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Naphthalimide derived fluorescent probes with turn-on response for Au^{3+} and the application for biological visualization

Yan Li^a, Yanxin Qiu^b, Jianjian Zhang^a, Xinyue Zhu^a, Bin Zhu^a, Xiaoyan Liu^a, Xiaoyu Zhang^b, Haixia Zhang^{a,*}

^a State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China

^b Institute of Physiology, School of Basic Medical Sciences, Lanzhou University, Lanzhou 730000, China

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ABSTRACT

The 4-*N,N*-dimethyl-1,8-naphthalimide based fluorescent probes have been explored for selective detection of Au^{3+} . Both probes show a pronounced fluorescence enhancement response to Au^{3+} . Hydroxy is introduced as ligand of Au^{3+} for Probe 1 and the newly designed Probe 2 contains an alkyne moiety to recognize Au^{3+} through an irreversible $\text{C}\equiv\text{C}$ bond hydrolysis reaction. Probe 1 exhibits higher performance such as faster response, lower detection limit of 0.050 μM and the better responsive effect in 99.5% water system compared with most of probes published. The Probe 2 displays high stability to pH, suitable water solubility, wider linear range (0–100 μM) to Au^{3+} , and live-cells imaging with low cytotoxicity.

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1. Introduction

As one of the important noble metals, in recent years, gold has attracted special attention in light of their versatile chemical and photophysical properties (Arcadi, 2008; Hashmi and Rudolph, 2008; Krause and Winter, 2011; Li et al., 2008). Gold-based drugs, such as solganol, sanocrysin and auranofin, are valuable for the treatment of a wide variety of diseases including rheumatic arthritis, asthma, malaria, cancer, and HIV (Gabbiani et al., 2007; Ott, 2009). However, in sharp contrast to the beneficial effects, it is well-known that Au^{3+} is potentially toxic to humans. A concentration of 200 μM could cause over 90% cytotoxicity for the Au^{3+} salt solution (Connor et al., 2005). HAuCl_4 (10–15 μmol) causes agglutination and hemolysis of erythrocytes suspended in 1 mL of saline (Jandl and Simmons, 1957; Kundu et al., 2012).

On the basis of these observation, it is urgent to establish a new method to detect Au^{3+} in a variety of samples. Fluorospectrophotometry is undoubtedly the best choice for this purpose owing to its high sensitivity and selectivity, visibility, real-time detection and easiness of manipulating (Beija et al., 2009; Ding et al., 2015; Guo et al., 2014; Vendrell et al., 2012; Yuan et al., 2013). The design of fluorescent chemosensor is usually based on specific reactions mediated by the analyte of interest. To date,

fluorescent probes based on various fluorophore units including rhodamine (Egorova et al., 2009; Emrulloğlu et al., 2013; Jou and Kim, 2009; Karakuş et al., 2015; Seo et al., 2014; Song et al., 2014; Wang et al., 2011; Yang et al., 2009; Yuan et al., 2011), fluorescein (Kambam et al., 2015; Patil et al., 2012; Seo et al., 2012), BODIPY (Park et al., 2012a; Üçüncü and Emrulloğlu 2014; Wang et al., 2016; Wang et al., 2012; Yang et al., 2016), naphthalimide (Choi et al., 2013; Dong et al., 2010), coumarine (Do et al., 2010; Park et al., 2012b; Wang et al., 2013), rhodamine-BODIPY coupling (Cao et al., 2011; Karakuş et al., 2014) dyes, have been developed to detect gold ions and the possible reaction mechanism mainly include: (1) hydrolysis reaction of alkynyl (Choi et al., 2013) or Schiff base (Wang et al., 2016) promoted by Au^{3+} ; (2) conversion of thiocarbonyl compounds into their carbonyl analogues promoted by Au^{3+} (Park et al., 2012b); (3) only few works are based on the chelation-enhanced fluorescence (CHEF) (Wang et al., 2011). Among these probes, there are one or more problems existed, such as cytotoxicity, poor water solubility, small Stokes shift and failed to differentiate Au^{3+} from other alkynophilic metal ions.

