Fluorescent Behavior of 2-(3,4,5,6-Tetrafluoro-2-hydroxyphenyl)imidazo-[1,2-*a*]pyridine in the Presence of Metal Perchlorate

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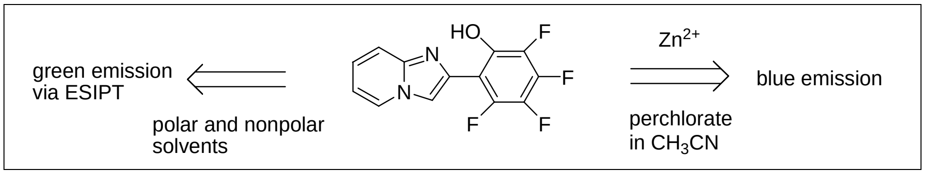

2-(3,4,5,6-Tetrafluoro-2-hydroxyphenyl)imidazo[1,2-*a*]pyridine (**1**) emits long wavelength light around 540 nm both in polar and in nonpolar solvents. Zn^{2+} perchlorate in acetonitrile causes the intermediate wavelength emission around 430 nm, which is ascribed to the species where the imidazole nitrogen atom and the phenolate oxygen atom bridge Zn^{2+}. In the presence of Hg^{2+} and Al^{3+} perchlorates, short wavelength emission around 370 nm is strongly increased and this fluorescent enhancement is attributable not to the coordination of Hg^{2+} and Al^{3+} to **1** but to the formation of the salt of perchloric acid of **1**.

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INTRODUCTION

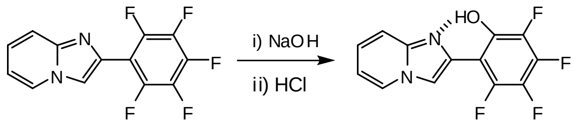
Fluorescence of 2-(2-hydroxyphenyl)benzazoles *via* the excited state intramolecular proton transfer (ESIPT) has been widely studied from the viewpoint of photophysics [1]. The benzazoles emit long wavelength fluorescence around >480 nm *via* the ESIPT process of the excited state of the intramolecularly hydrogen bonded enol in nonpolar solvent. The intensity of short wavelength fluorescence around 380 nm, which arises from the excited state of the intermolecularly hydrogen bonded rotamer, gradually increases in accordance with increase of the polarity of solvent [2,3]. In our continuing research on the function of polyfluoro-benzene derivatives [4], we have reported that 2-(3,5,6-trifluoro-2-hydroxy-4-methoxyphenyl)-benzoxazole and -benzothiazole emit similar long wavelength fluorescence in nonpolar solvents and exclusively emit the intermediate wavelength fluorescence around 450 nm in a polar solvent such as acetonitrile and methanol, which is assumed to emit from the excited state of the corresponding phenolate anions of these fluorophores. The strongly electron-withdrawing fluorine atoms of these fluorophores make it possible to exchange the phenolic proton with a metal cation in a neutral methanol solution to result in the enhancement of the intermediate wavelength fluorescence. These properties can be applied to the fluorescent probes that can sense magnesium and zinc cations [5]. On the other hand, 2-(2-hydroxyphenyl)imidazo[1,2-*a*]-pyridine is well established to have a similar fluorescence *via* the ESIPT process, where the 1-nitrogen atom plays a role as strong acceptor of the intramolecular hydrogen bonding [6,7]. Therefore, it is expected that 2-(3,4,5,6-tetrafluoro-2-hydroxy-phenyl)-imidazo[1,2-*a*]pyridine (**1**) strongly captures a metal cation, because it has strong recognition-sites: tetrafluorophenolate and the 1-nitrogen atom of the imidazopyridine ring. In this paper, we demonstrate the fluorescent behavior of **1** in the presence/absence of metal perchlorate.

