Photosensitizer That Selectively Generates Singlet Oxygen in Non Polar Environments: Photophysical Mechanism and Efficiency for BODIPY Dimer.

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Photosensitizer That Selectively Generates Singlet Oxygen in Nonpolar Environments: Photophysical Mechanism and Efficiency for a Covalent BODIPY Dimer

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ABSTRACT: Photosensitizers that selectively generate singlet oxygen in non polar/polar microenvironments are highly desirable for photodynamic therapy of tumor but not yet reported. BODIPY (boron-dipyrromethene complexes) covalent dimer **1** is such a photosensitizer that forms singlet oxygen only in hexane, cyclohexane, and toluene significantly but not in polar solvents. Its corresponding monomer is not photoactive in any solvents for forming singlet oxygen. To reveal the mechanism, we measured the excited triplet-, singlet-, and ground-state properties as well as singlet oxygen generation capability with laser flash photolysis, fluorescence spectroscopy, time-correlated single photon counting, and absorption spectroscopy in various solvents. The striking difference is due to the fact that the excited dimer (excimer) undergoes very fast intramolecular charge transfer (ICT) that makes intersystem crossing noncompetitive in polar solvents, while ICT is negligible in nonpolar solvents.

efficiency	
non polar solvents:	**0.30**
polar solvents:	**0.00**
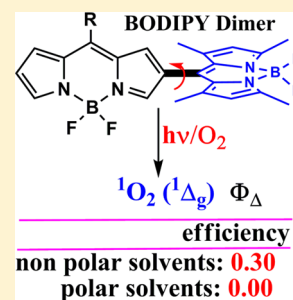
INTRODUCTION

Singlet oxygen,[1] $O_2(^1\Delta_g)$, is a very active transient species that reacts with many kinds of organic or biomolecular compounds, including DNA and proteins.[2−5] These reactions result in irreversible cellular damage and cell death for both normal tissues and malignant tumors in the photodynamic therapy (PDT) of cancer.[6,7] Photosensitizer (PS), the producer of singlet oxygen in the presence of light and oxygen, flows through various tissues with blood cycling but selectively accumulates within malignant tumors after intravenous injection. During the period of PS building up in tumors, a PS in blood can generate singlet oxygen and causes the damage to normal tissues. A PS that is inactive in blood but active in non polar tumors is highly desirable. Activatable photo-sensitizers by various strategies have been reported,[8] a few of them are related to the environment polarity.[9,10] Scherz showed that Pd-bacteriopheophorbide formed singlet oxygen almost exclusively in organic solvents, but it also generated hydroxyl radicals and superoxide radicals in aqueous medium,[9] therefore it is not selective in phototoxity to tumors. Nagano reported that a PS can be switched on by binding to the protein target of low polarity.[10]

We found that a BODIPY dimer (**1** in Figure 1) showed a high sensitivity to solvent polarity in generating singlet oxygen. Porphyrin and phthalocyanine are efficient PSs,[11] but their ability for generating singlet oxygen is not remarkably affected by the microenvironment in which they are located. BODIPY monomer molecules are generally not effective at producing singlet oxygen but can emit fluorescence very efficiently[12−16] unless they are brominated or iodized.[15,17−20] However, the particular halogenated BODIPY monomer molecules also showed no dependence on solvent polarity in their ability to produce singlet oxygen.[20] BODIPY dimers, however, such as **1**, can effectively produce $O_2(^1\Delta_g)$ by photosensitization, as found by other groups and us recently,[21−23] which is in contrast with many dye dimers that are usually not photoactive for singlet oxygen formation. The unique property of BODIPY dimers leads us to further study their mechanism in photosensitization. During the process we found that the BODIPY dimer is a singlet-oxygen photosensitizer that shows selectivity to the hydrophobicity/lipophobicity of the surrounding environment.

