ORGANIC
LETTERS

2011
Vol. 13, No. 21
5774–5777

Rational Design and Synthesis for Versatile FRET Ratiometric Sensor for Hg^{2+} and Fe^{2+}: A Flexible 8-Hydroxyquinoline Benzoate Linked Bodipy-Porphyrin Dyad

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Received August 29, 2011

ABSTRACT

A flexible 8-hydroxyquinoline benzoate linked Bodipy-porphyrin dyad has been designed, synthesized, and characterized. Binding of this dyad with Hg^{2+}/Fe^{2+} induced just the opposite (promoting/restraining) influence on energy transfer from the Bodipy donor to the porphyrin acceptor, resulting in a remarkably different ratio change of two signal emissions, endowing this dyad as the first Bodipy-porphyrin-based versatile fluorescence resonance energy transfer (FRET) ratiometric sensor for Hg^{2+} and Fe^{2+} ions, respectively.

Fluorescent chemosensors, in particular those for detecting heavy metal ions such as Hg^{2+}, Pb^{2+}, and Cd^{2+}, with high sensitivity and simplicity have attracted increasing attention in recent years.[1,2] However, among many reported fluorescent intensity-based sensors, the change in the fluorescence intensity, the sole sensing signal for the target analyte(s), is readily perturbed by environmental factors.[3] In contrast, a ratiometric sensor, employing the ratio of two emissions at different wavelengths as the detecting signal, can minimize the above-mentioned environmental effects by self-built-in corrections of two signal peaks and therefore provide more precise measurement relative to single-channel detection.[4]

Ratiometric sensors have been designed to mainly function following either the intramolecular charge transfer (ICT) or the fluorescence resonance energy transfer (FRET) sensing mechanisms. ICT ratiometric sensors usually for a single analyte have been reported with few

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10.1021/ol202338c

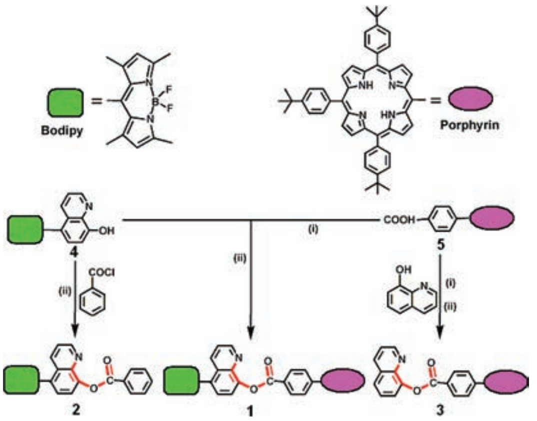
examples for multianalytes.[5] However, for many ICT-based fluorescence sensors, significant overlap between two relatively broad signal emissions usually makes it difficult to accurately determine the ratio of the two signal emissions. Theoretically, this problem can be avoided by employing FRET ratiometric sensors, in which the donor emission at relative short wavelength induces the acceptor emission at longer wavelength due to the resonance between the donor emission and the acceptor absorption.[6] As a consequence, FRET-based ratiometric sensors working for single-biomolecule or single-ion detection such as for Hg^{2+} and Zn^{2+} have started to attract great research interest in biological and chemical sensing fields.[7] Noticeably, Schultz and co-workers also reported the FRET ratiometric sensor for dual biomolecules (protein kinase C and A).[8] However, there appears still no exploration on the FRET ratiometric sensor simultaneously responding to multimetal ions.

It is worth noting that either a Boron-dipyrromethene (Bodipy) or porphyrin moiety has been widely employed as a good signal moiety of a fluorescence sensor due to their advantageous photophysical characteristics.[9] The dyads simultaneously containing Bodipy and porphyrin moieties were revealed to exhibit effective energy transfer properties owing to the favorable optical overlap between these two chromophores.[10] Furthermore, larger pseudo-Stoke's shift (> 100 nm) between the maximum emission wavelengths of Bodipy and porphyrin moieties favors ruling out the influence of excitation backscattering on fluorescence detection, rendering the Bodipy-porphyrin dyad as having great potential as an excellent FRET ratiometric sensor.[11] It is noteworthy, however, that reports on Bodipy-porphyrin dyads have been limited to the energy transfer properties without the exploration on their FRET-based ratiometric sensing properties thus far.

