Enhancement of near-infrared emission of neodymium-doped monoclinic gadolinium phosphate nanophosphors by surface coating with calcium phosphate

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ABSTRACT
Core/shell-type nanoparticles composed of GdPO₄ₓ mol% Nd³⁺/calcium phosphate (CaPO) (0 ≤ x ≤ 5) were synthesized by a precipitation method, as nontoxic bio imaging phosphors that can emit near-infrared (NIR) light under NIR excitation. The GdPO₄ₓ mol% Nd³⁺ core, obtained in a single-phase form of the monoclinic rare-earth orthophosphate structure, exhibited characteristic emissions attributed to the f–f transitions of Nd³⁺. The strongest emission peak was observed at 1061 nm under excitation at 800 nm in a sample containing 3 mol% of Nd³⁺. The average particle size of GdPO₄: 3 mol% Nd³⁺ was 42 nm, indicating that nano-sized particles were successfully obtained. Although the average particle size of the core/shell-type GdPO₄: 3 mol% Nd³⁺/CaPO nanophosphor was slightly increased to 54 nm by a second calcination in the surface coating process, the CaPO shell was well formed with a thickness of 3 nm around the GdPO₄: 3 mol% Nd³⁺ core. With surface coating with the CaPO shell, the NIR emission intensity increased to 4.2 times higher than that of GdPO₄: 3 mol% Nd³⁺. This emission intensity was significantly higher than that of indocyanine green, moreover, which is used in practice as an organic bioimaging reagent.

1. Introduction

Nanophosphors have been actively studied as bioimaging materials lately because of their low light-scattering intensity [1–4]. Several studies on bioimaging applications of semiconducting quantum dots (QDs) [5–7] and up-conversion nanophosphors [8–11] have been energetically reported. Unfortunately, QDs are unsuitable for in vivo use, because they possess toxic elements such as cadmium, arsenic, lead and mercury. Although a core/shell-type QD in which a ZnS shell is coated with a CdSe core has been proposed, it is difficult to completely suppress Cd elution [5,12]. The up-conversion phosphors capable of converting near-infrared (NIR) light to visible light exhibit a fatally low quantum yield, as multiphoton excitation in their emission mechanism is inevitable [13].

Besides nanophosphors, organic fluorescent dyes that emit visible light under irradiation with short wavelengths such as ultraviolet (UV) light have also been proposed [14–16]. Excitation by UV rays often causes damage to cells and tissues due to overheating, however, and contrasts with images are reduced by the autofluorescent background.

As one means of solving the above problems, application of a fluorescent material that is excited by NIR light and emits NIR light to bioimaging has been proposed. NIR light in the range of 700 to 1400 nm, in particular, is usually referred to as the “optical transmission window” of tissues. NIR light in the optical transmission window penetrates deep into the tissue, but phototoxicity is less damaging to the living body, and any decrease in image contrast due to tissue autofluorescence and scattering loss is suppressed [17,18]. Indocyanine green (ICG) is the only clinical example of an organic fluorescent pigment that emits NIR light under NIR excitation in the range of 700 to 1400 nm [19]. Unfortunately, however, the emission intensity is insufficient, and the penetration depth is limited.

Because of this situation, ceramic nanophosphors that are excited by NIR light and emit strong NIR light have attracted increasing attention, and it is considered significant to develop such nanophosphors with biological compatibility, non-toxicity, and thermal and chemical stability. As candidates, nanophosphors containing neodymium (Nd³⁺) as a luminescent ion are promising candidates for bioimaging, because they...
show efficient NIR luminescence at around 880, 1060 and 1340 nm due to the f–f transition of Nd$^{3+}$ under NIR excitation at 808 nm [20–23]. Their emission mechanism is classified into the down-shifting process, and its quantum yield is generally higher than that of the up-conversion process.

