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A fluorescence turn-on sensor for the detection of palladium ions that operates through *in situ* generation of palladium nanoparticles†

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A simple and straightforward fluorescence method for the detection of palladium ions at low concentrations has been developed. The mode of operation of the sensor involves *in situ* generation of palladium nanoparticles (PdNPs), which promote a selective deiodination reaction of iodo-BODIPY that forms highly fluorescent H-BODIPY.

Palladium species are versatile and widely used catalysts for numerous chemical transformations employed for the production of fine chemicals, therapeutic drugs, and polymers.[1] Pd is also extensively used in various commercial materials such as automobile catalytic converters, jewellery, dental alloys, fuel cells, medical instruments, and electronics.[2] However, palladium released by these materials or present in pharmaceuticals has raised great concern because it can adversely affect human health and the environment.[3] It is known that palladium species in body organs disturb a variety of cellular processes and cause serious physiological disorders including memory loss, dizziness, migraine headaches, allergies, immune system impairment, and facial paralysis.[2] As a result, the threshold level of palladium in pharmaceutical products is strictly limited to be no more than 5–10 ppm and the maximum daily human dietary intake of palladium is restricted to less than 1.5–15 μg.[4] Consequently, efficient methods for monitoring these low levels of palladium in industrial and pharmaceutical settings, as well as in environmental samples, are highly desirable.

Conventional methods for palladium detection include atomic absorption spectroscopy (AAS), HPLC coupled with solid-phase microextraction, and inductively coupled plasma atomic emission (ICP-AES/OES), X-ray fluorescence, and inductively coupled plasma mass spectrometry (ICP-MS).[5] Although being the most sensitive and reliable techniques, ICP and AAS require costly instrumentation and time-consuming manipulations. In contrast, a solution fluorescence-based sensing protocol would be highly advantageous because it would enable simple, cost-effective, rapid, and sensitive detection of palladium species in a high throughput fashion.

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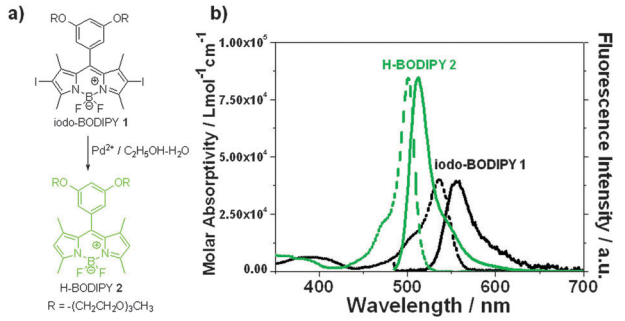
A few fluorescence-based probes have been reported recently for the detection of palladium species.[6] One type relies on changes in photoinduced energy/electron transfer governed emission intensities caused by the formation of Pd^{2+}-specific coordination induced complexes.[7] The others employ Pd-mediated chemical reactions (*i.e.*, Tsuji–Trost reaction, oxidative cyclization) to transform non-emissive dyes into highly fluorescent products.[8] Although these sensors are based on conceptually appealing designs, they possess several important drawbacks. In general, the sensing systems exhibit poor selectivity for palladium, and they require the use of media that contain a high proportion of organic solvents, as well as extended reaction times at elevated temperatures.

In the investigation described below, we have developed a simple fluorescence turn-on sensing system for the detection of palladium. In this system, palladium nanoparticles (PdNPs), generated from Pd salts, serve as an *in situ* catalyst for efficient C–I bond cleavage reactions of a profluorescent iodo-dye. The strategy used to design the sensor was stimulated by earlier observations that show that PdNPs can be readily prepared by reduction of Pd^{2+} precursors[9] and that they arguably serve as catalysts for C–C coupling reactions.[10]

Boron dipyrromethane (BODIPY) dyes were selected as the chromophores to demonstrate this concept. BODIPYs exhibit high fluorescence quantum yields, high extinction coefficients, and excellent photostability.[11] In addition, their spectroscopic properties can be easily tuned by simple synthetic modifications. The singlet excited states of BODIPY derivatives that contain heavy atom substituents at C2 and C6 positions are known to undergo rapid intersystem crossing to generate the corresponding triplets, a process which leads to markedly decreased fluorescence efficiencies.[12] As a result of this phenomenon, reactions in which heavy iodine atoms are excised from a BODIPY core have been explored as turn-on transduction schemes for the detection of DNA by Herrmann *et al.*,[13] and for the detection of gold ions by our group.[14] In the current work, we employed iodo-BODIPY **1** as a profluorescent probe for the detection of palladium (Scheme 1). The emission properties of **1** and its corresponding deiodinated derivative **2** were elucidated to demonstrate that they are suitable for this approach (Table S1, ESI†). As expected, the fluorescence



