



## Characterization of 5-chloro-8-methoxyquinoline appended diaza-18-crown-6 as a chemosensor for cadmium

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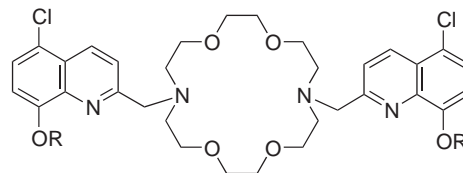
**Abstract**—5-Chloro-8-methoxyquinoline appended diaza-18-crown-6 (**1**) selectively responds to Cd<sup>2+</sup> over other tested metal ions via a large increase in fluorescence. In addition, **1** selectively binds Cd<sup>2+</sup> over Zn<sup>2+</sup>. Compound **1** may be useful in measuring Cd<sup>2+</sup> concentrations in waste effluent streams and in food products. © 2001 Elsevier Science Ltd. All rights reserved.

Cadmium is widely dispersed in the environment; nevertheless due to human activity levels of cadmium have increased dramatically in many areas.<sup>1</sup> Increased levels of cadmium are a result of mining, smelting, fossil fuel combustion and industrial use. Furthermore, cadmium is found in phosphate fertilizers and is concentrated in sewage sludge,<sup>2</sup> which is often used as a fertilizer. These sources lead to dietary cadmium exposure, and in certain areas there is evidence of increasing cadmium content in food.<sup>3</sup> Biological effects of chronic cadmium exposure include renal dysfunction, calcium metabolism disorders and an increased incidence of certain forms of cancer.<sup>2</sup> Due to the adverse biological effects of cadmium, and because cadmium is accumulated in tissues, there is a need for improved methods for the detection and monitoring of cadmium levels in environmental samples, industrial waste effluent and tissue samples.

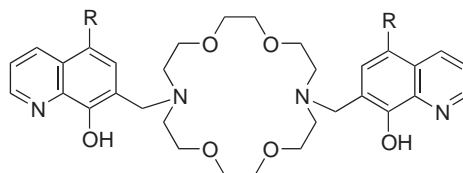
We have developed compounds capable of selectively responding, via an increase in fluorescence, to several specific metal ions. Our efforts have resulted in the identification and characterization of compound **1**<sup>4</sup> as an effective fluorescent chemosensor for cadmium, as described in the present paper. Compound **1** is related to **3** and **4**, which are chemosensors for Mg<sup>2+</sup> and Hg<sup>2+</sup>, respectively, that were developed in our laboratories.<sup>5,6</sup> However, in **1** the quinolines are attached at C-2 rather than at C-7 as in **3** and **4**; the attachment site of quinolines to macrocyclic ligands greatly influences

metal ion affinities of the ligands.<sup>4</sup> As a chemosensor, **1** selectively binds and selectively responds to Cd<sup>2+</sup> and may find application in monitoring Cd<sup>2+</sup> levels in waste effluent streams and in food products.

Other compounds have been reported that respond to Cd<sup>2+</sup> via increases in fluorescence.<sup>7</sup> However, these compounds generally do not display significant selectivity for Cd<sup>2+</sup> over other related transition metal ions. One notable exception is an anthrylazamacrocycle reported by Czarnik and co-workers which responds selectively to Cd<sup>2+</sup> via electrophilic aromatic cadmiation.<sup>7a</sup> Selective ion responses can originate through selective association with the target analyte and/or selective response to the target analyte. The compound



**1** R = -CH<sub>3</sub>  
**2** R = -H



**3** R = -Cl  
**4** R = -NO<sub>2</sub>

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**Table 1.** Photophysical properties of **1** and its complexes with various metal ions<sup>a</sup> in methanol

