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Cyclen-Conjugated Rhodamine Hydroxamate as Pd^{2+}-Specific Fluorescent Chemosensor

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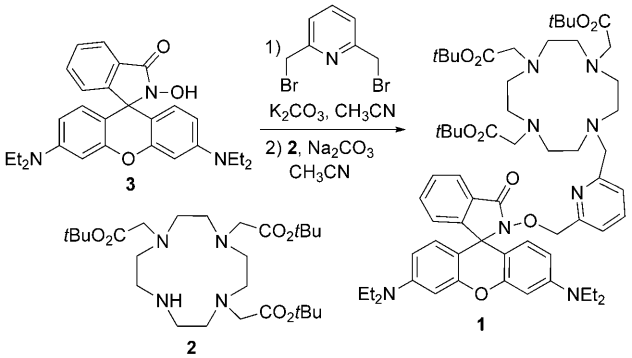
Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday

Palladium is widely used in various materials, such as dental crowns, fuel cells, jewelry, automobile, and catalysts.[1] And palladium-catalysed reactions, such as Buchwald–Hartwig, Heck, Sonogashira, and Suzuki–Miyaura reactions, are increasingly important because of their advantages in forming difficult bonds.[2,7a] However, even after several purification steps, residual palladium species, which can be hazardous to human health,[3] are often found in the final products. In particular, owing to its ability to coordinate with DNA, thiol-contaning amino acids, proteins, and vitamin B_6, palladium is known to potentially disturb several cellular processes.[4] Because the proposed dietary intake is between <1.5 and 15 $\mu g\,day^{-1}$ per person and the threshold for palladium in drugs is <5–10 ppm, the products obtained after palladium-catalyzed reactions need extensive purification and analysis.[4,5]

Therefore, analytical methods are urgently needed for the sensitive and selective detection of palladium in a high-throughput fashion. The typically used analytical methods, such as atomic absorption spectrometry, plasma emission spectroscopy, solid-phase microextraction high-performance liquid chromatography, X-ray fluorescence, etc., require high cost and heavy instrumentation.[6] A fluorescent chemosensor method would be more desirable because it is less labor-intensive and highly sensitive. Recently, a few fluorescent-sensing systems for palladium species utilizing either coordination-based sensing methods or palladium-catalyzed chemical reactions have been reported.[7] Most palladium chemosensors show interference by platinum species owing to their similar chemical properties.

Over the past few years, we have developed fluorescent sensing systems for the selective detection of metal ions using rhodamine–amide fluorophores.[8] Whilst the ring-closed spirolactam form is nonfluorescent and colorless, the corresponding open form is strongly fluorescent and pink colored. Judicious choice of ligand attached to the spirolactam ring could selectively bind with a metal ion to induce ring opening and eventually turn on the fluorescence signal.

Cyclen derivatives are commonly used as ligands owing to their strong coordination ability to many transition metal ions.[9] Recently, a few research groups have reported cyclen-linked fluorescent chemosensors for the detection of metal ions.[10] The pyridine moiety is also well known as a good ligand for metal ions.[11] Thus, we envisioned that the introduction of a cyclen moiety and a pyridine into the rhodamine hydroxamate could provide a well-organized coordination platform for metal ions, as shown in Scheme 1. The rhodamine–cyclen probe (**1**) was prepared in two steps: 1) 2,6-bis(bromomethyl)pyridine, K_2CO_3, CH_3CN, RT, 2) **2**, Na_2CO_3, CH_3CN, reflux, from the known rhodamine hydroxamic acid **3**[8c] (Scheme 1).



Scheme 1. Synthesis of the rhodamine-cyclen conjugate **1**.

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Probe **1** shows neither color nor fluorescence in H_2O (DMSO 1%, v/v) solution indicating that it exists in the spirocyclic form predominantly as expected. On treatment with 5.0 equiv of Pd^{2+} ions, probe **1** (10 μM) exerts strong fluorescence signal at 581 nm in H_2O (DMSO 1%, v/v). In addition, the solution changes from colorless to pink-red color upon addition of Pd^{2+} ions. Probe **1** monitors Pd^{2+} ions in the pH 7–9 range (see the Supporting Information).

