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Hg(II)-Mediated Intramolecular Cyclization Reaction in Aqueous Media and Its Application as Hg(II) Selective Indicator

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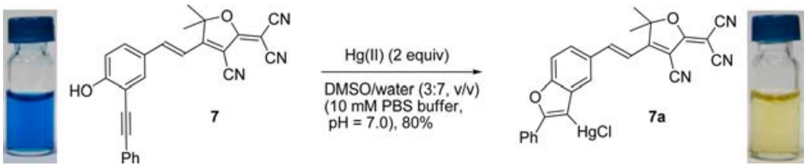
ABSTRACT



The Hg(II)-specific intramolecular cyclization reaction of ethynyl phenols was carried out for the first time in semiaqueous media at ambient temperature. The reaction unit (ethynyl phenol) was coupled with a malononitrile derivative (signal unit), which afforded the chromogenic Hg(II) indicator 7. The reaction of the chromogenic Hg(II) indicator 7 was further optimized in DMSO/water (3:7, v/v) (10 mM PBS buffer, pH = 7.0). Compound 7 displays a color change from blue to pale yellow in the presence of Hg(II).

Many metal ions are necessary to sustain life, and they are precisely controlled in ecology and biology. Nevertheless, one heavy metal ion, Hg(II), is extremely toxic and possesses no benign effect. The toxicity of the Hg(II) cation is related to the fact that biological ligands such as proteins, DNA, and enzymes can coordinate with mercury cations. Consequently, toxic levels of Hg(II) cause significant damage to the brain, kidney, stomach, and central nervous system.[1] Therefore, detection of toxic Hg(II) ions in environmental and biological samples is of primary interest. Many different chemical sensors have been developed as prototype tools for detecting toxic Hg(II). Since Czarnik's seminal work,[2] analyte-specific reaction indicators[3] have attracted considerable attention and become an important research area in supramolecular chemistry. This approach relies on an irreversible chemical reaction rather than on reversible interactions.[4] Consequently, all the characteristics, including sensitivity and selectivity, depend on a Hg(II)-specific reaction instead of a shape-recognition process (lock and key concept). Thus far, most of the reported Hg(II) selective reaction-based detection strategies can be classified as Hg(II)-specific hydration reactions of alkynes or alkenes[5] or reactions related to the thiophilic nature of Hg(II), which constitute the majority of Hg(II) selective reaction-based indicators. This thiophilic nature of Hg(II) is interrelated to many different Hg(II) selective reactions, including intramolecular cyclic guanylation of

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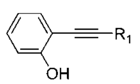
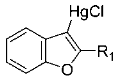
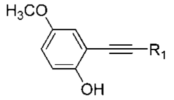
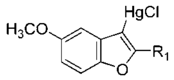
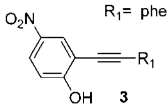
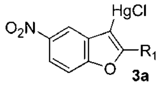
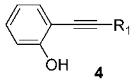
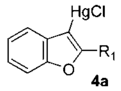
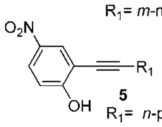
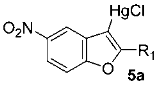
thiourea derivatives,[6] ring-opening of spirocyclic systems,[7] desulfurization–lactonization reactions,[8] desulfurization of thiocarbonyl compounds,[2,9] deprotection of dithiol-protected aldehydes,[10] and hydrolysis reactions of thioethyl carbamate.[11] Some of the above Hg(II) indicators have their own novel Hg(II)-specific reaction, which displayed different advantages. For example, a rarely known hydrolysis reaction of thioethyl carbamate was first used as a Hg(II)-specific reaction, which enabled us to synthesis the coumarin-based Hg(II) indicator in a single step from commercially available starting materials.[11] Since then, our interests have been further extended to finding Hg(II)-specific reactions that have never been used for detecting Hg(II) analytes. This approach necessarily includes a new reaction methodology and a better understanding of existing mechanisms. Here, we report the first (to the best of our knowledge) Hg(II)-mediated synthesis of benzofuranylmercury derivatives from ethynyl phenol substrates in a semiaqueous solution. Hg(II)-specific intramolecular cyclization between phenol and acetylene occurs to form a benzofuranylmercury chloride, which was characterized by X-ray crystallograpy. This methodology was further applied to develop a Hg(II) selective indicator.

