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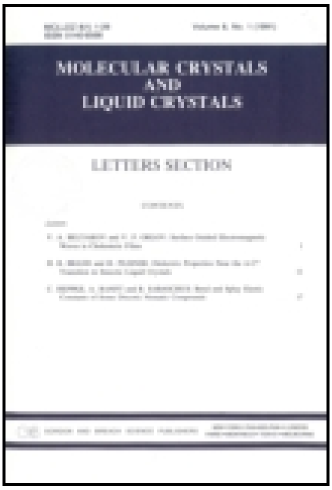

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Through-Bond Energy Transfer Cassettes: Pyrene-Bisindolylmaleimide Dyads with Large Pseudo-Stokes Shifts

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Through-Bond Energy Transfer Cassettes: Pyrene-Bisindolylmaleimide Dyads with Large Pseudo-Stokes Shifts

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An energy transfer cassette was reported with energy donor (pyrene) and energy acceptor (bisindolylmaleimide) incorporated together. The pyrene and bisindolylmaleimide units are connected through carbon-nitrogen single covalent bond. The intramolecular repulsion prevents the coplanarization of pyrene and bisindolylmaleimide units, thereby forcing them act as independent chromophores centers. Upon photoexcitation, there exists highly efficient energy transfer from the pyrene (energy donor) to the bisindolylmaleimide (energy acceptor) unit predominantly through Coulombic coupling. At such a short separation, the orbital overlap (Dexter-type) interaction was completely isolated between chromophoric units by virtue of the orthogonal arrangement. Excited at 340 nm, PBM has similar emission quantum yield to bisindolylmaleimide and expanded the Stokes shift to 232 nm. Computational study for PBM was carried out based on DFT. Careful analysis of energy-minimized structure and frontier molecule orbitals support the efficient energy transfer in PBM. Favorable photophysical properties, such as efficient energy transfer, strong emission, and large Stokes shift make it an attractive functional molecule.

Keywords Energy transfer; pyrene-bisindolylmaleimide; Stokes shift; orthogonal arrangement; frontier molecule orbitals

Introduction

During the past decade, energy-transfer (**ET**) from a host molecule (donor) to a guest molecule (acceptor) has gained tremendous importance in the areas of DNA sequencing, biological imaging, artificial light-harvesting, molecular probe, and OLEDs [1–5]. Electronic excitation energy transfer (**EET**) is the ubiquitous mechanism for energy transfer in multichromophoric systems [6]. Based on the model of **ET** cassettes, fluorescent molecules

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were developed to increasing the solid-state emission of the guest molecule, enlarging the Stokes shift to eliminate self-absorption, and tuning emission color. **EET** mechanisms, characterized by their different distance dependences, include Forster-type "Coulombic" interactions, Dexter-type exchange interactions, and other contributions to short-range coupling due to orbital overlap effects [7]. The typical model of **EET** is the fluorescence resonance energy transfer (**FRET**), which has been widely applied in designing ratiometric probes for bioimaging applications [8]. However, for **FRET** systems, to achieve the largest energy transfer efficiency, sufficiently large spectral overlap is necessary between the donor emission and the acceptor absorption, which also limit the wavelength difference between the two emission peaks. The through-bond energy transfer (**TBET**), in which the donor and the acceptor moieties are linked by a conjugated bond, dosed not need spectral overlap between donor emission and acceptor absorption and could afford a large wavelength difference between the two emission peaks by choosing suitable dye pairs [9].

Understanding mutually exclusive energy transfer at short separation is needed to yield deep insight into coherence in quantum energy transfer. Detailed analysis of such short-distance energy transfer conjugated with or without orbital overlap and the design of novel luminescent molecules offering large Stokes shift for biological application are of significant. Herein, the synthesis and photophyscial properties of a double chromophoric system (pyrene-bisindolylmaleimide derivative) were reported to act as an energy-transfer cassette that can be applied potentially in fluorescent probes, photodynamic therapy, and other nonlinear optics. The present molecular system integrates pyrene (energy donor) and bisindolylmaleimide (energy acceptor) moieties at the distance of a single covalent bond and enforces a sterically driven orthogonality between the two chromophores. The perpendicular arrangement of the incorporated chromophores results in negligible orbital overlap, thereby isolating efficient energy transfer through Coulombic interactions at short separations. The incorporated dye exhibits a remarkable pseudo-Stokes Shift of ca. 230 nm, which is promising for biological application.

