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Stimuli Responsive Reversible Switching of Intersystem Crossing in Pure Organic Material for Smart Photodynamic Therapy

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Abstract: Photosensitizers (PSs) with stimuli responsive reversible switchable of intersystem crossing (ISC) is highly promising for smart photodynamic therapy (PDT), but achieving this goal remains a tremendous challenge. This study introduces a strategy to obtain such reversible switching of ISC in a new class of PSs, which exhibit stimuli initiated twisting of conjugated backbone. We present a multidisciplinary approach that includes femtosecond transient absorption spectroscopy and quantum chemical calculations to show remarkably enhanced ISC efficiency (Φ_{ISC}), switching from nearly 0 to 90%, via increasing the degree of twisting, providing an innovative mechanism to promote ISC in these organic structures. This leads us to propose here and demonstrate the concept of smart PDT, where pH-induced reversible twisting maximizes the ISC rate, and thus enables strong photodynamic action only under pathological stimulus (such as pH, hypoxia or enzyme). The ISC process is turned off to deactivate PDT ability, when the PS is transferred or metabolized away from pathological region.



Introduction

ISC is a radiationless transition from a singlet excited state of a molecule to its triplet excited state, which underlies a variety of applications in many diverse fields such as in PDT and phosphorescence imaging as well as in photovoltaics and photocatalytic reactions.^[1] The current ISC-related studies mainly focus on the Φ_{ISC} enhancement and/or activatable ISC

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Figure 1. Schematic illustration of reversible switching of ISC and potential application in smart PDT. (a) Novel strategy to design of a POM with pH-reversible conjugated backbone twisting (CBT) for reversible switching of ISC. (b) Only inside the tumor the ISC of smart photosensitizer (PS) can be switched on to generate cytotoxic singlet oxygen (¹O₂) for PDT and switched off when PS is transferred or metabolized away from the tumor region.

with single-time switching feature, because activatable ISC with the enhanced Φ_{ISC} improves efficiency and precision of theranostics.^[2] Further development of reversible ISC that allows a repeatable and selective tuning of triplet excited state towards certain stimulus is particularly valuable for theranostics applications. It is of outmost importance, if reversibly switchable ISC could be achieved in response to pathological stimulus, such as pH, hypoxia or enzyme. This would greatly benefit the development of more advanced PDT that is currently infeasible by using activatable ISC. The underlying reason is that reversibly switchable ISC has an ability to be turned off to deactivate PDT action when a PS is transferred or metabolized away from pathological region. This will help overcome the general limitations plaguing the current PDT paradigm, such as unavoidable damage to normal tissues and long lasting cutaneous photosensitivity. To the best of our knowledge, obtaining such reversibly switchable ISC remains a tremendous challenge and no demonstration of such smart PDT therapy, as proposed here, has been reported.

The key challenge to achieve reversible switching of ISC lies in the inability to shut off ISC after activation, because current strategies to enhance ISC leave little room for other functionalities. In addition, majority of materials with high Φ_{ISC} are noble metal complexes (such as iridium and platinum

complexes), that generally suffer from intrinsic problems such as high costs and metal-induced toxicity.^[3] Considering the inherent biocompatibility and low cost,^[4] obtaining reversible switching of ISC in pure organic materials (POMs) is more desirable for practical applications. For an efficient ISC to exist in POMs, their chemical structure typically requires incorporating specific moieties: aromatic carbonyls, heteroatoms, or halogens.^[5] Aromatic carbonyls exhibit strong spin-orbit coupling (SOC) at the carbonyl oxygen which allows for intrinsic ISC.^[6] According to the El-Sayed rule, presence of heteroatoms (such as nitrogen or sulfur), can enhance SOC because of the involvement of different type orbitals in radiationless transitions between singlet and triplet manifolds, ${}^{1}(n, \pi^{*}) \rightarrow {}^{3}(\pi, \pi^{*})$ being a typical example.^[7] Halogens, which combine the benefits of aromatic carbonyls and heavy atom effect, have also been widely used in enhancing ISC. Clearly, rigid incorporation of these moieties into conjugated backbone makes achieving reversible switching of ISC especially challenging, despite the ever-growing demands in reversible switching of ISC for the emerging applications.

In a ground breaking research reported here, we introduce the concept of smart PDT, where we show by study of the structureproperty relationships in a series of *p*-phenyleneethynylenebased derivatives (named PE1-4), that exceptionally enhanced ISC can be effected by a twist in the conjugated backbone. We present a design of a small POM (PE5) which exhibits reversible switching of ISC through pH-reversible conjugated backbone twist (CBT). Figure 1 schematically presents this design and the concept of smart PDT which is pH-activatable. Figure 2. (a) Molecular structure of PE1-4 and their corresponding Φ_{ISC} . (b) Normalized absorption (solid) and fluorescence (dash dot) spectra.