Intramolecular alkoxymercuration reactions were first reported in 1984,[12] and the utility of similar reactions has been proven many times in the literature.[13] Unfortunately, the alkoxymercuration reaction is known to proceed best in acetic acid, which is not suitable for Hg(II) selective reaction-based detection strategies due to the harsh acidic conditions and longer reaction times. Here, we hypothesized that a more reactive phenolic OH may be able to accelerate the reaction. Various ethynyl phenol substrates were tested for the cyclization reaction, as shown in Table 1; simple phenol did not induce the formation of the desired product or of any other products (entry 1). To activate the phenolic OH more, electronic effects were examined. A nitro group on phenolic substrate **3** afforded cyclized product **3a** with 93% yield in 10 min, while methoxylated substrate **2** did not result in any desired product even after an extended time. To obtain a simple Hg(II) indicator, less substituted phenolic substrates **4** are highly desired. However, substrate **4** was unreactive under the same conditions. Surprisingly, the reaction with an alkyl group on ethynyl nitrophenol **5** proceeded faster than **3**, affording **5a** in 95% yield after only 2 min (entry 5).

Table 1. Various Phenolic Substrates in the Hg(II)-Mediated Cyclization Reaction[a]

entry	substrate	product	yield[b]	time
1	 R_1 = phenyl		No Reaction	
2	 R_1= phenyl		No Reaction	
3	 **3** R_1 = phenyl	 **3a**	93%	10 min
4	 **4** R_1= *m*-nirtophenyl	 **4a**	No Reaction	
5	 **5** R_1= *n*-pentyl	 **5a**	95%	2 min

[a] All reactions were run on a 17 mM scale (phenolic substrate). $HgCl_2$ (2 equiv, in water) was added to a solution of the substrate in DMSO at 25 °C. The final solvent ratio (water/DMSO = 1/4, v/v) was carefully adjusted (cf. the Supporting Information). [b] Isolated yields.

Most of the unknown compounds were characterized by ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry. However, not all of the ^{13}C NMR spectra of the products in Table 1 were clear, and we found that ^{13}C NMR spectra of benzofuranylmercury chloride compounds were not reported in the literature.[11] The unavailability of the ^{13}C NMR spectra should be related to the fact that two Hg isotopes (^{199}Hg and ^{201}Hg) possess spin quantum numbers that interact with the ^{13}C isotope. To confirm the product of the cyclization reaction (or the expected mechanism), a single crystal of **5a** was grown from a mixture of ethyl acetate and *n*-hexane by slow evaporation of the solvent. The X-ray structure of **5a** clearly proves that the Hg(II)-specific reaction affords the benzofuranylmercury chloride derivative (Figure 1).

An interesting feature of the cyclization reaction of phenolic substrates to benzofuranylmercury derivatives is that the cyclization products change the conjugation pathway of the phenolic substrates (Table 1, see entries 3 and 5). We thus imagined that this reaction could be used to produce a specific Hg(II)-mediated color change, provided a suitably colored phenol derivative could be obtained. To test this hypothesis, π-extended **7** was designed and prepared from 4-formyl-2-iodophenyl acetate, as shown in Scheme 1. Compound **6** was obtained in 92% yield by Sonogashira coupling between 4-formyl-2-iodophenyl acetate

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and phenyl acetylene. Compound **6** was then condensed with a malononitrile derivative. Deacetylation occurred simultaneously to afford **7** in 44% yield.

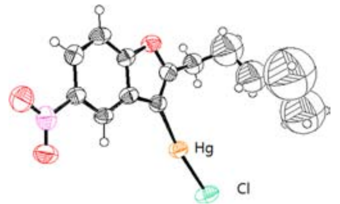
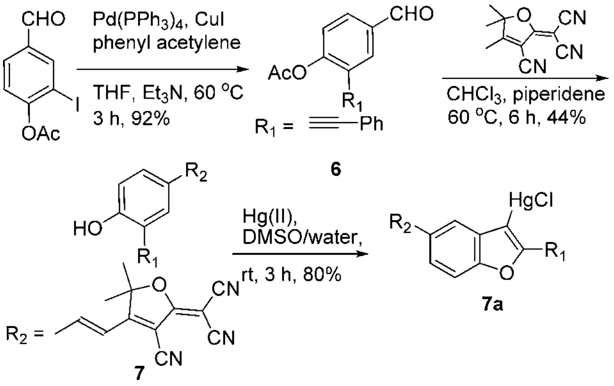
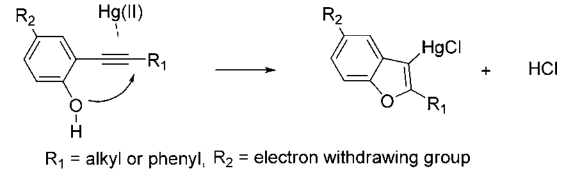


Figure 1. Single-crystal X-ray diffraction structure of **5a**. Thermal ellipsoids are scaled to the 50% probability level. Disorder of alkyl group was found in the X-ray structure of **5a**.

