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A highly selective Cd^{2+} sensor of naphthyridine: fluorescent enhancement and red-shift by the synergistic action of forming binuclear complex

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Abstract

A new series of fluorophore derivatives from 1,8-naphthyridine have been developed. Compound D1 is the first naphthyridine PET sensor that can signal Cd^{2+} selectively with fluorescent enhancement and red-shift. A binuclear complex structure has been demonstrated in the D1–Cd^{2+} complex.

In recent years, the fluorescent sensing of transition and heavy metal ions has become an important research field advancing rapidly.[1] It is noticeable that fluorescent sensors recognize metal ions mainly by forming single-nuclear complex.[2] In few literature, binuclear metal complex was used as the report mechanism for the signal response.[3,4] To form a stable binuclear metal complex, a receptor should meet certain requirement of having well-organized multidentate chelation sites and of providing a rigidity-suitable cage with a favorable size. An appropriate metal–metal synergistic effect is another integrant to ensure the formation of a binuclear complex. All these factors contribute to the high selectivity of the fluorescent sensors of this kind.

This study focused on 1,8-naphthyridine based on the following considerations. Firstly, the bridging coordination mode could form two metal centers by the two nitrogen atoms on positions 1 and 8,[5] and auxiliary chelating groups could be incorporated at the 2 and 7 positions: so a special cage-like receptor may enforce two metal centers so close that a synergistic effect is expected. Lippard and coworkers have explored a series of 1,8-naphthyridine derivatives as potential multidentate ligands and reported a Cu-complex as the first 1,8-naphthyridine binuclear complex.[6]

Secondly, superior to many ligands without fluorescence, 1,8-naphthyridine derivatives could possibly work as a reporter to transfer the binding character by fluorescent changes.[7] According to our experience in fluorophore design,[8] the introduction of different electron-donating substituents at position 4 could result in intensive fluorescence by forming an intramolecular charge-transfer (ICT) system; such a small fluorophore might be competitive to many of the available large fluorescent markers in the field of sensors.

Although considerable attention has been paid to chemosensors for the cadmium ion,[9] which is ubiquitous in nature and toxic to a broad spectrum of organisms, there is still room for further improvement. Moreover, even some 1,8-naphthyridines are known as ligands, and the derivatives designed as fluorescent sensors for the cadmium ion have not been previously reported.

Therefore, in the present work, emphases are on the development of 1,8-naphthyridine based fluorophores and

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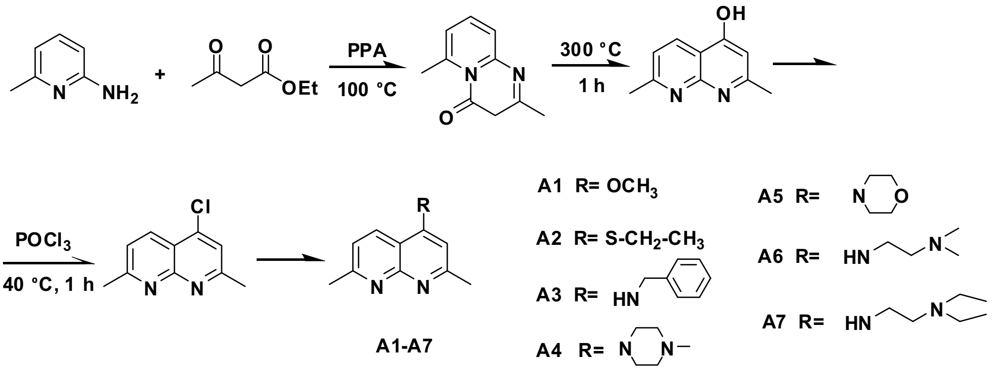


Scheme 1. Synthesis of derivatives of 4-substituted 2,7-dimethyl-1,8-naphthyridine (yields: A1 90%; A2 45%; A3 39 %; A4 72%; A5 75%; A6 51%; A7 43%).

the subsequent modifications for multidentate binuclear chelator as a novel fluorescent sensor. Experiment indicated that D1 could signal Cd^{2+} selectively with considerable fluorescent red-shift and enhancement, and a synergistic action was demonstrated in the D1–Cd^{2+} complexation.

