

Cu²⁺- and Hg²⁺-Selective Chemosensing by Dioxocyclams Having Two Appended Pyrenylacetamides

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Two new chemosensors **1** and **2** derived from 5,12- and 5,7-dioxocyclams were prepared and their signaling behaviors toward transition metal ions were investigated. Chemosensors **1** and **2** showed very efficient responses toward Cu²⁺ and Hg²⁺ ions. Ratiometric analysis of the fluorescence changes in pyrene monomer and excimer emissions clearly demonstrated the Cu²⁺- and Hg²⁺-selective signaling behavior. The signaling mechanism of the chemosensors is due to conformation changes upon complexation with metal ions and the inherent quenching nature of the complexed Cu²⁺ and Hg²⁺ ions themselves.

Key Words: Dioxocyclams, Chemosensing, Pyrene, Cu²⁺ selectivity, Hg²⁺ selectivity

Introduction

The selective detection of transition and heavy metal ions is very important in various fields of chemical and biological science as well as in the protection of our environment.¹ Cu²⁺ is an important transition metal ion that not only plays an important role in various biological processes in the human body,² but also exerts toxic impacts on our environment.³ There are many sophisticated systems for the efficient and selective determination⁴ and visualization of Cu²⁺ ions.⁵ Even so, a great deal of effort continues to focus on the construction of devices that are able to signal the presence of transition and heavy metal ions from various sources.⁶

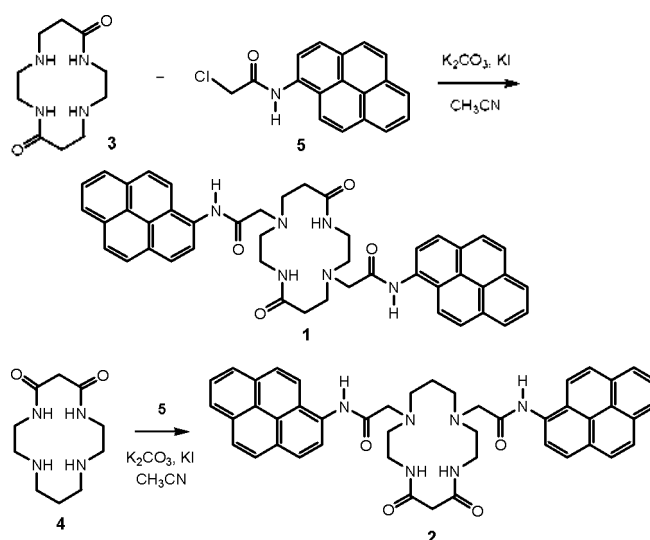
Cyclams and cyclens are attractive molecular frameworks for the development of transition metal ion selective chemosensors, medicines, and supramolecular systems with unique functions.⁷ Dioxocyclams, which have two amine and two amide functions in a cyclic framework, have also attracted considerable interest. They have been used to act as chemosensors for the recognition of Cu²⁺ and Hg²⁺ ions⁸ and to construct supramolecular systems containing Ni²⁺ and Cu²⁺.^{9,10} Among the two common dioxocyclams, 5,12-dioxocyclam has been relatively unexploited compared with its 5,7-analogue¹¹ in spite of its attractive structural characteristics suitable for the construction of supramolecular systems containing transition metal ions.¹²⁻¹⁴ Hegedus *et al.* reported that mono- and bis-5,12-dioxocyclams having pyridine caps and their Cu²⁺ complexes, and various other 5,12-dioxocyclam derivatives were potential ligands for Gd³⁺ ions and DNA bis-intercalating and cleaving agents.¹⁵ In this paper, we present new chemosensor systems that are derived from 5,7- and 5,12-dioxocyclams for the signaling of transition metal ions. Compounds **1** and **2** exhibited a pronounced selective fluorescent chemosensing behavior toward Cu²⁺ and Hg²⁺ ions, which could be readily analyzed by ratiometry using changes in monomer and excimer emissions of pyrene fluorophore.