RESULTS AND DISCUSSION

The hydroxyimidazopyridine **1** was synthesized by hydroxylation of 2-(pentafluorophenyl)imidazo[1,2-*a*]-pyridine (**2**) with sodium hydroxide in 73% yield. The compound **2** was prepared by condensation of bromomethyl pentafluorophenyl ketone and 2-amino-pyridine. The *ortho*-substituted position in hydroxylation was determined by ^{19}F NMR analysis. Substitution at *para* position, as was observed in hydroxylation of 2-(-pentafluoro-phenyl)-benz-oxazole, was anticipated, but no formation of any *para*-substituted product was detected. The selective *ortho* substitution seems to be ascribed to the relatively strong coordination of sodium cation to the imidazole nitrogen atom of **2** to result in the acceleration of the *ortho* attack by the accompanying hydroxide. In the ^{1}H NMR spectrum of **1** in $CDCl_3$, the hydroxy proton appears highly deshielded (13.97 ppm) and the 3-hydrogen atom couples with the 6-fluorine atom at 4.0 Hz, suggesting a planar ground-state conformation with an intramolecular hydrogen bond, as shown in

Scheme 1. It should be noted that no similar H-F coupling appears in the compound **2**.

Scheme 1



2 **1**

In the fluorescence spectra of **1**, long wavelength emission *via* the ESIPT process in a nonpolar solvent such as toluene is blue-shifted to λ_{em} = 540 nm, compared with that (λ_{em} = 588 nm in cyclohexane) of the analogous non-fluorinated 2-(2-hydroxyphenyl)imidazo[1,2-*a*]-pyridine **3** [6]. Similarly, long wavelength emission of **1** *via* the ESIPT process is exclusively observed in dioxane. This is in sharp contrast to that of **3**, which in dioxane fluoresces short wavelength emission at λ_{em} = 379 nm from the excited state of the intermolecularly hydrogen bonded rotamer, together with the emission *via* the ESIPT process. These fluorescent properties suggest the rather rigid intramolecular hydrogen bonding at an excited state of **1**. Weak emission *via* the ESIPT process appears also in acetonitrile and its fluorescence quantum yield was estimated to be Φ_f = 0.015. However, no intermediate wavelength emission attributable to the phenolate anion of **1**, such as is observed in the cases of the fluorinated 2-(2-hydroxyphenyl)benzoxazoles, is detected (Figure 1). But in protic solvent such as methanol-water (9/1), intermediate wavelength emission appears faintly, with no emission *via* the ESIPT process.

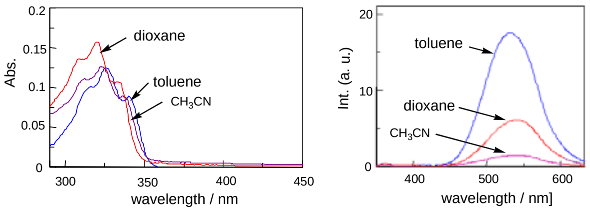


Figure 1. Absorption and fluorescence spectra of **1** in toluene, in dioxane, and in acetonitrile. [**1**] = 1.0x10^{-5} M, λ_{ex} = 326 nm.

The pH dependence of the absorption was measured in the methanol-water solution (Figure 2). Absorbance at a longer wavelength around 350 nm is noticed under basic conditions; this is attributable to the phenolate species of **1**. The pK_a value was estimated to be 8.6±0.1 based on the curve fitting method using the absorbance change at 350 nm. Excitation at 350 nm under basic conditions does not show any meaningful enhancement of intermediate wavelength emission. These facts indicate that the quantum yield of the phenolate species of **1** is small.

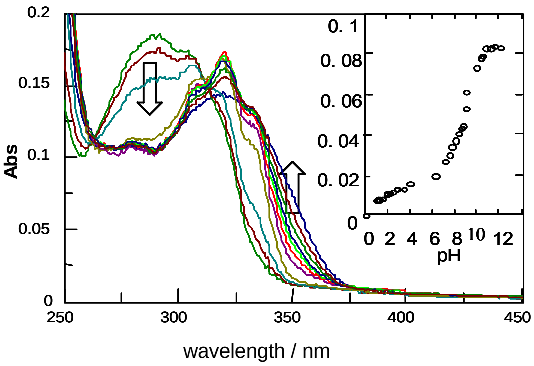


Figure 2. Spectral change of **1** between pH 1 and pH 12. [**1**] = 1.0x10^{-5} M, solvent: MeOH / H_2O = 9 / 1, [NaCl] = 0.1 M. The inset shows the absorbance change at 350 nm.

