Facile Synthesis of Black Phosphorus Nanosheet@NaReF₄ Nanocomposites for Potential Bioimaging

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Abstract: Black phosphorus nanomaterials (BPN) have been well developed in tumor therapy. However, lack of diagnostic function limits the development of BPN in biomedicine. Lanthanide-doped nanoparticles are considered as versatile materials for fluorescence or magnetic resonance imaging. Integration of BPN with lanthanide-doped nanoparticles was rarely reported owing to the complex synthesis processes and poor modification effect. Herein, we report a simple and general method for synthesizing BPN@NaReF₄ (Re: Gd or Y, Yb, Er) nanocomposite. TEM and XRD characterization confirm efficient combination of BPN and NaGdF₄ or NaYF₄:Yb,Er (18.2 mol %) after one-step mixing. The FTIR and XPS spectra were used to prove the generation of PO₄³⁻-Gd and P-Gd coordination bonds and clarify ligand exchange mechanism. The anchored nanoparticles on BPN were stable and become hydrophilic. The prepared BPN@NaGdF₄ exhibit the signals of photoacoustic and magnetic resonance imaging. The obtained BPN@NaYF₄:Yb,Er (18.2 mol %) have the potential in fluorescence bioimaging. We believe that this work will expand the applications of BPN in diagnosis and therapy together.

Keywords: black phosphorus; rare-earth nanoparticle; nanocomposites; magnetic resonance imaging; photoacoustic imaging

1. Introduction

Black phosphorus, a two-dimensional semiconductor, has attracted much attention from researchers in recent years due to its unique layer-dependent properties [1]. The black phosphorus nanosheet (BPN), exfoliated from its bulk counterpart, exhibits outstanding optical, electronic, thermal, and catalytic performances, and, thus, may be widely applied in optoelectronics [2], energy conversion [3], and biomedicine [4]. Nevertheless, to meet the diversified demand in varied fields, the functionality of black phosphorus nanomaterials should be further improved, especially when used in biomedicine.

With the advantages of high specific area, good biocompatibility, and photothermal/photodynamic properties, BPN was well studied for tumor treatment and showed great therapy performance [5,6]; however, lack of diagnostic function limits the development of BPN in clinical use. To improve it, imaging medium, such as Cy7 dyes [7] or iron oxide [8], was loaded with BPN, realizing bioimaging and therapy together. Sadly, the binding force between BPN and contrast medium is an electrostatic interaction which will cause uncontrollable aggregation of nanomaterial and medium leakage [9,10]. Thus, continual effort in developing effective strategies should be made to endow BPN with bioimaging functions, such as fluorescence imaging or magnetic resonance imaging, which is very common and powerful in clinics [11].

Lanthanide-doped nanoparticles, also called rare-earth nanoparticles (NaReF₄), have been developed as an important class of functional nanomaterials for many years. Bene-
fiting from the inner-layer electron transition, lanthanide-doped nanoparticles commonly exhibit light emission with large anti-stokes shift, long luminescence lifetimes, and excellent photostability [12,13]. Moreover, Gd$^{3+}$ based complex and nanoparticle yield magnetic resonance signals [14]. Thus, lanthanide-doped nanoparticles were widely used for disease diagnosis, including fluorescence imaging and magnetic resonance imaging [15–17]. In this regard, integration of lanthanide-doped nanoparticles with BPN to form 0D-2D heterostructure will be an upward trend, realizing integrated diagnostic and therapy. Unfortunately, to the best of our knowledge, the rare-earth nanoparticles were married with BPN just via electrostatic attraction which often suffers inefficient modification and intricate procedures including charged polymer coating or surface modification [18,19]. A simple method of combining rare-earth nanoparticles with BPN is desirable and worthwhile for nanotechnology development.

In this work, we synthesized BPN@NaReF$_4$ (Re: Gd or Y, Yb, Er) heterostructure by a simple process. As the schematics illustration show in Figure 1, the oleic acid-capped NaReF$_4$ in cyclohexane was directly mixed with BPN in water. After vortexing overnight, the NaReF$_4$ in the oil phase was transferred to the aqueous phase and integrated with BPN, forming NaReF$_4$ coordinated BPN nanocomposites. The prepared BPN@NaGdF$_4$ nanocomposites exhibit photoacoustic and magnetic resonance signals and the BPN@NaYF$_4$:Yb,Er (18.2 mol %) demonstrate fluorescence emission, showing the potential application in bioimaging.

