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Synthesis and Photophysical Properties of Fluorescein Esters as Potential Organic Semiconductor Materials

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Abstract

Fluorescein (1), a known fluorescent tracer in microscopy with high photophysical properties, was esterified to have fluorescein ethyl ester (2) and *O*-ethyl-fluorescein ethyl ester (3) in excellent yields. All of them were investigated for the photophysical and electrochemical properties as potential organic semiconductor materials. Absorptions and emission spectra were taken in various solvents, compound 2 showed emission maxima at $\lambda_{max} = 545$ and compound 3 showed $\lambda_{max} = 550$ nm. Optical band gap energy (E_g) was calculated for 1–3 and the values were found in between 2.34 – 2.39 eV. Possibility of shifting emission maxima was studied in various pH (5–9) buffers, and finally the thermal stability was examined using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Increasing of conjugation system of 2 and 3 were studied by HOMO and LUMO distributions of 1–3. Experimental results showed that compounds 2 and 3 have excellent photophysical and electrochemical properties hence can be used as excellent organic semiconductor materials.

Keywords Fluorescein · Fluorescein ester · Fluorescence · Optical band gap · Organic semiconductor

Introduction

Photo- and electroactive organic compounds, bearing high π -conjugate structures and/or fused aromatic system, have gained great attraction in most scientific, academic, and industrial societies due to their excellent potential application in full-color-flat-panel displays and solid-state light source [1]. In recent years, organic semiconductor devices (e.g. organic solar cells, OSCs; organic field effects transistors, OFETs; and organic light-emitting diodes, OLEDs etc.)

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made from organic compounds, got enormous achievements attributed to their comparatively low energy consumption, high efficiency and thermal stability. Their realistic color tunability can be further improved through chemical structural modification of those organic compounds. Organic molecules could also be used to produce thin, light, transparent, flexible, and efficient devices [2]. For example, OLED screens are mainly used in digital devices such as advanced television systems, desktop and laptop computer monitors, portable small sized systems such as smartphones, media players, digital cameras, and portable gaming consoles etc. However, some important characteristics should be considered before using an organic molecule in an organic semiconductor device. Figure 1 shows the electron distribution on the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) level of organic semiconductor [3], the energy difference between HOMO and LUMO is defined as energy gap. The energy gap determines the minimum energy that can be absorbed by the molecules. The ionization potential is defined as the minimum energy required when taking an electron from HOMO to the vacuum, whereas electronic affinity is defined as the minimum energy released when supplying an electron from the vacuum level to LUMO. This energy gap is also known



Fig. 1 Electron distribution on the HOMO and LUMO level of Organic semiconductor [3]

as optical band gap energy (E_g) . If E_g is larger than 4 eV for a molecule, it acts as an insulator, and if it is lower than 3 eV, it acts as semiconductor, therefore, E_g plays a vital role in selecting an organic molecule as organic semiconductor material [4].

Fluorescein (1) is a synthetic organic molecule with open/ cyclic form (Fig. 2), it is powder with dark orange/red in color, soluble in water as well as in alcohol. It was first synthesized in 1871 [5]. It is commonly used as a fluorescent tracer in microscopy, a type of dye laser, and in forensics and serology to detect latent blood stains [6]. Compound 1 has a *p*Ka of 6.4, and its ionization equilibrium leads to pH-dependent absorption and emission over the range of 5 to 9. In addition, the fluorescence lifetimes of the protonated and deprotonated forms of compound 1 are approximately 3 and 4 ns, which allows for pH determination through nonintensity-based measurements. The lifetimes can be recovered using time-correlated single photon counting or phasemodulation fluorimeter. Compound 1 has an isosbestic point (equal absorption for all pH values) at 460 nm [7].