Thus, it is still a challenge to develop versatile fluorescent probes to cater to the requirements of practical application. The naphthalimide derivatives have been extensively used as fluorescent chemosensors for pH, metal cations, and anions in recent years (Li et al., 2012). Recent development of the naphthalimide-based chemosensors for the detection of Au^{3+} are summarized in Table S1. Using the rigid naphthalimide structure as chromophore

* Corresponding author.

E-mail address: zhanghx@lzu.edu.cn (H. Zhang).

is attractive for several reasons: Firstly, the synthesis of 4-substituted naphthalimides is easy from 4-bromonaphthalic anhydride with a high yield (De Silva et al., 1997; Gan et al., 2002; Wintgens et al., 1994). Additionally, the photophysical properties of naphthalimide structure are strongly affected by the nature of the substituent (e.g. amino or nitro group), a strong push-electron group at the 4 position of the ring can emit strong fluorescence and have a high photo stability, the moderate fluorescence emission wavelength, large Stokes shift and high fluorescence quantum yield (Chang et al., 1999; Tao and Qian, 1999).

Therefore, we successfully designed and synthesized two novel “turn-on” type fluorescent probes derived from naphthalimide structure for Au^{3+} detection with high sensitivity, large Stokes shift and rapid responsive time. Hydroxy is introduced as ligand of Au^{3+} for Probe 1 and the newly designed Probe 2 contains an alkyne moiety that recognize Au^{3+} through an irreversible $\text{C}\equiv\text{C}$ bond hydrolysis reaction. Probe 1 showed the better response effect under physiological conditions, Probe 2 successfully achieved Au^{3+} bioimaging of cell nucleus.

2. Results and discussion

2.1. Synthesis and characterization of Probe 1 and Probe 2

The detailed synthetic procedure of Probe 1 and Probe 2 was depicted in Supporting Information and Scheme 1. The reaction between 4-N,N-dimethyl-1,8-naphthalic acid anhydride and hydroxylamine hydrochloride in ethanol afforded Probe 1. Then the alkynes group, incorporated to sense gold ions, was introduced through nucleophilic substitution reaction of Probe 1 with propargyl bromide in the presence of sodium hydride in tetrahydrofuran, which formed the Probe 2. The structures of compound 1 and probes were confirmed by ^1H NMR, ^{13}C NMR and HRMS (ESI) in Figs. S10–S17 (Supporting Information).

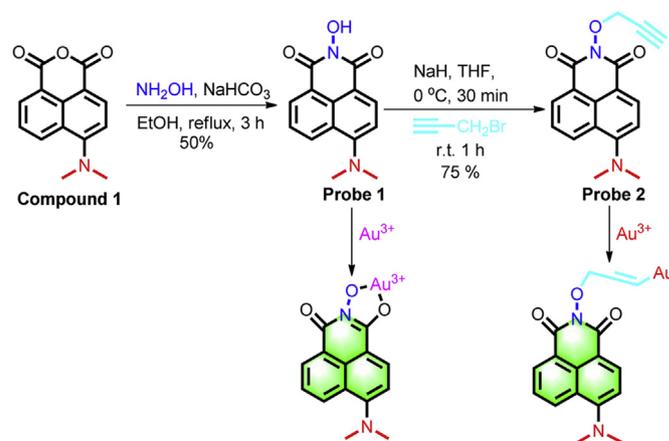
2.2. Optimization of experimental conditions

To achieve the highly sensitive and selective detection of Au^{3+} , different experimental parameters such as solvents (Fig. S1, Supporting Information), pH values (Figs. S2–S3, Supporting Information) and response time (Fig. S4, Supporting Information) were studied.

The mixture of water and ethanol was chosen as solvent to evaluate the response of the probes to Au^{3+} , since they are friendly environmental. The medium of H_2O -ethanol (v:v, 6:4) was proved to be highly efficient for the sensing process of Probe 2, however, the emission intensity was unceasingly increased when water content was higher than 60% in the Probe 1- Au^{3+} system. This difference can be attributed to that higher water content is more beneficial to the conversion of $-\text{OH}$ to O^- in Probe 1, which can effectively block the photo induced electron transfer process.

