

A New BODIPY Derivative Bearing Piperazine Group

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A new BODIPY derivative bearing piperazine group was synthesized and its fluorescent changes towards metal ions as well as pH are studied. The title compound displayed a moderate selectivity for Hg^{2+} among the metal ions examined.

Key Words : Fluorescent chemosensor, BODIPY, Hg^{2+} sensor

Introduction

Fluorescent chemosensors for ions appear to be particularly attractive due to the simplicity and high detection limit of the fluorescence.¹ Over the last few years, 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) derivatives have been utilized as useful fluorophores because of their advantages, such as high excitation coefficients, high fluorescence quantum yields and high stability against light and chemical reactions.² Recently, the fluorescent chemosensors based on the BODIPY have been applied as metal ion sensor,³ pH sensor,⁴ NO sensor,⁵ etc.

Mercury contamination through oceanic and volcanic emission,⁶ gold mining,⁷ or solid waste incineration has been an important issue because of its severe immunotoxic, genotoxic, and neurotoxic effects. Accordingly, considerable attention has been devoted to the development of new fluorescent chemosensors for the detection of Hg^{2+} .⁸

We report herein the synthesis and X-ray crystal structure of a new BODIPY derivative **1** bearing a piperazine group

and its fluorescent changes towards metal ions as well as pH. Compound **1** displayed a moderate fluorescent change with Hg^{2+} among the metal ions examined. Furthermore, the reversible protonation/deprotonation of **1** in aqueous solution was also studied.

Results and Discussion

4-(4-Methylpiperazin-1-yl)benzaldehyde **3** and 2,4-dimethylpyrrole was reacted to give compound **1** as a red powder in 21% yield after flash chromatography (MC: MeOH = 50:1) followed by a further separation *via* preparative TLC (MC:MeOH = 50:1, v/v) (Scheme 1). Compound **2** was synthesized by the reported procedure.⁹

In the X-ray structure of **1** (Figure 1), the phenyl and pyrrole rings are planar, with an average deviation of 0.0019 and 0.0235 Å, respectively. The dihedral angle between the phenyl and pyrrolyl rings is 75.09°, which may be influenced by intramolecular interaction of hydrogen bonds (C1-H1A \cdots F1 and C12-H12C \cdots F2, C1-H1C \cdots F2, C12-H12A

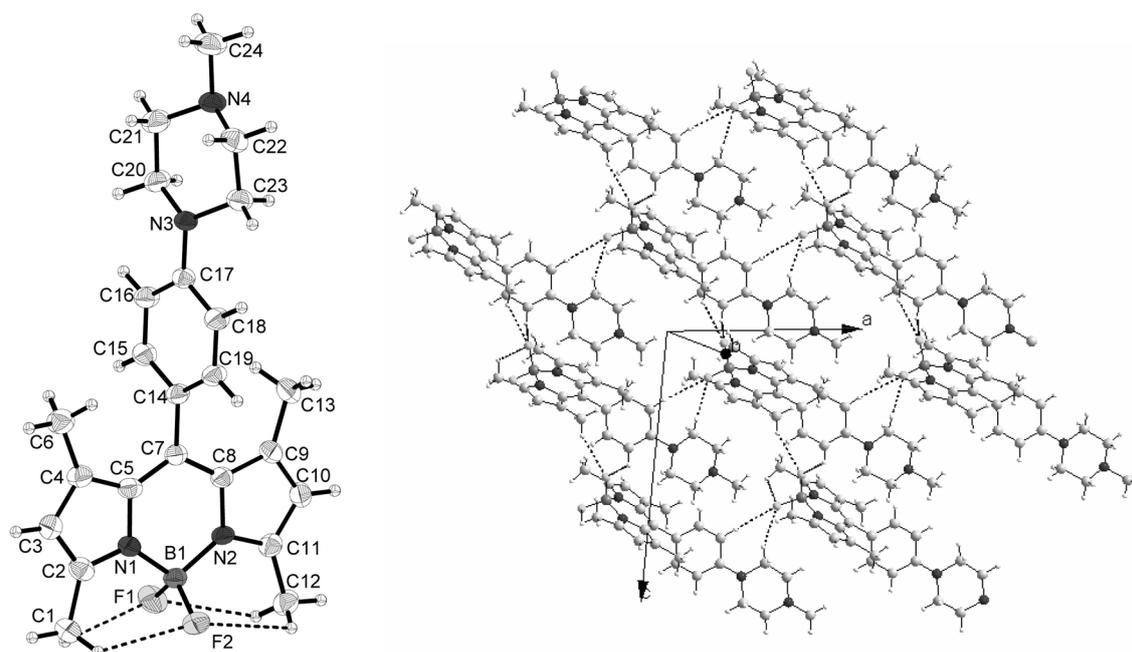
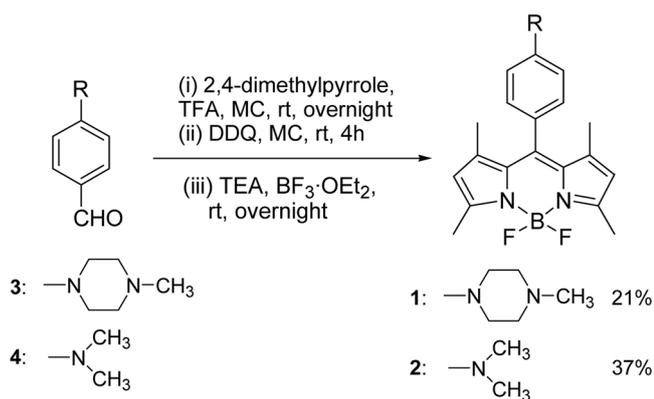