RESULTS AND DISCUSSION

The BODIPY dimer **1** shows the different UV−vis absorption from that of the monomer **2** (Figure 1). An additional band at 525 nm occurs in the dimer **1**, which is due to the exciton coupling between the two BODIPY π−systems in dimer **1**.[24] The degree of the coupling is a function of the dihedral angle θ, which can be changed by the rotation along the bridging C−C bond (Figure 1). θ is almost 90° in the crystal of dimer **1**[22] but expected to be variable continuously when it is dissolved in a liquid solvent. The plot of absorbance of the dimer **1** in DMF and cyclohexane at the band maximum against concentration (2−10 μM) is linear, and no new bands were observed with the increase in its concentration, indicating that no intermolecular aggregation occurred.

Using diphenylisobenzofuran (DPBF) as the chemical trapper of $O_2(^1\Delta_g)$,[25] we quantified the $O_2(^1\Delta_g)$ production
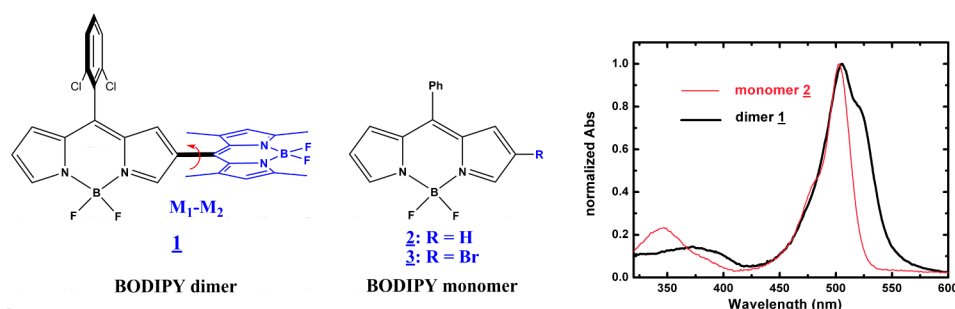
Figure 1. Left: chemical structure of dimer **1** and monomer **2**. Right: normalized absorption spectra of dimer **1** and monomer **2** in hexane.
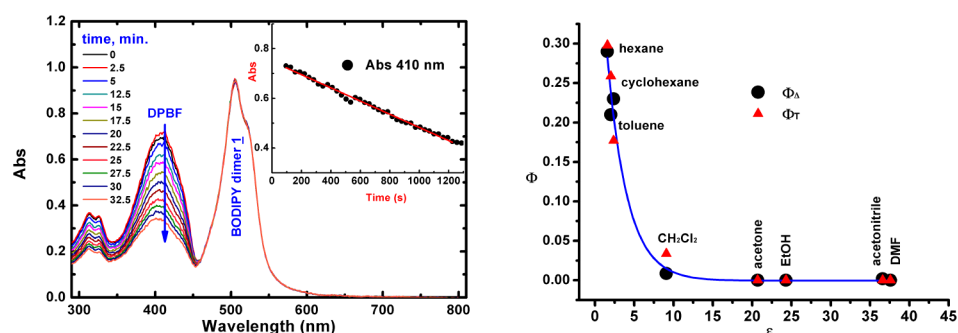

Figure 2. Left: change of absorption spectra of DPBF in the presence of dimer **1** in cyclohexane. Right: quantum yield for triplet (Φ_T) and singlet oxygen (Φ_Δ) formation in various solvents as a function of the solvent polarity.
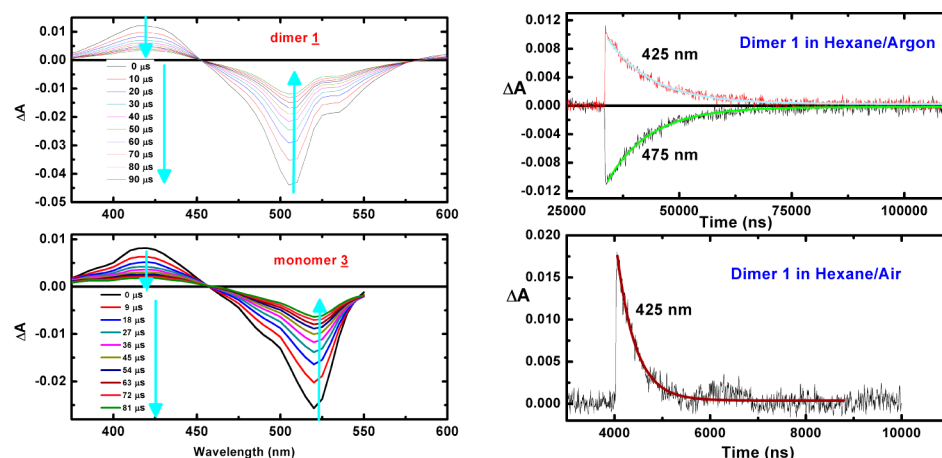

