ABSTRACT

Title of dissertation: *N*-METHYL-4-PICOLINIUM ESTERS AS PHOTOREMOVABLE PROTECTING GROUPS BASED ON PHOTOINDUCED ELECTRON TRANSFER

Chitra Sundararajan, Doctor of Philosophy, 2005

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The goal of this project is to develop an improved photoremovable protecting group (PRPG) for the carboxylate functionality that can be released using high wavelength light through a photoinduced electron transfer (PET) process.

The *N*-methyl-4-picolinium group has been demonstrated to be an efficient PRPG. Various carboxylic acids and amino acids as well as diethyl phosphate were released from their corresponding *N*-methyl-4-picolinium esters in high yields upon sensitized irradiation. The quantum yields for photorelease were also found to be satisfactory.

Some advantages of the picolinium esters over previous PRPGs include their aqueous solubility, ease of protection and removal, clean and fast release, harmless byproducts, and high reduction potential. This latter property is especially desirable as it allows for protection of carboxylic acids that can be easily reduced and also widens the

choice of photosensitizers and wavelengths of light used for deprotection. Several photosensitizers were shown to effect PET and the subsequent fragmentation of the picolinium esters.

High wavelength visible light sensitizers were also employed and successfully released the picolinium group. To our knowledge, this is the first report of high wavelength (450-525 nm) release of PRPGs using a PET process, and proceeding with high chemical and effective quantum yields.

In order to further improve the efficiency of this system by suppressing back electron transfer, a mediated relay electron transfer strategy was used to release the picolinium group. Two triplet sensitizers, benzophenone and xanthone, were found to effectively carry out a relay electron transfer to the picolinium esters and release the free substrates in high yields. The quantum yields of release were higher than in the direct sensitized case.

The successful release of picolinium esters by both direct and mediated electron transfer prompted us to study the corresponding covalently linked systems. Several carbazole linked picolinium esters failed to release the free acids upon photolysis. In the mediated case however, the benzophenone linked picolinium esters released the free acids efficiently.

N-METHYL-4-PICOLINIUM ESTERS AS PHOTOREMOVABLE PROTECTING GROUPS BASED ON PHOTOINDUCED ELECTRON TRANSFER

By

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List of Abbreviations

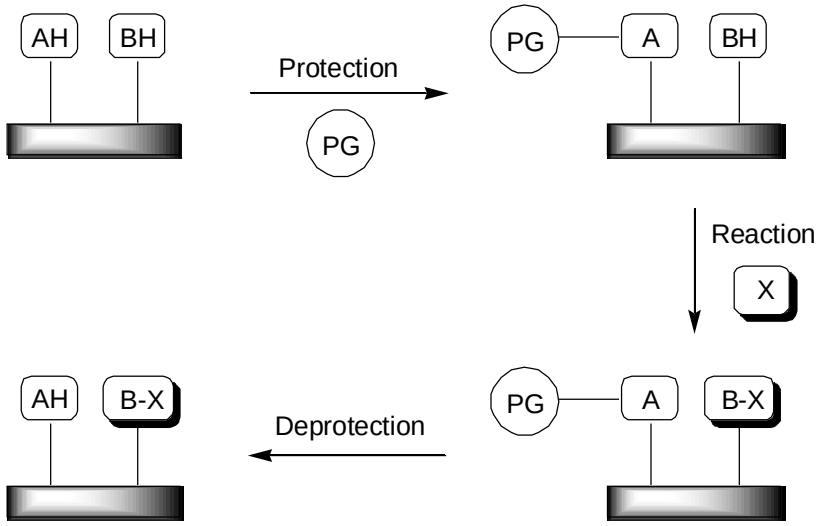
9-MC	9-Methyl carbazole
ATP	Adenosine triphosphate
BET	Back electron transfer
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
CH_3OH	Methanol
CV	Cyclic voltammetry
DCC	Dicyclohexylcarbodiimide
DMA	*N*,*N*-dimethylamine
DMF	Dimethyl formamide
DPA	9,10-Diphenylanthracene
EtOH	Ethanol
HMDS	Hexamethyldisiloxane
ISC	Intersystem crossing
LFP	Laser flash photolysis
Nd:YAG	Neodium yttrium aluminium garnet
NMR	Nuclear magnetic resonance
PET	Photoinduced electron transfer
PRPG	Photoremovable protecting group
RET	Relay electron transfer
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMB	*N*,*N*,*N*',*N*'-Tetramethylbenzidine
TPA	Triphenylamine
UV	Ultraviolet
hν	Light energy

