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Regular Article

Synthesis and bioimaging of biodegradable red fluorescent organic nanoparticles with aggregation-induced emission characteristics

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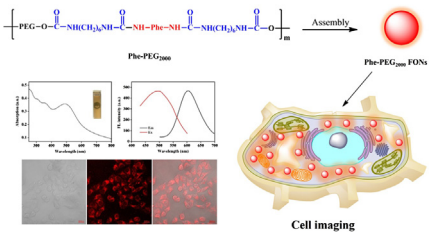
GRAPHICAL ABSTRACT

Biodegradable and biocompatible fluorescent organic nanoparticles with aggregation-induced emission feature were fabricated via a two-step conjugation reaction and utilized for bioimaging.



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ABSTRACT

Fluorescent organic nanoparticles (FONs) with aggregation-induced emission (AIE) features have recently emerged as promising fluorescent probes for biomedical applications owing to their excellent optical properties, designability and biocompatibility. Significant progress has been made recently for synthesis and biomedical applications of these AIE-active FONs. However, only very limited reports have demonstrated the fabrication of biodegradable AIE-active FONs with red fluorescence emission. In this study, a novel strategy has been developed for the preparation of biodegradable AIE-active polyurethanes (PUs) through a two-step polymerization, in which the diisocyanate-terminated polyethylene glycol (NCO-PEG-NCO) was synthesized and subsequently conjugated with diamine-containing AIE dye (NH_2-Phe-NH_2). The successful synthesis of AIE-active Phe-PEG_{2000} PUs is evidenced by a series of characterization techniques. Because of the formation of AIE-active amphiphilic PUs, the final copolymers can self-assemble into spherical nanoparticles, which exhibit strong luminescence and high water dispersion. The biological evaluation results suggest that the AIE-active Phe-PEG_{2000} FONs possess low toxicity and desirable cell permeability. Therefore, we anticipate that these AIE-active FONs with biodegradable potential will trigger much research enthusiasm and effort toward the creation of new AIE-active materials with improved properties for various biomedical applications.

1. Introduction

With the rapid development of nanotechnology, fluorescence nanoparticles with advanced functionality have received great

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attention in visualizing biological processes [1], metabolism [2,3] and pharmacokinetics [4] due to their good photostability, tunable size and ease of surface functionalization. To date, typical fluorescence probes including inorganic and organic nanoparticles or organic-inorganic hybrid materials have been extensively used in biosensing and cell imaging [5–11]. Although each kind of fluorescent nanoparticle has its own characteristics, the fluorescence probes based on organic dyes have attracted much research interest by virtue of their tunable chemical structure and properties, biodegradable potential and biocompatibility. In particular, red/near-infrared organic luminescent materials are essential in bioimaging. To reach red emission, dye molecules generally have large planar rings with extended conjugation or strong π-conjugated electron-donating and accepting groups. Although these red fluorophores are strongly emissive in their molecularly when dissolved in solution, the emission signals are often weakened or even annihilated in aggregates, due to what is known as the notorious aggregation-caused quenching (ACQ) effect [12,13]. Conventional organic dyes have a tendency to aggregate, which is highly depend on their intrinsic hydrophobicity, and the excited state often decays via non-radiative channels, which reduces the brightness and sensitivity in biological applications. Various chemical and physical approaches have been employed to prevent fluorophore aggregation, but they have met with only limited success. Interestingly, some propeller-like organic dyes show distinctive fluorescence phenomena with aggregation-induced emission (AIE) characteristics [12,14–17]. These fluorogens generally contain rotor structures and exhibit low frequency vibration motions in dilute solutions. However, in aggregated states, instead of quenching, AIEgens emit efficiently due to the restriction of intramolecular rotations (RIR) and the lack of energy dissipation via non-radiative channels. Since the first discovery by Tang and coworkers in 2001, luminescent materials with AIE features have attracted extensive research interest for applications such as electroluminescent devices, bio-sensing, and cell imaging. Up until now, a wide variety of AIE dyes have been designed and synthesized based on the mechanism of RIR. In our previous work, we prepared a series of AIE-active FONs, which were utilized for cell imaging, by various fabricated approaches [18–27]. Even so, synthesizing AIE-active probes with better biocompatibility, biodegradability and red/near-infrared emission is essential for bioimaging applications.

