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UNEXPECTED FLUORESCENT BEHAVIOR OF A NEW PH CHEMOSENSOR BASED UPON BIS-4-PIPERIDINE-1,8-NAPHTHALIMIDE LINKED BY THE DIETHYLENETRIAMINE

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Dedicated to Professor Dr. Albert Eschenmoser on the occasion of his 85th birthday

Abstract – A new fluorescent chemosensor **3** based upon bis-4-piperidine-1,8-naphthalimide linked by the diethylenetriamine was synthesized, and its fluorescent properties were also investigated. Different from other bis-1,8-naphthalimides, no changes in the fluorescence spectra of **3** in the presence of metal cations was observed, and it displayed an unexpectedly strong fluorescence quench in weakly acidic aqueous solutions. Its p*Ka* value (7.25) indicated that it would be suited as a new pH fluorescent chemosensor to monitor changes at the physiological pH range.

INTRODUCTION

Currently, the design and synthesis of fluorescent devices for the sensing and reporting chemical species is of very importance for biological and environmental applications.[1-5] Due to their fluorescent properties and special interactions with some biomolecules, mono-1,8-naphthalimides are frequently used as the fluoroionophores to prepare fluorescent chemosensors for metal cations and protons.[6-9] To the best of our knowledge, however, little attention has been paid to the fluorescent properties of the bis-1,8-naphthalimides. Chovelon *et al.* described the changes in the fluorescence spectra of bis-1,8-naphthalimide analog **1** (Figure 1) in the presence of metal cations (Zn^{2+}, Ni^{2+} and Ce^{3+}) and protons.[10] Staneva *et al.* reported Fe^{3+} and Cr^{3+}-induced fluorescence spectra changes of

bis-1,8-naphthalimide analog **2** (Figure 1).[11] Obviously, introducing the different groups (*e.g.*, *N,N*-dimethylaminoethylamino group) on the 4-position of **1** could lead to compound **2** with different photophysical properties. Therefore, in this paper we want to introduce the piperidine group on the 4-position of **1**, and investigate the fluorescent properties of a new bis-1,8-naphthalimide analog **3** (Figure 1) based on bis-4-piperidine-1,8-naphthalimide linked by the diethylenetriamine.

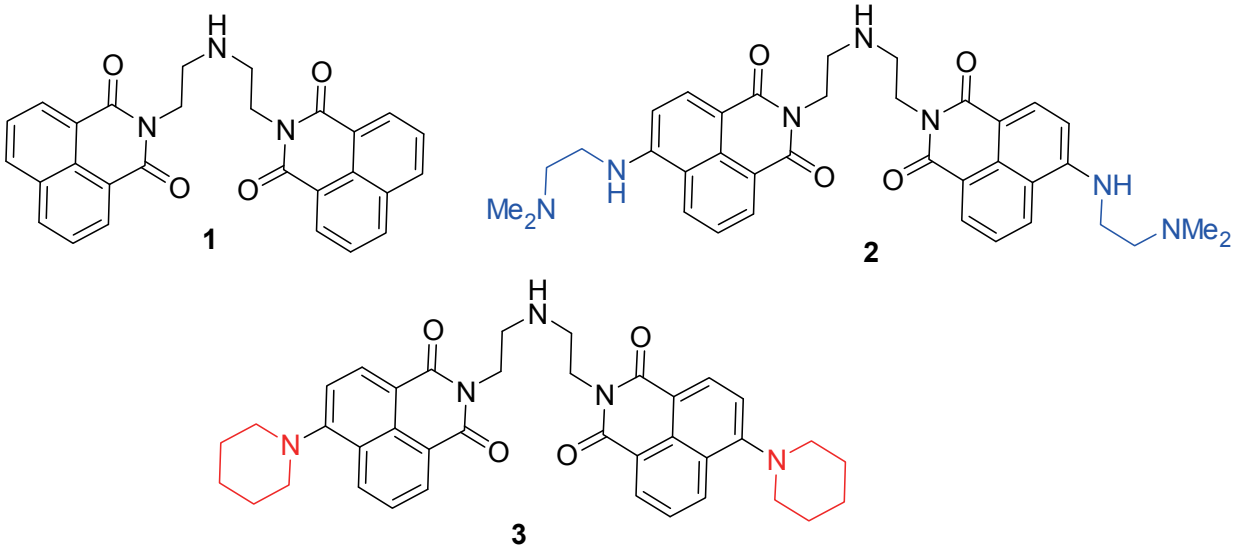
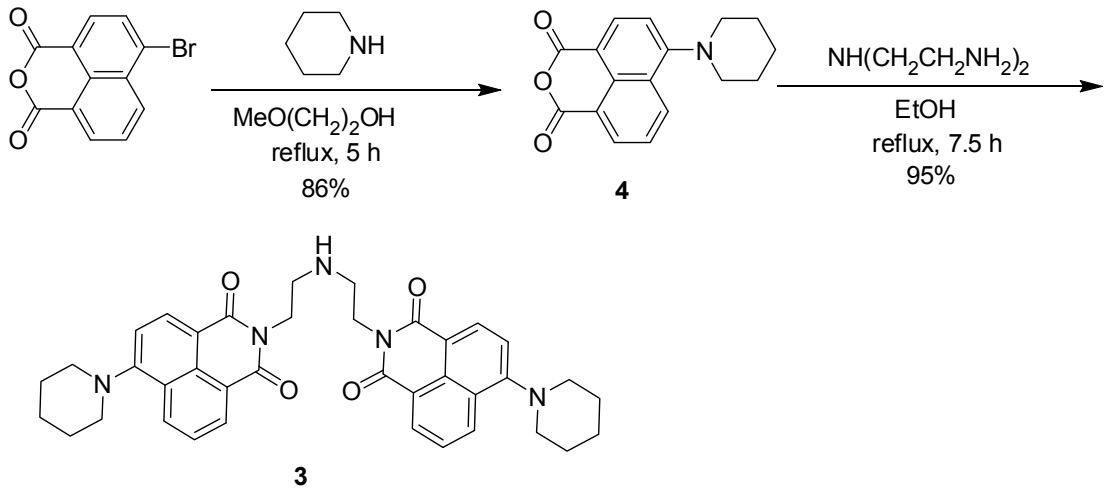