Design and basic optical properties. Our previous studies found that POMs with side-chain ammonium group could be used as a highly-efficient photosensitizer for PDT,^[8] which means that these POMs may have considerable Φ_{ISC} for efficient ¹O₂ generation. However, the underlying mechanism of highly efficient ¹O₂ generation in these POMs so far remained unclear. To reveal a relationship between the molecular structure and ISC, a series of similar POMs (PE1-4) were designed and synthesized (Figure 2a, Scheme S1). PE1 and PE2 were used to study the ISC properties that were individually influenced by carboxyl and ammonium salt. PE3 was used to validate the interaction between carboxyl and ammonium salt, and PE4 was used to verify the effect of side-chain length on this interaction. The steady-state absorption and fluorescence spectra exhibited similar absorption and emission bands owing to their comparable conjugated backbone (Figure 2b). Both the absorption and the PL spectra of PE1, PE3, and PE4 were slightly red-shifted compared to those of PE2. This is because of a considerably extended conjugated system after the introduction of carboxyl groups. All photophysical parameters are presented in Table 1.

Table 1. Summary of key optical parameters for the POMs in this study.

POM	λ _{abs} ^[a] (nm)	λ _{FL^[d] (nm)}	t _{isc} [c] (ps)	<i>k_{ISC}</i> ^[d] (×10 ¹⁰ s ⁻¹)	Φ_{ISC}
PE1	380	433	197	0.5	1%
PE2	356	408	87	1.1	3%
PE3	370	440	1.3	77	83%
PE4	356	414	1.0	100	90%

[a] Lowest-energy absorption maximum wavelength. [b] Fluorescence maximum wavelength. [c] ISC lifetime [d] ISC rate.

To get a solid evidence of the ISC process, we deciphered the excitation dynamics of all samples using femtosecond transient absorption (fs-TA) spectroscopy. Figure 3a shows 2D colorcoded fs-TA spectra of PE1-4 upon excitation at 350 nm, from which we can identify the evolution of the primary excited state. For all the samples, the initial signal was dominated by a negative absorption band (white box). These negative absorption bands should be attributed to stimulated emission because their profiles are consistent with corresponding fluorescence spectra (red dashed line at the bottom of Figure 3a). The variations in the position of stimulated emission were caused by differences in the fluorescence onset for each POM (Figure 2b). Any more detailed information associated with the negative absorption bands is unattainable because of strong instrumental noise. This is however not the key point of the present study. Over time, PE1-4 showed a broad positive absorption band that emerges quickly within 2 ps timeframe (Figure 3a). This positive absorption band was assigned to corresponding excited-state absorption (ESA). To distinguish singlet ESA from triplet ESA, fs-TA plots at different delay times were extracted from Figure 3a and presented in Figure S1 and

Results and Discussion







Figure 3. Experimental evidence of ISC. (a) 2D pseudo-colour fs-TA spectra of PE1-4 obtained with time delays from 0 to 2900 ps (350 nm, 0.3 mW). The fluorescence spectrum of corresponding sample is presented in red dashed line to show the stimulated emission band. (b) fs-TA plots of PE1-4 at different pump-probe delay times. Rising arrow represents population of triplet excited state while drop down arrow represents the depopulation of singlet excited state. The presence of an isosbestic point (marked by black dotted circle) indicates the appearance of two different species, which usually represents the occurrence of ISC. (c) Population dynamics of PE1-4, which illustrate the dynamics of the singlet excited state formation followed by the singlet to triplet transformation through ISC, and triplet decay. Green ball and blue star represent the singlet and triplet-excited state population.

Figure 3b. Within a 2 ps timeframe (Figure S1), PE1-4 exhibited red-shifted yet intensity-growing ESA, along the prolonged delayed time, indicating the formation of new ESA species. Upon further increase in delay time (Figure 3b), PE3 and PE4 exhibited two distinctive ESA bands, including a gradually decreased peak around 535 nm and a continuously rising peak around 580 nm. Dynamic decay trace of PE3 at 500 nm revealed two decay components at 1.1 ps and 1216 ps (Figure 3c). The appearance of these long-lived components is consistent with the 1.78 ns fluorescence lifetime obtained by time-correlated single photon counting (Figure S2). Therefore, the former peak of PE3 around 535 nm was assigned to singlet ESA. The peak around 535 nm almost totally decays within 1 ps (Figure 3a), while the peak around 580 nm lived up to 1000 ps (Figure S3). Considering that a triplet excited state has a longer lifetime than a singlet excited state, it is reasonable to assign the latter peak around 589 nm to the triplet ESA. With same method, in Figure 3a, we figured out the singlet (green box) and the triplet (black box) ESA in PE1, PE2, and PE4. Notably, the occurrence of an obvious isosbestic point in PE3 and PE4 is of particular interest. The positive nature of the isosbestic point is usually an indication of a singlet-to-triplet ISC process.^[9] Overall, these results presented a solid evidence for ISC in both PE3 and PE4.

