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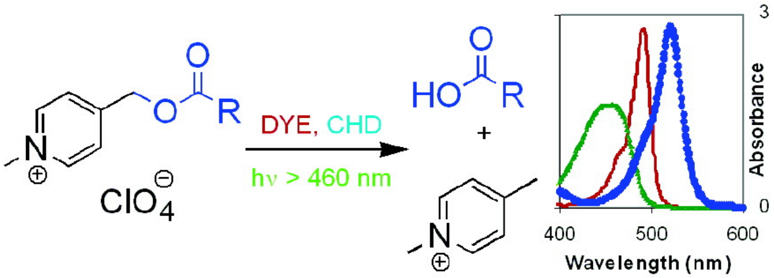

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Photorelease of Carboxylic Acids, Amino Acids, and Phosphates from *N*-Alkylpicolinium Esters Using Photosensitization by High Wavelength Laser Dyes

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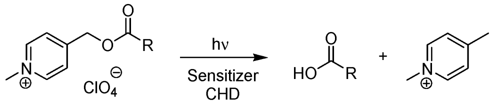
The development of selective bond-breaking reactions that are triggered by the absorption of a photon is a fundamental goal of photochemistry. These reactions also have many practical applications. For example, photolithographic techniques create nanometer-scale images on a surface by selectively breaking bonds in a photoinitiator molecule, creating free radicals or cations. These intermediates, in turn, react in a way to modify the solubility of a photoresist coating.[1] The photochemical generation of free radicals has also been exploited in synthetic chemistry.[2,3] An additional family of applications utilizes photochemical bond breaking with the goal of releasing stable molecules, rather than reactive intermediates. In synthetic chemistry, such systems are referred to as “photoreleasable protecting groups” (PRPGs),[4] and in biophysical applications they are referred to as “caged molecules” (e.g., caged ATP or caged neurotransmitters).[5,6]

Widely used PRPGs, including ortho-nitrobenzyl alcohol derivatives,[7] benzoin esters,[8] phenacyl groups,[9] and aryl ketones,[10−12] generally require ultraviolet (UV) light (<420 nm) for activation. This requirement has both practical and fundamental limitations. As a practical matter, photolysis with UV light requires expensive glassware, specialized light sources, and additional safety precautions. As a fundamental matter, UV light is limiting, because these wavelengths are often absorbed by the protected molecule and/or the matrix. Thus, one challenge is to develop wavelength-tunable PRPGs and, specifically, to develop photorelease technology that utilizes visible light.[13] In a series of articles we have advocated the design of PRPGs that are activated through an electron transfer from a photosensitizer molecule[14,15] or tethered chromophore.[16] In this way, it is possible to decouple the light absorption step from the photorelease chemistry, making it possible to independently optimize both. Our most recent efforts involved electron-transfer reactions from either a photosensitizer or a reduced mediator to *N*-alkyl-4-picolinium esters (**1**) (Scheme 1). Herein we are pleased to report a system capable of efficiently releasing carboxylic acids, amino acids, and phosphates using high wavelength visible light.

Scheme 1. Photofragmentation of *N*-Alkyl-4-picolinium Esters



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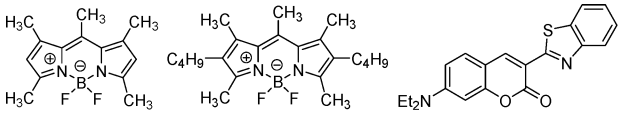
The properties of the *N*-alkyl-4-picolinium (NAP) protecting group have been described earlier.[17] The corresponding alcohol can be coupled to carboxylic acids, protected amino acids, and phosphates using standard ester synthesis techniques, which are described in detail in the Supporting Information. High-wavelength photorelease of carboxylic acids (**1a**, **1b**), *N*-carbonylbenzyloxy (cbz)-protected amino acids (**1c**, **1d**), and diethyl phosphate (**1e**) was effected through tungsten lamp (>400 nm, 300 W) irradiation of the NAP esters (CH_3CN solution), the radical scavenger 1,4-cyclohexadiene (CHD, 1.7 M),[17] and a visible light-absorbing photosensitizer. These solutions were purged with N_2, irradiated for the prescribed periods of time, and then analyzed by ^{1}H NMR spectroscopy. The protected substrates are released in good, and in most cases nearly quantitative, yields, based on converted **1**.

Chart 1 illustrates the photosensitizers employed in these reactions. The dyes, PM 546 and PM 597, are pyrromethene dyes that were originally developed for use in lasers.[18,19] Consequently, these chromophores have strong, sharp absorption bands in the visible region of the spectrum (Table 1). Coumarin 6 is also a laser dye.[20]

Chart 1. Structures of PM 546, PM 597, and Coumarin 6



PM 546 (**4**) PM 597 (**5**) Coumarin 6 (**6**)