Figure 1. Schematic illustrations of BPN@NaReF$_4$ synthesis and corresponding experimental process.

2. Materials and Methods
2.1. Materials

Bulk black phosphorus crystals were synthesized via a chemical vapor transport method according to our previously reported procedures [20]. N-Methyl-2-pyrrolidone (NMP, 98%), cyclohexane (99.5%), methanol (99.8%), and ethanol (AR) were obtained from Aladdin Biochemical Technology Co., Ltd. (Shanghai, China). Hydrochloric acid (~36%) and sodium hydroxide (>98%) were purchased from Sinopharm Chemical Reagent Co., Ltd. Yttrium(III) acetate hydrate (99.9%), ytterbium(III) acetate hydrate (99.9%), erbium(III) acetate hydrate (99.9%), gadolinium(III) acetate hydrate (99.9%), and oleic acid (OA, 90%) were purchased from Alfa Aesar (Haverhill, MA, USA). Ammonium fluoride (>98%) and 1-Octadecene (90%) was purchased from Sigma-Aldrich (St. Louis, MO, USA). All chemicals were used as received without further purification.
2.2. Characterization

Low-resolution TEM images were taken from a Talos L120C G2 (USA) instrument operated at 120 kV. Powder X-ray diffraction (XRD) patterns were recorded using a Rigaku Mini Flex 600 with Cu Kα radiation (λ = 1.5406 Å). UV-Vis spectra were recorded using a UV-1800 instrument (Shimadzu, Kyoto, Japan). Fluorescence spectra were obtained on an FLS1000 fluorescence spectrometer (Edinburgh Instruments, Livingston, UK). Scanning electronmicroscopy (SEM) images were carried out in a JSM-7800F (JEOL) scanning electron microscope. Raman spectra were obtained using a Renishaw inVia Qontor confocal microscope with a 532 nm laser. FTIR spectra were obtained on a Nicolet iN10 MX instrument (Thermo Scientific, Waltham, MA, USA). X-ray photoelectron spectroscopy (XPS) was performed on an AXIS Ultra DLD (Shimadzu, Kyoto, Japan). Inductively coupled plasma mass spectrometry (ICP-MS, iCAP Q, Thermal Fisher, Waltham, MA, USA) was used to determine the concentration of black phosphorus and gadolinium. Photoacoustic signal was obtained on a VEVO LAZR-X (Fujifilm VisualSonics, Toronto, Canada). The magnetic resonance images and T1 relaxation rate were acquired on the 0.5 T MesoMR23-060H-I (Niumai Electronic Technology, Suzhou, China).

2.3. Synthesis of Black Phosphorus Nanosheets

Bulk BP (200 mg) was ground with NMP and then dispersed in NMP (100 mL). The mixture was first tip-sonicated (working 2 s, interval 2 s, power 650 W) for 3 h in an ice bath, followed by ice bath sonication for 12 h at 300 W. The resulting suspension was centrifuged at 7000 rpm for 20 min, and the collected supernatant was then centrifuged at 14,000 rpm for 20 min. The precipitate was washed with DI water three times and dispersed in the aqueous solution for further use. The concentration of BPN dispersion was determined by ICP-MS.

2.4. Synthesis of NaGdF4 Nanoparticles

Oleic acid capped NaGdF4 (NaGdF4-OA) nanoparticles were prepared using the thermal coprecipitation method according to the literatures [21]. Briefly, oleic acid (4 mL), 1-octadecene (6 mL), and an aqueous solution (2 mL) containing Gd(CH3COO)3 (0.4 mmol) were added to a 50 mL two-neck round-bottom flask. The mixture was stirred at 150 °C for 1 h to remove the water. After the mixture was cooled to room temperature, a methanol solution (5 mL) containing NaOH (1 mmol) and NH4F (1.2 mmol) was added to the flask. The mixture was then stirred at 50 °C for 2 h, followed by maintaining the temperature at 100 °C for another 30 min. Subsequently, the mixture was heated to 280 °C and kept for 2 h under nitrogen atmosphere. After cooling down to room temperature, the oleic acid capped NaGdF4 nanoparticles were collected by centrifugation and washed three times with ethanol. The nanoparticles were dispersed in cyclohexane for further use.

