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BODIPY-DERIVATIVES AS PHOTOSENSITIZERS IN PHOTODYNAMIC THERAPY: THE RELATIONSHIP BETWEEN ELECTRONIC PROPERTIES AND LIGHT ABSORPTION EFFICIENCY

Nguyen Phuong Nga[1], Doan Thuy Duong[1] and Nguyen Thi Thu Ha[2, *]
[1]*Student of Faculty of Chemistry, Hanoi National University of Education*
[2]*Faculty of Chemistry, Hanoi National University of Education*

Abstract. In this study, the structural and electronic properties of BODIPY and its twelve derivates, including meso-amino, meso-alkoxy, meso-phenyl, meso-alkyl and other compounds, were investigated using an accurate and broadly parametrized self-consistent tight-binding quantum chemical method named GFN2-xTB. The influence of the substituent groups on the geometrical parameters, the HOMO-LUMO gap, and electronic properties of BODIPYs was analyzed. The obtained results have shown that the presence of substituents at the R2 position did not significantly change the structural parameters of BODIPY. The electron-acceptor or electron-donor substituents in the meso-position have different effects on the electronic parameters of the molecules. A correlation between the global electrophilicity index and the HOMO-LUMO gap was found. Among the studied systems, the BODIPY-derivative with a $-NO_2$ group at the meso-position was evaluated as the most promising candidate for photosensitizers in PDT.

Keywords: BODIPY, GFN2-xTB, photosensitizers.

1. Introduction

Photosensitizers (PSs) are molecules which absorb light and transfer the energy from the incident light into another nearby molecule. PSs are crucial in photodynamic therapy (PDT) because they generate toxic reactive oxygen species. More recent PSs have been engineered to achieve i) high absorption and emission efficiency, ii) improved specificity to targets through targeting vectors or target-specific activation mechanisms, and iii) dual modality for imaging and therapy [1, 2].

Boron-dipyrromethene-4,4-Difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) has grown in importance in scientific research because of its intense fluorescent activity. BODIPY has been identified as a new generation of photosensitizers for application in photodynamic therapy. The design and synthesis of novel derivatives of BODIPY with target properties has attracted a lot of attention from experimental and theoretical researchers.

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Contact Nguyen Thi Thu Ha, e-mail: ntt.ha@hnue.edu.vn

Recently, a variety of BODIPY-based PSs have been reported, such as iodinated BODIPY derivatives [3], styryl/distyryl BODIPY-based photosensitizers [4], aza-BODIPY [5], etc. Theoretical studies have also been conducted to study the structural and electronic properties of BODIPY and its derivatives [6-8]. Theoretical calculations can provide useful information for designing and synthesizing novel BODIPY derivatives.

In this study, we used an up-to-date calculation method based on the density functional theory tight-binding approach to study the structural and electronic properties of BODIPY and its derivates, clarify the influence of the substituent groups, and, from there, predict promising candidates for application as photosensitizers in PDT.

2. Content

2.1. Computational details

2.1.1. Models

The structure of BODIPY and the scheme of substituting functional groups at R1, R2 positions are presented in Figure 1. Based on the substituents of R1, R2, the studied compounds are denoted as shown in Table 1. The B2 molecule can be considered as homologous to BODIPY, except that the C atom in the conjugate system at the R1 position was replaced by an N atom, similar to that in pyrolle heterocycles. The B3 - B13 are BODIPY-derivatives, in which functional groups with different electronic properties (electron-donors/electron-acceptors) are substituted at the R2 position.

