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Microwave-Assisted Synthesis and Fluorescent Properties of 4-Phenyl-1,8-naphthalimide

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Abstract: 4-Phenyl-1,8-naphthalimide was synthesized by imidation of commercially available 4-bromo-1,8-naphthalic anhydride, followed by Suzuki coupling with phenyl boronic acid, both under microwave heating. The microwave-assisted reactions were found to be faster and more efficient than reactions carried out by heating in oil-baths. While this compound was quite fluorescent in solvents such as chloroform, methanol and ethanol, it is virtually non-fluorescent in DMSO; however, upon the addition of water to DMSO solutions of this dye, fluorescence was restored, suggesting a tendency for aggregation-induced emission. The fluorescent properties of 4-phenyl-1,8-naphthalimide were found to be influenced by salt concentrations, likely as a result of hydrophobic effects. While this dye does not show binding to DNA, presence of bovine serum albumin leads to effective fluorescence quenching.

Keywords: aggregation-induced emission; fluorescence; microwave-assisted synthesis; 1,8-naphthalimide; solvent-dependence

1. Introduction

1,8-Naphthalimide (1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione) is an old chromophore and fluorophore useful in a wide range of applications. The 1,8-naphthalimide scaffold is simple and readily amenable to chemical modifications for the fine-tuning of its photochemical properties. To date, this class of fluorophores has been shown to be useful in fluorescent sensing of ions, cellular imaging [1–4], and DNA binding and associated anticancer activities [5–7].

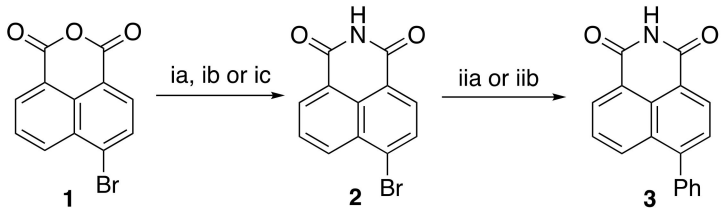
We are interested in developing fluorophores that are sensitive to the environment for applications in biological systems. In this respect, fluorophores that possess different fluorescent properties in different solvents, ionic strength, and hydrophobic environments are useful reporters to study these molecular systems. Toward this goal, 4-phenyl-1,8-naphthalimide, which has not been reported previously, represents an attractive core structure for the sensing of hydrophobic environments. We wish to report the synthesis of 4-phenyl-1,8-naphthalimide and its photochemical properties. It should be noted, however, that a rather large number of *N*-alkyl/aryl-4-aryl-1,8-naphthalimide derivatives have been reported in the literature.

2. Results and Discussion

2.1. Synthesis of Compounds

The synthesis of 4-phenyl-1,8-naphthalimide is rather straightforward (Scheme 1). The literature demonstrated the imidation of 4-bromo-1,8-naphthalic anhydride by heating with ammonium hydroxide [8,9]; however, this approach is inconvenient due to evolution of ammonia gas in the reaction mixture. Previous work by Song and co-workers showed efficient imidation of 4-bromo-1,8-naphthalic

anhydride with formamide under microwave heating using a non-commercial microwave reactor [10]. It is noteworthy that microwave-assisted reactions can be highly sensitive to the parameters of the reactor and reaction conditions [11]; it is, therefore, of importance to carry out these reactions in commercially available microwave reactors with reproducible control of microwave power output, temperature and pressure (see Figures S11 and S12 for temperature, pressure and power profiles of the reactions carried out in this work). It was found that while the imidation of 4-bromo-1,8-naphthalic anhydride with ammonium acetate in acetic acid (step ia, Scheme 1) or ammonia in dioxane (step ib, Scheme 1) took 24 and 48 h under heating to give 4-bromo-1,8-naphthalimide in 22% and 21% yields, respectively; 4-bromo-1,8-naphthalic anhydride was consumed in the reaction with ammonium acetate in 20 min, as indicated by TLC, with microwave heating at 60 °C (step ic, Scheme 1) in a CEM microwave reactor, leading to the isolation of the desired product in a 54% yield.



