DOI: 10.1002/ejoc.201001500

Construction and Properties of a Phototriggered Cd^{2+} Release System

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Keywords: Photochemistry / Cadmium / Sensors / Fluorescence / Synthetic methods

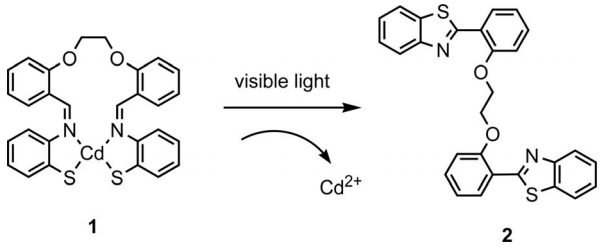
A phototriggered Cd^{2+} release complex has been prepared by using benzothiazoline as a ligand. With visible-light ($\lambda \geq 400$ nm) irradiation, bound Cd^{2+} can be released from the complex, and the ligand is converted into a benzothiazole derivative. Accompanying the process of photoconversion, turn-on fluorescence is observed. The fluorescence intensity increases with photoconversion until Cd^{2+} is completely released, which provides a convenient method to monitor the phototriggered Cd^{2+} release process.

Introduction

The phototriggered release of molecules is not only a powerful mechanistic tool for the characterization of reactive intermediates in chemical synthesis[1] and the activation and transport of small molecules,[2] but it also has practical applications in catalysis and chemotherapy.[3] Currently, the light-activated release of metal ions has attracted considerable interest because some biologically active metals make them an essential cofactor in numerous enzymes that are critical for life.[4] Metal photodelivery may be a valuable tool for the delivery of heavy metal ions to study the mechanisms of metal-ion trafficking and applications, such as chemotherapy, where toxic metal ions could be released to induce cell death by catalyzing DNA and RNA cleavage or by binding active sites of proteins competitively with essential metals.[5]

Cadmium is a toxic metal that inhibits biological function.[6] Cadmium treatment affects transcription of many genes, including those related to oxidative stress response; unfolded protein response; protein synthesis, transport, and degradation; apoptosis; cell cycle; and immune function. It is known that cadmium forms a strong bond with sulfur and can therefore displace essential metal ions such as Zn^{2+} and Ca^{2+} from the binding sites of certain enzymes.[7] Zn, for instance, represents an essential structural and functional component of many proteins, including those involved in DNA and RNA processing;[8] therefore, the competition of Cd with Zn changes enzymatic activities, resulting in cell death, which may provide a new strategy for chemotherapy.

In this paper, we design and prepare a phototriggered Cd release system (Scheme 1) by using benzothiazoline as a ligand. In comparison to other known photorelease systems,[4a,9] the system presented herein has some significant features: (1) It is a visible-light trigger. (2) The release process can be monitored by fluorescence intensity. (3) Photocyclization is observed instead of photocleavage during photochemical reaction of the ligand, in most cases. It was found that in such a system, Cd^{2+} can be efficiently released with a phototrigger.



Scheme 1. Outline of the phototriggered Cd^{2+} release system.

Results and Discussion

Synthesis of Complex 1

Complex **1** was designed and prepared in terms of the report that metal ions induce rearrangements of bisbenzothiazolines to Schiff base chelates.[10] Complex **1** was obtained starting from salicylaldehyde, which reacted with 1,2-dibromoethane in acetonitrile to afford dialdehyde **4** in 80% yield. Condensation of dialdehyde **4** with 2-aminobenzothiol in absolute ethanol produced benzothiazoline **3** in 86% yield. Addition of cadmium acetate in methanol to a solution of **3** in methanol afforded orange crystalline **1** in 96% yield (Scheme 2).