Ligand	Absorption		Fluorescence			log $K_a^b$	log $K_a^c$
	$\lambda$ (nm)	$\epsilon$ (M <sup>-1</sup> cm <sup>-1</sup> )	$\lambda$ (nm)	$\Phi$	$\tau$ (ns)		
<b>1</b>	247	$1.1 \times 10^5$	420	0.007	1.7	–	–
	311	$1.2 \times 10^4$					
<b>1</b> ·K <sup>+</sup>	247	$6.6 \times 10^4$	406	0.061	3.0	$5.2 \pm 0.1$	$5.3 \pm 0.2$
	309	$8.9 \times 10^3$					
<b>1</b> ·Ca <sup>2+</sup>	249	$9.2 \times 10^4$	426	0.58	18	$3.26 \pm 0.04$	<sup>d</sup>
	322	$9.5 \times 10^3$					
<b>1</b> ·Sr <sup>2+</sup>	244	$6.8 \times 10^4$	418	0.21	12	$4.8 \pm 0.1$	<sup>d</sup>
	313	$9.3 \times 10^3$					
<b>1</b> ·Ba <sup>2+</sup>	249	$6.7 \times 10^4$	419	0.086	4.2	$5.6 \pm 0.1$	$5.6 \pm 0.1$
	321	$8.7 \times 10^3$					
<b>1</b> ·Zn <sup>2+</sup>	251	$9.0 \times 10^4$	458	0.48	36	$3.98 \pm 0.04$	<sup>e</sup>
	324	$9.4 \times 10^3$					
<b>1</b> ·Cd <sup>2+</sup>	252	$9.5 \times 10^4$	450	0.66	33	$6.1 \pm 0.1$	<sup>f</sup>
	332	$1.0 \times 10^4$					
<b>1</b> ·Hg <sup>2+</sup>	253	$1.0 \times 10^5$	458	0.003	1.0	>7	<sup>f</sup>
	342	$5.8 \times 10^3$					
<b>1</b> ·Tl <sup>+</sup>	248	$7.7 \times 10^4$	424	0.004	1.3	$6.0 \pm 0.2$	<sup>f</sup>
	312	$8.3 \times 10^3$					
<b>1</b> ·Pb <sup>2+</sup>	247	$6.6 \times 10^4$	447	0.008	1.5	$7.0 \pm 0.2$	<sup>f</sup>
	315	$7.8 \times 10^3$					
<b>1</b> ·Cu <sup>2+</sup>	247	$1.1 \times 10^5$	–	–	–	$5.8 \pm 0.1$	<sup>e</sup>
	322	$1.2 \times 10^4$					
<b>1</b> ·Ni <sup>2+</sup>	250	$9.5 \times 10^4$	–	–	–	<10 <sup>3</sup>	<10 <sup>3</sup>
	311	$9.5 \times 10^3$					

<sup>a</sup> Perchlorate salts of metal ions were used except for Tl<sup>+</sup> and Pb<sup>2+</sup>, with which acetate salts were used.

<sup>b</sup> Values determined via spectroscopic titration.

<sup>c</sup> Values determined<sup>4</sup> via calorimetric titration.

<sup>d</sup> No measurable heat other than heat of dilution indicating the  $\Delta H$  and/or log  $K$  is small.

<sup>e</sup> Complex precipitated and log  $K_a$  values were not determined.

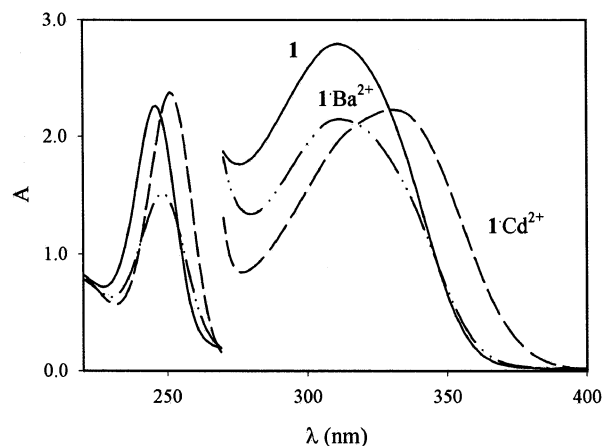
<sup>f</sup> Not measured calorimetrically.

reported by Czarnik responds selectively, by an increase in fluorescence, to Cd<sup>2+</sup> over Zn<sup>2+</sup>; however, it apparently does not selectively bind to Cd<sup>2+</sup> over Zn<sup>2+</sup>.<sup>8</sup> Compound **1** selectively binds and selectively responds to Cd<sup>2+</sup> over Zn<sup>2+</sup>.

