



Unexpected high photothermal conversion efficiency of gold nanospheres upon grafting with two-photon luminescent ruthenium(II) complexes: A way towards cancer therapy?



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ABSTRACT

The design and development of functional hybrid nanomaterials is currently a topic of great interest in biomedicine. Herein we investigated the grafting of Ru(II) polypyridyl complexes onto gold nanospheres (Ru@AuNPs) to improve the particles' near infrared (NIR) absorption, and ultimately allow for application in photothermal cancer therapy. As demonstrated in this article, these ruthenium(II) complexes could indeed significantly enhance gold nanospheres' two-photon luminescence (PTL) intensity and photothermal therapy (PTT) efficiency. The best dual functional nanoparticles of this study were successfully used for real-time luminescent imaging-guided PTT in live cancer cells. Furthermore, *in vivo* tumor ablation was achieved with excellent treatment efficacy under a diode laser (808 nm) irradiation at the power density of 0.8 W/cm² for 5 min. This study demonstrates that the coupling of inert Ru(II) polypyridyl complexes to gold nanospheres allows for the enhancement of two-photon luminescence and for efficient photothermal effect.

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1. Introduction

Photothermal therapy (PTT) uses photon absorbers to convert optical energy into thermal energy to kill cancer cells. PTT has recently received extensive attention among researchers [1–11]. Gold nanoparticles are the most widely explored class of nanoagents due to their low toxicity and good biocompatibility. These properties make gold nanoparticles a promising platform for various biomedical applications, particularly for cancer diagnosis and treatment [12–14]. Over the past several years, gold nanorods [15] and nanoshells [16]-based near infrared (NIR) hyperthermia agents have been employed to photothermally kill cancer cells. However, gold nanorods have a low photostability since their NIR

absorbance peak diminishes after a significant period of laser irradiation due to the “melting effect” [17]. Also, gold nanoshells are too large (diameter > 100 nm) for tissue accumulation and elimination [18].

Gold nanospheres (AuNPs) have significant advantages over other nanoparticles due to their small size, rapid synthesis and easy bioconjugation to various ligands such as DNA, peptides, antibodies and small guest molecules. These properties make them especially attractive as biological sensors [19,20]. However, the poor NIR absorbance of naked gold nanospheres limits their application in photothermal therapy [21,22]. It was recently demonstrated that aggregated gold nanospheres [23] and hollow gold nanospheres [24] can serve as agents for photothermal cancer therapy. However, the “melting effect” still occurs upon irradiation with a strong laser and the generated photothermal heat often melting hollow or anisotropic Au nanostructures into solid spheres, which indicates poor photothermal stability and thus easy loss of NIR surface plasmon resonance (SPR) properties. Herein, we propose a new

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strategy involving the adsorption of molecules with strong two-photon absorption onto the surface of AuNPs as antenna species to improve the particles' NIR absorption, and ultimately allow for photothermal cancer therapy.

Ru(II) polypyridyl complexes, owing to their more diverse stereochemistry than organic compounds, water-solubility, large Stokes shifts, good photostability and strong two-photon luminescence (TPL), have emerged as novel and promising candidates for biological probing and environmental monitoring [25–28]. To date, a few luminescent Ru(II) complex-functionalized AuNPs have been developed [29–33], and two examples of Ru(II)-functionalized AuNPs have been used for one-photon luminescent cellular imaging in living cells [31,33]. However, to the best of our knowledge, there is no report of the impact of Ru complexes on the efficiency of photothermal therapy or two-photon property of gold nanomaterials. More specifically, in this paper, we study: (1) how do the TPL and PTT of gold nanoparticles change after grafting terminal phenanthroline groups of Ru(II) complexes of various length (Fig. 1); (2) how does the size of these hybrid nanoparticles influence their PTT efficiency and TPL. The results showed that Ru(II) complexes can improve the AuNPs' photothermal therapy efficiency and the two-photon luminescence in a significant manner.

2. Materials and methods

2.1. Materials and instruments

Ruthenium chloride hydrate (Alfa Aesar, USA), bpy (2,2'-bipyridine, Sigma Aldrich, USA), MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Sigma Aldrich, USA), DMSO (dimethyl sulfoxide, Sigma Aldrich, USA), Rhodamine B (Sigma–Aldrich, USA) and DPBF (1,3-diphenyliso-benzofuran, Sigma Aldrich, USA) were used as received. Water with a resistivity of 18.2 MΩ cm, which was used throughout the experiments, was purified with a Milli-Q system from the Millipore Company (USA). The complex [Ru(bpy)₂(pdppz)]Cl₂ (**Ru2**, bpy = 2,2'-bipyridine, pdppz = phenanthro[4,5-abc]dipyrido[3,2-h:2', 3'-j]phenazine) was synthesised as previously described by our group [34].