In the present paper, we design and synthesize a flexible 8-hydroxyquinoline benzoate(8-HQ-B) linked Bodipy-(8-HQ-B)-porphyrin dyad (**1**), Scheme 1. Employment of the flexible 8-HQ-B bridge receptor not only facilitates the energy transfer process but also provides versatile binding affinity for Hg^{2+} and Fe^{2+} cations, respectively, endowing dyad **1** as the first FRET chemosensor toward both Hg^{2+} and Fe^{2+}. For the purpose of comparative study, the reference compounds of Bodipy-(8-HQ-B) (**2**) and porphyrin-(8-HQ-B) (**3**), Scheme 1, were also synthesized and characterized by a range of spectroscopic methods.

Figure 1A compares the electronic absorption spectra of **1**–**3** recorded in DMF. As can be seen, the electronic absorption spectrum of the dyad **1** is a linear superimposition of the individual components of **2** and **3**, with the absorption at 506 nm resulting from the Bodipy moiety and the bands of 420, 550, 591, and 648 nm from the porphyrin chromophore (another porphyrin-originating band at 515 nm was largely obscured by the Bodipy absorption at 506 nm), indicating the absence of strong ground-state electronic interaction between these two components in **1**. In contrast, upon the irradiation of 470 nm where the Bodipy unit absorbs most of the light, the dyad **1** gives not only the Bodipy emission at 516 nm but also the porphyrin emission at 650 nm (Figure 1B). However, the emission intensity of Bodipy in **1** becomes significantly decreased (over 95%) in comparison with that of **2**, while the porphyrin emission exhibits an obvious fluorescence enhancement relative to that of **3** under the same experimental conditions. Furthermore, the mixture of **2** and **3** (1:1) only produces the Bodipy emission similar to that of **2** at the corresponding excitation, Figure 1B, indicating no intermolecular energy transfer between the Bodipy moiety of **2** and porphyrin chromophore of **3**. These results clearly show the occurrence of energy transfer from the Bodipy donor to the porphyrin acceptor in dyad **1**, with an FRET efficiency (Φ_{ENT}) of 95.4%,[12] suggesting that the flexible 8-HQ-B bridge moiety can facilitate the energy transfer process in dyad **1**, as expected.[13]

Scheme 1. Synthesis of 8-Hydroxyquinoline Benzoate Linked Bodipy and/or Porphyrin Derivates **1**–**3**[a]



[a] (i) $SOCl_2$, reflux; (ii) TEA, THF, 50 °C.

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The crystal analysis for Bodipy-(8-HQ-B) (**2**) shows that Bodipy-(8-HQ-B) crystallizes in a monoclinic system containing two slightly different configuration molecules per unit cell, Figure S1 and Table S1 (Supporting Information, SI). The presence of two methyl groups at C-1 and C-7 positions of the Bodipy core induces the almost orthogonal configuration between the 8-HQ and Bodipy moieties with dihedral angles of 78.65° and 80.54°, respectively, in two molecules, leading to a lesser extent to nonradiative energy loss from the Bodipy moiety. This renders the Bodipy moiety as a good potential energy donor in the Bodipy-porphyrin bichromophoric system, as mentioned above. More notably, the distances of C–O (esterified hydroxyl oxygen atom), locating in the range of 1.363–1.405 Å, clearly indicate their typical single-bond nature in contrast to the obviously double bond of C–O (carbonyl oxygen atom) with a bond length of 1.184–1.188 Å, in turn revealing the excellent flexible bridging nature of the 8-HQ-B receptor.

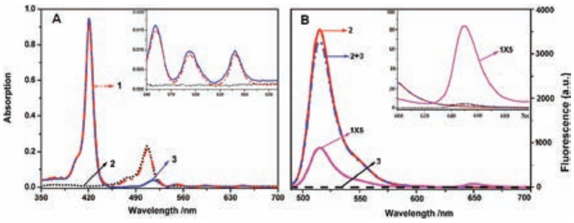

Figure 1. Electron absorption spectra (A) and emission spectra (B) of **1**–**3** at 2 μM in DMF with excitation of 470 nm.