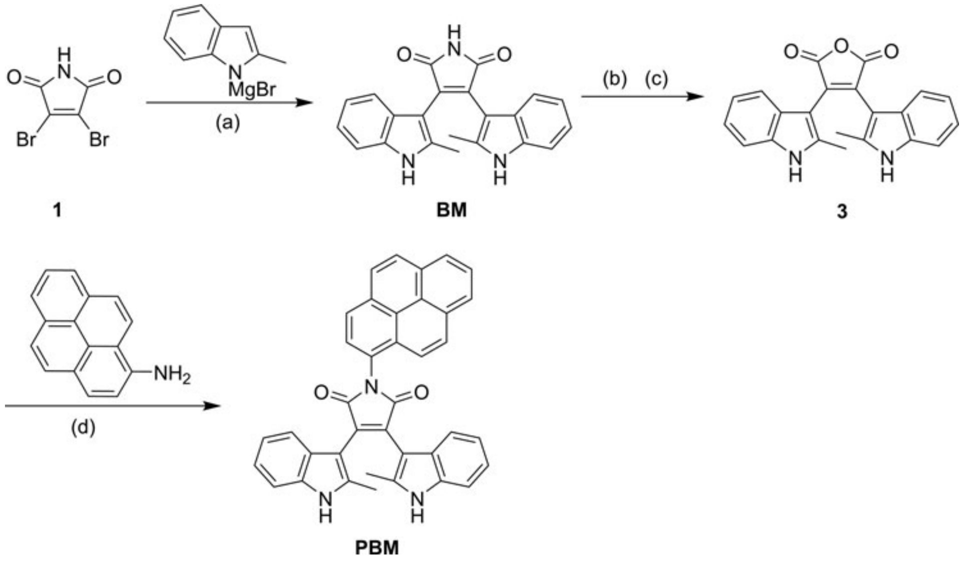
Experimental

General Procedures and Materials

All solvents used in reaction were carefully dried according to the standard procedure and stored over 4Å molecular sieve. All the reagent-grade chemicals were purchased from Aldrich, Acos, or Alfa Aesar and used without further purification. Melting points were determined on a Mel-Temp® IA9200 digital melting point apparatus in a glass capillary and were uncorrected. All synthesized compounds were routinely checked by TLC and ^{1}H NMR. TLC was performed on aluminum-backed silica gel plates (Merck DC. Alufolien Kieselgel 60 F254).

Synthesis

Synthetic routes of the target compound, pyrene-bisindolylmaleimide (**PBM**), are outlined in Scheme 1. The synthesis of **PBM** started from dibromomaleimide (**1**), which was coupled with two equivalents of 2-methylindole-MgBr and yielded bis-2-methylindolylmaleimide (**BM**) [10, 11]. Followed by the hydrolysis of **2** in KOH aqueous solution, bis-2-methylindolylmaleic acid anhydride was obtained with the nitrogen atom replaced by oxygen atom [12]. Subsequent imidization of bis-2-methyindolemaleic anhydride with 1-aminopyrene yielded the target compound **PBM**.



Scheme 1. Synthetic route and conditions: (a) toluene/Et$_2$O/THF (5:1:1), refl. 24 h; (b) 10% aq. KOH, refl. 40 min; (c) 2N HCl; (d) CH$_3$OCH$_2$CH$_2$OH, refl. 24 h.

Bis-2-methylindolylmaleic acid anhydride (50 mg, 0.14 mmol) and 1-aminopyrene (35 mg, 0.16 mmol) dissolved in 2-methoxyethanol (25 mL). Three drops of triethylamine was added to the solution. The mixture was heated to reflux for about 24 h. The reaction process was monitored by TLC. After the bis-2-methylindolylmaleic acid anhydride was disappeared. The reaction mixture was cool to ambient temperature and poured to water (25 mL). The mixture was extracted with ethyl acetate (25 mL×3). The collected organic phase was dried over MgSO$_4$. After filtration, the solvent was evaporated in vacuum. The crude product was purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:2) as the eluant, affording dark red solid of **PBM** (61 mg, yield, 78%). mp: 324 – 328°C.

