



Synthesis and fluorescence properties of difluoro[amidopyrazinato-*O,N*]boron derivatives: a new boron-containing fluorophore

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ABSTRACT

New boron-containing fluorophores, difluoro[amidopyrazinato-*O,N*]boron (APB) derivatives, were prepared from amidopyrazines. The fluorescence properties of APB were successfully modulated by an aryl substitution at the C8 position.

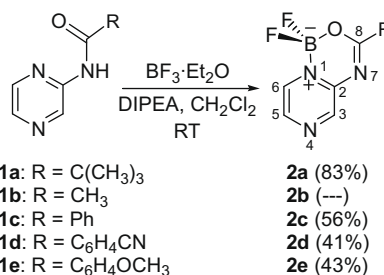
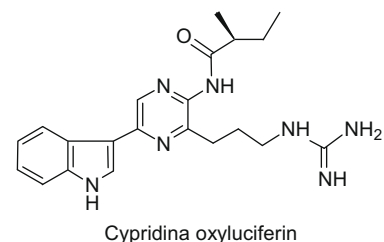
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Cypridina oxyluciferin (Scheme 1) and coelenteramide are the light-emitter compounds for bioluminescence of the ostracod *Cypridina*¹ and the jellyfish *Aequorea*,² respectively. These light-emitter compounds have an amidopyrazine core structure. We investigated the fluorescence properties of the derivatives of *Cypridina* oxyluciferin and coelenteramide and found that the excited singlet states of these compounds have an intramolecular charge transfer (ICT) character and show fluorescence solvatochromism.³ Because fluorescent compounds are widely used in many applications, such as fluorescent sensors for biological imaging and light-emitting components for organic light-emitting devices,⁴ one of our goals is to design a new fluorescent compound based on *Cypridina* oxyluciferin and coelenteramide. We attempted to modify the chemical structure of amidopyrazine using the methodology for preparing boron dipyrromethene (BODIPY).⁵ We then successfully prepared new boron-containing fluorophores, difluoro[amidopyrazinato-*O,N*]boron (APB) derivatives (**2**), by the reactions of amidopyrazines (**1**) with BF₃ (Scheme 1). In this Letter, we describe the synthesis and fluorescence properties of these APB derivatives **2**.

Pivalamidopyrazine **1a** was treated with BF₃·Et₂O in the presence of *N,N*-diisopropylethylamine (DIPEA) at room temperature to give 8-*t*-butyl APB (**2a**) in 83% yield.⁶ Although acetamidopyrazine **1b** also reacted with BF₃·Et₂O in the presence of DIPEA, we could not isolate **2b** from the complex mixture of products. This result suggests that deprotonation of the methyl group at C8 induces decomposition of **2b**. Therefore, it would be preferable to use an amidopyrazine having a tertiary or aryl group at C8 for preparing APB compounds. We were also able to convert benzamidopyrazine **1c** and its derivatives **1d** and **1e** to the corresponding APBs **2c–e** in 40–60% yields. Crystal structure analysis of **2a** confirmed its APB skeleton (Fig. 1A).⁷ The boron-containing ring is slightly distorted by the introduction of the sp³ boron atom. The core bicyclic ring

of **2a** shows a bond length alternation (Fig. 1B). Unfortunately, however, APBs (**2**) were slowly decomposed to give **1** by solvolysis in a protic solvent such as methanol.

UV–vis absorption and fluorescence spectra of the APB derivatives (**2**) were measured in cyclohexane, chloroform, and acetonitrile.^{8,9} It was confirmed that the excitation spectra of the fluorescence agree with the corresponding absorption spectra. The spectral data are summarized in Table 1. Figure 2 shows representative spectra in chloroform. The lowest energy absorption bands of **2a** and **2c** in chloroform were observed at 331 and 353 nm, respectively, and fluorescence emission maxima (λ_f) of **2a** and **2c** were observed at 384 and 402 nm with quantum yields



Scheme 1. Structure of *Cypridina* oxyluciferin and synthesis of APB **2**.

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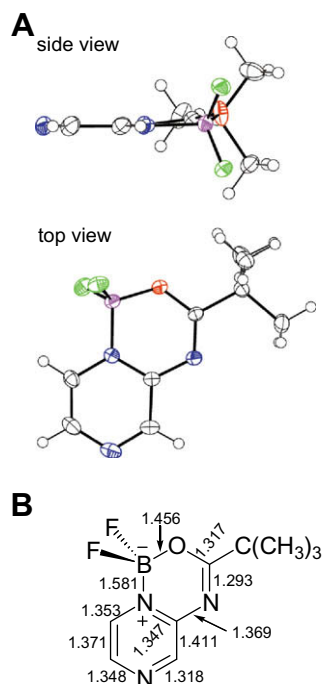


Figure 1. Molecular structure of **2a** (A) with the atomic displacements drawn at the 50% probability level and selected bond distances in a partial structure of **2a** (B).