GdPO$_4$ is very attractive for use with some host material candidates, because it offers high thermal stability and low water solubility, resulting in low cytotoxicity and biological capabilities suitable for bioimaging phosphors [24]. GdPO$_4$ forms several allotropic structures such as monoclinic, hexagonal and tetragonal structures, depending on the synthesis conditions [25–30]. For monoclinic GdPO$_4$:Nd$^{3+}$, however, only the optical properties of the submicron-sized phosphors have been reported [21]. Investigation of the optical properties of nano-sized monoclinic GdPO$_4$:Nd$^{3+}$ is significant because the optical properties are correlated with the particle size, morphology, crystal structure and local symmetry around the Nd$^{3+}$ ion. We, therefore, focused on the synthesis of monoclinic GdPO$_4$:Nd$^{3+}$ nanophosphors.

When applying nano-sized phosphors, it is important to suppress decreases in fluorescence intensity due to the large surface proportions. Since the excited electrons relax non-radiatively through the surface trap levels, surface defects may also result in short lifetimes and low quantum yields. The optical properties of nanophosphors depend strongly on such surrounding conditions as organic ligands, water molecules and carbonate ions in solvents, moreover, because of the dangling bonds formed on the surface [31].

In order to improve the photoluminescence properties and stability, it is effective to cover the surfaces of the nanophosphors thinly with an inactive substance to form a core/shell-type structure and to suppress interactions between the core and the solvent [32–35]. In this study, we focused on core/shell-type nanophosphors with monoclinic GdPO$_4$:Nd$^{3+}$ as the core and calcium phosphate (CaPO) as the shell. Some materials based on CaPO, such as hydroxyapatite (Ca$_{10}$(PO$_4$)$_6$(OH)$_2$), exhibit an excellent practical biological capability as biomaterials, because CaPO is contained in biological hard tissues such as bones and teeth. Monoclinic GdPO$_4$:Nd$^{3+}$ and core/shell-type GdPO$_4$:Nd$^{3+}$/CaPO nanophosphors were therefore synthesized, and their NIR luminescent properties under NIR excitation were characterized.

2. Experimental

2.1. Materials

Gadolinium oxide (Gd$_2$O$_3$, 99.9%) was purchased from Shin-Etsu Chemical Co. Ltd. (Japan). Neodymium oxide (Nd$_2$O$_3$, 99.9%) was purchased from Kishida Chemical Co. Ltd. (Japan). Nitric acid (HNO$_3$), ammonium dihydrogen phosphate solution ([NH$_4$]$_2$HPO$_4$, 99.0%), ethylene glycol (EG, 99.5%), ethanol (99.5%), citric acid (CA, 98.0%), and calcium nitrate tetrahydrate (Ca(NO$_3$)$_2$·4H$_2$O, 98.5%) were purchased from FUJIFILM Wako Pure Chemical Co. (Japan). Indocyanine green (ICG) for use as a luminescent reference substance was purchased from Tokyo Chemical Industry Co., Ltd. (Japan). All reagents in this study were used as received without further purification.

2.2. Synthesis of monoclinic GdPO$_4$·x mol% Nd$^{3+}$ nanoparticles

Monoclinic GdPO$_4$:x mol% Nd$^{3+}$ (0 ≤ x ≤ 5) nanophosphors were synthesized by a precipitation method using ethylene glycol (EG) as a surfactant [36]. Gd$_2$O$_3$ and Nd$_2$O$_3$ were dissolved in diluted HNO$_3$, and their concentrations were then adjusted to 0.5 mol dm$^{-3}$ and 0.05 mol dm$^{-3}$ with deionized water, respectively. A mixture of 8.3 cm$^3$ of 0.6 mol dm$^{-3}$ (NH$_4$)$_2$HPO$_4$, 6.0 cm$^3$ of EG, and 20 cm$^3$ of deionized water was heated with a magnetic stirrer until it reached 50°C. A stoichiometric mixed solution of the 0.5 mol dm$^{-3}$ Gd(NO$_3$)$_2$ and 0.05 mol dm$^{-3}$ Nd(NO$_3$)$_2$ aqueous solutions was added dropwise to the above (NH$_4$)$_2$HPO$_4$ solution containing EG, and the mixed solution was then stirred for 3 h. Here, the amount of the (NH$_4$)$_2$HPO$_4$ solution was adjusted to 1.25 times the stoichiometric ratio. After the pH of the solution reached 1, it was centrifuged, and the precipitate was washed with deionized water and ethanol. The precipitate was dried at 80°C overnight and subsequently calcined at 900°C for 90 min in a muffle furnace (Isuzu, EPTR-26K), because monoclinic GdPO$_4$ was obtained by the calcination of hexagonal GdPO$_4$ at 800°C and above [27,28]. The obtained powder was ground in an agate mortar and then ultrasonically dispersed in 15 cm$^3$ of ethanol.

