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Short note

Near-infrared off-on fluorescent probe for fast and selective detection of palladium (II) in living cells

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Dedicated to professor Chen-Ho Tung on the occasion of his 80th Birthday for his research accomplishments and contributions to photochemistry.

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ABSTRACT

The frequent use of palladium in industry may lead to palladium contamination in the final pharmaceutical products, which raises health risks due to their potential toxicity. In this work, a novel near-infrared fluorescent probe **NIR-Pd** for the detection of palladium (II) has been developed. The probe exhibits excellent sensing properties such as rapid detection of palladium within a few minutes, selectively and sensitively detects palladium in solution. The limit of detection was calculated to be 134.6 nM. Moreover, the probe was successfully used for near-infrared fluorescence imaging of palladium in living cells.

1. Introduction

Palladium is widely used as efficient catalysts in the fields of material science, drug discoveries, organic catalytic reactions, and fuel cells, etc [1–3]. However, the frequent use of palladium in the catalyst industry may lead to its significant accumulation in the water, food and even in the final medicinal products, which raises hard-to-ignore health and environmental risks due to its potential toxicity. Palladium ions can bind to thiol-containing amino acids, proteins (silk fibroin, casein and many enzymes), DNA or other macromolecules (e.g. vitamin B_6) and thereby may disturb a variety of cellular processes [4,5]. Thus, the threshold for palladium in the end products is strictly limited from European Agency for the Evaluation of Medicinal Products (EMEA) to be 5–10 ppm, and the proposed maximum dietary intake of palladium is less than 1.5–15 μg per day per person [6]. Consequently, it is necessary to develop convenient and effective assay methods to detect low levels of the palladium species in various samples.

Typical analytical methods used for quantification of palladium species include inductively coupled plasma mass spectrometry (ICP-MS), atomic absorption spectrometry (AAS), solid phase micro extraction-high performance liquid chromatography (SPME-HPLC), etc [7,8]. However, these methods often require complicated sample preparation steps, rigorous experimental conditions, sophisticated instrumentation, and well-trained individuals. Thus, recent research activities on palladium detection have been focused onto fluorescent and colorimetric methods because of their operational simplicity, low cost, and real time monitoring [9–11]. Fluorescent probes and sensors for highly selective and sensitive detection of palladium are especially attractive [12–35]. In a landmark paper, Koide and coworkers developed an innovative fluorescent sensing system for palladium species based on Pd(0)-catalyzed Tsuji-Trost allylic oxidative insertion reaction [12]. The developed probe was proved to be useful for measuring low concentrations of palladium. Since then, a majority of fluorescent probes have been developed for the detection of palladium based on Pd-triggered cleavage reaction as a result of its excellent selectivity and the mild sensing conditions. However, many reported sensing systems have been limited due to long response time (need several hours to achieve saturation point) [13,29,33], rigorous test conditions (additional additives, such as PPh_3, tri-2-furylphosphine (TFP) or TFP-$NaBH_4$, etc.) [30,35], which greatly

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restricted their practical applications. Moreover, most of them have emission in the visible region [16,20,24], and examples of near-infrared (NIR) fluorescent palladium probes are still sparse.

NIR fluorescence probes have become a promising tool in bioimaging, because the light in this wavelength region (650–900 nm) shows minimum biological damage, deep tissue penetration, and low auto-fluorescence in living systems [36–38]. In this article, a new NIR probe **NIR-Pd** was designed by employing a modified hemicyanine dye (**HD-NH$_2$**) as the fluorophore [39–41], and terminal allyl ether moiety which has been demonstrated to be favorable for selective palladium recognization as the recognition group [12,17,20,42]. We expected the intramolecular charge transfer (ICT) process of hemicyanine dye may be blocked with an allyl carbamate group resulted in much diminished fluorescence due to the electron-withdrawing effect of the allyl carbamate (Scheme 1). Upon reacting with palladium, the efficient deallylation and decarboxylation will restore the fluorophore and elicit fluorescence. As reported in this paper, such a probe shows excellent selectivity and high sensitivity for palladium (II) over other metal ions under physiological condition, and was successfully applied for palladium imaging in living cells.

