



Preliminary study on singlet oxygen production using $\text{CeF}_3:\text{Tb}^{3+}@\text{SiO}_2\text{-PpIX}$



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HIGHLIGHTS

- $\text{CeF}_3:\text{Tb}^{3+}$ nanoparticles were prepared via sol–gel route.
- Surface modification by SiO_2 layer and bioconjugation with PpIX were performed.
- Radioluminescence spectra indicate an energy transfer from Tb^{3+} to PpIX.
- X-ray-induced singlet oxygen production was observed.

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ABSTRACT

Luminescent properties and singlet oxygen production using $\text{CeF}_3:\text{Tb}^{3+}$ -based nanoparticles modified with SiO_2 and protoporphyrin IX (PpIX) were studied. $\text{CeF}_3:\text{Tb}^{3+}$ nanopowder was prepared via sol–gel route, with subsequent surface coating by SiO_2 layer and the conjugation with photosensitive PpIX molecules. Radioluminescence spectra suggest an energy transfer from Ce^{3+} to Tb^{3+} ions and from Tb^{3+} to molecules of PpIX photosensitizer. The energy transfer was confirmed by photoluminescence decay curves. Singlet oxygen production was detected using a reaction of $^1\text{O}_2$ with 3'-(p-aminophenyl) fluorescein (APF) chemical probe after X-Ray excitation. Qualitative changes in time resolved photoluminescence spectra in the region of 520 nm indicate $^1\text{O}_2$ generation. Studied nanocomposites may be good candidates for the application in X-ray induced photodynamic therapy.

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1. Introduction

CeF_3 single crystal was intensively studied in first half of 1990's due to intended application in high energy physics (Auffray et al., 1996). In powder form it is a known phosphor and widely studied compound in various fields (Liu et al., 2011). Its luminescent properties are given by $5d - 4f$ transitions enabled by $4f^{15}d^0$ electron configuration of the valence shell of Ce^{3+} ions. CeF_3 features low toxicity and high chemical stability (Kong et al., 2007); its luminescence can be characterized by high quantum yield, low phonon energy (Guo, 2006), relatively large Stokes shift (Li and Lin, 2010). Changes in the luminescence spectrum of CeF_3 can be achieved by doping with appropriately chosen Ln^{3+} ion. Tb^{3+} as a

dopant in CeF_3 host matrix causes the emission in the green spectral part as a result of an effective energy transfer (ET) from Ce^{3+} to Tb^{3+} ions (Kong et al., 2008). Surface modification and/or biofunctionalization of CeF_3 has been studied, recently (Kong et al., 2007; Li and Lin, 2010). Based on the above-mentioned characteristics, $\text{CeF}_3:\text{Tb}^{3+}$ can also be used as a material of choice for biomedical applications, e.g. for modern methods of cancer treatment, such as X-ray induced photodynamic therapy (PDTX).

PDTX drugs consist of surface-modified scintillating nanoparticles (NPs) biofunctionalized with photosensitizer (PS), which accumulate preferentially in the tumor and after the X-ray irradiation cause an effective destruction of cancer cells (Chen and Zhang, 2006). The X-ray irradiation causes the excitation of scintillating nanoparticles and emitted secondary radiation activates the photosensitizer (e.g. porphyrin), which produces reactive oxygen species (ROS). Emission lines of Tb^{3+} overlap with the

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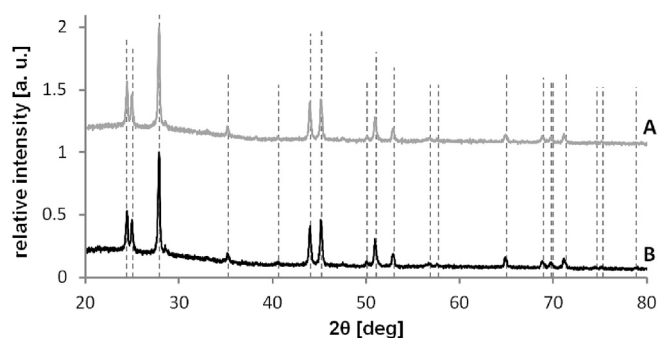


Fig. 1. Diffractograms of $\text{CeF}_3:\text{Tb}^{3+}@\text{SiO}_2\text{-PpIX}$ (A) and $\text{CeF}_3:\text{Tb}^{3+}@\text{SiO}_2$ (B) in comparison with standard data of CeF_3 from ICDD PDF-2 database (Card No. 00-008-0045, dashed lines).

absorption bands of protoporphyrin IX (PpIX); therefore, the efficient energy transfer from donor to acceptor and production of singlet oxygen are expected (Bulin et al., 2013). The processes leading to the $^1\text{O}_2$ production are well understood (Chen, 2008). Preparation of the material for PDTX applications includes three main steps: synthesis of nanoparticles with appropriate luminescent and morphological characteristics, surface modification of nanoparticles and biofunctionalization with photosensitizer. Materials in wide range of size up to tens of nm are usable for PDTX (Morgan et al., 2009).

This work presents a proof-of-concept research focused on the preparation and study of the luminescent properties of the composite nanomaterial which is based on the $\text{CeF}_3:\text{Tb}^{3+}$ nanoparticles prepared via sol–gel route and modified with SiO_2 and PpIX, having their prospective application in PDTX in mind.