The effect of metal cation on the emission of **1** was investigated in acetonitrile using metal perchlorates, which are conventionally used as sources of metal cations. Alkali metal cations (Li^+, Na^+, K^+, Rb^+, Cs^+), alkaline earth metal cations (Mg^{2+}, Ca^{2+}, Ba^{2+}), Cd^{2+}, and Ag^+ cations do not cause any meaningful changes in fluorescence or absorption, even though 100 molar ratio of cations were added. However, Zn^{2+}, Hg^{2+}, and Al^{3+} cations bring about fluorescence enhancement; it was found that the fluorescence wavelength is dependent on the added metal perchlorate. Zn^{2+} perchlorate causes a new fluorescence of the intermediate wavelength emission (λ_{em} = 430 nm) (Figure 3b) and an increase in absorbance at longer wavelength around 350 nm (Figure 3a). From these spectral behaviors, we assume that the species where the imidazole nitrogen atom and the phenolate oxygen atom bridge Zn^{2+} is formed and that the coplanarity causes the 430 nm emission [1c,5,8]. In the case of Hg^{2+} perchlorate, absorbance around 350 nm gradually increases, as the concentration of Hg^{2+} perchlorate increases in the range of 0 to 0.45 molar ratio of **1**. But in the more concentrated range, it reverses direction and decreases with the increase of the concentration of Hg^{2+} perchlorate (Figures 4a and 4'). In contrast, the absorbance around 280 nm and the 370 nm emission simply increase in these concentrations (Figure 4b). Such spectral behavior suggests the formation of two species: one is a species similar to that of Zn^{2+}, which absorbs at longer wavelength, but in this case has rather low quantum yield of the intermediate wavelength emission [5a], and the other is a species that causes the 370 nm emission. Two similar species seem to be formed with Al^{3+} perchlorate, but the formation of the species causing the red-shifted absorption is only detected in quite low concentrations of Al^{3+} perchlorate (Figure 5a). Another species absorbing around 280 nm emits the strong 370 nm fluorescence (Figure 5b). It should be added that the intensity of the 370 nm emission is very sensitive to the water-proportion of the acetonitrile solution; 1.75% of water reduces the intensity to 1/7.5.

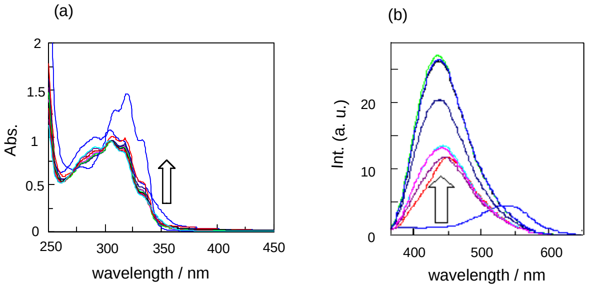


Figure 3. Absorption (a) and fluorescence (b) spectral changes with increase of Zn^{2+}. [**1**] = 1.0×10^{-4} M for absorption spectra and 1.0×10^{-5} M for fluorescence spectra, [Zn^{2+}] = 0~10 equivalent of **1**, Zn^{2+}: $Zn(ClO_4)_2 \cdot 6H_2O$, solvent: acetonitrile, λ_{ex} = 350 nm.