2. Experimental

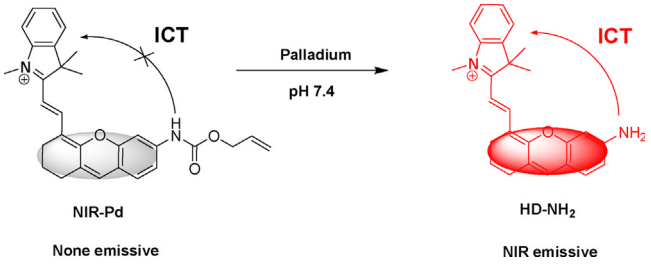
2.1. Materials and instruments

All reagents were purchased from commercial suppliers and used without further purification. Solvents used were purified by standard methods prior to use. ^{1}H NMR spectra were recorded on a Varian Model Mercury 400 MHz spectrometer. ^{13}C NMR spectra were recorded on a Varian Model Mercury 150 MHz spectrometer. Spectrometer UV–vis spectra were acquired on a Hitachi U-2900 double beam UV–vis spectrophotometer. Fluorescence spectra were measured by Hitachi F-2500 fluorescence spectrophotometer. Electrospray ionization (ESI) mass spectra were acquired with Agilent 1100 Series LC/MSD and AB SCIEX Triple TOFTM 5600+ mass spectrometer. All spectra were recorded at room temperature, except for the confocal laser scanning microscopic images. The stock solutions (10 mM) of the metal ions were prepared in H_2O. The salts used in the stock aqueous solutions of metal ions were $AgNO_3$, $CoSO_4{\cdot}7H_2O$, $CuCl_2{\cdot}2H_2O$, $FeCl_3{\cdot}6H_2O$, $HgCl_2$, $MgSO_4$, $NiCl_2{\cdot}6H_2O$, $ZnCl_2$, $CaCl_2$, $MnSO_4{\cdot}H_2O$, $PbCl_2$, $LiBr{\cdot}H_2O$, NaBr, KBr, $BaCl_2{\cdot}2H_2O$, and $AlCl_3{\cdot}6H_2O$. The working solution of **NIR-Pd** (1 mM) was prepared in ethanol. The detection solutions of **NIR-Pd** were freshly prepared for spectroscopic measurements.

2.2. Synthesis

2.2.1. Synthesis of compound *3*

The precursor chlorocyanine dye (compound **1**) and N-boc-2-hydroxyaniline (compound **2**) were prepared following the procedures reported in the literature [39,43].



Scheme 1. Structure of **NIR-Pd** and the proposed sensing mechanism.

To a solution of compound **1** (400.0 mg, 0.65 mmol), compound **2** (272.0 mg, 1.30 mmol) and K_2CO_3 (180.0 mg, 1.30 mmol) dissolved in anhydrous CH_3CN (20 mL) under an inert atmosphere, and the mixture was stirred for 4 h at 50 °C. The reaction mixture was concentrated under reduced pressure to give crude solid, then purified by silica gel column chromatography (CH_2Cl_2/CH_3OH = 40:1) to give compound **3** as dark green solid (250.0 mg, yield 46.1%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.91 (dd, J = 14.2, 2.0 Hz, 2H), 7.38–7.32 (m, 2H), 7.23 (q, J = 6.3, 5.1 Hz, 6H), 7.18 (d, J = 7.4 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 6.76–6.70 (m, 1H), 6.08 (d, J = 14.2 Hz, 2H), 3.65 (s, 6H), 2.79 (t, J = 6.2 Hz, 4H), 2.10–2.01 (m, 2H), 1.51 (s, 9H), 1.38 (s, 12H). ^{13}C NMR (150 MHz, Chloroform-*d*): δ 172.35, 164.36, 160.23, 152.71, 142.80, 142.09, 140.99, 130.48, 128.59, 124.90, 123.25, 122.00, 112.33, 110.32, 108.84, 104.98, 100.68, 80.56, 48.90, 32.14, 28.36, 27.86, 24.72, 21.11. ESI–MS (m/z): $[M]^+$ Calcd. for $[C_{43}H_{50}N_3O_3]^+$: 656.38; found 656.40.