 $\begin{array}{c} & & & & \\ & & & \\ HO \\ & & & \\ HO \\ \hline \\ H$

Fig. 2 Structures of fluorescein

Due to the high photophysical properties of compound 1 (λ_{abs} = 494 and $\lambda_{emission}$ ~ 512 nm in water), it has been functionalized with an isothiocyanate (-N = C = S) group (FITC, Chart 1) and the formed product has been studied for their physicochemical, photophysical properties before its application in biological implications as FITC-conjugates [8–22]. Compound 1 has also been functionalized on the top ring with a carboxylic acid group (FCA) [23] for the preparation of peptide/glycosides conjugates [24-29]. Hydroxyl groups of 1 have also been functionalized (FCA-OR) [30] for various purposes [31–42], such as artificial photosynthesis and solar energy conversion [33]. A detailed search gives us the information that fluorescein derivatives were derived from cyclic form (Fig. 2, cyclic form) rather than open form of 1 (Fig. 2, open form) and have been studied for the detection of membrane-bound DNA [43], detection of damaged nucleic acids [44], measurement of mammalian phosphoinositide-specific phospholipase C activity [45] and proteolytic activities [46].

Early this year, Shumin Feng and co-workers reported that alkyl protected fluorescein enhanced its fluorescence properties [47]. In addition to this article, a review on 2017, done by Elisabete Oliveria and co-others after they had reviewed 265 articles, concluded that derivatization of fluorescein (hydroxyl protection, esterification, hydrazone formation as well as metal complexes formation) also enhanced the fluorescence properties a lot [48]. Since fewer conjugated π -bonds give lower λ_{max} (towards the UV) while more conjugated π -bonds give higher λ_{max} (towards the visible), we assumed that, it might be due to the free acid group of 1, which might have been responsible for cyclic formation of 1. It should be noted that if cyclic formation occurs in 1, the conjugated π -bonds became less, resulting in lower λ_{max} , and if it stays in open form, the conjugated π -bonds get more, resulting in higher λ_{max} . Based on this hypothesis, we therefore, designed and synthesized fluorescein ethyl ester (2) and ethyl protected fluorescein ethyl ester (3) and compared the photophysical properties with 1, and distributions of HOMO and LUMO of 1-3 were studied to get more theoretical information, for further uses as potential organic semiconductor materials candidates. A resonance structure and conjugated π -bonds in those compounds (1–3) are shown below (Scheme 1).

Experimental Section

General

Chemicals and solvents were commercial reagent grade and were used without further purifications. Melting points were determined on a Barnstead electrothermal digital melting point apparatus model IA9100, BIBBY scientific





Scheme 1 Resonance structures and conjugated π -bonds in 1–3

limited, Stone, Staffordshire, ST15 0SA, UK. IR spectra were recorded on a Jasco FT/IR-6600 spectrometer, Japan. NMR spectra were taken using an Agilent Technologies 400 MHz premium shielded NMR spectrometry, CA, USA. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed using an Agilent 6320 ion trap mass spectrometer fitted with an electrospray ionization (ESI) ion source (Agilent Technologies, Palo Alto, CA, USA) with direct injection. UV-vis spectra were measured using a Genesys G10S UV-Vis spectrophotometer (Thermo scientific, CA, USA). For the compounds studied, the measurements were performed using various solvent and quartz cells with a path length of 10.00 mm. The UV-vis spectra in solution were measured over the range of 200-700 nm. Based on each spectrum, the optical band gap was calculated according to Equation (i), which represents the optical band gap expressed in eV, and λ_{ae} denotes the absorption edge wavelength expressed in nm [4, 49–51]. Fluorescence spectra were recorded on JASCO spectrofluorometer FP-8200 (Japan). Thermogravimetric analysis (TGA) spectra were recorded on a Perkin Elmer model Pyris 1 (Perkin Elmer Life and Analytical Sciences, Shelton, CT, USA). Differential scanning calorimetry (DSC) spectra were recorded on a Perkin Elmer model 4000 (PerkinElmer, Inc. Waltham, MA, USA). The geometrical, distribution of HOMO and LUMO, energy levels were performed using the Gaussian 16 program package using Becke's three-parameter hybrid functional with Lee-Yang-Parr correlation functions (B3LYP) and the 6-31G(d) atomic basis set.