Scheme 1. Synthesis of 4-phenyl-1,8-naphthalimide. *Reagents and conditions*: (ia). $NH_4{}^+CH_3COO^-$, CH_3COOH, reflux, 24 h; (ib). NH_3 in dioxane, 60 °C, 48 h; (ic). $NH_4{}^+CH_3COO^-$, CH_3COOH, microwave, 60 °C, 2 h; (iia). $Pd(P(C_6H_5)_3)_4$, $PhB(OH)_2$, DMF/H_2O, reflux, 8 h; (iib). $Pd(P(C_6H_5)_3)_4$, $PhB(OH)_2$, DMF/H_2O, microwave, 70 °C, 30 min.

Subsequent Suzuki coupling of 4-bromo-1,8-naphthalimide with phenol boronic acid was carried out both by heating in oil-baths and in a CEM microwave reactor. A rather poor yield (22%) was obtained when the reaction was carried out by heating under reflux for 8 h in oil baths (step iia, Scheme 1), even when molar equivalents of tetrakis(triphenylphosphine) palladium(0) catalyst was used. On the other hand, 4-phenyl-1,8-naphthalimide was isolated in a moderate yield (77%) when the reaction mixture was subjected to microwave heating at 70 °C for 30 min (step iib, Scheme 1), where 5 mol% of catalyst was used.

2.2. Solvent-Dependent Absorption and Emission Spectroscopic Properties of 4-Phenyl-1,8-naphthalimide

The absorption spectra of 4-phenyl-1,8-naphthalimide in methanol, ethanol and DMSO were very similar (Figure 1a, solid lines), showing a maximal absorbance at 350 nm and a weaker absorption peak at 260 nm. The absorption at ca. 260 nm was found to be very intense in chloroform. 4-Phenyl-1,8-naphthalimide showed solvent-dependence in its emission profiles. As can be seen in Figure 1a (dotted lines), the emission spectrum of this dye in chloroform showed a blue-shift, as compared with those in methanol and ethanol, while the emission is the highest in ethanol (with a fluorescent quantum yield of 0.12 using fluorescein as a standard). The fluorescence is, however, quenched in DMSO (fluorescent quantum yield of 0.003) (as can be seen in Figure 1b).

2.3. Fluorescent Emission of 4-Phenyl-1,8-naphthalimide in Aqueous-Organic Solvent Mixtures

When the fluorescence spectra of 4-phenyl-1,8-naphthalimide in DMSO–water were recorded, a drastic change in fluorescent emission was observed with the addition of water. Thus, at a 1-μM dye concentration, there is a small red-shift in emission upon addition of water, and a *ca*. seven-fold increase in emission intensity was seen in 99.9% water (Figure 2a). Similar trends were observed in 10 and 50 μM dye concentrations (Figure 2b,c); however, the dye appears to precipitate at 99.9% and 80% water at these two dye concentrations, respectively. This behavior is in agreement with the literature observations of aggregation-induced emission (AIE) [12–14]. It is worth noting that all fluorescent measurements were performed after samples were left to equilibrate for two hours. It was found that

this equilibrium is of importance for all the subsequent measurements in aqueous environments, i.e., DNA binding, salt-dependence and protein binding experiments. This AIE-like property, however, is not observed in ethanol–water mixtures (Figure 2d).