Results and Discussion

Compounds **1** and **2** were prepared by the reaction of 5,12-dioxocyclam **3** and 5,7-dioxocyclam **4** with 2-chloro-*N*-pyren-1-yl-acetamide **5** (K₂CO₃, KI, CH₃CN). The resulting yields were 72% and 81%, respectively. The structure of compounds **1** and **2** differed in the position of the two oxo moieties and the two appended pyrenes in the dioxocyclam backbone, thus yielding so-called *trans*- and *cis*-isomers, respectively.

UV-vis spectra of **1** and **2** in acetate buffer, pH 4.8/DMSO solution (1:1, v/v), revealed intense absorption bands near 345 nm, which is characteristic of pyrene moiety. No significant changes in absorbance or absorption maximums were observed upon interaction with representative alkali (Na⁺, K⁺), alkaline earth (Mg²⁺, Ca²⁺), and transition metal ions (Fe²⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺, Ag⁺, Cd²⁺, Hg²⁺, Pb²⁺).

The fluorescence spectrum of compound **1** in 50% aqueous



Scheme 1. Synthesis of pyrene appended dioxocyclam chemosensors.

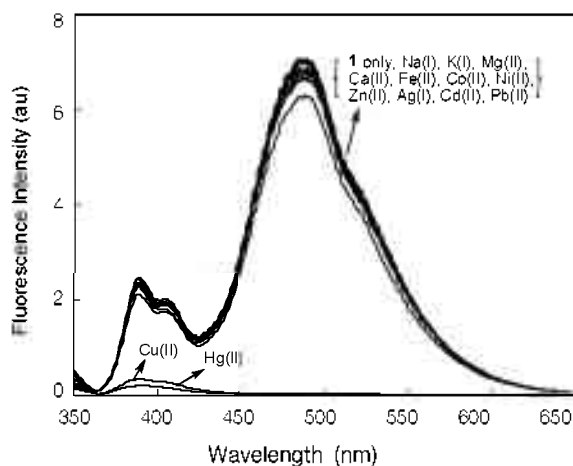


Figure 1. Fluorescence spectra of **1** in the presence of various metal ions in 50% aqueous DMSO. [**1**] = 5.0×10^{-6} M, [M^{n+}] = 5.0×10^{-4} M, pH = 4.8 acetate buffer (10 mM), λ_{ex} = 340 nm. The pH value refers to the acetate buffer solution before mixing with DMSO.

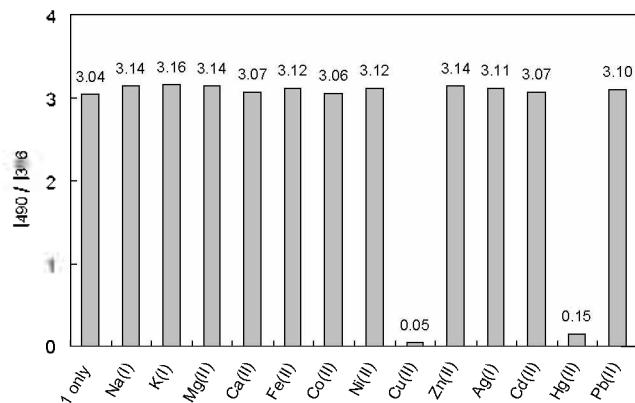


Figure 2. Ratiometric analysis of fluorescence intensity ratio (I_{490}/I_{386}) of **1** in the presence of various metal ions. In 50% aqueous DMSO, [**1**] = 5.0×10^{-6} M, [M^{n+}] = 5.0×10^{-4} M, pH = 4.8 acetate buffer (10 mM), λ_{ex} = 340 nm.

