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Investigation of photophysical properties of 1,8-naphthalimides with an extended conjugation on naphthalene moiety via Suzuki coupling reaction

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ABSTRACT

Five 4-substituted 1,8-naphthalimides (**1**-**5**), with an extended conjugation on the naphthalene ring, have been synthesized via Suzuki coupling reaction. These derivatives showed a large Stokes shift (up to 200 nm) and longer emission due to the increase of conjugation. Besides strong solvation effect, the low quantum yield were observed in protic solvents compared to in aprotic solvents. The anion forms of **1**-**5** obtained from reacting with NaH gave a significant red-shift for both absorption and emission spectra. These results provided a new strategy for preparation of fluorescent dyes with a long emission on the basis of 1,8-naphthalimde structure by using Suzuki coupling reaction.

1. Introduction

1,8-naphthalimides (NIs) and derivatives is a fluorescent molecule family with various applications in chemical, biological, and medical fields [1]. NIs are able to specifically intercalate to base-pairs of DNA to form a strong intermolecular complex, which in further induces strand break and inhibits nucleic acid synthesis as anticancer agents and antivirus therapeutics [2]. Several NIs (i.e., 3-amino-1,8-naphthalimide and 3-nitro-1,8-naphthalimide) have entered into phase II clinical trials [3]. Abundant photophysical properties is another extremely important feature of NIs [4]. Many NIs and derivatives show strong luminescence, high photo stability, and large Stock-shift, which allow NIs functionalized as fluorescent brighteners, solar energy collectors, laser dyes, and fluorescent cellular imaging agents [5]. Since the unique structure, NIs show many unique photophysical properties, including ICT (internal charge transfer), PET(photoinduced electron transfer), and DF (dual fluorescence) [6]. These feature have been intensively investigated and applied to design fluorescence sensors for detection of various molecules [7]. Another interesting feature of NIs is that the optical properties of NIs highly rely on the nature of substituents on naphthalene ring, particularly at positon 3 and 4, which provides an excellent strategy to attune the properties of NIs as needed [8].

As fluorescent dyes and imaging agents, NIs show a typical emission in the range of 350–500 nm, which overlaps the intrinsic fluorescence generated by biomolecules (e.g., Tryptophan and NADP/NADPH) in living cells. The interference from the background fluorescence significantly limits the biological applications of NIs dyes [9]. Therefore, developing new derivatives of NI with a long emission is highly desirable. Since the photophyscial properties of NIs is dramatically sensitive to the substituent at position 4 on the naphthalene ring, the electronic properties of the substituent significantly affect the spectral features of NIs. A strong electron-donating group at position 4 may cause a strong fluorescence due to the charge transfer, and the electron-withdrawing group leads to a weak fluorescence for the intersystem crossing [10].

Suzuki coupling reaction is one of the most efficient approaches to construct a carbon-carbon bond by coupling an organoboron species with a halide using a palladium catalyst under basic condition, which was first published in 1979 by Akira Suzuki [11]. Suzuki coupling reaction can be conducted in both of organic and aqueous media, which significantly increase the scope of applications in synthetic chemistry [12]. Compared to other metal-catalyzed organic reactions (i.e., Kharash coupling and Negishi coupling), the key advantages of Suzuki coupling reaction include commercial availability of boronic acids, mild reaction conditions, less toxic nature, tolerance to active function groups, and less sensitivity to moisture [13]. Currently, Suzuki coupling reaction has been widely used for preparation of polymers, ligands, natural products, and pharmaceuticals contain biaryl or substituted aromatic structures [14].

In this research, five 4-substituted 1, 8-naphthalimides (**1**-**5**) have been synthesized for investigation of spectral properties. A conjugated moiety is appended to naphthalene ring at positon 4 by using Suzuki coupling reaction, which has been intensively used for organic synthesis, but is rarely reported for preparation of derivatives of 1,8-naphthalimides. The influence of conjugation, heteroatoms and charge to spectral properties (i.e., absorption and emission) of 1,8-naphthalimide

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have been investigated. These results provide a new strategy to prepare fluorescent dyes based on 1,8-naphthalimide structure with a long emission.

2. Experimental

2.1. General

All reagents used for synthesis and measurements were purchased from Sigma-Aldrich (MO, USA), Fisher Scientific (USA), TCI (USA), Alfa Aesar (USA) and Acros Organics (USA) in analytical grade and were used as received, unless otherwise stated. Absorbance spectra were collected by Cary Series Uv–vis Spectrophotometer (Agilent Technologies). Fluorescence measurements were all performed by using a FluoroMax-4 Spectrofluorometer (Horiba Jobin Yvon, USA). All of fluorescence spectra were recorded in a 1 cm quartz cuvette. The excitation and emission slits were set at 2 nm. ^{1}H and ^{13}C NMR spectra were recorded on (^{1}H 300 MHz, ^{13}C 75 MHz) Bruker 300 Ultra-Shield spectrometer at room temperature. The HRMS data was collected in the Nebraska Center of Mass Spectrometry at University of Nebraska-Lincoln by using GCT Mass Spectrometer (Water, USA).