Scheme 1 (a) Overview of the sensing method using iodo-BODIPY **1** to detect Pd^{2+}. *In situ* generated PdNPs from Pd salts in C_2H_5OH–water trigger the conversion of iodo-BODIPY **1** to H-BODIPY **2**, which results in turn-on fluorescence. (b) Absorption and emission spectra of iodo-BODIPY **1** and H-BODIPY **2** in C_2H_5OH–water (1 : 4, v/v).

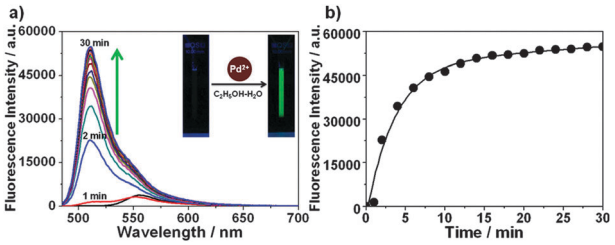


Fig. 1 (a) Time-dependent emission spectra of iodo-BODIPY **1** (5 μM) upon treatment with $PdCl_2$ (20 μM) in ethanol–water solution (1 : 4, v/v) at 25 °C. λ_{ex} = 465 nm. Inset contains photographs of solutions of probe **1** in the absence (left) and presence (right) of $PdCl_2$ after incubation for 30 min under UV light (365 nm) illumination. (b) Relative fluorescence intensities at 510 nm as a function of incubation time.

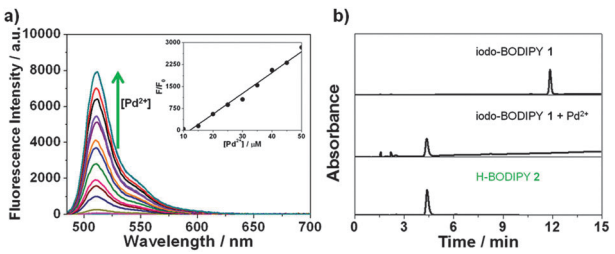


Fig. 2 (a) Fluorescence titration spectra of iodo-BODIPY **1** (5 μM) in the presence of different concentrations of Pd^{2+} in ethanol–water (1 : 4, v/v) at 25 °C. [Pd^{2+}] = 0, 0.5, 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100 μM. λ_{ex} = 465 nm. Each spectrum was obtained 30 min after addition of Pd^{2+}. Inset shows a plot of the relative fluorescence intensity at 510 nm as a function of [Pd^{2+}]. (b) HPLC chromatograms of **1** without Pd^{2+} (top); with Pd^{2+} treatment in ethanol–water (1 : 4, v/v) for 30 min at 25 °C (middle); **2** only (bottom).

quantum yield of iodo-BODIPY **1** (Φ_{PL} = 0.017) is greatly reduced compared to that of the reduced analog **2** (Φ_{PL} = 0.55).

To demonstrate the feasibility of the new *in situ* generated NP-based palladium sensing system, we first investigated the generation of PdNPs from Pd salts in aqueous media under mild reducing conditions. To probe this feature, $PdCl_2$ was selected as a representative palladium species. Among several possible reducing agents, aqueous ethanol was selected for its rapid promotion of the Pd^{2+} to Pd^0 conversion, leading to aggregation and generation of PdNPs. Accordingly, using UV-Vis spectroscopy we showed that PdNPs are readily generated by mixing $PdCl_2$ in aqueous ethanol at room temperature under an air atmosphere (Fig. S1, ESI†). The conversion of Pd^{2+} to PdNPs resulted in generation of a dark colloidal solution, accompanied by a smooth increase in the shorter wavelength absorption band in a manner that is similar to the palladium monolayer protected clusters reported by Murray and co-workers.[15] Transmission electron microscopy (TEM) analysis further showed that the PdNPs, formed by rapid reduction of the Pd salts, have a nearly spherical shape with an average diameter of *ca.* 4.2 nm (Fig. S3, ESI†).