Table 1. Deprotection Yields of NAP Esters

dye	ester	R	time (min)[a]	% acid formed[b,c]	% ester consumed[b,c]
4	**1a**	$CH_2C_6H_5$	5	92 (80)[d]	90 (100)[d]
4	**1b**	$CH(C_6H_5)_2$	5	100 (96)[d]	100 (100)[d]
4	**1c**	*N*-cbz-glycine	5	77	78
4	**1d**	*N*-cbz-serine	5	100	100
4	**1e**	$PO(OCH_2CH_3)_2$	20	97	100
5	**1a**	$CH_2C_6H_5$	20	87	96
5	**1b**	$CH(C_6H_5)_2$	20	84	80
5	**1c**	*N*-cbz-glycine	20	87	87
5	**1d**	*N*-cbz-serine	20	100	100
5	**1e**	$PO(OCH_2CH_3)_2$	60	100	100
6	**1a**	$CH_2C_6H_5$	20	100	100
6	**1b**	$CH(C_6H_5)_2$	20	100	100
6	**1c**	*N*-cbz-glycine	20	76	75
6	**1d**	*N*-cbz-serine	20	97	100
6	**1e**	$PO(OCH_2CH_3)_2$	60	100	100

[a] Photolysis solution was 2.5−3.0 mL of a 3.5 mM solution of ester and sensitizer, 1.7 M CHD in CH_3CN. [b] Yields were determined by ^{1}H NMR integration of the α-C−H protons relative to an internal standard. [c] Estimated error ±5%. [d] Isolated yields from preparative experiments.

The visible light photorelease follows the same mechanism we characterized earlier for several UV-absorbing sensitizers (Scheme 2). This is supported by three observations. First, the oxidation potentials (E_{ox}) and the singlet state energies of the three sensitizers (E_{oo}, in electron volts) along with the reduction potential for the picolinium esters ($E_{red} = -1.1$ V) can be applied to eq 1 to estimate the driving force (ΔG_{CT}, in kilocalories per mole) for the charge-transfer step (Table 2). In each case, an exergonic electron-transfer reaction is predicted in CH_3CN.

$$\Delta G_{CT} = 23.06(E_{ox} - E_{red} - E_{oo} + 0.06) \qquad (1)$$

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Scheme 2. Photorelease Mechanism

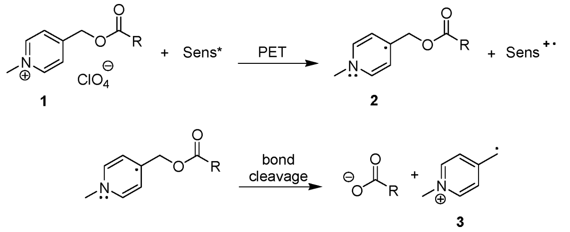

Table 2. Photophysical Parameters of the Photosenstizers[21−24]

dye	E_{ox} (V)	E_{00} (V)	λ_{max} (nm)	ϵ ($M^{-1}cm^{-1}$)	τ (ns)	k_q ($10^9 M^{-1} s^{-1}$)	$\Phi\epsilon$ ($M^{-1} cm^{-1}$)
4	1.22	2.50	493	81 000	5.6	2.8	4500
5	1.01	2.32	525	68 000	4.2	1.3	1700
6	1.02	2.65	467	54 000	3.1	7.6	630

Second, the NAP esters react rapidly with the singlet states of the three sensitizers. This was established by fluorescence quenching experiments using NAP ester **1a**. Stern−Volmer analysis of these data, along with literature values for the singlet lifetimes of the dyes, gives rate constants $k_q > 10^9$ M^{-1} s^{-1} (Table 2).

Third, laser flash photolysis (LFP) experiments show the formation of the expected radical intermediates. Figure 1 illustrates such an experiment carried out with PM 546 and ester **1a**. Immediately following the laser pulse (355 nm, 10 ns, 10−20 mJ), we detect a sharp transient absorption band at ca. 410 nm, along with a negative signal corresponding to photobleaching of the dye. We also generated the cation radical of PM 546 by using pyromellitic dianhydride as the acceptor and observed a transient signal that was nearly identical to that derived from **1a**, along with the known signal for the acceptor anion radical at 660 nm.[20] LFP experiments with PM 597 give similar results (in this case the cation radical absorbs at 420 nm). Previous LFP experiments on similar PM dyes gave similar results.[21] We were unable to detect a signal that could be assigned to the coumarin 6 cation radical. It is possible that this species does not possess an absorption band that is sufficiently distinct from the starting materials.

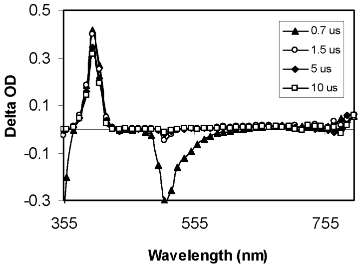

Figure 1. Transient absorption spectra of PM 546 with **1a**.

