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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
Cite This: J. Am. Chem. Soc. XXXX, XXX, XXX−XXX
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Upconversion-like Photolysis of BODIPY-Based Prodrugs via a One-Photon Process

Wen Lv,[†] Yafei Li,[†,‡] Feiyang Li,[§] Xin Lan,[∥] Yaming Zhang,[†,‡] Lili Du,[∥] Qiang Zhao,[§] David L. Phillips,[∥] and Weiping Wang*[,†,‡]

[†]Laboratory of Molecular Engineering and Nanomedicine, Dr. Li Dak-Sum Research Centre, The University of Hong Kong-Karolinska Institutet Collaboration in Regenerative Medicine, The University of Hong Kong, Hong Kong, China

[‡]Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

[§]Key Laboratory for Organic Electronics and Information Displays & Jiangsu Key Laboratory for Biosensors, Institute of Advanced Materials, Nanjing University of Posts and Telecommunications, Nanjing 210023, China

[∥]Department of Chemistry, The University of Hong Kong, Hong Kong, China

Supporting Information

ABSTRACT: Photochemical reactions at lower energy than the absorption window are currently achieved by multi-photon processes, including two-photon absorption and photon upconversion, which have limited energy utilization efficiency. Here, we report a one-photon strategy based on triplet−triplet energy transfer (TTET) between a photosensitizer and a photocleavable molecule to achieve photolysis at low energy. To verify this concept, we chose platinum(II) tetraphenyltetrabenzoporphyrin (PtTPBP) as the photosensitizer and synthesized a boron-dipyrromethene (BODIPY)-based prodrug as the photocleavable molecule. Photolysis of the prodrug is achieved by TTET upon excitation of PtTPBP at 625 nm with a photolysis quantum yield of 2.8%. Another demonstration shows an unexpected higher photolysis quantum yield than the direct excitation at 530 nm. This strategy opens a new path for achieving photolysis at long wavelengths, benefiting the applications in biological studies, photopharmacology, and photoresponsive drug delivery.

Photochemistry plays an important role in designing controllable molecules, which offers promising optical tools for chemical, biological, and medical applications.[1−4] Photolysis or photocleavage reactions can be used to release desired functional molecules at appropriate times and locations with light excitation.[5,6] The reactions normally occur following excitation with light at the absorption wavelengths of the photocleavable molecule. In biological and medical applications, substantial efforts have been focused on increasing the excitation wavelength because long-wavelength light exhibits deeper tissue penetration depths and lower photocytotoxicity.[7,8]

One strategy is to develop long-wavelength light-excitable photocleavable groups or photocages, including derivatives of coumarin,[6,9] boron-dipyrromethene (BODIPY),[10,11] and Ru(II) complexes.[12] These compounds, however, usually require multi-step organic syntheses and have relatively low photolysis quantum yields compared to short-wavelength light-excitable photocleavable groups.[10,11] The second strategy is to use two-photon excitation.[13,14] Due to the small two-photon absorption cross sections of current photocages, high-power femtosecond pump lasers are required for two-photon excitation.[15] The third strategy is to excite photocages utilizing upconversion luminescence systems, including lanthanide-doped upconversion nanoparticles (UCNPs)[16] and triplet−triplet annihilation-based upconversion (TTA-UC).[17,18] However, the theoretical upconversion quantum yield of these upconversion systems is less than 0.5, since at minimum two photons are required to produce one upconverted photon.[15,19,20] Internal energy consumption during multi-step energy-transfer processes further decreases upconversion quantum yields, resulting in low photolysis efficiencies. Therefore, a simple energy-transfer strategy is highly desired for photolysis with long-wavelength light excitation. Here, we present a one-photon upconversion-like strategy, where light at lower energy than the onset of absorption of the photocleavable group can achieve the high-energy-demanding cleavage reaction based on a triplet−triplet energy transfer (TTET) process.