$$E_{g}(eV) = h \times f = h \times c/\lambda_{a} \cdot e \approx 1240/\lambda_{a} \cdot e(nm)$$
(1)

Synthesis

Synthesis of Fluorescein Ethyl Ester (2)

Fluorescein (1, 3.32 g, 0.01 mol) was dissolved in 50 mL of absolute ethanol, a catalytic amount of concentrate sulfuric acid was added and the mixture was refluxed for overnight.

Solvent was evaporated under vacuum, ethyl acetate was added and subsequently washed with water, 5% NaHCO₃, brine and dried over anhydrous Na₂SO₄, filtered, and the solvent was evaporated to obtain compound **2** (3.35 g, 93%) as white powder. Mp. 241–242 °C [52–54].

Synthesis of Ethoxyfluorescein Ethyl Ester (3)

Fluorescein (1, 30.00 g, 90.000 mmol) was suspended in DMF (30 mL) in a 500 mL round bottom flask equipped with magnetic stirrer. K_2CO_3 (2.2 equiv.) was added to the reaction mixture followed by the addition of ethyl iodide (2.2 equiv. $g \sim 16$ mL, d = 1.94). The reaction mixture was stirred at room temperature until the starting materials were fully consumed (approximately for 24 h). The reaction was diluted with 500 mL water and the pale-yellow color solid precipitation was collected by filtration followed by washing it with excess amount of water (100×3), afforded analytical pure **3** (26.00 g, 82%). $R_f = 0.5$ (Ethyl acetate: *n*-hexane = 3: 7). Mp. 151–152 °C [54].

Results and Discussion

Esterification of fluorescein (1) was carried out in the presence of catalytic amount of concentrate sulfuric acid in ethanol to afford fluorescein ethyl ester (2) in an excellent yield (93%). *O*-Ethyl fluorescein ethyl ester (3) was also prepared from fluorescein (1) with ethyl iodide in the presence of potassium carbonate (K_2CO_3) in DMF at room temperature for 24 h in very good yield (82%) (Scheme 2).

Photophysical properties of synthesized fluorescein esters were evaluated to see the possibility of using these materials as organic semiconductor materials (i.e. OLEDs/OSCs). Initially, absorbance and fluorescence spectra were taken under various solvents in constant concentration $(2.77 \times 10^{-5} \text{ M for}$ absorbance; $6.94 \times 10^{-7} \text{ M}$ for fluorescence) at room temperature to see which solvent would give higher absorbance and emission. Figure 3A, C and E show the absorption spectra of compounds **1**, **2** and **3** in ethanol, methanol, water,



Scheme 2 Synthesis of fluorescein esters 2 and 3



Fig. 3 Absorbance and emission spectra of compounds 1–3 in different solvents with λ_{max} (nm), A absorbance of compound 1, B emission of compound 2, E absorbance of compound 3, F emission of compound 3

 $\epsilon \times 10^4$

2.4

2.3

23

2.1

1.9

1.7

1.7

1.9

 $(L \text{ mol}^{-1} \text{ cm}^{-1})$

 $\lambda_{FL} (nm)$

 $6.44 \times 10^{-7} \text{ M}$

in

515

515

522, 550

520, 550

524, 546

520 548

521, 549

Solvent 1 2 3 $\lambda_{abs}\left(nm\right)$ $\epsilon \times 10^4$ $\epsilon \times 10^4$ $\lambda_{FL} \ (nm)$ $\lambda_{abs} (nm)$ $\lambda_{FL} (nm)$ $\lambda_{abs} (nm)$ (L mol⁻¹ cm⁻¹) (L mol-1 cm-1) in in in in in $7.53 \times 10^{-7} \text{ M}$ $3.10 \times 10^{-5} \text{ M}$ 2.77×10^{-5} $6.94 \times 10^{-7} \text{ M}$ $2.57 \times 10^{-5} \text{ M}$ М 500 523 1.8 469, 508 0.8 460, 490 518, 547 Ethanol 527

