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N-Bridged Annulated BODIPYs: Synthesis of Highly Fluorescent Blue-shifted Dyes

Yanping Wu, John Mack, Hua Lu,* Xuqiong Xiao, Zhifang Li, and Zhen Shen

Abstract: A series of novel BODIPY dyes has been prepared through the introduction of an N-bridged annulated *meso*-phenyl ring at one of the β -positions of the BODIPY core. An unusual blue shift of the main spectral bands is observed, since the fusion of a *meso*-substituent results in a marked relative destabilization of the LUMO. The greater rigidity of the ring-fused structure leads to very high fluorescence quantum yields. The position of the main spectral bands can be fine-tuned by introducing electron withdrawing and donating groups onto the *meso*-phenyl ring.

Boron dipyrromethene (BODIPY) dyes are a well-known class of fluorophores, that have been widely used as laser dyes, fluorescent labels in fluorescence imaging and indicator dyes in sensor applications in recent decades.^[1] In recent years, the number of papers published on the synthesis and properties of these dyes has been rapidly growing. The key advantages offered by BODIPYs are their high photostabilities and advantageous spectroscopic properties, as well as their facile synthesis and structural versatility.^[2] Most of the recent research on BODIPYs has focused on structural modifications that result in red-shifts of the absorption and emission band maxima, such as, 1) aryl, ethynylaryl and styryl substitution at the 1-, 3-, 5-, and/or 7-positions, 2) aromatic ring fusion, 3) replacing the meso-carbon atom with an aza-nitrogen atom to form an dye, or combinations thereof,^[3] aza-BODIPY and dimerization.[4]

The fusion of polycyclic aromatic compounds to the *meso*and β -positions of BODIPY provides another more rarely used strategy for shifting the main spectral bands to the farred of the visible region and the near infrared (NIR).^[5] Reports on this type of structural modifications are relatively few in number and have involved only the use of Se and Te bridging atoms, which have red-shifted spectral bands.^[6] To the best of our knowledge, the introduction of an Nbridging atom at one of the β -positions has not been reported previously. Although it is well known that the wavelengths of the band maxima of the absorption and fluorescence bands can be fine-tuned so that they lie anywhere from the green region of the visible to the NIR

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region, only a few *meso*-heteroatom substituted BODIPYs have exhibited a hypsochromic shift of the main spectral bands so that blue region emission is observed.^[7] Core-modification is another strategy that has been used to form difluoroboron complexes which exhibit blue region emission but this type of dye does not retain the conventional BODIPY core, which causes the favorable photophysical properties of this family of dyes.^[8] Herein, we report the synthesis of a series of novel *meso*, β -annulated N-bridged BODIPY dyes, which exhibit highly unusual spectroscopic properties that can be readily rationalized through a comparison of spectroscopic data with the results of theoretical calculations.



Scheme 1. Synthesis and molecular structures of a series of meso, β -annulated N-bridged BODIPYs. Reagents and conditions: I) TFA, CH₂Cl₂, rt, 1 h; II) DDQ, rt, 30 min; III) Et₃N, BF₃:Et₂O, rt, 30 min; IV) PPh₃, o-DCB, 150°C, 24 h.

Precursors 1a-f were prepared through the TFAcatalvzed condensation reaction of ortho-nitrobenzaldehyde with pyrrole, oxidized dipyrromethanes with DDQ, and complexed with BF₃ under base condition. The ortho-nitro group on the meso-phenyl substituent has been used to form a C-N bond via an intramolecular reductive cyclization approach that is referred to as a Cadogan reaction.^[9] The N-bridged meso-annulated BODIPYs were isolated in overall yields of 26-50%. All of the target compounds were unambiguously characterized by high-¹H and ¹³C resolution mass spectrometry, NMR spectroscopy.