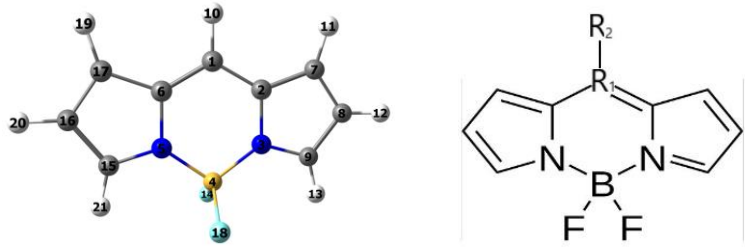
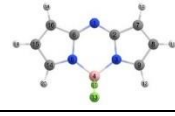
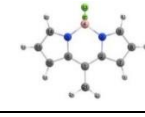
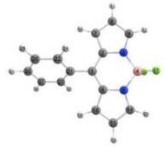
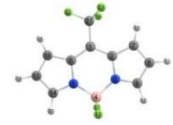
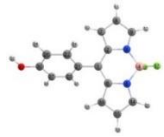
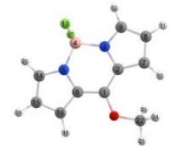
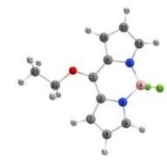
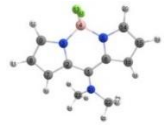
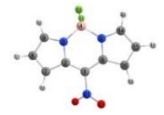


Figure 1. Structure of BODIPY and scheme of substituting functional groups at R1, R2 positions

Table 1. Notations for BODIPY and its derivatives

Compound	R_1	R_2	Optimized Structure	Compound	R_1	R_2	Optimized Structure
B1 (BODIPY)	C	H		B8	C	Cl	
B2	N	H		B9	C	CH_3	

B3	C	Phenyl		B10	C	CF_3	
B4	C	PhOH		B11	C	OMe	
B5	C	NH_2		B12	C	OEt	
B6	C	NMe_2		B13	C	OPh	
B7	C	NO_2					

2.1.2. Computational methods

All optimization and energy calculations were performed using an accurate and broadly parametrized self-consistent tight-binding quantum chemical method with multipole electrostatics and density-dependent dispersion contributions named GFN2-xTB (short for "Geometry, Frequency, Noncovalent, eXtended TB"). The accuracy of the method is benchmarked for a wide variety of systems [9-11]. The total energy of the systems obtained from GFN2-xTB is expression is given by

$$E = E_{rep} + E_{disp} + E_{EHT} + E_{IES+IXC} + E_{AES} + E_{AXC} + E_{Fermi} \quad (1)$$

where E_{rep}, E_{disp}, E_{EHT}, $E_{IES+IXC}$, E_{AES}, E_{AXC}, G_{Fermi} are the repulsion energy; the density-dependent dispersion energy; the extended Huckel-type energy; isotropic electrostatic (IES) and isotropic XC (IXC); the anisotropic electrostatic (AES) and anisotropic XC (AXC) energies; the chemical potential of electrons, respectively.

To investigate the electronic properties of the studied systems, we calculated and analyzed the vertical ionization potential (IP), vertical electron affinity (EA) and Global Electrophilicity Indexes (GEI). These parameters are calculated according to the following formulas:

$$IP = E(M^{+1}) - E(M) \quad (2)$$

$$EA = E(M^{-1}) - E(M) \quad (3)$$

$$GEI = (IP + EA)^2/8(IP - EA) \quad (4)$$

where, E(M), $E(M^{+1})$, and $E(M^{-1})$ are the total energy of the M molecule at the ground state and its ionized species in the same geometry.

The UV-VIS spectra of all studied systems were calculated using the simplified Tamm-Dancoff-Approach [12].

2.2. Results and discussions

2.2.1. Geometrical structures of BODIPY and BODIPY derivatives

Table 2 presents the geometrical parameters of BODIPY obtained by GFN2-xTB method in comparison to the references.

Table 2. Geometrical parameters of BODIPY

Parameter	**GFN2-xTB**	**Ref.** [13]
d(B-N5), Å d(B-N3), Å	1.550 1.550	1.555
<NBN, degree	106.98	
d(B-F14), Å	1.376	1.378
d(C15-N5), Å d(C9-N3), Å	1.326 1.326	1.329
d(C6-N5), Å d(C2-N3), Å	1.379 1.379	1.390

The geometrical parameters obtained by using the GFN2-xTB are in good agreement with the results calculated at the PCM-PBE0/6-311G (2d, p) level of theory, which confirms the coincidence of the GFN2-xTB method.

The geometrical parameters of BODIPY derivatives are shown in Table 3.