Chapter 1. Photoremovable Protecting Groups

1.1 Introduction

Protecting group chemistry occupies an important niche in organic chemistry. As chemical applications become more advanced, it is necessary to have utmost control and selectivity in chemical reactions. Protecting groups allow such selectivity in organic molecules having more than one reactive site (Figure 1.1). The other reactive sites can be temporarily blocked while the chemical reaction occurs selectively at the desired location. Upon completion of the reaction, the reactive sites can be restored by removing the protecting groups through chemical, electrolytic or photolytic means.

Figure 1.1 Protecting groups in organic synthesis



An ideal protecting group must satisfy the following requirements: ease of synthesis of the protected molecule, stability towards reaction conditions, efficient and

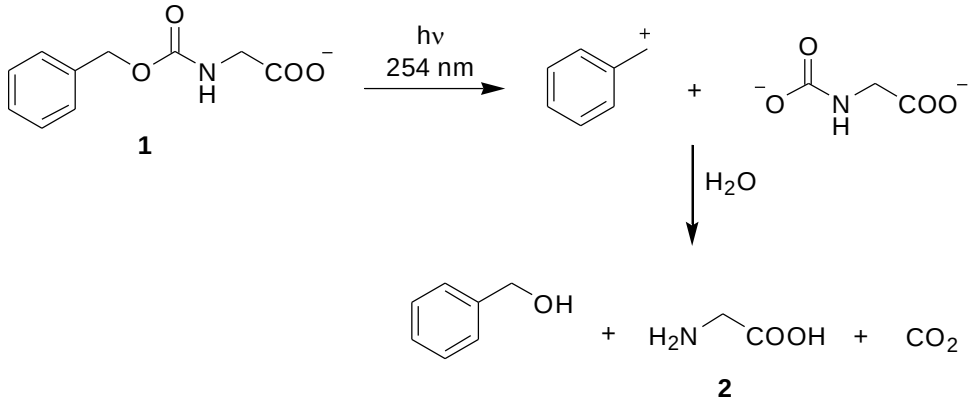
quantitative removal of the protecting group, formation of non-toxic and non-reactive byproducts, and facile separation of byproducts from the released molecule.

1.2 Photoremovable protecting groups

Photoremovable protecting groups are protecting groups that can be removed by exposure to light. These offer yet more control and specificity as light can be directed at specific sites (spatial control) and the light beam can be turned on and off as desired (temporal control). The energy of the beam can also be altered by using light of different wavelengths. There is also the added benefit of mild and neutral reaction conditions. Conventional protecting groups generally require harsh acidic or basic conditions for their removal which restricts their use to robust molecules. For more sensitive compounds, photoremovable protecting groups provide a better choice.

The very first photoremovable protecting group (PRPG) was discovered by J. A. Barltrop and P. Schofield in 1962. [1] They found that upon irradiation of benzyloxycarbonyl glycine **1** in a basic solution with light of 254 nm, the free amino acid glycine was released (Scheme 1.1).

