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# A rational approach to emission ratio enhancement of chemodosimeters via regulation of intramolecular charge transfer

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ABSTRACT

The sensitivity as well as dynamic range of a ratiometric probe is determined by the ratio of emission intensities at two wavelengths. Thus, it is highly desirable to acquire a large ratiometric fluorescence response at two wavelengths. However, ratiometric fluorescent signals are intrinsic characteristics of the particular probe–analyte interactions. The design for fluorescent probes with a large ratiometric signal remains a challenging task. There is still a lack of a proper approach to enhance the ratiometric fluorescence response for fluorescent chemodosimeters. Herein, we introduced a novel strategy to increase the emission ratios of a chemodosimeter via modulation of intramolecular charge transfer.



The development of fluorescent probes for analytes has received intense interest due to their applications in various areas.[1] Ratiometric fluorescent probes allow the measurement of emission intensities at two different wavelengths,[2] which should provide a built-in correction for environmental effects (i.e. canceling artifacts due to probe concentration variations) and can also enhance the dynamic range of fluorescence measurement.[1a,2] As the sensitivity as well as dynamic range of a ratiometric probe is determined by the ratio of emission intensities at two wavelengths,[2b,2] it is highly desirable to acquire a large ratiometric fluorescence response at two wavelengths. However, ratiometric fluorescent signals are intrinsic characteristics of the particular probe–analyte interactions,[2g] the design for fluorescent probes with a large ratiometric signal remains a challenging task.

Fluorescent chemodosimeters are molecular systems that use abiotic receptors to achieve analyte recognition with irreversible transduction of a fluorescent signal.[2d,2f,3] The design of a fluorescent chemodosimeter is usually based on a specific reaction induced by the analyte of interest. Consequently, high selectivity is often an advantageous feature of fluorescent chemodosimeters. This valuable characteristic has recently brought very intense attention for the development of fluorescent chemodosimeters.[2d,2f,3,4] For example, Wong and co-workers used an expanded porphyrin to construct a near-infrared-fluorescent chemodosimeter for mercury ions;[4c] Rurack and co-workers created a mercury ion fluorescent chemodosimeter on the basis of $Hg^{2+}$-triggered formation of a squaraine dye;[4d] Tae and co-workers developed a mercury ion fluorescent chemodosimeter based on the $Hg^{2+}$-promoted formation of 1,3,4-oxadiazoles from thiosemicarbazides;[4e] Hong and co-workers constructed a cyanide fluorescent chemodosimeter using a salicylaldehyde moiety.[4f] In spite of such advancement in the field of chemodosimeters, surprisingly, there is still a lack of a suitable approach to increase the ratiometric fluorescence response of chemodosimeters. This obviously limits the further development of fluorescent chemodosimeters and hampers their effective applications as the sensitivity and dynamic range of a ratiometric chemodosimeter are dependent on the ratiometric fluorescent signal. Thus, there is a need to develop an appropriate strategy for construction of fluorescent chemodosimeters with a large signal ratio.

Herein, we present a general strategy for enhancement of emission ratio of chemodosimeters. In principle, a ratiometric fluorescent signal is dependent on the wavelength shift and the intensity variation between the analyte-free probe and the analyte-interacted probe. Thus, to obtain a large ratiometric fluorescence response at two wavelengths, the spectra of a chemodosimeter should undergo a large wavelength shift (preferably complete-resolved) with sensible intensities before and after treatment with an analyte. We reasoned that this could be accomplished by spectral shift based on regulation of intramolecular charge transfer (ICT). Modulation of the electronic features of the substituents on a chemodosimeter could manipulate ICT to afford a large wavelength shift in the spectra of a chemodosimeter before and after treatment with an analyte. Therefore, a large signal ratio for fluorescent chemodosimeter could be obtained. Recently, we