Table 3. Geometrical parameters of BODIPY derivatives

Compound	**d(B-N), Å**	**<NBN, degree**	**d(C15-N5), d(C9-N3), Å**	**d(C6-N5), d(C2-N3), Å**
B2	1.554	105.39	1.323	1.389
B3	1.547	106.78	1.328	1.378
B4	1.546	106.79	1.329	1.377
B5	1.546	106.89	1.332	1.373
B6	(4-3) 1.534 (4-5) 1.540	106.04	1.333	(C2-N3) 1.373 (C6-N5) 1.378
B7	1.553	106.73	1.326	1.380
B8	1.550	106.80	1.328	1.379
B9	1.546	106.62	1.328	1.379
B10	(4-5) 1.551 (4-3) 1.548	106.60	1.325	(C6-N5) 1.383 (C2-N3) 1.378
B11	(4-3) 1.548 (4-5) 1.537	106.52	(C9-N3) 1.329 (C15-N5) 1.332	(C2-N3) 1.382 (C6-N5) 1.372
B12	(4-3) 1.548 (4-5) 1.537	106.54	(C9-N3) 1.329 (C15-N5) 1.332	(C2-N3) 1.382 (C6-N5) 1.372
B13	(4-3) 1.544 (4-5) 1.548	106.51	1.330	(C2-N3) 1.374 (C6-N5) 1.378

Obviously, the presence of different substitute groups does not cause a significant change in the key bond lengths in the pyrrole rings. A similar picture was obtained for the <NBN angle. Thus, all the BODIPY derivatives exhibit identical geometrical structures to those of the parent BODIPY.

2.2.2. Electronic properties of BODIPY and BODIPY derivatives

Table 4 presents the calculated electronic parameters for all studied systems. Figure 2 illustrates the trends of IP, EA, and GEI for the studied systems.

Table 4. Calculated electronic properties of BODIPY and its derivatives

Compound	IP (eV)	EA (eV)	GEI (eV)
B1	8.5153	1.8812	2.0366
B2	8.7749	2.4259	2.4700
B3	8.2784	2.0762	2.1609
B4	8.0786	2.0419	2.1209
B5	8.1950	1.1230	1.5347
B6	8.0973	1.3431	1.6494
B7	8.9618	2.8975	2.8990
B8	8.6412	2.2019	2.2823
B9	8.4208	1.857	2.0116
B10	8.8173	2.3743	2.4300
B11	8.3818	1.5713	1.8182
B12	8.3192	1.5406	1.7927
B13	8.2396	1.8090	1.9627

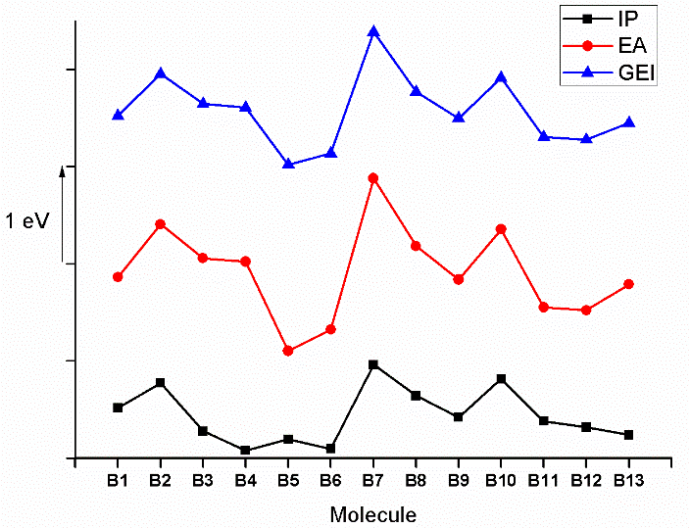


Figure 2. Trends of IP, EA, and GEI of BODIPY and its derivatives

It can be seen that, when the C atom at the R1 position of BODIPY was replaced by the N atom to form the B2, the IP and EA were significantly increased. A similar change was obtained for B7, B8, and B10 when in the molecule there is an electron acceptor at the R2 position. The maximum IP and EA values belong to the B7 compound with the presence of a -NO_2 group.