Scheme 1.1 Photoremoval of benzyloxycarbonyl group



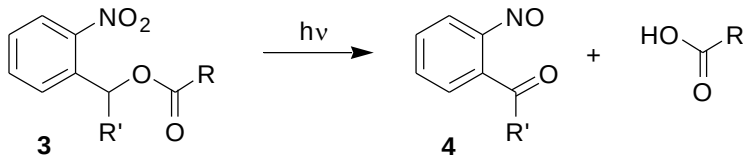
1 **2**

Since then, various photoremovable protecting groups have been developed for different functional groups and to cater to diverse requirements and applications. The properties desired in a PRPG are: (1) the protected molecule should be stable in the absence of light (2) the protecting group should absorb light at higher wavelengths than the substrate to avoid side reactions (3) the release of the substrate should be fast (4) the byproducts of the photorelease should be photoinert. There are several PRPGs which satisfy these criteria to different extents. The three most widely used PRPGs to date are based on *o*-nitrobenzyl derivatives, benzoin derivatives and phenacyl derivatives. The properties and photochemistry of these PRPGs will be discussed in detail in the following sections.

1.3 The *o*-nitrobenzyl group

Aromatic nitrocompounds having benzylic hydrogens *ortho* to the nitro group undergo a photochemical intramolecular rearrangement. This photoisomerisation reaction was used by Barltrop, Plant and Schofield in 1966 to develop the *o*-nitrobenzyl PRPG. [2]

Scheme 1.2 Photoremoval of *o*-nitrobenzyl group



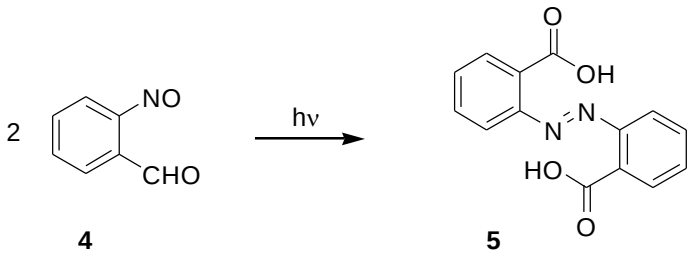
3 **4**

R' = H, Ph or $2\text{-}C_6H_5NO_2$

The initial study was carried out using 2-nitrobenzyl benzoate ($R=C_6H_5$; R'=H), and upon irradiation only 17% of benzoic acid was obtained (Scheme 1.2). The low yield was attributed to the transformation of the photoproduct, *o*-nitrosobenzaldehyde **4**, into

azobenzene 2, 2'-dicarboxylic acid **5** which acted as an internal light filter (Scheme 1.3). [3] This side-reaction was eliminated by adding carbonyl scavengers such as hydrazine or semicarbazide hydrochloride. Alternately, substituents on the benzylic methylene group, such as another *o*-nitrophenyl group (R'= 2-$C_6H_5NO_2$) were found to greatly improve the yield. After this modification, quantitative yields of the free carboxylic acids were obtained.