2.3. Synthesis of core/shell-type GdPO$_4$·x mol% Nd$^{3+}$/CaPO nanoparticles

The monoclinic GdPO$_4$:Nd$^{3+}$ nanoparticles were coated with calcium phosphate (CaPO) using a modified sol gel-based Pechini method to prepare a core/shell-type structure [37]. A small amount (0.0483 g) of citric acid (CA) was dissolved in a mixed solution of 75 cm$^3$ of deionized water and 25 cm$^3$ of ethanol (water/ethanol = 3/1 in volume). In order to obtain a shell thickness of 3 nm, 0.0293 g of Ca(NO$_3$)$_2$·4H$_2$O, 0.0110 g of (NH$_4$)$_2$HPO$_4$, and 4 g of EG acting as a crosslinker were added to the above CA solution and stirred at room temperature for 1 h. Finally, monoclinic GdPO$_4$:Nd$^{3+}$ nanoparticles dispersed in ethanol were added to this coating solution, and the mixture was stirred at room temperature for 2 h. After centrifugation, the resulting powder was dried at 100°C for 2
h and heated in a muffle furnace at 700°C, 800°C or 900°C for 15 min. Since the calcination temperature was higher than the boiling point of EG (198°C), the EG molecules adsorbed on the particle surface were removed by the calcination process. Accordingly, the influence of EG on the luminescent properties of the sample can be ignored.

2.4. Characterization

The sample composition was analyzed using X-ray fluorescence spectroscopy (XRF; Rigaku, ZSX Primus). The crystal structure was identified by X-ray powder diffraction (XRD; Rigaku Ultima IV) using Cu-Kα radiation (40 kV and 40 mA). The data were collected by step scanning over a 2θ range from 20° to 80° with a step size of 0.02° at a scan rate of 6° min⁻¹. The morphology of the core/shell-type nanoparticles was examined using a field emission scanning electron microscope (FE-SEM; JEOL, JSM-6701F). In addition, transmission electron microscope images were taken at an accelerating voltage of 300 kV (TEM; Hitachi H-9000NAR). The average particle size and particle size distribution were estimated by measuring the maximum diameter of 200 particles in one direction on the FE-SEM and the TEM photographs. In order to confirm the presence of Ca, P and O on the surfaces of the particles, the X-ray photoelectron spectra (XPS; ULVAC-PHI, PHI5000 VersaProve II) of the core/shell-type samples were measured using Al-Kα radiation (hν = 1486.6 eV). The NIR photoluminescence (PL) excitation and emission spectra were measured at room temperature using a fluorescence spectrometer (Horiba, Fluorolog-3), where the emission spectra were obtained for excitation at 800 nm and the excitation spectra were recorded for emission at 1060 nm.

3. Results and discussion

3.1. Characterization of monoclinic GdPO₄: x mol% Nd³⁺ nanoparticles

The composition of each sample was confirmed by XRF analysis to be almost stoichiometric. Figure 1 shows the XRD patterns of the GdPO₄: x mol% Nd³⁺ (0 ≤ x ≤ 5) samples synthesized at 900°C. All samples were obtained in the single-phase form, and the diffraction patterns were well indexed to that of the monoclinic GdPO₄ structure with a space group of P12₁/n1 (JCPDS No. 01-083-0657). Peak shifts to lower diffraction angles were observed with increases in the Nd³⁺ content (x), as seen in the magnified view, because Gd³⁺ (ionic radius: 0.119 nm for 8 coordination) [38] in the host material was partially substituted with larger Nd³⁺ (ionic radius: 0.125 nm for 8 coordination) [38] to form solid solutions.

