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Application of 2-(3,5,6-Trifluoro-2-hydroxy-4-methoxyphenyl)benzoxazole and -benzothiazole to Fluorescent Probes Sensing pH and Metal Cations

Kiyoshi Tanaka,* Tsutomu Kumagai, Hiroko Aoki, Makoto Deguchi, and Satoru Iwata

Faculty of Engineering, Seikei University, Musashino-shi, Tokyo 180-8633, Japan

tanaka@ge.seikei.ac.jp

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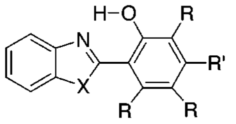
2-(3,5,6-Trifluoro-2-hydroxy-4-methoxyphenyl)benzoxazole (**3**) and benzothiazole analogue (**4**) are prepared by the two-step procedures from the corresponding 2-(pentafluorophenyl)benzazoles. Benzoxazole **3** is applicable to a fluorescent probe sensing magnesium cation, and **4** is suitable for sensing zinc cation. Both fluorophores **3** and **4** are sensitive to the pH change at pH 7−8, resulting in large fluorescence enhancement under basic conditions. Their high sensitivity to pH and selectivity in metal cations are ascribed to the high acidity of the fluorophenol moiety.

Introduction

2-(2-Hydroxyphenyl)benzoxazole (**1**) has been widely studied from the viewpoint of photophysics because of its dual emission via the excited-state intramolecular proton transfer (ESIPT).[1] In nonpolar solvent, **1** emits long-wavelength fluorescence (∼500 nm) exclusively via the ESIPT process of the exicited state of the intramolecularly hydrogen-bonded enol, and the intensity of short wavelength fluorescence (∼ 360 nm), which arises from the excited state of the intermolecularly hydrogen-bonded rotamer, gradually increases in accordance with an increase of the polarity of the solvent.[2,3] In continuing research on the function of polyfluorobenzene derivatives,[4,5] we have reported that 2-(3,4,5,6-tetrafluoro-2-hydroxyphenyl)benzoxazole (**2**) emits similar long-wavelength fluorescence in nonpolar solvent and exclusively emits the intermediate wavelength fluorescence around 440 nm in polar solvents such as acetonitrile, which is assumed to originate from the excited state of the phenolate anion of **2**.[6] Polyfluorophenol derivative is expected to be sensitive to a pH change of surrounds and also to complexation with a metal cation because of its rather high acidic property,[7] so that it is of interest to apply the intermediate wavelength fluorescence of the fluorinated benzoxazole derivative to an output signal for pH or metal cation sensor. On the other hand, a description of complexation of **1** or its benzothiazole analogue with a metal cation is limited to a few papers.[8,9] In this paper, we will describe pH-sensing fluorescence behavior of 2-(3,5,6-trifluoro-2-hydroxy-4-methoxyphenyl)benzoxazole (**3**) and -thiazole (**4**) and demonstrate that **3** is applicable to the fluorescent probe sensing magnesium cation and **4** is suitable for sensing zinc cation.



1: X=O, R=R'=H
2: X=O, R=R'=F
3: X=O, R=F, R'=OMe
4: X=S, R=F, R'=OMe

Results and Discussion

The benzoxazole **3** and thiazole **4** were synthesized in moderate yields by methoxylation of 2-(pentafluorophenyl)benzoxazole and -benzothiazole with sodium methoxide in methanol, followed by hydroxylation with sodium hydroxide. Substituted positions in **3** and **4** were determined by the ^{19}F NMR analysis. Ortho/para selectivity is an important problem in nucleophilic aromatic substitution of polyfluorobenzenes, and the selective para substitution in the first methoxylation was attained by the coexistence of methanol, which seems to interfere with the coordination of sodium cation to the azole-nitrogen atom to result in retardation of the ortho attack by the accompanied methoxide.[4,10] Para substitution of methoxide is important because it leads to the selective ortho substitution of the hydroxyl group in the second reaction (Scheme 1).