464, 501

465, 496

460, 520

462, 490

477, 517

460.490

481, 519

501

516

545

515

541

534

545

0.6

0.8

04

0.7

0.9

0.3

1.1

 Table 1 Photophysical properties of compounds 1–3 in respective solvents

0.6

1.7

0.04

0.02

2.5

0.02

0.3

512

510

530

520

540

520

540

480

486

510

462

509

460

509

Methanol

Water

CHCl₃

ACN

EtOAc

Acetone

THF

tetrahydrofuran, chloroform, acetonitrile, ethyl acetate and acetone, respectively. Figure 3B, D and F display/demonstrate the fluorescence spectra of compounds 1, 2 and 3 in the same solvents.

We found that polarity of the solvents playeds a crucial role in taking absorption/fluorescence spectra for compound 1-3. Since compound 1 possesses a free acid group, it was not properly dissolved in all the solvents studied and therefore it didn't show excellent absorption. But in case of compounds 2 and 3, absorption/emission spectra were perfect as expected. Bathochromic shift was observed in absorption/emission spectra depending on change in polarity of the solvent. According to electronic transition, electrons are promoted from their ground state to an excited state when an atom or molecule absorbs energy. In a molecule, the atoms can rotate and vibrate with respect to each other. These vibrations and rotations also have discrete energy levels, which can be considered as being packed on top of each electronic level. The electronic transitions involved in the ultraviolet and visible regions of these compounds [55, 56]. As shown in the Fig. 3A, C and E, all three compounds gave $n \rightarrow \pi^* / \pi \rightarrow \pi^*$ transitions. Emission spectra of 1-3

gave significant broad peaks at 480-600 nm because of the $\pi^* \rightarrow n / \pi^* \rightarrow \pi$ transitions. Photophysical properties of 1-3 in different solvents are illustrated in Table 1 in details. Molar absorptivity was calculated for 1-3 in the solvent evaluated. As shown in Table 1, compound 3 displayed a higher molar absorptivity than compound 2, which displayed a higher molar absorptivity than compound 1 in most cases.

457, 487

457, 480

460, 490

460, 490

456, 489

457.487

455, 485

Photographs of 1-3 were taken in standard methanolic solution under naked eye (Fig. 4A), 254 nm (Fig. 4B) and 365 nm (Fig. 4C), respectively. Compounds 1-3 having high luminescence in naked eyes. The photographs clearly indicate that compounds 1-3 having photophysical properties.

Emission spectra of compounds 1-3 at different pH (5-9) in THF were also taken to observe the stability of emission maxima and to clarify the correlation among the fluorescence behavior of 1-3 (Fig. 5). It was found that the emission maxima of **1** is lower in all the buffer solutions than in normal THF solutions. Emission maxima was obtained at 530 nm for normal THF solution (Fig. 5A) but shifted 4-7 nm (523 - 526 nm) for different pH buffer solutions (Fig. 5B). In case of compound 2 (545 nm)



Fig. 4 Luminescence properties of compounds 1-3 in MeOH: A under normal light, B under a 254 nm light, C under a 365 nm light



Fig. 5 Comparison of emission spectra of compounds 1–3 in THF (normal) vs THF (pH 5–9). A Emission of 1 in THF, B Emission of 1 in THF in various pH, C Emission of 2 in THF, D Emission of 2 in THF in various pH, E Emission of 3 in THF, B Emission of 3 in THF in various pH



Fig. 6 UV–Vis spectra recorded in ethanol, at room temperature for compounds 1-3. A Molar absorptivity vs wavelengths maxima of 1-3 in ethanol, B Molar absorptivity vs optical band gaps of 1-3 in ethanol

(Fig. 5C), it has also shifted 14–11 nm, becoming 531-534 nm (Fig. 5D). Fluorescence spectra were obtained with little differences for compound **3** in varying pH buffers. It should be noted that compound **3** showed 522 nm and a shoulder at 550 nm (Fig. 5E), but in case of different pH buffers, normalized wavelength at 532–534 nm was observed (Fig. 5F). Interestingly, all three compounds gave maximum emission at pH=7. It can be concluded that pH has no/negligible effect on emission maxima of compounds **1–3**.