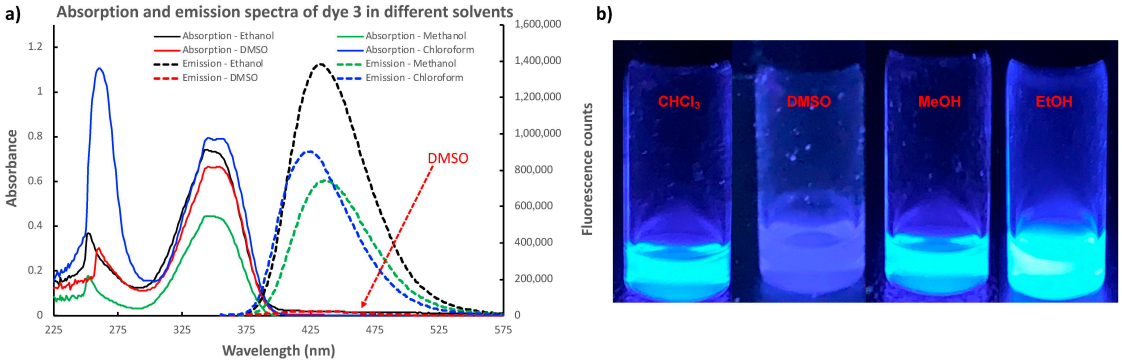


Figure 1. Photophysical properties of 4-phenyl-1,8-naphthalimide. (**a**). Absorption and emission profiles of 4-phenyl-1,8-naphthalimide in chloroform, DMSO, methanol and ethanol. Solid lines: absorption spectra recorded at 100 μM; dotted line: emission spectra recorded at 10 μM, excited at 345 nm; (**b**). pictures of 4-phenyl-1,8-naphthalimide in chloroform, DMSO, methanol and ethanol, excited with a handhold UV lamp (360 nm).

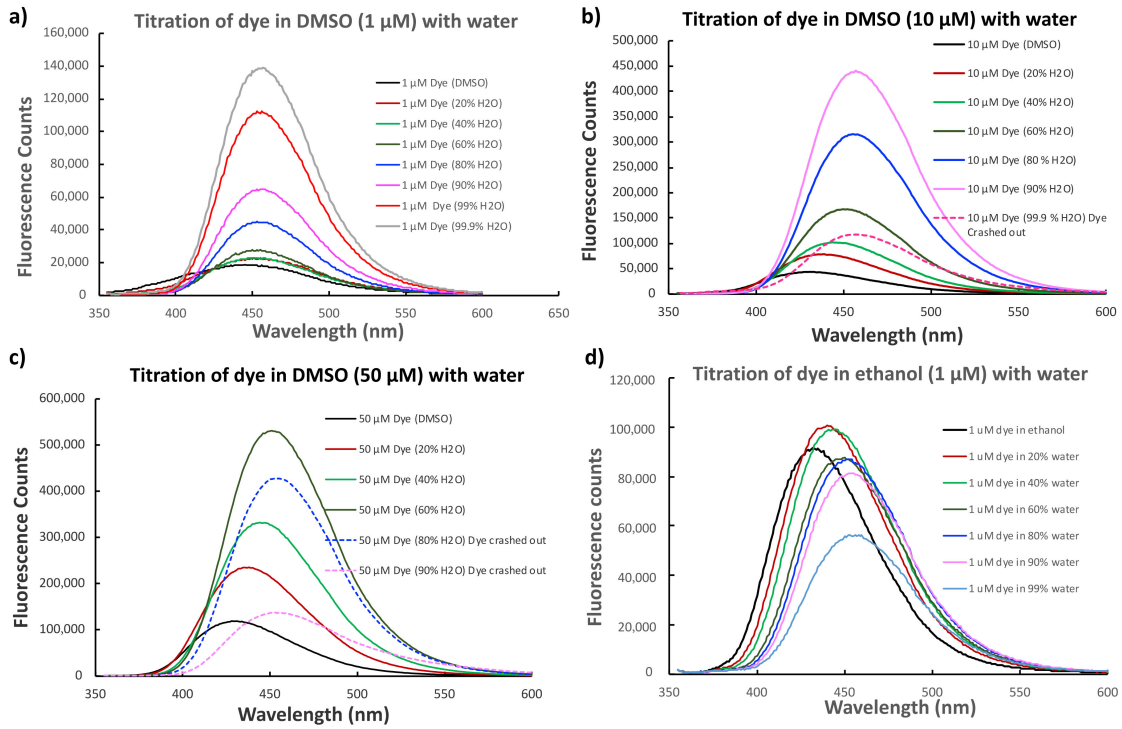


Figure 2. Changes in fluorescence intensity of 4-phenyl-1,8-naphthalimide in DMSO and ethanol upon addition of water. (**a**). 1 μM dye in DMSO, (**b**). 10 μM dye in DMSO, (**c**). 50 μM dye in DMSO, and (**d**). 1 μM dye in ethanol.

