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Benzene-fused BODIPYs: synthesis and the impact of fusion mode†

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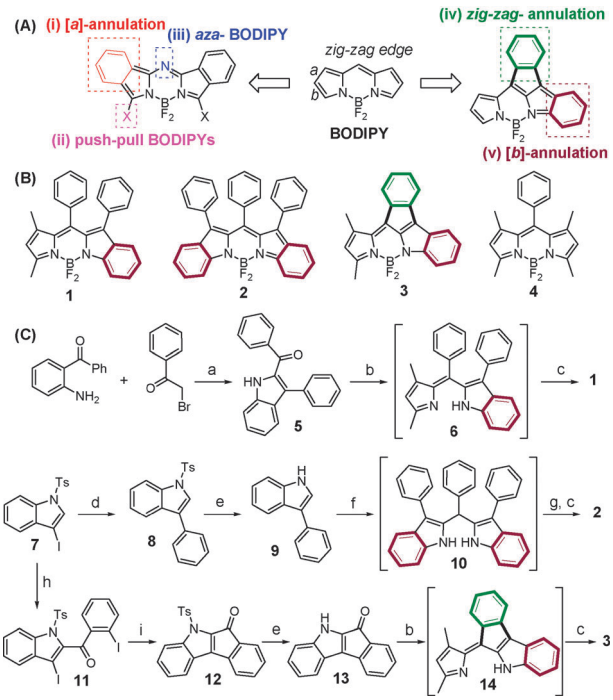
BODIPY derivatives with one or two benzene units fused at different positions are prepared using novel synthetic methods. The resulting dye 1 shows deep red fluorescence with a large Stokes shift. Dyes 2 and 3 are reported for the first time and 3 exhibits near infrared absorption. The impact of benzannulation at different positions of BODIPY is discussed, and the geometry and electronic structure are studied by DFT calculations.

4,4-Difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacene, abbreviated as BODIPY, represents a family of extremely versatile fluorophores which are currently attracting increasing interest among various research areas including bio-labeling/bio-imaging[1] and photovoltaic devices,[2] owing to their remarkable photophysical features, such as excellent thermal and photochemical stability, intense absorption, sharp fluorescence with high quantum yield, and outstanding inertness to the polarity and pH of the environment.[3] BODIPY derivatives that exhibit absorption and emission at the deep-red and near infrared (NIR) spectral regions (>650 nm) are highly desirable in both materials science[2e] and biotechnology.[3a] Various modification methods have been developed to access far-red or NIR BODIPYs (Scheme 1(A)), including (i) benzannulation at the *a* bond of the BODIPY skeleton by replacement of pyrrole with iso-indole;[4] (ii) functionalization at the α position of the pyrrole rings to generate a "push–pull" motif;[5] (iii) replacement of the *meso*-carbon by the nitrogen atom, *i.e.*, formation of aza-BODIPYs;[6] (iv) fusion of aromatic rings at the zig-zag edge of the BODIPY by oxidative cyclodehydrogenation reaction as reported by us;[7] and (v) annulation at the *b* bond of the BODIPY skeleton by replacement of the pyrrole rings with benzofuro[3,2-*b*]pyrrole, thianaphtheno-[3,2-*b*]pyrrole, and biphenyl-fused pyrrole units.[8] Indole can also be regarded as a benzannulated pyrrole. However, to the best of our knowledge, replacement of pyrrole rings in the BODIPY with indole units to generate indole-based BODIPYs has rarely been reported so far.[9] Moreover, the oxidative fusion strategy to introduce an aryl unit onto the zig-zag edge of BODIPY encountered a severe limitation, namely that the aryl unit must be suitably electron-rich.[7] Therefore, the phenyl ring without an electron-donating group cannot be successfully fused onto the zig-zag edge using this strategy.