Single-crystal X-ray structures were obtained for **2a**, **2c**, **2d** and **2f** (Figure. 1). Conventional BODIPY dyes typically contain a planar indacene plane. When substituents are introduced at the neighboring 1,7-positions, the *meso*-aryl ring lies in a near orthogonal manner to the BODIPY core. In contrast, the structures of **2c**, **2d** and **2f** have near planar conformations because the *meso*-phenyl ring is annulated at one of the β -positions of the fluorophore core. The average root-mean-square (rms) deviations are 0.0241, 0.0358 and 0.0546 Å for **2c**,

2d and 2f, respectively (Figure. 1). 2a adopts a slightly distorted conformation, since the pyrrole ring deviates from the mean plane (phenyl-pyridyl pyrrole rings) with an average dihedral angle of 8.5°, due to crystal packing effects caused by cocrystallization with triphenylphosphine oxide that is formed by the oxidation of triphenylphosphine during the ring fusion reaction (Scheme 1). In all four structures, the B–N2 bond is slightly longer than the B–N1 bond due to the molecular asymmetry. The N3–C3 and N3–C4 bond lengths lie in the 1.34–1.36 Å range, which is consistent with the values for a double bond and an intervening single bond, which has some double bond character.



Figure 1. X-ray crystal structures of 2a (top, left), 2c (top, right), 2d (bottom, left) and 2f (bottom, right). Both the top view and a perspective along the *y*-axis that runs through the boron and *meso*-carbon atoms. The thermal ellipsoids are scaled to the 30% probability level. Hydrogen atoms and solvent molecule are omitted for clarity in both views. Selected bond lengths (Å): B1-N1 1.537(3), B1-N2 1.548(2), C3-N3 1.346(2), C4-N3 1.372(2) for 2a. B1-N1 1.523(7), B1-N2 1.545(3), C3-N3 1.340(5), C4-N3 1.367(5) for 2c. (Å): B1-N1 1.534(3), B1-N2 1.545(3), C3-N3 1.350(3), C4-N3 1.363(2), C13-C11 1.730(2) for 2d. B1-N1 1.531(3), B1-N2 1.547(3), C3-N3 1.343(2), C4-N3 1.369(2), C13-O1 1.356(2) for 2f.

Intermolecular π - π interactions are observed with distances of 3.654, 3.647 and 3.747 Å for **2a**, **2c** and **2f**, respectively. In addition to these interactions, multiple short interatomic contacts are found within the crystal structures of **2c** and **2f**. These are not observed in the case of **2d**, since a solvent molecule lies between neighboring π -chromophores. Short intermolecular interactions with the solvent are still observed, however, such as





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Figure 2. Absorption and emission spectra of BODIPYs 2a-f in DCM, (λ_{ex} = 430 nm).

The photophysical properties of 2a-f were studied in toluene dichloromethane, THF and acetonitrile to obtain detailed information about the effect of structures that are conformationally locked through meso-phenyl substitution at the β-positions, Table S1. As shown in Figure 2, in dichloromethane the incorporation of an N-bridged annulated meso-phenyl ring results in a blue-shift of the absorption and emission band relative to those of conventional BODIPY dyes. Broadening of the main absorption band, which can be assigned as the main electronic band of the S_0-S_1 transition, is observed. The changes to the electronic structure that result in the observed blue shift have no effect on the morphology of the absorption band. A shoulder observed at shorter wavelength can be ascribed to a 0-1 vibrational band in a similar manner to the spectra of conventional BODIPY dyes.^[3] Broader and much weaker bands are observed in the UV region, which can be attributed to transitions to the S_2 or S_3 excited states (Figure 3). Although no emission is observed in the solid state, it should be noted that similar UV-visible absorption properties were observed for 2c in poly(methyl methacrylate) (PMMA) thin films (Supporting information, Figure S8).

The effect of introducing different substituents on the N-bridged fused *meso*-phenyl ring has been investigated. The introduction of an electron donating methoxy group at the *para*-position of the *meso*-phenyl ring to form **2f** results in a blue shift of 18 nm for the main spectral band relative to the analogous band of **2a** in toluene. The observed

absorption band maxima of **2a-f** depend on the polarity of the solvent, with a hypsochromic shift of ca. 17 nm when the solvent polarity changes on moving from the relatively non-polar toluene to more highly polar acetonitrile. A similar trend is observed in the emission band maxima (Table S1 in the Supporting Information).

Table 1. Spectroscopic properties of 2a-2f in dichloromethane at 298K.