First of all, the synthesis and the fluorescent properties of fluorophores were studied. As illustrated in Scheme 1, the key intermediate 4-chloro-2,7-dimethyl-1,8-naphthyridine was easily prepared from 2-amine-6-methylpyridine;[10] A1–A7 were facilely synthesized through the substitutions of chlorine atom by O, S, and N types of nucleophilic reagents. For comparison, the fundamental optical data of A1–A7 are listed in Table 1.

Whereas precursor 4-chloro-2,7-dimethyl-1,8-naphthyridine was not fluorescent, an intramolecular charge-transfer (ICT) system formed by the introduction of an electron-donating group at the 4-positions resulted in fluorescent emission. Furthermore, the characteristic of the substituent greatly influenced the luminescence: With electron-rich benzylamino group, strong fluorescence was observed in A3. The other two primary amine-substituted compounds (A6 and A7) also emitted intensively. For the compounds with relatively poor electron-donating substituents, A1 (methoxy group) and A2 (ethylthio group) show much weaker fluorescence than that of A3. Very weak fluorescence was also observed in A4 and A5, although strong electron-donating bisalkylamino was introduced. This could be explained by the formation of twisted intramolecular charge-transfer (TICT) state. It is safe to say that 4-amino-1,8-naphthyridine is a new class of fluorophores with small and simple molecular structure, and its fluorescent properties is considerably adjustable.

Table 1
Spectral data for A1–A7 (1.0×10^{-5} mol/L) in different solvents

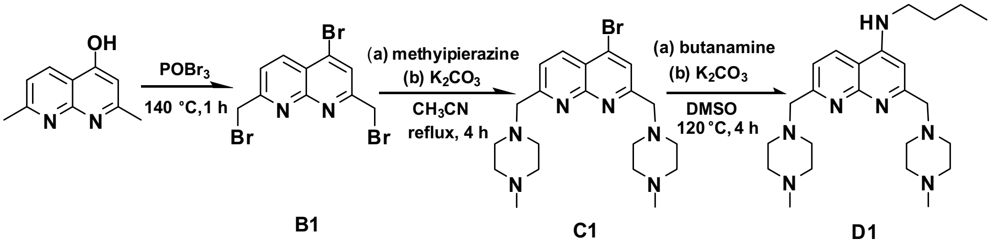
Compd	Solvent	λ_{abs} (nm)	$\log \varepsilon$	λ_{em} (nm)	Φ_F
A1	CH_2Cl_2	299	3.97	304	0.04
	C_2H_5OH	298	3.84	340	0.05
A2	CH_2Cl_2	315	4.19	309	0.03
	C_2H_5OH	316	4.08	312	0.03
A3	CH_2Cl_2	332	3.88	398	0.23
	C_2H_5OH	336	4.00	416	0.27
A4	CH_2Cl_2	316	3.97	310	0.04
	C_2H_5OH	315	3.93	315	0.04
A5	CH_2Cl_2	316	4.07	420	0.03
	C_2H_5OH	315	4.12	449	0.04
A6	CH_2Cl_2	333	4.05	404	0.12
	C_2H_5OH	336	3.94	414	0.14
A7	CH_2Cl_2	334	3.90	403	0.12
	C_2H_5OH	337	4.12	414	0.18

The fluorescence quantum yields (Φ_F) are estimated with quinine-sulfate ($\Phi_F = 0.55$ in 50 mM H_2SO_4 solution) as a standard.

Based on this promising fluorophore, we developed a new class of binuclear-type sensors. Scheme 2 summarizes the synthetic routes of B1, C1, and D1. Noticeably, when the 2,7-dimethyl-4-hydroxyl-1,8-naphthyridine was heated in phosphorous oxybromide, bromination on both hydroxy group and two methyl groups occurred, resulting in the good yield of the key intermediated B1. In this reaction, phosphorous oxybromide might form radicals, which induced the bromination on side-methyl group. This is the first report on multi-halogenated 1,8-naphthyridine derivatives synthesized by phosphorous oxybromide, which takes the advantages of the single product over the known procedure utilizing NBS, which always results in a multi-products distribution.[11]

In D1, piperazine was chosen as a chelating group because its nitrogen atoms were both ion receptors and electron donors for PET.[8a,b] Incorporation of piperazine units would induce a low basal fluorescence and would give the potential for fluorescence enhancement when the sensor bounds a suitable metal ion. The introduced partly rigid arms contributed a favorable ring size and multi-nitrogen atoms centers in D1's structure. When this multidentate ligand combined with suitable metal ions, it would hold the metal ion close and provide a coordination environment.