Quantification of ISC. To evaluate Φ_{ISC} we analyzed the singlet and the triplet population dynamics of PE1-4, which is presented in Figure 3c. The triplet ESA around 580 nm for PE3 and PE4 increased abruptly within 1 ps (Figure 3c), and remained almost unchanged from 10 to 100 ps (Figure 3a). This phenomenon indicates that ISC in PE3 and PE4 occurred guickly on a < 10 ps timescale. In sharp contrast, PE1 and PE2 exhibited a considerably longer singlet decay and ISC process on 100 ps time scale, indicating an unfavorable ISC in PE1 and PE2. It is well-documented that the dynamic growth trace of triplet ESA represents its ISC lifetime.^[10] Take PE4 as an example, the dynamic growth trace of PE4 at 589 nm showed that the triplet excited state is populated within 0.98 ps, and the rate of ISC $(k_{\rm ISC})$ is calculated to be $1.0 \times 10^{12} \, {\rm s}^{-1} \, (1/k_{\rm ISC})$. Dynamic decay trace of PE4 at 535 nm revealed a fast singlet decay with the lifetime of 0.9 ps. The efficiency of ISC $(\Phi_{ISC}=[1/t (T_1, rise)]/[1/t$ (S1, decay)]) was estimated based on previous studies.[11] As shown in Table 1, PE4 has a maximum Φ_{ISC} of 90%, which is a little higher than that of PE3 (83%), and almost two orders of magnitude greater than that of PE1 (1%) and PE2 (3%). From

these experimental results, it is reasonable to deduce that (*i*) the carboxyl group or ammonium salt alone has negligible effect on the enhancement of Φ_{ISC} in *p*-phenyleneethynylene-based conjugated system, and (*ii*) the interaction of carboxyl and ammonium salt groups is responsible for the exceptionally enhanced Φ_{ISC} in PE3 and PE4. Notably, Φ_{ISC} for PE4 is the largest among the Φ_{ISC} values reported for organic compounds, which is tremendously promising for triplet-state-based applications.

In addition, this study has also shed light on the mechanisms of switchable/reversible ISC: *(i)* Comparing the Φ_{ISC} of PE1 with that of PE3 or PE4, the mechanism that facilitates ISC originated from aromatic carbonyls which are put into specific conditions, where aromatic carbonyl oxygen and π -conjugated system are not in the same molecular plane. *(ii)* Negligible Φ_{ISC} in PE2 excluded the effect of the external heavy atom (bromine) on ISC, although external heavy atom effects have been observed in deuterated solvent (such as deuterated methanol and water).^[12] **Theoretical verification of CBT-induced ISC**. To elucidate the mechanism of ultra-efficient ISC in PE3 and PE4, we carried out time-dependent density functional theory (TD-DFT) calculations of the singlet and the triplet excited states. According to the perturbation theory, a smaller singlet-triplet energy gap (ΔE_{ST})

and greater spin-orbit coupling (SOC) constants facilitate higher $\Phi_{ISC}.^{[1c, 13]}$ On the basis of simple energetic arguments, the increased number of T_n states with small ΔE_{ST} (± 0.37 eV) that was found in PE3 and PE4 (Figure 4a and Table S1-4), resulted in a high ISC rate.^[14] Combining the energetic arguments and the analysis of SOC constants computed by means of the Dalton electronic structure program,^[15] the feasible $S_1 \rightarrow T_n$ channels were identified (Figure 4a and Tables S5-8). Clearly, the increased number of potential $S_1 \rightarrow T_n$ channels and several orders of magnitude larger SOC constants in PE3 and PE4 theoretically predict their ultrahigh Φ_{ISC} . The larger SOC constant in PE4 theoretically accounts for its higher Φ_{ISC} relative to PE3.

