme 1. Schematic showing the preparation of a glycosylated fluorescent bioprobes (An-Sh) which relied on the formation of specific interaction between phenylboronic acid and Sh. (Tp: triethyl phosphate, 4-FPBa: 4-Formylphenylboronic acid).

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