To investigate the effect of the metal binding on FRET in dyad **1**, the photophysical properties of **1** (2 μM) upon addition of different cations including Fe^{2+}, Co^{2+}, Hg^{2+}, Mn^{2+}, Cu^{2+}, Zn^{2+}, Ni^{2+}, Fe^{3+}, Cd^{2+}, Cr^{3+}, and Pb^{2+} ions (10 equal) in DMF/MeOH (98:2) were investigated, respectively, by electron absorption and fluorescence measurements. While the electronic absorption spectrum of **1** remained almost unchanged after addition of the tested metal ion, respectively, Figure S2 (SI), the fluorescence emission spectrum was found to change depending on the nature of metal ion added. As shown in Figure 2A, addition of Hg^{2+} lead to a significant decrease in the Bodipy emission (90.58% in comparison with that of dyad **1**, Figure S3, SI) and simultaneously a slight increase in the porphyrin emission, with the F_{516}/F_{650} ratio decreasing from 16.4 to 1.24, Figure 2B. In good contrast, addition of Fe^{2+} resulted in just the opposite change in the corresponding emission intensities: the Bodipy emission was remarkably enhanced (83.62% relative to that of **1**) and porphyrin emission, simultaneously, slightly diminished, with the F_{516}/F_{650} ratio increasing from 16.4 to 26.67, Figure 2B. The quantitative titration experiments of dyad **1** (2 μM) with an increasing amount of Hg^{2+}/Fe^{2+} in DMF/MeOH (98:2) suggest the 1:1 binding stoichiometry of Hg^{2+}/Fe^{2+}-**1**, with an approximate association constant (K_a) of 3.5×10^6 and 2.2×10^6, respectively, Figures 2C,D and S4 (SI). Additional support for this bonding mode also comes from the Job plot, Figure S5 (SI). Nevertheless, addition of other cations such as Zn^{2+}, Cd^{2+}, Co^{2+}, Mn^{2+}, Cu^{2+}, Ni^{2+}, Fe^{3+}, Cr^{3+}, and Pb^{2+} induced quite a small degree of change in these two corresponding emissions, Figure S6 (SI). Furthermore, a competition experiment of dyad **1** for Hg^{2+} and Fe^{2+} (1:1) in DMF/MeOH (98:2) lead to a fluorescence emission similar to that of Hg^{2+}-**1**: Bodipy emission decreases remarkably and porphyrin emission increases a little, indicating the better binding affinity of **1** for Hg^{2+} than for Fe^{2+}, Figure S6 (SI).

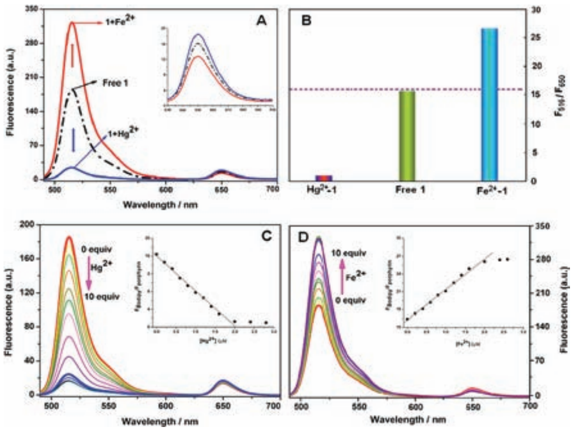

Figure 2. Fluorescence properties (A) and ratio of F_{516}/F_{650} (B) of dyad **1** (2 μM) in DMF/MeOH (98:2) upon adding Hg^{2+} and Fe^{2+} (10 equiv), respectively. The fluorescence emission spectra of dyad **1** (2 μM) in DMF/MeOH (98:2) upon addition of increasing amount (0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 1, 1.2, 1.4, 2, 4, 6, 8, and 10 equiv) of Hg^{2+} (C) and Fe^{2+} (D), respectively. The inset shows the linear response of the fluorescence intensity ratio (F_{516}/F_{650}) to low metal concentration with excitation of 470 nm.

The control experiments for the reference compounds **2** and **3**, as well as their mixture (1:1), were also conducted under the same conditions. As can be seen from Figure S7 (SI), among the tested cations, only the addition of Hg^{2+} led to an obvious decrease in the emission of the Bodipy moiety for **2** (but still to a lesser extent than that for **1** most probably due to the photoinduced electron transfer process).[9b] No remarkable spectroscopic response was revealed for **3** to all these cations. Moreover, the reference experiment for the mixture of **2** and **3** gives a result only similar to that of **2**, Figure S8 (SI). These results confirm the specific role of the flexible 8-HQ-B bridge receptor in dyad **1** on generating the intriguing FRET chemosensing properties toward Hg^{2+} and Fe^{2+} cations.