^{1}H NMR(400 MHz, DMSO-d_6): $\delta = 11.42$ (2H, s), 8.48 – 8.30 (6H, m), 8.20 – 8.15 (2H, m), 7.30 – 7.25 (4H, m), 7.07 – 6.70 (2H, m), 6.83 (2H, s), 2.30 (6H, s); ^{13}CNMR(100 MHz, DMSO-d_6): δ = 171.2, 138.3, 136.0, 131.9, 131.3, 131.0, 130.7, 129.0, 128.6, 127.8, 127.6, 127.2, 126.4, 126.23, 125.5, 124.8, 124.0, 122.9, 121.4, 120.1, 119.7, 111.2, 103.9, 13.7; MS(EI, 70 eV) m/z 555 (M$^+$); HRMS: calcd for C$_{38}$H$_{25}$N$_3$O$_2$: 555.1947, found 555.1954.

^{1}H and ^{13}C NMR Spectroscopy

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Brucker AM-400 spectrometer operating at frequencies of 400 MHz for proton 100 MHz for carbon in DMSO-d_6. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0$) as internal standard and expressed in parts per million. Spin multiplicities are given as *s* (singlet), *d* (doublet), *t* (triplet), and *m* (multiplet) as well as *b* (broad). Coupling constants (*J*) are given in Hertz.

Mass and High Resolution Mass Spectra (HRMS)

Mass spectra measured on a LC-MS (Waters UPLC-TQD) mass spectrometer. High resolution mass spectra (HRMS) were measured on Brucker microOTOF II Focus instrument.

UV-Vis and Emission Spectra

Absorption spectra were measured with PERSEE TU-1900 and Agilent 8453 spectrophotometer. Emission spectra were measured with Shimadzu RF-5301PC fluorescence spectrophotometer. Solvents used in photochemical measurement were spectroscopic grade and were purified by distillation. The stock solution of compounds (2×10^{-3} M) was prepared in THF, and a fixed amount of these concentrated solutions were added to each experimental solution. All the experiments were done repeatedly, and reproducible results were obtained. Prior to the spectroscopic measurements, solutions were deoxygenated by bubbling nitrogen through them.

Quantum Yield Measurements

The Φ_F values in solution were measured following a general method with quinine sulphate ($\Phi = 0.55$ in 50 mM H_2SO_4 solution) as a standard. Dilute solutions of compounds in THF were used. Sample solution was in quartz cuvettes and degassed for ~15 min. The degassed solution has absorbance of 0.05–0.09 at absorbance maxima. The fluorescence spectra were recorded 3–4 times and average value of integrated areas of fluorescence was used for the calculation of Φ_F in solution. The refractive indices of solvents at the sodium D line were used.

Theoretical Calculations

For the theoretical study of excited state photophysics of the compound, the *DMol*^{3} program packaged in *Material Studio* was used. The ground state geometries and the frontier molecular orbital of the compound were calculated using the density function theory (DFT) with the B3LYP hybrid functional and the double numerical plus *d*-functions (DND) atomic orbital basis set.

Results and Discussion

Figure 1 shows the absorption spectra of conjugate **PBM** and the corresponding model chromophores pyrene and **BM** in THF. Two major absorption bands were observed for **PBM**, one in the visible region around 350~550 nm, and the other one around 260~320 nm in the UV region. The broad absorption in the visible region including a shoulder at 350~435 nm can be assigned to the π–π^* transitions from the S_0 to S_1 and S_2 states. The absorption spectrum of conjugate **PBM** is almost the sum of the absorption spectra of pyrene centered around 336 nm and **BM** centered around 465 nm, indicating that **PBM** behaves as two separately conjugated chromophores connected through a single covalent bond. The ratio of molar extinction coefficients $\varepsilon_{\text{pyrene}}(336\ \text{nm})/\varepsilon_{\text{BM}}(465\ \text{nm})$ was estimated to be ca. 3.43 in the individual model chromophores, similar to that in the conjugate **PBM** ($\varepsilon_{\text{pyrene}}(342\ \text{nm})/\varepsilon_{\text{BM}}(465\ \text{nm}) = 3.82$). A slight red shift (5~6 nm) in the band corresponding to the bisindolylmaleimide moiety of the conjugate **PBM** indicates very weak electronic coupling between the two integrated chromophores.

