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A novel retro-reaction strategy toward designing a selective fluorescence Cu(II) chemodosimeter

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ABSTRACT

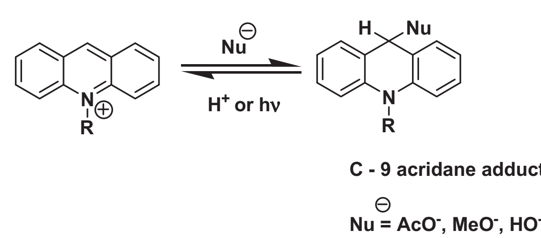
A novel C9 acridane-adduct, featuring ketobenzimidazole chelate, functions as a highly selective fluorescent chemodosimeter for Cu^{2+}, while other metal ions pose little interferences, if any. The signaling strategy operates via the Cu^{2+}-mediated retro-reaction, generating a strongly fluorescent acridinium ion at the expense of the weakly emitting probe.

Copper is essential for all plants and animals with many important cellular and enzymatic functions directly under its control.[1] At the same time, copper is also a toxic pollutant,[2] and exposures in humans beyond the physiological limits are known to cause some serious health disorders.[3] Consequently, designing the selective and sensitive Cu^{2+} chemosensors is an important goal for biological and environmental monitoring.[4] Because of the paramagnetic nature of Cu^{2+}, most chemosensors designed to detect it offer less sensitive and error prone luminescence quenching responses.[5] In a limited number of sensitive fluorescence turn-on Cu^{2+} sensors described to date,[6] the paramagnetically induced excited state deactivation is circumvented either via the chelation induced blocking of the quenching channel[7] or by turning the non-emitting n–π* state into the fluorescent π–π* state.[8]

In recent years, chemodosimeters have emerged as promising ion sensing motifs, because the accompanying ion-promoted chemical modifications often generate highly contrasting and easily quantifiable optical responses. The first fluorescence turn-on Cu^{2+} chemodosimeter was described by Czarnik and co-workers by the application of a spiro-ring-opening protocol on a chelating rhodamine derivative.[9] Following this elegant work, additional examples of Cu^{2+} chemodosimeters, based on the rhodamine platform or other signaling strategies, which include ring closures or hydrolytic reactions have been reported.[10] Despite impressive advances, the issues of delayed responses and/or varying degrees of cross affinities associated with a number of Cu^{2+} chemosensors/chemodosimeters necessitate the designing of new sensing approaches in order to elicit fast optical responses and optimizing the selectivity.

Acridinium salts are well-known to react with nucleophiles on their highly electrophilic C-9 position.[11,12] As illustrated in Scheme 1, certain C9 acridane-adducts of hydroxyl, methoxyl, or acetate anions are susceptible to retro-reactions under the acidic conditions or photoactivation.[13,14] Presently, we envisaged that a suitably designed C9 acridane-chelate adduct might also undergo retro-reaction upon interacting with strongly chelating metal ions, a process that could be exploited to develop optical metal ion sensors.

With this intent, we have synthesized C9 acridane–ketobenzimidazole adduct, designated as Acrida-B (Scheme 2), by reacting *N*-methylacridinium salt **1** with the enolate of a potentially chelating, 2-acetyl benzimidazole **2**[15] (Supplementary data). The rationale for the optical sensing is based on the premise that the coordination of metal ion with N, O binding site of Acrida-B would polarize the C–C



Scheme 1. Reversible nucleophilic addition on the acridinium ion.

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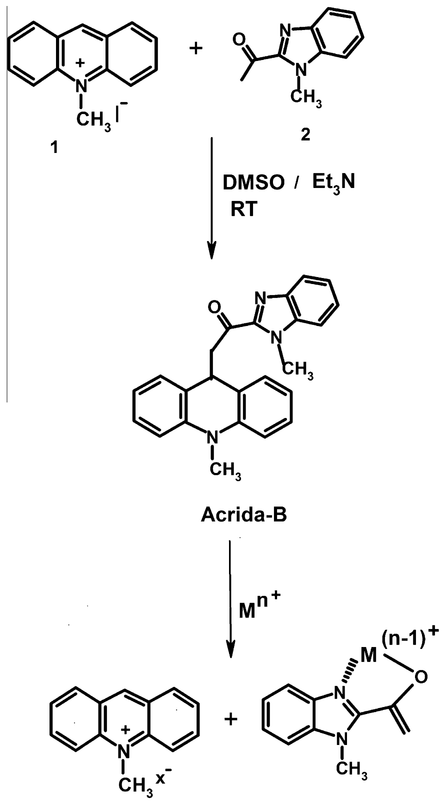

Scheme 2. Synthesis of C9 acridane–ketobenzimidazole adduct, Acrida-B, and the proposed metal ion (M^{n+})-mediated retro-reaction.

bond connecting acridane with ketobenzimidazole, while the acridane-N lone pair would provide the ultimate push to trigger the retro-reaction, thereby releasing the metal-coordinated chelate and the acridinium ion.[16] The available reports indicate the acridane motifs to be weakly emissive, while acridinium salts are known to be strongly fluorescent.[17] Thus, assuming Acrida-B to be also poorly emitting, we anticipated the fluorescence 'switch-on' response on account of the formation of non-coordinating, fluorescent acridinium ion in this process. From the results to follow, the probe, Acrida-B, has been found to function as a selective and sensitive fluorescent Cu^{2+} chemodosimeter, but not for other metal ions investigated.