For most of the PET sensors, both protonation and metal ions chelation work on the sites of the electron donors, which can inhibit PET and induce fluorescent



Scheme 2. Synthesis of derivatives of 2,7-dimethyl-1,8-naphthyridine (yields: B1 29%; C1 37%; D1 30%).

enhancement in a similar way. Protons frequently interfere with metal-ion fluorescence analysis, and thus the pH response experiment is particular important in a research work on PET metal ions sensors.

D1 did not exhibit any detectable fluorescent change between pH 13 and 10.4. When pH was further decreased, fluorescent maxima gradually decreased in intensity. A marked fluorescence decrease response with a 7 nm red-shift characterized the lower pH region between pH 5.5 and 4.0, but below pH 2.0 no obvious fluorescent change was observed (Fig. 1). Based on the fluorescent titration curve, the pK_a of D1 is about 5.18.

The pH-dependent spectra properties of D1 cannot be simply explained by piperazine protonation, but rather results from other processes associated with naphthyridine. The protonated nitrogen atoms of naphthyridine caused absorption increase and disrupted the whole conjugated electronic system of the ICT moiety, resulting in a fluorescence quenching of the latter.

A similar reduction in fluorescence was also found in A3 under an acidic condition (Supplementary data). For A3 without methylpiperazine, the protonation of the naphthyridine primarily caused the reduction of the fluorescence, which could test the proposed explanation of D1's fluorescent changes. These results demonstrated that D1 worked in a manner which was different from that of the usual PET sensor: it responded to proton mainly by fluorophore moiety instead of electron donor part, so the problem of interference from protonation of piperazine group could be ruled out to some extent in D1.

Fluorescence titrations with various transition-metal ions were performed to shed light on the binding properties of D1 with metal ions. These titration studies were conducted in a mixed solution containing Tris–HCl (0.01 M, pH = 7.0). D1 displayed a fluorescence quenching effect with Ag^+, Co^{2+}, Cr^{3+}, Cu^{2+}, Fe^{3+}, Hg^{2+}, Mg^{2+}, Ni^{2+}, and Zn^{2+} (Supplementary data); Only with Cd^{2+}, a different responding signal of considerable fluorescent enhancement and red-shift was observed (Fig. 2).

To examine the signal response toward Cd^{2+}, the absorption and emission responses of D1 were tested in different concentration of Cd^{2+}. As shown in Figure S2 (Supplementary data), upon the addition of Cd^{2+} to 1 equiv, there was an obvious increase in the absorption intensity. However, when another equivalence Cd^{2+} was added, the absorption intensity increased just slightly, with a final red-shift of 5 nm.

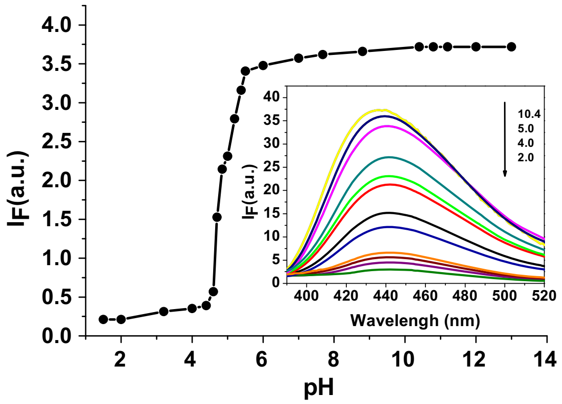


Fig. 1. Fluorescence intensity of D1 (1×10^{-5} M) as a function of pH in a mixed solution of ethanol and water (4:6, v/v) (pH adjusted by 75% $HClO_4$ or 10% $(CH_3)_4N^+OH^-$). Inset, dependence of the fluorescence intensity of D1 on pH.