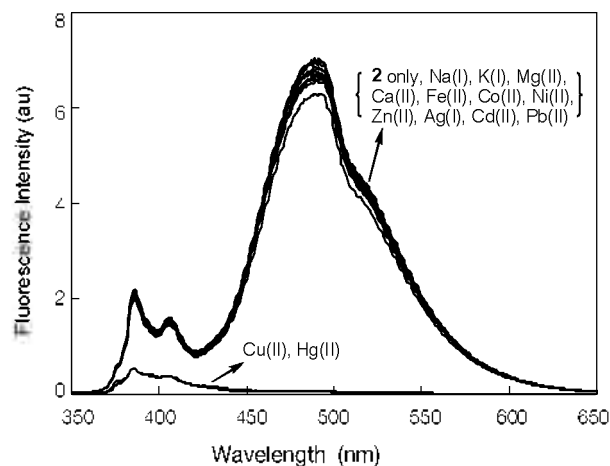


Figure 3. Fluorescence spectra of **2** in the presence of various metal ions in 50% aqueous DMSO. [**2**] = 5.0×10^{-6} M, [M^{n+}] = 5.0×10^{-4} M, pH = 4.8 acetate buffer (10 mM), λ_{ex} = 340 nm.

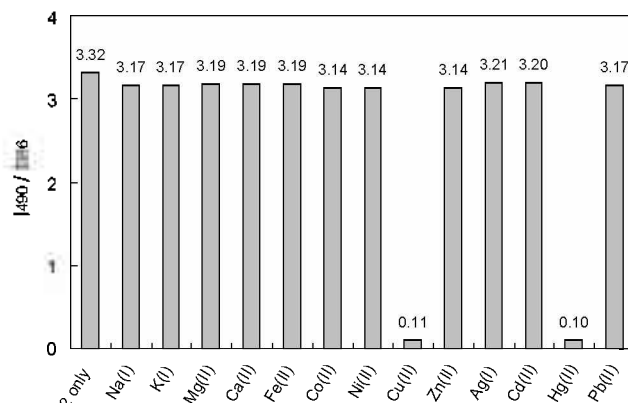


Figure 4. Ratiometric analysis of fluorescence intensity ratio (I_{490}/I_{386}) of **2** in the presence of various metal ions. In 50% aqueous DMSO, [**2**] = 5.0×10^{-6} M, [M^{n+}] = 5.0×10^{-4} M, pH = 4.8 acetate buffer (10 mM), λ_{ex} = 340 nm.

DMSO solution was characterized by a strong emission band at 490 nm along with moderate intensity bands at 386 nm and 404 nm. These strong and moderate intensity bands are attributed to the excimer and monomer emissions of pyrene, respectively.¹⁶ Compound **1** revealed a strong excimer emission in acetate buffer, pH 4.8/DMSO solution (1:1, v/v), which means that the two pyrene fluorophores of **1** were situated close enough to interact efficiently and yield strong excimer.

The influence of various metal ions on the fluorescence spectrum of compound **1** was determined. Highly efficient fluorescence quenching effects were obtained with Cu^{2+} and Hg^{2+} ions (Figure 1). The changes were particularly pronounced in excimer emissions at 490 nm. The quenching efficiency of metal ions on excimer at 490 nm was expressed as $[I/I_0]_{490}$, which is the ratio of fluorescence intensity in the presence (I) and absence (I_0) of metal ions. The $[I/I_0]_{490}$ values for Cu^{2+} and Hg^{2+} ions were 2.4×10^{-3} and 4.2×10^{-3} , respectively; yet the values for the other metal ions ranged between 0.89 and 1.0. The monomer emission at 386 nm was

also significantly affected by Cu^{2+} and Hg^{2+} ions. $[I/I_0]_{386}$ values varied between 0.86 for Zn^{2+} and 0.99 for Ca^{2+} , with the exception of 0.14 for Cu^{2+} and 0.09 for Hg^{2+} .