Figure 1. The chemical structures of bis-1,8-naphthalimide analogs **1**-**3**.

RESULTS AND DISCUSSION

As shown in Scheme 1, 4-bromo-1,8-naphthalic anhydride firstly reacted with piperidine in 2-methoxyethanol to give 4-piperidine-1,8-naphthalic anhydride **4** in a 86% yield.[5] Then compound **3** was obtained in a 95% yield by treating compound **4** with diethylenetriamine in ethanol. The structure of compound **3** was well characterized by ^{1}H NMR, ^{13}C NMR, HR-MS and mp.



Scheme 1. The synthetic route of **3**

Table 1. Photophysical properties of **3** (1×10^{-6} M) in the presence of different solvents

	DMF	DMSO	THF	acetone	*c*-hexane	MeCN	CH_2Cl_2	MeOH
λ_{Abs} (nm)	408	410	386	400	386	402	406	406
A	0.028	0.029	0.027	0.029	0.020	0.030	0.026	0.022
λ_F (nm)	528.8	536	513.4	523.6	472.4	527.4	516	532.4
Φ_F [a]	0.0118	0.008	0.300	0.071	0.144	0.276	0.431	0.0043
ν_A-ν_F (cm^{-1}) [b]	5600	5730	6430	5900	4740	5910	5250	5850

[a]The fluorescence quantun yields were obtained by quinine sulfate in 1 N H_2SO_4 (Φ_F = 0.55) as a reference; [b]ν_A-ν_F (cm^{-1}) is Stokes shift.

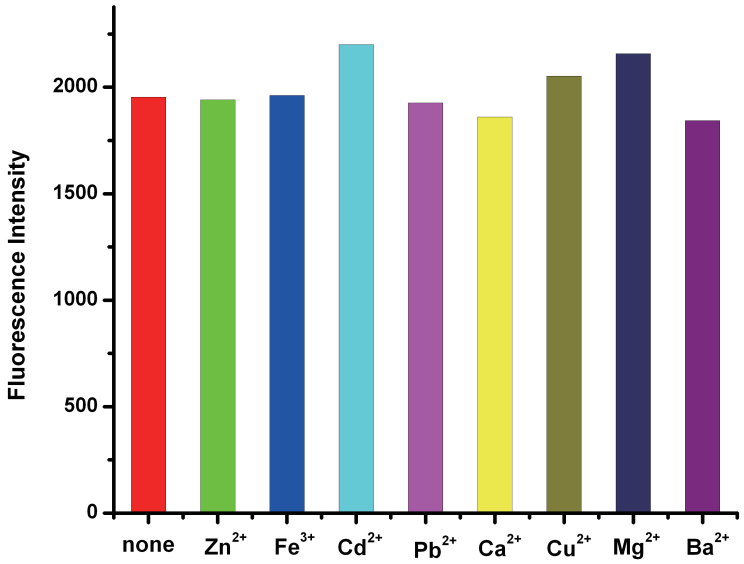


Figure 2. Variation of the fluorescent intensity at λ_{max} (513 nm) of compound **3** (1×10^{-6} M) in THF in the presence of 5.0 equiv. of the respective metal cations.