Phototriggered Cd^{2+} Release from Complex 1

Phototriggered Cd^{2+} release was performed with visible-light irradiation. Upon irradiation ($\lambda \geq 400$ nm, irradiation

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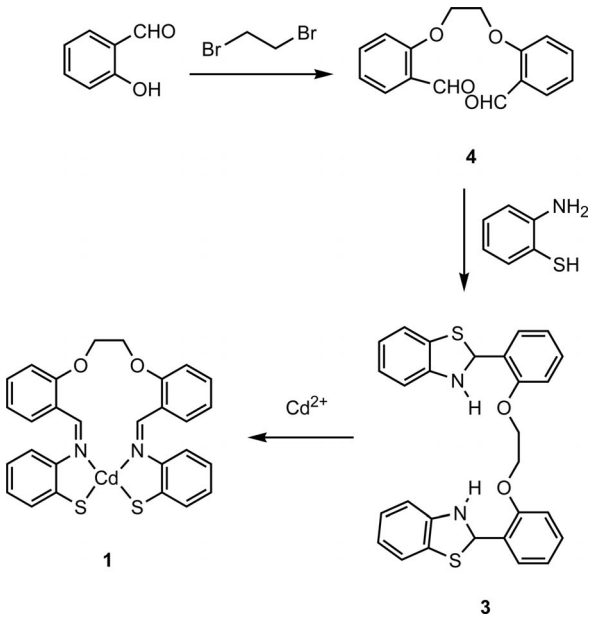


Scheme 2. Synthesis of complex **1**.

power: 0.23 W), the absorption of **1** (λ_{max} = 430 nm, ε = 6.95×10^3 L mol^{-1} cm^{-1} in DMSO) decreased and disappeared with an increase in irradiation time, and accompanying this process, a new band at 322 nm appeared (Figure 1). To elucidate the species that corresponded to the absorption of 322 nm, the product resulting from **1** with visible-light irradiation was isolated and analyzed. Both ^{1}H NMR spectroscopy and HRMS (see the Experimental Section) confirmed that the species corresponding to absorption at 322 nm is 1,2-bis[2-(benzothiazol-2-yl)phenoxy]ethane (**2**; Scheme 1). The result indicated that **1** was converted into **2** upon light irradiation and Cd^{2+} was released during the photoconversion process. As presented in Figure 1, the absorption at 430 nm disappeared completely when the solution of **1** was irradiated for about 240 min (irradiation time for complete Cd^{2+} release could be changed by changing the concentration of the solution or by changing the irradiating power). This suggested that Cd^{2+} was completely released during the conversion of **1** into **2**. This suggestion was also confirmed by TLC: it was found that the spot corresponding to **1** on the TLC plate (R_f = 0.15, petroleum/ethyl acetate = 2:1) disappeared and new spot attributable to **2** appeared (R_f = 0.56, petroleum/ethyl acetate = 2:1) after irradiation for 240 min. Further study found that the conversion of **1** into **2** is efficient and that a high quantum yield (Φ_f = 0.86) was obtained. Moreover, a control experiment also found that **2** was stable in solution and that it could not be converted back into **1** in the presence of Cd^{2+}, which indicates that the photorelease system is not reversible after visible-light irradiation.

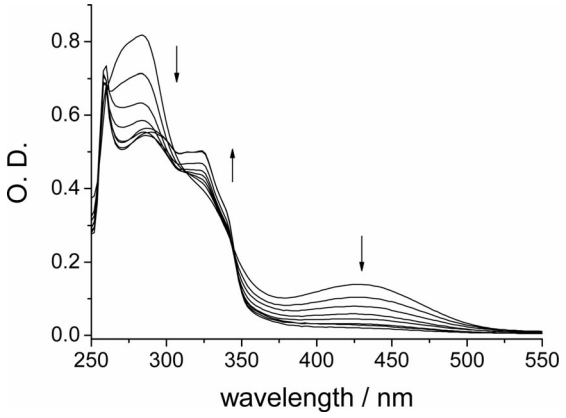


Figure 1. Absorption changes of **1** (20 μM in DMSO) upon visible-light irradiation ($\lambda \geq$ 400 nm, irradiation power = 0.23 W. Periods: 0, 40, 80, 120, 160, 200, 240, and 280 min).