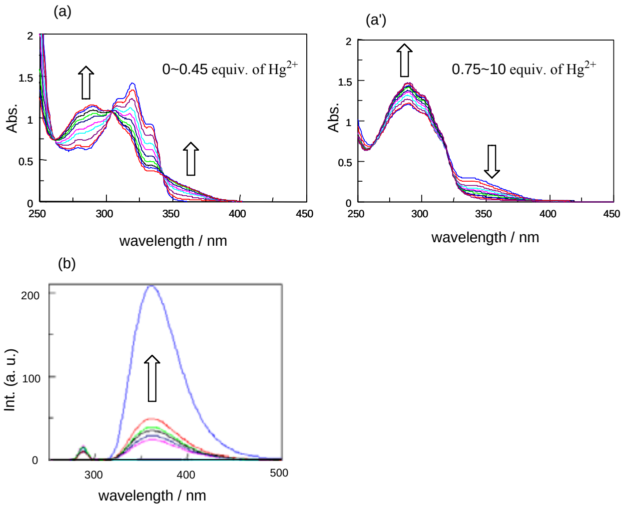


Figure 4. Absorption (a and a') and fluorescence (b) spectral changes with increase of Hg^{2+}. [**1**] = 1.0×10^{-4} M for absorption spectra and 1.0×10^{-5} M for fluorescence spectra, [Hg^{2+}] = 0~0.45 (a), 0.75~10 (a'), and 0~10 (b) equivalent of **1**, Hg^{2+}: $Hg(ClO_4)_2 \cdot 3H_2O$, solvent: acetonitrile, λ_{ex} = 284 nm.

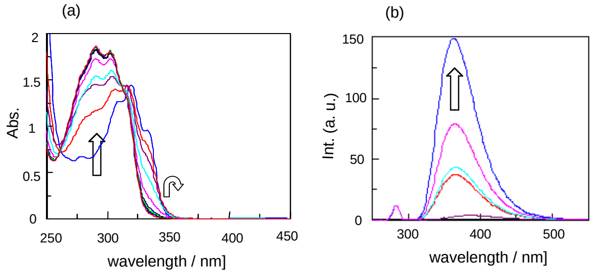


Figure 5. Absorption (a) and fluorescence (b) spectral changes with increase of Al^{3+}. [**1**] = 1.0×10^{-4} M for absorption spectra and 1.0×10^{-5} M for fluorescence spectra, [Al^{3+}] = 0~10 equivalent of absorption spectra and 0~2 equivalent of **1** for fluorescence spectra, Al^{3+}: $Al(ClO_4)_3 \cdot 9H_2O$, solvent: acetonitrile, λ_{ex} = 284 nm.

To determine the structure of the species causing the 370 nm emission, we studied the association behavior of Al^{3+} perchlorate using 2-(pentafluorophenyl)imidazo[1,2-*a*]pyridine (**2**) as a model of **1**. Similarly to **1**, increases in fluorescence around 350 nm and absorbance around 280 nm occur in acetonitrile due to the increase of Al^{3+} perchlorate (Figure 6: **2** and Al^{3+}). The Job's plot seems to support the formation of a 2:1 complex of **2** and Al^{3+} (Figure 7a). Isolation and crystallization of the product were attained by standing a mixture with a 2:1 ratio of **2** and $Al(ClO_4)_3 \cdot 9H_2O$ in hexane-acetone. The UV-vis spectra of the isolated compound **4** are the same as those of a mixture of **2** and $Al(ClO_4)_3 \cdot 9H_2O$ and the fluoresecent spectra also show the strong 350 nm emission (Figure 6). The ORTEP drawing taken in X-ray analysis shows that the ClO_4 moiety is sandwiched between two protonated imidazopyridines **2** (Figure 8) [9]. Thus, it is confirmed that the coordination of Al^{3+} is not participated to the complexation but the salt of perchloric acid is formed. The Job's plot (Figure 7a) will be explained by the assumption that the following hydrolysis is involved in the solvent.

$$Al(ClO_4)_3 \cdot 9H_2O \rightarrow 2HClO_4 + Al(ClO_4)(OH)_2 \cdot 7H_2O$$

The protonation will contribute to the coplanarity of the imidazopyridine ring and the pentafluorophenyl group to result in enhancement of the 350 nm emission.