Molar absorptivity (ε), wavelengths at the maxima ($\lambda_{max.}$), absorption edge wavelengths (λ_{edge}) and optical band gaps ($E_{optical \ band \ gap}$ eV) were calculated using UV–Vis spectra for compounds **1–3** in ethanol, and were depicted in Fig. 6. The values are presented in the Table 2.

As expected, the UV–Vis spectra of 1-3 showed peak maxima at 498 nm (optical band gap ~ 2.36 eV), 508 nm (2.34 eV), and 458 & 488 nm (2.37 – 2.39 eV), respectively (Fig. 6 & Table 2). The obtained optical band gap values are consistent with standard organic semiconductor

Table 2 Values of the molar absorptivites and wavelengths at the maxima, absorption edge wavelengths and experimental optical band gaps for compounds 1–3

Entry	$\epsilon \times 10^3$ L mol ⁻¹ cm ⁻¹	λ_{\max} (nm)	$\lambda_{edge} (nm)$	$E_{\rm optical\ band\ gap}\ { m eV}$
1	18.2	498	527	2.36
2	7.57	508	531	2.34
3	23.9	458	521	2.37
	18.7	488	517	2.39

materials, thus compounds 1, 2 and 3 are suitable for organic semiconductors materials.

Differential scanning calorimetry (DSC) was taken under nitrogen atmosphere for compounds 1–3 to study their thermodynamic stability (Fig. 7). As shown in Fig. 6, from the DSC curve, compound 1 has a glass transition (T_g) peak at 77 °C without exhibiting other phase transitions, whereas compound 2 gave a glass transition peak at 102 °C and underwent crystallization (T_c) at 151 °C. On the other hand, compound 3 gave all three phases transition with glass transition (T_g) peak at 53 °C, crystallization (T_c) peak at 140 °C and melting (T_m) peak at 153 °C. From the data analysis of DSC, it turneds out that, compound 2 has more thermodynamic stability than compounds 1 and 3.

Thermogravimetric analysis (TGA) was also taken under nitrogen atmosphere for compounds 1-3 to study their thermodynamic stability (Fig. 8). It can be seen from the TGA curve in Fig. 7 that the compounds 1-3 have thermal decomposition temperature (5% weight loss temperature) at 70, 144 and 245 °C, respectively. From the DSC and TGA it can be concluded that compounds 2 and 3 have more thermal stability than 1, thus can better serve as excellent candidates of organic semiconductor materials which are necessary for light emitting devices.

Molecular modeling is an iterative process of analyzing and predicting compound with desired properties. In order to have a better understanding of the molecular features, fluorescein derivatives were optimized and calculated by Gaussian 16 program package. The stability of compound 1 is important for this scenario because we are focusing on the development of stable fluorescein compounds. Hence, Bond Dissociation Energy (BDE), a crucial indicator to evaluate the stability of the compound, has been computed.





