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BODIPY Dyes

Towards *meso*-Ester BODIPYs with Aggregation-Induced Emission Properties: The Effect of Substitution Positions**

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Abstract: Three *meso*-ester boron dipyrromethene (BODIPY) dyes have been synthesized and functionalized with aggregation-induced emission (AIE)-active tetraphenylethene or triphenylethene moieties. It was found that functionalizing at the different positions of the BODIPY core resulted in the final dye having different emission properties in response to aggregation: from aggregation-induced quenching (ACQ) to being AIE active. X-ray crystallographic analysis was thus performed to provide an explanation for these differences.

Many organic luminogens, owing to their planar structure, suffer from an aggregation-induced quenching (ACQ) effect, which can reduce their effectiveness in applications. In 2001, Tang's group first discovered a new class of organic luminogens, which displayed the opposite effect of ACQ.[1] These luminogens, such as hexaphenylsilane (HPS) and tetraphenylethene (TPE), are non-emissive in dilute solutions but their emission intensifies on forming nano-aggregates in the presence of poor solvents. This is mainly due to their propeller-like structures that suppress π–π interactions and cause restriction-to-intramolecular rotation upon aggregation. Tang thus coined the term "Aggregation-Induced Emission" (AIE) for the intriguing property that this group of luminogens possess.[2] AIE-active luminogens outshine their ACQ-counterparts in many applications and overcome problems previously associated with ACQ luminogens. This has made the design and applications of AIE luminogens a hot research topic for the past decade.[3]

There has been intensive focus on the development of bioprobes with far-red and near infrared (NIR) emission. Such fluorescent probes are particularly preferred over visible-emitting ones because they have low phototoxicity, low auto-fluorescent background, and the ability to penetrate deeper into tissue samples, thus making them especially useful for in vivo experiments and procedures.[4] A few established classes of organic luminogens have been reported to achieve the highly desired far-red and NIR emission. One of these is 4,4-difluoro-4-borata-3a,4a-diaza-*s*-indacene (BODIPY) dyes.[5] BODIPY dyes are well known for their chemical stability, high fluorescence quantum yield, and versatile functionalization at various positions of the BODIPY core to tune its photophysical properties. A number of fluorescent bioprobes based on the BODIPY structure have been developed for bioimaging, but not many have managed to reach far-red and NIR emission.[6]

Recently, our group reported the unique synthesis of *meso*-ester-substituted BODIPY dyes that were able to push the emission range beyond 600 nm (of normal BODIPY dyes) into the far-red and NIR region.[7] Positive results were obtained for bioimaging applications of these dyes as well. Encouraged by this successful study, we envisaged to introduce the AIE properties to BODIPY dyes of such designs with the ultimate aim to develop an AIE-active fluorescent probe with far-red and NIR emission. To the best of our knowledge, the first example of an AIE BODIPY was reported by Tang and co-workers, through functionalizing the *meso*-position with an AIE-active triphenylamine moiety, and several other AIE-active BODIPY dyes were successively reported.[8] All these reported cases are based on functionalizing the *meso* group with either AIE-active moieties or sterically bulky groups, which hinders close π–π stacking.

By considering previous successful studies of introducing AIE properties to conventionally ACQ luminophores by functionalizing them with AIE-active moieties (e.g. HPS and TPE),[3g,9] we attempted to do the same for our *meso*-ester BODIPY. However, the introduction of AIE properties into our *meso*-ester BODIPY system was not as straightforward as we had anticipated. Herein, we wish to report our attempts and findings, where we have successively synthesized three *meso*-ester BODIPY dyes (**1**–**3**), each with AIE-active TPE or triphenylethene functionalized at different positions of the core (Scheme 1), to produce derivatives that are either ACQ (**1**), slightly ACQ (**2**), or AIE-active (**3**). X-ray crystallographic analysis

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[**] *BODIPY = Boron dipyrromethene.*