Figure 1. X-ray crystal structure of compound **1**.



Scheme 1. Synthesis of compound **1** and **2**.

...F2) between F atoms and methyl groups. By intermolecular hydrogen bonds (C16-H16···F2, C20-H20A···F2, C13-H13A···F1, C18-H18···F1), the molecules of **1** are linked into a complex sheet (Figure 1).

Ag⁺, Ca²⁺, Cd²⁺, Co²⁺, Cu²⁺, Cs⁺, Hg²⁺, K⁺, Mg²⁺, Mn²⁺, Na⁺, Ni²⁺, Pb²⁺ and Zn²⁺ ions were used to evaluate the metal ion binding properties of **1**. Fluorescent studies were conducted in acetonitrile-water (95:5, v/v) and using a 1 μM concentration of compound. The fluorescence emission changes of **1** upon the addition of various metal ions (100 eq.) are illustrated in Figure 2. The fluorescence spectra were obtained by excitation into the BODIPY fluorophore at 495 nm, and both the excitation and emission slits were 3 nm. As shown in Figure 2, compound **1** displayed a moderate fluorescent quenching effect with Hg²⁺ and a moderate fluorescent enhancement with Zn²⁺ among the metal ions examined. Compound **1** also displayed relatively small fluorescent enhancement upon the addition of Pb²⁺ and Mn²⁺. The fluorescent enhancements of compound **1** upon the addition of Zn²⁺, Pb²⁺ or Mn²⁺ can be explained by the blocking of the PET mechanism process from amine moiety.^{1a} On the other hand, if a quenching metal ion such as Hg²⁺ (*via* enhanced spin-orbital coupling)¹⁰ binds tightly to the

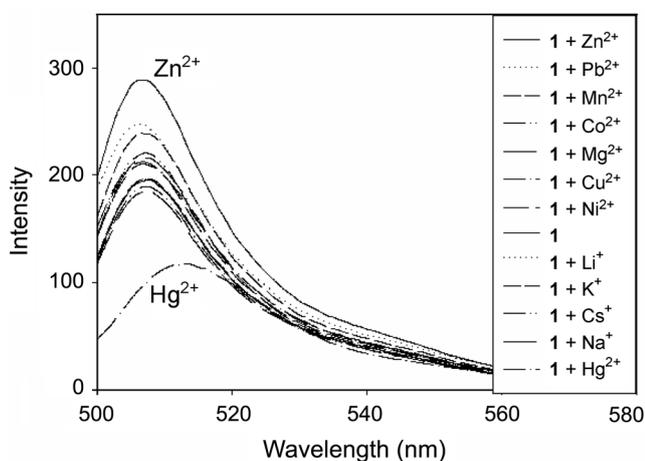


Figure 2. Fluorescence spectra of **1** (1 mM) upon the addition of various metal ions (perchlorate salts) in CH₃CN-water (95:5, v/v) (excitation at 495 nm).

ligand, intracomplex quenching takes place.