-	λ_{abs}	λ_{em}	Δv^a	${\pmb \phi}_{\sf F}{}^{\sf b}$	7 _F ^c	$k_{\rm r}^{\rm d}$	k _{nr} e		
	nm	nm	cm ⁻¹		ns	10 ⁸ s ⁻¹	10 ⁸ s ⁻¹		
2a	458	478	914	0.99	4.71	2.10	0.02		
2b	464	486	975	0.82	4.90	1.67	0.37		
2c	467	488	921	0.87	5.00	1.74	0.26		
2d	461	485	1074	0.99	5.11	1.94	0.02		
2e	462	486	1069	0.98	6.24	1.57	0.03		
2f	446	471	1190	0.99	5.81	1.70	0.02		

[[]a] Stokes-shift. [b] fluorescence quantum yield. [c] fluorescence halflifetime. [d] radiative rate constant. [e] non-radiative rate constant.

In all of the solvents investigated, the fluorescence quantum yields of **2a-f** are relatively high, in a similar manner to classical BODIPY dyes,³ with values as high as 1.00 in non-polar toluene. This is probably related to the enhanced structural rigidity that is introduced when a *meso*-phenyl ring is fused at one of the neighboring β-pyrrole positions of the BODIPY core. The fluorescence decay profiles of **2a-f** could be described with a single-exponential fit with fluorescence lifetimes in the 4.40–6.75 ns range in all of the solvents investigated. Only minor solvatokinetic effects are observed in the rate of decay constants. As expected, the non-radiative decay constants are very small and significantly lower than those that have been reported previously for non-bridged BODIPY.^[10]

In order to investigate the influence of structural modifications on the spectroscopic and electronic properties, density functional theory (DFT) was used to carry out ground-state geometry optimizations by using the B3LYP functional and 6-31G(d) basis sets of the Gaussian 09 software package,^[11] for **2a-f** and for a series of deprotonated species. The polarized continuum model (PCM) was used to provide an acetonitrile solvation environment. The CAM-B3LYP functional was preferred for use in time-dependent density functional theory (TD-DFT) calculations, since it contains a long range correction that provides more accurate results for transitions with charge transfer character.^[12]



angular nodal patterns of the HOMOs and LUMOs of selected *meso*-annulated BODIPYs and the parent *meso*-phenyl-BODIPY model compound **3**. The HOMO-LUMO gap values are highlighted with red diamonds and are plotted against a secondary axis. Calculations were performed at the CAM-B3LYP/6-31G(d) level of theory in an acetonitrile solvation environment.

Table 2 provides the predicted trends in the lowestenergy transitions for 2a-f, and the deprotonated species. A marked blue-shift is predicted for the main spectral bands of 2a-f relative to that of the parent meso-phenyl-BODIPY 3. Figure 3 shows key trends associated with the frontier molecular orbitals of 2a, 2c and 2f and the parent mesophenyl-BODIPY 3. The angular nodal patterns of the frontier orbitals of 2a, 2c and 2f differ markedly from those of 3, and there are significant MO coefficients across the entire chromophore. This results in a significant destabilization of LUMO and HOMO relative to the analogous MOs of 3. There is a greater destabilization of the LUMO, since the LUMO has a large MO coefficient at the meso-carbon, which is the point of attachment for the fused pyridine ring that is introduced, but this atom lies on a nodal plane in the HOMO. This means that there is an increase in the magnitude of the HOMO-LUMO gap (Figure 3), and hence there is a blue-shift of the absorption band wavelength relative to that of 3 (Table 2). This is unusual, since most other structural modifications that have been reported for BODIPYs tend to result in a relative destabilization of the HOMO or stabilization of the LUMO and hence in a narrowing of the HOMO-LUMO gap.^[3] The fine tuning of the λ_{max} values through changes to the mesoaryl ring can also be readily explained. The introduction of an electron donating methoxy group to form 2f further destabilizes the LUMO relative to 2a, since there is a large MO coefficient at the para-position of the meso-phenyl ring. In contrast, there is almost no effect on the HOMO because the methoxy group is attached at an angular nodal plane.

Table 2. Calculated excited wavelength (λ) , oscillator strengths (f) and the related wave functions of *meso*-annulated BODIPYs **2a-f** and the parent *meso*-phenyl-BODIPY model compound **3** in acetonitrile calculated by using the CAM-B3LYP functional with 6-31G(d) basis sets and the PCM.