The sensing behavior of the system, promoted by *in situ* generation of PdNPs, was investigated by simply adding $PdCl_2$ to a solution of iodo-BODIPY **1** in ethanol–H_2O (1 : 4, v/v) at 25 °C. Upon addition of $PdCl_2$, the absorption and emission bands of **1** at $\lambda_{max,abs}$ = 535 nm and $\lambda_{max,em}$ = 555 nm, respectively, undergo a rapid and large decrease in intensities. In addition, concomitant increases take place in the intensities of absorption and emission bands at $\lambda_{max,abs}$ = 501 nm and $\lambda_{max,em}$ = 512 nm, respectively, which are characteristic of the deiodinated product, H-BODIPY **2** (Fig. 1 and see ESI†). Importantly, in the absence of Pd^{2+}, iodo-BODIPY **1** in aqueous ethanol (1 : 4, v/v) at 25 °C is stable for more than 2.5 h under continuous visible irradiation (λ_{ex} = 465 nm) (Fig. S11, ESI†).

Notably, the fluorescence turn-on process, associated with the production of bright green fluorescence, occurs in less than 2 min, and it reaches saturation within 30 min at room temperature (Fig. 1). As large as a 560-fold enhancement in the fluorescence intensity at $\lambda_{max,em}$ = 510 nm is observed upon addition of 4 equiv. Pd^{2+} to a solution of **1**. This new fluorescence emission is easily discernible to the naked eye under 365 nm irradiation (Fig. 1a inset). In Fig. 2a is shown the fluorescence sensing response of **1** (5 μM) to different concentrations of $PdCl_2$ in the range of 0–100 μM after incubation times of 30 min. As expected, the fluorescence intensities at 510 nm increase with increasing $PdCl_2$ concentrations in this range. Subsequent data analysis shows that a linear relationship (R^2 = 0.98) exists between the normalized fluorescence intensities at 510 nm and $PdCl_2$ concentrations in the 10–50 μM (1–5 ppm Pd content) range (Fig. 2a, inset).

LC-MS analysis showed that H-BODIPY **2** is the sole BODIPY-derived product generated in the assay solution upon addition of $PdCl_2$ (Fig. 2b), thus confirming that the formation of PdNPs promote C–I bond cleavage of iodo-BODIPY **1**. Whether PdNPs can directly react with **1** to result in deiodinated **2**, or merely act as a reservoir for an active soluble Pd(0) species is not currently known.[10] However, under the assay conditions, deiodination always coincides with the formation of PdNPs.

Similar fluorescence turn-on responses were observed when other aqueous alcohols (*i.e.*, isopropyl alcohol, 1-propanol) were employed, but negligible fluorescence intensity changes were observed when a reducing alcohol was not present (*i.e.*, acetone, acetonitrile, or DMSO in water), or when the alcohol contains amine groups susceptible to coordinate to and stabilize mononuclear Pd species (*i.e.*, 3-amino-1-propanol in water) (Fig. S8, ESI†). The results of these control experiments suggest that the conversion of iodo-BODIPY **1** to H-BODIPY **2** upon addition of Pd^{2+} salts does not occur without formation of PdNPs.

The sensing response of the system comprised of **1** toward other metal ions was explored using the conditions established above (ethanol–H_2O (1 : 4, v/v), 25 °C). Spectroscopic analyses,

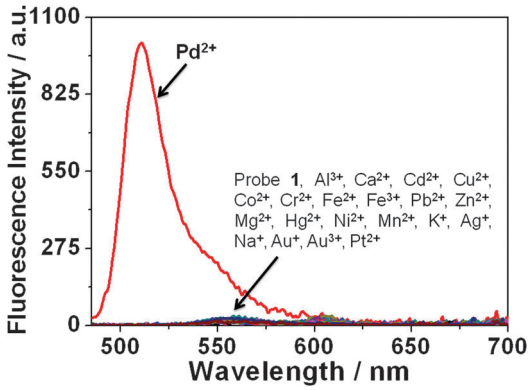


Fig. 3 Fluorescence emission spectra of iodo-BODIPY **1** (5 μM) in ethanol–water (1 : 4, v/v) containing various metal ions (as their chloride salts except for $AgNO_3$), measured 30 min after addition of each metal ion at 25 °C. [metal ion] = 20 μM for Pd^{2+} and 50 μM for all other metal ions. λ_{ex} = 465 nm.

