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Photolytic Release of Carboxylic Acids Using Linked Donor–Acceptor Molecules: Direct versus Mediated Photoinduced Electron Transfer to *N*-Alkyl-4-picolinium Esters

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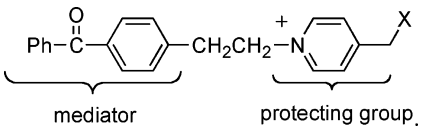
ABSTRACT



Efficient photorelease ($\Phi = 0.7$) of carboxylic acids is achieved with a covalently linked mediator (benzophenone) protecting group (*N*-alkyl-4-picolinium ester) molecule. The mechanism involves initial photoreduction of the mediator, followed by rapid electron transfer to the protecting group.

The controlled photochemical release of functional molecules is a general goal in photochemistry. In the past decade a series of useful molecular systems known as "phototriggers", "photoremovable protecting groups" (PRPGs), or "caged molecules" have been developed.[1] In these systems a functional molecule is deactivated through covalent attachment to a protecting group. The latter is then released at a specified time and located through UV or visible irradiation. Successful PRPGs include various ester derivatives of 2-nitrobenzyl alcohol,[2] benzoin,[3] and phenacyl alcohol,[4] as well as various aryl ketone derivatives.[5] Such PRPGs have been used in diverse applications such as multistep synthesis,[1b] the fabrication of combinatorial libraries,[6] time-resolved X-ray crystallographic studies of enzymatic reactions,[7] and the temporal or spatial manipulation of cellular process.[8] Despite this remarkable progress, several problems remain to be addressed. One of these is controlling the light wavelengths required for photorelease. With most PRPGs, the triggering photon is absorbed directly by the protecting

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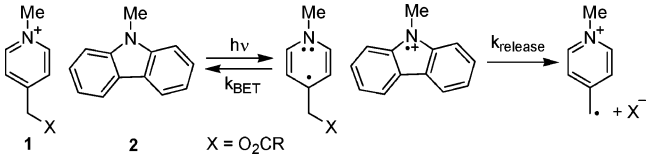
group and the requisite wavelengths are determined by its chromophore. As a rule it is difficult to extend the conjugation of PRPG chromophores without adversely affecting the bond cleavage rates and selectivity, although some recent progress has been reported.[9]

Our approach to the issue of wavelength control has been to decouple the light absorption and bond-breaking steps in PRPGs through the use of electron-transfer sensitization.[10] In these systems, light is absorbed by an electron-donor sensitizer. The excited-state sensitizer then encounters and transfers an electron to the protecting group, triggering a bond-breaking event, releasing the protected molecule. It was demonstrated that phenacyl esters could be used in this way.[11] Photoinduced one-electron reduction with a variety of sensitizers was shown to promote rapid and high yield release of carboxylic acids. However the very negative reduction potential (ca. −2.2 V vs SCE) of the phenacyl group limits the range of sensitizers that can be employed. Subsequent efforts have focused on the *N*-alkyl-4-picolinium esters (NAP) (**1**, Scheme 1).[12] The NAP group is reduced at less

Scheme 1. Release of Carboxylate Ions from NAP Group



negative potentials (−1.1 V vs SCE) than the phenacyl group, allowing activation by a wider variety of photoreductants. In fact a recent report shows that the NAP group can be activated using high-wavelength laser dyes.[13]

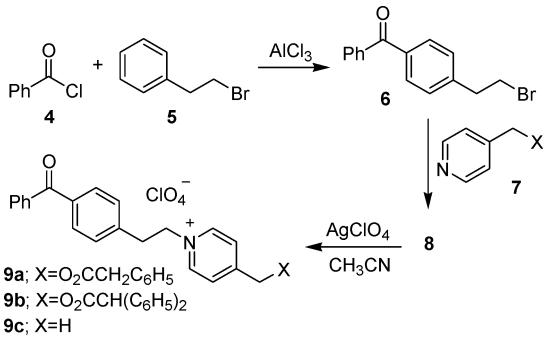
One limitation imposed by the sensitization approach is that the quantum yields for deprotection depend on the concentration of the NAP ester. This is because the bimolecular electron transfer step competes with unimolecular relaxation of the excited sensitizer. A potential solution to this problem is to covalently tether the sensitizer to the protecting group. However, the problem then becomes competition between back electron transfer (BET) and the desired bond-breaking step. In fact, this problem was encountered in our attempts to create a useful PRPG by linking an anthracene donor to a phenacyl ester group. This PRPG was found to be stable to prolonged irradiation, despite the fact that unlinked analogues of this system release carboxylates with high efficiencies.[14]

