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Highly absorbing multispectral near-infrared polymer nanoparticles from one conjugated backbone for photoacoustic imaging and photothermal therapy

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ABSTRACT

Semiconducting polymers with specific absorption are useful in various applications, including organic optoelectronics, optical imaging, and nanomedicine. However, the optical absorption of a semiconducting polymer with a determined structure is hardly tunable when compared with that of inorganic semiconductors. In this work, we show that the optical absorption of polymer nanoparticles from one conjugated backbone can be effectively tuned through judicious design of the particle morphology and the persistence length of polymers. Highly absorbing near-infrared (NIR) polymers based on diketopyrrolopyrrole-dithiophene (DPP-DT) are synthesized to have different molecular weights (MWs). The DPP-DT polymer with a large molecular weight and high persistence length exhibited remarkably high optical absorption with a peak mass extinction coefficient of 81.7 L g^{-1} cm^{-1}, which is one of the highest value among various photothermal agents reported to date. Particularly, the polymer nanoparticles with different sizes exhibit broadly tunable NIR absorption peaks from 630 to 811 nm. The PEGylated small polymer dots (Pdots) show good NIR light-harvesting efficiency and high non-radiative decay rates, resulting in a relatively high photothermal conversion efficiency in excess of 50%. Thus, this Pdot-based platform can serve as promising photothermal agents and photoacoustic probes for cancer theranostics.

1. Introduction

Organic semiconductor materials have received considerable attention in recent years owing to their fascinating physical properties and extensive applications [1,2]. Semiconducting polymers are macromolecules characterized by a system of delocalized π-electrons by hopping, tunneling, and related mechanisms, which can result in intriguing and tunable optical and electrical properties [3]. Owing to these outstanding characteristics, semiconducting polymers have been widely used in photonics, sensing, solar energy conversion, and biomedicine [4–6]. There is also a great deal of interest in the development of nanoparticle systems given their broad potential applications in biological medicine [7]. In particular, semiconducting polymer dots (Pdots) represent an emerging nanotechnology in the energy and health fields [8–11]. Pdots exhibit high brightness and rapid emission rates, show excellent photostability, and are nontoxic, with demonstrated utility in a wide range of applications such as cellular labeling [12,13], in vivo imaging [14,15], photoacoustic imaging [16,17], single-particle tracking [18], and biosensing [19,20]. Semiconducting polymer-based multifunctional nanoparticles have also been demonstrated to have theranostic applications because of their flexible matrix for accommodating drugs, photosensitizers, and other imaging contrast agents [21–23].

Photothermal therapy (PTT) is an attractive therapeutic methodology that employs the conversion of absorbed near-infrared (NIR) light into thermal energy to ablate cancerous

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cells. PTT has received tremendous attention in the field of cancer therapy because of its specific selectivity to cancer-targeting sites and minimal invasion to the surrounding normal tissues. Thus, it would be highly desirable to shift the wavelength of irradiation light to the "therapeutic window" (600–900 nm) to achieve the maximum penetration depth for solid tumors, while minimizing the scattering and absorption of photons by the tissue in order to reduce damage to surrounding healthy tissues. Currently, many light-absorbing inorganic and organic photothermal agents are being extensively explored as efficient photothermal materials for in vivo cancer therapy, such as gold nanomaterials [24–26], carbonous nanostructures [27,28], transition-metal dichalcogenides [29,30], copper sulfide nanoparticles [31], magnetic nanoparticles [32], and organic dyes [33] and polymers [34]. However, most of these thermotherapy agents are not utilized in clinical practice due to their potential long-term toxicity and poor drug metabolism and pharmacokinetic (DMPK) properties. Therefore, the development of therapeutic agents that can serve as imaging agents to monitor the biodistribution and DMPK of these photothermal probes is essential. Recently, researchers designed and synthesized a class of biocompatible conjugated polymer nanoparticles as highly effective photothermal agents for the PTT ablation of cancer in vivo [35,36]. Pu et al. proposed an intraparticle molecular orbital engineering approach to enhance both the photoacoustic brightness and PTT efficiency of semiconducting polymer nanoparticles for amplified theranostics [37]. In another recent report, Liu et al. developed nanoscale metal-organic particles with rapid clearance for the imaging-guided PTT of cancer [38]. These are encouraging achievements in cancer therapeutics and have stimulated the extensive development of NIR photothermal techniques.

