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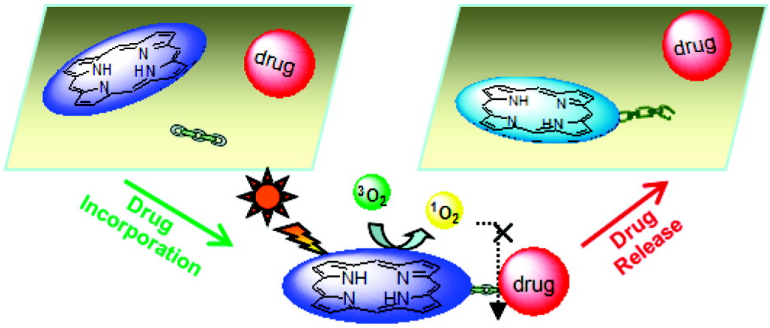

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Site-Specific Prodrug Release Using Visible Light

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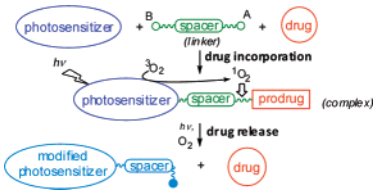
Prodrug approaches are widely used in drug discovery, and the release of the parent drugs is generally through enzymatic activation and can be site-specific when unique activating enzymes and appropriate chemical environment are present at the target site.[1] An external and nonenzymatic activation providing more direct controls over the course of drug release would be attractive. Herein, we report a novel site-specific prodrug system, in which visible light is employed to trigger drug release.

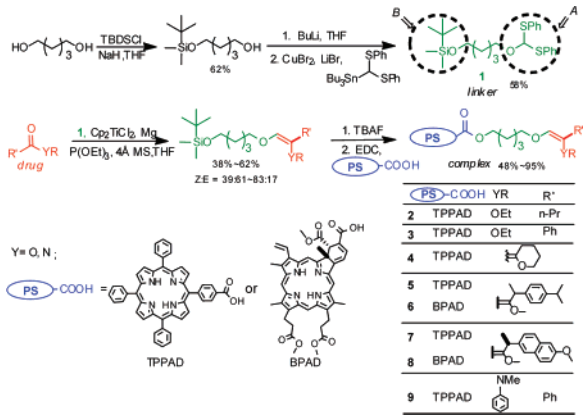
UV light triggerable prodrugs have been reported.[2] However, the poor tissue-penetrating nature of UV light, less than 1 mm, hampers their clinical utility. In fact, only visible light between 650 to 800 nm can penetrate tissue effectively, and some photosensitizers with a strong absorption band within this range have been developed as photomedicines using photodynamic therapy (PDT).[3] The chemical basis of PDT relates to the ability of the visible-light-activated photosensitization to convert normal triplet oxygen into singlet oxygen, which reacts with various biomolecules to cause cell modification or death.[3] Taking advantage of the reactivity of singlet oxygen, especially its [2 + 2] cycloaddition with double bonds to ultimately give carbonyl fragments via a dioxetane intermediate,[4] Breslow and co-workers have developed photocleavable cyclodextrin carriers for photosensitizers.[5] Using the similar photosensitization−singlet oxygenation−dioxetane decomposition trilogy, we envisioned that a "photodynamic" prodrug system could be engineered to release drugs bearing carbonyl functionalities.

In our system, a drug bearing a carbonyl group is incorporated onto the periphery of a photosensitizer, by a linker, to furnish a sensitizer−drug complex. The carbonyl group of the drug becomes part of the double bond linkage. After systemic administration, selective irradiation at the diseased site by visible light triggers the photosensitizing moiety of the local complex to generate singlet oxygen, which then migrates and oxidatively cleaves the olefin linkage to release the drug (Scheme 1). Due to the fact that the [2 + 2] cycloaddition generally competes ineffectively with the "ene" reaction and the [4 + 2] cycloaddition in singlet oxygenation of alkenes,[6] our major challenge was the elaboration of an olefin linkage to ensure the desired chemoselectivity during photooxygenation. Highly electron-rich alkenes, such as those heavily substituted by hetero groups, have been reported to favor the [2 + 2] mode.[7,8] Furthermore, hetero substituents tend to direct the attack of the singlet oxygen to the side of the double bond, a phenomenon known as the "cis-directing effect",[9] which can be used to secure the [2 + 2] selectivity if that side of the olefin lacks an abstractable allylic hydrogen. Based on these considerations, a 1,2-dihetero-substituted alkene, preferably in Z-configuration, presents itself as an ideal olefin linkage for our system. These species can be readily generated from esters or amides by a recently reported alkoxymethylenation methodology using a titanium−carbene complex.[10] In addition, Steglich esterification[11] provides a facile and mild way to attach the resulting prodrug module to photosensitizers bearing a carboxyl group.

Scheme 1. General Diagram of Drug Incorporation and Release



Scheme 2. Synthesis of Linker and Photosensitizer−Drug Complexes



A linker was designed to have functional groups (**A** and **B**) at either end of a spacer arm (Scheme 1). **A** is a dithioorthoformate to alkoxymethylenate carbonyl-bearing drugs, while **B** is a silyl-protected hydroxyl to esterify carboxyl-bearing photosensitizers. Simple alkyl chains or complex structures like steroids can be used as spacers to fine-tune the pharmacokinetic (PK) profile of the complexes.

As proof-of-principle, linker **1** was readily prepared by a three-step synthesis from 1,5-pentandiol (Scheme 2). Simple esters (aliphatic, aromatic and lactone) and amides as drug mimics and methyl esters of NSAIDs (ibuprofen and naproxen) were connected with photosensitizers of a tetraphenylporphyrin monoacid derivative (TPPAD) or benzophenylporphyrin monoacid derivative (BPAD, verteporfin analogue) to give complexes **2** to **9**, comprising both *Z*- and *E*-isomers (Scheme 2).