Figure 2 depicts the photoluminescence emission spectra of the monoclinic GdPO₄: x mol% Nd³⁺ (0 < x ≤ 5) powders under excitation at 800 nm. Three characteristic peaks due to the f–f transitions of Nd³⁺ were observed in the NIR region at 890 nm, 1061 nm and 1341 nm, which were attributed to ⁴F₃/2→⁴I₉/₂, ⁴F₃/2→⁴I₁₁/₂ and ⁴F₃/2→⁴I₁₃/₂ transitions, respectively. Among the samples synthesized in this study, the highest emission intensity was obtained at x = 3. The GdPO₄ : 3 mol% Nd³⁺ phosphor is therefore used for synthesis of core/shell-type materials hereafter.

An FE-SEM image of the GdPO₄: 3 mol% Nd³⁺ particles is presented in Figure 3. Monoclinic GdPO₄: Nd³⁺ nanoparticles were successfully synthesized without significant grain growth. The morphology of the particles was spherical, and the particle size was about 100 nm. This is probably due to EG molecules adsorbed on the surface of the as-prepared GdPO₄: Nd³⁺ particles, which suppressed excessive particle growth in the calcination process. A more detailed observation
conducted by TEM later, as shown in Figure 4(a), revealed that the particles on the SEM image consisted of aggregates of smaller particles with an average size of 42 nm. In any case, the GdPO$_4$: 3 mol% Nd$^{3+}$ nanoparticles are potential candidate materials for bioimaging applications, since the particle size suitable for bioimaging is in the range of 10 to 200 nm.

### 3.2. Characterization of core/shell-type GdPO$_4$: x mol% Nd$^{3+}$/CaPO nanoparticles

The core/shell-type structure of the GdPO$_4$: 3 mol% Nd$^{3+}$/CaPO particles was confirmed by TEM observation. Figure 4 shows TEM photographs of the GdPO$_4$: 3 mol% Nd$^{3+}$ nanoparticles (a) without surface coating and the core/shell-type GdPO$_4$: 3 mol% Nd$^{3+}$/CaPO nanoparticles synthesized at (b) 700°C, (c) 800°C and (d) 900°C. In comparison with the (a) uncoated GdPO$_4$: 3 mol% Nd$^{3+}$ particles, two distinguishable parts were recognized in the (b) core/shell-type GdPO$_4$: 3 mol% Nd$^{3+}$/CaPO particles synthesized at 700°C, which is to say the formation of a core/shell-type structure was confirmed. The high-contrast core comprising GdPO$_4$: 3 mol% Nd$^{3+}$ composed of heavy elements was uniformly covered with a bright CaPO shell composed of relatively lighter elements. The average particle size of the core/shell-type particles was 54 nm, where the thickness of the CaPO shell was 3 nm. The particles size increased slightly from 42 to 54 nm with formation of the core/shell-type structure due to a second calcination conducted in the surface coating process. As is clear from Figure 4(b–d); moreover, the CaPO shell gradually reacted with the GdPO$_4$: 3 mol% Nd$^{3+}$ core at the core/shell boundary with increases in the calcination temperature from 700°C to 900°C, until the boundary finally disappeared at 900°C.

Figure 5 shows the XPS of the core/shell-type GdPO$_4$: 3 mol% Nd$^{3+}$/CaPO nanoparticles. The Ca 2p spectra can be deconvoluted into two components, ($\alpha$) 351.0–351.3 eV and ($\beta$) 347.6–347.9 eV. These binding energies observed in the present samples were consistent with those of calcium phosphate [39,40]. These results indicate that calcium was present on the surface of the core/shell-type samples, even though the core/shell boundary disappeared when the calcination temperature exceeded 800°C.