Figure 3. Left: Transient absorption spectra of BODIPY dimer **1** and brominated monomer **3** in degassed hexane with 355 nm laser excitation. Right: Triplet decay and ground-state recovery of BODIPY dimer **1** in argon-saturated (top right) and air-saturated (bottom right) hexane.

photosensitized by **1** and **2** in various solvents upon irradiation at 510 nm (Figure 2).

During the selective irradiation at **1** in air-saturated cyclohexane, the absorption of DPBF decreased, but that of **1** remained unchanged. The quantum yields of singlet oxygen formation (Φ_Δ) of **1** in different solvents are compared in Figure 2. The most striking feature is that Φ_Δ in nonpolar solvents is over 0.20 but essentially decreased to nothing in polar solvents, whereas the BODIPY monomer **2** did not show the ability for photosensitized oxidation to DPBF in either polar or nonpolar solvents. To our knowledge, such a polarity-dependent PS is unprecedented and offers an additional degree of control in the photosensitized production of O$_2$ ($^1\Delta_g$) for PDT. The mechanism for such a PS is still unknown and elucidated by the following investigation. All such dimers synthesized in our previous report[22] showed the selectivity to

solvent polarity, but the dimer of higher polarity is more sensitive.

BODIPY monomer generally does not yield its excited triplet state (T$_1$), so one cannot be certain that BODIPY dimer can generate T$_1$ and transfer its energy to molecular oxygen for the production O$_2$ ($^1\Delta_g$). In fact there has been no identification of T$_1$ for the BODIPY dimers, although it became known very recently that the dimer can generate O$_2$ ($^1\Delta_g$).[21−23] We hence measured the transient absorption (TA) of **1** by laser flash photolysis (LFP).

For the monomer **2**, no TA signal was detected by LFP in the nanosecond to microsecond time range in any solvent. The dimer **1**, however, did show strong TA signal (Figure 3) in nonpolar solvents, such as hexane, cyclohexane, and toluene, but it was not the case in polar solvents. To make the assignment of the TAS for the dimer **1** to be T$_1$, a brominated
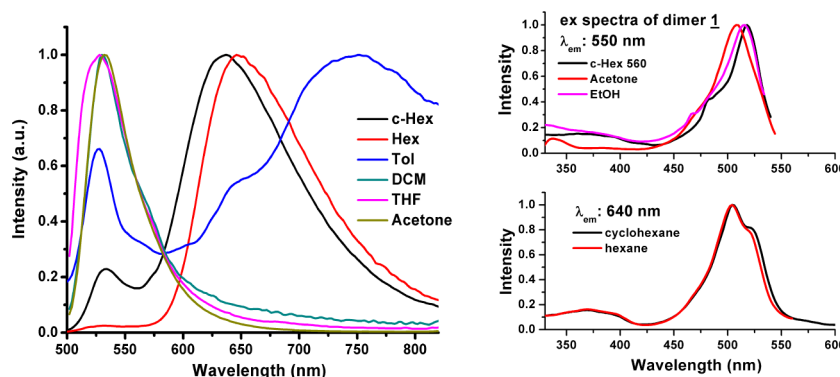
Figure 4. Left: Normalized fluorescence spectra of BODIPY dimer **1** (10 μM) in different solvents with excitation at 480 nm. Right: The normalized excitation spectra for **1** for emission band I (top right, emission wavelength = 550 nm) and band II (bottom right, emission wavelength = 640 nm) in different solvents.

monomer **3** was used in the LFP study for a comparison (Figure 3, bottom left). The heavy atom effect of the Br atom in the monomer **3** leads to a 46% quantum yield for its triplet formation (Φ_T), so that we were able to assign the TA spectra of **3** as T_1-T_n absorption very recently.[20]

Figure 3 shows the time evolution of the TA spectra of the dimer **1**, which showed a positive peak with the maximum at 420 nm and a negative peak with the minimum at 510 nm. Both the shape and position are very similar to the T_1-T_n absorption spectra of the BODIPY **3**. This similarity indicates the positive signal of the dimer **1** is also T_1-T_n absorption. The following spectral behavior is also typical of the T_1-T_n absorption. The minimum of the negative absorptions exhibited peaks matching the maximum of the corresponding ground-state absorption. The positive bands are separated from the ground-state bleaching with well-defined isosbestic points.