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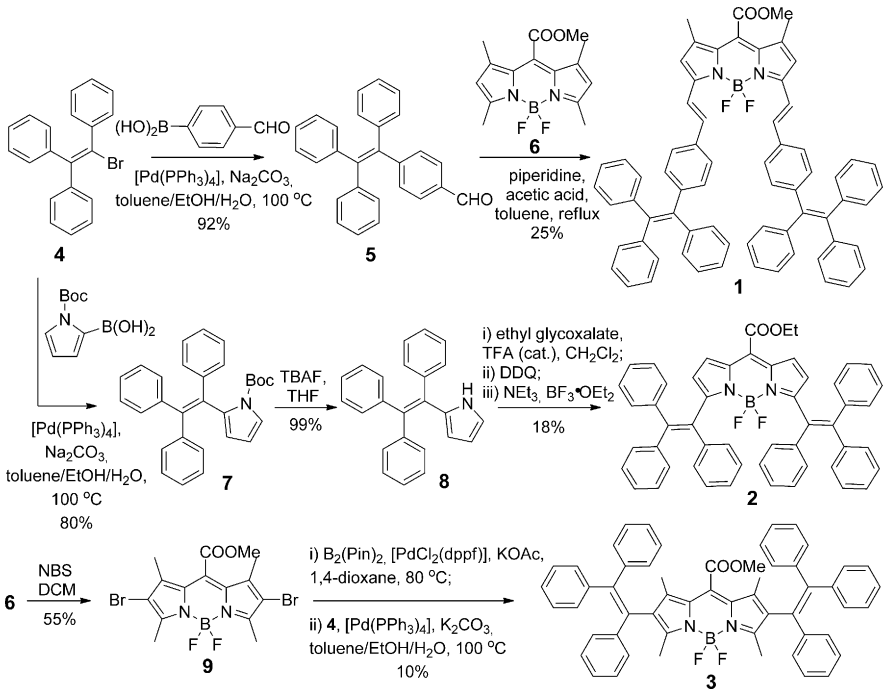

Scheme 1. Synthesis of TPE and triphenylethene substituted BODIPYs **1**–**3**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; pin = pinacol.

was performed, and this demonstrated that functionalizing the BODIPY core at different positions with TPE/triphenylethene resulted in a different packing manner, thus explaining the different properties observed.

In BODIPY **1**, the two AIE-active TPE units were connected to the α-position of the BODIPY core through an ethylene linkage. It was synthesized simply by Knoevenagel condensation between the *meso*-ester BODIPY **6**[7] and the TPE monoaldehyde **5**, which was obtained by simple Suzuki coupling from **4**. Investigations into the emission properties of BODIPY **1** in response to increasing the concentration of poor solvent (water) revealed that the compound, much to our dismay, exhibited ACQ properties (see Figure S1 in the Supporting Information). Building on the assumption that the AIE-active TPE units are too far from the BODIPY core, we decided to bring the AIE-active moiety closer by substituting the *meso*-ester BODIPY core with triphenylethene at the two α-positions (BODIPY **2**). Suzuki coupling between 1-bromo-1′,2,2′-triphenylethene and *N*-Boc pyrrole-2-boronic acid yielded **7**, which underwent a tetra-*n*-butylammonium fluoride (TBAF) deprotection of the *tert*-butoxycarbonyl (Boc) protecting group to give the triphenylethene-substituted pyrrole **8**. BODIPY **2** was then synthesized with **8** by using a standard synthetic procedure for the *meso*-ester BODIPYs.[7] It was found that BODIPY **2** had a slight ACQ tendency as well (see Figure S1 in the Supporting Information). On our third try, we chose to substitute the *meso*-ester BODIPY core at the two β-positions with triphenylethene. *N*-bromosuccinimide (NBS) bromination was first carried out on **6** to produce **9**. Subsequent Pd-catalyzed Miyaura borylation followed by Suzuki coupling reaction with **4** gave the product BODIPY **3**. To our delight, BODIPY **3** exhibited the much desired AIE properties.