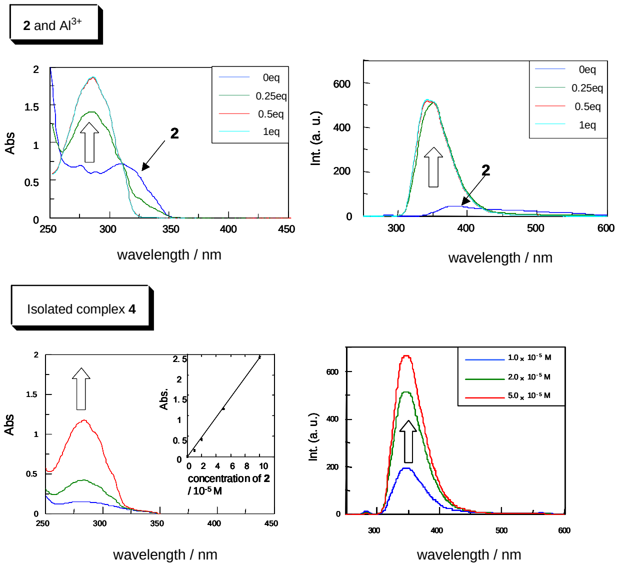


Figure 6. **2** and Al^{3+}; Spectral change of **2** with increase of Al^{3+}. [**2**] = 1.0×10^{-4} M, Al^{3+}: $Al(ClO_4)_3 \bullet 9H_2O$, solvent: acetonitrile. Isolated complex **4**; Concentration dependence on spectra of isolated complex.

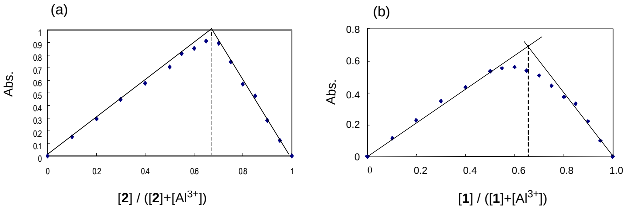


Figure 7. Job plots of (a) **2** and Al^{3+}; (b) **1** and Al^{3+}. [**2**] = [**1**] = 1.0×10^{-4} M, Al^{3+}: $Al(ClO_4)_3 \cdot 9H_2O$, solvent: acetonitrile.

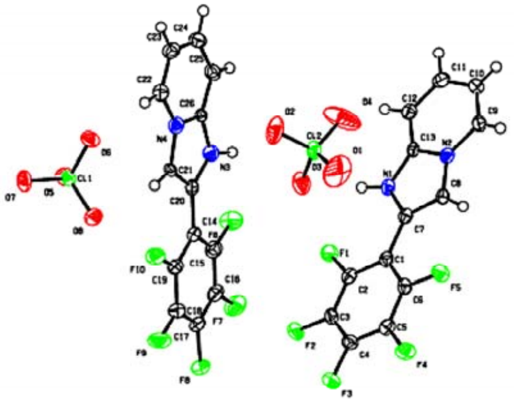


Figure 8. ORTEP view of the compound **4**.

Based on the spectral behavior and the Job's plot (Figure 7b), a species similar to **4** is deduced for the case of **1** and $Al(ClO_4)_3 \cdot 9H_2O$. Preferential formation of the similar species is assumed to be dependent on the acidity of metal perchlorates. So the pH values of the methanol-water solution of Zn^{2+}, Hg^{2+}, and Al^{3+} perchlorates were measured and are summarized in Table 1. The pH value of **1** ([**1**] = 1.0×10^{-4} M) under the same conditions is 7.1. If these values are assumed to be comparable to those in acetonitrile, acidic Al^{3+} perchlorate forms the salt of perchloric acid of **1** even in rather low concentration, while the neutral Zn^{2+} perchlorate forms the species in which the phenolate participates even in higher concentrations. Hg^{2+} perchlorate provides an intermediate acidity between Zn^{2+} and Al^{3+} perchlorates and so both species can coexist under low concentration, but under higher concentration the medium becomes more acidic to result in the formation of the salt of perchloric acid of **1**, leading to the enhancement of the 370 nm emission.

Table 1

The pH values of aqueous methanol solutions of metal perchlorates[1)]

	concentration of perchlorate	
	1.0×10^{-4} M	1.0×10^{-3} M
$Al(ClO_4)_3 \cdot 9H_2O$	4.1	3.7
$Hg(ClO_4)_2 \cdot 3H_2O$	6.8	4.4
$Zn(ClO_4)_2 \cdot 6H_2O$	7.0	7.1

1) Solvent: MeOH / H_2O = 9 / 1, [NaCl] = 0.1 M.