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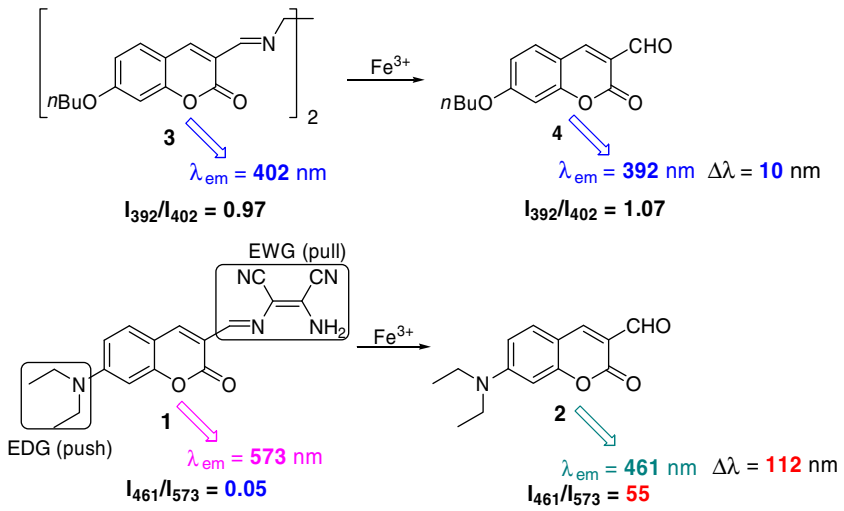
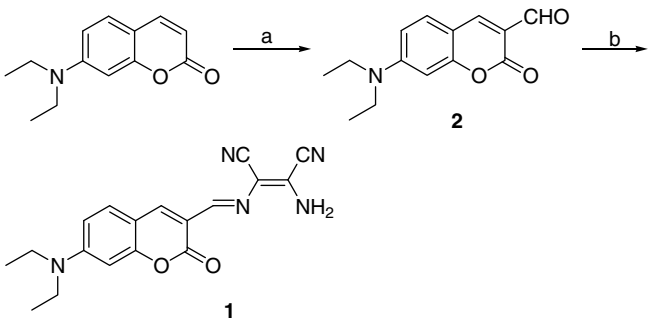



**Figure 1.** Design of chemodosimeter **1** with a large signal ratio.

have identified coumarin Schiff base **3** (Fig. 1) as a fluorescent chemodosimeter for $Fe^{3+}$, which only has a very low signal ratio due to poor wavelength shift (only 10 nm).[5] Thereby, for proof of principle, chemodosimeter **3** appeared to be a suitable platform to illustrate the possibility of our strategy. Modifications of compound **3** with a strong electron-donor group such as diethylamino moiety and a potent electron-withdrawing group such as diaminomaleonitrile moiety give rise to compound **1**, which should have a significant red-shift when compared to compound **3** due to effective ICT induced by the electron push-pull system. However, if the electron-withdrawing diaminomaleonitrile moiety is released by $Fe^{3+}$-promoted Schiff base hydrolysis, the ICT process will be blocked. This should induce a large blue-shift in the emission spectrum of hydrolysis product **2** in comparison to that of compound **1**. Thus, the fluorescent spectra of compounds **1** and **2** should be resolved very well by regulation of the ICT process. This should lead to a large signal ratio for chemodosimeter **1**. Notably, although modifications of spectral features by ICT have been documented, the concept of ICT regulation in a chemodosimeter for generation of a large ratiometric fluorescence response was unknown.

Compound **1** was readily synthesized in two steps (Scheme 1). A reported procedure was used to synthesize the intermediate,[6] 7-diethylaminocoumarin-3-aldehyde **2**, which was then reacted with diaminomaleonitrile to afford compound **1**.[7] The structures of the intermediate and the final product were confirmed by NMR, ESI-MS, and elementary analysis.

The emission spectrum of compound **1** displayed a maximum emission around 573 nm, which is red-shifted about 171 nm when




**Scheme 1.** Synthetic route to compound **1**. Reagents and conditions: (a) $POCl_3$, DMF, 60 °C, 6 h; (b) diaminomaleonitrile, $C_2H_5OH$, room temperature, 24 h.