Furthermore, the molecular geometries of PE1-4 were studied to gain an insight into the underlying mechanism responsible for the ultrahigh Φ_{ISC} . As shown in Figure 4b and Figure S4, both PE3 and PE4 display a large torsion angle between central benzene ring and the adjacent benzoate groups, indicating a significant CBT, while PE1 and PE2 display nearly planar structure. The twisted geometry in PE3 and PE4 is attributed to the electrostatic attraction between the positively-charged quaternary ammonium salt and the negatively-charged carboxyl moiety. From these experimental and theoretical insights, it was



Figure 4. TD-DFT study of the CBT-dominant ISC. (a) Schematic diagrams showing the computed energy levels and the probable ISC channels from the S₁ state to higher- or lower-lying triplet states (T_n). The triplet states in gray region are those levels with energy higher than $E_{S1} + 0.37$ eV or lower than $E_{S1} - 0.37$ eV. The triplet states marked in green contain the same transition configuration compositions as S₁. Average spin-orbit coupling (SOC) constants between S₁ and the involved triplet states (the larger SOC, the higher ISC possibility) are also shown. (b) Optimized molecular geometries. Electrostatic interaction between positively-charged side-chain ammonium salt and negatively-charged terminal carboxyl group twists the conjugated backbone. The CBT was evaluated roughly by the torsion angle between central benzene moiety and adjacent benzoate groups. (c) Experimental validation of CBT-enhanced ISC. Flatting the twisted structure of PE4 into planar one to switch off its ISC via host-guest complexion in which negative-charged water-soluble pillar[5]arene (WP5) shields the positively-charged ammonium salt and thus disrupts the electrostatic interaction.

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reasonable to attribute the ultrahigh Φ_{ISC} in PE3 and PE4 to the twisted conjugated backbone.

Demonstration of CBT-enhanced ISC. The CBT-induced Φ_{ISC} was theoretically confirmed by TD-DFT calculations (Figure S5), in which the simplified conjugated backbone was extracted and the electronic structure calculations for planar and twisted geometries were carried out. In planar geometry ISC between S₁ and T_n is suppressed owed to a large ΔE_{ST} between S₁ and T_{1,4}, and small SOC constant between S₁ and T_{2,3}. The EI-Sayed rule^[16] states that the rate of ISC is considerably large if the

radiationless transition involves a change in orbital type.^[17] The out-of-plane (molecular plane) π -type orbitals in a planar geometry give the major contribution to the S₁ and the closely lying T₂ and T₃ states (Figure S6). Thus, the orbital angular momentum operator cannot efficiently couple these states, leading to small values of SOC constant. Meanwhile, in the twisted geometry ISC is enhanced because of an in-plane projection of π -character orbitals, giving the major contribution to T₂ and T₃ states.



Figure 5. pH-reversible ISC and intracellular pH-activatable PDT. (a) Schematic illustration of pH-reversible structure. (b) pH-reversible ISC, which was demonstrated by triplet excited state-induced assumption of ADMA. (c) Schematic illustration of the photophysical and photochemical processes taken place in PE5-mediated PDT. After ISC, the excited $T_{2,3.4}$ states decay back to T_1 through internal conversion. The energy in T_1 is then transferred to molecular oxygen to generate ¹O₂ for PDT. (d) ¹O₂ emission generated by PE5 in D₂O with different pH value. (e) Micrographs of intracellular ¹O₂ generation in HeLa cells. Scale bar: 40 µm. The non-fluorescent ¹O₂ probe can be transferred into green fluorescence by ¹O₂. 5,10,15,20-Tetrakis(1-methyl-4-pyridinio)porphyrin tetra(p-toluenesulfonate) (TMPyP₄) is a frequently used PS for PDT and here as a comparison to highlight the pH-activatable ability of PE5. (f) pH-activatable PDT of PE5. Scale bar: 160 µm. The green color represents live cells, and the red color represents dead cells.

The in- and out-of-plane orbitals can now be coupled (Figure S6), resulting in a larger SOC constant. In addition, the $S_0 \rightarrow S_2$ transition is forbidden in the planar geometry, but weakly allowed in the twisted geometry, opening up a potential $S_2 \rightarrow T_4$ ISC channel.