Scheme 1. Synthesis of Hg(II)-specific Indicator



Scheme 2. Proposed Mechanisms of Hg(II)-Mediated Intramolecular Cyclization



The cyclization reaction of **7** was monitored by UV−vis spectroscopy. We found that the progress of the Hg(II)-specific reaction of **7** is inversely proportional to the absorbance of **7** at 608 nm (Figure 2). This characteristic absorbance change of **7** enabled us to monitor the progress of the reaction with a UV−vis spectrophotometer. It should be noted that the reaction was complete in 3 h, and **7a** was isolated in 80% yield under the conditions listed in Table 1. The isolated product was confirmed by ^{1}H NMR spectroscopy and high-resolution mass spectrometry. From these results, it can be concluded that compound **7** underwent Hg(II)-mediated intramolecular cyclization in aqueous buffered media (Scheme 2). The reaction was further optimized by increasing the PBS buffer content from 30% to 70% in DMSO (Supporting Information, Figure S1). Under the optimal conditions, the reaction of **7** (11 μM) was fast enough to reach completion in 20 min in the presence of 2 equiv of Hg(II). In the absence of Hg(II), the absorption maximum of compound **7** was observed at 608 nm, as illustrated in Figure 2. After addition of 2 equiv of $HgCl_2$, further spectral changes were not observed after 20 min.

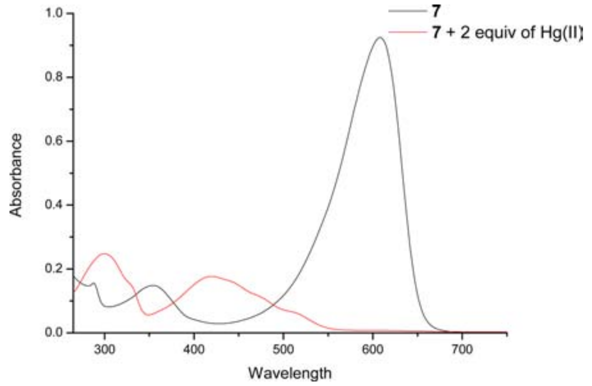


Figure 2. UV−vis spectra of indicator **7** (11 μM) in DMSO/water (3:7, v/v) (10 mM PBS buffer, pH = 7.0), recorded before and 20 min after the addition of $HgCl_2$ (2 equiv, 6.60×10^{-3} M in water) at 25 °C.

To test the selectivity of compound **7**, 2 equiv of each cation (Cu(I), Cu(II), Au(III), Co(II), Hg(II), Fe(III), Zn(II), Ag(I), Pb(II), Na(I), Pt(II), Fe(II), Ni(II), Al(III), Mg(II), K(I), Cd(II), and Ca(II)) were added to solutions of **7** (11 μM) in DMSO/water (3:7, v/v) (10 mM PBS buffer, pH = 7.0), and the absorbance spectra were recorded 20 min later. As shown in Figure 3a, the absorbance band at 608 nm completely disappeared in the presence of Hg(II). In this case, a dramatic color change was also observed, from blue to pale yellow (Figure 3b). Although a slight color change was observed for Au(III) due to the alkynophilicity of gold ions,[14] no color change was seen upon the addition of other metals. In the presence of gold ions, the solution shows a different color as well (Figure 3b).

Competition experiments were also carried out by adding 2 equiv of Hg(II) to the buffered solutions in the presence of 2 equiv of other metal ions, as shown in Figure 3c. The presence of other metal ions did not interfere with the detection of Hg(II) ions, which indicates that the system of compound **7** and Hg(II) was barely affected by these coexistent ions (Figure 3c).

The sensitivity of **7** to Hg(II) was evaluated upon the addition of various amounts of Hg(II) to solutions of **7**. The reactions were carried out for 20 min to ensure completion of the reaction, and the absorbance at 608 nm was recorded (Figure 4a). To obtain the detection limit, four independent UV−vis titrations were carried out at

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(14) For Au(III) indicators using alkynes, see: Seo, H.; Jun, M. E.; Egorova, O. A.; Lee, K.-H.; Kim, K.-T.; Ahn, K. H. *Org. Lett.* **2012**, *14*, 5062–5065 and references cited therein.