The calculated BDE value of "C-O" bond in the lactone of cyclic **1** is 52.06 kcal/mol, which is much lower than the common "C-O" bond (109.3 kcal/mol), means the cyclic state is readily to be formed [57]. Meanwhile, the energy of

singlet (S₁) and triplet (T₁) states of cyclic **1** are calculated to be 94.24 kcal/mol, 86.96 kcal/mol respectively, all of which are higher than the value of "C-O" BDE, indicating that the cyclic **1** is also not stable and can easily undergo





Fig. 9 A Stability analysis of cyclic and open state compound 1, B Optimized structure and distribution of HOMO and LUMO of cyclic and open state compound 1

photodegradation to form the open **1** as illustrated in Fig. 9A. Additionally, distributions of HOMO and LUMO of **1** also apparently show that open form gets more conjugated systems because the HOMO and LUMO of open **1** are located mainly on the xanthene system while cyclic **1** are separated located on xanthene and isobenzofuran

systems, respectively, as depicted in Fig. 9B, which is consistent with optical properties discussed above. Therefore, on the one hand, it is necessary to prevent the cyclic ring formation by protecting carboxyl group with inert substituents, while on the other hand, steric hindrance also has to be taken into consideration that to avoid the carboxylate to

	1				
Entry	HOMO (eV)	LUMO (eV)	$S_1 (eV)$	T1 (eV)	
1 _{open}	-5.53	-2.36	2.65	1.58	
1 _{cyclic}	-6.03	-1.29	4.09	3.60	
2	-5.52	-2.34	2.66	1.59	
3	-5.81	-2.76	2.53	1.50	

Table 3 Values of the calculated data of compound 1–3

be attacked by nucleophile. Additionally, the acidic phenol group on xanthene system is another unstable factor because it is easy to lose proton under base conditions. Calculated Mulliken charge value of the proton is 0.416 a.u., and the value of BDE is 79.11 kcal/mol, even close to the phenol BDE [58]. All of the data indicate that protection of phenol group is also important. Hence, we used large steric hindrance group, ethyl groups, to stabilize and protect the active compound **1**.

Likewise, HOMO and LUMO distributions of compound 2 and 3 are all dispersed on the xanthene rings, which are significant proofs of the increasing conjugated system as summarized in Table 3. All of the data we calculated were well associated with the experimental ones, which are direct evidences to verify our ideas, illustrating our molecular design strategy is on the right way.

Optimized structure and distribution of HOMO and LUMO of compounds **2** and **3** is depicted in Fig. 10.



Fig. 10 Optimized structure and distribution of HOMO and LUMO of compounds 2 and 3

Conclusion

Fluorescein esters (2 and 3) only have open form rather than cyclic/open form of fluorescein (1), and therefore having more conjugated π -bonds, contributing to giving higher λ_{max} in most of the organic solvents studied. Fluorescein (1) and esters (2 and 3) are having high luminescence in naked eyes. Synthesized esters (2 and 3) are also stable in different pH (5-9), which leads to no significant difference in λ_{max} values. Both 2 and 3 have optical band gap (E_{α}) in between 2.34 – 2.39 eV. Fluorescein esters (2) have more thermodynamic stability than compounds 1 and 3. Considering the above-mentioned properties, it can be concluded that modified fluorescein esters 2 and 3 can be excellent organic semiconductor materials. It should be noted that since fluorescein esters 2 and 3 have neither cyclic form nor free acid group, and have displayed excellent photophysical properties in all the solvent evaluated as well as no changes in emission spectra in different pH, these compounds can be used as fluorescent tracer and for the synthesis of conjugates. HOMO and LUMO distributions of compounds 1-3 significantly prove the increasing conjugated system of 2 and 3. Further uses of these materials in devices will be studied and the results will be explored in due courses.

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Authors' Contributions G.A.E. Mostafa performed absorbance and fluorescence measurements; A.S. Mahajumi checked the literature, wrote the part of manuscript, H. AlRabiah and A.A. Kadi provided the equipment's and laboratory facilities, revised the manuscript; Y. Lu performed HOMO–LUMO calculation and wrote the part of manuscript; A.F.M.M. Rahman conceived the research thought, designed the experimental scheme, edited the manuscript.

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Data Availability Unreported NMR, IR and Mass spectra for compounds **1–3** are given in supporting information files, samples and all other data and materials from this manuscript will be made available on request.

Declarations

Competing Interests The authors declare no conflict of interest/competing interests.

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