Studies have found that photolysis can occur from the first excited triplet state (T_1) in addition to the first excited singlet state (S_1).[21,22] We hypothesize that a photocleavable molecule could be sensitized to the T_1 state by a photosensitizer with a higher T_1 energy level and a lower S_1 energy level through TTET process to achieve the photolysis reaction of interest. The lower S_1 energy level of the photosensitizer results in longer absorption wavelengths than that of the photocleavable molecule, allowing lower energy photons to be used for excitation. The effect of which is like upconversion-based photolysis, in that a low-energy photon is used to achieve a higher-energy photolysis reaction. In the strategy, the T_1 state of the photocleavable molecule is populated by the photosensitizer through TTET. Since photolysis can occur from the T_1 state of the photocleavable molecule, TTA is not necessary. Therefore, a second photon is not required for the cleavage (Figure 1). This one-photon upconversion-like photolysis offers a simpler energy-transfer process compared with the

Received: August 21, 2019

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DOI: 10.1021/jacs.9b09034

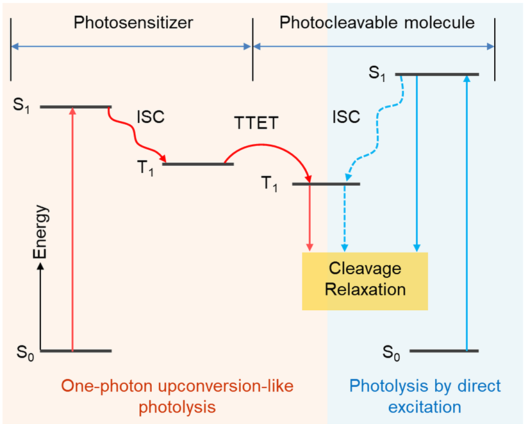

Figure 1. Jablonski diagram of the one-photon upconversion-like photolysis via a TTET process (red lines) and the photolysis by direct excitation at the absorption wavelengths of photocleavable molecules (blue lines). Other possible relaxation pathways from excited states are not shown in the diagram. S_0, ground singlet state; S_1, first excited singlet state; T_1, first excited triplet state; ISC, intersystem crossing; TTET, triplet−triplet energy transfer. The S_0 energy levels of the photosensitizer and photocleavable molecule are set at the same level.

traditional TTA-UC-based photolysis (Figure S1), which means less internal energy consumption and more efficient energy utilization.

Based on the energetic requirements described above, a photosensitizer should have a higher T_1 energy level but a lower S_1 energy level than the photocleavable molecule to achieve the photolysis. Therefore, we chose *meso*-methyl position-substituted BODIPY (BODIPY1) and platinum(II) tetraphenyltetrabenzoporphyrin (PtTPBP) as the photocage and photosensitizer, respectively (Figure 2A). We further designed and synthesized a photocleavable prodrug, BODIPY1-Cb, by modifying BODIPY1 with an anticancer drug molecule, chlorambucil (Cb) (Supporting Information). BODIPY1-Cb exhibited absorption and emission spectra with peaks at 543 and 570 nm, respectively (Figure 2B and Figure S2A). From its emission peak, the S_1 energy level of BODIPY1-Cb was calculated to be 2.18 eV.[23] PtTPBP is a common photosensitizer with S_1 energy level of 1.8 eV.[24] Compared with BODIPY1-Cb, PtTPBP has a lower S_1 energy level and longer maximum absorption wavelength (613 nm, Figure 2B), necessary in order to function as a low-energy photosensitizer.