The bleaching recovery at ground-state absorption (475 nm) is concomitant with the decay at 425 nm, indicating that as the positive T_1-T_n absorption decays the ground state is repopulated. The presence of the isosbestic points suggests that the decay of T_1 generates only ground-state S_0. The curves can all be well fit by the monoexponential function, indicating that only one triplet state species is present in the solutions. The triplet lifetime (τ_T) is computed to be 49 and 43 μs for **1** and **3**, respectively, in argon-saturated hexane, which are sufficiently long for photosensitizing the production of singlet oxygen.

In air-saturated hexane solution, the τ_T is shortened dramatically (Figure 3) to 0.38 and 0.41 μs for **1** and **3**, respectively. The rate constant by oxygen quenching can be then evaluated to be (1.31 and 1.21) $\times 10^9$ M^{-1} s^{-1} for **1** and **3**, respectively, which are close to the diffusion rate constant. This effective oxygen quenching also suggests that the positive absorptions are indeed due to T_1-T_n triplet absorptions.

The triplet quantum yield (Φ_T) for **1** was also measured in different solvents. The solvent effect on Φ_T value is the same as that of Φ_Δ value (Figure 2), suggesting that O$_2$ ($^1\Delta_g$) is indeed generated by T_1.

The LFP study shows that intersystem crossing (ISC) in the dimer can effectively compete with radiation and internal conversion (IC) processes, although its monomer cannot. LFP, however, does not answer why T_1 of **1** is produced efficiently in nonpolar solvents but not in polar solvents. We then measured the singlet excited-state (S_1) properties of **1** in different solvents. The fluorescence spectra of dimer **1** are very dependent on the solvents (Figure 4).

In polar solvents, only one narrow band I at 530 nm was observed, which shows similar band shape and position to the emission of monomer **2**. One additional broad band II at 640 nm occurred in nonpolar solvents, while the intensity of the 530 nm band is decreased. In toluene, the third broad peak III at 750 nm occurred. Bands II and III are structureless and broad, which are typical of the excimer or charge-transfer emission.

The excitation spectra of the emission band I match the absorption shape of the BODIPY monomer (Figure 4 right top), suggesting that band I is the monomer-like emission.

For the fluorescence bands II and III, however, the excitation spectra are similar to the absorption of the dimer **1** (Figure 4 right bottom), indicating that the emission bands II and III are caused by the dimer **1** in which two BODIPY moieties are not independent but strongly interacting each other. Also noted is that the triplet excited state forms only when band II or III is present, suggesting that the emitting species for the band II or III is the precursor of the triplet state.

On the basis of the observation, we conclude the following mechanism (Figure 5). The ground state of dimer **1** can be
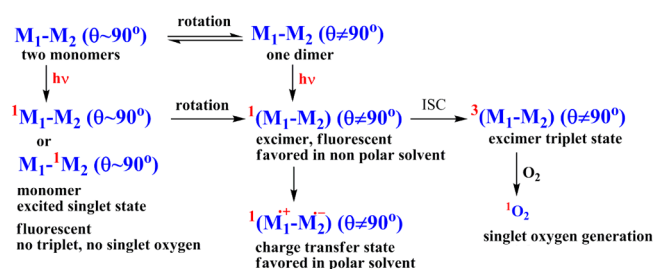

Figure 5. Photophysical mechanism for dimer **1** to generate singlet oxygen.

classified as two types: (i) The first type is M$_1$-M$_2$ ($\theta \approx 90°$), in which the electronic interaction is negligible so that two BODIPY moieties M$_1$ and M$_2$ can be essentially considered as two independent monomers. The crystal structure of **1** has revealed that the dihedral angle θ is 90 $\pm$ 0.5° due to the strong steric hindrance caused by the four methyls;[22] this perpendicular conformation must be also present in the solvent liquid. (ii) The second type is M$_1$-M$_2$ ($\theta \neq 90°$), a true dimer, in which the rotation causes the significant overlap of the electron cloud of M$_1$ and M$_2$; each moiety is not independent

any more. A dynamic and fast equilibrium holds between (i) and (ii) (Figure 5).