The data of absorption (λ_A), fluorescence (λ_F), quantum yield of fluorescence (Φ_F), and Stokes shift (ν_A-ν_F) of **3** in the different organic solvents were listed in Table 1. Due to the good solubility for the HTM ions and the fluorescent quantun yields (Φ_F), tetrahydrofuran (THF) was chosen as the solvent for all the measurements. Firstly, the metal-induced fluorescence changes of **3** in THF solution were investigated. As shown in Figure 2, an enhancement or reducement of fluorescent intensity of **3** in the presence of different metal cations (such as Zn^{2+}, Fe^{3+}, Cd^{2+}, Pb^{2+}, Ca^{2+}, Cu^{2+}, Mg^{2+}, and Ba^{2+}) has not been observed. Then the influence of protons on the fluorescent intensity of **3** was also tested in water over a pH range of 3.04-9.34. The parameters of absorption and fluorescent spectra of **3** in water of different pH were listed in Table 2. As outlined in Figure 3, compound **3** exhibited high sensitivity to the presence of protons. For

example, from pH 8.20 to 4.88, a dramatic decrease in the fluorescent intensity of **3** was observed. That is, the fluorescent intensity of **3** was greatly reduced when the solution became acidic. Meanwhile, the fluorescent intensity of **3** at pH 8.20 was more than 17 times of that at pH 3.04. It should be noteworthy that the fluorescent intensity of **3** was absolutely observed in water, while the fluorescent intensity of **1** and **2** was observed in mixture solution (*e.g.*, MeCN/H_2O or MeOH/H_2O).[10,11] The pH dependence of fluorescent intensity could be analyzed with below equation to give the pK_a value.

$\log[(I_{Fmax}- I_F)/(I_F-I_{Fmin})] = pH-pK_a$

Table 2. Parameters of absorption and fluorescent spectra of compound **3** (1×10^{-6} M)[a]

	Compound **3**
λ_{Abs} (pH 3.04) [nm]	416
A	0.014
λ_{Abs} (pH 8.20) [nm]	410
A	0.013
λ_F (pH 3.04) [nm]	545.6
Φ_F (pH 3.04)	0.002969
λ_F (pH 8.20) [nm]	531.8
Φ_F (pH 8.20)	0.021948
pK_a	7.25

[a]Compound **3** was characterized at 288 K in water of different pH.

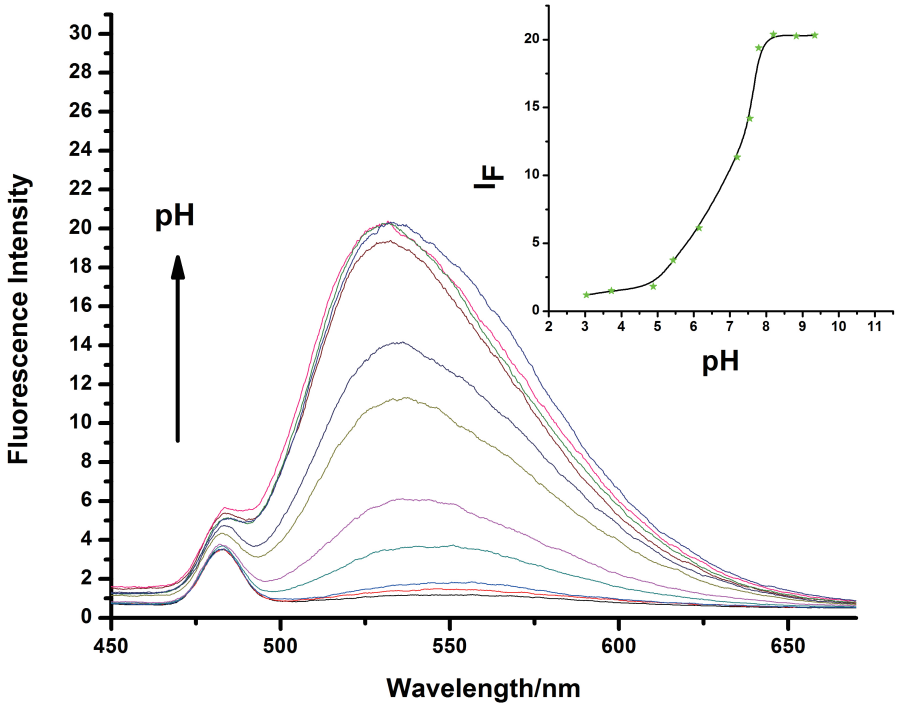


Figure 3. Changes in the fluorescence spectra of **3** as a function of pH in water. Inset: Fluorescence intensity of **3** *vs.* pH (pH adjusted by $HClO_4$ or $N^+Me_4OH^-$) in water.