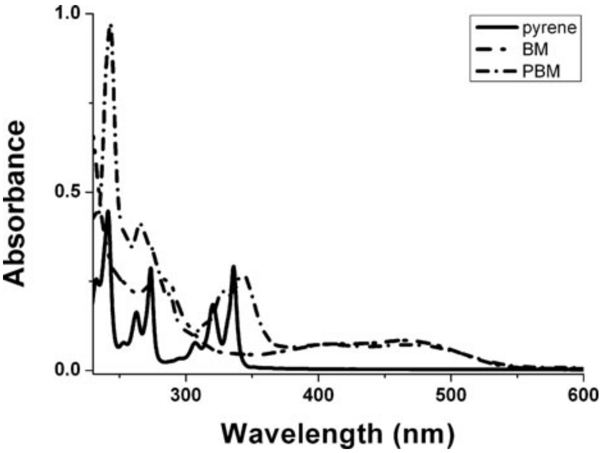


Figure 1. Absorption spectra of **PBM** (1.0×10^{-5} M) in THF.

Figure 2 shows the emission spectra of conjugate **PBM**, **BM**, and pyrene. Pyrene, the energy donor, has no emission in the wavelength range 500–700 nm, where the **BM** and the bisindolylmaleimide moiety in **PBM** exhibits fluorescence centered at 572 nm. **BM**, the energy acceptor, excited at 340 nm, shows relatively weak fluorescence. Negligible fluorescence from the pyrene (energy donor) moiety in **PBM** supports the energy transfer to the acceptor bisindolylmaleimide moiety. The fluorescence intensity of the bisindolylmaleimide moiety through energy transfer ($\lambda_{ex} = 340$ nm) is similar to that for the direct excitation (470 nm) of conjugate **PBM**. Excitation spectra of PBM monitored at 572 nm shows clearly the peak at 340 nm with similar intensity of 484 nm, confirming efficient energy transfer the pyrene moiety to the bisindolylmaleimide moiety. Consistent with the absorption spectra, a red shift (8 nm) in the bisindolylmaleimide emission band of the **PBM** indicates a weak electronic coupling between the substituents. The pseudo-Stokes shift is estimated to be 232 nm, which is expanded more than the 96 nm Stokes shift of **BM** (excited at the longest maximum absorption 466 nm). Due to the blue emission pyrene

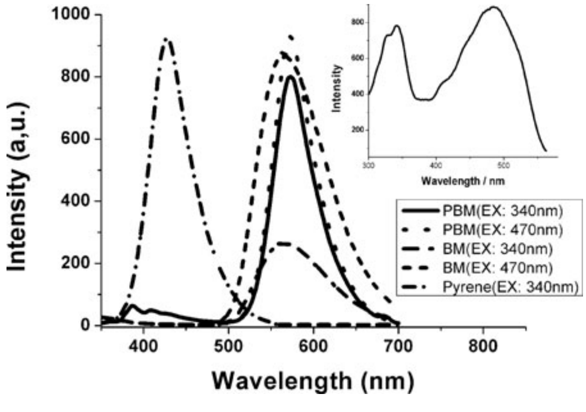


Figure 2. Fluorescence emission spectra of pyrene, **BM**, and **PBM** (1.0×10^{-5} M) in THF. Insert: Excitation spectra of **PBM** in THF monitored at 572 nm.