A fluorescence titration experiment of **1** (10 μM) with Pd^{2+} ions was conducted in water (DMSO 1%, v/v) at 25°C. Upon each addition of Pd^{2+} ions, the solution was incubated for 30 minutes and then fluorescence intensity was measured. About 2.0 equivalents of Pd^{2+} ions were required for saturation of the fluorescence intensity under the titration conditions (Figure 1a). The UV/Vis absorption spectrum of **1** shows a distinctive absorption at 480–610 nm with a clear color change from colorless to pink in the presence of Pd^{2+} ions (see the Supporting Information). The fluorescence titration experiment of **1** at 10 μM with Pd^{2+} ions demonstrates that the detection of Pd^{2+} ions is possible at the 85 nM level. Under these conditions, the fluorescence intensity of the solution of **1** is linearly proportional to the concentration of Pd^{2+} ions (Figure 1b).

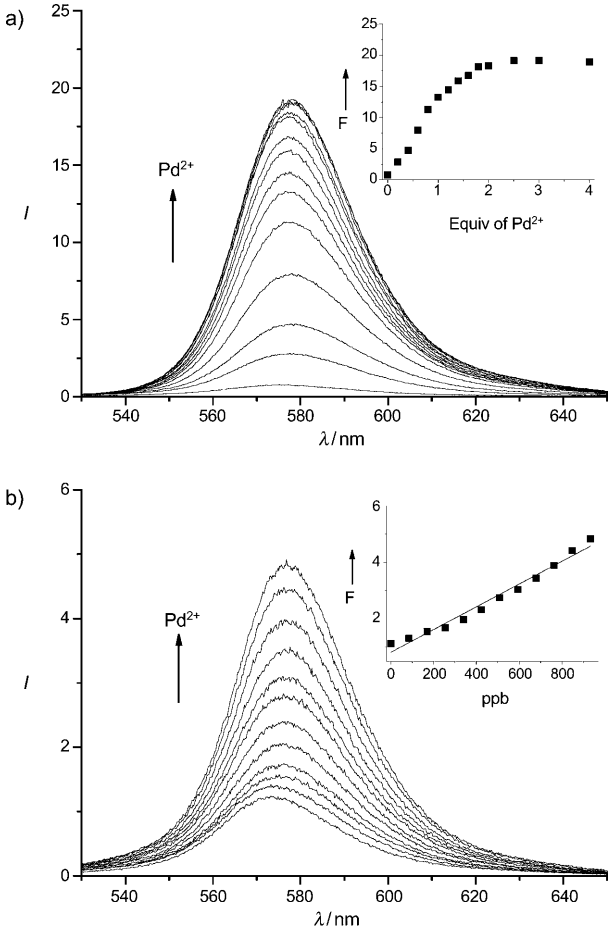


Figure 1. Fluorescence intensity changes of **1** upon addition of Pd^{2+} in H_2O (DMSO 1%, v/v). Each spectrum is measured 30 min after each Pd^{2+} addition at 25°C with excitation at 520 nm. a) **1** (10 μM). Inset: plot of fluorescence intensities at 581 nm depending on the equivalents of Pd^{2+}. b) **1** (10 μM) upon addition of Pd^{2+} (by 85 ppb). Inset: plot of fluorescence intensities at 578 nm depending on the concentration of Pd^{2+} ions.

The Job plot[12] shows that **1** forms a 1:2 complex with Pd^{2+} ions (see the Supporting Information). The binding constant (log $K = 10.26$), which was calculated by the Benesi–Hildebrand method[13] in water (DMSO 1%, v/v) from the fluorescence titration experiments based on a 1:2 binding model, showed strong binding bewteen **1** and Pd^{2+} ions. The addition of excess sodium cyanide to a mixture of **1** and Pd^{2+} ions decreases the fluorescence intensities of the solution and leads to disappearance of the pink color (see the Supporting Information). This result implies the reversible binding properties of **1** with Pd^{2+} ions in aqueous solutions.