Herein we report photochemical studies on linked donor−NAP molecules. Attempts to achieve efficient photorelease with a simple sensitizer, 9-alkylcarbazole, are unsuccessful. It is argued that this is due to rapid BET. However, efficient photorelease is achieved using mediated electron transfer. In particular, it is shown that a covalently tethered benzophenone chromophore can, upon photoexcitation, abstract an electron from an external donor. The resulting benzophenone anion radical then transfers an electron to the NAP group, triggering release of a carboxylate ion.

Mediated electron transfer (also called electron-transfer cosensitization)[15] has been shown to substantially increase the quantum yields of a variety of PET-initiated processes.[16] In our embodiment of this scheme, initial electron transfer occurs between a donor and an excited-state mediator. The reduced mediator then relays an electron to the substrate in a subsequent ground-state electron-transfer process. This approach avoids the problem of having a rapid, exergonic back electron transfer reaction compete with the desired bond scission process.

Scheme 2 shows the linked mediator−acceptor systems that we studied. Benzophenone (BP) was chosen as the

Scheme 2. Synthesis of Linked Mediator−NAP Molecule



mediator for the following reasons. (1) Its reduction potential (−1.68 V) is more negative than that of the picolinium esters.[17] Thus electron transfer is expected to occur rapidly and irreversibly to the acceptor. (2) BP is a very well characterized chromophore with a relatively high wavelength absorption maximum (380 nm). (3) BP undergoes rapid intersystem crossing. This means that the geminate radical ion pair formed following electron abstraction from the donor will be in the triplet state as well. That, in turn, should reduce BET and make the overall photorelease process more efficient.[18]

The linked mediator−acceptor synthesis is fairly straightforward (Scheme 2). Friedel−Crafts acylation of 1-phenyl-

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2-bromoethane **5** forms 4-(2-bromoethyl)benzophenone **6**. The latter is combined with the appropriate 4-picolylester **7** to form the linked system **9**. Three of these ions were synthesized: a phenylacetate ester (**9a**), a diphenylacetate ester (**9b**), and a nonreactive system having no leaving group (**9c**).

Results from photolysis of **9a** and **9b** are shown in Table 1. In these experiments the linked esters were dissolved in

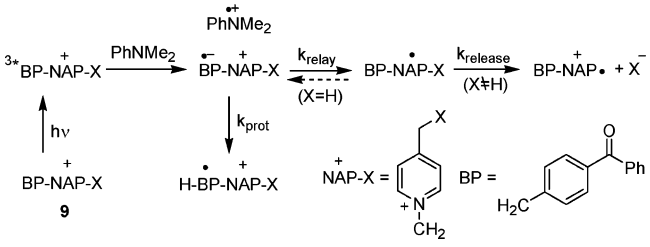
Table 1. Photolysis of Mediator−NAP Molecules with DMA

linked ester	conditions	% acid formed	% **9** consumed	% **9c** formed
9a	2 h, MeOH	70	76	
9b	2 h, MeOH	63	62	
9a	2 h, MeOH, CHD	41	46	40

CH_3OH along with an electron donor, *N.N*-dimethylaniline (DMA, 10−15 mM). These solutions were purged with N_2 and then irradiated with wavelengths >320 nm. The product mixtures were then analyzed by ^{1}H NMR spectroscopy. As shown in Table 1, the acids are formed cleanly and account for all, or nearly all, of the consumed esters. To confirm the identity of the product, photolysis of **9a** was carried out on a larger (3×) scale. The product, $PhCH_2CO_2H$, was isolated in pure form (73% yield), and its ^{1}H NMR spectrum was found to be indistinguishable from that of an authentic sample. With only DMA added, we could not identify any byproduct associated with the picolinium benzophenone portion of the molecule. However, when photolysis was carried out with a radical scavenger, 1,4-cyclohexadiene (CHD), quantitative yields of the expected byproduct **9c** were observed. For compound **9a** the quantum yield of acid release was determined using monochromatic irradiation at 380 ± 10 nm to be $\Phi = 0.72$.