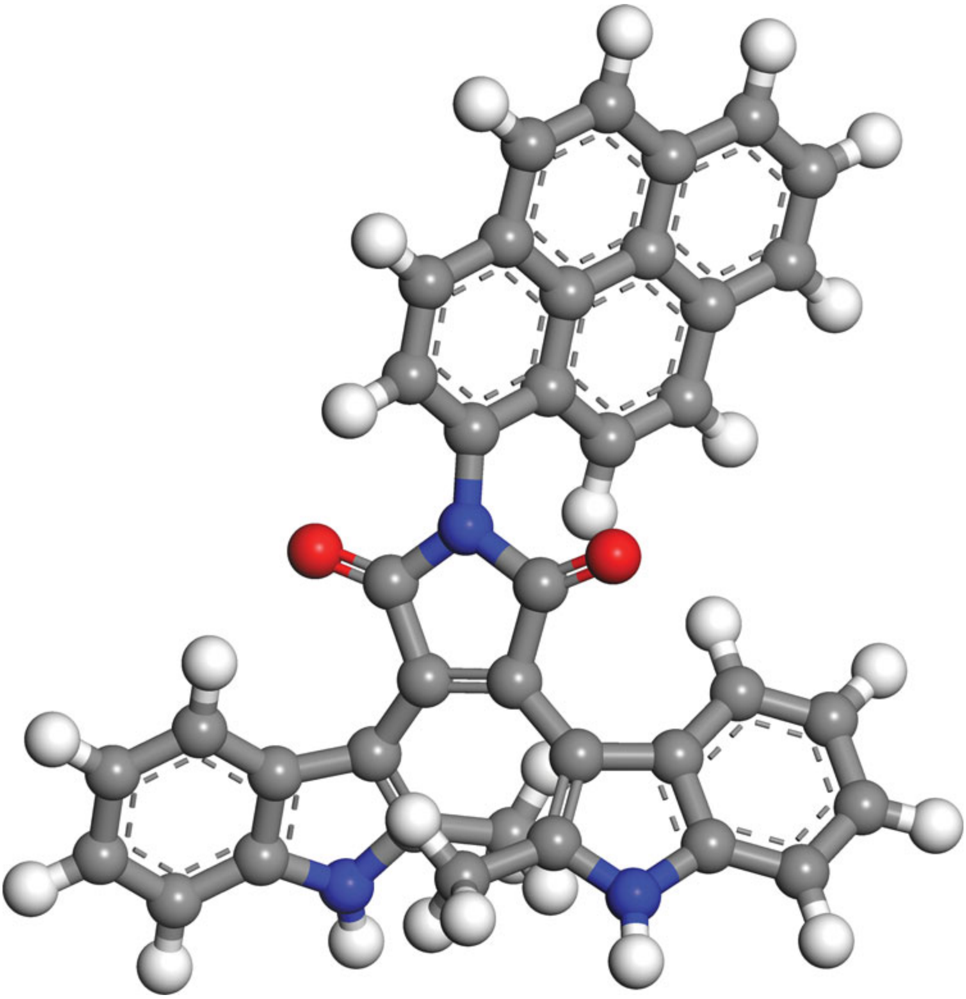


Figure 3. Energy-minimized geometric structure of **PBM**.

moiety introduced, the excitation wavelength can be shifted to shorter wavelength to a large extent. Thus, the pseudo-Stokes shift is magnified. The fluorescence quantum yield of **PBM** is estimated to be ca. 0.25, marginally higher than that of **BM** ($\Phi_F = 0.27$).

Various solvents were used in the measurement of fluorescence emission properties, such as chloroform, acetonitrile, DMSO, ethanol, hexane, dioxane, ethyl acetate, and toluene. Very weak emission was observed in most of the solvent. Only in toluene, **PBM** shows medium fluorescence emission relative to that in THF, with the quantum yield estimated to be ca. 0.16. And similar extent of energy transfer was also observed for **PBM** in toluene.