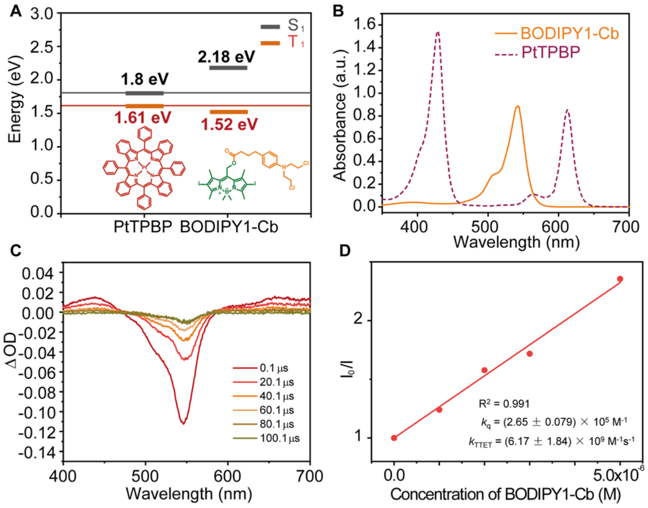

Figure 2. (A) S_1 and T_1 energy levels and chemical structures of the photosensitizer (PtTPBP) and the photocleavable molecule (BODIPY1-Cb). (B) Absorption spectra of BODIPY1-Cb and PtTPBP in dichloromethane ($c = 10^{-5}$ M). (C) Nanosecond transient absorption spectra of BODIPY1-Cb (10^{-5} M) in N_2-saturated toluene. $\lambda_{ex} = 355$ nm. (D) Stern−Volmer plot of phosphorescence intensity quenching of PtTPBP (10^{-5} M) by BODIPY1-Cb through a TTET process in a N_2-saturated methanol solution containing 5% toluene and 10% dichloromethane ($n = 3$). k_q is the phosphorescence intensity quenching constant of PtTPBP during the TTET process, k_{TTET} is the rate constant of the TTET process.

From the phosphorescence spectrum of PtTPBP (Figure S2B), the T_1 energy level of PtTPBP was calculated to be 1.61 eV.[23] Since BODIPY1-Cb did not exhibit a clear phosphorescence peak, time-dependent density functional theory (TD-DFT) was used to calculate its T_1 energy level, which was determined to be 1.52 eV (Figure S3). The results show that PtTPBP has a higher T_1 energy level but a lower S_1 energy level than BODIPY1-Cb (Figure 2A), satisfying the energy requirement for the one-photon upconversion-like photolysis. The nanosecond transient absorption spectra of BODIPY1-Cb exhibited a bleaching of the absorbance band at 546 nm (Figure 2C) with a lifetime of 21.82 ± 10.11 μs (Table S1). The T_1 lifetime of PtTPBP (42.92 ± 0.80 μs) was determined from the phosphorescence lifetime at 770 nm. The long T_1 lifetime of both BODIPY1-Cb and PtTPBP supports an efficient TTET process from ^{3}PtTPBP* to ^{3}BODIPY1-Cb*. The TTET rate constant (k_{TTET}) was calculated to be (6.17 ± 1.84) × 10^9 M^{-1} s^{-1} (Figure 2D), which is comparable to literature k_{TTET} values (approximately 10^9 M^{-1} s^{-1}).[25,26]

To demonstrate whether cleavage relaxation occurs from the T_1 state of BODIPY1-Cb, we irradiated BODIPY1-Cb with a 530 nm LED (Figure 3A). The irradiation within the absorption window of BODIPY1-Cb can directly promote the molecule to the S_1 state. The heavy atoms in BODIPY1-Cb can enhance intersystem crossing (ISC) and facilitate conversion from the S_1 state to the T_1 state. In air-saturated solutions, the decomposition of BODIPY1-Cb and generation of free Cb were mainly due to the cleavage relaxation from the S_1 state, since the T_1 state of BODIPY1-Cb could be quenched by oxygen molecules. In N_2-saturated solutions, a much higher cleavage efficiency was observed (Figure 3B and Table S2), which indicates that BODIPY1-Cb can be cleaved from its T_1 state. Almost all BODIPY1-Cb was decomposed after 10 s of the irradiation at 44 mW/cm^2, which released 48.31 ± 1.05% of free Cb with generation of byproducts as photolysis of other BODIPY-modified molecules did.[11]

Photolysis of BODIPY1-Cb by photosensitization with PtTPBP was assessed by irradiating a N_2-saturated solution containing the two molecules with a 625 nm LED and analyzing the reaction mixture with high-performance liquid chromatography (HPLC) (Figure S4). A new peak located at ∼11.2 min was observed along with the disappearance of the BODIPY1-Cb signal at ∼29.0 min. The new peak showed the same elution time as that of free Cb and as the peak from the BODIPY1-Cb solution treated with 530 nm light. The generation of Cb was further confirmed by the mass spectrometric analysis of the reaction mixture (Figures S5−S7). In contrast, irradiation of BODIPY1-Cb alone with 625 nm light did not cleave BODIPY1-Cb to release Cb. These results demonstrate that the photolysis of BODIPY1-Cb can be achieved by irradiation of PtTPBP with 625 nm red light,