To evaluate the selectivity of probe **1**, fluorescence responses of **1** (10 μM) to other biologically relevant metal ions in water (DMSO 1%, v/v) were examined. Upon addition of 5.0 equivalents of metal ions (Fe^{3+}, Fe^{2+}, Au^{3+}, Hg^{2+}, Zn^{2+}, Pb^{2+}, Ca^{2+}, Co^{2+}, Mn^{2+}, Mg^{2+}, Cu^{2+}, Cd^{2+}, Al^{3+}, Cr^{3+}, Au^{+}, Ag^{+}, Na^{+}, Li^{+}, Pt^{2+}, Ru^{3+}, Rh^{2+}, Ni^{2+}, K^{+}, and Ba^{2+}) at 25°C, only Pd^{2+} ions induced significant fluorescence-intensity enhancement. Other metal ions did not cause any significant changes in fluorescence intensity (Figure 2a).[14] This result implies that the selectivity of **1** toward Pd^{2+} ions over other metal ions is extremely high. More importantly, competitive Pt^{2+} ions afforded no enhancement in fluorescence intensity. Fluorescence interference by the presence of other metal ions was negligible, except for Hg^{2+} ions which are known to bind strongly with the cyclen moiety (Figure 2b).[10c]

The fluorescence selectivity and colorimetric selectivity of **1** were well-matched. Whilst the binding of **1** (10 μM) with Pd^{2+} ions resulted in obvious colorless to pink-red color changes in aqueous solutions, no significant color changes were promoted by other metal ions (Figure 3).

To confirm the cooperative effects of the pyridine and the cyclen moieties of **1** for the selective binding with Pd^{2+} ions, we tested the corresponding rhodamine hydroxamates with either a pyridine or a cyclen moiety (see the Supporting Information). These model compounds exerted poor metal-ion selectivities and very weak binding properties with Pd^{2+} ions, which implies that the two binding sites, the pyridyl and the cyclen-tri(*tert*-butyl ester) groups, of **1** bind cooperatively with Pd^{2+} ions to display the observed selectivity. Scheme 2 shows a proposed binding complex, where all three binding groups participate in the complexation with Pd^{2+} ions.

Next, we conducted experiments to detect palladium complexes in aqueous solutions to demonstrate the potential applications of this palladium-ion probe. We first compared fluorescence intensity changes of **1** induced by different palladium complexes ($PdCl_2$, $Pd(NO_3)_2$, $[K_2PdCl_4]$, $Pd(OAc)_2$, and $[Pd(PPh_3)_4]$). The palladium complexes were dissolved in dimethyl sulfoxide (10 mM) at 25°C and then added to the solutions of **1** (10 μM) in water (DMSO 1%, v/v). The