From the concentration-dependent studies with several metal ions, we found that only Cu^{2+} induced relatively pronounced variations in both the ground and the excited state profiles of the probe. The absorption spectrum of Acrida-B in MeOH/H_2O (8:2 v/v) in Tris–HCl buffer (5 mM, pH 7) displayed a maximum at 289 nm, attributable to the electronic transitions of the acridane moiety.[18]

As shown in Figure 1, the spectrophotometric titration with Cu^{2+} (0–1000 μM) revealed progressive decline in the probe maxima, while a new maxima centered at 356 and 400–450 nm region evolved concurrently. Unlike the Cu^{2+}, the probe's UV–vis behavior was essentially insensitive up to 10^4 μM of perchlorates of Na^+, K^+, Li^+, Ca^{2+}, Ba^{2+}, Mg^{2+}, Zn^{2+}, Ni^{2+}, Co^{2+}, Cd^{2+}, Ag^+, and Pb^{2+}, with only slight absorbance increase (5–15%) being observed at the 289 nm maximum, but without producing any longer wavelength bands, as seen in the case of Cu^{2+} (Supplementary data).

Acrida-B, upon excitation (λ_{ex} = 356 nm) displayed, typical of the acridane systems, a very poorly emissive band centered at 399 nm. As depicted in Figure 2, with increasing exposures to Cu^{2+}, the probe's emission at 399 nm gave way to a new, strongly emissive band in the range 400 to 600 nm with the maximum intensity centered at 490 nm.

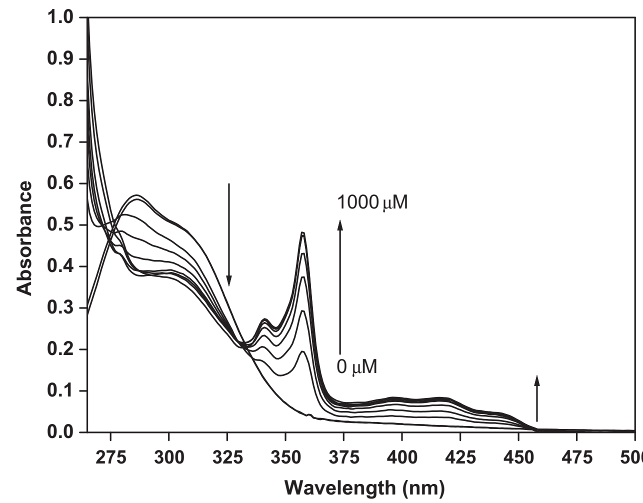

Figure 1. Absorbance response of Acrida-B (10 μM) to increasing Cu^{2+} (0–1000 μM) in MeOH/H_2O (8:2 v/v) Tris–HCl buffer (5 mM, pH 7).

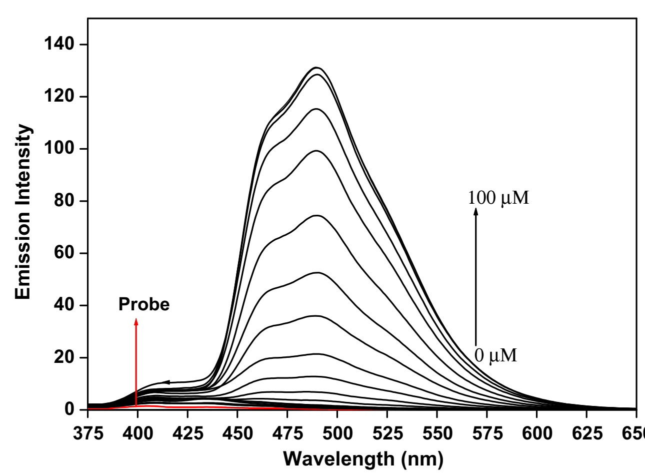

Figure 2. Fluorescence response of Acrida-B (1 μM) with increasing Cu^{2+} (0–100 μM) in MeOH/H_2O (8:2 v/v).Tris–HCl buffer (5 mM, pH 7).

By saturating Cu^{2+} (100 μM), the emission intensity at 490 nm peaked, displaying more than 67-fold enhancement with respect to that of the free probe at 390 nm. The Cu^{2+}-modified emission behavior, with regard to both the energy and shape, was found to essentially conform to that reported for *N*-methylacridinium ion.[19] Clearly, the Cu^{2+}-induced fluorescence turn-on response is the result of Cu^{2+}-mediated retro-reaction,[20] generating a strongly fluorescent acridinium ion at the expense of a weakly emitting probe.