Absorption and fluorescence spectra of the toluene solution of **3** are essentially the same as those of the

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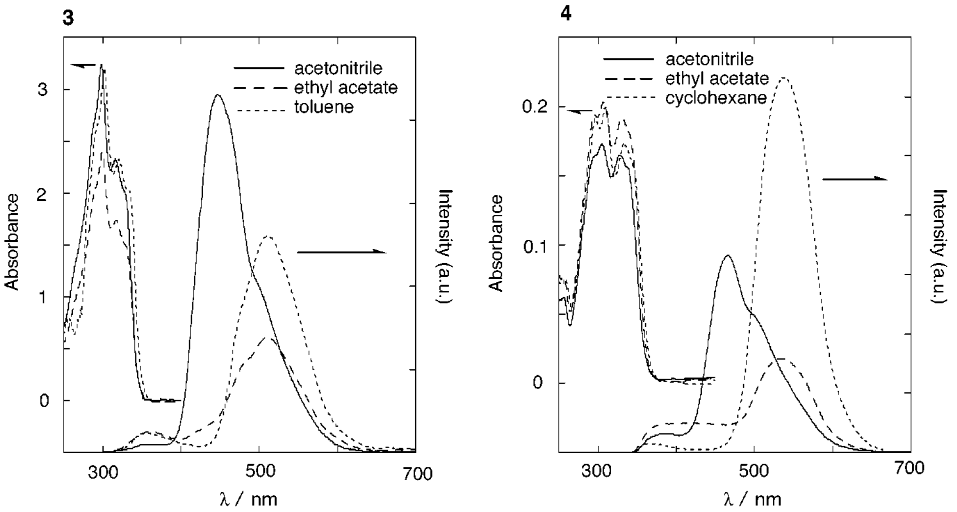
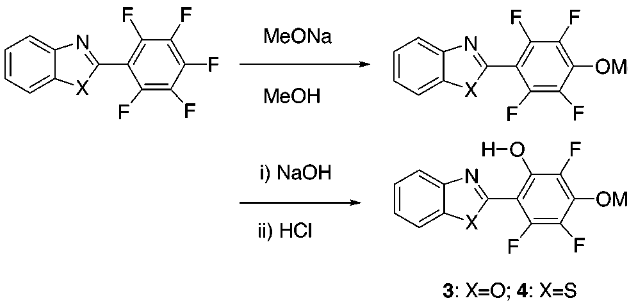


Figure 1. Absorption and fluorescence spectra of **3** and **4** in various solvents. $\lambda_{ex} = 298.5$ nm for **3** and 306.5 nm for **4**: $[\mathbf{4}] = 1.0 \times 10^{-5}$ M, $[\mathbf{3}] = 9.6 \times 10^{-5}$ M and 2.4×10^{-5} M for absorption and fluorescence spectra, respectively.

Scheme 1



benzoxazole **2**, and slightly red-shifted absorption and fluorescence are notable.[6] Fluorescence spectra of the ethyl acetate solution show a slight shoulder due to the intermediate wavelength fluorescence around 447 nm, along with the appreciable 513 nm emission, and those of the acetonitrile solution indicate the 447 nm emission as the main fluorescence. Absorption and fluorescence spectra of the benzothiazole **4** are similar to those of **3**, and fluorescence spectra of the acetonitrile solution show the intermediate wavelength fluorescence around 465 nm (Figure 1). Fluorescence intensities of **3** and **4** in acetonitrile are very small, but additions of methanol to the solutions bring about the considerable enhancement of the intermediate wavelength fluorescences and their intensities increase in proportion to methanol, as shown in Figure 2. A gradual increase in the absorbance at longer wavelength around 350 nm is also remarkable. It is another noteworthy behavior of **3** that fluorescence quantum yield is highly sensitive to the concentration; for example, the fluorescence quantum yield of the methanol solution of 1×10^{-5} M is $\Phi_f = 0.03$ and that of the 2×10^{-7} M solution is substantially enhanced to almost 12 times of that of the 1×10^{-5} M solution. Relative absorbance of the longer wavelength band is considerably large in dilute solution.[6,11] The fluorescence quantum yield of **4** is not so largely affected by the concentration, but a similar trend is still observed, with two times fluorescence quantum yield being estimated for the 2×10^{-7} M solution, compared to that of the 1×10^{-5} M solution (Figure 3).

Spectral changes caused by the concentration and the polarity of the solvent point out that under the polar environment **3** or **4** equilibrates with its phenolate anion, which emits the intermediate wavelength fluorescence and absorbs at longer wavelength.[6,12,13] A larger fluorescence quantum yield of **3** than **4** supports the formation of **3** (anion) in preference to that of **4** (anion) in methanol. To understand the ease of formation of **3** (anion), ab initio calculations were performed for the ground states of the anions of **3** and **4**.[14] Optimized structures, net charges of the selected atoms based on Mulliken population analysis, and dipole moments are collected in Figure 4. Calculations suggest that a coplanar conformation of **4** (anion) is preferable to a twisted one, and this coplanarity is ascribed to an ionic interaction between the anionic phenolate oxygen atom and the cationic sulfur atom.[15] With **3** (anion), a twisted conformation is optimized, and it will come from an electronic repulsion between the phenolate and oxazole oxygen atoms. The large dipole moment of **3** (anion), compared to **4** (anion), is another notable property, and this polarity will be one of the reasons why the formation of **3** (anion) is easy in polar methanol solution.