The excitation of (ii), the true dimer, leads directly to a singlet excimer $^1(M_1\text{-}M_2)$ which can be partially converted to its T_1 by ISC and then yields singlet oxygen by transferring its triplet energy to molecular oxygen. An excimer is usually observable only in nonpolar solvent. Intramolecular excimer formation for covalently linked BODIPY dyes was also previously reported.[26]

The charge transfer in an excimer occurs quickly in polar solvents, and the resulting charge-separation state is also stabilized by polar solvents so that ISC is not competitive to form triplet state. This explains why $^1O_2$ is not formed in polar solvent for 1. The presence of the charge-transfer state is evidenced by the additional fluorescence emission in toluene. Charge-transfer emission is generally weak and not easily observed, but toluene is a solvent that is often used to detect charge-transfer emission.[27,28]

The excitation of (i) $M_1\text{-}M_2$ ($\theta \approx 90°$), two monomers, leads to either $^1M_1\text{-}M_2$ or $M_1\text{-}^1M_2$. It is known that BODIPY monomers do not form triplet state effectively but do emit fluorescence, which is the band I at 530 nm. We also measured the fluorescence lifetimes at 530 nm for 1 in various solvent. The decays are all biexponential with $\tau_1 = 1.5$ ns for M_1 and $\tau_2 = 5.5$ ns for M_2. The lifetimes showed no dependence on the polarity of solvents, indicating no photoinduced electron transfer (PET) in $^1M_1\text{-}M_2$ to form $M_1^{\bullet+}\text{-}M_2^{\bullet-}$. This is due to the fact that no electronic coupling is existent when M_1 and M_2 are perpendicular each other. The rotation in $^1M_1\text{-}M_2$ or $M_1\text{-}^1M_2$, however, can also lead to the excimer formation.

The fluorescence decay of the excimer is also non-mono-exponential because θ is not a fixed value due to the rotation.

■ CONCLUSIONS

In summary, we have demonstrated that the BODIPY dimer 1 sensitizes $O_2(^1\Delta_g)$ production in nonpolar solvents but not in the polar ones. The striking difference is due to the fact that the excited dimer (excimer) undergoes very fast intramolecular charge transfer (ICT) in polar solvents that makes ISC noncompetitive, while ICT is negligible in nonpolar solvents. The true precursor of singlet oxygen is the triplet excimer, while the intramolecular rotation is the factor that determines if the excimer can be formed. Such a polarity-dependent $O_2(^1\Delta_g)$ production efficiency could play a crucial role in many applications, including photoinduced cell death selectively for PDT. The unique polarity-dependent properties of 1 may also be beneficial for applications requiring the controlled release of oxidizing/oxygenating species in amphiphilic systems.

■ EXPERIMENTAL SECTION

The synthesis and characterization for the compounds 1−3 have been previously described.[22,29] Solvents are of analytical grade and used after redistillation.

Ground-state UV−vis absorption spectra were recorded on a StellarNet BLACK Comet C-SR diode array miniature spectrophotometer connected to deuterium and halogen lamp by optical fiber using 1 cm matched quartz cuvettes at room temperature. Fluorescence spectra were recorded using Edinburgh Instruments FLS920 fluorospectrometer, with 2 nm slits for excitation at 480 nm and emission from 490 to 830 nm. All spectra were corrected for the sensitivity of the

photomultiplier tube. The fluorescence quantum yield (Φ_f) was computed by using

$$\Phi_f = \Phi_f^0 \cdot \frac{F_s}{F_0} \cdot \frac{A_0}{A_s} \frac{n_s^2}{n_0^2} \tag{1}$$

in which F is the integrated fluorescence intensity, A is the absorbance at excitation wavelength, and n is the refractive index of the solvent used, and the subscript 0 stands for a reference compound and s represents samples. Rhodamine 6G in ethanol was used as the reference ($\Phi_f = 0.95$).[30] The sample and reference solutions were prepared with the same absorbance (A_i) at the excitation wavelength (near 0.090 in a 1 cm quartz cell). All solutions were air-saturated.