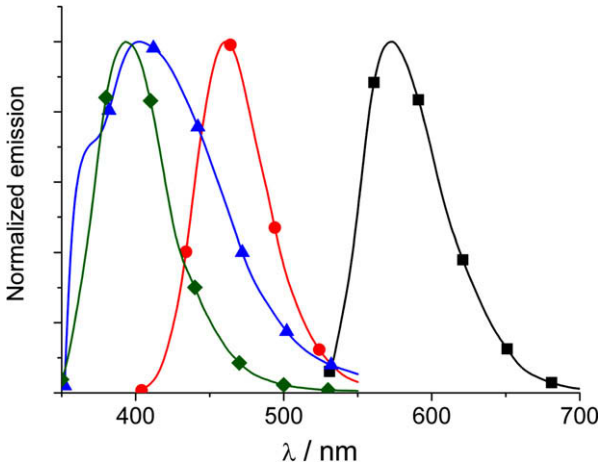



**Figure 2.** The normalized emission spectra of **1** (■), **2** (●), **3** (▲), and **4** (◆) in MeOH/$H_2O$ (99:1).

compared to that of the reference compound **3** (Fig. 2). This drastic red-shift is apparently attributed to ICT. The emission spectrum of compound **2** exhibited a maximum emission around 461 nm, which has a 69 nm red-shift in comparison with that of compound **4**, consistent with the fact that diethylamino moiety is a stronger electron-donor than *n*butoxy group.

As shown in Figure 3, compound **1** (5 μM) exhibited no observable changes in the ratios of emission intensities at 461 and 573 nm ($I_{461}/I_{573} = 0.05$) in the absence of $Fe^{3+}$ in MeOH/$H_2O$ solution (99:1). By contrast, upon addition of $Fe^{3+}$, a significant enhancement in the ratio was observed even after 1 min, and the ratio reached maximum after about 35 min. Thus, an assay time of 35 min was chosen to further explore the sensitivity and selectivity of **1** toward $Fe^{3+}$. Furthermore, after treatment of compound **1** with $Fe^{3+}$ for 35 min, addition of an excess of EDTA, a chelating agent for $Fe^{3+}$, had no evident effect on the emission spectra (Fig. S1), demonstrating the irreversible nature of this hydrolysis process promoted by $Fe^{3+}$. As it is known that Schiff bases are sensitive to metal-promoted hydrolysis[8] and that $Fe^{3+}$ could facilitate imidazolidine and phosphate ester hydrolysis by coordinated acidic water molecules,[9] we hypothesized that $Fe^{3+}$ could also hydrolyze Schiff bases in an analogous way. The hydrolysis product, coumarin aldehyde **2**, was separated and confirmed by a comparative study with

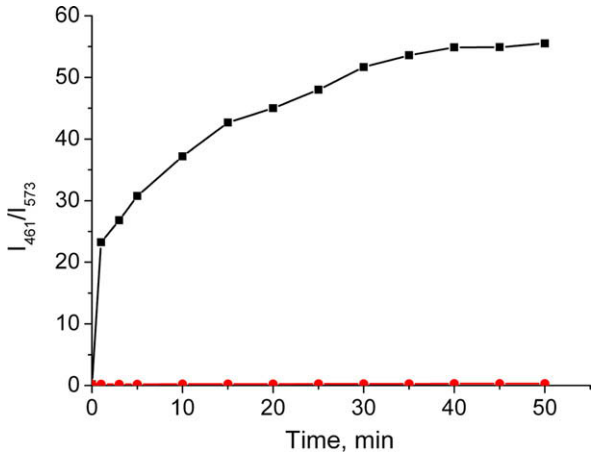



**Figure 3.** Reaction-time profile of chemodosimeter **1** (5 μM) in the absence (●) and presence (■) of $Fe^{3+}$ (20 equiv). The emission ratio of intensities at 461 and 573 nm ($I_{461}/I_{573}$) was plotted versus time.

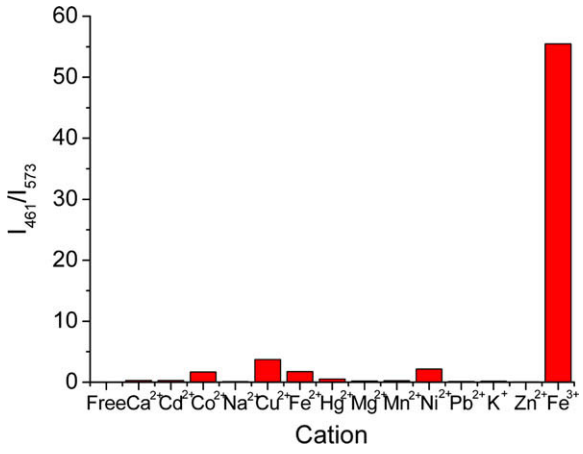



**Figure 5.** Emission ratios ($I_{461}/I_{573}$) for chemodosimeter **1** (5 μM) to various metal ions (20 equiv) on excitation at 389 nm.

a standard compound **2** through TLC, $^1$H NMR, MS, excitation and emission spectra (Fig. S2).