Polymeric micelles are convenient vehicles that could efficiently solubilize hydrophobic AIE dyes by encapsulating them within the core of the micelles at different concentrations. Therefore, biodegradable and biocompatible polyurethanes (PUs) may be a promising candidate for this application [28,29]. Since first introduced as implantable biomaterials in 1967, biodegradable PUs have been widely explored for numerous applications in medicine including regenerative medicine, drug delivery systems, and implantable bioelectronics [30–38]. PUs, which consist of alternating hard and soft segments, are known as one of the most versatile polymers, and their properties can be tailored by employing a variety of soft segment and chain extenders (diol, diamine). Poly(ethylene glycol) (PEG) has the advantage of non-toxicity, non-immunogenicity and hydrophilicity and has been approved for use in biomedical applications by the U.S. Food and Drug Administration (FDA) [39,40]. Hence, PEG is one of the desired diol soft segments for designing PU-based block polymers. The PEG coating on the surface of micelles can increase circulation time by reducing the interactions with serum proteins. Based on the advantages of PUs and PEG, the self-assembled PU-based AIE-active FONs have tremendous potential in cell imaging and other biomedical applications.

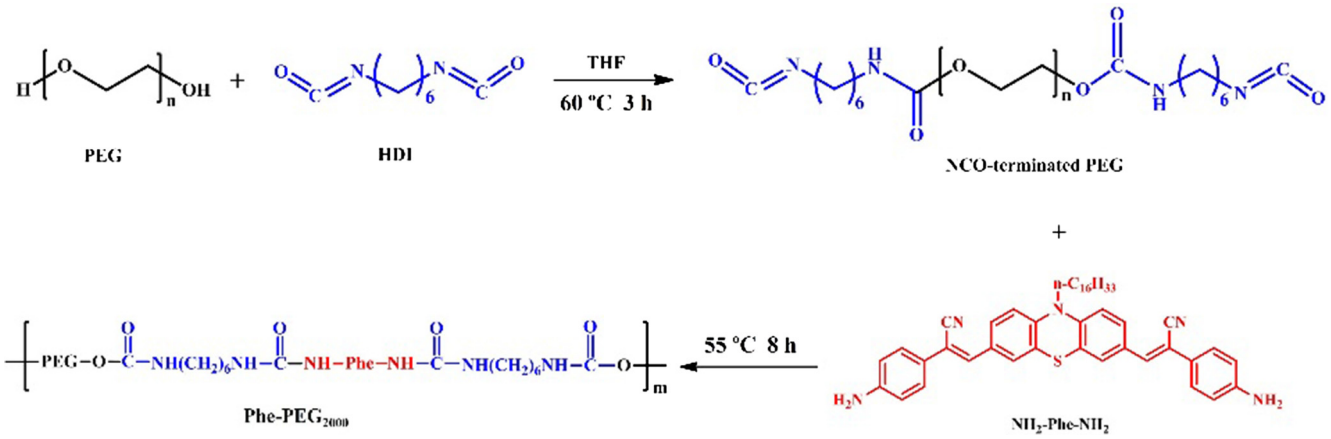
In this work, we constructed biodegradable and biocompatible amphiphilic PU-based block copolymers with alternating PEG_{2000} segments and AIE dyes in a "two-step" strategy. The detailed procedure is displayed in Scheme 1. Briefly, diisocyanate-terminated PEG (NCO-PEG-NCO) was conjugated with diamine AIE dye (NH_2-Phe-NH_2) to form AIE-active copolymers with biodegradable bonds. The ultimate biodegradable PUs were amphiphilic polymers that could self-assemble into spherical micelles in aqueous solutions with encapsulated hydrophobic AIE dyes in their interior.

2. Experimental procedures

2.1. Materials and measurements

All of the chemical agents were used as received without any further purification. Polyethylene glycol (*M*w = 2000 Da), hexamethylene diisocyanate (HDI) and stannous octoate were analytical grade and purchased from Aladdin (Shanghai China). Tetrahydrofuran (THF) was distilled from sodium in the presence of benzophenone. The intermediate NH_2-Ph-NH_2 was prepared according to methods in the literature [41–43].

^{1}H nuclear magnetic resonance (NMR) spectra were measured on a Bruker Avance-400 (400 MHz) spectrometer using TMS as internal reference and $CDCl_3$ as the solvent. The Fourier transform infrared (FT-IR) spectra were obtained on a Nicolet 5700. An F-4500 FL spectrometer with a slit width of 10 nm was used to determine the fluorescent properties of Phe-PEG_{2000} in water or THF



Scheme 1. Schematic showing the preparation of biodegradable AIE-active red FONs through the two-step conjugation reaction between NCO-PEG-NCO and NH_2-Phe-NH_2.