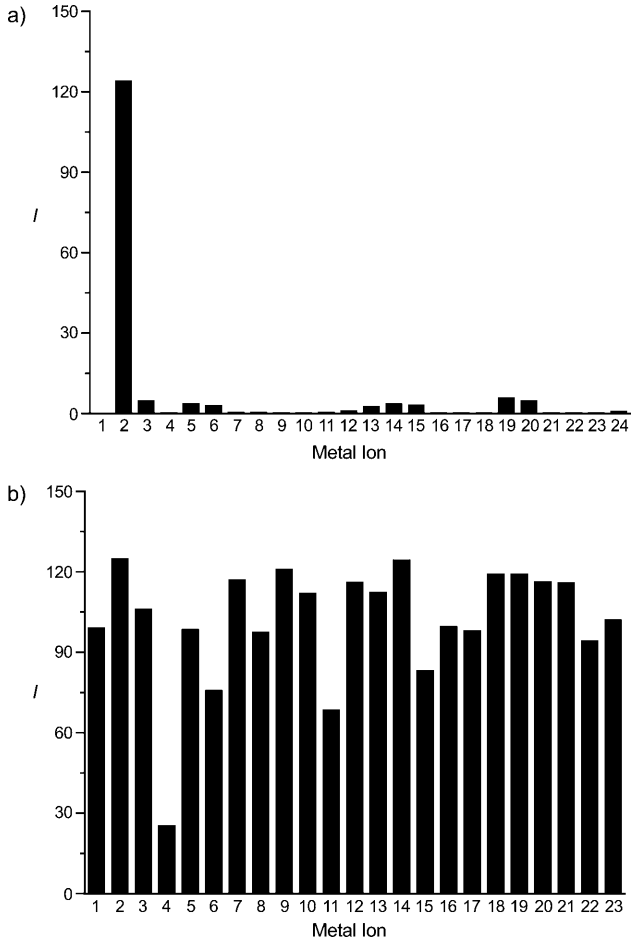


Figure 2. Fluorescence intensity changes of **1** (10 μM) in H_2O (DMSO 1%, v/v) at 581 nm. a) In the presence of metal ions (5.0 equiv): 1 none, 2 Pd^{2+}, 3 Fe^{3+}, 4 Fe^{2+}, 5 Hg^{2+}, 6 Zn^{2+}, 7 Pb^{2+}, 8 Ca^{2+}, 9 Co^{2+}, 10 Mn^{2+}, 11 Mg^{2+}, 12 Cu^{2+}, 13 Cd^{2+}, 14 Al^{3+}, 15 Cr^{2+}, 16 Ag^{+}, 17 Na^{+}, 18 Li^{+}, 19 Pt^{2+}, 20 Ru^{3+}, 21 Rh^{2+}, 22 Ni^{2+}, 23 K^{+}, 24 Ba^{2+}. b) In the presence of Pd^{2+} ions (5.0 equiv) and other metal ions (5.0 equiv). 1 none, 2 Fe^{3+}, 3 Fe^{2+}, 4 Hg^{2+}, 5 Zn^{2+}, 6 Pb^{2+}, 7 Ca^{2+}, 8 Co^{2+}, 9 Mn^{2+}, 10 Mg^{2+}, 11 Cu^{2+}, 12 Cd^{2+}, 13 Al^{3+}, 14 Cr^{3+}, 15 Ag^{+}, 16 Na^{+}, 17 Li^{+}, 18 Pt^{2+}, 19 Ru^{3+}, 20 Rh^{2+}, 21 Ni^{2+}, 22 K^{+}, 23 Ba^{2+}.

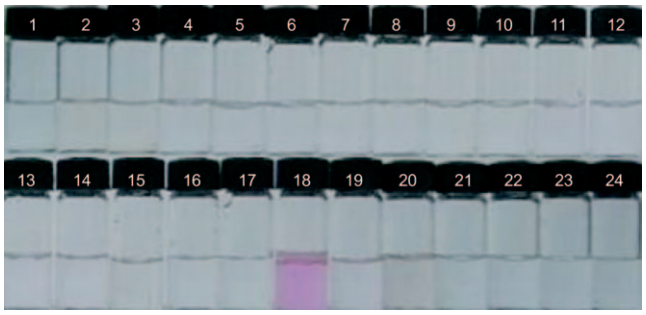
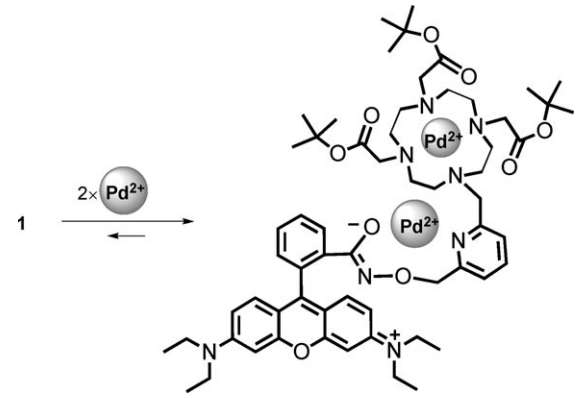