The effect of pH on the fluorescence spectra along with absorption spectra was investigated under the conditions of [**3** or **4**] = 1×10^{-5} M in methanol/water (9:1) and the

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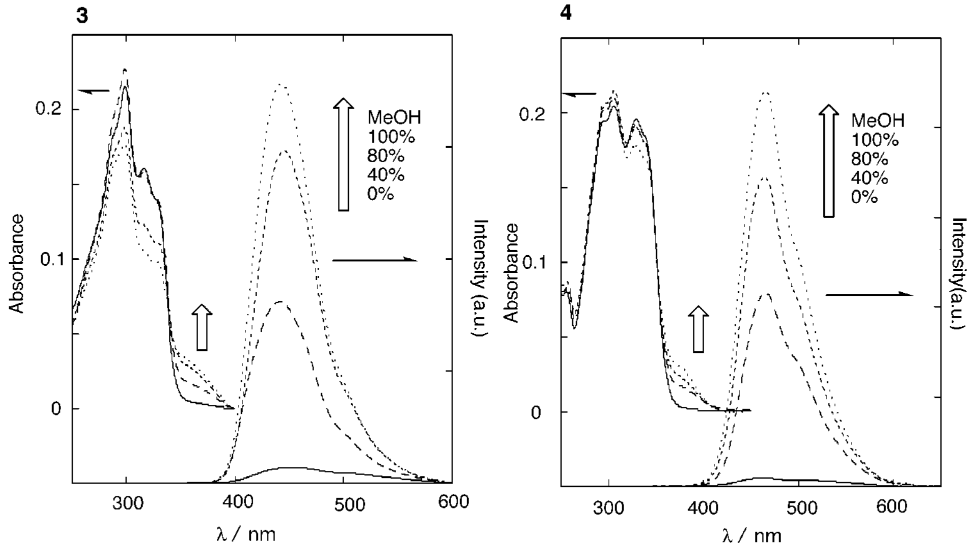

Figure 2. Absorption and fluorescence spectra of **3** and **4** in a mixture of acetonitrile and methanol: $[\mathbf{3}] = [\mathbf{4}] = 1.0 \times 10^{-5}$ M, $\lambda_{ex} = 298.5$ nm for **3**, 306.5 nm for **4**.

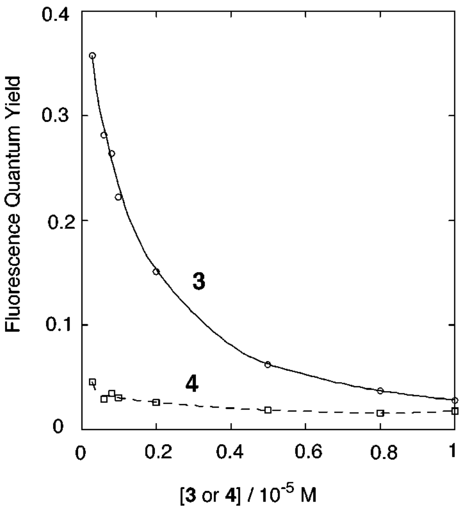

Figure 3. Concentration dependence of fluorescence quantum yields of **3** and **4** in methanol. $\lambda_{ex} = 300$ nm.

constant ionic strength (0.1 M) (Figure 5). Results show that the fluorescence intensity of **3** or **4** is almost zero under acidic conditions and increases under basic conditions. The fluorescence quantum yields were estimated to be $\Phi_f = 0.233$ for **3** and $\Phi_f = 0.228$ for **4** at pH 10.3. It is also notable that the absorbance at longer wavelength (345 nm for **3** or 371 nm for **4**) increases under basic conditions. Typical titration curves are depicted in Figure 6. The sharp titration curves show that **3** and **4** are fairly sensitive to the change at pH 7–8. For the demonstration of the pH sensing of **3** and **4**, changes in the fluorescence intensity are checked in the presence of 2-, 3-, or 4-aminopyridines in methanol. In both cases of **3** and **4**, only 4-aminopyridine brings about large fluorescence enhancement and that is attributed to relatively high basicity ($pK_a = 9.1$) of 4-aminopyridine, compared to 2- and 3-aminopyridines ($pK_a = 6.9$ and $pK_a = 6.0$, respectively).