Scheme 1.3 Formation of secondary photoproduct **5**



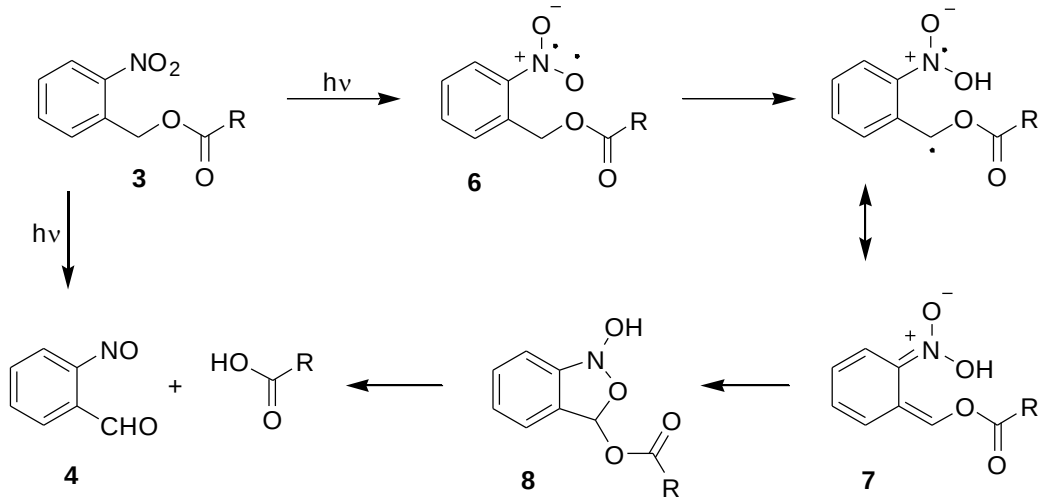
4 **5**

The *o*-nitrobenzyl group has been used to protect a variety of functional groups and the syntheses of the protected molecules are simple and high-yielding. Carboxylic acids are protected as their esters by reacting the carboxylic acids with *o*-nitrobenzyl bromide in the presence of a strong base. Hydroxyl groups are converted to the corresponding ethers by reacting the alcohols with *o*-nitrobenzyl bromide or by reacting alkyl halides with *o*-nitrobenzyl alcohol. Amines are protected as their carbamates by treating the amine with *o*-nitrobenzyl oxycarbonyl chloride. Phosphates can also be protected as their *o*-nitrobenzyl phosphate esters.

Photoremoval of the *o*-nitrobenzyl group is effected by using light of wavelengths greater than 320 nm in pyrex glassware. [3] Deprotection yields are usually quantitative. The mechanism for deprotection of the *o*-nitrobenzyl group was investigated by Schupp et al. [4] who proposed that the release occurred through a photoisomerization of *o*-

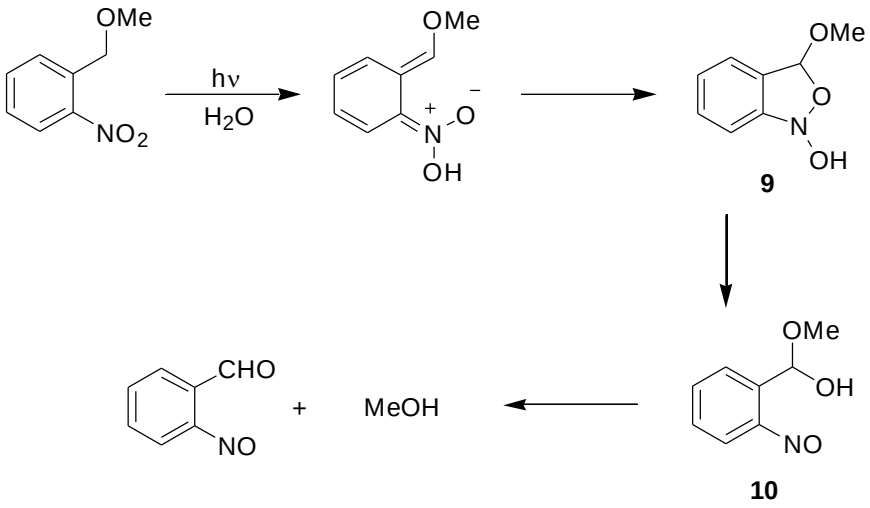
nitrobenzyl group into *o*-nitrosobenzaldehyde (Scheme 1.4) and the released fragment. The primary photochemical step is an intramolecular hydrogen abstraction by the excited nitro group, followed by electron redistribution to the *aci*-nitro form **7** which then rearranges to the nitroso derivative **8**. Ring opening of the cyclic structure **8** releases the free acid and the *o*-nitrosobenzaldehyde **4**.

Scheme 1.4 Mechanism of photorelease in *o*-nitrobenzyl derivatives.



Recently, Wirz et al. have investigated the mechanism more thoroughly by laser flash photolysis using *o*-nitrophenyl methyl ethers. They have managed to detect the cyclic intermediate **9** as well as a 2-nitrosobenzyl hemiacetal intermediate **10** hitherto undetected. [5] They proposed the revised mechanism in Scheme 1.5 to explain the formation of the hemiacetal derivative, and suggest that the cyclic intermediate collapses to the hemiacetal **10** which then eliminates the free hydroxyl group.

Scheme 1.5 Revised mechanism for *o*-nitrobenzyl derivatives proposed by Wirz et al.