2.2. Synthesis

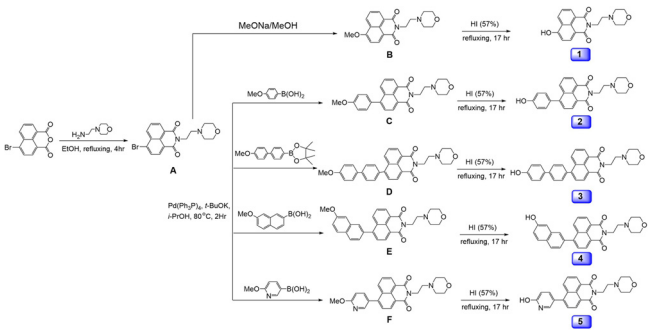
The designed molecules (**1**-**5**) are synthesized from commercially available 4-bromo-1,8-naphthalic anhydride via a three-step reaction as illustrated in Scheme 1.

6-bromo-2-(2-morpholinoethyl)-1H benzo[de]isoquinoline1,3 (2 H)-dione (**A**). 4-bromo-1,8-naphthalic anhydride (1.11 g, 4.0 mmol) was mixed with 2-morpholinoethanamine (1.04 g, 8.0 mmol) in ethanol (40 mL) under reflux for 4 h. After cooling reaction mixture to room temperature, a yellow solid was collected by suction filtration. The crude product was purified by column chromatography (silica gel 200–400 mesh, 60 Å) eluted by EtOAc to yield a white solid (1.38 g, 89%). Melting point (m.p.): 165–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.6 (t, J = 4.5 Hz, 4 H), 2.7 (t, J = 6.6 Hz, 2 H), 3.7 (t, J = 4.6 Hz, 4 H), 4.3 (t, J = 6.9 Hz, 2 H), 7.8 (t, J = 7.9 Hz, 1 H), 8.0 (d, J = 7.8 Hz, 1 H), 8.4 (d, J = 7.8 Hz, 1 H), 8.5 (d, J = 8.5 Hz, 1 H), 8.6 (d, J = 7.2 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.4, 53.8, 56.2, 67.1, 122.2, 123.1, 128.1, 129.0, 130.3, 130.6, 131.1, 131.3, 132.0, 133.3, 163.8.

6-hydroxy-2-(2-morpholinoethyl)-1H-benzo[de]isoquinoline-1,3(2 H)-dione (**1**) A mixture of **A** (194 mg, 0.5 mmol) and sodium methoxide methanol solution (5.4 M, 0.5 mL) were refluxed in anhydrous methanol (5 mL) for 10 h. After cooling to room temperature, the reaction mixture was poured into cold water to collect precipitate as the crude product, which was purified by column chromatography (silica, 220–400 mesh). Dichloromethane and ethyl acetate (1:2) were used as elution solvents. A light yellow solid (**B**) was obtained as the product (141 mg, 83%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.5–3.0 (m, 6 H), 3.6–3.9 (m, 4 H), 4.1 (s, 3 H), 4.3–4.5 (m, 2 H), 7.0 (d, J = 9.6 Hz, 1 H), 7.7 (t, J = 7.9 Hz, 1 H), 8.5–8.6 (m, 3 H), ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 53.4, 55.9, 56.3, 66.2, 105.2, 114.9, 122.2, 123.5, 126.0, 128.9, 129.5, 131.7, 133.7, 161.0, 164.0, 164.6. **B** (208.6 mg, 0.5 mmol) and 11 ml of hydro iodic acid (57%) were refluxed for 17 h. Then, the precipitation was collected by centrifuge using water to wash solid. The precipitation was dissolved in acetone and the solution was purified by column chromatography (silica, 220–400 mesh, ethyl acetate/CH_2Cl_2). **1** was collected as a white solid (141 mg, 70%). ^{1}H-NMR (400 MHz, DMSO-D_6) δ: 2.4–2.8 (m, 6 H), 3.4–3.8 (m, 4 H), 4.0–4.2 (m, 2 H), 7.1 (d, J = 8.8 Hz, 1 H), 7.7 (t, J = 5.7 Hz, 1 H), 8.3 (d, J = 8.2 Hz, 1 H), 8.4 (d, J = 8.1 Hz, 1 H), 8.5 (d, J = 8.6 Hz, 1 H), ^{13}C-NMR (100 MHz, DMSO-D_6) δ: 36.6, 53.7, 55.9, 66.3, 110.5, 112.9, 122.3, 122.7, 126.1, 129.3, 129.8, 131.6, 134.2, 143.1, 161.1, 163.6, 164.2. TOF EI$^+$: M^+ m/z 328.1423 (calcd.), 328.1487(found).