The effective rate of a photorelease system can be characterized by $\Phi\epsilon$, which is the product of the quantum yield for photorelease and the molar absorptivity of the light absorbing species. For many of the nitrobenzyl-based systems, $\Phi\epsilon$ values range from 95 to 300, depending on the derivative employed.[25] A recent report demonstrates that this can be increased to ca. 2500 using UV-absorbing triplet sensitizers.[25] We carried out preliminary quantum yield measurements for the present system using **1a** at 3.5 mM in CH_3CN with 1.5 M CHD. These solutions were illuminated, using a Xe-lamp/monochromator/radiometer system, at the absorption maximum of the dye. The $\Phi\epsilon$ values derived from these experiments (630−4500 M^{-1} cm^{-1}, depending on the dye) are comparable to, and in the case of PM 546 exceed, those previously reported. It should be emphasized that these values were obtained at a single concentration of the acceptor and are thus limited by the efficiency of singlet quenching by **1**. We anticipate that a substantial increase in these rates can be obtained if the dyes were covalently tethered to the NAP group or if the photolyses were carried out in constrained media where the effective concentration of the quencher is higher. These approaches are currently being explored.

Acknowledgment. We would like to thank the National Science Foundation for their financial support of this work and Prof. N. Blough for assistance with the quantum yield determinations.

Supporting Information Available: Transient absorption spectra, fluorescence data, synthesis, and characterization data for esters **1a**−**e** data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reiser, A. In *Photoreactive Polymers: The Science and Technology of Resists*; Wiley-Interscience: New York, 1989; pp 178−225.
(2) Yoon, U. C.; Jin, Y. X.; Oh, S. W.; Park, C. H.; Park, J. H.; Campana, C. F.; Cai, X.; Duesler, E. N.; Mariano, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 10664−10671.
(3) Griesbeck, A. G.; Heinrich, T.; Oelgemoller, M.; Lex, J.; Molis, A. *J. Am. Chem. Soc.* **2002**, *124*, 10972−10973.
(4) Pellicciolli, A. P.; Wirz, J. *Photochem. Photobiol. Sci.* **2002**, 441−458.
(5) Il'ichev, Y. V.; Schwoerer, M. A.; Wirz, J. *J. Am. Chem. Soc.* **2004**, *126*, 4581−4595.
(6) Corrie, J. E. T.; Trentham, D. R. In *Caged Nucleotides and Neurotransmitters*; Morrison, H., Ed.; Wiley: New York, 1993; Vol. 2, pp 243−305.
(7) Misra, A.; Tripathi, S.; Misra, K. *Ind. J. Chem., Sect. B* **2002**, *41*, 1454−1459.
(8) Pirrung, M. C.; Fallon, L.; Lever, D. C.; Shuey, S. W. *J. Org. Chem.* **1996**, *61*, 2129−2136.
(9) Givens, R. S.; Weber, J. F. W.; Conrad, P. G., II; Orosz, G.; Donahue, S. L.; Thayer, S. A. *J. Am. Chem. Soc.* **2000**, *122*, 2687−2697.
(10) Atemnkeng, W. N.; Louisiana, L. D., II; Yong, P. K.; Vottero, B.; Banerjee, A. *Org. Lett.* **2003**, *5*, 4469−4471.
(11) Pika, J.; Konosonoks, A.; Robinson, R. M.; Singh, P. N. D.; Gudmundsdottir, A. D. *J. Org. Chem.* **2003**, *68*, 1964−1972.
(12) Literák, J.; Wirz, J.; Klán, P. *Photochem. Photobiol. Sci.* **2005**, *4*, 43−46.
(13) Blanc, A.; Bochet, C. G. *J. Org. Chem.* **2002**, *67*, 5567−5577.
(14) Banerjee, A.; Falvey, D. E. *J. Org. Chem.* **1997**, *62*, 6245−6251.
(15) Banerjee, A.; Lee, K.; Falvey, D. E. *Tetrahedron* **1999**, *55*, 12699−12710.
(16) Lee, K.; Falvey, D. E. *J. Am. Chem. Soc.* **2000**, *122*, 9361−9366.
(17) Sundararajan, C.; Falvey, D. E. *J. Org. Chem.* **2004**, *69*, 5547−5554.
(18) Pavlopoulos, T.; Boyer, J. H. *Proc. SPIE- Int. Soc. Opt. Eng.* **1994**, *2115*, 231−239.
(19) Pavlopoulos, T.; Boyer, J. H.; Thangaraj, K.; Sathyamoorthi, G.; Shah, M. P.; Soong, M. L. *Appl. Opt.* **1992**, *31*, 7089−7094.
(20) Drexhage, K. D. *Dye Lasers*; Springer-Verlag: New York, 1977; Vol. 1.
(21) Jones, G., II; Kumar, S.; Klueva, O.; Pacheco, D. *J. Phys. Chem. A* **2003**, *107*, 8429−8434.
(22) Lai, R. Y.; Bard, A. J. *J. Phys. Chem. B* **2003**, *107*, 5036−5042.
(23) Jones, G., II; Griffin, S. F.; Choi, C.-y.; Bergmark, W. R. *J. Org. Chem.* **1984**, *49*, 2705−2708.
(24) Gould, I. R.; Shukla, D.; Giesen, D.; Farid, S. *Helv. Chim. Acta* **2001**, *84*, 2796−2812.
(25) Wöll, D.; Walbert, S.; Stengele, K.-P.; Albert, T. J.; Richmond, T.; Norton, J.; Singer, M.; Green, R. D.; Pfleiderer, W.; Steiner, U. E. *Helv. Chim. Acta* **2004**, *87*, 28−45.

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