Fluorescence lifetime of S_1 state was measured by time-correlated single photon counting method (Edinburgh FLS920 spectrophotometer) with excitation at 379 nm by a portable diode laser (69 ps fwhm), and emission was monitored at the peak maximum. The lifetime values were computed by the F900 software coming with the instrument.

Nanosecond TA measurements were obtained using LP920 (Edinburgh Instruments). The excitation source was a Q-switched Nd/YAG laser (BRIO) of 4 ns full width at half-maximum with third-harmonic (355 nm) generation. The 355 nm beam was directed onto one side of a 1 cm square silica cell containing the sample (absorbance around 0.2) after bubbling Ar gas during 20 min. The transient transmission variations were monitored at right angles to the excitation in a crossbeam arrangement using a 450 W xenon flash lamp, a mono-chromator, a photomultiplier, and a digitized oscilloscope interfaced with a desktop computer. The power of the incident 355 nm laser pulse in the sample was ~5 mJ. The triplet quantum yield Φ_T was obtained by comparing the ΔA_T of the optically matched sample solution at peak maximum in a 1 cm cuvette to that of the reference using the equation:[31]

$$\Phi_T = \Phi_T^{ZnPc} \cdot \frac{\Delta A_T}{\Delta A_T^{ZnPc}} \cdot \frac{\Delta \varepsilon_T^{ZnPc}}{\Delta \varepsilon_T} \tag{2}$$

where the superscript represents the reference, ΔA_T is the absorbance of the triplet transient difference absorption spectrum at the selected wavelength, and $\Delta \varepsilon_T$ is the triplet state molar absorption coefficient, which is obtained by eq 3.

$$\Delta \varepsilon_T = \varepsilon_S \frac{\Delta A_T}{\Delta A_S} \tag{3}$$

where ΔA_S and ΔA_T are the absorbance change of the triplet transient difference absorption spectrum at the minimum of the bleaching band and the maximum of the positive band, respectively, and ε_S is the ground-state molar absorption coefficient at the UV−vis absorption band maximum. Both ΔA_S and ΔA_T were obtained from the triplet transient difference absorption spectra.

Singlet oxygen quantum yield (Φ_Δ) determinations were carried out using the chemical trapping method.[32] Typically, a 3 mL portion of the respective PS solutions that contained DPBF was irradiated at 510 nm in air-saturated toluene. Φ_Δ value was obtained by the relative method using methylene blue as the reference (eq 4):

$$\Phi_\Delta = \Phi_\Delta^{ref} \frac{k}{k^{ref}} \cdot \frac{I_a^{ref}}{I_a} \tag{4}$$

where Φ_{Δ}^{ref} is the singlet oxygen quantum yield for the standard (0.79);[7] k and k^{ref} are the DPBF photobleaching rate constants in the presence of the respective samples and standard, respectively; and I_a and I_a^{ref} are the rates of light absorption at the irradiation wavelength of 510 nm by the samples and standard, respectively. Their ratio can be obtained by eq 5.

$$\frac{I_a^{ref}}{I_a} = \frac{1 - 10^{-A_{670}^{ref}}}{1 - 10^{-A_{670}}} \tag{5}$$

To avoid chain reactions induced by DPBF in the presence of singlet oxygen, the concentration of DPBF was lowered to $\sim 3 \times 10^{-5}$ mol dm^{-3}. A solution of sensitizer (absorbance ~ 0.80 at the irradiation wavelength) that contained DPBF was prepared in the dark and irradiated in the 510 nm. DPBF degradation was monitored by UV–vis absorption spectrum. The error in the determination of Φ_{Δ} was $\sim 10\%$ (determined from several Φ_{Δ} values).

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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