6-(4-hydroxyphenyl)-2-(2-morpholinoethyl)-1H benzo[de] isoquinoline-1,3(2 H)-dione (**2**) A mixture of **A** (195 mg, 0.5 mmol) and (4-methoxyphenyl)boronic acid (98 mg, 0.65 mmol) were refluxed with t-BuOK (61.5 mg, 0.55 mmol), and $Pd[P(Ph)_3]_4$(28.9 mg, 5%) in isopropyl alcohol (5 mL) for 2 h at 80 °C. After cooling to room temperature, the reaction mixture was extracted by dichloromethane to collect crude product, which was purified by column chromatography (silica, 220–400 mesh). Dichloromethane and ethyl acetate (3:1) were used as elution solvents. A light yellow solid (**C**) was obtained as the product (166 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.6 (t, J = 5.2 Hz, 4 H), 2.7 (t, J = 6.9 Hz, 2 H), 3.7 (t, J = 4.5 Hz, 4 H), 3.9 (s, 3 H), 4.4 (t, J = 7.1 Hz, 2 H), 7.1 (d, J = 8.7 Hz, 2 H), 7.4 (d, J = 8.7 Hz, 2 H), 7.7 (t, J = 7.8 Hz, 2 H), 8.3 (d, J = 8.4 Hz, 1 H), 8.6 (d, J = 7.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.1, 53.7, 55.4, 56.1, 66.9, 76.6, 77.0, 77.4, 114.1, 121.2, 122.8, 126.7, 126.9, 127.7, 128.8, 130.1, 130.9, 131.0, 131.1, 132.8, 146.8, 159.9, 164.1, 164.3. **C** (200 mg, 0.48 mmol) was refuxed in HI (57%, 11 mL) for 14 h. The reaction mixture was added into cold water (20 mL) to collect a yellow solid. The crude product was purified by column chromatography (silica gel 200–400 mesh, 60 Å) eluted by EtOAc:CH_2Cl_2 = 5:1 to yield **2** as a yellow solid (174 mg, 90%). ^{1}H NMR (300 MHz, DMSO-D_6) δ: 2.4–2.7 (m, 6 H), 3.5 (m, 4 H), 4.2 (m, 2 H), 6.9 (d, J = 8.5 Hz, 2 H), 7.3 (d, J = 8.5 Hz, 2 H), 7.7 (d, J = 7.6 Hz, 1 H), 7.8 (t, J = 7.9 Hz, 1 H), 8.3 (d, J = 8.5 Hz, 1 H), 8.5 (t, J = 6.4 Hz, 2 H), 9.8 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.3, 54.0, 56.0, 66.8, 116.1, 121.0, 122.7, 127.6, 128.1, 128.6, 129.3, 129.8, 131.0, 131.3, 131.7, 133.0, 134.8, 146.9, 158.4, 163.7, 163.9. TOF EI$^+$: M^+ m/z 402.1579 (calcd.), 402.1594(found).

6-(4′-hydroxy-[1,1′-biphenyl]-4-yl)-2-(2-morpholinoethyl)-1H-benzo[de]isoquinoline-1,3(2 H)-dione (**3**) A mixture of **A** (194 mg, 0.5 mmol) and 4′-methoxybiphenyl-4-boronic acid pinacol ester (201 mg, 0.65 mmol) were refluxed with t-BuOK (61.5 mg, 0.55 mmol), and $Pd[P(Ph)_3]_4$(28.9 mg, 5%) in isopropyl alcohol (5 mL) for 2 h at 80 °C. After cooling to room temperature, the reaction mixture was extracted by dichloromethane to collect crude product, which was purified by column chromatography (silica, 220–400 mesh). Dichloromethane and ethyl acetate (3:1) were used as elution solvents. A yellow solid (**D**) was obtained as the product (212 mg, 86%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.7-2.5 (t, J = 5.5 Hz, 4 H), 2.78 (t, J = 6.6 Hz, 2 H), 3.6–3.8 (m, 4 H), 3.9 (s, 3 H), 4.4 (t, J = 6.6 Hz, 2 H), 7.0 (d, J = 8.7 Hz, 2 H), 7.4–7.8 (m, 8 H), 8.4 (d, J = 8.1 Hz, 1 H), 8.6–8.7 (m, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 37.0, 53.8, 55.3, 56.2, 67.0, 121.5, 122.5, 122.8, 126.8, 127.8, 128.1, 130.0, 130.3, 130.8, 131.2, 132.0, 132.1, 133.9, 136.9, 141.0, 146.8, 159.5, 164.1, 164.3. **D** (200 mg, 0.41 mmol) was refuxed in HI (57%, 11 mL) for 14 h. The reaction mixture was added into cold water (20 mL) to collect a yellow solid. The crude product was purified by column chromatography (silica gel 200–400 mesh, 60 Å) eluted by EtOAc:CH_2Cl_2 = 5:1 to yield **3** as a yellow solid (171 mg, 88%). ^{1}H-NMR (300 MHz, DMSO-D_6) δ: 2.5–2.6 (m, 6 H), 3.4–3.6 (m, 4 H), 4.2 (s, 2 H), 6.9 (d, J = 7.8 Hz, 2 H), 7.5–7.7



Scheme 1. The synthetic route to prepare **1**-**5**.

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