2.5. Synthesis of NaYF4:Yb,Er (18.2 mol %) Nanoparticles

Oleic acid capped NaYF4:Yb,Er (18.2 mol %) nanoparticles were also prepared by the thermal coprecipitation method according to our previous work [22]. The Y(CH3COO)3 (0.32 mmol), Yb(CH3COO)3 (0.072 mmol) and Er(CH3COO)3 (0.008 mmol) aqueous solution was mixed with oleic acid (3 mL) and 1-Octadecene (7 mL). After stirring at 150 °C for 1 h, the mixture was cooled to room temperature, and then NaOH (1 mmol) and NH4F (1.2 mmol) dissolved in methanol was added followed by stirring at 50 °C for 2 h. Next, the mixture was heated to 100 °C and kept for another 30 min. After purging with nitrogen, the reaction mixture was heated to 290 °C and kept for 1.5 h before cooling down to room temperature. The resulting nanoparticles were collected by centrifugation washed with ethanol. The oleic acid capped NaYF4:Yb,Er (18.2 mol %) nanoparticles were finally obtained and dispersed in cyclohexane.
2.6. Synthesis of Ligand-Free Nanoparticles

Ligand-free rare-earth nanoparticles were prepared according to a procedure in the literature, with slight modification [23]. The oleic acid capped nanoparticles were dispersed in ethanol (1 mL), and after adding hydrochloric acid (1 mL, 1 M), the mixture was ultrasonicated for 1 min. The ligand-free nanoparticles were collected by centrifugation at 14,000 rpm for 20 min and washed with ethanol three times. The ligand-free rare-earth nanoparticles were redispersed in water for the MRI test.

2.7. Synthesis of BPN@NaReF₄ Nanocomposites

The oleic acid capped NaGdF₄ or NaYF₄:Yb,Er (18.2 mol %) in cyclohexane (2 mL, 50–500 µg mL⁻¹) was directly mixed with BPN aqueous solution (2 mL, 100 µg mL⁻¹). After vortex overnight, the nanoparticles in cyclohexane were transferred to water and integrated with BPN in the meantime. The BPN@NaGdF₄ or BPN@NaYF₄:Yb,Er (18.2 mol %) nanocomposites were collected from the aqueous phase by centrifugation.

3. Results

3.1. Characterization of BPN@NaGdF₄ Nanocomposites

NaGdF₄ nanocrystals were used as the representative lanthanide-doped nanoparticles to examine the integration between BPN and NaReF₄. First, the BPN and NaGdF₄ were synthesized separately and characterized with TEM, XRD, absorption spectra, and Raman spectra.

As the XRD pattern shows in Figure S1, the exfoliated black phosphorus nanosheets still have the crystal structure. The lateral size of obtained BPN was 100–200 nm (Figure 2A). The optical bandgap derived from the BPN absorption spectrum was ~2.18 eV (Figure 3A,B), indicating the ultrathin thickness of the obtained BPN [24]. The Raman spectrum (Figure 3C) shows three characteristic peaks at 361, 438, and 466 cm⁻¹, assigned to the modes of $A_g^1$, $B_{2g}$, and $A_g^2$, respectively, demonstrating the puckered orthorhombic lattice structure of the exfoliated BPN [25].

Figure 2. The TEM images of BPN (A), NaGdF₄ (B), and BPN@NaGdF₄ (C); (D) XRD pattern of the as-synthesized BPN@NaGdF₄ nanocomposites.
The synthesized NaGdF₄ nanoparticles, capped by oleic acid, have high uniformity in size (average size of ~8.3 nm) as shown in Figure 2B and Figure S2. The XRD pattern proves that the obtained NaGdF₄ nanoparticles are composed of pure hexagonal NaGdF₄ crystals (Figure S1).

After the integration of NaGdF₄ and BPN, the product was collected from the aqueous phase. As Figure S3 shows, the amount of NaGdF₄ nanoparticles was decreased which indicates the possible combination of BPN and NaGdF₄. From the TEM image in Figure 2C, we can see that the nanoparticles were distributed on the surface of BPN and no free nanoparticles were found. XRD pattern in Figure 2D shows combined diffraction peaks of BPN and NaGdF₄ nanocrystal. After NaGdF₄ coating, the Raman peaks of BPN experience a slight red shift, indicating that the NaGdF₄ nanoparticles were successfully loaded on the BPN [26]. To investigate the loading capacity of BPN for NaGdF₄ nanoparticles, different amounts of NaGdF₄ nanoparticles were added in the oil phase. After the reaction, the collected products were characterized with TEM (Figure S4). It is obvious that the numbers of loaded NaGdF₄ nanoparticles are increased with the elevated feeding ratios of NaGdF₄ to BPN and keep constant when the ratio is higher than 2. Above all, these results confirm the efficient integration of NaGdF₄ with BPN via this simple experimental method.