The calculated pK_a value was 7.25 (288 K). Interestingly, the influence of protons on the fluorescent intensity of **3** was completely different from its other bis-1,8-naphthalimide analogs **1** (pK_a = 7.53) and **2**(pK_a = 6.85).[10,11] For example, the fluorescent intensity of **3** was greatly reduced as the solution became acidic, while the fluorescent intensity of **1** and **2** were greatly reduced as the solution became alkali. The difference of the chemical structures between **3** and **1** (hydrogen atom) or **2** (*N,N*-dimethylaminoethylamino group) was only the different substituents on the 4-position of bis-1,8-naphthalimide. The proposed mechanism for the observed quenching process for **3** in the weakly acidic conditions was due to the formation of intramolecular hydrogen bond between the nitrogen atom of diethylenetriamine and oxygen atoms of aminonaphthalimide.

In summary, a new fluorescent chemosensor **3** based upon bis-4-piperidine-1,8-naphthalimide linked by the diethylenetriamine was synthesized, and its fluorescent properties were also investigated. Different from other bis-1,8-naphthalimides, no changes in the fluorescence spectra of **3** in the presence of metal cations was observed, and it displayed an unexpectedly strong fluorescence quench in weakly acidic aqueous solutions. It would be suited as a new pH sensor to monitor changes in the physiological pH conditions.

EXPERIMENTAL

All solvents and reagents were used as obtained from commercial sources without further purification. The solutions of metal ions were prepared from $Zn(ClO_4)_2·6H_2O$, $Fe(ClO_4)_2·6H_2O$, $Ca(ClO_4)_2·4H_2O$, $Mg(ClO_4)_2$, $Ba(ClO_4)_2$, $Pb(ClO_4)_2$, $Cd(ClO_4)_2$, and $Cu(ClO_4)_2$, respectively, and were dissolved in distilled THF. Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were performed with silica gel plates using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd.). Melting points are uncorrected. Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker Avance DMX 400 MHz instrument in $CDCl_3$ (^{1}H at 400 MHz and ^{13}C at 100 MHz) using TMS (tetramethylsilane) as the internal standard. High-resolution mass spectra (HR-MS) and mass spectra (MS) were carried out with APEX II Bruker 4.7T AS instrument and HP 5988 instrument, respectively. All pH measurements were carried out with a pH-meter PHS-3C (Chengdu Century Fangzhou Science& technology Co., Ltd.). Fluorescent spectra were determined on a Hitachi F-4500 spectrophotometer. UV-visible spectra were determined on a Hitachi U-3310 spectrophotometer.

Synthesis of compound 4. A mixture of 4-bromo-1,8-naphthalic anhydride (2.77 g, 10.0 mmol), and piperidine (1.97 mL, 20 mmol) in 2-methoxyethanol (25 mL) was refluxed for 5 h, then the reaction mixture was cooled to room temperature to afford a yellow solid after filtration, which was purified by recrystallization from EtOH to give 2.41 g (86%) of **4** as the orange needles. Mp 170-171 ^{o}C (lit.,[12] 175-176 ^{o}C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.58 (d, J = 7.6 Hz, 1H), 8.50 (d, J = 8.4 Hz, 1H), 8.44 (d, J

= 8.8 Hz, 1H), 7.73 (t, *J* = 7.6 Hz , 1H), 7.20 (d, *J* = 8 Hz, 1H), 3.31 (t, *J* = 5.6 Hz, 4H), 1.88-1.93 (m, 4H), 1.74-1.78 (m, 2H); EI-MS m/z: 281(M^+, 83), 280 ($[M-1]^+$, 100).

Synthesis of compound 3. A mixture of **4** (351mg, 1.25 mmol), and diethylenetriamine (0.054 mL, 0.5 mmol) in absolute EtOH (20 mL) was refluxed for 7.5 h under an argon atmosphere. After removal of EtOH, the residue was purified by preparative thin-layer chromatography (PTLC) using CH_2Cl_2/MeOH (20:1, v/v) as eluent to afford 299 mg (95%) of **3** as a yellow solid. Mp 115-116 ^oC; ^1H-NMR (400 MHz, $CDCl_3$): δ 8.28-8.37 (m, 6H), 7.60 (t, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 4.34 (t, *J* = 6.4 Hz, 4H), 3.11-3.21 (m, 12H), 2.80 (s, 1H), 1.86-1.90 (m, 8H), 1.72-1.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 164.2, 132.5, 130.9, 130.3, 129.8, 126.1, 125.1, 122.9, 115.8, 114.5, 54.5, 47.4, 39.3, 26.2, 24.3; HRMS: Calcd. for $C_{38}H_{40}N_5O_4$ $(M+H)^+$: 630.3075. Found: 630.3083.

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