2.4. Fluorescent Properties of 4-Phenyl-1,8-naphthalimide in the Presence of DNA

We next examined the fluorescence properties of 4-phenyl-1,8-naphthalimide in the presence of DNA. As can be seen from Figure 3a, the presence of an octadecamer $d(CG)_9$ (0.01 μM) in 100 mM NaCl, which is known to adopt B-DNA form [15], did not lead to significant changes in the fluorescent profile of 4-phenyl-1,8-naphthalimide over a range of dye concentrations. This is also the case for a 30-mer

DNA duplex d(AT)$_{15}$ in 100 mM NaCl (Figure 3c). In 4 M NaCl, however, a rather moderate increase in fluorescence intensity was seen for d(CG)$_9$ (Figure 3b), which adopts the left-handed Z-DNA form [15]. Furthermore, little difference was seen in the emission profiles of 4-phenyl-1,8-naphthalimide in the presence of a single- (d(TGGTATATCTCCTTCTTAAAG)) and double-stranded mixed sequence 21-mer (Figure 3d).

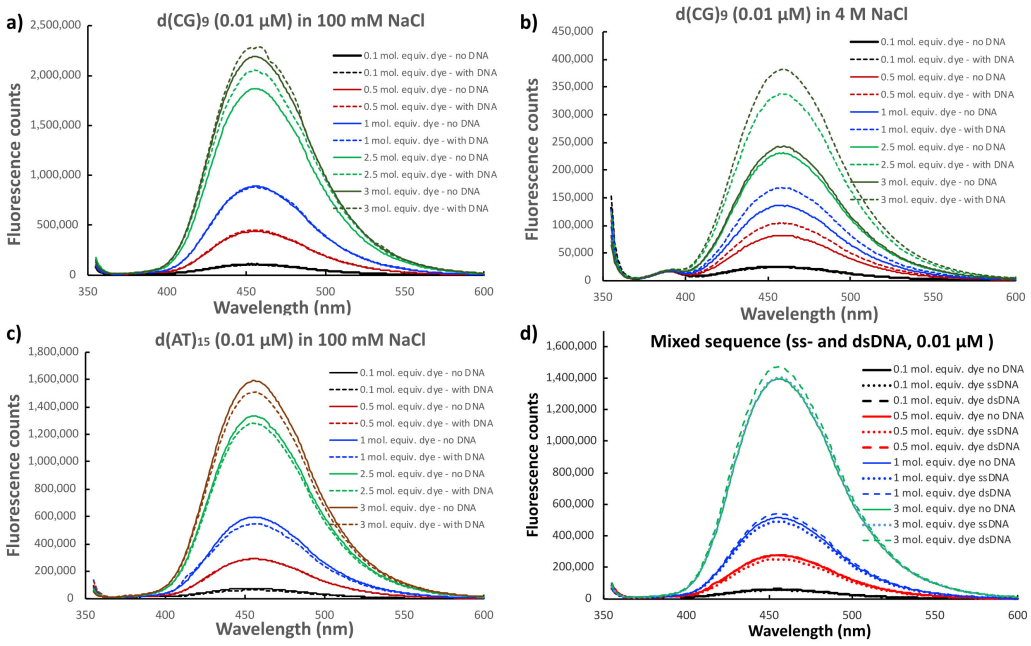


Figure 3. Fluorescence profiles of 4-phenyl-1,8-naphthalimide in the presence of DNA. (**a**). d(CG)$_9$ in 100 mM NaCl; (**b**). d(CG)$_9$ in 4 M NaCl; (**c**). d(AT)$_{15}$ in 100 mM NaCl; and (**d**). mixed sequence ss- and ds-21-mer, d(TGGTATATCTCCTTCTTAAAG).

2.5. Salt Concentration-Dependent Fluorescence

We evaluated the fluorescence emission of 4-phenyl-1,8-naphthalimide in the presence of various salts at concentrations ranging from 0.1 to 4 M. As shown in Figure 4, a general trend in the decrease of fluorescence intensity at 456 nm was observed with the increase of salt concentrations, but the degree of decrease was smaller with the increase of calcium chloride concentration where emission is rather concentration-independent above 1 M $CaCl_2$. This observation is supportive of the scenario where high salt concentrations lead to the disruption of hydration of 4-phenyl-1,8-naphthalimide, which is rather hydrophobic, resulting in the reversal of aggregation-induced emission.