Fluorescence of 2

Turn-on fluorescence was detected during the process of Cd^{2+} photorelease. It was found that weak fluorescence of **1** (λ_{em} = 371 nm, Φ_f = 0.03) was detected in DMSO when using an excitation wavelength of 324 nm; the fluorescence did, however, increase significantly during the conversion of **1** into **2** by the phototrigger. As presented in Figure 2, the fluorescence intensity increased as the irradiation time was increases, and the largest fluorescence intensity was obtained with an irradiation time of 240 min. At that time, the conversion of **1** into **2** was complete.

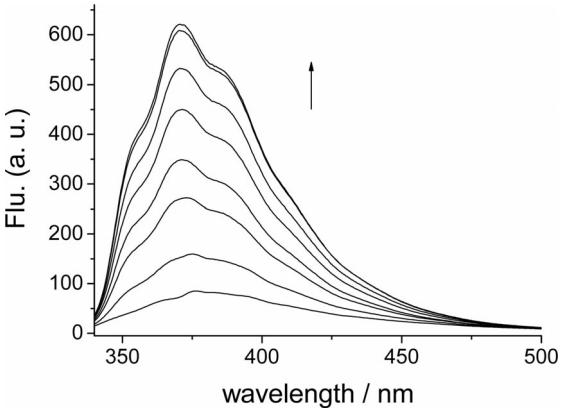


Figure 2. Fluorescence changes of **1** (20 μM, in DMSO) upon visible-light irradiation ($\lambda \geq$ 400 nm, irradiation power: 0.23 W. Periods: 0, 40, 80, 120, 160, 200, 240, and 280 min, λ_{ex} = 324 nm).

To elucidate the fluorescence properties of **2**, pure **2** was prepared and investigated. The absorption and fluorescence spectra of **2** are presented in Figure 3. It was found that the absorption and emission profiles of **2** were similar to those of pure compound **2**, and the absorption (λ_{max} = 322 nm) and emission (λ_{max} = 371 nm) maxima were at the same position (Figures 1 and 2 vs. Figure 3). Strong fluorescence of **2** (λ_{em} = 371 nm) was observed in DMSO with an excitation wavelength of 324 nm, and a large fluorescence quantum yield (Φ_f = 0.87) was obtained. In addition, control experiments showed that benzothiazole **2** is photostable, and no distinct changes in absorption or fluorescence was detected after the solution of **2** was irradiated for 240 min with visible light. Moreover, the absorption spectra and ^{1}H

NMR spectroscopy confirmed that no significant binding between **2** and Cd^{2+} was detected.

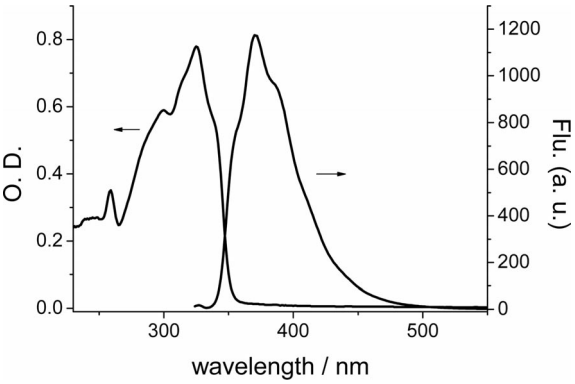


Figure 3. Absorption and fluorescence of pure compound **2** (20 μM in DMSO, λ_{ex} = 324 nm).

Fluorescence Monitoring of Phototriggered Cd^{2+} Release

The kinetics of Cd^{2+} photorelease at different irradiation times were also investigated by monitoring the fluorescence changes of **2**. As presented in Figure 4, the fluorescence intensity of **2** increased as the irradiation time was increased until the photorelease of Cd^{2+} was complete. The correlation between the fluorescence intensity and the irradiation time is excellent before release is complete, which indicates that the amount of Cd^{2+} released could be manipulated by controlling the irradiation time, which is beneficial for drug release in terms of quantity, location, and time.