Herein, we report convenient synthetic routes to replace the pyrrole with indole to achieve indole-based BODIPY **1** and bisindole-based



Scheme 1 (A) Various approaches towards BODIPYs with longer absorption and emission wavelengths. (B) Benzene-fused BODIPYs synthesized in this study. (C) *Reagents and conditions*: (a) DMF, 90 °C, 16 h, 72%; (b) 2,4-dimethylpyrrole, $POCl_3$, DCM, r.t., 12 h; (c) $BF_3{\cdot}OEt_2$, TEA, DCM, 2 h, 42% for **1** from **5**, 20% for **2** from **9**, 24% for **3** from **13**; (d) phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene, 110 °C, 24 h, 81%; (e) 10% NaOH, DMSO, EtOH, 50 °C, 94%; (f) benzaldehyde, 37% HCl, MeOH/EtOH, r.t., 12 h; (g) DDQ, DCM, refluxing, 2 h; (h) i: LDA, THF, −78 °C, 2 h; ii: 2-iodobenzoylchloride, r.t., 12 h, 21%; (i) Cu, DMF, 140 °C, 3 h, 95%.

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BODIPY **2**, which can also be regarded as benzo[*b*]-fused BODIPYs (Scheme 1(B)). Meanwhile, a novel strategy to prepare BODIPY **3** with one benzene unit fused at the *b* bond and one benzene ring fused at the zigzag edge will also be demonstrated. Their geometries, electronic structures and photophysical properties are investigated to afford a fundamental understanding of these new benzene-fused BODIPY dyes. A tetramethyl-BODIPY dye **4** was also prepared for comparison.[10]

The asymmetric benzo[*b*]-fused BODIPY **1** was synthesized through a two-step synthetic route (Scheme 1(C)). The alkylation–condensation between 2-amino-benzophenone and 2-bromoacetylphenone gave 2-benzoyl-3-phenylindole **5** in 72% yield.[11] Compound **5** was then reacted with 2,4-dimethylpyrrole in the presence of $POCl_3$, followed by addition of triethylamine (TEA) and complexation with $BF_3{\cdot}OEt_2$ to afford the benzo[*b*]-fused BODIPY **1** as a deep red solid in a total yield of 42%. This method likely can be used to prepare a series of benzo[*b*]-fused BODIPY derivatives since the alkylation–condensation sequence between *o*-amino ketones and α-bromo ketones provides ready access to a wide variety of 2-acylindoles.[11] The symmetric BODIPY **2** was prepared through the condensation of indole derivatives with the corresponding aldehyde. The Suzuki coupling reaction of *N*-tosyl-3-iodoindole **7** with phenylboronic acid gave the *N*-tosyl-3-phenylindole **8** in 88% yield. After hydrolysis, the resulting 3-phenylindole **9** was reacted with benzaldehyde in the presence of concentrated hydrochloric acid to produce the key intermediate **10**.[12] Without further purification, this intermediate was dissolved in anhydrous dichloromethane (DCM) followed by oxidation with DDQ and complexation with borontrifluoride to afford the dibenzo[*b*]-fused BODIPY **2** as a blue dye in an overall 20% yield. To synthesize compound **3**, we attempted the condensation of a fused indole–ketone intermediate **13** with pyrrole for the first time. Compound **7** was treated with strong base LDA for lithiation at the 2-position, then reacted with 2-iodobenzoyl-chloride to generate **11**. This compound was then treated with activated copper for intra-molecular Ullmann coupling reaction to give **12**,[13] which after hydrolysis afforded the key intermediate benzene-fused keto-indole **13**. Using a similar synthetic methodology to BODIPY **1**, BODIPY **3** was successfully prepared as a pink-red solid in an overall yield of 24% from **13**. The structures of all these compounds were unambiguously identified by NMR spectroscopy and mass spectrometry (ESI†).