It should be noted that the optical bandgap of BPN@NaGdF₄ calculated from the absorption spectrum is generally consistent with BPN (Figure 3A,B). Due to the layer-dependent bandgap, the optical bandgap can reflect the thickness and aggregation degree [27]. Thus, it is concluded that the rigid NaGdF₄ nanoparticles can prevent aggregation of BPN after loading them.

### 3.2. Mechanism of BPN@NaGdF₄ Preparation

To investigate the reason why NaGdF₄ can be bound with BPN, the FTIR and XPS spectra were acquired. For the FTIR spectrum of BPN@NaGdF₄ nanocomposites (Figure 4A), the peaks at 2920, 2854, 1554, and 1454 cm⁻¹ disappeared, unlike with OA capped NaGdF₄, which confirms removal of the OA [22]. According to the literature, the BPN is easily oxidized and PO₄³⁻ can be generated on the surface of BPN [28,29]. From the FTIR spectrum of BPN, we can recognize the peaks located in the 1115–975 cm⁻¹ range which are from PO₄³⁻ [30,31]. The XPS spectra (Figure 4B) also show the binding energy of PO₄ for the BPN@NaGdF₄ sample. Thus, the PO₄³⁻ were indeed existed on the as-prepared BPN and BPN@NaGdF₄ nanocomposites.
It is well known that the $\text{PO}_4^{3-}$ can easily replace the $\text{CO}_2^{-}$, as the $\text{PO}_4^{3-}$ has a stronger coordination ability for rare earth than carboxyl [32,33]. In this case, we believe that the oleic acid with $\text{CO}_2^{-}$ was displaced by $\text{PO}_4^{3-}$ on the BPN, and $\text{PO}_4^{3-}$-Gd coordination was formed. Thus, the NaGdF$_4$ nanoparticles can be integrated with BPN.

In addition to the coordination of $\text{PO}_4^{3-}$ for Gd element, the P-Gd coordination [34] has also been studied. As shown in Figure 4B–D, after the combination of BPN and NaGdF$_4$, the XPS peaks of P 2p and Gd 4d are shifted to higher binding energy while the Gd 3d XPS peaks exhibit no change, indicating strong interaction between P and Gd atoms. By XPS-peak-differentiation-imitating analysis for P 2p and Gd 4d XPS spectra [35,36], there are two new emerged peaks that can all be assigned to P-Gd coordination.

Generally, the coordination bond is stable. In this case, we examined whether the anchored NaGdF$_4$ on BPN can be dropped or not. The prepared BPN@NaGdF$_4$ nanocomposites in water were stirred vigorously overnight and TEM was conducted. In Figure S8, almost no free NaGdF$_4$ nanoparticles can be observed. Thus, the anchored NaGdF$_4$ nanoparticles on BPN by this method are stable.

Above all, we concluded that the $\text{PO}_4^{3-}$ groups on BPN replace the $\text{CO}_2^{-}$ contained oleic acids on the surface of NaGdF$_4$ and $\text{PO}_4^{3-}$-Gd as well as P-Gd coordination bonds are formed, realizing firm integration of NaGdF$_4$ and BPN.

To prove the generality of such synthesis method, NaYF$_4$:Yb,Er (18.2 mol %) nanoparticles with an average size of 22 nm were prepared to modify BPN (Figure 5A,B). After the modification process, the amount of NaYF$_4$:Yb,Er (18.2 mol %) nanoparticles in upper cyclohexane was reduced (Figure S9) and the TEM image of the product shows that the NaYF$_4$:Yb,Er (18.2 mol %) nanoparticles were effectively anchored on BPN (Figure 5C).
Consequently, we believe that the described experimental method in this work can be used to integrate other lanthanide-doped nanoparticles with BPN.

Figure 5. TEM image of OA capped NaYF₄:Yb,Er (18.2 mol %) nanoparticles (A) and the corresponding size distribution (B); (C) TEM image of BPN@NaYF₄:Yb,Er (18.2 mol %) nanocomposites.