Actually dyad **1** possesses two potential binding positions with a metal ion, namely the 8-HQ-B unit and porphyrin core. The downfield shifts of quinoline protons ($\Delta\delta$ = 0.117, 0.071, and 0.043 ppm) together with the observation of the porphyrin pyrrole proton signal at δ = −2.742 ppm in the ^{1}H NMR spectrum of the mixture of **1** and $HgCl_2$ (10 equal) in $CDCl_3$ indicate the binding of the quinoline moiety with Hg^{2+} in Hg^{2+}-**1**, Figure S9 (SI). This, in combination with the 1:1 binding stoichiometry of Hg^{2+}-**1** as revealed above, indicates the proposed binding mode for **1** with Hg^{2+}, Figure S10 (SI). This should be also true for Fe^{2+}-**1** due to the very similar absorptions and emission wavelengths of Fe^{2+}-**1** and Hg^{2+}-**1**. On the basis of the above spectroscopic properties, it can be concluded that Hg^{2+}-/Fe^{2+}-binding with the 8-HQ-B receptor in dyad **1** induces just the opposite effect on the energy transfer between Bodipy and porphyrin moieties: Hg^{2+}-binding promotes the energy transfer process and Fe^{2+}-binding just inhibits this process, resulting in the reverse change of the ratio of $F_{Bodipy}/F_{porphyrin}$.[8]

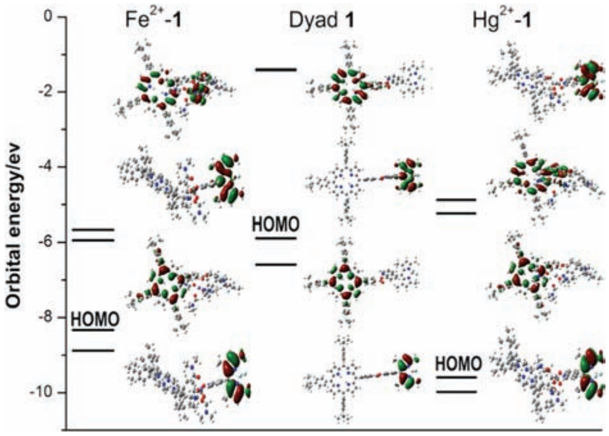

Figure 3. Calculated HOMO and LUMO energy levels of porphyrin and Bodipy moieties in Fe^{2+}-**1**, dyad **1**, and Hg^{2+}-**1** with their corresponding orbital maps. It is worth noting that the two orbital energy levels of LUMO for porphyrin and Bodipy moieties in **1** are too close to be distinguished in the figure.

To understand the just opposite influence of the binding of 8-HQ-B with Hg^{2+} and Fe^{2+} on energy transfer in dyad **1**, density functional theory (DFT) calculations were carried out on the basis of the above proposed structures. The HOMO–LUMO gap for the porphyrin acceptor was revealed to be smaller than that of the Bodipy donor in metal-free dyad **1** (4.49 vs 5.18 eV), Hg^{2+}-**1** (4.35 vs 5.10 eV), and Fe^{2+}-**1** (2.67 vs 2.94 eV) respectively, Figure 3 and Table S2 (SI), which renders it possible to induce the FRET process from Bodipy to porphyrin moieties. In addition, calculation results also indicate that binding of 8-HQ-B with Hg^{2+}/Fe^{2+} results in the somewhat twisted molecular configuration relative to that of dyad **1**, Figure S11 (SI), which in turn induces the changes in distance and orientation between the donor and acceptor transition dipoles and thus affecting energy transfer efficiency. In the case of Hg^{2+}-**1**, the decrease in the distance between the donor and acceptor, transition dipoles, 1.28 Å, Table S2 (SI), most probably as the principal effective factor, leads to an enhancement in the energy transfer between Bodipy and porphyrin moieties. However, binding of the 8-HQ-B receptor in **1** with Fe^{2+} induecs partial restraint in intramolecular energy transfer due to the nonradiative quenching in the excited states assocaied with the unpaired electrons in Fe^{2+}. These results are in good correspondence with the experimental findings as detailed above.

In summary, a flexible 8-HQ-B linked Bodipy-porphyrin system with interesting fluorescence properties associated with the intramolecular energy transfer process has been developed. This dyad exhibits versatile selectivity for Hg^{2+} and Fe^{2+} ions due to the just opposite influence on the intramoleculr energy transfer upon binding with these two cations, rendering it the first example of a Bodipy-porphyrin-based FRET ratiometric sensor for multimetal ions. This result is helpful for developing novel versatile FRET ratiometric sensors with potential applications in chemical and biological fields.

Acknowledgment. Financial support from the Natural Science Foundation of China, Ministry of Education of China, and Fundamental Research Funds for the Central Universities, Beijing Municipal Commission of Education, Fundamental Research Funds for the Central Universities, and University of Science and Technology Beijing is gratefully acknowledged.

Supporting Information Available. Synthesis and characteristics of **1**–**3**; spectroscopic properties of **1**–**3** upon adding different metal ions in DMF/MeOH (98:2); ^1H NMR spectra of **1** with $HgCl_2$ (10 equiv) in $CDCl_3$; crystal structure and data refinements of **2**; and calculational details. This materials are available free of charge via the Internet at http://pubs.acs.org.