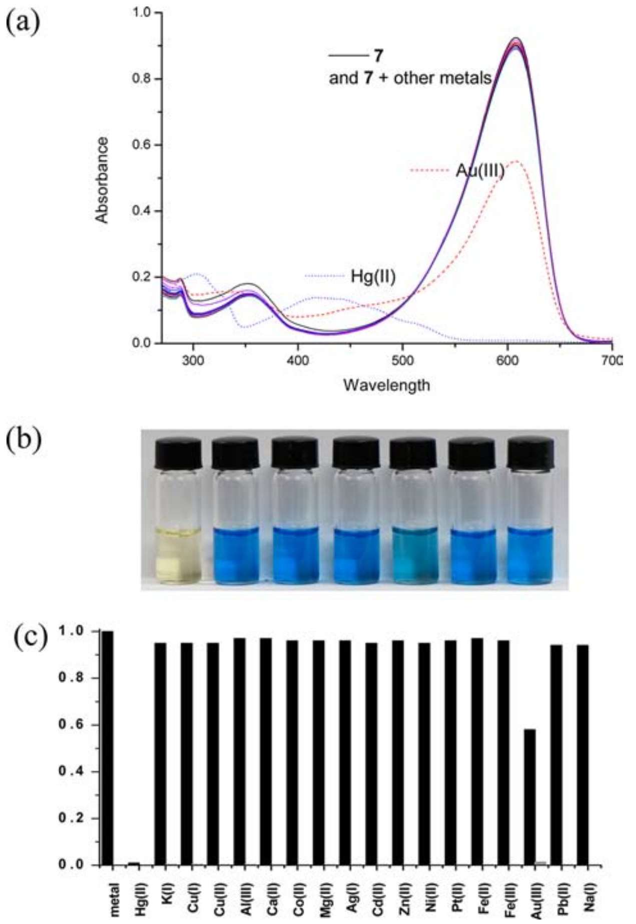

Figure 3. (a) Absorbance responses of **7** (11 μM) with various metal ions (2 equiv) in DMSO/water (3:7, v/v) (10 mM PBS buffer, pH = 7.0). All measurements were conducted 20 min after the addition of various ions. (b) Observed color change of **7** (11 μM) seen without or with various metals (2 equiv) in DMSO/water (3:7, v/v) (10 mM PBS buffer, pH = 7.0). From left to right: Hg(II), no metal, Cd(II), Cu(III), Au(III), Ni(II), Ag(I). (c) Metal-ion selectivity of **7** (11 μM). The black bars represent the absorbance of **7** at 608 nm in the presence of other cations (2 equiv). The gray bars represent the absorbance that occurs upon the subsequent addition of 2 equiv of Hg(II) to the above solution.

Hg(II) concentrations from 0 to 5.5 μM, which afforded average values with the standard deviation (σ = 0.0028) and the linear slope (absorbance vs Hg(II) concentration, m = 64198 M^{-1}, and R^2 = 0.9995) shown in Figure S2 (Supporting Information). The corresponding detection limit was determined to be 0.13 μM based on the expression 3σ/m.[15] As mentioned above, Hg(II) triggered a color change of **7**; the colorimetric detection limit can be less than 8.3 μM, as shown in Figure 4b.

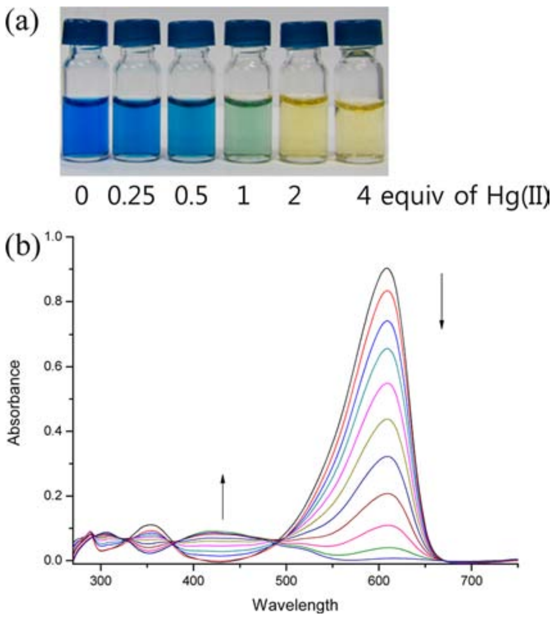

Figure 4. (a) UV–vis spectra were recorded 10 min after adding various quantities of Hg(II) (0–2 equiv of Hg(II)) to compound **7** (11 μM) in DMSO/water (3:7, v/v) (10 mM PBS buffer, pH = 7.0). (b) Observed color change seen 10 min after adding various quantities of Hg(II) (0–4 equiv of Hg(II)) to compound **7** (33 μM) in the above conditions.

In conclusion, we disclosed a Hg(II)-specific intramolecular cyclization reaction of ethynyl phenols in semiaqueous media at ambient temperature. The reaction was further optimized and utilized as a Hg(II)-specific reaction for the application of **7** as a Hg(II) indicator. Compound **7** displays a color change from blue to pale yellow in the presence of Hg(II). More importantly, this stepwise approach that discovered a new analyte-specific reaction, which affords an analyte-specific indicator, could result in new research avenues in supramolecular analytical chemistry.

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Supporting Information Available. Experimental procedures, structural proofs, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.