2.6. Fluorescent Properties of 4-Phenyl-1,8-naphthalimide in the Presence of Bovine Serum Albumin

Given the hydrophobic nature of 4-phenyl-1,8-naphthalimide and its solvent-dependent fluorescent behavior, we next examined the fluorescent profiles of this dye in the presence of bovine serum albumin (BSA). Figure 5 shows that fluorescence of 4-phenyl-1,8-naphthalimide is virtually completely quenched by BSA, although at a very large molar ratio (above 20 µM BSA for 0.5 µM dye). While the detailed cause of this quenching remains to be elucidated, this observation suggests the potential to use 4-phenyl-1,8-naphthalimide derivatives to survey protein surface hydrophobicity, which remains a topic of challenge [16,17].

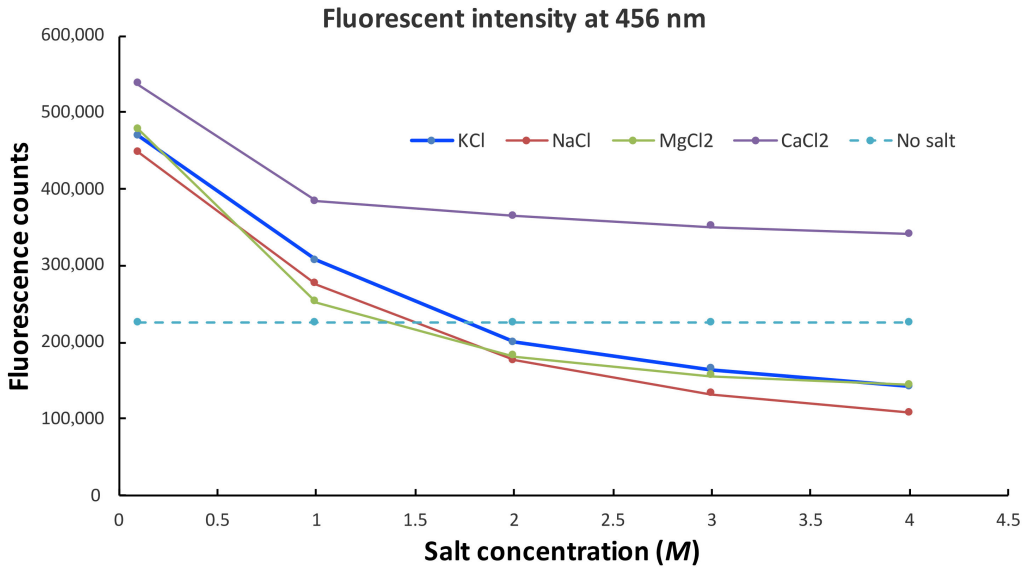


Figure 4. Salt-dependent fluorescence of 4-phenyl-1,8-naphthalimide. The dye solutions were all prepared at 1 μM.

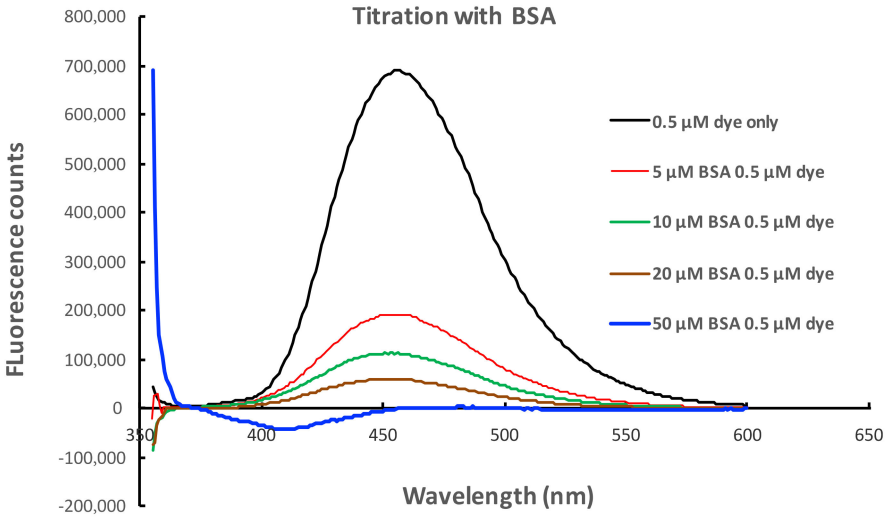


Figure 5. Quenching of 4-phenyl-1,8-naphthalimide by BSA. The fluorescence spectra with BSA samples were derived after subtraction of that of BSA of corresponding concentrations.