Figure 3. Color changes of **1** (10 μM) in the presence of metal ions (5.0 equiv) in H_2O (DMSO 1%, v/v): 1 none, 2 Fe^{3+}, 3 Fe^{2+}, 4 Hg^{2+}, 5 Zn^{2+}, 6 Pb^{2+}, 7 Ca^{2+}, 8 Co^{2+}, 9 Mn^{2+}, 10 Mg^{2+},11 Cu^{2+}, 12 Cd^{2+}, 13 Al^{3+}, 14 Cr^{3+}, 15 Ag^{+}, 16 Na^{+}, 17 Li^{+}, 18 Pd^{2+}, 19 Pt^{2+}, 20 Ru^{3+}, 21 Rh^{2+}, 22 Ni^{2+}, 23 K^{+}, 24 Ba^{2+}.



Scheme 2. Proposed structure of the 1:2 complex between **1** and Pd^{2+} ions.

resultant solutions were incubated for 30 minutes at 25°C prior to fluorescence measurements. It was possible to detect most palladium(II) complexes in aqueous solutions by fluorescence and colorimetry methods (Figure 4). Although palladium(0) complex $[Pd(PPh_3)_4]$ shows relatively small fluorescence intensity changes, it is still possible to detect palladium(0) complexes in aqueous solutions.

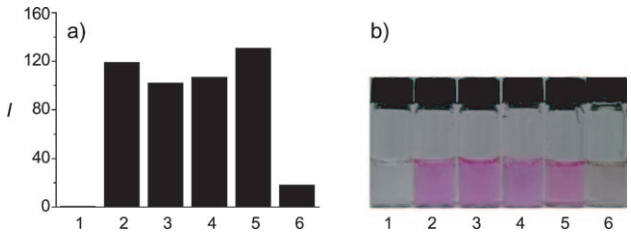


Figure 4. a) Fluorescence intensity changes and b) color changes of **1** (10 μM) in the presence of palladium complexes (5.0 equiv) in H_2O (DMSO 1%, v/v) at 25°C (at 578 nm): 1 none, 2 $PdCl_2$, 3 $Pd(NO_3)_2$, 4 $[K_2PdCl_4]$, 5 $Pd(OAc)_2$, 6 $[Pd(PPh_3)_4]$.

Next, we carried out experiments to detect residual Pd^{2+} ions in glass reactors.[7f] Solutions of each palladium(II) complex, $PdCl_2$, $Pd(NO_3)_2$, $[K_2PdCl_4]$, and $Pd(OAc)_2$ in tetrahydrofuran were stirred in a flask for 3 hours at room temperature, then the flask was cleaned according to the usual laboratory washing procedure (brushed with detergent, washed with water and acetone, then oven-dried). A solution of probe **1** in water (DMSO 1%, v/v) was added to the cleaned flask and stirred overnight at room temperature prior to fluorescence measurements (see the Supporting Information). The observed fluorescence intensities of the prepared samples showed that most of the flasks still had significant amounts of residual palladium species (Figure 5). This result implies that this probe system could be effectively used to detect residual Pd^{2+} complexes in aqueous solutions.