The normalized absorption and emission spectra of BODIPYs **1**–**3** in THF are shown in Figure 1 and the data are summarized in Table S1 (see the Supporting Information). BODIPY **1** is the most red-shifted with absorption maximum (λ_{abs}) at 673 nm compared to **6** with λ_{abs} at 511 nm due to the largest extent of conjugation, but suffers the shortest Stoke's shift of just 18 nm and fluorescence quantum yield (Φ = 4.7%). The extent of conjugation of BODIPY **2** is lower than that of BODIPY **1** and thus its absorption maximum is shorter at 619 nm. It has the largest Stoke's shift of 78 nm amongst the three dyes and a quantum yield of 6.4% in dilute solution (see the Supporting Information). The β,β′-substitution of triphenylethene onto the *meso*-ester BODIPY core leads to lesser extent of conjugation compared to α,α′-substitution, thus BODIPY **3** is the least

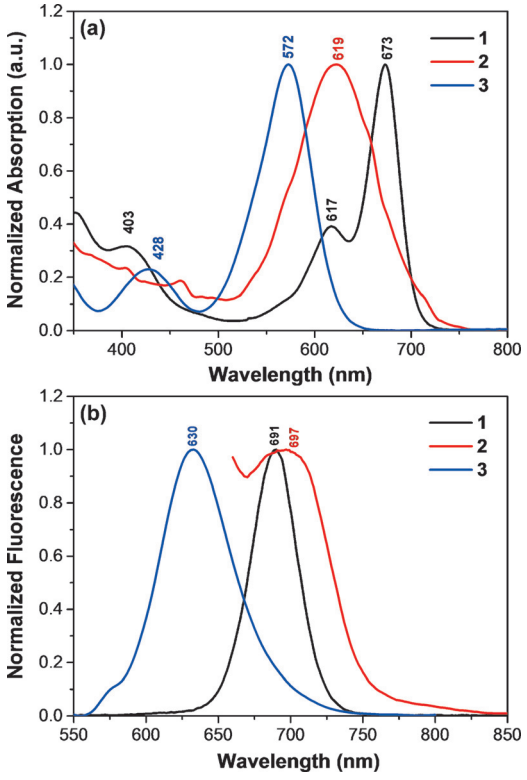

Figure 1. Normalized UV/Vis absorption (a) and fluorescence (b) spectra of BODIPYs **1**–**3** in THF solution.

red-shifted, absorbing at 572 nm and emitting at 630 nm. Its quantum yield is 2.9% in dilute solution and 10.0% in crystalline form (see the Supporting Information). Time-dependent DFT (B3LYP/6-31G*) calculations predicted similar absorption spectra, with the absorption maximum at 667.5 nm (oscillator strength $f=0.7009$) for **1**, 642.0 nm ($f=0.3028$) for **2**, and 545.6 nm ($f=0.4182$) for **3** (see the Supporting Information), which is in agreement with the observed experimental trend. Fluorescence spectra of thin film state is only observable for BODIPY **2** (faintly) and BODIPY **3** (intensively), and the corresponding emission wavelengths are red-shifted slightly owing to aggregation (Figure S2, see the Supporting Information). Fluorescence was fully quenched in thin film for **1** owing to its ACQ nature.

The AIE properties of BODIPY **3** were investigated in THF/H_2O solution at a concentration of 100 μM (Figure 2). The fluorescence intensity in the presence of 90% water (poor solvent) increased 14 times compared to in pure THF, showing a bright red-emission. However, BODIPY **2** experienced mild quenching of fluorescence when the percentage of water (poor solvent) increased from 0 to 70%, but emission increased again at 80% and 90% (see Figure S1 in the Supporting Information). BODIPY **1** showed an obvious ACQ effect with fluorescence almost entirely quenched after the addition of 70% water onwards (see Figure S1 in the Supporting Information).