The effect of metal cation on the emissions of **3** and **4** in methanol was next investigated, and the change in the fluorescence intensity in the presence of a 50 molar ratio of metal cation is summarized in Figure 7. Among alkali and alikaline earth metal cations, **3** recognizes magnesium cation to bring about large fluorescence enhancement and slightly recognizes calcium cation to cause appreciable fluorescence enhancement. For other alkali and alkaline earth metal cations, a meaningful fluorescence change is not detected. From the observation that, in an aqueous methanol solution (methanol/water = 9:1), magnesium cation causes the similar fluorescence enhancement but calcium cation has no meaningful effect on the fluorescence intensity, **3** can be regarded as a probe sensing magnesium cation selectively. It should be added that fluorescence enhancement of **3** with magnesium cation is in sharp contrast to no appreciable change in fluorescence of the nonfluorinated benzoxazole **1**. On the other hand, fluorescence intensity of **4** is not affected by alkali metal cations but **4** is reversely quenched with all kind of alkaline earth metal cations, which is comparable to quenching by ammonium cation.

Dramatic fluorescence enhancement of **3** with magnesium cation may be interpreted by the formation of a complex **5** ($X = O$, $M^{n+} = Mg^{2+}$), where the benzoxazole and phenolate rings lie on the same plane by the bridging magnesium cation, and this coplanarity and the anionic property of the phenolate ring bring about large fluorescence enhancement.[16] The formation of the coplanar anion type of **3** is supported by the red-shifted absorption ($\lambda_{ab} = 359$ nm),[6,8,12,13] excitation of which also results in the same fluorescence enhancement (Figure 8). The curve fitting of the fluorescence intensity according to the Benesi–Hildebrand plot supported the formation of a 1:1 complex of **3** and magnesium cation, its binding constant being estimated to be $K = 5.4 \times 10^3$ M^{-1} in methanol (Figure 9). The curve fitting of the absorbance change gave similar results. On the other hand, **4** is reversely quenched with magnesium cation, and this quenching will be explained by the assumption that the equilibrium between **4** and **4** (anion) shifts to the **4** side under the presence of magnesium cation, which is supported by the

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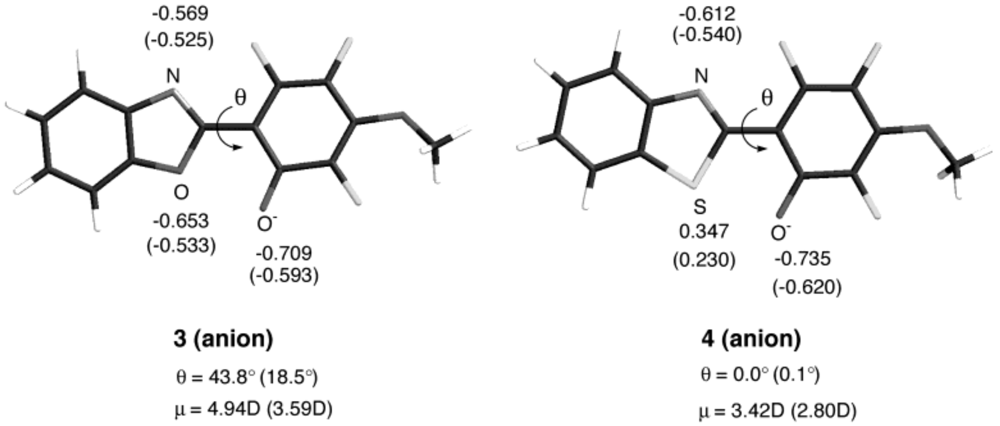


Figure 4. RHF/6-31G** (B3LYP/6-31G**)-optimized structures of **3** (anion) and **4** (anion), net charges of the selected atoms based on Mulliken population analysis, and dipole moments (μ). θ: dihedral angle between benzazole and phenyl rings.