In conclusion, we have developed a Pd^{2+}-selective chemosensor based on rhodamine hydroxamate with a cyclen-tri-

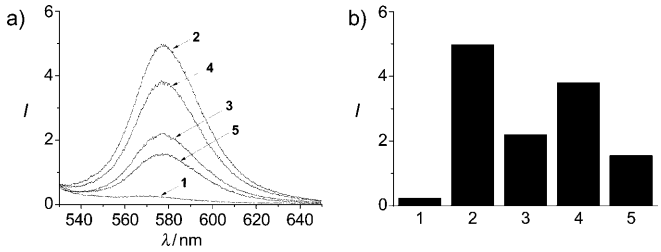


Figure 5. a) Fluorescence intensities of **1** (20 μM) in H_2O (DMSO 1%, v/v) prepared from the flasks contaminated by the following palladium complexes: 1 none, 2 $PdCl_2$, 3 $Pd(NO_3)_2$, 4 $[K_2PdCl_4]$, 5 $Pd(OAc)_2$. b) Fluorescence intensities at 578 nm.

(*tert*-butyl ester) and a pyridine moiety as binding units. This chemosensor binds specifically with Pd^{2+} ions to induce a strong fluorescence enhancement and color changes in aqueous solution. This probe system could discriminate Pd^{2+} over Pt^{2+} ions by fluorescence and colorimetry. We have also demonstrated the detection of residual palladium(II) species in 'cleaned' glass flasks.

Experimental Section

General Methods

Acetonitrile was distilled over calcium hydride under nitrogen immediately prior to use. All reactions were carried out under a nitrogen atmosphere. Chromatographic purification were performed on silica gel (230–400 mesh) with the solvent systems indicated. All recorded melting points are uncorrected. NMR spectra were recorded with reference to tetramethylsilane as an internal standard. Organic extracts were dried over anhydrous $MgSO_4$.

*Synthesis of Probe **1***

Rhodamine derivative **3** was prepared according to the known procedure.[8c] The cyclen derivative **2** was prepared according to the known procedure.[15]

2,6-Bis(bromomethyl)pyridine (70 mg, 0.24 mmol) and potassium carbonate (30 mg, 0.24 mmol) was slowly added to a solution of **3** (54 mg, 0.12 mmol) in acetonitrile (4 mL) at 0 °C. After 30 min, the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc = 3:1 to 1:1, v/v) to give 36 mg (0.06 mmol, 47%) of white solid.

Sodium carbonate (25 mg, 0.24 mmol) and compound **2** (60 mg, 0.12 mmol) were added to a solution of the white solid (75 mg, 0.12 mmol) in acetonitrile (5 mL). The solution was heated at reflux for 48 h and the reaction mixture was filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH: 10/1 to 9/1, v/v) to give **1** (119 mg, 0.11 mmol, 92%) as a white solid: $R_f = 0.33$ (CH_2Cl_2/MeOH = 10:1); m.p. 130–135 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (d, $J = 6.8$ Hz, 1H), 7.47–7.43 (m, 3H), 7.07–6.98 (m, 3H), 6.37 (d, $J = 8.8$ Hz, 2H), 6.31(s, 2H), 6.17 (d, $J = 8.4$ Hz, 2H), 4.84 (s, 2H), 3.57 (bs, 2H), 3.32 (q, $J = 7.2$ Hz, 8H), 3.17–2.29 (broad, 22H), 1.43 (s, 9H), 1.31 (s, 18H), 1.17 ppm (t, $J = 7.2$ Hz, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 172.6$, 165.8, 158.0, 155.9, 153.5, 151.0, 148.7, 136.9, 133.3, 128.7, 128.4, 124.1, 122.7, 122.5, 122.2, 107.9, 105.0, 97.7, 82.2, 82.1, 78.8, 65.6, 59.5, 56.4, 55.7, 50.8, 44.3, 28.0, 12.8 ppm; IR (film): $\tilde{\nu} = 2972$, 2932, 2900, 2837, 2450, 2359, 2337, 1721, 1634, 1612, 1544, 1512, 1454, 1427, 1368, 1310, 1265, 1224, 1157, 1116, 1076, 1017, 751 cm^{-1}; HRMS(FAB) *m/z* calcd for $C_{61}H_{86}N_8O_9$ ($M+Na^+$) 1097.6415; found 1097.6409.

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Keywords: chemosensor · fluorescent probes · palladium · rhodamine · cyclen

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