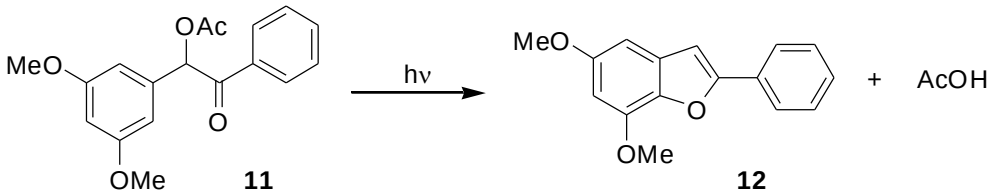
The *o*-nitrobenzyl group is now the most widely used PRPG, and has been used to protect carboxylic acids, amino acids, alcohols, amines, nucleic acids, carbohydrates and phosphates. [3,6-8] It has found extensive applications in release of biologically useful molecules such as neurotransmitters, nucleotides, peptides, etc. [9,10] Its popularity is due to several advantages such as ease of protection and removal, quantitative yields upon deprotection and the use of light above 320 nm for deprotection, at which even the most light-sensitive amino acid, tryptophan is unaffected.

However, the *o*-nitrobenzyl group suffers from several disadvantages. The rate of release is slow (in the millisecond range) since the initial photochemical step is followed by a series of chemical steps before release of the substrate. This limits its application in systems where a fast release step is required. Also, the nitrosoaldehyde byproduct is highly reactive and is harmful to biological systems. There is the added complication of formation of azo intermediates that act as internal light filters.

1.4 The benzoin group (desyl)

The benzoin group was introduced as a PRPG for carboxylic acids by Sheehan, Wilson and Oxford in 1971. [11] They discovered that irradiation of benzoin esters results in a photocyclization reaction yielding the free acids and 2-phenylbenzofuran. The reaction was found to be highly dependent on the nature and position of ring substituents, with methoxy groups providing the best yields. Optimal results were obtained with 3', 5'-dimethoxybenzoin (DMB) esters (Scheme 1.6).

Scheme 1.6 Photoremoval from the benzoin group



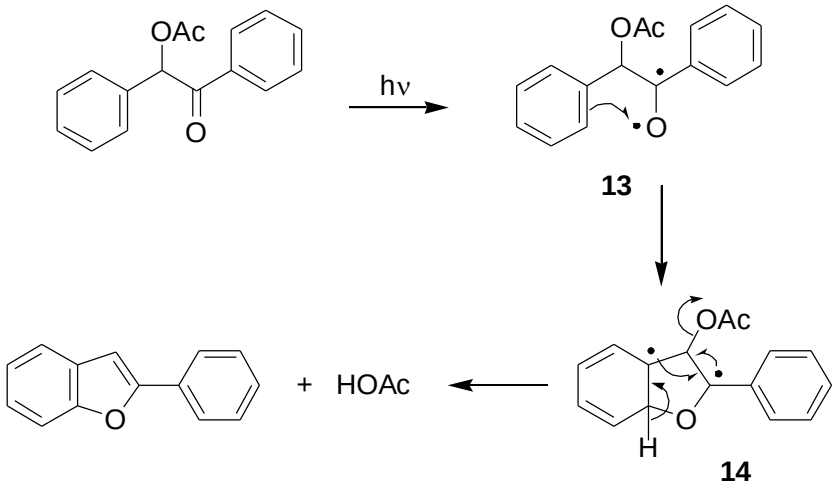
The benzoin group has been used to protect carboxylic and amino acids, [12] alcohols, [13] amines [14] and phosphates. [15] Protection of carboxylic acids is achieved by treating the acid with benzoin bromide in the presence of a base to give benzoin esters. [12] Alcohols and amines are protected as their carbonates [13] and carbamates, [14] respectively.

Deprotection of benzoin esters is usually performed in benzene using a high-pressure mercury lamp with a pyrex filter. The deprotection yields were found to be dependent on the solvent as well as the leaving group. Various research groups have investigated the mechanism of deprotection of the benzoin protecting group. It was shown that substituents on the aromatic ring, nature of the leaving group, and solvent all strongly influence the mechanism as well as reaction efficiency of the benzoin

phototriggers. Some of the important mechanistic work carried out on the benzoin group is discussed below in chronological order.

