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A simple but effective colorimetric and far-red to near-infrared fluorescent probe for palladium and its application in living cells

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ABSTRACT

In this work, a new colorimetric and far-red to near-infrared fluorescent turn-on probe for rapid detection of palladium was reported. This probe uses a readily available seminaphthorhodafluor dye as the fluorophore and an allylcarbonate moiety as the reaction site. Based on the Pd^0-triggered cleavage reaction, this probe shows rapid (within 2 min), selective, and sensitive response for palladium with different oxidation states (Pd^0, or Pd^{2+} and Pd^{4+} in the presence of PPh_3) in almost wholly aqueous solution under mild conditions, accompanied by distinct color changes and significant fluorescent turn-on signal in the far-red to near-infrared region. The detection limit of this probe for Pd^0 was determined to be as low as 1.6 nM in solution. In addition, a sensitive bioimaging of palladiun in living cells can be achieved with a low level of this probe (2 μM), indicating the new developed probe has great potential for palladium detection in both solution and living systems.

1. Introduction

Palladium (Pd) is a rare but very useful metal that can be used in numerous areas including catalytic converters, electronics, medical instruments, dentistry, hydrogen purification, fuel cells, groundwater treatment and jewelry *etc.* [1–3]. In modern organic chemistry, a large number of carbon-carbon bond formation reactions are facilitated by palladium catalysts, which have been widely used for production of various functional compounds and drug molecules [4–6]. However, the wide use of palladium has resulted in a high level of residual palladium in water systems and soil, which is harmful to public health [7–9]. Strong evidence showed that palladium can bind to biomolecules like proteins, DNA, thiol-containing amino acids and disturb cellular processes [10]. Due to the potential hazardous effects, the threshold limit of palladium in drugs was set as 5–10 ppm and the proposed dietary intake should be less than 1.5–15 mg per person per day by European Agency for the Evaluation of Medicinal Products (EMEA) [11]. Consequently, much effort have been given to the development of methods for the detection of palladium, such as those using atomic absorption spectrometry (AAS), inductively coupled plasma atomic emission spectrometry (ICP-AES), inductively coupled plasma mass spectrometry (ICP-MS), solid phase microextraction high-performance liquid chromatography (SPMME-HPLC), and capillary zone electrophoresis (CZE) *etc*. [12–15]. However, these methods need sophisticated sample pretreatment procedures and complicated apparatus. In addition, they are time consuming and not suitable for real-time detection in living systems. Therefore, development of new biocompatible methods for convenient and rapid detection of palladium is still very important.

Optical methods, particularly dual colorimetric and fluorescent detection methods, on the other hand, provide simple but effective detection with many advantages such as easy operation, high sensitivity, real-time visual detection and good biocompatibility, and therefore are becoming more attractive for palladium detection [16–18]. Over the past few years, a number of colorimetric and/or fluorescent probes for palladium have been developed [19–47]. However, many of them need to use high content of organic solvent (up to 90%, v/v) and/or require a long detection time (> 20 min, see Table S1 in the Supplementary Data), which greatly limited their real applications. In addition, most of these probes showed fluorescence changes in the short wavelength window (< 600 nm), which limited their biological applications due to the interference of background autofluorescence of biomolecules [48–53]. Since fluorescent probes in the far-red to near-infrared (600–900 nm) region are well-known to have low autofluorescence background, low phototoxicity, and good tissue penetration ability [54–57], there is a strong interest in the development of colorimetric and fluorescent probes with fluorescence readout in the far-red to near-infrared region, good water solubility and a fast response for palladium.

Herein, we report a new colorimetric and fluorescent palladium probe (probe **SNARF-Pd** in Scheme 1) that meets these standards. This

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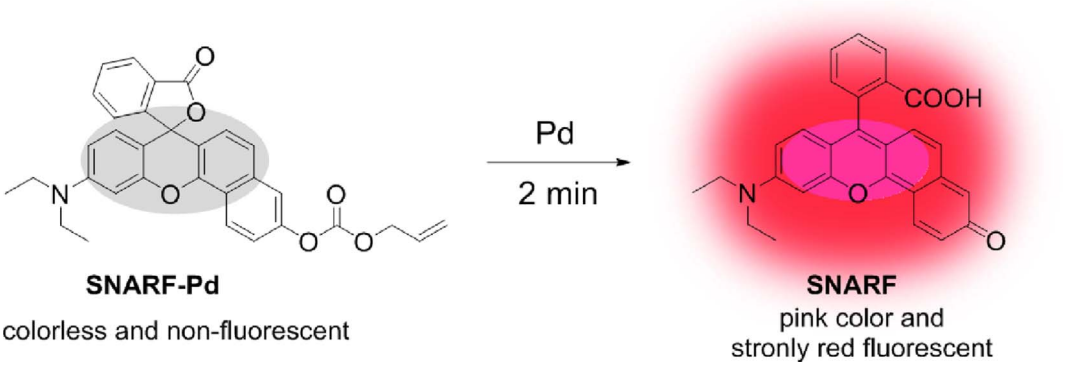


Scheme 1. A new colorimetric and fluorescent probe for detection of palladium.

probe uses a readily available seminaphthorhodafluor (**SNARF**) dye as the fluorophore and an allylcarbonate moiety as the reaction site. Importantly, this probe not only can be readily prepared, but also can be used to detect palladium in almost wholly aqueous solution with excellent sensing properties, including rapid response (within 2 min), high selectivity and sensitivity (detection limit: 1.6 nM), and distinct color changes and significant fluorescent turn-on signal changes in the far-red to near-infrared region. Besides, a low level of this probe (2 μM) can be used to image micromolar levels of palladium in living cells, indicating this probe holds great potential as a new molecular tool for palladium detection in both aqueous solution and living systems.