Photoacoustic imaging (PAI), as an emerging noninvasive biomedical imaging modality based on optical excitation and ultrasound detection [39], has attracted considerable interest primarily because of its superiority to traditional optical imaging technologies, e.g., low acoustic scattering, nonionizing radiation, high depth-to-resolution ratio, high sensitivity, multiscale capacity from organelles to organs, and inherent background-free and speckle-free features [40–43]. In particular, PAI has the capability to provide structural, functional, and molecular information of biological tissues and has enabled the clear visualization of deep tumors in preclinical and clinical studies [44–47]. Because both photoacoustic and photothermal approaches involve thermoplastics, it may be useful to integrate PAI and PTT using the same probes, thereby permitting imaging-guided therapy. Therefore, an ideal photoacoustic and photothermal agent should have a large absorption coefficient, good biocompatibility, good photostability, and well-controlled surface functionalization, which are important characteristics for clinical practice in cancer therapeutics.

In this work, we designed and synthesized the highly absorbing NIR polymer diketopyrrolopyrrole-dithiophene (DPP-DT) with different molecular weights. The nanoparticles of different sizes were characterized for their optical absorption, NIR light-harvesting efficiency, and photothermal conversion efficiency. Intriguingly, these nanoparticles from one conjugated backbone showed intense tunable absorption from 630 nm to 811 nm. The polymer with high persistence length exhibited remarkably high optical absorption with a peak mass extinction coefficient of 81.7 L g^{-1} cm^{-1}, which was much higher than most of photothermal agents. In vitro cellular assays and in vivo animal experiment indicate these Pdots are promising PTT and PAI contrast agents for photoacoustic imaging and photothermal cancer treatment.

2. Results and discussion

2.1. Design and synthesis of highly absorbing NIR semiconducting polymers

The specific optical absorption of semiconducting polymers is critical for their optoelectronic and biomedical applications. Because of the planar structures and strong electron deficiency, the value of diketopyrrolopyrrole derivatives has been increasingly recognized in the development of organic optoelectronic devices. Nelson et al. demonstrated that semiconducting polymers with higher MWs (120 kDa) led to substantially enhanced mass extinction coefficients that were 1.4-fold larger than those of fractions with lower MWs (20 kDa) [48]. Unfortunately, the high molecular weights of semiconducting polymers always cause poor solubility in tetrahydrofuran, preventing subsequent nanoprecipitation. In this context, we designed and synthesized a series of long side-

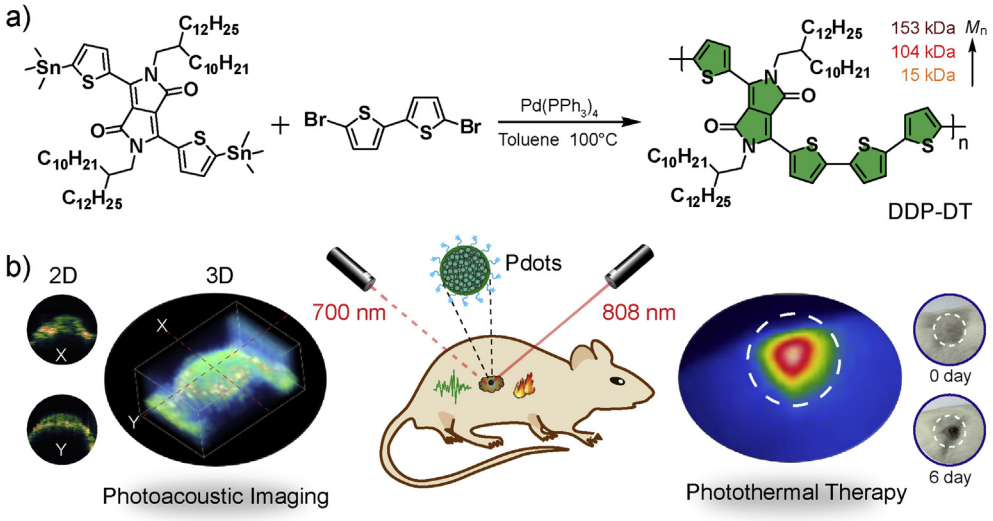

Fig. 1. (a) Synthetic route and chemical structure of the conjugated polymer DPP-DT via Stille polymerization. (b) Schematic illustration of PEGylated DPP-DT Pdots as a photoacoustic imaging and photothermal therapy agent.