3. Materials and Methods

3.1. Instrumentation

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.3 MHz, respectively, with a Bruker Avance 400 NMR spectrometer (Billerica, MA, USA). Coupling constants (*J*) and chemical shifts are given in ppm and hertz (Hz), respectively. Deuterated solvents were purchased from C/D/N Inc. EI (electron impact) and FAB (fast atom bombardment) mass spectra were obtained with a Thermo Scientific DFS mass spectrometer (Waltham, MA, USA); ESI (electrospray) spectra were measured with a Bruker HCT Plus ion-trap mass spectrometer (Billerica, MA, USA).

3.2. Chromatography

Silicycle silica gel (230-]–400 mesh) was used for flash chromatography. Thin layer chromatography (TLC) was performed on Silicycle F-254 silica TLC plates (Silicycle, Québec City, QC, Canada) with methanol–dichloromethane (5:95, *v*/*v*).

3.3. Solvents and Chemicals

Solvents and reagents were purchased from Sigmaaldrich, Thermofisher or TCI and used without purification.

3.4. UV/vis and Fluorescent Spectroscopy

Absorption spectra were recorded using a Genesys 10S UV-Vis Spectrophotometer (Thermo Scientific, Waltham, MA, USA). Fluorescence spectra were recorded using a PTI Photon Technology International fluoremeter (Birmingham, NJ, USA). The strip size was set at 1 nm, integration was performed at 1 sec, and the slit width was set at either 2 or 6 nm depending on the experiment.

3.5. Synthesis of 4-Bromo-1,8-naphthalimide

3.5.1. Method A (Conventional Heating with Ammonium Acetate)

4-Bromo-1,8-naphthalic anhydride (300 mg, 1.08 mmol) was heated with ammonium acetate (256 mg, 3.32 mmol) in acetic acid (5.0 mL) under reflux for 24 h. Upon cooling, the mixture was evaporated under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and extracted with water (10 mL). The layers were separated, and the aqueous layer was back extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel. The fractions, which were eluted with dichloromethane–methanol (98:2 *v*/*v*), were combined and concentrated under reduced pressure to give 4-bromo-1,8-naphthalimide (65 mg, 22%) as a yellow solid.

3.5.2. Method B (Conventional Heating with Ammonia in Dioxane)

4-Bromo-1,8-naphthalic anhydride (300 mg, 1.08 mmol) was heated in a solution of ammonia in dioxane (5.0 mL, 0.5 *M*) in a sealed Reacti® vial at 60 °C for 48 h with occasional manual mixing. Upon cooling, the products were evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and extracted with water (10 mL). The layers were separated, and the aqueous layer was back extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane–methanol (98:2 *v*/*v*), were combined and concentrated under reduced pressure to give 4-bromo-1,8-naphthalimide (61 mg, 21%) as a yellow solid.

3.5.3. Method C (Microwave Heating with Ammonium Acetate)

4-Bromo-1,8-naphthalic anhydride (300 mg, 1.08 mmol) was reacted with ammonium acetate (250 mg, 3.25 mmol) in acetic acid (5 mL) in a CEM Discover microwave reactor (Matthews, NC, USA) at 60 °C (60 psi and 60 W) for 10 min. Microwave heating was repeated for another 10 min to ensure complete consumption of the anhydride, as indicated by TLC. Upon cooling, the products were concentrated under reduced pressure and the residue was dissolved in dichloromethane (10 mL) and extracted with water (10 mL). The layers were separated, and the aqueous layer was back extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel. The fractions, which were eluted with dichloromethane–methanol (98:2 *v*/*v*), were combined and concentrated under reduced pressure to give 4-bromo-1,8-naphthalimide (161 mg, 54% yield) as a yellow solid.

