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Near IR Emitting Red-Shifting Ratiometric Fluorophores Based on Borondipyrromethene

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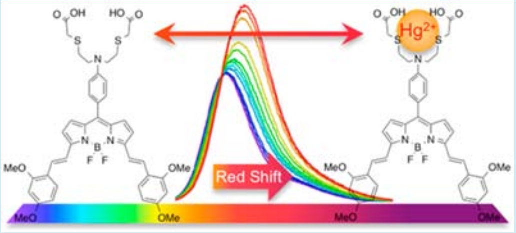
S *Supporting Information*

ABSTRACT: Two distyryl-BODIPY-based NIR red-shifting ratiometric fluorescent probes are reported: **KBHR-1** for pH and **KBAHgR-1** for Ag^+ and Hg^{2+}. **KBHR-1** showed a red-shifting ratiometric response to pH in the NIR region. The identical fluorophore core structure applied to **KBAHgR-1** with a different recognition moiety resulted in a ratiometric response to Ag^+ and Hg^{2+} in the NIR region.



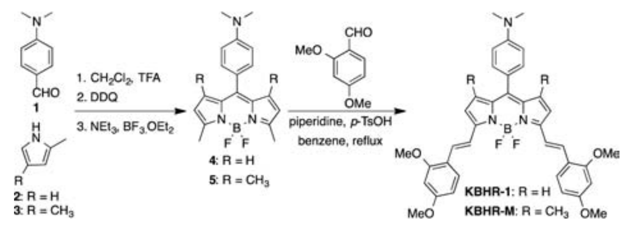
The design and synthesis of fluorescent chemosensors and probes continuously attracts considerable attention because fluorescence-based detection methods are known for their simplicity and high sensitivity.[1] In particular, self-calibrating ratiometric probes contribute to improved signal stability and reproducibility and allow for simplified quantitative measurements.[2] Fluorescent dyes emitting in the near-infrared (NIR) spectral region beyond 650 nm profit from significantly lower light scattering compared to those emitting in the visible region.[3] Therefore, for applications in heavily pigmented and highly scattering media, NIR emitting ratiometric fluorescent compounds are of considerable interest in chemical and biological fields.[4] Boron dipyrromethene (BODIPY) fluorescent dyes generally have advantageous optical characteristics, such as high extinction coefficients, high fluorescence quantum yields, narrow emission bandwidths, and relatively high photostabilities.[5] Therefore, BODIPY dyes are considered useful in a variety of research fields.[6] Because the original BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) emits at a relatively short wavelength (around 500 nm), various approaches have been presented to obtain NIR-emitting BODIPY derivatives.[7]

The photoinduced intramolecular charge-transfer (ICT) mechanism[8] has been applied to ratiometric fluorescent sensing and probe systems.[9] When an electron-donating group is conjugated to a fluorophore, the molecule upon light excitation undergoes ICT from the electron donor to the fluorophore acting as electron acceptor, which shifts the fluorescence emission to longer wavelength compared to the bare fluorophore. When this electron-donating group coordinates with an ion, the intramolecular charge transfer is blocked, resulting in the blue shift of fluorescence emission compared to the ion-free state.[10] Most BODIPY-based ICT-type ion-responsive fluorophores carry a dialkylamino substituent at the 3- and 5-positions acting as electron donor, while the BODIPY core acts as the electron acceptor. While this type of ratiometric fluorophore shows NIR fluorescence emission in the absence of target ion, an emission blue-shift toward the visible region is induced upon target ion binding.[11]

To the best of our knowledge, BODIPY-based NIR emitting ratiometric fluorescent dyes responding with a spectral red-shift to ion recognition have only been reported once.[4b] The same applies to boratriazaindacene (aza-BODIPY)-based compounds.[4c] In addition, the flexibility in molecular design of these ratiometric fluorescent compounds in regard to adaptation to other analytical targets was low. In this work, we present a distyryl-BODIPY-based NIR red-shifting ratiometric fluorophore substituted with electron-donating 2,4-dimethoxystyryl moieties at the 3- and 5-positions and a dialkylamino substituent at the 8-position as ion recognition site with the aim of obtaining BODIPY-based NIR emitting ratiometric fluorophores having broad utility.