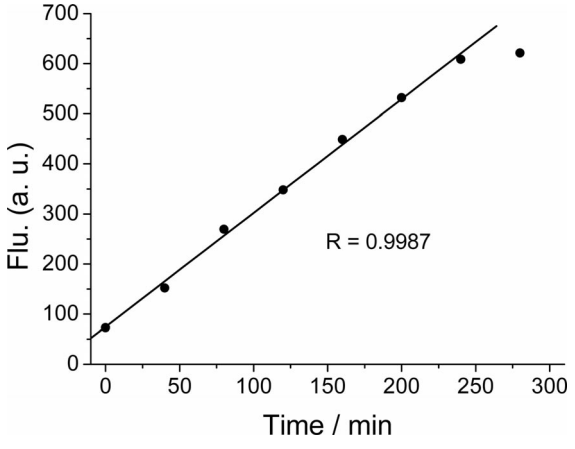


Figure 4. The kinetics of Cd^{2+} photorelease with different irradiation times (monitoring fluorescence intensity of **2** at 371 nm).

Binding Ratio and Binding Constant of the Complex

The binding ratio and the binding constant of complex **1** were determined by titration of ligand **3** with Cd^{2+}. Absorption changes of ligand **3** (20 μM in DMSO) with the addition of Cd^{2+} [$Cd(OCOCH_3)_2$, 0.01 M in H_2O] are presented in Figure 5. Upon addition of Cd^{2+} to a solution of **3** (λ_{max} = 318 nm, $\varepsilon = 1.1 \times 10^4$ L mol^{-1} cm^{-1}) in DMSO, a new band at 430 nm appeared, which corresponded to the absorption of complex **1**. UV/Vis titration experiments for the system Cd^{2+}–**3** showed the formation of a 1:1 ligand–metal species (Figure 5, inset). Monitoring the changes at 430 nm upon Cd^{2+} addition, a large binding constant (log K = 7.24) was obtained by nonlinear least-squares treatment of the titration profile.[11] The large binding constant indicates that the concentration of free Cd^{2+} in the background is very low, which is one of key requirements in practical use.

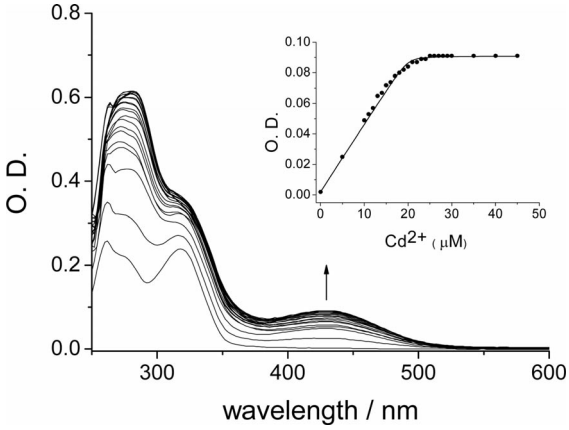
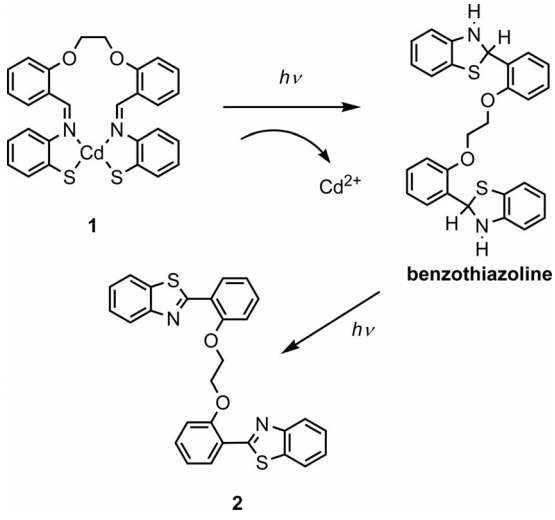


Figure 5. Titration of 20 μM of ligand **3** with $Cd(OCOCH_3)_2$ in DMSO. The inset is the plot of the optical density of **1** (at 430 nm) against the amount of Cd^{2+}.