2. Material and methods

2.1. Materials and instrumentation

All chemicals and solvents were purchased from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 600 NMR spectrometer, and resonances (δ) are given in parts per million relative to tetramethylsilane (TMS). Coupling constants (*J* values) are reported in hertz. High-resolution mass spectrometry (HR-MS) spectra were obtained on a Bruker microTOF-Q instrument. UV–Vis and fluorescence data were collected on an Agilent Cary-100 UV–Vis spectrophotometer and an Agilent Cary Eclipse fluorescence spectrophotometer, respectively. Cell imaging was performed in an inverted fluorescence microscopy with a 20 × objective lens with excitation wavelength at 460–560 nm.

2.2. Synthesis of probe *SNARF-Pd*

SNARF was prepared from commercially available 2-(4-(diethylamino)-2-hydroxybenzoyl)benzoic acid and 1,6-dihydroxynaphthaiene (Scheme 2) according to the literature report [58].

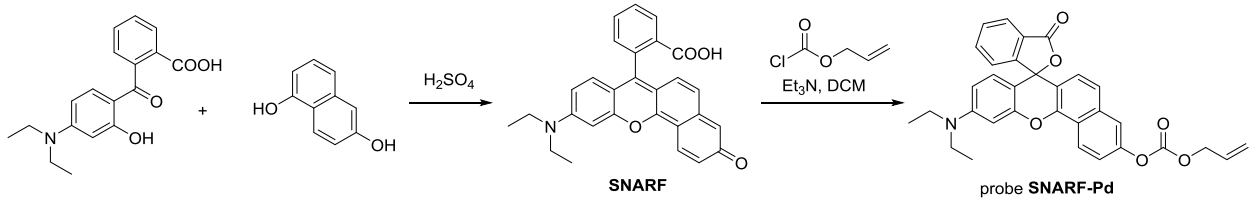
Probe **SNARF-Pd** was prepared as the following procedure: **SNARF** (144 mg, 0.33 mmol) and triethylamine (142 μL) were dissolved in 5 mL of dry dichloromethane in a 50 mL flask. The mixture was stirred in an ice bath. Next, allyl chloroformate (305 μL, 1.33 mmol) was added to the solution under stirring. The mixture was stirred in an ice bath for another 15 min and then continued to be stirred at room temperature overnight. After evaporation of the solvent, the residue was dissolved in dichloromethane (20 mL). The solution was washed with brine (3 × 20 mL), dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography on silica gel with petroleum ether:ethyl acetate (5:1, v/v) as eluent to afford a white solid (75 mg, yield 44%). Mp. 88–90 °C. ^{1}H NMR (600 MHz, DMSO-d6) δ 8.68 (d, *J* = 9.1 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.66 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.60 (d, *J* = 8.9 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 6.85–6.75 (m, 2H), 6.63–6.51 (m, 2H), 6.04 (ddt, *J* = 16.4, 10.9, 5.5 Hz, 1H), 5.45 (dd, *J* = 17.3, 1.8 Hz, 1H), 5.34 (d, *J* = 10.5 Hz, 1H), 4.81–4.78 (m, 2H), 3.41 (q, *J* = 8.1, 7.6 Hz, 4H), 1.14 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d6) δ 168.9, 152.9, 152.8, 151.7, 150.1, 149.3, 146.6, 135.7, 134.5, 131.6, 130.2, 128.7, 126.1, 125.1, 124.7, 124.2, 124.0, 122.9, 121.7, 121.3, 119.1, 112.8, 109.3, 104.1, 97.3, 83.4, 69.0, 43.8, 12.4. HR-MS (ESI): *m/z* calculated for $C_{32}H_{28}NO_6^+$ [M + H^+] 522.19111, found: 522.19009.

2.3. General spectrophotometric experiments

Stock solutions of probe **SNARF-Pd** and $Pd(PPh_3)_4$ were prepared in DMSO and THF with a concentration of 1.0 mM, respectively. The stock solutions of other analytes including K_2PdCl_6, Na_2PdCl_4, $Pd(OAC)_2$, $PdCl_2$, $CaCl_2$, $ZnCl_2$, $MgCl_2$, $NiCl_2$, $CuCl_2$, $Ce(NO_3)_3$, $AgNO_3$, $CoCl_2$, $CdCl_2$, $FeCl_2$, $AlCl_3$, $MnCl_2$, $SrCl_2$, KCl, $LiClO_4$, NaCl, $BaCl_2$ and $HgCl_2$ were prepared in ultrapure water. The stock solution of PPh_3 was prepared in ethanol. Unless otherwise stated, both the absorption and fluorescence experiments were conducted in 3 mL of PBS buffer solution (10 mM, pH 7.4) with probe **SNARF-Pd** (10 μM) and an appropriate amount of analyte at 37 °C. For fluorescence measurements, excitation was set at 564 nm and slit widths were set at 5.0 and 5.0 nm for excitation and emission, respectively.

2.4. Imaging of palladium in living cells

HeLa cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% FBS (Fetal Bovine Serum), 100 U/mL penicillin and 100 μg/mL streptomycin in a 5% CO_2, water saturated incubator at 37 °C, and then were seeded in a 12 well culture plate for one night before cell imaging experiments [19,53]. In the experiment of cell imaging, as a control, living cells were incubated with **SNARF-Pd**



Scheme 2. Synthetic route for probe **SNARF-Pd**.