The varying results prompted us to further investigate the underlying reasons behind the effect of functionalization positions of AIE-active moieties on the emission response in the event of aggregation. We opted to perform single-crystal XRD analysis on the three BODIPY dyes to ascertain how packing of molecules during aggregation differs (Figure 3).[10] Molecules of BODIPY **1** are arranged in an anti-parallel manner, where bulky TPE units of alternating molecules interact with each other at the sides, whereas the BODIPY are packed close together through face-to-face π–π stacking with a short distance of 3.827 Å. This suggests the easy formation of aggregates, thereby leading to the efficient quenching of fluorescence. Hence, BODIPY **1** exhibits ACQ properties. As the AIE-active triphenylethene moieties are positioned closer to the BODIPY core in the case of BODIPY **2**, the BODIPY cores no longer have the flexibility and capability to pack as closely together face-to-face as compared to BODIPY **1**. Molecules of BODIPY **2** are also arranged in an anti-parallel fashion with triphenylethene moieties of adjacent molecules interacting with each other on both sides. The BODIPY cores between adjacent molecules are unable to arrange face-to-face as they are being forced apart. BODIPY cores of alternating molecules, however, do face each other with a distance of 9.250 Å. Quenching of fluorescence is thus not as efficient as that of BODIPY **1**, which explains the much milder ACQ effect observed for BODIPY **2**. Molecules of BODIPY **3** are arranged in a manner such that the adjacent BODIPY cores are not directly facing each other. The packing seems to be stabilized by some [C–H···π] interaction between the BODIPY core and a proton of a phenyl ring from the adjacent molecule with a distance of 2.914 Å. Excimers due to π–π stacking between BODIPY cores cannot be formed in the event of aggregation and thus BODIPY **3** exhibits AIE properties.

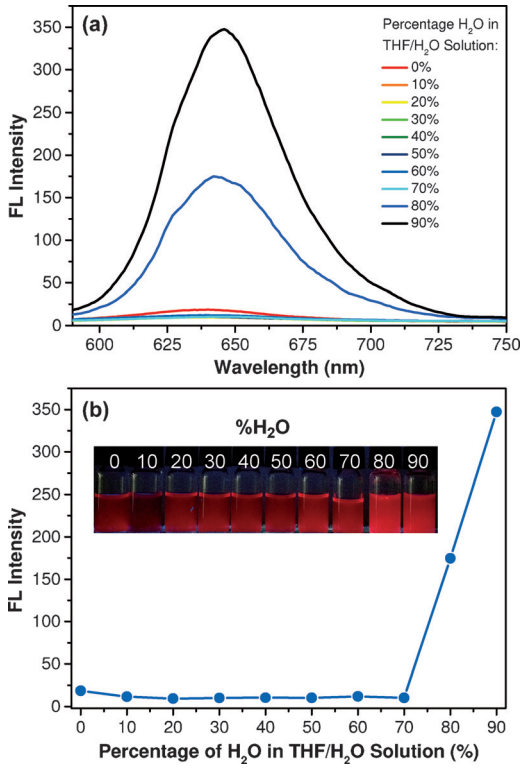

Figure 2. (a) FL spectra of BODIPY **3** in THF/water solutions of different proportions (100 μM). (b) The change of the maximum FL intensity with the percentage of water. Insert are photos taken under UV lamp (360 nm).