Microanalysis (C, H, and N) were carried out on a Vario EL cube

elemental analyzer. ¹H NMR spectra were recorded on a Varian INOVA500NB NMR spectrometer with (CD₃)₂SO as solvent at room temperature. All chemical shifts are given relative to tetramethylsilane (TMS). Electrospray ionization mass spectra (ESI-MS) were recorded on an LCQ system (Finnigan MAT, USA). The morphology and the microstructure of the Ru@AuNPs were characterized by transmission electron microscopy (TEM, JEM2010-HR, 200 KV), energy dispersive X-ray spectrometer (EDX, S-520/INCA 300, Japan) and field-emission scanning electron microscope (FE-SEM, JSM-6330F). The X-ray photoelectron spectroscopy (XPS, ESCALab250, Thermo VG) with 200 W Al KR radiation in twin anode. All core level XPS spectra were calibrated using C_{1s} photoelectron peak at 284.6 eV as the reference. Dynamic light scattering and zeta potential experiments were determined by dynamic laser light scattering equipment (DLS, Brooken Haven BI-200SM). The average hydrodynamic diameter and the zeta potential of the Ru@AuNPs were measured 6 times for each solution, with the average of all the runs reported. UV–Vis–NIR spectra were recorded on a UV-3150 spectrophotometer (Shimadzu). Emission spectra were recorded on a PerkinElmer LS55 spectrofluorophotometer at room temperature. A diode laser (808 nm) from Hi-Tech Optoelectronics Co., Ltd. (Beijing, China) and Xenon Light Source (450 nm, MAX-302, ASAHI Spectra, USA) were used in this study.

2.2. Synthesis and characterization

2.2.1. Synthesis of 2-diethoxymethyl-1H-imidazo[1,10]-phenanthroline (PIPOEt)

To a solution of sodium ethoxide (0.6 g, 26.1 mmol of Na in 20 mL dry ethanol) were added 1,10-phenanthroline-5,6-diamine (2.7 g, 12.7 mmol) and ethyl diethoxyacetate (2.7 g, 15.1 mmol). The mixture was refluxed for 24 h, cooled to room temperature, and the solvent was removed under vacuum. The residue was dissolved in water, neutralized with acetic acid, and extracted with ethyl acetate. The combined organics were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was subjected to flash column chromatography (CHCl₃/EtOAc = 2:1). Yield: 78%. ¹H NMR (500 MHz, CDCl₃-d₆): δ 9.45 (d, J = 8.0 Hz, 2H), 9.18 (d, J = 8.5 Hz, 1H), 7.60 (dd, J = 8.5 Hz, 1H), 5.48 (s, 1H), 3.49–3.70 (m, 4H), 1.26 (t, 6H, J = 8.0 Hz). ESI-MS (CH₃OH) m/z: 323 [M+H]⁺.

2.2.2. Synthesis of 1H-imidazo[1,10]-phenanthroline-2-carbaldehyde (PIPCHO)

Water (6 mL) and 37% hydrochloride acid (3 mL) were added to a THF (20 mL) solution of 2-diethoxymethyl-1H-imidazo[1,10]-phenanthroline (1.3 g, 4.0 mmol). After refluxing for 24 h, the reaction mixture was neutralized with saturated sodium bicarbonate and extracted with EtOAc (3 × 70 mL). The extract was washed with brine (2 × 50 mL), filtered, and evaporated to dryness. The residue was chromatographed on silica gel (Hexane/EtOAc 1:3). Yield: 78%. ¹H NMR (500 MHz, CDCl₃-d₆): δ 10.35 (s, 1H), 9.60 (d, J = 8.0 Hz, 2H), 9.34 (d, J = 7.5 Hz, 1H), 7.83 (dd, J = 8.0 Hz, 1H). ESI-MS (CH₃OH) m/z: 248 [M+H]⁺.

2.2.3. Synthesis of [Ru(bpy)₂(PIPCHO)](ClO₄)₂

cis-[Ru(bpy)₂Cl₂]·2H₂O (0.2 g, 0.4 mmol) and 1H-imidazo[1,10]-phenanthroline -2-carbaldehyde (0.1 g, 0.4 mmol) in ethanediol (10 mL) were heated to 125 °C for 8 h under N₂. The cooled reaction mixture was diluted with water (30 mL). Saturated aqueous sodium perchlorate solution was added under vigorous stirring and filtered. The dark red solid was collected and washed with small amounts of water, and diethyl ether, then dried under a vacuum and purified by column chromatography on alumina with acetonitrile-toluene (5:1 v/v) as the eluant. The solvent was removed under reduced pressure, and red microcrystals were obtained. Yield: 80%. Anal. Calcd

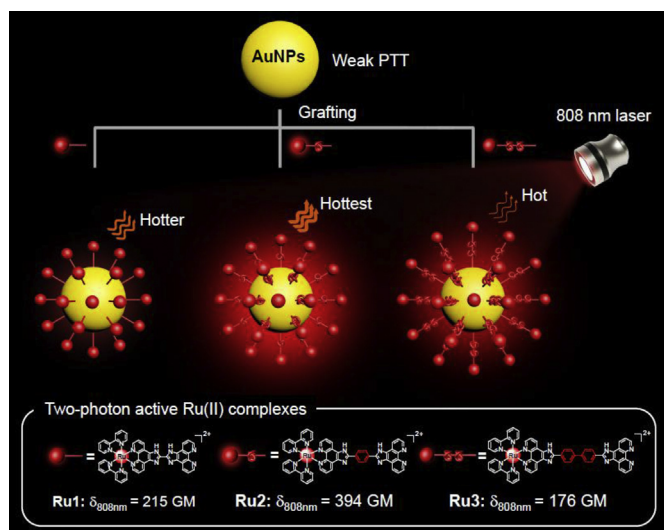


Fig. 1. Schematic illustration of the three different Ru(II) complexes (**Ru1**, **Ru2**, **Ru3**) grafted onto gold nanoparticles (Ru1@AuNPs, Ru2@AuNPs, Ru3@AuNPs) of the change of two-photon luminescence and of the photothermal efficiency of the Ru@AuNPs. GM is the unit of two-photon absorption cross-section δ ($1 \text{ GM} = 1 \times 10^{-50} \text{ cm}^4 \text{ s}^{-1} \cdot \text{photon}^{-1}$).

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