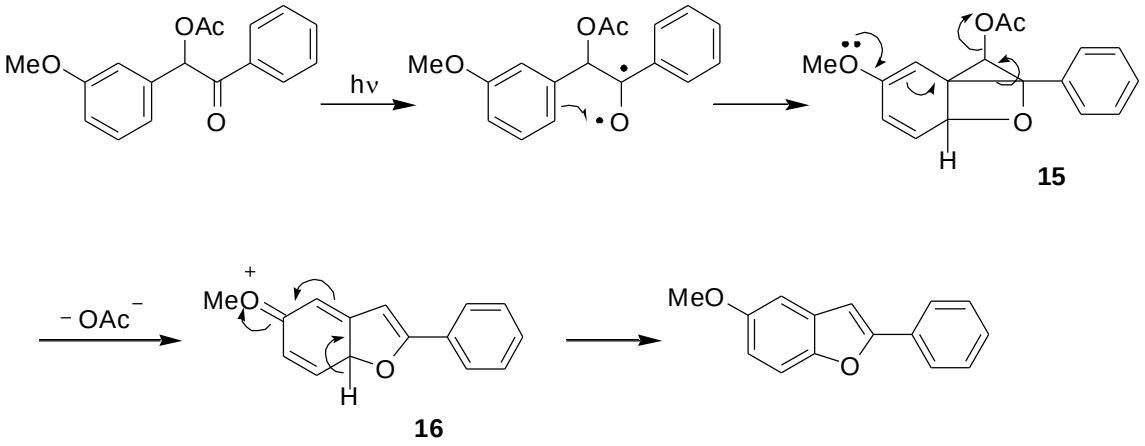
Based on the original study of photorelease of benzoin esters, Sheehan et al. proposed that the mechanism of deprotection involves a n-π* transition of the carbonyl group, followed by the formation of a diradical intermediate **13** (Scheme 1.7). [16] Based on quenching studies, they suggested that the reaction proceeds from the triplet excited state for unsubstituted benzoins esters and 3'-methoxybenzoin esters.

Scheme 1.7 Proposed mechanism for photorelease from benzoin esters



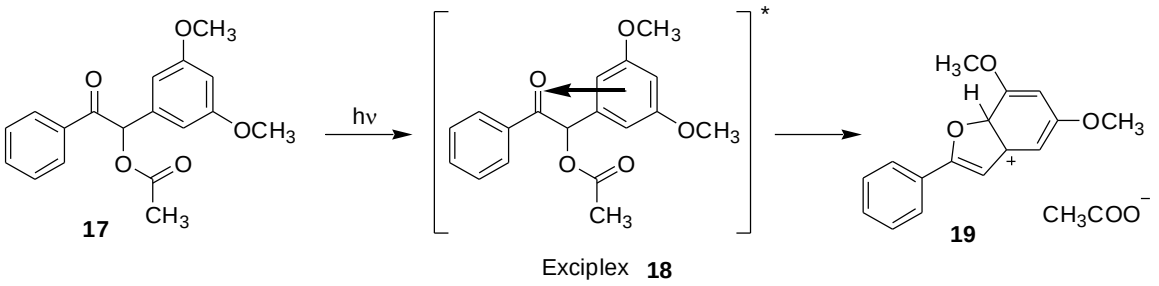
Sheehan et al. later modified this mechanism to explain the effect of methoxy substitution on the ring on the rate of cyclization. [11] They proposed a Paterno-Buchi reaction forming an oxetane intermediate **15**, which undergoes ring opening and subsequent loss of the acetate leaving group to give benzofuran (Scheme 1.8).