The pronounced changes in fluorescence intensity induced by Cu^{2+} and Hg^{2+} ions were visualized more easily by ratiometric analysis using the fluorescence intensity ratio of excimer and monomer emissions at 490 nm and 386 nm, I_{490}/I_{386} (Figure 2). The I_{490}/I_{386} ratio was very small for Cu^{2+} (0.05) and Hg^{2+} (0.15) ions, yet the other metal ions revealed relatively constant values between 3.04 and 3.16.

The chemosensing properties of *cis*-isomer **2** were also investigated by fluorescence measurements and found to be quite similar to those of *trans*-isomer **1**. The changes in fluorescence of compound **2** were prominent in the presence of Cu^{2+} and Hg^{2+} ions (Figure 3), and the profile of the variations in excimer and monomer emissions was almost identical to compound **1**. The fluorescence intensity ratio of monomer and excimer emissions, I_{490}/I_{386} , was very small for Cu^{2+} (0.11) and Hg^{2+} (0.10) ions (Figure 4); yet the other metal

ions revealed relatively constant changes, having a ratio between 3.14 and 3.32.

The signaling mechanism of the chemosensors is due to conformation changes upon complexation with metal ions and the inherent quenching nature of the complexed Cu²⁺ and Hg²⁺ ions themselves. As can be understood from the fluorescence spectra of Figures 1 and 3, compounds **1** and **2** in free state existed in conformations where two pyrene moieties situated close enough neighbor to yield strong excimer. However, when the guest ions complex with the carboxamide function as well as dioxocyclam moiety of **1** or **2**, the two pyrene moieties move away from each other. This is like a butterfly spreading its wings and subsequently the excimer emissions of pyrene do not occur.¹⁷ At the same time the quenching nature of the complexed Cu²⁺ and Hg²⁺ ions also significantly reduce the monomer emissions of pyrene.¹³

Confirmation of selective interaction of **1** with Cu²⁺ or Hg²⁺ ions was attempted by NMR, IR, and MALDI mass spectrometry measurements. The ¹H NMR spectrum of **1** in the presence of Cu(OAc)₂ or Hg(OAc)₂ was considerably broadened and provided no valuable information. However, the IR spectra of **1** was influenced by Cu(ClO₄)₂, as indicated by the significant shift of the stretching band of the carbonyl group from 1650 to 1621 cm⁻¹. MALDI mass measurements provided additional evidences for the complex formation by revealing an intense peak for [1+Cu]⁺ at *m/z* = 805.26 and [2+Cu]⁺ at *m/z* = 805.22.

Fluorescence titration of **1** with Cu²⁺ ions afforded a smooth titration curve (Figure 5). The stoichiometry of the **1**-Cu²⁺ complex was estimated by a Job's plot and found to be 1:1. The concentration dependent changes were analyzed by a nonlinear curve fitting procedure,¹⁵ and the association constant *K*_{assoc} for the **1**-Cu²⁺ system was found to be larger than 10⁷ M⁻¹. On the other hand, titration of **1** with Hg²⁺ ions resulted in a less clear titration break and the *K*_{assoc} value was found to be 2.0 × 10⁵ M⁻¹. From these concentration dependent changes, detection limits for Cu²⁺ and Hg²⁺ ions were determined to be 1.34 × 10⁻⁶ M and 4.76 × 10⁻⁶ M, respectively.²⁰ Similarly, the *cis*-isomer **2** also formed a 1:1 complex with Cu²⁺ ions, the *K*_{assoc} value for the **2**-Cu²⁺ system was larger than 10⁷ M⁻¹, and the detection limit for the determination of Cu²⁺ ions was 1.14 × 10⁻⁶ M.