The synthesis of the proton-responsive NIR red-shifting ratiometric fluorophore series (**KBHR-1** and **KBHR-M**) is shown in Scheme 1. 8-[(Dimethylamino)phenyl]-substituted

Scheme 1. Synthesis of KBHR-1 and KBHR-M



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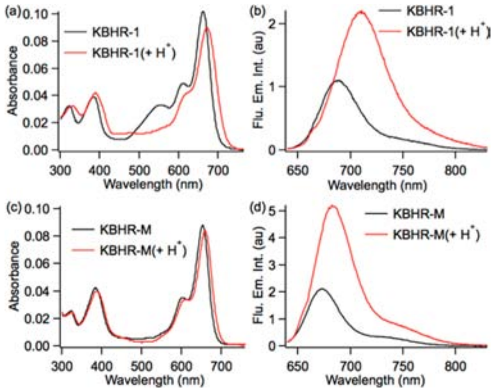

Figure 1. Absorbance (a) and fluorescence emission (b) spectra of **KBHR-1** and absorbance (c) and fluorescence emission (d) spectra of **KBHR-M** at 1 μM concentration in 1:1 THF/water or THF/1 M HCl solutions (excited at 653 nm for **KBHR-M** and 662 nm for **KBHR-1**).

BODIPY cores (**4**, **5**) are synthesized by condensation of pyrrole derivatives and aromatic aldehydes, oxidation, and complex reaction with boron trifluoride. **KBHR-1** and **KBHR-M** were obtained by Knoevenagel condensation of **4** and **5** with 2,4-dimethoxybenzaldehyde.

Figure 1 shows the absorbance spectra and fluorescence emission spectra of **KBHR-1** and **KBHR-M** in 1:1 THF/water or THF/1 M HCl aqueous solutions, respectively. Compared to the THF/water solution, the peaks of maximum absorbance and fluorescence emission of **KBHR-1** were red-shifted from 662 to 672 nm (absorbance) and from 686 to 711 nm in the presence of 1 M HCl. This red shift is thought to be due to the enhancement of the ICT process from the electron-donating 2,4-dimethoxystyryl moieties at the 3, 5-positions to the phenyl moiety at the 8-position with the protonation of the dimethylamino moiety.

It has been previously reported that the introduction of electron-donating groups to the 8-position of the BODIPY core results in quenching of the fluorescence emission by a photoinduced electron-transfer (PET) mechanism.[8] The emission is recovered upon the binding of a target cation to the electron-donating moiety (often a dialkylamino group). Several fluorescent probes covering the spectral range from the visible to the NIR wavelength region relying on this type of OFF/ON switching have been realized.[12] In the present work, the electron-donating 2,4-dimethoxystyryl moieties at the 3,5-positions have the role of suppressing the PET-based fluorescence quenching by the dialkylamino group at the 8-position. The free energy change of the PET process can be described by the Rehm−Weller equation and is influenced by the reduction potential and the excitation energy of the fluorophore core.[13] The introduction of electron-donating groups into the 3,5-positions[7c] and the long wavelength emission lower the reduction potential and the excitation energy, respectively. Therefore, it is expected that the free energy change of the PET process is increased, resulting in PET suppression and the observation of an ICT-related spectral behavior. To investigate the ICT process of this molecular structure in detail, the relation between the degree of red-shift and the dihedral angle θ between the BODIPY core and the aromatic moiety at the 8-position was evaluated. It has been reported that the relative spatial orientation of the (dimethylamino)phenyl moiety and the BODIPY moiety are more strongly twisted in the presence of two methyl groups at the 1- and 7-positions of the molecule.[14] Therefore, **KBHR-M**, having the structure of **KBHR-1** with the addition of two methyl substituents (1,7-dimethyl derivative), is expected to show a reduced degree of π-conjugation, caused by the increased dihedral angle of the aromatic substituent at the 8-position,[15] leading to a suppression of ICT from the 2,4-dimethoxystyryl moieties to the aromatic moiety at the 8-position. In accordance with this theory, a smaller red-shift response to protonation was experimentally observed for **KBHR-M** compared to **KBHR-1** (in Table 1).