From the ultraviolet absorption curves, it was found that within the wide scope of pH range from 3 to 10, no changes of absorption intensity and wavelength shift were observed for Probe 2, because there are no sensitive groups against H^+ and OH^- in the structure of Probe 2, which displayed a high stability to pH. For Probe 1, the absorption intensity was stable at pH range from 3 to 6, however, a slight decrease in absorption intensity and a platform between 380 nm and 450 nm were observed when pH is higher than 6. The reason is that the pKa calculated is 7.06 for Probe 1 and $-\text{OH}$ converts into O^- under the condition of alkaline.

In the probe- Au^{3+} system, the maximum emission intensity was obtained for Probe 1 at pH 7.4, while lower pH values were beneficial to the emission of Probe 2- Au^{3+} system. The different phenomena can be attributed to that pH 7.4 was favorable to the



Scheme 1. Synthesis of probes and the response to Au^{3+} .

complexation between Probe 1 and Au^{3+} to block the PET process, although more alkaline environment is beneficial to the formation of O^- , competition occurred in metal-hydroxy complex will reduce the complexing ability between Au^{3+} and hydroxyl. For Probe 2, acidic environment was more conducive to facilitate the hydrolysis of alkynyl in the presence of Au^{3+} . Considering better suitability for cell image, pH 7.4 was used for both probes in the later experiments.

The time dependent experiment was established under optimal conditions. The emission intensity reached its maximum value at 5 min for Probe 1 and 10 min for Probe 2, which exhibited that both probes have fast response to Au^{3+} .

Therefore, 99.5% water (pH 7.4, 10 mM PBS) in ethanol was used as the solvent, the emission intensity was recorded after 5 min for Probe 1- Au^{3+} system. 60.0% water (pH 7.4, 10 mM PBS) in ethanol was used and the emission intensity was recorded at 10 min for Probe 2- Au^{3+} system.

2.3. Specificity of probes towards metal ions

It is of great importance to evaluate the selectivity of the new sensing systems. Twenty four metal ions in H_2O -ethanol solution, including Ca^{2+} , Cd^{2+} , Co^{2+} , Fe^{2+} , Fe^{3+} , Hg^{2+} , K^+ , Li^+ , Mg^{2+} , Mn^{2+} , Na^+ , Sr^{2+} , Ba^{2+} , Zn^{2+} , Al^{3+} , Ag^+ , Pb^{2+} , Cr^{3+} , Cu^{2+} , Ni^{2+} , Cu^+ , Pd^{2+} , Au^+ and Au^{3+} ions were investigated. Free probes have a negligible fluorescence intensity, however, addition of Au^{3+} made the emission intensity increasing 145 times ($50 \mu\text{M Au}^{3+}$) for Probe 1 and 14 times ($100 \mu\text{M Au}^{3+}$) for Probe 2, displaying an efficient OFF-ON behavior (Fig. S5, Supporting Information). These results indicated that both probes have high selectivity towards Au^{3+} . Probe 1 responded to Au^+ too, but the sensitivity was much lower than to Au^{3+} , which resulted from the disproportionation reaction of Au^+ .

To get a further insight into the sensing and anti-interference properties of probes toward Au^{3+} , the competitive experiments were carried out with other metal ions in the presence of Au^{3+} . It was found that fluorescence enhancement caused by the mixture of Au^{3+} with most other metal ions was similar to that caused by Au^{3+} alone, which indicated that most of metal ions have little effect on the sense of Au^{3+} . However, it was worth noting that an approximately 3.6-fold increase and 73% decrease of fluorescence intensity of Probe 2- Au^{3+} complex were observed when Au^{3+} was mixed with Ag^+ or Mn^{2+} , respectively (Fig. S6, Supporting Information). For both probe- Au^{3+} system, fluorescence quenching caused by Mn^{2+} or Cr^{3+} results from the paramagnetic shielding effect of the both ions. Ag^+ may play a catalytic role in the Probe 2- Au^{3+} system to accelerate the reaction rate between Probe

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