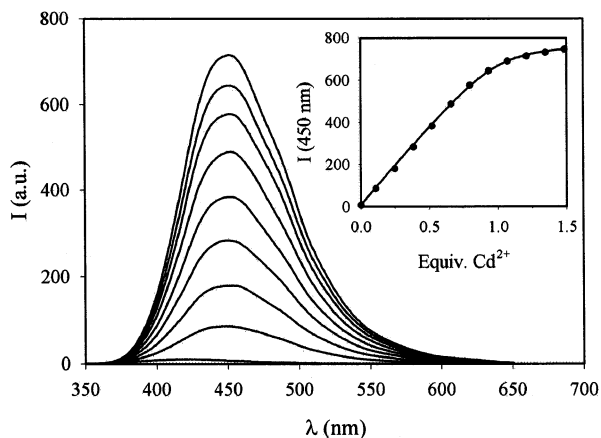
As reported for other lariat ethers containing hydroxyquinoline derivatives,<sup>4–6,9</sup> **1** was able to bind a variety of metal ions. In particular, in methanol solutions<sup>10</sup> it formed stable 1:1 complexes with alkali, alkaline earth (with the exception of Mg<sup>2+</sup>), transition and post-transition metal ions (in particular Cu<sup>2+</sup>, Zn<sup>2+</sup>, Cd<sup>2+</sup>, Hg<sup>2+</sup>, Tl<sup>+</sup> and Pb<sup>2+</sup>) (Table 1). It is of interest that complexation with alkali and alkaline earth metal ions did not, in general, cause strong changes in absorption bands of **1**, only decreases in extinction coefficients ( $\epsilon$ ), accompanied in some cases with very small red shifts (for an example with Ba<sup>2+</sup> see Fig. 1). These changes were more significant with transition and post-transition metal ions. Larger red-shifts (ca. 20 nm) and smaller decreases in  $\epsilon$  values were observed with complexes of **1** with these ions (for an example with Cd<sup>2+</sup> see Fig. 1).

The effects of metal ion complexation on the luminescence properties of **1** were dramatic. The fluorescence spectrum of **1** in methanol solution exhibited only a moderately weak band (Table 1). With various metal cations, the complexation process led to an enhance-

ment of the fluorescence intensity and an increase of the  $\tau$  value, accompanied by a relatively small shift (up to 38 nm) of the wavelength maximum. For example, a large increase in fluorescence of **1** was observed upon addition of Ca<sup>2+</sup> ions (enhancement factor<sup>11</sup> (E.F.) = 83). This increase was less prominent with the heavier alkaline earth ions (E.F. = 30 and 12 for Sr<sup>2+</sup> and Ba<sup>2+</sup>, respectively).



**Fig. 1.** Absorption spectra of methanol solutions of **1** ( $2.5 \times 10^{-5}$  M) (—) and its complexes with Ba<sup>2+</sup> (---) and Cd<sup>2+</sup> (— · —) (both as their perchlorate salts at  $2.5 \times 10^{-4}$  M).



**Fig. 2.** Fluorescence spectra of **1** ( $2.5 \times 10^{-5}$  M,  $\lambda_{\text{exc}} = 311$  nm) in methanol alone and after addition of increasing amounts of  $\text{Cd}^{2+}$  (perchlorate salt). Inset: the corrected value of the intensity read at 450 nm versus the equivalents of added  $\text{Cd}^{2+}$ .

Multiple transition and post-transition metal ions formed stable complexes with **1**, and in some cases the resulting complexes were highly fluorescent. Complexes of **1** with  $\text{Ni}^{2+}$  and  $\text{Cu}^{2+}$  proved to be non-fluorescent, as expected, since with these ions energy- and electron-transfer processes are usually accessible, providing a fast deactivation route to the ground state. Possibly for the same reason, complexation of **1** with  $\text{Hg}^{2+}$ ,  $\text{Tl}^+$  and  $\text{Pb}^{2+}$  did not cause increases in fluorescence. In contrast, highly fluorescent complexes were formed with  $\text{Zn}^{2+}$  and  $\text{Cd}^{2+}$  ions (E.F. = 69 and 94 for  $\text{Zn}^{2+}$  and  $\text{Cd}^{2+}$ , respectively). These ions have  $d^{10}$  configurations and do not introduce low energy metal-centered or charge-separated excited states so energy- and electron-transfer processes do not occur. In addition, with these ions large increases in  $\tau$  values were observed (Table 1). The fluorescence intensities of **1**- $\text{Zn}^{2+}$  and **1**- $\text{Cd}^{2+}$  complexes were very similar to those observed for the **1**- $\text{Ca}^{2+}$  complex. However, complexes of **1** with the former ions gave a 30 nm red shift of  $\lambda_{\text{em}}$ , similar to the shifts in the absorption spectra of the same complexes. Notably, because the observed fluorescence quantum yields of these complexes were high, detection of metal ion complexation at low concentration was possible.