carried out 30 min after addition of 4.0 equiv. of each of the metal ions, show that large fluorescence turn-on response occurs only in the presence of Pd^{2+}. Importantly, none of the other metal species, including Al^{3+}, Ca^{2+}, Cd^{2+}, Cu^{2+}, Co^{2+}, Cr^{2+}, Fe^{2+}, Fe^{3+}, Pb^{2+}, Zn^{2+}, Mg^{2+}, Hg^{2+}, Ni^{2+}, Mn^{2+}, K^{+}, Ag^{+}, Na^{+}, Au^{+}, Au^{3+}, and Pt^{2+}, causes changes in the emission profile of probe **1** (Fig. 3). The excellent selectivity displayed by the sensor is attributed to the highly specific formation of the PdNPs, which mediate the C–I bond cleavage reaction of **1**. However, the fluorescence enhancement induced by palladium is interfered with by other ions that have higher standard reduction potentials (E^0) than that of Pd^{2+} to Pd (E^0 = +0.915 V). For example, the addition of Pd^{2+} to a solution of probe **1** containing either Au^{3+}, Ag^{+}, Pt^{2+}, or Hg^{2+} leads to negligible increases in fluorescence intensities at 510 nm.[16] This phenomenon is likely a consequence of the ability of these metal ions either to promote oxidation of Pd^0 to form Pd^{2+}, hence preventing the growth of PdNPs, or to generate catalytic inactive alloyed NPs.

The rate constant for the Pd^{2+}-induced conversion of iodo-BODIPY **1** to H-BODIPY **2** in ethanol–water (1 : 4, v/v) at 25 °C, determined using initial rate data, was found to be k_{obs} = 3.15 (±0.26) × 10^3 M^{-1} min^{-1} (see ESI†). The rate of this process is enhanced by increasing the amount of ethanol, raising the temperature of the solution, and/or by adding additional reducing agents (*i.e.*, $NaBH_4$) (Fig. S16–S18, ESI†). By doing so, one can increase the analytical sensitivity of the assay. The limit of detection (LOD) for Pd^{2+} on the basis of a signal-to-noise ratio (S/N > 3) was determined to be 0.01 μM of $PdCl_2$ (Pd content = 1 ppb), when $NaBH_4$ (0.5 mM) is added as a reductant to a solution of probe **1** (5 μM) in ethanol–water (1 : 4, v/v) at 25 °C (Fig. S19, ESI†). This LOD is well below the specified threshold limit established for the Pd content in active pharmaceutical ingredients (APIs, 5–10 ppm),[4] a finding that highlights one meritorious feature of the new, simple Pd sensing system.

The new sensing protocol is also applicable to assaying other palladium species, which behave similarly to $PdCl_2$ under the detection conditions (ethanol–H_2O (1 : 4, v/v), 0.5 mM $NaBH_4$, 25 °C). Accordingly, enhancement in fluorescence intensity, sensitivities of **1** to palladium species was found to fall in the order $Pd(NO_3)_2$ ≈ $Pd(OAc)_2$ ≈ $PdCl_2$ ≈ Na_2PdCl_4 > $Pd(PPh_3)_4$ > $PdCl_2(PPh_3)_2$ ≈ $PdCl_2(dppf)_2$ (Fig. S20, ESI†). As shown below, simple sample preparation ensures reliable detection regardless of palladium speciation.

Finally, an application of the new sensor to the determination of residual Pd content in synthetic compounds prepared by palladium-catalyzed reactions was explored. Specifically, the amount of Pd in a biphenyl derivative **3**, synthesized by using a Suzuki–Miyaura cross coupling reaction and purified by column chromatography, was assayed (Scheme S1, ESI†). Our fluorometric analysis showed that the purified **3** (38 μg) contains 2.0 ± 0.1 ppm of Pd (Fig. S21, ESI†). The results demonstrate the practical utility of the new sensing system for the quantitative analysis of Pd in the synthetic intermediate prepared by palladium-catalyzed reactions.

In conclusion, the study described above has led to the development of a highly sensitive fluorescence sensing system for the detection and quantitation of palladium species. The sensor relies on the reductive deiodination reaction of iodo-BODIPY promoted by PdNPs, which are generated *in situ* by the reduction of palladium salts in ethanol–water mixtures. The new method for generating a strong (>560-fold) and specific turn-on response to Pd species has potential practical applications for the quantitative and qualitative assay of Pd species in environmental and chemical samples.

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