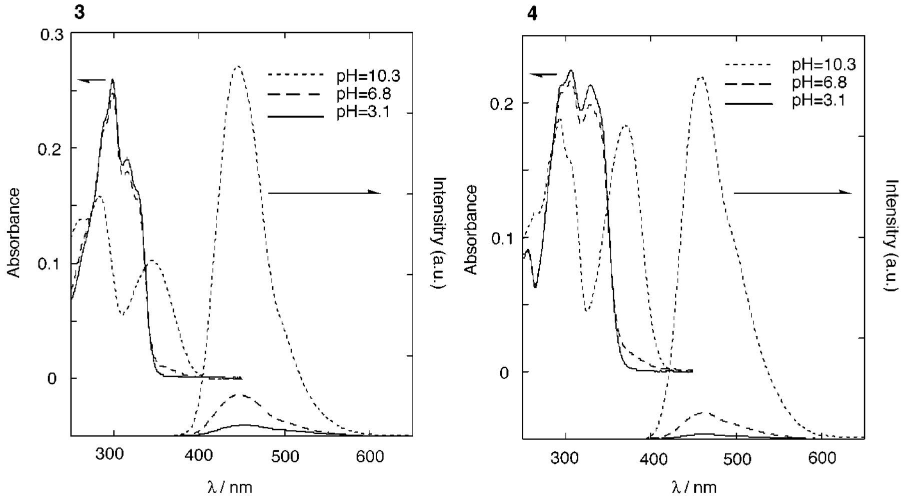


Figure 5. Absorption and fluorescence spectra of **3** and **4** under acidic and basic conditions: [**3**] = [**4**] = 1.0 × 10^{-5} M, [NaCl] = 0.1 M, 20 °C; solvent MeOH/H_2O = 9/1. λ_{ex}= 298.5 nm for **3** and 306.5 nm for **4**.

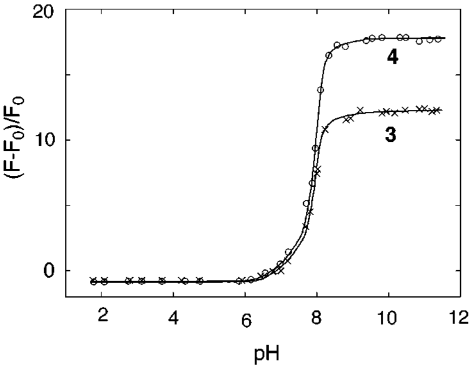
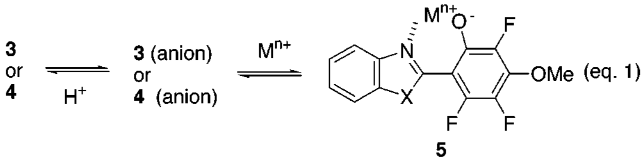


Figure 6. Dependence of pH on fluorescence intensity of **3** and **4**: [**3**] = [**4**] = 1.0 × 10^{-5} M, [NaCl] = 0.1 M, 20 °C; solvent MeOH/H_2O = 9/1. λ_{ex} = 298.5 nm for **3**, 306.5 nm for **4**. F_0 stands for fluorescence intensity without hydrochloric acid and sodium hydroxide.

decrease of absorbance at longer wavelength around 370 nm (Figure 8). This equlibrium shift to the **4** side will be led by the slightly acidic conditions, which is caused by magnesium cation and methanol, and is also the case with other alkaline earth metal cations and with ammonium cation. It is noteworthy that the benzoxazole ring complexes with magnesium cation more strongly to form the stable **5** (X = O, M^{n+} = Mg^{2+}), compared to the benzothiazole ring, and this stability shifts the equilibrium to the complex side (eq 1).



Among transition metal cations such as silver, zinc, cadmium, nickel, copper, and mercury cations together with lead and aluminum cations, **3** recognizes zinc and aluminum cations and **4** does only zinc cation in methanol to cause fluorescence enhancement, accompanied by the increase in absorbance at longer wavelength. The curve fitting of the fluorescence intesity again supported the formations of 1:1 complexes of **3** or **4** with the corresponding metal cations, and their estimated association constants are summarized in Figure 9. With regard to cadmium cation, both **3** and **4** cause the fluorescence enhancement at low concentration of cadmium cation, but the fluorescence intensity gradually decreases at relatively high concentration of cadmium cation. This behavior is rationalized by the assumption that the ability of complexation of **3** and **4** with cadmium cation is not so large that once formed complexes are degraded into **3**