As a conclusion, long wavelength emission of **1** *via* the ESIPT process is exclusively observed even in polar solvent such as acetonitrile and no intermediate and short wavelength emissions attributable to the phenolate anion and the intermolecularly hydrogen bonded rotamer of **1**, respectively, are detected. In the presence of Li^+, Na^+, K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, Cd^{2+}, Ag^+, Zn^{2+}, Hg^{2+}, or Al^{3+} perchlorate in acetonitrile, only Zn^{2+} perchlorate causes an enhancement of the intermediate wavelength emission (λ_{em} = 430 nm), which is ascribed to the species where the imidazole nitrogen atom and the phenolate oxygen atom bridge Zn^{2+}. In the presence of Hg^{2+} and Al^{3+} perchlorates, short wavelength emission (λ_{em} = 370 nm) was strongly increased and this fluorescent enhancement is attributable not to the coordination of Hg^{2+} and Al^{3+} to **1** but to the formation of the salt of perchloric acid of **1**.

EXPERIMENTAL

General Methods. The FTIR spectra were run as KBr pellets. The UV-vis and fluorescent spectra were recorded in toluene, dioxane, or acetonitrile of the highest quality for spectroscopy (KOKUSAN Chemical Co.) without further purification. The chemical shifts are given in δ/ppm downfield from tetramethylsilane as an internal standard for ^1H nmr spectra and downfield from trifluoroacetic acid as an external standard for ^{19}F nmr spectra, respectively; J values are given in Hz. The fluorescence quantum yields were estimated relatively, on the basis of $\Phi_f = 0.78$ for 2-phenylbenzoxazole in cyclohexane [10].

2-(Pentafluorophenyl)imidazo[1,2-*a*]pyridine (2). A solution of bromomethyl pentafluorophenyl ketone (3.00 g, 10.4 mmol) in 30 mL of DMF was added dropwise to a solution of 2-aminopyridine (0.98 g, 10.4 mmol) in 30 mL of DMF. The mixture was stirred at 60 °C for 2 h and then ethyl acetate was added to the reaction mixture. The mixture was washed with water, with 5% aqueous sodium hydrogen-carbonate, and with brine. The mixture was dried over anhydrous magnesiun sulfate and evaporated. The resulting residue was chromatographed on silica gel (hexane/ethyl acetate = 1/1) to give 2.51 g (85% yield) of **2**. Recrystallization from hexane-ethyl acetate was carried out to give white needles of **2**: mp 153-154 °C; FT/IR (KBr): *ν* 3163, 3043, 1655, 1636, 1548, 1528, 1520, 1510, 1505, 1471, 1366, 1088, 985, 973, 756 cm^{-1}; UV-vis (CH_3CN): λ_{max} (log ε/L mol^{-1} cm^{-1}) 275.5 (4.04), 310 nm (4.04); ^1H nmr (400 MHz, CD_3CN): δ 6.92 (td, 1H, J = 6.8, 1.2 Hz), 7.30 (ddd, 1H, J = 9.2, 6.8, 1.2 Hz), 7.58 (1H, d, J = 9.2 Hz), 8.14 (s, 1H), 8.38 (dt, 1H, J = 6.8, 1.2 Hz); ^{19}F nmr (376 MHz, CD_3CN): δ -87.8 (m, 2F), -81.3 (t, 1F, J = 21.8 Hz), -65.6 (m, 2F). *Anal.* Calcd for $C_{13}H_5F_5N_2$: C, 54.94; H, 1.77; N, 9.86. Found : C, 54.85; H, 1.52; N, 9.87.