	State ^[a]	λ _{cal} [nm] ^[b]	λ _{exp} [nm] ^[c]	$f^{[d]}$	Wavefunction [e]					
neutral BODIPY compounds										
3	S ₁	410	503 ^[3]	0.51	H → L (95%)					
2a	S ₁	390	451	0.48	H → L (97%)					
2b	S ₁	396	457	0.47	H → L (97%)					
2c	S ₁	397	460	0.46	H → L (97%)					
2d	S ₁	393	454	0.48	H → L (97%)					
2e	S ₁	397	456	0.45	H → L (97%)					
2f	S ₁	386	439	0.48	H → L (97%)					
deprotonated anion species										
2a	S ₁	370		0.36	H → L (96%)					
2b	S ₁	371		0.34	H → L (96%)					
2c	S ₁	376		0.33	H → L (96%)					
2d	S ₁	376		0.34	H → L (96%)					
2e	S ₁	377		0.33	H → L (96%)					
2f	S ₁	367		0.36	H → L (96%)					

[a] Excited state. [b] Calculated absorption wavelength in acetonitrile. [c] Experimental absorption wavelength in toluene. [d] Oscillator strength. [e] MOs involved in the transitions, H = HOMO, L = LUMO.

The pH dependence properties of the absorption and fluorescence bands were analyzed through the sequential

addition of Et₃N (TEA) to a MeCN solution of 2a (Figure 4). Upon addition of TEA, new bands are observed at 420 and 350 nm in the absorption spectrum, and there is a marked decrease of the intensity at 451 nm. An isosbestic point is observed at 425 nm, which is consistent with the quantitative formation of a deprotonated species. In a similar manner, there is a stepwise blue shift of the emission band at 472 nm along with a decrease in intensity. A new blue-shifted emission band is observed at 437 nm, along with an isosbestic point at 462 nm. This results in a change in the color of the fluorescence emission from cyan to blue (Figure 4). Upon addition of trifluoroacetic acid (TFA), the deprotonated species recovers its original colour and fluorescence properties. No concentration dependence is observed in the emission spectrum of 2a (Supporting information, Figure S9), and the same trends are observed in the absorption spectra upon addition of increasing concentrations of TEA to a dilute solution of 2a (1 ×10⁻⁶ M) in MeCN (Supporting information, Figure S10), so aggregation effects do not contribute significantly to the observed spectral properties.

The spectroscopic properties can be explained based on a comparison with the results of TD-DFT calculations, which predict a marked blue-shift of the main spectral band upon deprotonation of the N-bridging atom to form an anionic species (Table 2). There is a marked blue-shift of the main bands in the absorption and emission spectra, since a phenyl-pyridyl-pyrrole fused-ring π -system is formed (Scheme 2) when the N-bridging atom is sp² hybridized and this results in a further relative destabilization of the LUMO.



Figure 4. Absorption and emission spectra of **2a** (10⁻⁵ M) in MeCN upon addition of increasing concentrations of Et₃N (0–10 equiv). $\lambda_{ex} = 400$ nm. Pictures showing the fluorescence change that is caused by the addition of TEA and TFA upon excitation at 365 nm using a UV lamp (bottom).



Scheme 2. The structure change of fluorophore after addition of TEA and TFA.

A series of novel BODIPY dyes has been synthesized through the introduction of an N-bridged annulated mesophenyl ring at one of the π -positions of the BODIPY core. A blue shift of the main spectral bands is observed, since the fusion of a meso-substituent at one of the neighboring π position carbons results in a marked relative destabilization of the LUMO and hence an increase in the HOMO-LUMO gap. The position of the main spectral bands can be successfully fine-tuned in the blue region by introducing electron withdrawing and donating groups onto the mesophenyl ring, thus extending access for the use of the BODIPY chromophore in applications to a wider portion of the optical spectrum, since the favorable photophysical properties that are typically reported for this class of dye are retained. For example, the greater rigidity of the ring-fused structure leads to very high fluorescence quantum yield across a wide range of organic solvents with differing polarity values. The *p*H dependence of the emission properties due to deprotonation of the N-bridging atom could also potentially be used to form ratiometric probes in non-aqueous media.

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Highly Fluorescent

Blue-Shifted BODIPY Dyes

meso-annulation

 Φ_F as high as 1.0

 $\Phi_{\rm F} \sim 0.053$