The UV-vis-NIR absorption spectra of compounds **1–4** and the normalized emission spectrum of **1** are shown in Fig. 1. BODIPY **1** shows a relatively broad absorption band with maximum at 512 nm (log ε = 4.62, ε: molar extinction coefficient in M^{-1} cm^{-1}), with a slight red-shift by 12 nm relative to **4** (λ_{max} = 500 nm, log ε = 4.90). It exhibits an emission band centered at 655 nm with a fluorescence quantum yield of *ca.* 10% in DCM. Interestingly, a very large Stokes shift of 143 nm was observed, which makes this dye attractive for bio-imaging application after modification at the 3-methyl site.[14] BODIPY **2** displays an even broader absorption band (covering from 500 nm to 700 nm) with a more red-shifted λ_{max} of 568 nm. However, no fluorescence was observed. BODIPY **3** exhibits three absorption bands, an intense band at 391 nm with a relatively large coefficient (log ε = 5.0), a band at 518 nm, which is similar to that of BODIPY **1**, and a broad band ranging from 600 nm to 1100 nm, indicating a highly extended π-delocalization caused by fusion of a benzene ring at the zigzag edge of the BODIPY core.

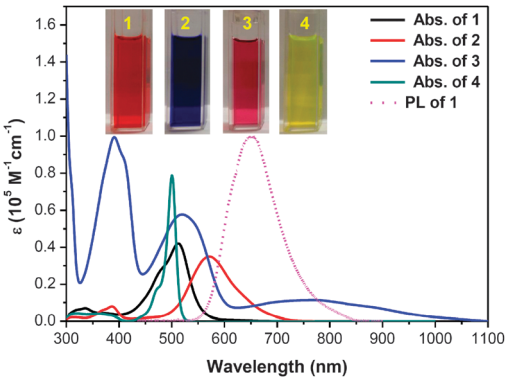

Fig. 1 UV-vis-NIR absorption spectra of **1–4** and normalized emission spectra of **1** in DCM. Inset is the photograph of the solutions of **1–4**.

The electrochemical properties of **1**, **2** and **3**, together with **4** for comparison, were investigated by cyclic voltammetry in DCM solution containing 0.1 M tetra-*n*-butylammonium hexafluorophosphate as the supporting electrolyte. As shown in Fig. 2, compounds **4**, **1** and **2** all exhibit one quasi-reversible oxidation wave and one reversible reduction wave with half-wave potentials at 1.05 V, −1.68 V for **4**, 1.11 V, −1.24 V for **1**, and 1.20 V, −0.70 V (*vs.* Fc^+/Fc) for **2**, respectively. The half-wave potentials of the oxidation waves of these three compounds show only a slight difference, while the reduction potentials exhibit a positive shift from **4** to **1** then to **2**, indicating that fusion of a benzene ring at the b bond of BODIPY can efficiently decrease the LUMO energy level, but shows a less impact on the HOMO energy level. HOMO energy levels of −5.68 eV, −5.79 eV, −5.88 eV and LUMO energy levels of −3.32 eV, −3.69 eV, −4.19 eV were estimated for **4**, **1** and **2**, respectively, based on the onset potential of the first oxidation and reduction waves. Compound **3** displays one reversible oxidation wave with a half-wave potential of 0.78 V and two reversible reduction waves with half-wave potentials of −0.85 V and −1.61 V. The HOMO energy level was estimated to be −5.44 eV, 0.33 eV higher than that of **1**, while the LUMO energy level is −4.08 eV, 0.39 eV lower than that of **1**. Thus, the fusion of a benzene unit at the zigzag edge of BODIPY can effectively extend the π-delocalization, resulting in an efficiently narrowed energy gap.[7] Electrochemical energy gaps of 2.36 eV for **4**, 2.10 eV for **1**, 1.69 eV for **2** and 1.36 eV

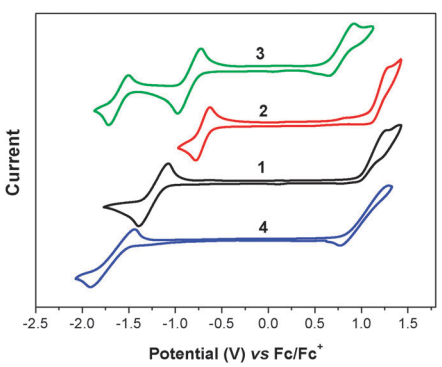

Fig. 2 Cyclic voltammograms of **1–4** in DCM with 0.1 M Bu_4NPF_6 as a supporting electrolyte, AgCl/Ag as a reference electrode, Au disk as a working electrode, Pt wire as a counter electrode, and a scan rate of 50 mV s^{-1}. Fc^+/Fc was used as external reference.