Photoirradiation of the final complexes was carried out in NMR tubes at room temperature using filtered visible light. Progress of the reactions was monitored and quantified by NMR and GC with internal standardization. Since dioxetanes decompose instantly at the injection temperature (220 °C), GC offers the advantage of showing the total amount of releasable drug from the complex. The step-by-step NMR spectra of the photoirradiation show the rapid decay of the starting complex, accompanied by the increase of the released drug and the remaining dioxetane. Signals of the porphyrin backbone are barely changed as the photooxygenation took place

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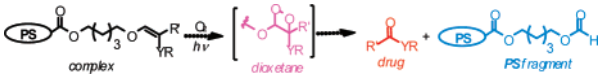
Table 1. Visible-Light-Triggered Drug Release



entry[a]	complex	solvent	concn (mM)	time (min)	yield by NMR[b] (%)	yield by GC[c] (%)
1	**2Z**	C_6D_6	7	4	93	94
2	**2Z**	$CDCl_3$	3	3	91	>95
3	**2Z**	$CDCl_3/CD_3OD = 4:1$	4	3	93	>95
4	**2Z**	CD_3COCD_3	4	8	>95	>95
5[d]	**2Z**	CD_3COCD_3	5	60	>95	>95
6	**3Z**	C_6D_6	3	1	>95	91
7	**4Z**	C_6D_6	10	3	94	90
8	**5Z**	C_6D_6	15	2.5	92	>95
9	**6Z**	C_6D_6	4	6	94	>95
10	**7Z**	C_6D_6	8	7	88	>95
11	**8Z**	C_6D_6	7	3	>95	86
12	**2E**	$CDCl_3$	2	1	35[e]	33
13	**9**[f]	C_6D_6	8	5	>95	88

[a] All the experiments were carried out at room temperature, and yields are based on conversions ≥ 95%. [b]Yield of the total [2 + 2] cycloaddition products. [c]Yield of total releasable esters or amides. [d]DABCO (6 equiv) was added. [e]"ene" products were generated in 56% yield. [f]A $Z/E = 4$:1 mixture was used as starting materials.

exclusively on the side chain, leaving the chromophore intact. The dioxetane intermediate was confirmed by ESI-MS.

The high yields of the visible-light-triggered drug release were solvent-independent, as evident by the photooxygenation of **2Z** in solvents of varied polarity (Table 1, entries 1 to 4). The involvement of singlet oxygen in drug release was confirmed as the progression of the photooxygenation of **2Z** in deuterated acetone was severely hampered when 1,4-diazabicyclo[2.2.2]octane (DABCO), a singlet oxygen quencher, was added (entry 5). Quantitative and rapid releases of ethyl benzoate, δ-valerolactone, methyl esters of ibuprofen, and naproxen were observed in the photooxygenation of **3Z** to **8Z** (entries 6 to 11). It is remarkable that the competing "ene" reaction and the [4 + 2] cycloaddition were completely suppressed in these reactions. The equal efficiency of drug release from either TPPAD or BPAD based complexes indicated the choice of photosensitizer can be flexible. It is noteworthy that even though some dioxetane intermediates persisted immediately after the end of the photooxygenation, they completely decomposed within hours at room temperature. In fact, the simultaneous and complete dioxetane cleavage for drug release *in vivo* would be expected, due to the ubiquitous presence of amines and trace metals in human tissues, which are reported to catalyze the dioxetane decomposition.[12] Unfortunately, the "ene" reaction predominated the photooxygenation of **2E**, giving the [2 + 2] cycloaddition products in only 35% yield (entry 12), which is in direct contrast to the complete [2 + 2] selectivity of the precedent singlet oxygenation of some *E*-configurated enediol ethers.[7] The dramatic reactivity difference between **2Z** and **2E** is attributed to the different results of the cis-directing effect of the alkoxy substituents: for the *Z*-isomer, two same-side alkoxy groups "lock" the attack of singlet oxygen to their side of the double bond as expected, while, for the E-isomer, each side of the double bond has an alkoxy group and the extra alkyl group at the disubstituted side provides an additional directing effect for the incoming singlet oxygen, leading to the predominant "ene" reaction. Clearly, the HOMO−LUMO interaction between singlet oxygen and the olefin substitutents played a more decisive role than the electron richness of the olefin in determining the chemoselectivity of these reactions. Interestingly, the photooxygenation of a $Z/E = 4:1$ diastereomer mixture of **9** showed complete release of amide from both *Z*- and *E*-isomers, although the latter was more sluggish (entry 13). This could be due to the pronounced activating effect of the enamino nitrogen. Our results indicated that a Z-configured complex should be chosen for future clinical applications.

In conclusion, a proof-of-principle photodynamic prodrug system has been established, which allows for rapid drug incorporation and highly efficient drug release upon visible light irradiation. The advantages of this system are multifold: (1) the external, light-triggered activation would provide superior controls over the location and the onset of drug release; (2) the system itself is sufficiently flexible that both the linker and the photosensitizer can be rationally modified or functionalized; (3) as shown here, well-established photosensitizers such as verteporfin can be directly utilized so that their PK and clinical profiles can serve as good reference points for new photosensitizer−drug complexes; (4) since esters and amides provide some of the most common prodrug derivatives, our system provides a solution to deliver these prodrugs site-specifically; (5) from a PDT perspective, bifunctional drugs can be developed to have the complementary drug simultaneously released at the site where PDT is performed, to bring about a synergistic therapeutic effect.

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Supporting Information Available: Experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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