To gain insight into the practical application of **1** in Cu²⁺ and Hg²⁺ analysis, cross-selectivity over other common metal ions was evaluated. The fluorescence changes of **1** induced by 10 equiv of Cu²⁺ or Hg²⁺ ions were measured in the presence of 100 equiv potential interfering metal ions. Interference by the coexisting metal ions was expressed by the changes in the fluorescence intensity ratio of excimer emissions at 490 nm and monomer emissions at 386 nm, *I*₄₉₀/*I*₃₈₆. For Cu²⁺ ions, the interference from other metal ions was insignificant. The ratio *I*₄₉₀/*I*₃₈₆ decreased from 3.04 and varied in a narrow range between 0.08 (Co²⁺) and 0.21 (Fe²⁺) (Figure 6). For Hg²⁺ ions, the values also decreased from 2.31 and ranged between 0.13 (Cu²⁺) and 0.4 (Pb²⁺). *cis*-Isomer **2** also revealed similar selective responses in the presence of common coexisting metal ions. For Cu²⁺ ions, the ratio *I*₄₉₀/*I*₃₈₆ decreased from 4.26 and varied in a narrow range between 0.12 (Ni²⁺) and

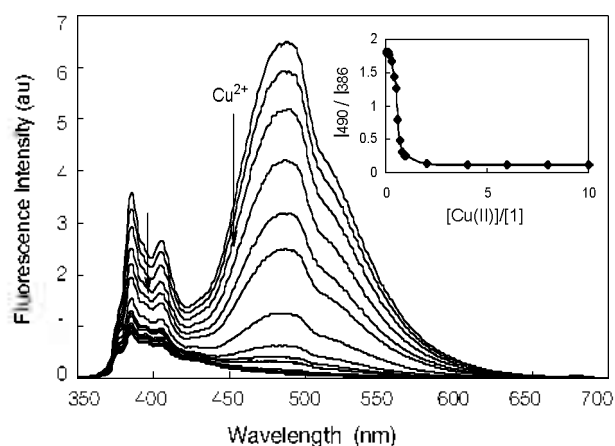


Figure 5. Titration of chemosensor **1** with Cu²⁺ ions. Inset shows the changes in fluorescence intensity ratio (*I*₄₉₀/*I*₃₈₆). In 50% aqueous DMSO, [1] = 1.0 × 10⁻⁵ M, pH = 4.8 acetate buffer (10 mM), λ_{ex} = 340 nm.

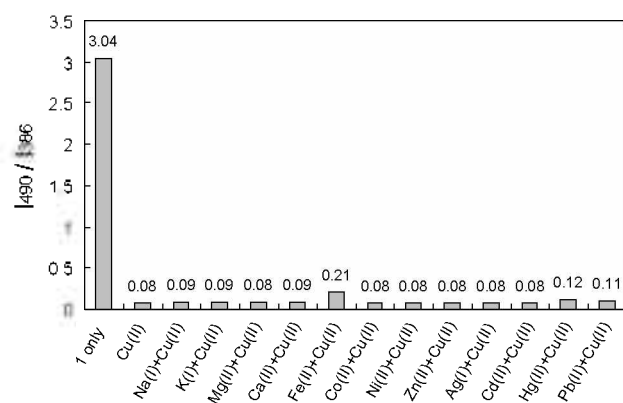


Figure 6. Cross-selectivity of **1**-Cu(II) system with various metal ions. In 50% aqueous DMSO, [1] = 5.0 × 10⁻⁶ M, [Cu²⁺] = 5.0 × 10⁻⁵ M, [Mⁿ⁺] = 5.0 × 10⁻⁴ M, pH = 4.8 acetate buffer (10 mM), λ_{ex} = 340 nm.

0.20 (Fe²⁺). These observations revealed that the compounds **1** and **2** could selectively signal Cu²⁺ and Hg²⁺ ions in the presence of common coexisting metal ions.

In conclusion, we prepared simple chemosensor systems for the signaling of Cu²⁺ and Hg²⁺ ions by combining two isomeric dioxocyclams with pyrenylacetamide moieties. The prepared compounds exhibited selective responses towards Cu²⁺ and Hg²⁺ ions. The signaling is due to the conversion between the conformations exhibiting monomer and excimer emissions by the two pyrene moieties. Fluorescence changes of the chemosensors were readily analyzed ratiometrically to selectively signal the Cu²⁺ ions in micromolar or Hg²⁺ ions in submillimolar concentration ranges.