DOI: 10.1021/jacs.9b09034
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

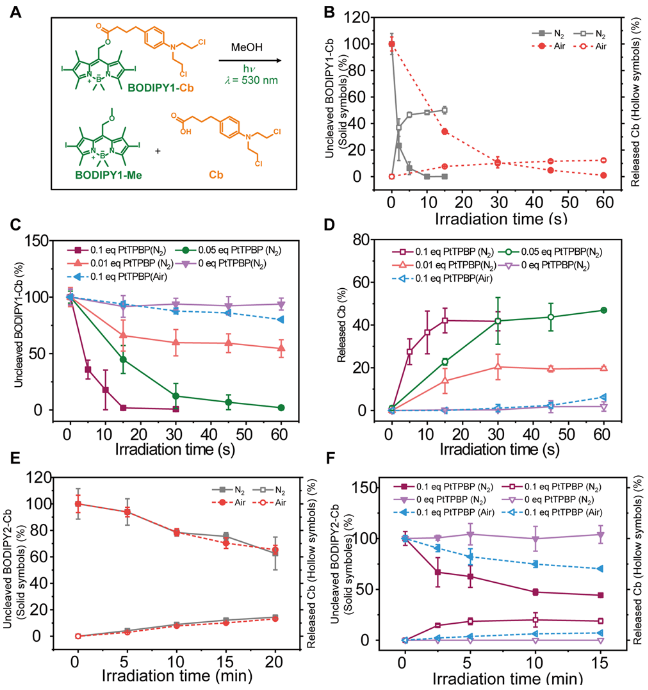

Figure 3. (A) Photolysis reaction of BODIPY1-Cb. Photolysis rate of BODIPY1-Cb (B−D) and BODIPY2-Cb (E, F) after irradiation with 530 nm light (B, E) or 625 nm light (C, D, and F) for different time periods. All irradiations were done with an LED at 44 mW/cm². $n = 3$.

which has deeper tissue penetration depths than the green light at 530 nm.[7,8]

To evaluate the influence of photosensitizer concentration on the TTET-based photolysis, different molar equivalents of PtTPBP were used in the photolysis assay of BODIPY1-Cb upon 625 nm light irradiation in N_2-saturated solutions. As expected, the release of Cb by the cleavage of BODIPY1-Cb was accelerated with increasing molar equivalents of PtTPBP (Figure 3C,D), which is attributed to the accelerated TTET process with increased molar ratios of PtTPBP to BODIPY1-Cb. In the presence of 0.1 equiv of PtTPBP, 30 s of the irradiation at 44 mW/cm² decomposed almost all the BODIPY1-Cb and released 41.74 ± 4.46% of free Cb, which is close to the percentage of released Cb by direct irradiation of BODIPY1-Cb with 530 nm light. The corresponding photolysis quantum yield Φ_{BC} was calculated to be ∼2.8% using Reinecke's salt actinometry (Table S2).[27,28] The TTET-based photolysis was also investigated in air-saturated solutions, which showed approximately 68 times decrease in photolysis quantum yield (Figure 3C,D and Table S2) due to the quenching of both ^{3}PtTPBP* and ^{3}BODIPY1-Cb* by oxygen molecules.[29]