2-(2,3,5,6-Tetrafluoro-2-hydroxyphenyl)imidazo[1,2-*a*]pyridine (1). A mixture of **2** (250 mg, 0.88 mmol) and crushed sodium hydroxide (350 mg, 8.75 mmol) in 10 mL of dioxane was stirred at 80 °C for 44 h. Water was added to the reaction mixture and the aqueous mixture was washed with ethyl acetate and, after being acidified with 1 *M* of hydrochloric acid, the mixture was extracted with ethyl acetate. The extracts were washed with water and brine, and dried over anhydrous sodium sulfate. The extracts were evaporated to leave a residue which was chromatographed on silica gel with eluents of hexane/ethyl acetate (1/1) to give 180 mg (73%) of white solid **1**. Further purification was performed by recrystallization from hexane-acetone to give white crytals of **1**: mp 262-263 °C; FT/IR (KBr): ν 3173, 3152, 1638, 1517, 1483, 1430, 1366, 1083, 991, 860, 755, 739 cm^{-1}; UV-vis (toluene): λ_{max} (log ε/L mol^{-1} cm^{-1}) 313 (sh, 4.03), 326 (4.12), 340 nm (3.97); ^{1}H nmr (400 MHz, $CDCl_3$): δ 6.95 (dd, 1H, J = 6.8, 7.2 Hz), 7.34 (dd, 1H, J = 9.2, 6.8 Hz), 7.63 (d, 1H, J = 9.2 Hz), 8.03 (d, 1H, J = 4.0 Hz), 8.22 (d, 1H, J = 7.2 Hz), 13.97 (s, 1H); ^{19}F nmr (376 MHz, $CDCl_3$): δ –96.6 (td, 1F, J = 20.3, 5.6 Hz), -87.9 (ddd, 1F, J = 20.3, 7.8, 5.6 Hz), -81.6 (td, 1F, J = 20.3, 2.3 Hz). –66.3 (dddd, 1F, J = 20.3, 7.8, 4.0, 2.3 Hz). *Anal*. Calcd for $C_{13}H_6F_4N_2O$: C, 55.33; H, 2.14; N, 9.93. Found: C, 55.21; H, 2.04; N, 9.84.

Compound 4 from 2 and $Al(ClO_4)_3{\cdot}9H_2O$. A mixture of **2** (200 mg, 0.70 mmol) and $Al(ClO_4)_3{\cdot}9H_2O$ (170 mg, 0.35 mmol) was dissolved in a minimum amount of acetone. After a slightly excess amount of hexane was added to the mixture, the resulting solution was allowed to stand at room temperature for 5 days. The formed crystals were collected on a filter and washed with a cooled mixture of acetone and hexane (1/3) several times, giving 40 mg (30%) of colorless crystals **4**: mp 155-157 °C; FT/IR (KBr): ν 3393, 1659, 1521, 1505, 1116, 1089, 986 cm^{-1}; UV-vis (CH_3CN): λ_{max} (log ε/L mol^{-1} cm^{-1}) 284 nm (4.37); ^{1}H nmr (400 MHz, CD_3CN): δ 7.54 (td, 1H, J = 6.4, 1.2 Hz), 8.00 (d, 1H, J = 9.2 Hz), 8.04 (ddd, 1H, J = 9.2, 6.4, 1.2 Hz), 8.46 (s, 1H), 8.67 (dt, 1H, J = 6.4, 1.2 Hz); ^{19}F nmr (376 MHz, CD_3CN): δ -85.1 (m, 2F), -74.4 (tt, 1F, J = 20.7, 4.0 Hz), -63.6 (m, 2F). *Anal*. Calcd for $C_{13}H_6ClF_5N_2O_4$: C, 40.59; H, 1.57; N, 7.28. Found: C, 40.78; H, 1.56; N, 7.30.

Crystal data for 4: $C_{26}H_{12}Cl_2F_{10}N_4O_8$, M = 769.29, monoclinic, space group P 1 21/c 1, a = 5.2084(11), b = 27.495(6), c = 19.252(4) Å, $\alpha = 90^{\circ}$, β = 91.0712(9), γ = 90, V = 2756.5(10) Å^3, T = 123.1 K, Z = 4, D_c = 1.854 g cm^{-3}, λ = 0.7107 Å, 5905 reflections measured, 16800 unique (R_{int} = 0.028). R_1 = 0.055 and R_w = 0.139.

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