The P 2p spectra are also deconvoluted into three components, (a) 135.4–135.6 eV, (b) 134.3–134.5 eV and (c) 132.9–133.1 eV. The binding energy of the $\gamma$ peak was consistent with the value of PO$_4^{3–}$ [39–42],
while the $\alpha$ and $\beta$ peaks were derived from $\text{H}_2\text{PO}_4^{-}$ and $\text{HPO}_4^{2-}$, respectively [42]. The ratios of the $\gamma$ peak to the total $P_{2p}$ peak in the samples calcined at 700°C, 800°C and 900°C were 57.6%, 52.8% and 50.4%, respectively. The ratio decreased when the calcination temperature was raised to 800°C and above, indicating
that the PO$_4^{3-}$ species was reduced and the shell was broken.

The O 1s spectra were deconvoluted into two peaks at ($\alpha$) 532.5–533.1 eV and ($\beta$) 531.0–531.6 eV. The former and latter were attributed to hydroxide and phosphate, respectively [42]. The proportions of the $\beta$ peak calcined at 700°C, 800°C and 900°C were 67.4%, 54.7% and 58.1%, respectively. They decreased at 800°C and above, indicating that the surface modification increased with increases in the calcination temperature. These results also support the collapse of the core/shell type structure at high temperatures.

Figure 6 shows XRD patterns of the core/shell-type GdPO$_4$: 3 mol% Nd$^{3+}$/CaPO nanoparticles synthesized at 700°C, 800°C and 900°C. Except for the increase in crystallinity, no significant change was observed in the XRD patterns, even when the temperature was raised, and only monoclinic GdPO$_4$ was detected in the single-phase form with no degradation or phase transformation. No calcium phosphate or other calcium compound was detected, probably because the amount of Ca was too low to be detected or the Ca compound had an amorphous form. In addition, no obvious shift in the diffraction peak located at around 54° was observed after calcination at 700°C, indicating that the reaction of CaPO with GdPO$_4$: 3 mol% Nd$^{3+}$ was limited to the core/shell interface and Ca$^{2+}$ did not diffuse into the GdPO$_4$: 3 mol% Nd$^{3+}$ core. These results indicated that the optimum heating temperature for synthesizing the core/shell-type nanoparticles was 700°C. At this temperature, the CaPO$_4$ shell was successfully formed as a thin layer over the GdPO$_4$: 3 mol% Nd$^{3+}$ core without overreaction.

Figure 7 compares the photoluminescence emission spectra of the core/shell-type GdPO$_4$: 3 mol% Nd$^{3+}$/CaPO nanophosphors synthesized at 700°C, 800°C and 900°C under excitation at 800 nm with that of GdPO$_4$: 3 mol% Nd$^{3+}$ nanophosphors without the CaPO shell as a reference. As in the case of the GdPO$_4$: 3 mol% Nd$^{3+}$ nanoparticles alone, all the core/shell-type particles showed characteristic emission peaks of Nd$^{3+}$ at 870, 1060 and 1336 nm corresponding to $^4F_{3/2} \rightarrow ^4I_{5/2}$, $^4F_{3/2} \rightarrow ^4I_{7/2}$ and $^4F_{3/2} \rightarrow ^4I_{9/2}$ transitions. Among the samples synthesized in this study, that calcined at 700°C showed the strongest emission intensity, which was 4.2 times that of the GdPO$_4$: 3 mol% Nd$^{3+}$ core without the CaPO shell. Since the CaPO shell passivated the surface of GdPO$_4$: 3 mol% Nd$^{3+}$, the presence of surface defects acting as luminescent killers was reduced. As a result, the emission intensity increased.
The emission intensity of the core/shell-type nanoparticles decreased with increases in the calcination temperature, however, as shown in Figure 8. The luminescent intensity of phosphors generally increases with improvements in their crystallinity, and it usually increases as the synthesis temperature increases. In this study, the opposite result was obtained. This degradation was caused by a reaction of the GdPO₄: 3 mol% Nd³⁺ core with the CaPO shell, as already seen in the TEM photograph in Figure 4. Although the crystallinity of the GdPO₄: 3 mol% Nd³⁺ core was increased by calcination at 800°C and 900°C, the production of impurity phases at the core/shell boundary probably suppressed the emission intensity. Hence, the luminescence characteristics were lowered, instead of raised when the calcination temperature was too high.