The fluorescent spectra of chemodosimeter **1** in the presence of different concentrations of $Fe^{3+}$ ions are displayed in Figure 4. When increasing concentrations of $Fe^{3+}$ ions were introduced, the intensity of the emission maximum at 573 was decreased with the concomitant appearance of a strong peak around 461 nm, due to formation of compound **2**. This great shift up to 112 nm in the emission spectra enabled the nearly complete separation of the emission peaks before and after treatment with $Fe^{3+}$, which should contribute favorably for a large signal ratio change. Indeed, chemodosimeter **1** displayed a remarkable enhancement of emission intensity ratios ($I_{461}/I_{573}$) from 0.05 to 55 (an 1100-fold enhancement) on $Fe^{3+}$ treatment (Fig. 5). It is noteworthy that such a magnitude of signal ratio variation for a chemodosimeter is highly sought but rarely reported. By contrast, reference chemodosimeter **3** exhibited a very small signal ratio change ($I_{392}/I_{402}$) from 0.97 to 1.07 (1.1-fold enhancement) upon treatment with $Fe^{3+}$ due to only a 10 nm wavelength shift. The dramatic change in visual fluorescence color of chemodosimeter **1** in the absence and presence of $Fe^{3+}$ further supported the large ratiometric emission response (the inset in Fig. 4). These data clearly established the effectiveness of our strategy through regulation of ICT for signal ratio enhancement. In addition, Figure 5 also indicated that this strategy allowed judiciously designed chemodosimeter **1** not only to have a large signal ratio but also to possess an excellent selectivity for $Fe^{3+}$.

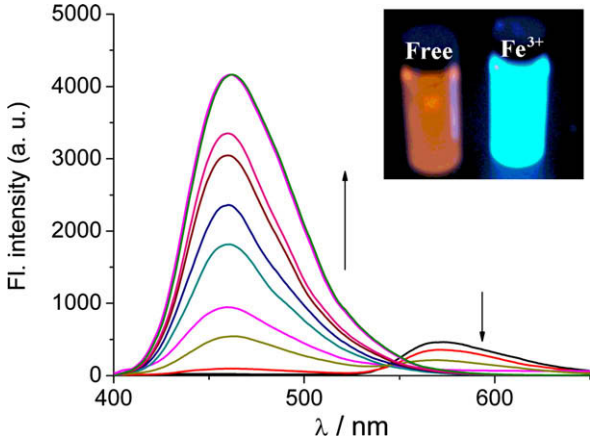



**Figure 4.** The emission spectra of chemodosimeter **1** (5 μM) with the addition of $Fe^{3+}$ ions (0–20 equiv) on excitation at 389 nm. The inset shows the visual fluorescence emission of chemodosimeter **1** only (left) and chemodosimeter **1** +20 equiv. of $Fe^{3+}$ ions (right) on excitation at 365 nm using UV lamp.

In summary, we have introduced a novel strategy to increase the emission ratio of a chemodosimeter. Modulation of the electronic features of the substituents on a chemodosimeter could manipulate ICT for generation of a large wavelength shift in the spectra of a chemodosimeter before and after treatment with an analyte. This should elicit a large ratiometric response. For proof of concept, we have employed chemodosimeter **1** as an example to successfully illustrate this effective strategy. Although fluorescent chemodosimeters are considered as attractive alternatives in sensing system design, the field of chemodosimeters is still largely unexplored. We believe that this powerful strategy should open a new avenue for further advance of the chemodosimeter field, in particular, in the construction of fluorescent chemodosimeters with a high ratiometric emission response for interesting applications in diverse areas.

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## Supplementary data

The supplementary data includes detailed experimental procedures and full characterization data for all compounds synthesized, and some spectra of the chemodosimeter. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tetlet.2008.09.029.

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