Experimental Section

General. 1-Aminopyrene, 1,4,8,11-tetraazacyclotetradecane-5,7-dione (5,7-dioxocyclam) and 1,4,8,11-tetraazacyclotetradecane-5,12-dione (5,12-dioxocyclam) were purchased from Aldrich Chemical Co. and Chematech and used without further purification. Flash chromatography was performed with silica gel (particle size 0.040 – 0.062 mm). IR spectra

were obtained using a FT-IR spectrophotometer. UV-vis spectra were recorded with a Jasco V-550 spectrophotometer. Fluorescence spectra were measured on an Aminco-Bowman Series 2 Spectrophotometer. All solvents used for the measurements of UV-vis and fluorescence spectra were obtained from Aldrich Chemical Co. as 'spectroscopic grade'. ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz) were recorded on a Varian VNS spectrometer. Chemical shifts are reported relative to residual peaks of DMSO- d_6 for ^1H NMR and ^{13}C NMR spectra. Mass spectral data were obtained with a MALDI spectrometer. 2-Chloro-*N*-pyren-1-ylacetamide **5** was prepared by the reaction of 1-aminopyrene with chloroacetyl chloride following the reported procedure.²¹

Preparation of 1. A mixture of 5,12-dioxocyclam (50 mg, 0.19 mmol) and 2-chloro-*N*-pyren-1-yl-acetamide (117 mg, 0.4 mmol) was heated under reflux in the presence of K_2CO_3 (78 mg, 0.56 mmol) and KI (66 mg, 0.4 mmol) in acetonitrile (7 mL). After 24 h, the precipitate formed was filtered and washed with acetonitrile and water. The product was purified by precipitation from aqueous DMSO solution. Yield: 72%. ^1H NMR (DMSO- d_6 , 600 MHz) δ 10.01 (s, 2H), 8.20-8.02 (m, 18H), 3.52 (s, 4H), 3.05 (s, 4H), 2.87 (s, 4H), 2.75 (s, 4H), 2.40 (s, 4H); ^{13}C NMR (DMSO- d_6 , 150 MHz) δ 171.8, 170.6, 132.0, 131.3, 131.0, 129.0, 127.5, 127.3, 127.0, 126.6, 125.5, 125.3, 125.2, 124.9, 124.4, 124.1, 122.9, 57.3, 53.2, 51.5, 36.8, 34.0; HR-MS (FAB, *m*-NBA) found 743.3351, calcd for $\text{C}_{46}\text{H}_{43}\text{N}_6\text{O}_4$ 743.3346.

Preparation of 2. Compound **2** was prepared from 5,7-dioxocyclam following the same procedure as for **1**. Yield: 81%. ^1H NMR (DMSO- d_6 , 600 MHz) δ 10.19 (s, 2H), 8.33-8.01 (m, 18H), 3.51 (s, 4H), 3.40 (s, 4H), 3.13 (s, 2H), 2.77 (d, 8H), 1.85 (s, 2H); ^{13}C NMR (DMSO- d_6 , 150 MHz) δ 171.0, 167.3, 132.0, 131.2, 130.8, 128.8, 127.6, 127.0, 126.7, 125.6, 125.3, 124.7, 124.6, 124.2, 123.8, 122.8, 59.8, 54.4, 53.8, 45.6, 38.6, 27.0; HR-MS (FAB, *m*-NBA) found 743.3353, calcd for 743.3346.