We further tested our hypothesis using another photocleavable molecule with a shorter T_1 lifetime and lower photoreaction efficiency. We designed the molecule BODIPY2-Cb, whose chemical structure is similar to that of BODIPY1-Cb but without iodine modification and with fluorine substitution of methyl groups (Scheme S1). BODIPY2-Cb exhibited similar absorption and emission spectra with BODIPY1-Cb (Figures S8 and S9), but with a shorter T_1 lifetime (1.91 ± 0.01 μs) (Table S1 and Figure S10). The lack of iodine atoms in BODIPY2-Cb led to inefficient ISC.[30] Therefore, photolysis of BODIPY2-Cb upon direct irradiation at 530 nm mainly occurs from the S_1 state under both N_2- and air-saturated conditions. This conclusion is supported by the negligible difference in photolysis efficiencies under the both conditions (Figure 3E and Table S2). The T_1 energy level of BODIPY2-Cb was calculated to be 1.42 eV (Figure S11), which is lower than that of PtTPBP (1.61 eV), enabling energy transfer to occur from ^{3}PtTPBP* to ^{3}BODIP2-Cb*. As shown in Figure 3F, irradiation at 625 nm also cleaved BODIPY2-Cb in the presence of PtTPBP. The photolysis efficiency of BODIPY2-Cb was lower under the air-saturated conditions than under the N_2-saturated conditions, which is due to the decreased T_1 lifetime of both PtTPBP and BODIPY2-Cb by oxygen molecules. The results demonstrate that the one-photon upconversion-like photolysis strategy can be applied to photocleavable molecules with a short T_1 lifetime and low photoreaction efficiency.

An unexpected result was obtained when we analyzed the photolysis quantum yield of BODIPY2-Cb. The photolysis quantum yield upon sensitization by PtTPBP at 625 nm was 5-fold greater than that upon direct 530 nm light irradiation without photosensitization (Table S2). This means that our one-photon upconversion-like strategy can achieve photolysis of BODIPY2-Cb with a longer excitation wavelength as well as higher photolysis quantum yield than direct photolysis from excitation at its absorption wavelength. The result is unexpected, because one-photon upconversion-like excitation has more energy transfer processes than direct excitation and is supposed to have a lower photolysis quantum yield. This experimental observation has not been previously reported in upconversion-based photolysis, which usually has a much lower photolysis quantum yield than direct photolysis due to the extra photon upconversion process and energy transfer from upconversion systems to photocleavable molecules (Figure S1). The result is presumably attributable to the facts that the cleavage relaxation from the T_1 state is more efficient than that from the S_1 state for BODIPY2-Cb and the TTET process is more efficient than ISC in terms of populating ^{3}BODIPY2-Cb*. This study provides new insight into decreasing excitation energy while increasing photolysis efficiency for some photocleavable molecules.

In summary, we have demonstrated that photocleavable molecules can undergo photolysis by populating the T_1 state with longer-wavelength-absorbing photosensitizers. The process requires that the photosensitizers have higher T_1 energy levels but lower S_1 energy levels than the photocleavable molecules. The one-photon upconversion-like photolysis strategy could be applied to other pairs of photosensitizers and photocleavable molecules that fulfill the energy matching. Finding suitable pairs, especially for photosensitizers with absorption in the near-infrared range, is a challenging but worthwhile exploration. Compared to TTA-UC-based photolysis, the one-photon upconversion-like photolysis requires a simpler energy-transfer process, which is attractive for practical applications. Furthermore, our method can increase both the excitation wavelength and the photolysis efficiency of photocleavable molecules. Like the application of TTA-UC-based photolysis, the photosensitizers and BODIPY-based prodrugs could be encapsulated within the hydrophobic core of polymeric nanoparticles in aqueous solutions, which achieves photorelease of drugs in biological systems. Therefore, this TTET-based one-photon upconversion-like photolysis offers a new platform for improving the performance of photoactivation systems for applications in biological studies, photoactivated chemotherapy, and targeted drug delivery.

DOI: 10.1021/jacs.9b09034
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b09034.

General experimental considerations, detailed procedures, and additional supporting data, including Figures S1–S22, Tables S1 and S2, and Scheme S1 (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*wangwp@hku.hk

ORCID

Qiang Zhao: 0000-0002-3788-4757

Weiping Wang: 0000-0001-7511-3497

Notes

The authors declare the following competing financial interest(s): A PCT application was filed with No. PCT/CN2019/101689.

■ ACKNOWLEDGMENTS

This work was supported by Dr. Li Dak-Sum Research Fund (Start-up Fund) of The University of Hong Kong, Seed Fund for Basic Research of The University of Hong Kong (No. 201711159053), Guangdong-Hong Kong Technology Cooperation Funding Scheme (No. 2017A050506016), and Young Scientists Fund of the National Natural Science Foundation of China (No. 81803469). The computations were performed using research computing facilities provided by Information Technology Services, The University of Hong Kong.

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