The proposed mechanism, shown in Scheme 3, is supported by LFP experiments, as well as the product studies,

Scheme 3. Photorelease through Mediated Electron Transfer



and thermodynamic considerations described above. Figure 1a shows transient spectra taken following pulsed laser photolysis of **9b** with DMA in MeOH. The peak at 470 nm is assigned to the well-known absorption of the DMA cation radical. Not detected are the peaks for the H-bonded BP anion radical (640 nm) or the BP ketyl radical (545 nm).[19] Thus, we conclude that the relay step, in which an electron

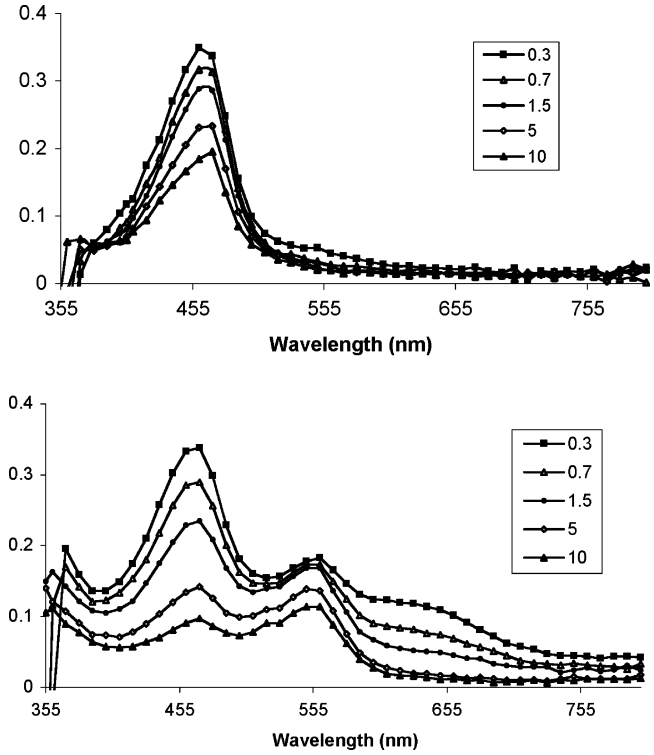


Figure 1. Transient absorption spectra from pulsed laser photolysis of **9a** (top) and **9c** (bottom) in MeOH with added DMA. Times indicated are in μs.

is transferred from the benzophenone anion radical to the NAP group, occurs too rapidly (<100 ns) to be observed with our instrument. Electron-transfer reactions between DMA and BP triplet state have been studied in some detail.[19] The geminate radical ion pair partitions between solvation, forming the ion radicals, and proton transfer, forming benzophenone ketyl radical. It is interesting to note that with **9a** and **b**, no ketyl radical is detected. This implies that relay electron transfer and the subsequent C−O bond scission occur more rapidly than geminate proton transfer. Although rate of this process in CH_3OH has not been characterized, rates of ca. 5×10^8 s^{-1} have been determined in other polar solvents.[20]

The nonreactive model system, **9c**, shows different behavior. In this case, LFP results in the formation of the $DMA^{+\bullet}$, along with $BP^{-\bullet}$ and ketyl radical. Indeed, the transient spectra immediately following LFP of **9c** are very similar to those from unlinked DMA/BP. In the case of **9c**, each of these transients decay in a non-first-order way and each shows a different half-life. The BP anion radical decays with the shortest half-life (0.61 μs), the DMA cation radical decays with a somewhat longer half-life (2.7 μs), and $BPH^{\bullet}$ shows a still longer half-life (5.6 μs). There are two reasons why the reduced BP intermediates are longer lived with this