References

- (a) de Silva, A. P.; Gunaratne, H. Q. N.; Gunlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515. (b) Nolan, E. M.; Lippard, S. J. *Chem. Rev.* **2008**, *108*, 3443.
- (a) Rurack, K. *Spectrochim. Acta Part A* **2001**, *57*, 2161. (b) Xie, J.; Ménand, M.; Maisonneuve, S.; Métivier, R. *J. Org. Chem.* **2007**, *72*, 5980.
- (a) Krämer, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 772. (b) Corami, F.; Capodaglio, G.; Turetta, C.; Bragadin, M.; Calace, N.; Petronio, B. M. *Ann. Chim-Rome* **2007**, *97*, 25.
- (a) Dujols, V.; Ford, F.; Czarnik, A. W. *J. Am. Chem. Soc.* **1997**, *119*, 7386. (b) Torrado, A.; Walkup, G. K.; Imperiali, B. *J. Am. Chem. Soc.* **1998**, *120*, 609. (c) Zheng, Y.; Huo, Q.; Kele, P.; Andreopoulos, F. M.; Pham, S. M.; Leblanc, R. M. *Org. Lett.* **2001**, *3*, 3277. (d) Martinez, R.; Espinosa, A.; Tarraga, A.; Molina, P. *Org. Lett.* **2005**, *7*, 5869. (e) Royzen, M.; Dai, Z.; Canary, J. W. *J. Am. Chem. Soc.* **2005**, *127*, 1612. (f) Xiang, Y.; Tong, A.; Jin, P.; Ju, Y. *Org. Lett.* **2006**, *8*, 2863. (g) Qi, X.; Jun, E. J.; Xu, L.; Kim, S.-J.; Hong, J. S.; Yoon, Y. J.; Yoon, J. *J. Org. Chem.* **2006**, *71*, 2881. (h) Martinez, R.; Zapata, F.; Caballero, A.; Espinosa, A.; Tarraga, A.; Molina, P. *Org. Lett.* **2006**, *8*, 3235. (i) Liu, J.; Lu, Y. *J. Am. Chem. Soc.* **2007**, *129*, 9838.
- (a) Zeng, L.; Miller, E. W.; Fralle, A.; Isacoff, E. Y.; Chang, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 10. (b) Que, E. L.; Chang, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 15942. (c) Swamy, K. M. K.; Ko, S.-K.; Kwon, S. K.; Lee, H. N.; Mao, C.; Kim, J.-M.; Lee, K.-H.; Kim, J.; Shin, I.; Yoon, J. *Chem. Commun.* **2008**, 5915. (d) Jung, H. S.; Kwon, P. S.; Lee, J. W.; Kim, J. I.; Hong, C. S.; Kim, J. W.; Yan, S.; Lee, J. Y.; Lee, J. H.; Joo, T.; Kim, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 2008.
- Que, E. L.; Domaille, D. W.; Chang, C. J. *Chem. Rev.* **2008**, *108*, 1517.
- (a) Kimura, E. *Tetrahedron* **1992**, *48*, 6175. (b) Liang, X.; Sadler, P. J. *Chem. Soc. Rev.* **2004**, *33*, 246. (c) Bergamini, G.; Ceroni, P.; Balzani, V.; Cornelissen, L.; van Heyst, J. *J. Mater. Chem.* **2005**, *15*, 2959.
- (a) Mu, H.; Gong, R.; Ma, Q.; Sun, Y.; Fu, E. *Tetrahedron Lett.* **2007**, *48*, 5525. (b) Song, K. C.; Kim, M. H.; Kim, H. J.; Chang, S.-K. *Tetrahedron Lett.* **2007**, *48*, 7464.