To better comprehend the geometrical, electronic, and optical properties of **PBM**, a comprehensive computational investigation using Material Studio. To reduce the run times in the first instance, the ground-state energy-minimized structures were calculated using DFT and LDA/DN basis set. Further refinement and optimization on structures were then undertaken using B3LYP/DND basis set. Figure 3 shows the optimized geometric

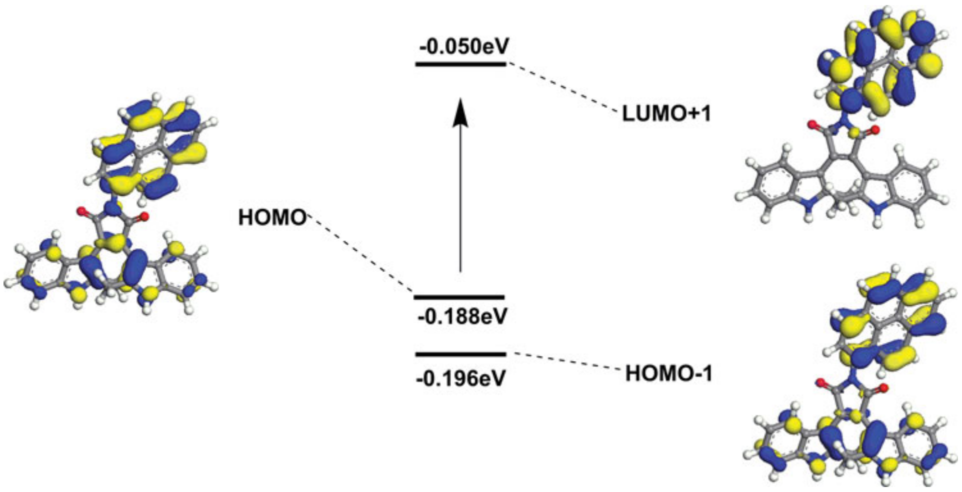


Figure 4. Electron density distributions and energies of the frontier orbitals of **PBM**.

structure of **PBM**. The conjugate nature of individual chromophores was confirmed from the analysis of the optimized structure, with comparable bond lengths corresponding to conjugate carbon-carbon single and double bonds. As shown in Figure 3, the pyrene donor moiety twisted out of the malimide plane by 60.5°. Consequently, the pyrene and bisindolylmaleimide units act as independent chromophores and not as a conjugate system. And also, the quantum yield of **PBM** can be maintained similar to that of **BM** due to the rigidity of the carbon framework. It would appear that a steric rather than electronic effect is controlling non-radiative decay. Because of the steric hindrance between H of pyrene and O of imide, the pyrene unit rocks back and forth rapidly between two extreme points.

The electron distribution model of the HOMO (H), HOMO-1 (H−1), and LUMO+1 (L+1) are illustrated in Fig. 4. Examination of the electron density distribution in the frontier molecular orbitals helps for understanding the electronic interactions between the constituent pyrene and bisindolylmaleimide moiety of **PBM**. According to the calculation, the transition H→L+1 and H−1→L+1 are possible with the oscillator strength (f) 0.099 and 0.228, respectively. The absorption of **PBM** calculated as 484 nm (H→L+1) and 372 nm (H−1→L+1), which is in good agreement with the experimentally observed absorption band. In H and H−1, the electron density distribution spread over the whole molecule. In contrast, L+1 is localized in pyrene moieties. Such delocalization increases the energy gap between H−1/H and L+1. This could be contributed to large steric repulsion between hydrogen and oxygen atoms, preventing rotation about the internuclear bond and leading to noncoplanar arrangements. The large difference of electron density distribution between H/H−1 and L+1 clearly support the efficient charge transfer excitation to pyrene moiety of **PBM**.

Conclusions

In conclusion, the donor-acceptor conjugate **PBM** was designed and synthesized at the separation distance of a single bond. The intramolecular hindrance configured the orthogonality of **PBM** and led to the individuality of the two chromophores. Upon photoexcitation at 340 nm, an efficient energy transfer from the pyrene (donor) to the bisindolylmaleimide with the pseudo-Stokes shift estimated to be 232 nm. The orthogonality of the chromophore enforced by the steric barrier allows the donor and acceptor moieties to be held at a distance of a single bond, maximizing the Coulombic coupling and nullifying any contribution from orbital overlap to energy transfer. Computational results of frontier orbitals clearly suggest that energy transfer predominantly occurs by through-bond interactions. Wide excitation range and large pseudo-Stokes shift make the energy transfer of **PBM** a potential candidate for biological applications [13]. Progress is underway in our lab to functionalize **PBM** further.

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