We also attempted to synthesize core/shell-type GdPO₄: 3 mol% Nd³⁺/CaPO nanophosphors with different thicknesses by controlling the amount of starting reagents used to form CaPO shells. The thickness of the CaPO shells did not increase too much, however, as observed in Figure S1, although the starting reagent was increased to obtain CaPO shells with thicknesses of (a) 11.25 nm and (b) 15 nm. These results indicate that it is difficult to control the thickness of CaPO shells by a simple method. XRF analysis revealed that the surface calcium ratio increased with increases in the Ca-containing starting material. The atomic percentages of Ca were 0.008, 0.012, 0.12 and 0.17 at% for the samples that obtained shell thicknesses of 3.75 nm, 7.5 nm, 11.25 nm and 15 nm, respectively. No significant change was observed in their XRD patterns, however, as shown in Figure S2, even when the amount of Ca-containing starting material was increased. Furthermore, there were no Ca-containing crystalline phases. As can be seen from the magnification in Fig. S2(b), there was no peak shift with increases in the Ca³⁺ content, indicating that Ca²⁺ did not diffuse into the lattice of the GdPO₄: 3 mol% Nd³⁺ core.

These results suggest the presence of an extra Ca-containing compound not used in the coating as an amorphous phase in the sample, or an insufficient Ca content to be detected by XRD analysis. Figure S3 depicts the dependence of the relative emission intensity on the amount of Ca-containing starting material. The sample synthesized to obtain the CaPO shell with a thickness of 3.75 nm exhibited the strongest emission intensity. The relative emission intensity decreased with increases in the Ca content, however, and did not change even if the amount of Ca was further increased. This result is consistent with the fact that the thickness of the CaPO shell did not increase monotonously. In the present study, therefore, an appropriate CaPO shell was obtained by adjusting the amount of Ca-containing starting material to obtain a shell with a thickness of 3.75 nm.

Finally, the emission intensity of the core/shell-type GdPO₄: 3 mol% Nd³⁺/CaPO nanophosphors was compared with that of indocyanine green (ICG), a green organic dye clinically applied as a bioimaging reagent. Figure 9 depicts the photoluminescence emission spectra of core/shell-type GdPO₄: 3 mol% Nd³⁺/CaPO nanophosphors synthesized at 700°C and indocyanine green. It is evident that the emission intensity of our sample was significantly higher than that of ICG: the emission intensity was 114 times that of ICG at 1060 nm.

4. Conclusions

Core/shell-type GdPO₄: x mol% Nd³⁺/CaPO (0 ≤ x ≤ 5) nanophosphors were successfully synthesized using a modified sol gel-based Pechini method. The monoclinic GdPO₄: x mol% Nd³⁺ nanoparticles were covered homogenously with a 3 nm thin CaPO layer, although no calcium phosphate or other calcium compound was detected by XRD. The mean particle size of the core/shell-type nanoparticles was 54 nm, which is suitable for bioimaging materials because it is in the range of 10 to 200 nm. The core/shell-type nanoparticles could emit NIR light at 870, 1060 and 1336 nm due to the f–f transitions of Nd³⁺ under excitation at 800 nm. Both the excitation and emission light were in the range of 700 to 1400 nm, which is known as the “optical transmission window” of tissue, and the maximum intensity was obtained for the sample containing 3 mol% of Nd³⁺. Furthermore, the emission intensity of the core/shell-type GdPO₄: 3 mol% Nd³⁺/CaPO nanophosphors was significantly larger than that of ICG. Based on these results, core/shell-type GdPO₄: 3 mol% Nd³⁺/CaPO nanophosphors are promising candidates for use as a bioimaging material.
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Disclosure statement

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