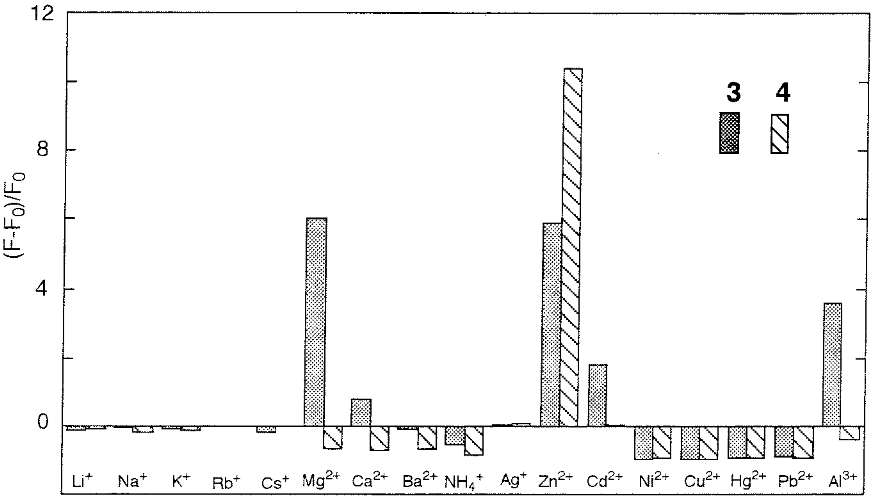


Figure 7. Effects of metal cations on fluorescence intensity of **3** and **4**: [**3**] = [**4**] = 1.0 × 10^{-5} M in methanol, [metal cation] = 5.0 × 10^{-4} M, λ_{ex} = 298.5 nm for **3** and 306.5 nm for **4**. F_0 stands for fluorescence intensity without metal cation, *F* for fluorescence intensity with metal cation. Thiocyanate salts are used for alkali and alkaline earth metal cations and ammonium cation. For other metal cations, perchlorate salts are used.

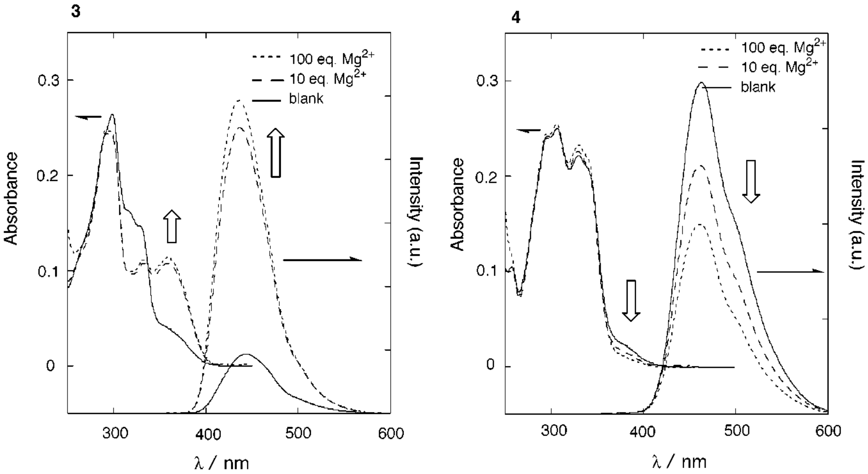


Figure 8. Absorption and fluorescence spectra of **3** and **4** in the presence of magnesium cation: [**3**] = [**4**] = 1.0 × 10^{-5} M in methanol, λ_{ex} = 298.5 nm for **3** and 306.5 nm for **4**.

and **4** under acidic conditions, generated by cadmium cation and methanol, giving rise to fluorescence quenching (Figure 10, eq 1). Another interesting behavior is observed in the case of mercury cation. Thus, fluorescence intensity of **3** or **4** decreases but absorbance at longer wavelength reversely increases, as the concentration of mercury cation increases. The change in absorbance in the case of **4** is too small to evaluate the association constant, whereas in the case of **3** the 1:1 complexation and its association constant (K = 5.9 × 10^5 M^{-1}) could be evaluated by the curve fitting of the absorbance change. Observations that excitations in longer wavelength bands resulted in no fluorescence in both cases of **3** and **4** indicate rather low quantum yields of **5** (X = O and S, M^{n+} = Hg^{2+}). It should be added that fluorescence behavior of **3** and **4** with nickel, copper and lead cations is similar to those with mercury cation.

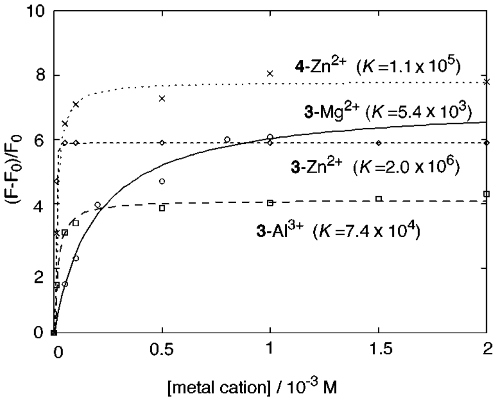


Figure 9. Fluorescence enhancement of **3** and **4** in methanol upon addition of metal cation: [**3**] = [**4**] = 1.0 × 10^{-5} M, λ_{ex} = 298.5 nm for **3**, 306.5 nm for **4**. F_0 stands for fluorescence intensity without metal cation, *F* for fluorescence intensity with metal cation. Estimated association constants (K/M^{-1}) are shown in parentheses.