Consistent with the nondescript spectrophotometric results, the fluorescence of Acrida-B (1 μM) also showed virtually no responses to the added Na^+, K^+, Li^+, Ca^{2+}, Ba^{2+}, Mg^{2+}, Zn^{2+}, Ni^{2+}, Co^{2+}, Cd^{2+}, Ag^+, and Pb^{2+} at 100 μM, the concentration at which Cu^{2+} induced a remarkably efficient fluorescence signaling. Further study revealed that at 10-fold or higher concentrations than Cu^{2+}, some of the metal ions (Mg^{2+}, Zn^{2+}, Ni^{2+}, Co^{2+}, and Cd^{2+}) did exhibit responses, however, the fluorescence enhancements were significantly truncated, being only in the range of two to fivefold (Supplementary data).

Fluorescence-derived Job's plot (Supplementary data) indicated 1:1 binding stoichiometry. In order to evaluate the selective chemodosimeter action of Acrida-B toward Cu^{2+}, we initially measured the fluorescence responses at 490 nm in the presence of

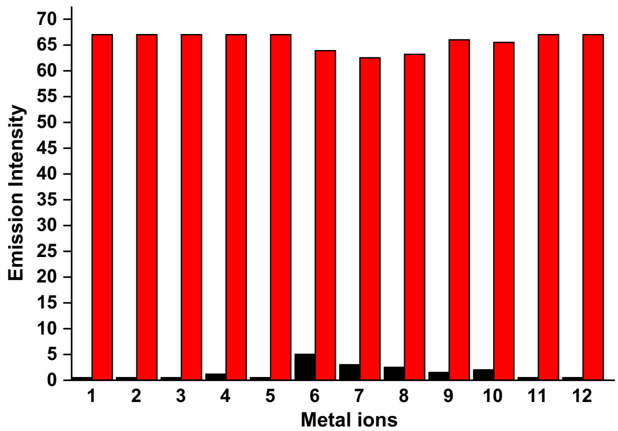

Figure 3. Selective binding studies of Acrida-B (1 μM, MeOH/H_2O (8:2 v/v) at pH 7.0) by fluorescence intensities' measurements at 490 nm. The black bars represent emission intensities after adding 1000 μM perchlorates of each of (1) Na^+, (2) K^+, (3) Li^+, (4) Ca^{2+}, (5) Ba^{2+}, (6) Mg^{2+}, (7) Zn^{2+}, (8) Ni^{2+}, (9) Co^{2+}, (10) Cd^{2+}, (11) Ag^+, (12) Pb^{2+}. The red bars indicate emission intensities after adding 100 μM of Cu^{2+} to each of the above solutions.

1000 μM each of Na^+, K^+, Li^+, Ca^{2+}, Ba^{2+}, Mg^{2+}, Zn^{2+}, Ni^{2+}, Co^{2+}, Cd^{2+}, Ag^+, and Pb^{2+}. As shown in Figure 3, the fluorescence was amplified by a maximum of fivefold, depending upon the identity of the metal ions. Thereafter, addition of 100 μM of Cu^{2+} caused the fluorescence intensity to enhance by 62–67-fold, nearly the same as observed with Cu^{2+} alone at this concentration. These results reflect a very strong binding affinity of Cu^{2+} toward the ketobenzimidazole chelate of Acrida-B. By contrast, several back-ground metal ions reveal a significantly weaker binding even in relatively higher concentrations than Cu^{2+}.

It is noteworthy that, of the different metal perchlorate (100 μM) added to a colorless solution of the probe (1 μM), only Cu^{2+} instantly produced a yellowish fluorescent solution, thereby allowing 'naked eye' recognition of this metal ion (Supplementary data).

Response times of 1–15 min and temperatures from ambient to 50 °C have been reported for certain known Cu^{2+} chemodosimeters.[9,10b,c,h,i] By contrast, Acrida-B generates optical responses spontaneously at room temperature, allowing rapid detection of Cu^{2+}. Moreover, the present probe does not suffer significant interferences from Zn^{2+}, Ni^{2+}, Cd^{2+}, Pb^{2+}, and Co^{2+} even in concentrations 10 times higher than Cu^{2+}.[21] Furthermore, high sensitivity of the probe toward Cu^{2+} is evident from the detection limit of 4.16×10^{-8} M calculated from the fluorescence data (Supplementary data). The observation of linear fluorescence response against increasing Cu^{2+} concentration implies that Acrida-B could be used for the detection of submillimolar of Cu^{2+}.

In conclusion, we have disclosed a new chemodosimeter strategy based on a novel metal ion-mediated retro-reaction of an acridane–ketobenzimidazole adduct. The high selectivity, sensitivity, and fast optical response confer the probe with a potential for the chemical and environmental tracking of Cu^{2+} at submicromolar levels. Several other metal ions afford no or less pronounced optical perturbations even in relatively higher concentrations to make any significant impact on the discrimination of Cu^{2+}. Importantly, the present strategy promises wider sensing capabilities if chelates exhibiting selective metal ion binding could be incorporated into the acridane motif.

Acknowledgments

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Supplementary data

Supplementary data (synthesis of Acrida-B, ^{1}H NMR/^{13}C NMR data, spectrophotometric studies with various metal ions, relative fluorescence experiment, job's plot, fluorimetric response of Acrida-B and the detection limit) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.044.

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