2.2.2. Synthesis of compound *4*

Compound **3** (250.0 mg, 0.32 mmol) was placed in a flask containing anhydrous CH_2Cl_2 (10 mL), and the solution was stirred at 0 °C under nitrogen atmosphere for 30 min. CF_3COOH (3 mL) was slowly introduced to the mixture via a syringe, and the reaction mixture was warmed to room temperature and stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure to give crude solid, then purified by silica gel column chromatography (CH_2Cl_2/CH_3OH = 40:1) to give compound **4** as dark green solid (128.0 mg, yield 60.6%).^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.94 (d, J = 14.1 Hz, 2H), 7.38–7.32 (m, 2H), 7.26 (d, J = 6.6 Hz, 2H), 7.17 (t, J = 7.4 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 7.06 (t, J = 8.2 Hz, 1H), 6.46–6.39 (m, 2H), 6.34 (dt, J = 7.8, 1.3 Hz, 1H), 6.06 (d, J = 14.2 Hz, 2H), 3.64 (s, 6H), 2.72 (t, J = 6.2 Hz, 4H), 2.09–1.98 (m, 2H), 1.40 (s, 12H). ^{13}C NMR (150 MHz, Chloroform-*d*): δ 172.39, 164.61, 160.98, 149.05, 142.80, 142.25, 140.95, 130.61, 128.59, 124.89, 122.99, 122.03, 110.36, 109.43, 104.22, 101.26, 100.24, 48.91, 31.70, 27.80, 24.43, 21.14. ESI–MS (m/z): $[M]^+$ Calcd. for $[C_{38}H_{42}N_3O]^+$: 556.33; found 556.50.

2.2.3. Synthesis of ***HD-NH$_2$***

Compound **4** (100 mg, 0.18 mmol) and triethylamine (0.1 mL, 0.71 mmol) were placed in a flask containing DMF (10 mL), and the mixture was heated at 110 °C for 3 h. The solvent was then removed under reduced pressure. The crude product was purified by silica gel flash chromatography using CH_2Cl_2/CH_3OH (20:1) as eluent to give compound **HD-NH$_2$** as blue-green solid (42.0 mg, yield 58.1%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.49 (d, J = 14.0 Hz, 1H), 7.44–7.33 (m, 3H), 7.25–7.20 (m, 2H), 7.13–7.03 (m, 2H), 6.91 (d, J = 8.6 Hz, 1H), 6.60 (s, 2H), 5.89 (d, J = 14.1 Hz, 1H), 3.62 (s, 3H), 2.74 (t, J = 6.1 Hz, 2H), 2.64 (t, J = 6.2 Hz, 2H), 1.92 (t, J = 6.1 Hz, 2H), 1.76 (s, 6H). ^{13}C NMR (150 MHz, Chloroform-*d*): δ 173.10, 163.91, 156.62, 155.88, 142.75, 141.42, 140.59, 140.03, 129.47, 128.59, 125.10, 122.51, 122.00, 116.58, 114.90, 114.17, 109.96, 98.91, 98.14, 49.29, 28.60, 27.22, 24.34, 20.72. ESI–MS (m/z): $[M]^+$ Calcd. for $[C_{26}H_{27}N_2O]^+$: 383.21; found 383.30.

2.2.4. Synthesis of ***NIR-Pd***

Compound **HD-NH$_2$** (51.0 mg, 0.10 mmol) was placed in a flask containing anhydrous CH_2Cl_2 (10 mL), and the solution was stirred at 0 °C under nitrogen atmosphere. Triethylamine (0.1 mL, 0.71 mmol) was introduced to the mixture via a syringe. Then, allyl chlorocarbonate (0.1 mL) was slowly introduced to the mixture via a syringe and the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated under reduced pressure to give crude solid, then purified by silica gel column chromatography (CH_2Cl_2/CH_3OH =

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