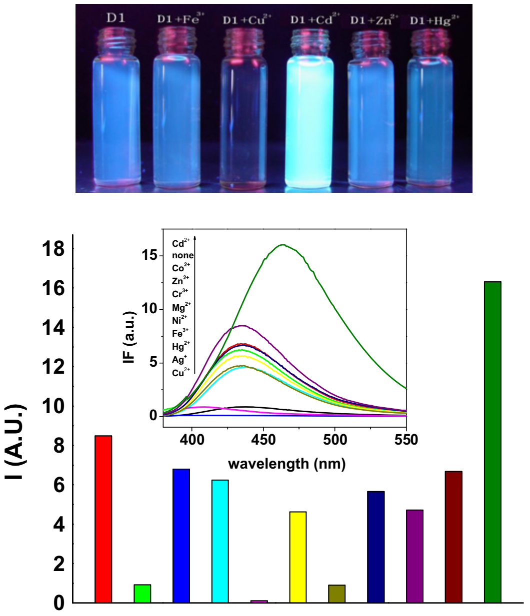


Fig. 2. The fluorescence intensity change profile of D1 (1.0×10^{-5} M) in a mixture (7:3, v/v) of ethanol and an aqueous Tris–HCl (0.01 M, pH = 7.00) buffer solution in the presence of selected metal ions (5.0×10^{-5} M). Inset: Corresponding fluorescent spectra of D1 in the presence of different metal ions. (The photo was taken under a handheld UV (365 nm) lamp after the addition of metal ions.)

The addition of Cd^{2+} dramatically changed the fluorescence spectra. When less than 0.4 equiv Cd^{2+} was added, the fluorescent intensity was gradually decreased with a red-shift. After the addition of more than 0.5 equiv of Cd^{2+}, a band at 450 nm appeared with a fluorescence increase. 1 equiv of Cd^{2+} ions increased the fluorescence intensity back to almost the same level as that of the background and shifted the fluorescence maximum to 458 nm. As the Cd^{2+} amount increased from 1 to 2 equiv, the fluorescent intensity increased linearly with an unobvious red-shift. No further spectra change was observed after Cd^{2+} was over 2 equiv, and a final twofold fluorescence enhancement and a 35 nm red-shift were achieved at the emission maximum (Fig. 3). Cd^{2+} titration experiments were repeated with several different concentrations (1×10^{-4} M, 1×10^{-5} M, 5×10^{-6} M) of D1, and all indicated that the 2 equiv Cd^{2+} is the necessary requirement for the constant complexation.

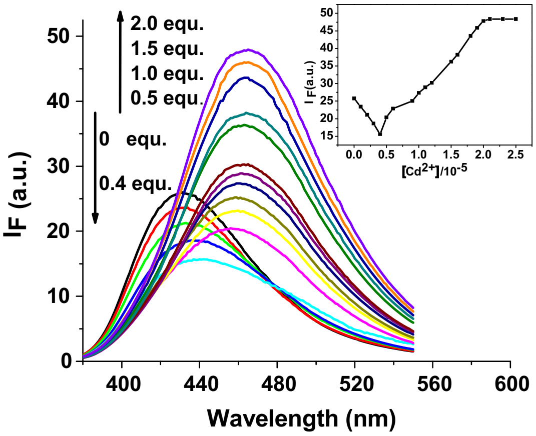


Fig. 3. Fluorescent spectra of D1 (1.0×10^{-5} M) in a Tris–HCl (0.01 M) solution (ethanol/water = 7:3, v/v, pH = 7.00) in the presence of different equiv of Cd^{2+}. Inset: Fluorescent intensity changes of D1 in the presence of different equiv of Cd^{2+}.

Spectra study clearly indicated that D1 can form binuclear complex with Cd^{2+}, and the two Cd^{2+} ions were caught by two steps. The calculation (Supplementary data) by Hyperchem 7.0 demonstrated two different binding modes in D1–Cd^{2+} complexation (Fig. 4), and the N–Cd^{2+} lengthes were close to the reported ones.[12]

D1 may coordinate the first Cd^{2+} ion by two nitrogen atoms on positions 1 and 8 of naphthyridine, resulting in a quenching fluorescence by reducing the electron density of the fluorophore. Then, the two arms of piperazines may get closer to provide a rigidity-suitable cage, which would favor the complexation of another Cd^{2+} ion. The complexation of the first Cd^{2+} would be rearranged as the second Cd^{2+} behaved as another metal center, which could give rise to the binuclear structure as shown in Figure 4. This kind of synergistic action may lead to the formation of a stable complex consisting of two metal ions. As the receptors reached a steady conformation by the cooperation of two accommodating Cd^{2+} ions, fluorescence enhancement was easily observed through a reduced PET process. This proposed mechanism could well explain the experimental phenomena of slight shift in emission spectra and little increase in the absorption maximum intensity, after the first coordination with Cd^{2+} ion.