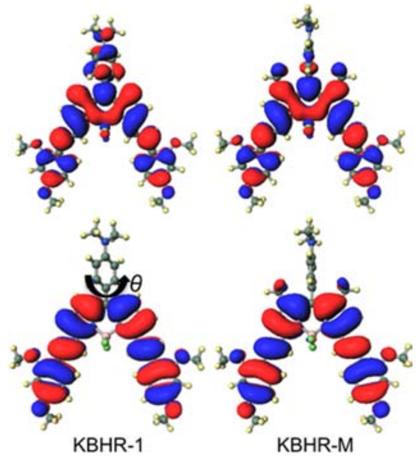

Figure 2. LUMOs (upper row) and HOMOs (lower row) of **KBHR-1** and **KBHR-M** calculated by using B3LYP/6-31G(D). The arrow indicates the definition of the dihedral angle θ.

The above-mentioned differences in the degree of the ICT process are clearly validated by quantum mechanical calculations. All of the optimized structures, orbital energies, and excitation energies were evaluated using density function theory (DFT) and time-dependent DFT (TD-DFT) methods with the B3LYP functional[16] and 6-31G(D) basis set.[17] The molecular structures, the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), and the definition of θ are shown in Figure 2. The S_1 states of **KBHR-1** and **KBHR-M** having large oscillator strengths are characterized as the HOMO−LUMO one-electron excited states, indicating that the maximum absorbance and the fluorescence emission wavelength are related to the S_1 states as has also been found in a previous study.[12c] The theoretical vertical excitation wavelengths for the S_0 structures of **KBHR-1** and **KBHR-M** in the gas phase are at 597 and 590 nm, respectively. They increase to 638 and 632 nm, respectively, in THF solvent as estimated with the polarizable continuum model (PCM) method. The magnitude of

Table 1. Wavelengths of Maximum Absorbance and Fluorescence Emission of KBHR-1 and KBHR-M (1 μM Dye in 1:1 THF/Water or THF/1 M HCl Aqueous Solutions

	λ_{abs}	λ_{abs} (+ H^+)	$\Delta\lambda_{abs}$[a]	λ_{flu}	λ_{flu} (+ H^+)	$\Delta\lambda_{flu}$[b]	ϕ	ϕ (+ H^+)
KBHR-1	662	672	10	686	711	25	0.08	0.21
KBHR-M	653	659	6	673	683	10	0.13	0.30

[a] λ_{abs} (+ H^+) − λ_{abs}. [b] λ_{flu} (+ H^+) − λ_{flu}.

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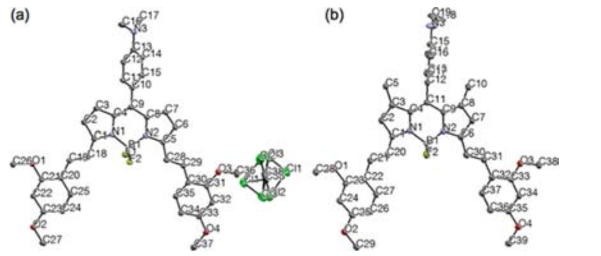


Figure 3. X-ray single-crystal structures of (a) **KBHR-1** and (b) **KBHR-M**.

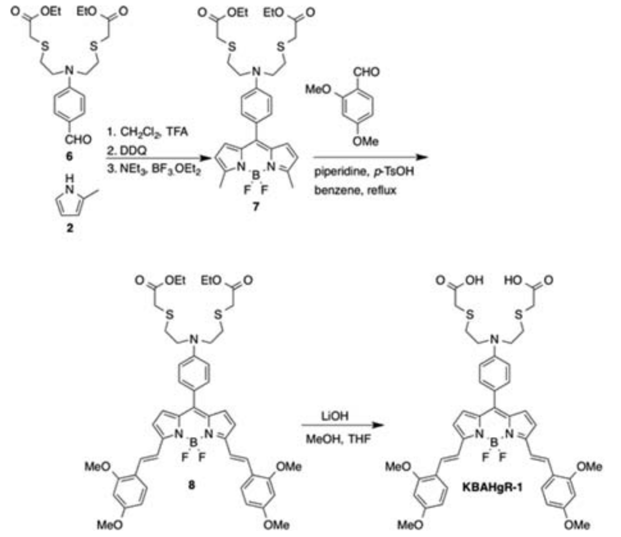
these blue-shifts (6−7 nm) from **KBHR-1** to **KBHR-M** is in agreement with the experimentally observed small blue-shifts of 9−13 nm in Table 1. **KBHR-1** has optimum dihedral angles θ of 51° and 47° for the S_0 and S_1 states, respectively, while those of **KBHR-M** are 90° and 89°. These results show that the (dimethylamino)phenyl moiety and the BODIPY core are more twisted with the addition of the 1,7-dimethyl moieties, as discussed above.