For B5, B6, B9, B11, B12, B13 molecules, in which an electron donor group is located at the R2 position, both the IP and EA are reduced in comparison with the pristine BODIPY. Meanwhile, for the B3 and B4 molecules, which contain phenyl and hydroxylphenyl groups at the R2 position, respectively, the changes in IP and EA are not identical. The IP values for these two compounds have been decreased, while the EA values have been found to be higher than that of the BODIPY molecule.

The Lewis acidity, expressed via the GEI value, of the BODIPY molecules is also affected by substituents. It can be seen that the B2, B3, B4, B7, B8, and B10 molecules exhibit greater GEI than BODIPY. The Lewis acidity, expressed via the GEI value, of the BODIPY molecules is also affected by substituents. It can be seen that the B2, B3, B4, B7, B8, and B10 molecules exhibit a greater GEI than the BODIPY. In contrast, the GEI values of B5, B6, B9, B11, B12, B13 derivatives are lower than the GEI of BODIPY.

Figure 3 illustrates the calculated UV-VIS spectra of all studied systems. Table 5 presents the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), the energy difference between HOMO and LUMO (E_g), and the maximum wavelengths (λ_{max}), obtained from the calculated UV-VIS.

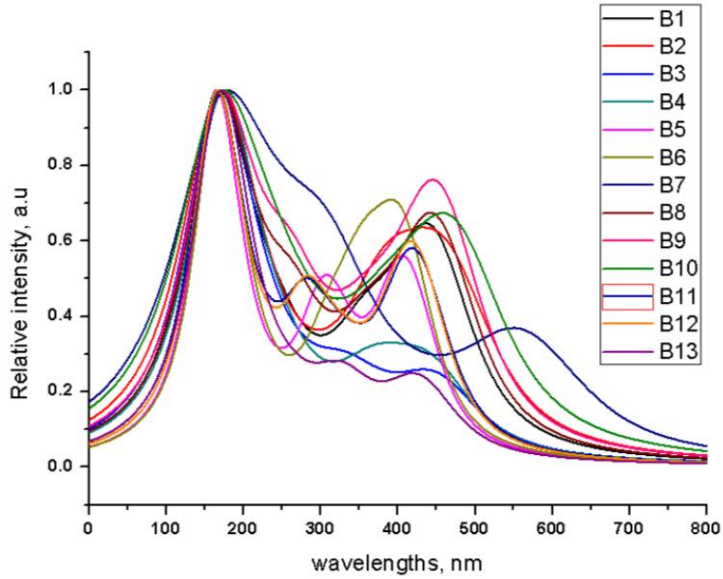
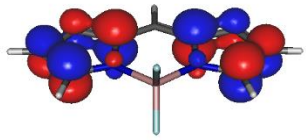
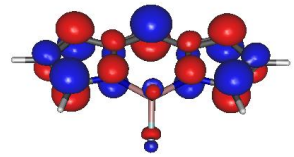
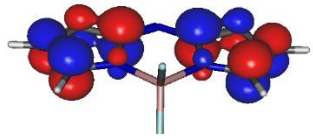
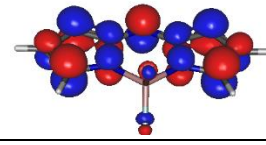
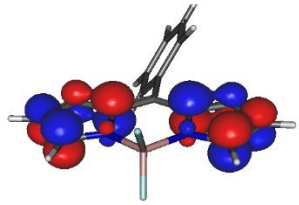
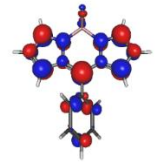
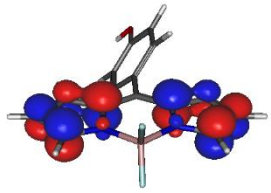
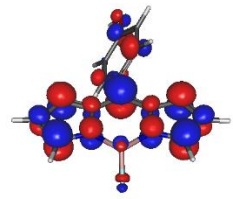
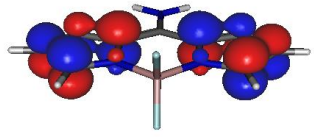
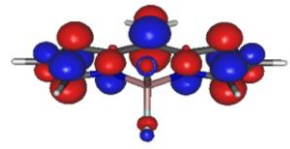
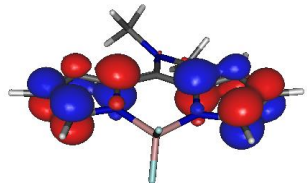
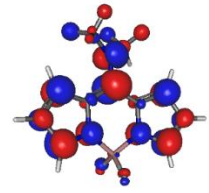
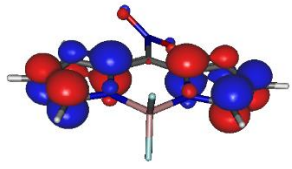
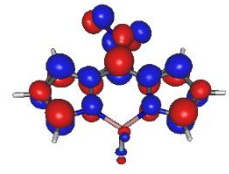
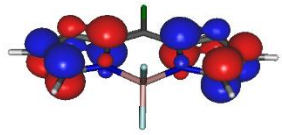
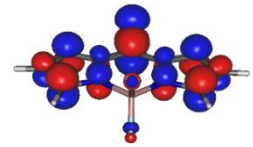
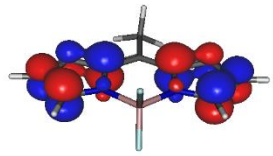
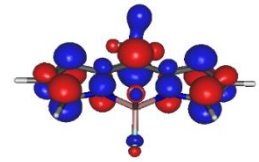
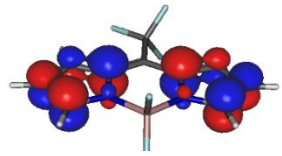
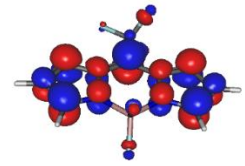
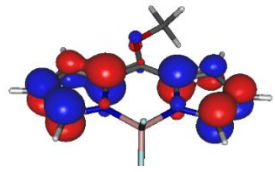
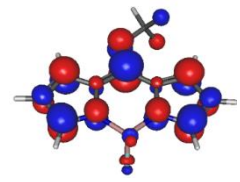
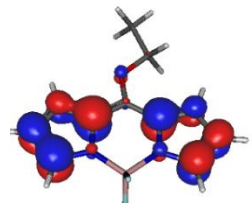
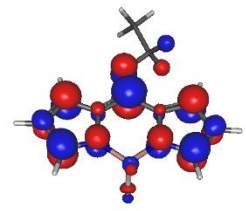
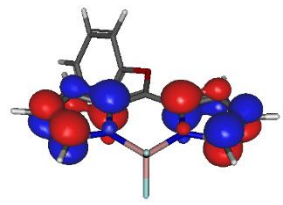
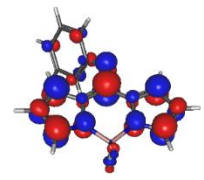