3.3. Bioimaging Properties of BPN@NaReF₄ Nanocomposites

The black phosphorus nanomaterials have been reported exhibit photoacoustic property owing to the excellent photothermal conversion and thermal stability [37–39]. We then examine the photoacoustic signal of BPN and BPN@NaGdF₄ nanocomposites. The photoacoustic signal of BPN was strongest when the excitation wavelength was 710 nm (Figure S10). The photoacoustic intensities all show good linear positive correlations with the concentrations of BPN (Figure 6A,B). The BPN@NaGdF₄ nanocomposites with 200 µg mL⁻¹ BPN display obvious photoacoustic imaging effect.

Figure 6. Photoacoustic intensity of BPN (A) and BPN@NaGdF₄ (B) with different concentrations of BPN and their linear fit. Inset: corresponding photoacoustic imaging; Relaxation rate R₁ (1/T₁) of ligand-free NaGdF₄ (C) and BPN@NaGdF₄ (D) versus Gd³⁺ concentration.
Gd-based chelates (Gd-DTPA, Gd-DOTA, etc.), as a class of T1 contrast agent, have been widely used in routine clinical magnetic resonance imaging (MRI) diagnosis [40,41]. NaGdF4 nanoparticles have also been well studied as contrast agent and show enhanced MRI effect [15,16]. In this case, the relaxation rate of NaGdF4 nanoparticles and BPN@NaGdF4 were evaluated. As shown in Figures 6C,D and S11, the NaGdF4 nanoparticles after BPN loading still exhibit comparable MRI signal compared with ligand-free NaGdF4.

The NaYF4:Yb,Er (18.2 mol %) nanoparticles are considered to be the more efficient NIR-to-visible upconverting nanomaterials, showing much potential in bioimaging application. As Figure 7 shows, when excited by a 980 nm laser, NaYF4:Yb,Er (18.2 mol %) nanoparticles have three emission peaks. After loading with BPN, the emission peaks in 507–575 nm range are quenched more severely owing to stronger absorption of BPN for shorter wavelength light (Figure 2A). The emerged emission peaks at 647 nm and 697 nm may be the results of light scattering or fluorescence emission of BPN. We speculate that there could be energy transfer between BPN and NaYF4:Yb,Er (18.2 mol %) and it will be further investigated in the future. In a word, the BPN@NaYF4:Yb,Er (18.2 mol %) nanocomposites still exhibit satisfied fluorescence emission for bioimaging application.

**Figure 7.** Room-temperature upconversion emission spectra of the oleic acid capped NaYF4:Yb,Er (18.2 mol %) nanoparticles dispersed in cyclohexane and BPN@NaYF4:Yb,Er (18.2 mol %) in water.

### 4. Conclusions

In this work, the BPN@NaReF4 (Re: Gd or Y, Yb, Er) nanocomposites were successfully synthesized via simple mixing. The formation mechanism of BPN@NaGdF4 is that the oleic acid on the surface of NaGdF4 can be substituted with the PO43− on the surface of BPN. Coordination bonds (PO43−-Gd and P-Gd) are generated between Gd and PO43− or P, so that the modified NaGdF4 on BPN are stable. The prepared BPN@NaGdF4 nanocomposites have the properties of photoacoustic and magnetic resonance imaging. The BPN@NaYF4:Yb,Er (18.2 mol %) nanocomposites in aqueous still show satisfied fluorescence emission and can be used for fluorescence bioimaging in future.

**Supplementary Materials:** The supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nano12193383/s1. Figure S1: XRD patterns of as-prepared BPN and NaGdF4; Figure S2: size distribution of the oleic acid capped NaGdF4 nanoparticles; Figure S3: pictures of reaction bottle containing NaGdF4 and BPN; Figure S4: TEM images of BPN@NaGdF4; Figure S5: SEM images of the BPN, NaGdF4 and BPN@NaGdF4 nanocomposites; Figure S6: XPS survey spectra; Figure S7: FTIR spectrum of as-synthesized BPN; Figure S8: TEM image of BPN@NaGdF4 nanocomposites after rigorously stirring overnight; Figure S9: pictures of reaction bottle containing NaYF4:Yb,Er (18.2 mol %) and BPN; Figure S10: Photoacoustic signal of BPN at different excitation wavelengths; Figure S11: magnetic resonance imaging of ligand-free NaGdF4 and BPN-NaGdF4 nanocomposites.
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**Data Availability Statement:** The data presented in this study are available on request from the first author.

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