Scheme 1.8 Modified mechanism for *m*-methoxy substituted benzoin esters



The reaction mechanism was found to be different for di-*m*-methoxy substituted benzoin esters as these reactions were not affected by triplet quenchers. Shi et al. performed nanosecond laser flash photolysis studies of various 3', 5'-dimethoxy benzoin esters. [17] They proposed a singlet mechanism involving interaction of the dimethoxybenzene ring with the singlet n, π* excited state of acetophenone via a singlet exciplex **18** (Scheme 1.9). They observed a short-lived cyclohexadienyl cation intermediate **19** as the precursor to the benzofuran product. According to this mechanism, the *m*-methoxy substituents activate the 2'-position of the benzene ring and thereby facilitate the intramolecular cyclization.

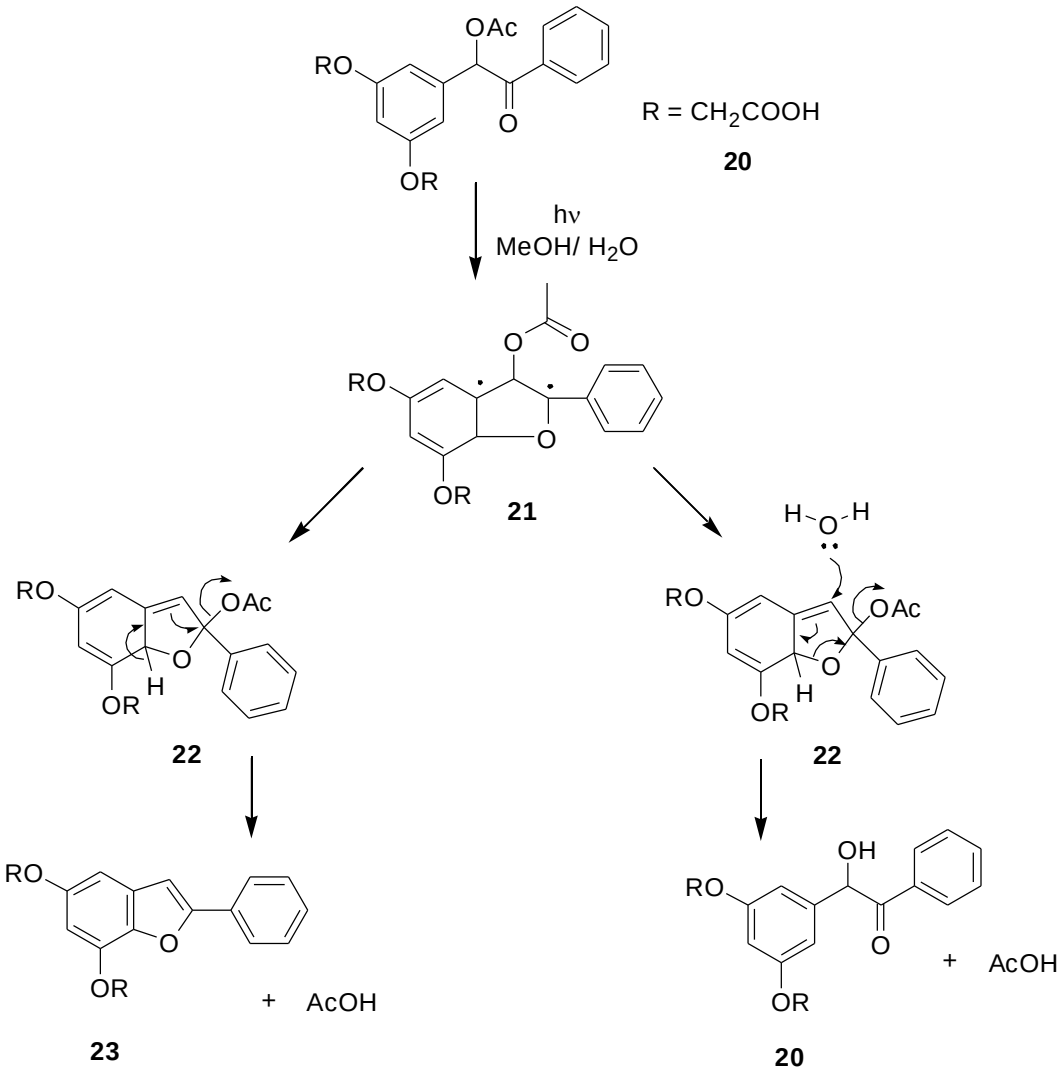
Scheme 1.9 Mechanism proposed by Shi et al.