Job's plot (Supplementary data) suggested that D1 finally formed a 1:2 complex with Cd^{2+} ion. The association constant was $K_1 = 0.75 \times 10^5\ M^{-1}$and $K_2 = 2.19 \times 10^5\ M^{-1}$ determined by a nonlinear least-square (Supplementary data), which corresponded to the first and second phase of the related line between the fluorescence intensity and concentration of Cd^{2+} shown in Figure

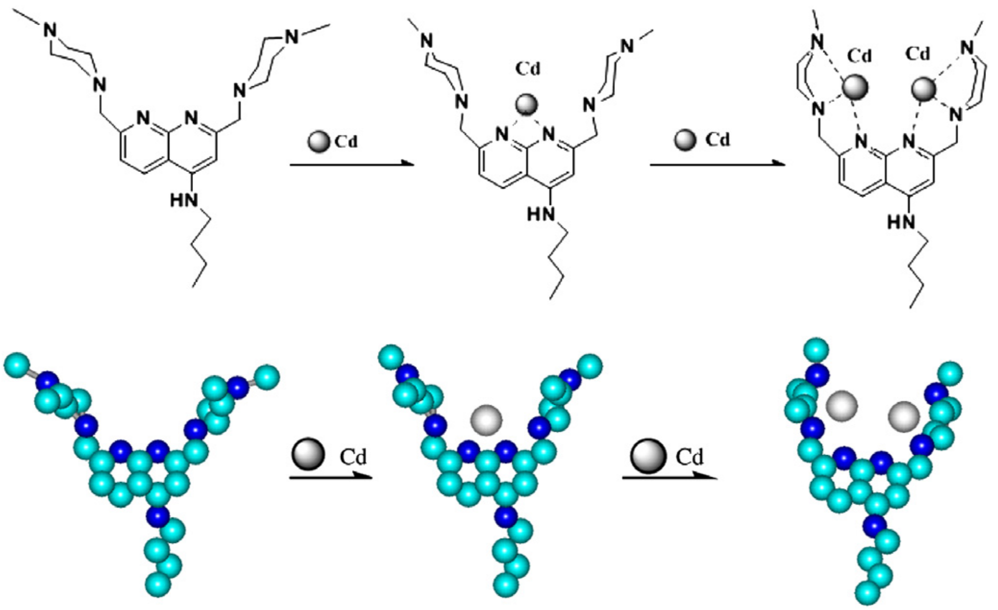


Fig. 4. Proposed D1–Cd^{2+} complex structure and the energy-minimized conformation by using Hyperchem software with the molecular mechanics subroutine.

3, respectively. We recently reported a new fluorescent Hg^{2+} sensor that disclosed an unusual positively cooperative complexation.[4] The fluorescence change led us to assume that D1–Cd^{2+} was another example of a positively cooperative complex.

A competitive metal-ion exchange experiment permitted further comparison of the binding properties of D1 (Supplementary data). The sensor D1 exhibited better selectivity to Cd^{2+} against most other metal ions, such as Ag^{+}, Co^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+}, Cr^{3+}, and Fe^{3+}. The emission of the sensor D1–Cd^{2+} complex was not remarkably affected by them. Only Hg^{2+} and Cu^{2+} induced fluorescence quench.

In conclusion, a series of new fluorophores derivative from 1,8-naphthyridine with tuneable optical properties have been developed. Based on our design of novel binuclear-complex utilizing synergistic action, we synthesized a fluorescent sensor with cage-like multidentate receptors, which are composed of naphthyridine and piperazines. D1 was the first 1,8-naphthyridine-based sensor that could exhibit a high selectivity and sensitivity for Cd^{2+} with fluorescent enhancement and red-shift by forming 1:2 complex with Cd^{2+} ions.

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Supplementary data

Supplementary data (synthesis and characterization of compounds, MR, NMR spectra, and spectroscopic data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.128.

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