δ_H(DMSO-d_6): 7.98 (1 H, dd, J = 7.4 and 8.5), 8.19 (1 H, d, J = 7.8), 8.27 (1 H, d, J = 7.8), 8.51 (1 H, dd, J = 0.8 and 7.5), 8.53 (1 H, dd, J = 0.8 and 8.5), 11.86 (1 H, s, NH, ex). δ_C(DMSO-d_6): 123.0, 123.7, 129.2, 129.6, 130.1, 130.6, 130.7, 131.3, 131.8, 133.1, 164.0, 164.1. ESI-MS found 275.9 $[M + H]^+$, $C_{12}H_6BrNO_2$ requires 274.9582. R_f: 0.52.

3.6. Synthesis of 4-Phenyl-1,8-naphthalimide

3.6.1. Method A (Conventional Heating)

4-Bromo-1,8-naphthalimide (50 mg, 0.18 mmol), phenolboronic acid (44 mg, 0.36 mmol) and tetrakis(triphenylphosphine)palladium(0) (105 mg, 0.194 mmol) were mixed with dimethylformamide (1 mL) followed by addition of a solution of sodium carbonate (224 mg, 181 mmol) in water (1 mL). After the mixture was heated under reflux for 8 h, the products were concentrated under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and extracted with saturated aqueous sodium bicarbonate (10 mL). The layers were separated, and the aqueous layer was back extracted with dichloromethane (2 × 5 mL). The combined organic layers were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel. The fractions, which were eluted with dichloromethane–methanol (98:2 *v*/*v*), were combined and concentrated under reduced pressure to give 4-phenyl-1,8-naphthalimide (5 mg, 10%) as a yellow solid.

3.6.2. Method B (Microwave Heating)

4-Bromo-1,8-naphthalimide (50 mg, 0.18 mmol), phenolboronic acid (66 mg, 0.55 mmol,) and tetrakis(triphenylphosphine)palladium(0) (11 mg, 0.0095 mmol) were mixed with dimethylformamide (1 mL) followed by addition of a solution of sodium carbonate (224 mg, 181 mMol) in water (1 mL). The mixture was heated in a CEM Discover microwave reactor at 70 °C (100 W, 60 psi) for 30 min. The products were concentrated under reduced pressure and the residue was then dissolved in dichloromethane (10 mL) and extracted with saturated aqueous sodium bicarbonate (10 mL). The layers were separated, and the aqueous layer was back-extracted with dichloromethane (2 × 5 mL). The combined organic layers were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane–methanol (98:2 *v*/*v*), were combined and concentrated under reduced pressure to give 4-phenyl-1,8-naphthalimide (38 mg, 77%) as a yellow solid. M.p. > 260 °C (Isopropanol). δ_H(DMSO-d_6): 7.54–7.63 (5 H, m), 7.78 (1 H, d, J = 7.3), 7.84 (1 H, t, J = 7.9), 8.23 (1 H, d, J = 8.4), 8.48 (1H, d, J = 7.0), 8.49 (1 H, d, J = 7.6), 11.80 (1 H, s, NH, ex). δ_C(DMSO-d_6): 122.2, 123.3, 127.8, 128.4, 129.0, 129.2, 129.6, 130.0, 130.1, 130.2, 130.5, 132.6, 138.8, 146.5, 164.4, 164.6. ESI-MS found 273.0784 (M^+), $C_{18}H_{11}NO_2$ requires 273.0790. R_f: 0.52.

3.7. Fluorescent Quantum Yield Measurement

The relative fluorescent quantum yield of dye **3** was determined against fluorescein as the standard (φ_f = 0.95) [18]. Briefly, a series of solutions of dye **3** were prepared (in ethanol and DMSO, respectively), with absorbance values below 0.1 and the absorption spectra were recorded using 10 mm fluorescence quartz cuvettes. The same was performed for the standard fluorescein in 0.1 M NaOH. The absorption spectra of the solvent were also recorded. The fluorescence spectra of the solutions in the 10 mm quartz fluorescence cuvette were then recorded and the integration of fluorescence intensity was calculated after solvent background correction. The slit width was set at 2 nm for this experiment. Linear plots were generated by graphing the integrated fluorescence counts against the absorbance values for calculation of relative fluorescent quantum yields.