This CBT-enhanced $\Phi_{\rm ISC}$ was further experimentally validated by host-guest complexion method. It is principally feasible to decrease $\Phi_{\rm ISC}$ through flattening the twisted conjugated backbone into a planar one. To validate this assumption, the positive-charged quaternary ammonium salt in PE4 was threaded into the cave of the negative-charged water-soluble pillar[5]arene (WP5) via host-guest complexion, to flatten the conjugated backbone (Figure 4c, Figure S7), because of the repulsive electrostatic interaction.^[18] The remarkably-decreased $\Phi_{\rm ISC}$ in as-prepared complex (WP5⊃PE4) from 90% to 0% highlighted the CBT-enhanced $\Phi_{\rm ISC}$ (Figure S8). Taken together, the computational and experimental data unambiguously

demonstrated the critical contribution of CBT to the exceptionally enhanced Φ_{ISC} .

pH-reversible ISC in POM. The availability of CBT-enhanced ISC offers unique opportunities to construct reversibly switchable ISC. Following this principle, we designed and synthesized a small inner salt-type POM (named PE5) with optimized isoelectric point of pH 6.0 (Figure 5a and Figures S9,10), which enables a significant twisting at pH 6.0 for high $\Phi_{\rm ISC}$ while a slight twist in normal biological environment (pH 7.4) with very low or negligible $\Phi_{\rm ISC}$. This is because PE5 exists in a zwitterionic form at pH 6.0 (Figure S9) in which electrostatic interaction results into a significant CBT leading to high $\Phi_{\rm ISC}$. At pH 7.4, PE5 exists mainly in anionic form losing the electrostatic interaction to drive the twisted geometry. The ISC on/off at pH 6.0 and 7.4 was experimentally confirmed by a typical triplet states-induced photodegradation of anthracene-9,10-diyl-bismethylmalonate (ADMA) in the presence of PE5 and molecular

oxygen (Figure 5b). The distinct consumption of ADMA demonstrated the ISC on at pH 6.0 and ISC off at pH 7.4. Most notably, PE5 exhibited a pH-reversible ISC for smart applications requiring switchable ISC (Figure 5b), which was unobtainable in previous studies. In addition, the excellent photostability and moderate absorption of PE5 was also demonstrated in Figure S11 and 12, highlighting their practical application in PDT.

pH-activatable PDT. Given the pH-reversible ISC, PE5 was further utilized as a smart organic PS for the proof-of-concept application in pH-activatable PDT (Figure S13). It is theoretically conceivable that PE5 can only produce ¹O₂ in tumor microenvironment (acid) due to the switch-on of ISC at pH 6.0. As anticipated, characteristic ¹O₂ emission of PE5 at 1270 nm demonstrated its pH-activatable ¹O₂ generation (Figure 5c). The ¹O₂ quantum yield (Figure S14) of PE5 was calculated to be 48% at pH 6.0 and 5% in a neutral environment (pH = 7.4). We stimulated the tumor microenvironment by adjusting the pH value of a culture solution.^[19] Intracellular ¹O₂ imaging in Figure 5d demonstrated the pH-activatable ¹O₂ of PE5. In contrast, commercial PS, TMPyP₄, exhibited undifferentiated $^{1}O_{2}$ generation, which causes unwanted damage to healthy cells or tissues. Finally, the in vitro PDT effect of PE5 was evaluated by assessing the cellular phototoxicity, in which green-emissive calcein AM (living cell) and red-emissive propidium iodide (PI, dead cell) cellular viability kit was used to distinguish the dead cells from the live cells (Figure 5e).[8b, 20] Compared with the unselective damage of TMPyP₄, PE5 possesses outstanding selectivity for the potential application in more precise photodynamic therapy of tumor cells. We would like to mention here that the application of PE5 to PDT in vivo may be limited by the fact that the excitation wavelength does not fall into the biological transparency window (750-900 nm). However, there are many plausible ways to overcome this hindrance via, for instance, using the upconverting nanophosphorsor even in situ photon upconversion in tissue and two-photon excitation in nearinfrared region.[20-21]

Conclusion

We have presented experimental demonstration and theoretical verification of CBT-enhanced ISC in *p*-phenyleneethynylenebased POMs, which not only reveals a concise yet reliable approach to design novel POMs with high Φ_{ISC} but also enables a deeper understanding of ISC switchability. Moreover, easily-tuneable ISC not only allows an advanced PDT paradigm with precision not currently achievable by available PS, but also opens up fascinating opportunities for triplet-state-related applications such as in switchable photochemical synthesis.

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Conflict of interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

A strategy to obtain reversible switching of ISC in a new class of organic small molecular photosensitizers by stimuli initiated twisting of conjugated backbone for smart photodynamic therapy.



Wenbo Hu, Tingchao He, Hui Zhao, Haojie Tao, Runfeng Chen, Lu Jin, Junzi Li, Quli Fan,*Wei Huang,* Alexander Baev, and Paras N. Prasad*

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Stimuli Responsive Reversible Switching of Intersystem Crossing in Pure Organic Material for Smart Photodynamic Therapy