The observed changes in the absorption and quantum yields of **1** induced by complexation processes were used for the determination of the association constants of **1** with the different metal ions in methanol (Table 1). The apparent association constants obtained from titrations monitored spectroscopically<sup>12</sup> are in excellent agreement with those measured previously via calorimetric titrations.<sup>4</sup> Observation of complex formation spectroscopically was possible at concentrations much lower than those required for calorimetric titrations. Consequently, it was possible to avoid problems with precipitation of ion complexes. As seen from the data in Table 1, **1** was selective for  $\text{Cd}^{2+}$  over  $\text{Zn}^{2+}$  and  $\text{Ni}^{2+}$ . Ligand **1** bound  $\text{Cd}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Tl}^+$  and  $\text{Pb}^{2+}$  with similar affinities; however, of these ions only  $\text{Cd}^{2+}$  formed a fluorescent complex with **1**. To verify that **1**

would form a stable fluorescent complex with  $\text{Cd}^{2+}$  in water, the association constant was determined spectroscopically using a  $\mu\text{M}$  concentration of **1** in water at pH 7.4; a lower limit of  $\log K_{\text{a}} = 4.3$  was measured with an E.F. = 100.

Complexation of  $\text{Cd}^{2+}$  with **1** resulted in a large increase in fluorescence intensity ( $I$ ) (Fig. 2), and among the metal ions that form strongly fluorescent complexes with **1**, significant selective affinity for  $\text{Cd}^{2+}$  was observed. Potential ion-sensing applications will call for **1** to be used in excess of metal ions in analyte solutions. In this case  $\text{Cu}^{2+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Tl}^+$  and  $\text{Pb}^{2+}$ , which form stable complexes with **1**, will not significantly interfere with determination of  $\text{Cd}^{2+}$ , provided that concentrations of these metal ions are not vastly higher than those of  $\text{Cd}^{2+}$ . In addition, while **1** forms relatively stable complexes with  $\text{Ba}^{2+}$  and  $\text{K}^+$ , they are not highly fluorescent (small  $\Phi$  values) and their  $\tau$  values are much shorter than that of the **1**- $\text{Cd}^{2+}$  complex.

These two behaviors of **1**, i.e. ion selectivity and intense fluorescent response to complex formation with  $\text{Cd}^{2+}$ , make **1** a promising candidate as a chemosensor for use in sensory devices for  $\text{Cd}^{2+}$ . Further experiments to evaluate the possible use of **1**, immobilized on a solid support, in an ion sensor are underway and results will be reported in due course.

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  - The experiments were performed in methanol to allow comparisons to  $\log K_a$  values measured calorimetrically.<sup>4</sup> Due to the low solubility of **1** in water (ca.  $1 \times 10^{-6}$  M) calorimetry experiments were performed in methanol. Nevertheless, as measured spectroscopically, **1** forms stable complexes with  $Cd^{2+}$  in water (vide infra), and the ion selectivities of **1** are expected to be the same in water as they are in methanol (for an example of ion selectivities of macrocycles in methanol compared to selectivities in water, see: Zhang, X. X.; Izatt, R. M.; Krakowiak, K. E.; Bradshaw, J. S. *Inorg. Chim. Acta* **1997**, *254*, 43).
  - An enhancement factor is the ratio of the quantum yield of a complex divided by the quantum yield of the uncomplexed ionophore.
  - Apparent  $\log K_a$  values were determined using a nonlinear least squares fit of titration data employing the program Sigma Plot 5.0.