- (a) Xian, H. B.; Xi, C. C.; Zhi, H. Z.; Zhi, A. Z.; Yun, T. C.; Shionoya, M.; Kimura, E. *Polyhedron* **1996**, *15*, 1203. (b) Bu, X. H.; Zhang, Z. H.; Cao, X. C.; Zhu, Z. A.; Chen, Y. T. *Transit. Metal Chem.* **1997**, *22*, 1. (c) Kimura, E.; Sasada, M.; Shionoya, M.; Koike, T.; Kurosaki, H.; Shiro, M. *J. Biol. Inorg. Chem.* **1997**, *2*, 74. (d) Chin, M.; Wone, D.; Nguyen, Q.; Nathan, L. C.; Wagenknecht, P. S. *Inorg. Chim. Acta* **1999**, *292*, 254. (e) Boyd, S.; Cabral, N. M.; Ghiggino, K. P.; Grannas, M. J.; McFadyen, W. D.; Tregloan, P. A. *Aust. J. Chem.* **2000**, *53*, 651. (f) Haines, R. I.; Baldwin, R. *Transit. Metal Chem.* **2002**, *27*, 284.
- (a) Xian, H. B.; Zhi, H. Z.; Dao, L. A. *Inorg. Chim. Acta* **1996**, *249*, 125. (b) Bu, X. H.; An, D. L.; Cao, X. C.; Zhang, R. H.; Clifford, T.; Kimura, E. *J. Chem. Soc. Dalton Trans.* **1998**, 2247. (c) Meyer, M.; Frémond, L. *Inorg. Chem.* **2004**, *43*, 5572. (d) Gasmier, A.; Barbe, J.-M.; Bucher, C.; Denat, F.; Moutet, J.-C. *Inorg. Chem.* **2008**, *47*, 1862.
- Mashuta, M. S.; Pimenov, K. V.; Grapperhaus, C. A. *Acta Crystallogr. C* **2002**, *58*, 226.
- (a) Hubin, T. J.; Tyryshkin, N.; Alcock, N. W.; Busch, D. H. *Acta Crystallogr. C* **2001**, *57*, 359. (b) Gavrish, S. P.; Lampeka, Y. D.; Lightfoot, P. *Inorg. Chim. Acta* **2004**, *357*, 1023.
- Meyer, M.; Frémond, L.; Tabard, A.; Espinosa, E.; Vollmer, G. Y.; Guillard, R.; Dory, Y. *New J. Chem.* **2005**, *29*, 99.
- (a) Comte, C.; Gros, C. P.; Guillard, R.; Khoury, R. G.; Smith, K. M. *J. Porphyr. Phthalocya.* **1998**, *2*, 377. (b) Kadish, K. M.; Shao, J.; Ou, Z.; Comte, C.; Gros, C. P.; Guillard, R. *J. Porphyr. Phthalocya.* **2000**, *4*, 639.
- (a) Wynn, T.; Hegedus, L. S. *J. Am. Chem. Soc.* **2000**, *122*, 5034. (b) Hegedus, L. S.; Greenberg, M. M.; Wendling, J. J.; Bullock, J. P. *J. Org. Chem.* **2003**, *68*, 4179. (c) Achmatowicz, M.; Hegedus, L. S.; David, S. *J. Org. Chem.* **2003**, *68*, 7661. (d) Todd, A.; Brugel, T. A.; Hegedus, L. S. *J. Org. Chem.* **2003**, *68*, 8409.
- (a) Winnik, F. M. *Chem. Rev.* **1993**, *93*, 587. (b) Kim, J. S.; Noh, K. H.; Lee, S. H.; Kim, S. K.; Kim, S. K.; Yoon, J. *J. Org. Chem.* **2003**, *68*, 597.
- Moon, S.-Y.; Youn, N. J.; Park, S. M.; Chang, S.-K. *J. Org. Chem.* **2005**, *70*, 2394.
- Rurack, K.; Kollmannsberger, M.; Resch-Genger, U.; Daub, J. *J. Am. Chem. Soc.* **2000**, *122*, 968.
- Kuzmic, P. *Anal. Biochem.* **1996**, *237*, 260.
- Shortreed, M.; Kopelman, R.; Kuhn, M.; Hoyland, B. *Anal. Chem.* **1996**, *68*, 1414.
- Kim, J. H.; Hwang, A.-R.; Chang, S.-K. *Tetrahedron Lett.* **2004**, *45*, 7557.