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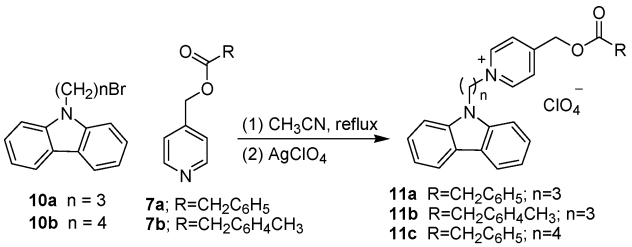
model system. First, simple picolinium ions are more difficult to reduce than the corresponding NAP esters, presumably because of the inductive effect of the acyloxy substituent.[12] Thus relay electron transfer is expected to be less exergonic in this system and perhaps reversible (the redox potentials were characterized in CH_3CN rather than CH_3OH). Second, in the esters, the relay electron transfer is coupled to an irreversible C−O bond heterolysis. On the other hand, with the model system, proton transfer from DMA cation radical to the $BP^{-\bullet}$ constitutes the only irreversible process. A more detailed kinetic study of these reactions is underway.

Also examined were linked systems, designed to undergo direct photoinduced electron transfer. As shown in Scheme 4, the electron donor, carbazole, was covalently tethered to

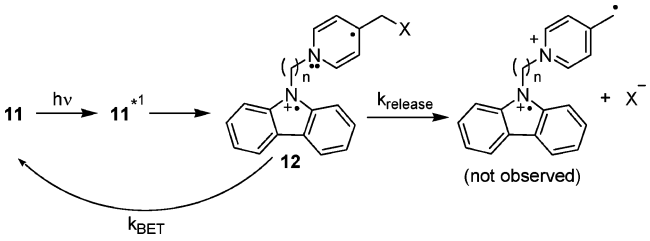
Scheme 4. Synthesis of Linked Donor−NAP Molecule



the NAP group. These include two propyl-linked esters, one of phenylacetic acid **11a** and one derived from 4-tolylacetic acid **11b**. A butyl-linked phenylacetic ester, **11c**, was also synthesized. These compounds were all prepared by nucleophilic substitutions of carbazole on 1,3-dibromopropane or 1,4-dibromobutane, followed by coupling of the resulting compound (**10**) with a 4-picolyl ester (**7**). These bromide salts were converted to the ClO_4^- salts (**11**) by treatment with $AgClO_4$.

Although the unlinked chromophore, 9-methylcarbazole, shows very efficient fluorescence, the linked systems **11a−c** show no measurable fluorescent emission. The free energy change for the excited state electron transfer is expected to be significantly exergonic ($\Delta G_{CT} = -33.2$).[12] On this basis, we infer that the desired intramolecular electron-transfer process occurs very rapidly. On the other hand, prolonged photolysis (8 h with a 300 W Hg lamp) of esters **11a−c** results in no measurable release of the corresponding acids. In contrast, analogous unlinked systems (e.g., Scheme 1)

Scheme 5. No Bond Scission in Donor−NAP Molecule



react with high efficiencies under these conditions.[12] LFP experiments on **11a−c** show none of the anticipated charge-transfer intermediates **12**, whereas the corresponding radical intermediates were easily detected in the unlinked cases.[12] Thus, we conclude that back electron transfer in **11** occurs much more rapidly than the C−O bond scission that would give the carboxylate anion. In the absence of any direct detection of the charge-transfer intermediates, it is difficult to estimate the rates of any of these processes. However, the lack of significant fluorescence from the linked systems and the fact that we could not detect reduced picolinium ion or carbazole cation radical by nanosecond LFP imply that both PET and BET are occurring on a subnanosecond time scale

These experiments emphasize the importance of addressing the issue of BET when designing linked donor−acceptor PRPGs. That **11b** would show rapid BET is, perhaps, unsurprising given that similar linked donor−acceptor molecules typically exhibit subnanosecond charge recombination lifetimes.[21] The successful and highly efficient photorelease with **9** illustrates the promise of using mediated electron transfer as a way of activating PRPGs, although practical applications have yet to be explored. In principle, this approach could be extended to visible light absorbing mediators.

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Supporting Information Available: Detailed procedures for synthesis of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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