Table 1
Electronic absorption and fluorescence of **2a** and **2c–e** in various solvents at 25 °C

Compound	Solvent	λ_{ab}/nm ($\epsilon/10^4$) ^a	λ_f/nm (Φ_f) ^b
2a	C ₆ H ₁₂	332 (0.86)	384 (0.078)
	CHCl ₃	331 (1.1)	384 (0.12)
	CH ₃ CN	329 (0.88)	386 (0.10)
2c	C ₆ H ₁₂	351 (2.6), 274 (1.7)	398 (0.18)
	CHCl ₃	353 (2.7), 274 (1.7)	402 (0.15)
	CH ₃ CN	349 (2.7), 268 (1.7)	395 (0.008)
2d	C ₆ H ₁₂	351 (2.0), 271 (1.4)	404 (0.013)
	CHCl ₃	354 (2.1), 271 (1.4)	408 (0.004)
	CH ₃ CN	351 (2.0), 266 (1.4)	n.d. ^c
2e	C ₆ H ₁₂	382 (3.0), 365 (3.2), 298 (1.2), 281 (1.2)	411, 396 (0.29)
	CHCl ₃	373 (2.9), 286 (1.1)	429 (0.16)
	CH ₃ CN	363 (2.9), 291 (1.1)	478 (0.062)

^a Absorption maximum (λ_{ab}) and extinction coefficient (ϵ in $\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$).

^b Fluorescence emission maximum (λ_f) and quantum yield (Φ_f).

^c Fluorescence was weak.

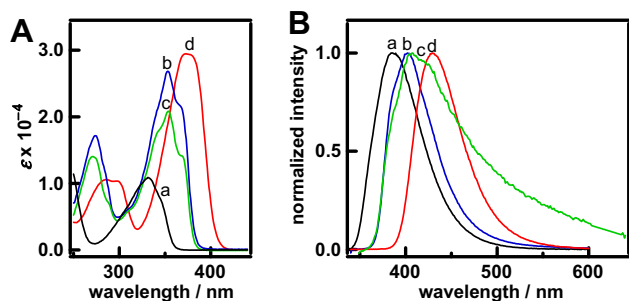


Figure 2. UV-vis absorption spectra (A) and fluorescence spectra (B) of **2a** (a), **2c** (b), **2d** (c), and **2e** (d) in chloroform at 25 °C.

(Φ_f) to be 0.12 and 0.15, respectively. This result indicates that the introduction of a phenyl group instead of a *tert*-butyl group at C8 induces 20 nm red shifts of the lowest energy absorption and fluorescence emission bands. Thus, the expansion of the π -electronic conjugation at C8 of the APB skeleton effectively modulates the spectroscopic characteristics. Another phenyl substitution effect appears to be an increase of the extinction coefficient of the lowest energy absorption band compared to that of **2a**. The absorption maxima (λ_{ab}) and the λ_f values of **2a**, **2c**, and **2d** indicate a slight dependency on solvent polarity,¹⁰ whereas the Φ_f value of **2c** in acetonitrile and that of **2d** were less than 0.01. On the other hand, 4-methoxyphenyl derivative **2e** showed fluorescence solvatochromism (Fig. 3). Although the lowest energy absorption bands of **2e** showed a small solvent-dependent variation at around 370 nm, the λ_f value of **2e** was red shifted with increased solvent polarity.¹⁰ This result indicates that the ICT character of the excited singlet state of **2e** is much greater than that of the ground state.

To better understand the observed structural and spectroscopic properties of the APB derivatives (**2**), DFT and time-dependent (TD) DFT calculations on **2** and amidopyrazines **1a** and **1c** were conducted at the B3LYP/6-31G(d) level (Table 2).^{11–14} Optimized structure of **2a** was very similar to the X-ray crystal structure of **2a**, whose boron-containing ring is bent. The HOMO and LUMO levels of **2a** and **2c** were lower than those of **1a** and **1c**, indicating that the electron-accepting character of the APB derivative is greater than that of the corresponding amidopyrazine. Although the excitation wavelengths (λ_{ex}) calculated for **2** were predicted to be shorter than their λ_{ab} values observed in cyclohexane, the relative differences in the λ_{ex} and λ_{ab} values among **2a** and **2c–e** agree well with each other. The finding that the oscillator strength (f) of **2c** is greater than that of **2a** also matches the difference in the ϵ values of the lowest energy absorption bands of **2a** and **2c**. Figure 4 shows the electron distribution of the HOMOs and LUMOs of **2c** and **2e**. While the HOMO and LUMO densities of **2c** are located on the APB skeleton, the HOMO and LUMO densities of **2e** are mainly localized on the 4-methoxyphenyl moiety and the APB skeleton, respectively. This result supports the premise that the excited singlet

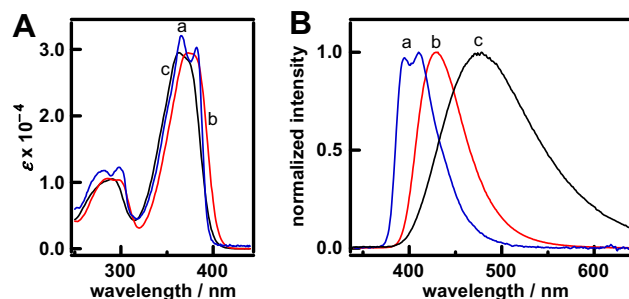


Figure 3. UV-vis absorption spectra (A) and fluorescence spectra (B) of **2e** in cyclohexane (a), chloroform (b), and acetonitrile (c) at 25 °C.