Possible Mechanism for the Photoreaction

A possible mechanism for the photoreaction consists of a two-step sequence involving the formation of benzothiazoline followed by oxidation and dehydration (Scheme 3).[12] Preliminary investigation found that benzothiazoline formation is a prerequisite to convert a Schiff base into benzothiazole by photon induction. Control experiments showed



Scheme 3. A possible pathway for the conversion of **1** into **2** by phototriggering.

that oxygen in the air played a minor role in the conversion reaction. A similar conversion yield of **2** (ca. 60%) was obtained when the irradiation of **1** was carried out in an air-saturated solution or in degassed solution, although the mechanism for the photoreaction in the absence of oxygen is not known. It is worth noting that complex **1** is stable at ambient temperature and no significant change (detection by absorption spectral) was detected when a solution of **1** was kept in the dark, which indicates that the conversion of **1** into **2** did not occur in the absence of light.

This study represents a platform for the development of controlled photorelease systems with fluorescence monitoring. Although the system presented herein has some shortcomings at present, including the inability to be performed in aqueous solution and the fact that both irradiation and excitation occur in the short wavelength region, the system has advantages that include controlled photorelease and turn-on fluorescence monitoring. A controlled photorelease system is a great benefit to drug delivery in terms of quantity, location, and time, which is a key goal for drug delivery science, as improved control maximizes therapeutic effect while minimizing side effects.[13] In addition, preliminary studies show that the system is not only suitable for Cd^{2+} release, but also for the release of other metal ions such as Zn^{2+} and Hg^{2+}. From a practical viewpoint, it is desirable for the system to be used in buffer solution with visible-light ($\lambda \geq 650$ nm) irradiation and excitation. Modifying molecular structure to meet the requirements, and exploring the applications in biological processing will be the subject of future studies.

Conclusions

In summary, a simple and efficient system for phototriggered Cd^{2+} release has been developed. It was demonstrated that Cd^{2+} can be released completely from metal–ligand complex **1** with a phototrigger. The system presented herein has some advantages including facile preparation, stable complex, turn-on fluorescence monitoring, and controlled photorelease.

Experimental Section

General Information: ^{1}H NMR spectra were recorded at 400 MHz with TMS as an internal reference and [D_6]DMSO as the solvent. HRMS spectra were recorded with a GC-TOF MS spectrometer. UV absorption spectra and fluorescence spectra were measured with an absorption spectrophotometer (Hitachi U-3010) and a fluorescence spectrophotometer (F-2500), respectively. All chemicals for synthesis were purchased from commercial suppliers, and solvents were purified according to standard procedures. Reactions were monitored by TLC silica gel plate (60F-254). Column chromatography was performed on silica gel (Merck, 70–230 mesh). A xenon lamp (500 W) with wavelength filter was used as light sources for photorelease (irradiation power: 0.23 W).