In the case of **KBHR-1**, the protonation of the (dimethylamino)phenyl moiety was also considered and denoted as **KBHR-1**(H^+) (see the Supporting Information). The calculation results indicate that the planarity of **KBHR-1**(H^+) stabilizes the LUMO because of the delocalization between the aromatic moiety and the BODIPY core. Moreover, the LUMO of the aromatic moiety of **KBHR-1**(H^+) (Figure S1, Supporting Information) has a larger amplitude than that of **KBHR-1** as shown in Figure 2. These results indicate that the protonation of **KBHR-1** enhances the ICT process from the electron-donating group substituted BODIPY core to the aromatic moiety at the 8-position and induces a significant red shift, as experimentally observed and shown in Table 1.

X-ray single-crystal structural analysis was performed to further determine the molecular structures of **KBHR-1** and **KBHR-M** (Figure 3). The dihedral angles between the planes of the BODIPY core and the aromatic substituent at the 8-position of **KBHR-1** and **KBHR-M** were 54° and 89°, respectively, supporting the results of the computational calculation. The results indicate that a smaller dihedral angle between the BODIPY core and the aromatic ring at the 8-position leads to a more intense red-shift upon protonation due to the enhancement of ICT. Therefore, **KBHR-1** can be regarded as an example of a donor−acceptor-type fluorophore system with the 2,4-dimethoxystyryl moieties acting as the electron donor and the 8-position substituted BODIPY as the electron acceptor, able to undergo ICT changing with the protonation of the dimethylamino moiety.

Based on the identical molecular design concept, a heavy metal ion responsive ratiometric fluoroionophore **KBAHgR-1** was synthesized by introducing a known ion recognition group.[18] The synthesis of **KBAHgR-1** is shown in Scheme 2. **KBAHgR-1** was basically synthesized in the same manner as **KBHR-1**, using a benzaldehyde derivative including a known heavy metal ion binding group (compound **6**), instead of (dimethylamino)-benzaldehyde. Finally, **KBAHgR-1** was obtained by hydrolysis of the diethyl ester (compound **8**). The absorption spectrum of **KBAHgR-1** shows a high-energy absorption band located at 380 nm (Figure S2). In a previous report, NIR distyryl BODIPY dyes were shown to be excitable by the indirect S_0−S_2 excitation.[12c] To prevent the fluorescence emission spectra from being affected by the excitation light, **KBAHgR-1** was also indirectly excited at 380 nm. Figure 4a shows the fluorescence emission spectra of **KBAHgR-1** in ethanol/HEPES buffer solution (10 mM, pH = 7.8) in the presence of several metal ions. As expected on the basis of the ICT process, spectral red shifts were observed with Ag^+ (from 685 to 695 nm) and Hg^{2+} (from 685 to 700 nm). In the case of other metal cations, only fluorescence emission intensity changes were observed. Parts b and c of Figure 4 show the fluorescence emission spectra of **KBAHgR-1** upon changing the Ag^+ and Hg^{2+} concentrations in the solution. An increase in the emission intensity accompanied by an ion concentration-dependent red shift was observed. The Ag^+ and Hg^{2+} concentration-dependent response curves shown in Figure 4d were obtained by ratiometric signal processing (emission intensity ratios at 695 nm/660 nm for Ag^+ and at 700 nm/670 nm for Hg^{2+}) applied to the spectral data shown in Figure 4b,c. Assuming a 1:1 complex formation between the ion-binding moiety of **KBAHgR-1** and Ag^+ or Hg^{2+}, a least-squares curve fitting relying on a theoretical chemical equilibrium was applied