Figure 3. Calculated UV-VIS spectra of BODIPY and its derivatives

Table 5. HOMO and LUMO, E_g, and λ_{max} of BODYPY and its derivatives

Compound	HOMO	LUMO	E_g, eV	λ_{max}, nm
B1 (BODIPY)			1.7907	434
B2			1.5367	435
B3			1.7951	439
B4			1.8001	398
B5			2.2019	404
B6			2.1451	395
B7			1.4024	550

B8			1.8388	430
B9			1.8561	441
B10			1.8561	450
B11			2.0646	416
B12			2.0775	416
B13			1.9919	421

The introduction of the substituents does not influence the HOMOs. For all studied systems, the HOMOs are mainly located on the pyrrole rings. Meanwhile, the LUMOs partially localize on the meso-position with a depletion of the pyrrole-systems compared to the HOMOs and a minor contribution to the BF_2 group. When bulky substitution groups like aromatic or conjugated systems are attached to the meso-position, the LUMOs appear to stretch into these groups.

It has been shown that, for the BODIPY family, the electron transition from HOMO to LUMO, which is assigned to the $\pi \rightarrow \pi^*$ transition, plays a crucial role in the first excitations [6, 14]. Among BODIPY derivatives, only B2 and B7 have E_g values less than BODIPY. It should be noted that these two molecules are also two species with higher IP, EA, and GEI values than BODIPY, as previously discussed. The presence of phenyl

and hydroxylphenyl at the R2 positions does not cause a significant change in the E_g of BODIPY. Meanwhile, the introduction of other substituents increases the E_g, and thus, causes a blue shift relative to the pristine BODIPY. In particular, the presence of an alkylamino group such as NH_2 (in B5), and NMe_2 (in B6) causes a shift to the higher energy of 0.4112 eV and 0.3544 eV, respectively. The correlation between GEI and E_g is illustrated in Figure 4.

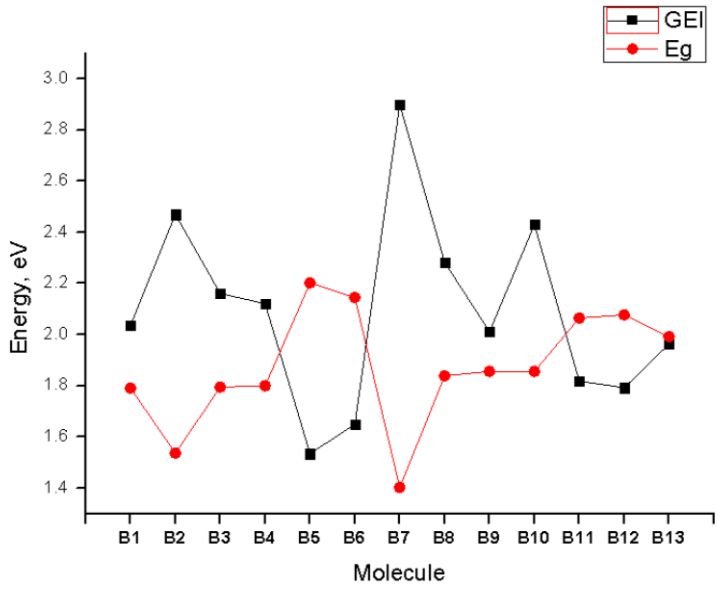


Figure 4. The correlation between GEI and E_g of BODIPY derivatives

In general, it can be seen that, as the GEI value increases, the E_g value will decrease. In other words, to shift the light absorption of BODIPY towards the long wavelength region, it is necessary to increase the global electrophilicity, i.e. Lewis acidity of the system.

An important criterion for a substance to be an effective photosensitizer in photodynamic therapy is that the molecule is able to adsorb in the region of 600-900 nm (therapeutic window). According to this criterion, the system with an absorption wavelength that can better penetrate into the tissue than BODIPY is B7. The introduction of the $-NO_2$ group to the R2 position greatly shifted the adsorption maximum of BODIPY to the longer wavelength region. The calculated λ_{max} for B7 is 550 nm, which is significantly longer than that of the parent BODIPY (434 nm). The B2 compound, similar to B7, has higher IP, EA, and GEI values than the pristine BODIPY. However, the maximum absorption wavelength of B2 (435 nm) is approximately BODIPY. It is noted that the structure of B2 only differs from that of BODIPY in the substitution of one C atom in the ring by one N atom. Therefore, it can be suggested that only the substitution of a functional group at the R2 position, not R1, which greatly increases the GEI, can shift the light absorption of BODIPY towards the long wavelength region. We do, however, acknowledge that further studies are necessary for confirmation of this idea.

3. Conclusions

In this work, the GFN2-xTB method was performed to study the structures and properties of BODIPY and its derivatives, and point out the correlation between the geometrical and electronic parameters. The obtained results have shown that the presence of substituents at the R2 position did not significantly change the structural parameters of BODIPY. The electron-acceptor or electron-donor substituents in the meso-position have different effects on the IP, EA, and GEI of the molecules. The introduction of an electron acceptor at the R2 position led to an increase in IP and EA. Meanwhile, the opposite effect is observed when electron-donor substituents are introduced. A correlation between GEI and E_g was found. The higher the GEI value, i.e., the greater the Lewis acidity, the lower the E_g. Among the studied systems, B7 was evaluated as the most promising candidate for photosensitizers in PDT.

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