Synthesis of Ligand 3 and Complex 1: Compounds **3** and **1** were prepared according to literature procedures,[10,14] and the detailed procedures are as follows: (a) To a solution of salicylaldehyde (6.1 g, 50 mmol) and 1,2-dibromoethane (4.7 g, 25 mmol) in acetonitrile (150 mL) was added potassium carbonate (6.9 g, 50 mmol) and potassium iodide (0.4 g, 2.5 mmol). The mixture was heated at reflux. When no starting material (salicylaldehyde) was detectable by TLC, the solution was concentrated and the crude product was added to water (100 mL). The solution mixture was extracted with dichloromethane (3 × 50 mL). The combined organic solution was dried with Na_2SO_4, the resulting solution was concentrated, and the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate, 2:1) to afford dialdehyde **4** (5.4 g) in 80% yield. (b) A solution of **4** (0.54 g, 2 mmol) in absolute ethanol (20 mL) was heated until **4** was dissolved completely, and the solution was then cooled to ambient temperature. To the solution was added a solution of 2-aminobenzothiol (0.5 g, 4 mmol) in absolute ethanol (10 mL), and the solution mixture was stirred at ambient temperature until **4** was no longer detectable by TLC. A small amount of deionized water (0.5 mL) was added slowly to the solution, and the solid was separated out. The crude product was washed with ethanol (3 × 10 mL) and water (10 mL) to afford target compound **3** (0.83 g) without further purification. Yield: 86%. M.p. 121–122 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.45 (d, J = 7.6 Hz, 2 H, ArH), 7.29 (t, J = 7.4 Hz, 2 H, ArH), 7.11 (d, J = 8.1 Hz, 2 H, ArH), 6.95 (t, J = 7.5 Hz, 2 H, ArH), 6.93–6.82 (m, 4 H, ArH), 6.80 (s, 2 H, ArH), 6.70–6.62 (m, 2 H, NH), 6.61–6.50 (m, 4 H, ArH), 4.41 (d, J = 3.1 Hz, 4 H, CH_2) ppm. HRMS (TOF, EI): calcd for $C_{28}H_{24}N_2O_2S_2$ [M]$^+$ 484.1279; found 484.1254. (c) To a boiling solution of **3** (484 mg, 1.0 mmol) in methanol (150 mL) was added dropwise a solution of cadmium acetate dihydrate (267 mg, 1.0 mmol) in methanol (10 mL). The mixture was heated at reflux for 15 min and then cooled down to ambient temperature. The orange crystalline solid was filtered off, washed with methanol (3 × 10 mL), and pure **1** (0.57 g) was obtained after drying under vacuum without further purification. Yield: 96%. M.p. >300 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.76 (s, 2 H, CH=N), 7.92–7.74 (m, 2 H, ArH), 7.52 (t, J = 7.8 Hz, 2 H, ArH), 7.28 (t, J = 7.8 Hz, 4 H, ArH), 7.22 (dd, J = 7.5, 1.7 Hz, 2 H, ArH), 7.10 (t, J = 7.5 Hz, 2 H, ArH), 6.87 (ddt, J = 9.0, 7.3, 3.8 Hz, 4 H, ArH), 4.62 (s, 4 H, CH_2) ppm. HRMS (TOF, EI): calcd. for $C_{28}H_{22}CdN_2O_2S_2$ [M – 1]$^+$ 595.0156; found 595.0393.

Preparation of Benzothiazole Derivative 2: A solution of **1** (100 mg) dissolved in DMSO (100 mL) was irradiated with a xenon lamp (500 W) until no starting material was detected by TLC. The mixture was concentrated, and the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate, 2:1) to afford **2**. M.p. 213–215 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, J = 8.1 Hz, 2 H, ArH), 8.03 (d, J = 8.1 Hz, 2 H, ArH), 7.73 (d, J = 7.7 Hz, 2 H, ArH), 7.48 (dt, J = 7.3, 1.8 Hz, 2 H, ArH), 7.41 (dt, J = 7.1, 1.1 Hz, 2 H, ArH), 7.31 (dt, J = 7.1, 0.9 Hz, 2 H, ArH), 7.21–7.17 (m, 4 H, ArH), 4.80 (s, 4 H, CH_2) ppm. HRMS (TOF, EI): calcd. for $C_{28}H_{20}N_2O_2S_2$ [M]$^+$ 480.0966; found 480.0991.

Acknowledgments

This work was supported by the National Nature Science Foundation of China (No. 21073214).

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Received: November 9, 2010
Published Online: January 20, 2011