Scheme 2. Synthesis of KBAHgR-1



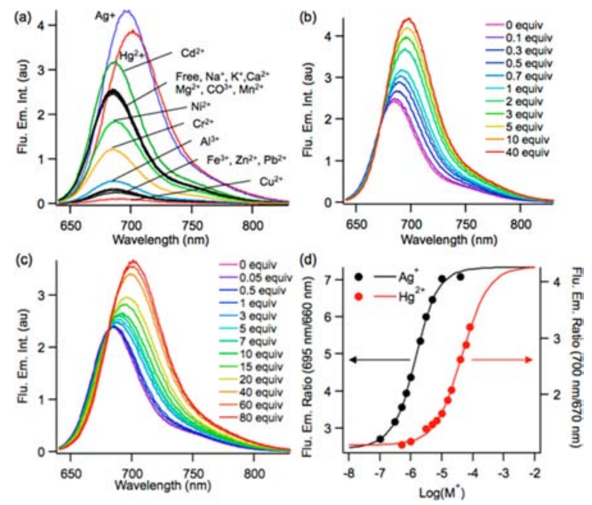


Figure 4. Fluorescence emission spectra of **KBAHgR-1** (1 μM) in ethanol/HEPES buffer (10 mM, pH = 7.8, 1:1) excited at 380 nm: (a) upon addition of 60 equiv of Ag^+, Hg^{2+}, Cd^{2+}, Co^{3+}, Mn^{2+}, Ni^{2+}, Cr^{2+}, Al^{3+}, Fe^{3+}, Zn^{2+}, Pb^{2+}, and Cu^{2+} (counteranion: NO_3^-); (b) in the presence of various Ag^+ concentrations; (c) in the presence of various Hg^{2+} concentrations; and (d) Ag^+ and Hg^{2+} concentration-dependent ratiometric response curve (fluorescence emission ratio 695 nm/660 nm for Ag^+; 700 nm/670 nm for Hg^{2+}).

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to the experimental data of Figure 4d, and the association constants, log K, were estimated to be 6.03 or 4.36, respectively. The binding to Hg^{2+} is weaker than for the identical chelating structure conjugated to a different BODIPY derivative (log K = 5.30).[18] The small dihedral angle between the aminophenyl chelating moiety and the BODIPY core in **KBAHgR-1** results in a stronger electronic conjugation of the aromatic nitrogen lone electron pair of the chelating moiety with the BODIPY core. It has been reported that pK_a values of 8-[(dimethylamino)-phenyl]-substituted BODIPYs decrease with decreasing dihedral angles.[14] For a similar reason, it is assumed that the more planar **KBAHgR-1** shows weaker Hg^{2+} binding and a different selectivity pattern compared to more twisted derivatives. Our results indicate that **KBAHgR-1** enables quantitative ratiometric detection of Ag^{+} and Hg^{2+} in the NIR spectral region. The literature reports many cation recognition sites with (dialkylamino)phenyl structure.[5b,6e] Therefore, the current molecular design can be adapted to the development of ratiometric sensing probes for targeting other cations.

In conclusion, two novel distyryl-BODIPY-based NIR red-shifting ratiometric probes, **KBHR-1** for protons and **KBAHgR-1** for Ag^{+} and Hg^{2+}, have been successfully designed and synthesized. The experimentally observed spectral behavior of **KBHR-1** has been theoretically confirmed by computational calculations. An identical electron-donor substituted BODIPY core fluorophore structure has been applied to proton, Ag^{+}, and Hg^{2+} detection with a simple exchange of the target recognition moiety at the 8-position. These results indicate that this molecular structure can be applied to obtain red-shifting ratiometric fluorescent probes for different ions simply by adapting the dialkylamino moiety, having potential applications in chemical and biological fields by taking advantage of the ratiometric probe system in the NIR spectral range.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, absorbance spectra of **KBAHgR-1**, NMR spectra, and crystallographic data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01299.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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