2. Experimental

2.1. Materials

$\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ (99.99%, Sigma–Aldrich), NH_4F (p. a., Lachema n. p. Brno) and $\text{Tb}(\text{NO}_3)_3$ were used as precursors and 2-methoxyethanol (EGME) ($\geq 99.0\%$, Sigma–Aldrich) as a solvent for synthesis of $\text{CeF}_3:\text{Tb}^{3+}$ nanoparticles. $\text{Tb}(\text{NO}_3)_3$ was prepared by dissolution of TbO_{2-x} ($\geq 99.9\%$) in an excess of concentrated nitric acid (p. a., PENTA) and subsequent evaporation of the reaction mixture and crystallization at room temperature.

Tetraethyl orthosilicate (TEOS) ($\geq 99.0\%$, Sigma–Aldrich) and (3-aminopropyl)triethoxysilane (APTES) ($\geq 98.0\%$, Sigma–Aldrich) were used for SiO_2 coating. The reaction was performed in diethylene glycol (DEG) (99%, Sigma–Aldrich) and catalyzed with

addition of triethylamine (TEA) ($\geq 99\%$, Sigma–Aldrich). Protoporphyrin IX ($\geq 95.0\%$, Sigma–Aldrich) and oxalyl chloride ($\geq 99.0\%$, Sigma–Aldrich) were used as starting materials for biofunctionalization. Anhydrous tetrahydrofuran (THF) ($\geq 99.9\%$, Sigma–Aldrich, distilled prior to use with sodium–potassium alloy under inert atmosphere) and anhydrous N,N-dimethylformamide (DMF) (99.8%, Sigma–Aldrich) were used as a solvent for biofunctionalization.

2.2. Sample preparation

$\text{CeF}_3:\text{Tb}^{3+}$ (1%) nanoparticles were synthesized via sol–gel route using a modified procedure that was described by (Kong et al., 2007). In a round-bottomed flask 18.00 mmol of NH_4F , 5.10 mmol of $\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ and 0.05 mmol of $\text{Tb}(\text{NO}_3)_3$ were dissolved in 100 mL of EGME. The mixture was stirred and heated to 200°C for 1 hour in N_2 atmosphere. After cooling to the room temperature, the reaction mixture was diluted with 100 mL of ethanol (p. a., Sigma–Aldrich). Nanoparticles were obtained after 5 min centrifugation at 4200 rot/min (14.6 cm rotor radius, 2880 g RCF). To remove absorbed molecules of the solvent, the product was washed with ethanol and re-centrifuged. $\text{CeF}_3:\text{Tb}^{3+}$ nanoparticles were dried in air at 40°C .

Technique of nanoparticles surface functionalization by SiO_2 layer was based on Bulin's et al. work (Bulin et al., 2013). Before the process the $\text{CeF}_3:\text{Tb}^{3+}$ powder was treated at 300°C in argon atmosphere to achieve higher intensity of radioluminescence of the sample. 420 mg of $\text{CeF}_3:\text{Tb}^{3+}$ were dispersed in 200 mL of DEG. 210 μL of APTES and 134 μL of TEOS were added simultaneously to the suspension under stirring and heating to 40°C . After 1 hour, 510 μL of DEG solution, containing 0.1 M TEA and 10 M distilled water, was added to the reaction mixture. The whole procedure was repeated three more times every 24 hours. Suspension was stirred for 48 hours at 40°C . As a result, a yellow colored suspension containing $\text{CeF}_3:\text{Tb}^{3+}@\text{SiO}_2$ was obtained.

In the first step of biofunctionalization, protoporphyrin IX dichloride (PpIX·2Cl) was prepared using Schotten–Baumann reaction: 30 mg of PpIX was dissolved in 1 mL of anhydrous THF and 1 mL of DMF, then 10 μL of oxalyl chloride was added. The reaction mixture was heated to 100°C on the oil bath for 2 hours. The prepared PpIX·2Cl solution was added to 120 mL of $\text{CeF}_3:\text{Tb}^{3+}@\text{SiO}_2$ suspension. The resulting reaction proceeded for 3 hours under the conditions described above. Finally, suspension with $\text{CeF}_3:\text{Tb}^{3+}@\text{SiO}_2\text{-PpIX}$ composite nanomaterial was prepared.

2.3. $^1\text{O}_2$ generation

APF commercial probe was used for the singlet oxygen

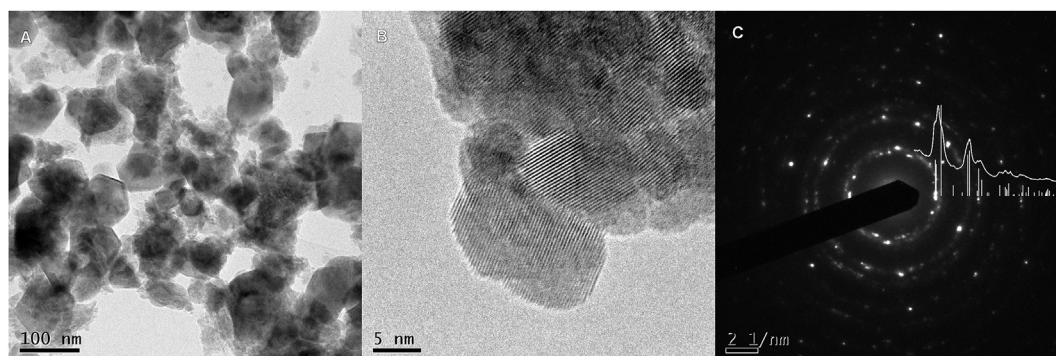


Fig. 2. TEM (A, B) and SAED (C) images of $\text{CeF}_3:\text{Tb}^{3+}@\text{SiO}_2$. SAED image was compared with standard data of CeF_3 ICDD PDF-2 database (Card No. 00-008-0045).

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