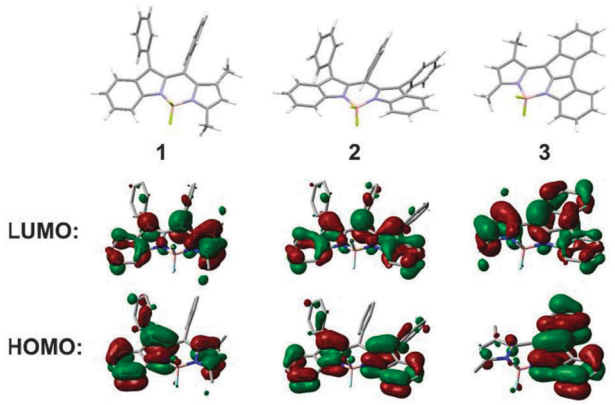

Fig. 3 Calculated geometry and frontier molecular orbital profiles of **1**, **2** and **3**. Hydrogen atoms are omitted for clarity.

for **3** were then calculated which are in agreement with their optical band gaps estimated from the onset of the lowest energy absorption band (2.40 eV for **4**, 2.23 eV for **1**, 1.76 eV for **2**, 1.28 for **3**).

In order to gain better insight into the molecular geometries, electronic structures, and optoelectronic properties, time-dependent density functional theory (TDDFT at B3LYP/6-31G*) calculations were performed for compounds **1–3**. The optimized structures and frontier molecular orbital profiles are shown in Fig. 3. For molecules **1** and **2**, the phenyl substitutions at *meso*- and β-positions are nearly perpendicular to the BODIPY plane, and the HOMO and LUMO are homogenously delocalized along the fused BODIPY system. **3** shows a nearly planar structure. The HOMO coefficients are mainly delocalized on the indole-fragment and the fused benzene ring at the zigzag edge, while the LUMO coefficients are homogenously dispersed along the whole conjugation system. The same tendency as the cyclic voltammetry was observed for the calculated HOMO and LUMO energy levels of **1**, **2** and **3**. The HOMO energy levels of **1** (−5.47 eV) and **2** (−5.40 eV) are almost the same, while a much lower LUMO level than that of **1** (−2.79 eV) was calculated for **2** (−3.21 eV). Meanwhile, a higher HOMO energy level (−5.19 eV) and a lower LUMO energy level (−3.25 eV) than those of **1** were also calculated for **3**. The computed absorption spectrum of **3** is in good agreement with the experimental results, with the calculated absorption maxima at 930.5 nm (HOMO → LUMO), 536.8 nm (HOMO − 1 → LUMO) and 401.1 nm (HOMO − 2 → LUMO) (ESI†).

In summary, BODIPY derivatives with one or two benzene rings fused at different positions (zigzag edge and/or *b* bond) were successfully prepared for the first time using new synthetic methods. The impacts of benzene-ring fusion at different positions were investigated by absorption/emission spectroscopy and electrochemical measurements assisted by DFT calculations. Compound **2** represents the first example of dibenzo[*b*,*g*]-fused BODIPY, and the synthetic method likely can be applied for the synthesis of other [*b*,*g*]-fused BODIPYs. Dye **3** shows NIR absorption due to the highly extended π-conjugation, and the new synthetic approach opens the door to introducing an aromatic unit without an electron-donating group onto the zigzag edge of the BODIPY core, which is essential to avoid intra-molecular charge transfer caused by the electro-donating groups. Dye **1** exhibits long wavelength fluorescence with a large Stokes shift, which makes it attractive for bio-imaging application, and this research is underway in our laboratories.

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