From the fluorescence titration experiments, the association constants of **1** with Hg²⁺ (Figure 3) and Zn²⁺ were observed to be 2800 and 480 M⁻¹, respectively (errors < 10%).¹¹ The job plots using the fluorescence changes indicated 1:1 binding for **1** with Hg²⁺ (Figure 4) and Zn²⁺.

Figure 5 displayed fluorescence emission spectra of **1** in aqueous nonbuffered solution (acetonitrile-water = 2:8, v/v) as a function of pH. By lowering the pH, fluorescence signal increase significantly. Werner et al. reported that compound **2** displayed a similar fluorescent change according to pH in methanol-water mixture (5:5, v/v).⁹ The pK_a value was reported as 3.3 in this solvent system.⁹ We repeated the same experiment in acetonitrile-water (2:8, v/v) and a similar pK_a value (3.5) was obtained. On the other hand, the pK_a value of compound **1** was calculated as 1.8 from pH titration experiments (Figure 5).¹¹ Virtually no dependence of absorption intensities versus pH was observed for both of these compounds (Figure 6). The pK_a difference between these two compounds can be explained by the better electron releasing effect of a piperazine group compared to a dimethyl group.

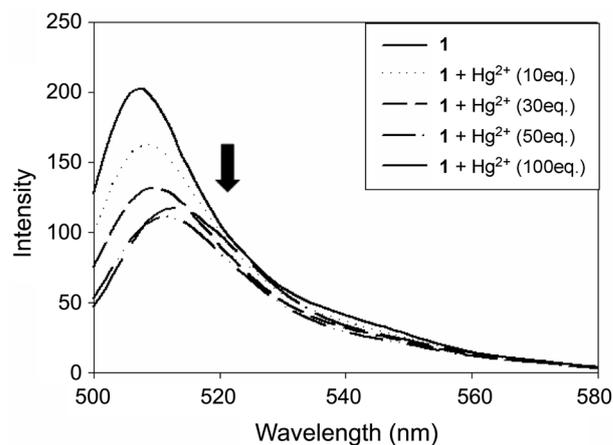


Figure 3. Fluorescence titrations of **1** (1 μM) with Hg²⁺ in CH₃CN-water (95:5, v/v) (excitation at 495 nm).

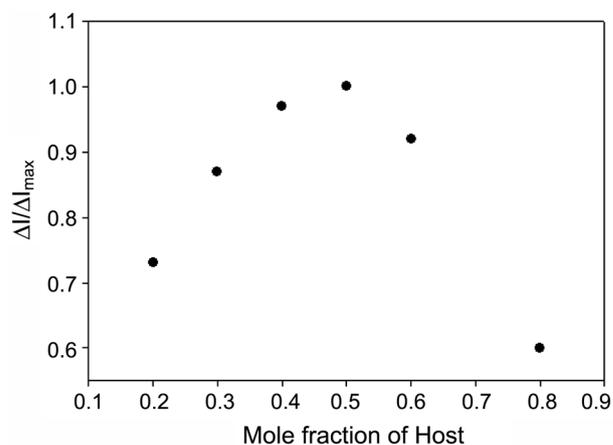


Figure 4. Job' plot between host **1** and Hg²⁺ using fluorescence emission changes in CH₃CN-water (2:8, v/v) (excitation at 495 nm, emission at 510 nm).

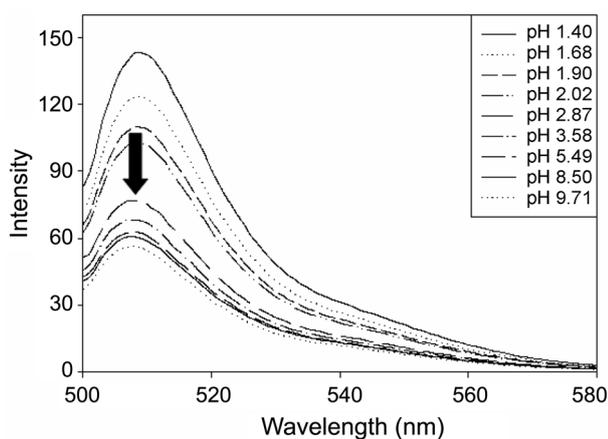


Figure 5. Fluorescence pH titrations of **1** ($1 \mu\text{M}$) in CH_3CN -water (2:8, v/v) (excitation at 495 nm).