Table 2
HOMO and LUMO and vertical wavelengths (λ_{ex}) and oscillator strengths (f) for the allowed transitions to the excited singlet states with the lowest excitation energies for **1** and **2** obtained by DFT and TDDFT calculations at the B3LYP/6-31G(d) level

Compound	HOMO/eV	LUMO/eV	λ_{ex}/nm	f
1a	-6.41	-1.31	263	0.12
1c	-6.55	-1.50	271	0.28
2a	-7.14	-2.58	301	0.18
2c	-6.76	-2.64	333	0.42
2d	-7.15	-3.08	334	0.62
2e	-6.24	-2.47	363	0.44

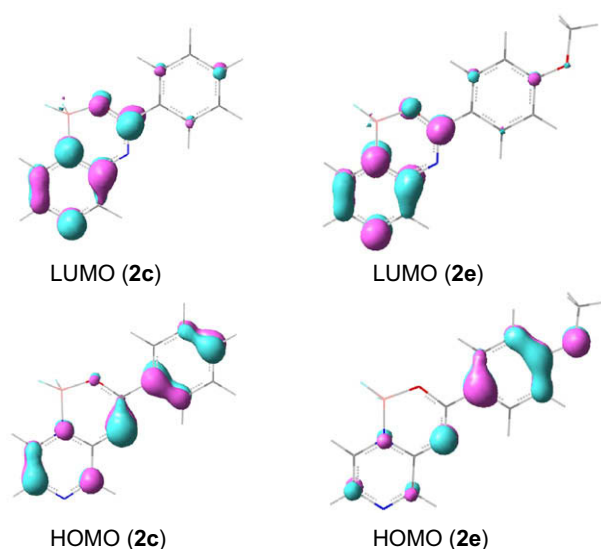


Figure 4. Frontier orbitals of **2c** and **2e** obtained by DFT calculations at the B3LYP/6-31G(d) level.

state of **2e** exhibits charge transfer from the 4-methoxyphenyl moiety to the APB skeleton.

In conclusion, we successfully prepared a new boron-containing fluorophore, APB **2**, by applying the conventional method for preparing BODIPY to amidopyrazine **1**. APB **2** is more fluorescent than the corresponding precursor **1**, and the fluorescence property of **2** was modulated by a substituent at C8. In particular, 4-methoxyphenyl derivative **2e** showed fluorescence solvatochromism. Further studies to reveal the redox property of APB and to modify APB for finding new light-emitting characters are now in progress.

Acknowledgment

We acknowledge technical assistances of computation for quantum chemical calculations from the Information Technology Center of UEC.

Supplementary data

Supplementary data (general experimental, synthesis of **1**, physical data of **2**, and DFT calculation data) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2010.01.072](https://doi.org/10.1016/j.tetlet.2010.01.072).

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- To a solution of **1a** (102 mg, 0.57 mmol) in dichloromethane (0.5 mL), diisopropylethylamine (0.14 mL, 0.76 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.16 mL, 1.13 mmol) were added at room temperature under Ar, and the reaction mixture was stirred over night. The reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (SiO_2 , chloroform/ethyl acetate) to give **2a** (108 mg, 83%) as colorless cubes.
- Single crystals of **2a** were obtained by recrystallization from hexane. Diffraction data were collected with a Rigaku AFC-8 CCD diffractometer using multi-layer confocal-mirror monochromated and focused $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) at 90 K. The structure was solved by direct methods using the program SIR-2004 [Burla, M. C.; Caliendo, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R., *J. Appl. Crystallogr.* **2005**, *38*, 381–388]. Refinements were carried out by a least-squares method on F^2 using the program SHELXL-97 [Sheldrick, G. M. *Acta Crystallogr. Sect. A*, **2008**, *64*, 112–122]. Crystal data are as follows: $\text{C}_9\text{H}_{12}\text{BF}_2\text{N}_3\text{O}$, $M = 227.03$, tetragonal, space group $I4_1/a$, $a = 16.380(2)$, $c = 16.240(3) \text{ \AA}$, $V = 4357.3(11) \text{ \AA}^3$, $Z = 16$, $D_x = 1.384 \text{ Mg m}^{-3}$, $\mu = 0.115 \text{ mm}^{-1}$, 3199 unique data, final $R(F) = 0.0390$, $wR(F^2) = 0.0976$ for 2827 observed data [$I > 2\sigma(I)$]. The crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 755766).
- Concentrations of **2** were $1.0\text{--}5.0 \times 10^{-5} \text{ M}$ for UV-vis absorption measurements and $1.0\text{--}5.0 \times 10^{-6} \text{ M}$ for fluorescence measurements.
- The authors thank a referee who pointed out that the data of excited state lifetime will increase the impact of this work. We unfortunately cannot obtain the data soon, because we do not have an instrument for fluorescence lifetime measurement. We would like to measure the data for preparing a full paper.
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