In conclusion, **3** and **4** were found to be very sensitive to the pH change at pH 7−8, giving rise to large fluorescence enhancement under basic conditions. They can be regarded as the very sensitive pH sensors, and the relatively large Stokes shift, compared to the conventional fluorophores such as fluorescein, is characteristic of them. For metal cation sensing, it was found that **3** was applicable to the fluorescent probe sensing mag-

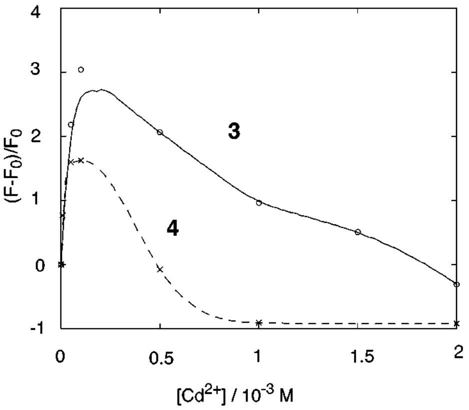


Figure 10. Fluorescence change of **3** and **4** in methanol upon addition of cadmium cation: [**3**] = [**4**] = 1.0×10^{-5} M, λ_{ex} = 298.5 nm for **3** and 306.5 nm for **4**. F_0 stands for fluorescence intensity without Cd^{2+}, F for fluorescence intensity with Cd^{2+}.

nesium cation strongly among alkali and alkaline earth metal cations and **4** was suitable for sensing zinc cation. The ease of exchange of phenolic proton with a metal cation in almost neutral methanol solution arises from the strongly electron-withdrawing fluorine atoms, and the strategy that phenol moiety is exchanged for fluorinated phenol moiety will be applicable to other probes recognizing metal cations.

Experimental Section

General Methods. The IR spectra were measured in KBr pellets. The 400 MHz ^{1}H and 376 MHz ^{19}F NMR spectra were measured for solutions of $CDCl_3$, unless otherwise noted. The chemical shifts are given in δ/ppm downfield from tetramethylsilane as an internal standard for ^{1}H NMR and from hexafluorobenzene as an external standard for ^{19}F NMR, respectively; J values are given in Hz. The absorption and fluorescence spectra were recorded at room temperature. Methanol, toluene, cyclohexane, ethyl acetate, and acetonitrile for spectroscopy were the highest quality from KOKUSAN Chemical Co. and were used without further purification. Fluorescence quantum yields were relatively estimated on the basis of $\Phi_F = 0.786$ for 2-phenylbenzoxazole in cyclohexane.[17] 2-(Pentafluorophenyl)benzoxazole was prepared according to the previously reported method.[6]

2-(3,5,6-Trifluoro-2-hydroxy-4-methoxyphenyl)benzoxazole (3). A mixture of 2-(pentafluorophenyl)benzoxazole (2.00 g, 7.02 mmol) and sodium methoxide (0.76 g, 14.1 mmol) in 60 mL of methanol was stirred at room temperature for 2 h. After removal of the solvent, the mixture was extracted with ethyl ether, and the extracts were washed with water and brine, dried over magnesium sulfate, and evaporated to leave a residue. Chromatography on silica gel (hexane) of the residue produced 1.58 g (76%) of 2-(2,3,5,6-tetrafluoro-4-methoxyphenyl)benzoxazole, which was recrystallized from hexane: white crystals; mp 87−88 °C; IR 2960 (CH), 1650 (C_6F_4), 1230 cm^{-1} (COC); ^{1}H NMR δ 7.88 (m, 1H), 7.65 (m, 1H), 7.43 (m, 2H), 4.22 (t, J = 1.8 Hz, 3H); ^{19}F NMR δ 23.5 (AA′BB′, 2F), 5.1 (AA′BB′, 2F). Anal. Calcd for $C_{14}H_7NF_4O_2$: C, 56.56; H, 2.38; N, 4.71. Found: C, 56.67; H, 2.19.; N, 4.71.

Thus obtained 2-(2,3,5,6-tetrafluoro-4-methoxyphenyl)benzoxazole (0.20 g, 0.67 mmol) and crushed sodium hydroxide (0.10 g, 2.50 mmol) were stirred at 50 °C for 48 h in 10 mL of dioxane. The mixture was acidified with 1 M hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water and brine, dried over magnesium sulfate, and evaporated to leave a solid. Chromatography on silica gel (hexane/ethyl acetate, 3:1) of the solid produced 0.18 g (91%) of **3**, which was recrystallized from hexane−ethyl acetate to give white crystals: mp 132−134 °C; IR 3100−2600 (OH), 2950 (CH), 1660 (C_6F_3), 1250, 1230 cm^{-1} (COC); ^{1}H NMR δ 12.27 (s, 1H), 7.77 (m, 1H), 7.68 (m, 1H), 7.45 (m, 2H), 4.19 (dd, J = 3.4, 1.8 Hz, 3H); ^{19}F NMR δ 23.4 (dd, J = 21.4, 10.9 Hz, 1F), 7.3 (d, J = 10.9 Hz, 1F), −0.5 (d, J = 21.4 Hz, 1F). Anal. Calcd for $C_{14}H_8NF_3O_3$: C, 56.94; H, 2.73; N, 4.75. Found: C, 57.03; H, 2.69.; N, 4.73.