3.8. DNA Binding

DNA binding experiments were carried out with 0.01 μM of ss- or ds-DNA and dye **3** (0.1–3 molar equivalents per DNA nucleobase) in Tris-HCl buffer (20 mM containing appropriate concentration of

salt). Solutions were left to equilibrate for two hours, and then excited at 345 nm and fluorescence emission was measured from 355–600 nm. The slit width was set at 6 nm for all the DNA binding experiments. Dye **3** solution (1 μM) was prepared in Tris-HCl buffer (20 mM Tris containing 100 mM NaCl and 8 mM EDTA, pH 7.5) containing 1%(*v*/*v*) DMSO. Tris-HCl buffer (20 mM, pH 7.5) contains 100 mM NaCl and 8 mM EDTA. DNA solutions were prepared at 1 μM in Tris-HCl buffer (20 mM, pH 7.5, containing 100 mM NaCl and 8 mM EDTA). The oligonucleotide samples, d(CG)9, d(AT)15 and mixed 21-mer (5′-d(CTTTAAGAAGGAGATATACCA)-3′) were constituted following compositions described in Tables S1–S4.

3.9. Fluorescence Measurement of 4-Phenyl-1,8-naphthalimide in Inorganic Salts of Different Concentration

Solutions of dye **3** (1 μM) in salts of different concentrations were prepared according to the composition described in Tables S5–S8. Solutions were left to equilibrate for two hours prior to fluorescence measurement. This sample equilibrium is of importance to ensure that no changes in fluorescence intensity were seen prior to binding experiments. For each sample, a blank without dye **3** was also prepared. The slit width was set at 6 nm for this experiment.

3.10. BSA Binding

BSA samples were prepared by mixing solutions of dye **3** (500 μL, 10 μM in 1%(*v*/*v*) aqueous DMSO, prepared by diluting 10 μL of 1 mM solution of dye **3** in DMSO with 9990 μL of milliQ water) and BSA (100 μL of appropriate concentrations), and diluted with PBS (100 μL, prepared by dissolving 80 g NaCl, 2 g KCl, 14.4 g $Na_2HPO_4{\cdot}2H_2O$ and 2.4 g KH_2PO_4 in 1 L milliQ water, with final pH of 8) and 1%(*v*/*v*) aqueous DMSO (200 μL). Solutions were left to equilibrate for two hours prior to fluorescence measurement. For each binding experiment, a control sample without dye **3** was used. The slit width was set at 6 nm for this experiment.

4. Conclusions

4-Phenyl-1,8-naphthalimide was synthesized in two steps from commercially available 4-bromo-1,8-naphthalic anhydride, both under microwave heating. This compound shows strong solvent-dependent fluorescent behaviors. While quite fluorescent in solvents such as chloroform, methanol and ethanol, this compound is virtually non-fluorescent in DMSO. Furthermore, 4-phenyl-1,8-naphthalimide shows strong AIE-like properties, where addition of water to solution of this dye in DMSO led to restoration of fluorescence. While virtually no difference in fluorescence emission profiles was seen in the presence of single-stranded and B-DNA, a moderate fluorescence enhancement was seen in the presence of Z-DNA. Lastly, the fluorescence of this dye is virtually completely quenched by bovine serum albumin. Taken together, incorporation of a benzene ring at the 4-position of 1,8-naphthalimide introduced interesting fluorescent properties that will enable future development of dyes that are likely specific for Z-DNA binding and hydrophobic environment. This aspect of research is currently ongoing in this lab.

Supplementary Materials: The following are available online, copies of NMR spectra, microwave reaction parameters, and sample preparation for fluorescence spectroscopic experiments.

Author Contributions: Conceptualization, F.B. and H.Y.; methodology, F.B., J.H., and H.Y.; experiment, F.B.; writing, review and editing, F.B, J.H., and H.Y.; supervision, H.Y. All authors have read and agreed to the published version of the manuscript.

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