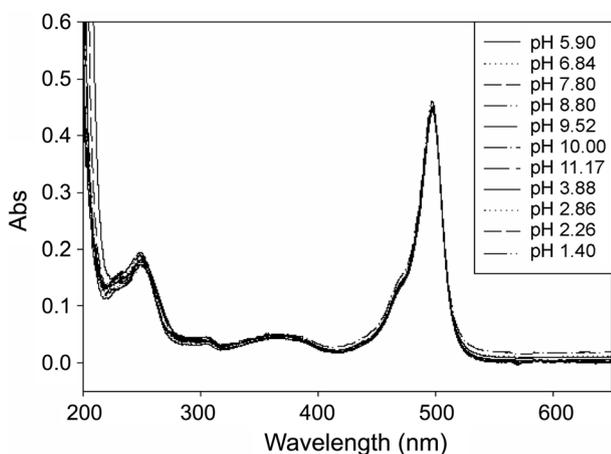


Figure 6. UV pH titrations of **1** ($15 \mu\text{M}$) in CH_3CN -water (2:8, v/v) (excitation at 495 nm).

In conclusion, we synthesized a new BODIPY derivative bearing a piperazine group (**1**) and explained X-ray crystal structure of this compound. Compound **1** displayed a moderate selectivity for Hg^{2+} among the metal ions examined. The pK_a value of this compound was productively compared to the aniline-type BODIPY (**2**).

Experimental

General methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Flash chromatography was carried out on silica gel 60 (230-400 mesh ASTM; Merck). Thin layer chromatography (TLC) was carried out using Merck 60 F_{254} plates with a thickness of 0.25 mm. Preparative TLC was performed using Merck 60 F_{254} plates with a thickness of 1 mm.

Melting points were measured using a Büchi 530 melting point apparatus, and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded using Bruker 500. Chemical shifts were expressed in ppm, using TMS as an internal standard. Mass spectra were obtained using a JMS-HX 110A/110A Tandem Mass Spectrometer (JEOL).

Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (Deposition No. CCDC-659972). That data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/perl/catreq.cgi> (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk)

4,4-Difluoro-8-[4-(4'-methylpiperazin-1'-yl)phenyl]-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene 1. 4-(4-Methylpiperazin-1-yl)benzaldehyde **3** (204.3 mg, 1 mmol) and 2,4-dimethylpyrrole (190.3 mg, 2 mmol) was dissolved in anhydrous methylene chloride (30 mL) under argon atmosphere. Trifluoroacetic acid (0.05 mL) was added and the solution was stirred at room temperature overnight. A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (227.0 mg, 1 mmol) in anhydrous toluene (30 mL) was added by syringe and the stirring was continued for another 4h. After the addition of triethylamine (6 mL), $\text{BF}_3 \cdot \text{OEt}_2$ (6 mL) was gradually added during 30 min in an ice-water bath followed by continuous stirring at room temperature overnight. The reaction solution was shaken with 10% aqueous sodium carbonate (80 mL) and the mixture was passed through a Celite pad and washed with MC (30 mL) to remove the black solid. The organic layer was washed with water, dried over anhydrous sodium sulfate. After concentration *in vacuo*, the residue was purified by flash chromatography (MC:MeOH = 50:1) followed by a further separation via preparative TLC (MC:MeOH = 50:1) procedure to afford a red powder (89.6 mg, 0.212 mmol, yield 21.2%). The analytical sample was recrystallized from ethyl acetate/hexane to get a red crystal: mp 235 °C; ^1H NMR (CDCl_3): δ 1.46 (s, 6H), 2.41 (s, 3H), 2.55 (s, 6H), 2.64 (t, 4H, $J = 4.8$ Hz), 3.29 (t, 4H, $J = 4.9$ Hz), 5.97 (s, 2H), 6.99 (d, 2H, $J = 8.7$ Hz), 7.10 (d, 2H, $J = 8.6$ Hz). ^{13}C NMR (CDCl_3): δ 14.3, 14.4, 45.7, 54.6, 115.6, 120.7, 125.3, 128.5, 131.6, 142.1, 142.9, 151.2, 154.7. HRMS: calcd. M^+ for $\text{C}_{24}\text{H}_{29}\text{BF}_2\text{N}_4$ 422.2453, found. 422.2469.

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