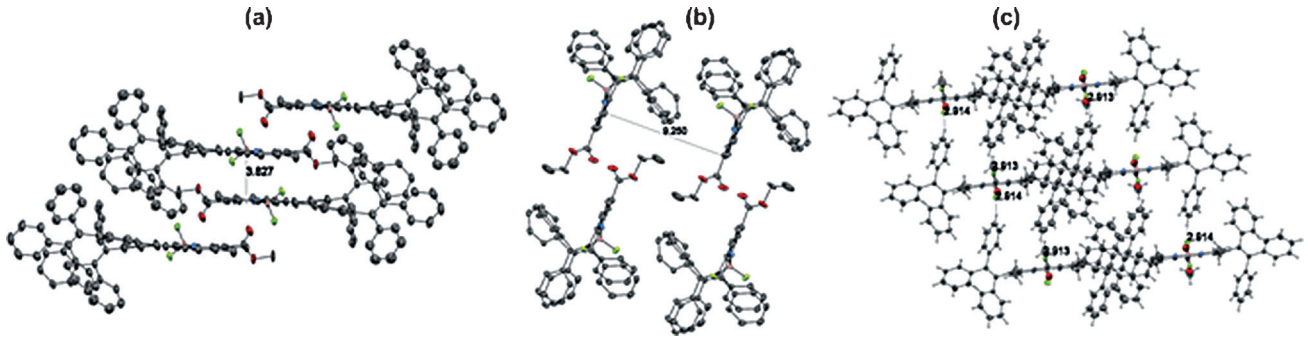

Figure 3. Packing structures of BODIPYs **1** (a), **2** (b), and **3** (c) obtained from single-crystal X-ray crystallographic analysis.

In summary, our research has demonstrated that the position of the AIE-active TPE or triphenylethene units on the BODIPY core is crucial to successfully incorporate AIE properties into the *meso*-ester BODIPY dyes, which will dispel a possible misconception that any luminogenic system can be rendered AIE-active just by functionalizing it with AIE-active moieties. The development of BODIPY **3** with AIE properties can serve as a potential fluorescent probe for bioimaging. More importantly, further functionalization and chemical modification can be performed at the α-methyl position by Knoevenagel condensation and/or hydrolysis of the ester at the *meso*-position, thus serving as a precursor to develop other AIE-active far-red and NIR BODIPY dyes for more specific functions in bioimaging and sensing applications.

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Keywords: aggregation-induced emission · bodipy · fluorescence · near-infrared · organic dyes

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[10] Crystallographic data for **1**: C70 H56 B F2 N2 O4, $M_w = 1037.97$; triclinic; space group *P-1*; $a = 9.8991(5)$ Å, $b = 19.1088(9)$ Å, $c = 20.4072(10)$ Å, $\alpha = 117.907(2)^\circ$, $\beta = 99.070(2)^\circ$, $\gamma = 90.009(2)^\circ$; $V = 3356.5(3)$ Å^3; $Z = 2$; $\rho_{calcd} = 1.027$ Mg/m^3; $R_1 = 0.1155$ ($I > 2\sigma(I)$), $wR_2 = 0.3384$ (all data). CCDC 1055168. Crystallographic data for **2**: C52 H39 B F2 N2 O2, $M_w = 772.66$; triclinic; space group *P*-1; $a = 9.4327(9)$ Å, $b = 12.4255(10)$ Å, $c = 17.7191(16)$ Å, $\alpha = 88.224(3)^\circ$, $\beta = 81.868(3)^\circ$, $\gamma = 87.318(3)^\circ$; $V = 2053.0(3)$ Å^3; $Z = 2$; $\rho_{calcd} = 1.250$ Mg/m^3; $R_1 = 0.0610$ ($I > 2\sigma(I)$), $wR_2 = 0.1713$ (all data). CCDC No.: 1055169. Crystallographic data for **3**: C57 H49 B F2 N2 O2.50, $M_w = 850.79$; monoclinic; space group *C 1 2/c 1*; $a = 37.1722(15)$ Å, $b = 9.4584(4)$ Å, $c = 26.3227(11)$ Å, $\alpha = 90^\circ$, $\beta = 91.7190(17)^\circ$, $\gamma = 90^\circ$; $V = 9250.6(7)$ Å^3; $Z = 8$; $\rho_{calcd} = 1.222$ Mg/m^3; $R_1 = 0.0985$ ($I > 2\sigma(I)$), $wR_2 = 0.2516$ (all data). CCDC 1055168 and 1055170 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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