2-(3,5,6-Trifluoro-2-hydroxy-4-methoxyphenyl)benzothiazole (4). A mixture of pentafluorobenzaldehyde (6.00 g, 30.6 mmol), 2-aminothiophenol (3.83 g, 30.6 mmol), and acetic acid (1 mL) in 50 mL of ethanol was stirred at 60 °C for 42 h. After the solvent was removed, the residue was extracted with ethyl acetate. The extracts were washed with aqueous sodium bicarbonate, water, and brine and dried over sodium sulfate. The extracts were evaporated to leave a residue that was chromatographed on silica gel (hexane/ethyl acetate, 5:1) to give 4.98 g (54%) of 2-(pentafluorophenyl)benzothiazole. Further purification was performed by recrystallization from hexane−ethyl acetate to give pale yellow crystals: mp 118−120 °C; IR 2900 (CH) and 1650 cm^{-1} (C_6F_5); ^{1}H NMR δ 8.21 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.59 (dt, J = 7.0, 1.3 Hz, 1H), 7.51 (dt, J = 7.1, 1.2 Hz, 1H); ^{19}F NMR δ 24.0 (m, 2F), 12.2 (tt, J = 21.1, 3.4 Hz, 1F), 1.7 (m, 2F). Anal. Calcd for $C_{13}H_4NF_5S$: C, 51.83; H, 1.34; N, 4.65. Found: C, 51.96; H, 1.33; N, 4.37.

A mixture of 2-(pentafluorophenyl)benzothiazole (1.00 g, 3.32 mmol) and sodium methoxide (0.30 g, 5.56 mmol) in 50 mL of methanol was stirred at room temperature for 2 h. After the solvent was removed, the residue was extracted with ethyl acetate. The extracts were washed with water and brine, dried over sodium sulfate, and evaporated to leave a residue that was recrystallized from hexane−ethyl acetate to give 0.74 g (71%) of 2-(2,3,5,6-tetrafluoro-4-methoxyphenyl)benzothiazole: white needles; mp 97−98 °C; IR 2950 (CH), 1640 (C_6F_4), 1200, 1160 cm^{-1} (COC); ^{1}H NMR δ 8.19 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.57 (m, 1H), 7.49 (m, 1H), 4.20 (tt, J = 1.7, 0.7 Hz, 3H); ^{19}F NMR δ 24.7 (AA′BB′, 2F), 7.6 (AA′BB′, 2F). Anal. Calcd for $C_{14}H_7NF_4OS$: C, 53.67; H, 2.25; N, 4.47. Found: C, 53.58; H, 2.15; N, 4.60.

A mixture of 2-(2,3,5,6-tetrafluoro-4-methoxyphenyl)benzothiazole (1.00 g, 3.19 mmol), crushed sodium hydroxide (1.28 g, 32.0 mmol), and 18-crown-6-ether (0.43 g, 1.63 mmol) in 75 mL of dioxane was stirred at 60 °C for 70 h. After acidification with 1 M of hydrochloric acid, the mixture was extracted with ethyl acetate. The extracts were washed with water and brine and dried over sodium sulfate. The extracts were evaporated to leave a residue that was chromatographed on silica gel with eluents of hexane/ethyl acetate/triethylamine (2:2:1) and then with eluents of hexane/ethyl acetate (1:1) to give 0.66 g (66%) of **4**. Further purification was performed by recrystallization from hexane−ethyl acetate to give pale yellow crystals: mp 157−158 °C; IR 3100−2600 (OH), 2950 (CH), 1650 (C_6F_3), 1210, 1170 cm^{-1} (COC); ^{1}H NMR δ 13.70 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 4.18 (t, J = 1.5 Hz, 3H); ^{19}F NMR δ 24.0 (dd, J = 22.0, 9.0 Hz, 1F), 6.9 (d, J = 9.0 Hz, 1F), −1.6 (d, J = 22.0 Hz, 1F). Anal. Calcd for $C_{14}H_8NF_3O_2S$: C, 54.02; H, 2.59; N, 4.50. Found: C, 54.06; H, 2.69; N, 4.35.

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