Recently Rock et al. have developed a water soluble cage based on 3',5'-DMB esters. [18] One of the major drawbacks of benzoin caged compounds is their poor solubility property. Rock and co-workers attempted to improve the solubility by modifying the DMB group. They introduced charged functionalities into the DMB group to give 3',5'-bis(carboxymethoxy)benzoin (BCMB) group.

They found that release of the acetate leaving group was accompanied by formation of BCMB **20** as the major photoproduct instead of benzofuran. To explain this, they proposed a mechanism involving a biradical intermediate **21** which undergoes an acetoxy migration to give a cyclic intermediate **22** which can undergo attack by water to give BCMB or rearomatize to give benzofuran (Scheme 1.10).

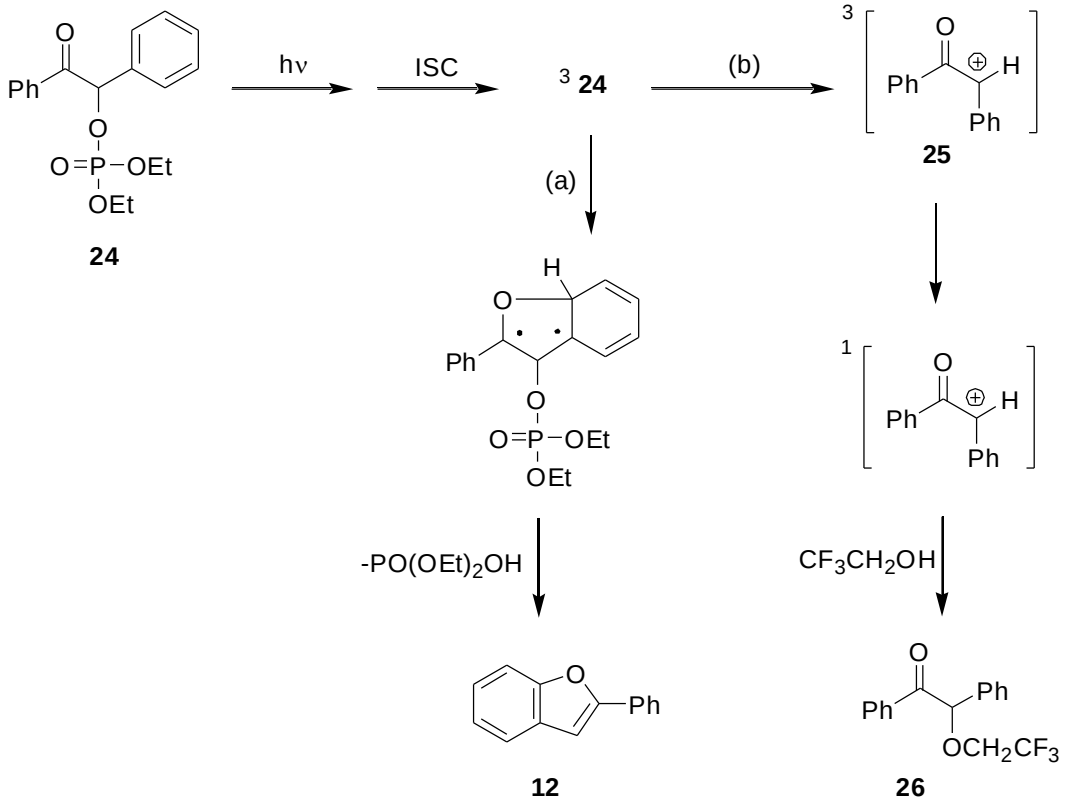
Scheme 1.10 Mechanism for water soluble benzoins proposed by Rock et al.



More recently, Rajesh, Givens and Wirz have proposed a mechanism of phosphate photorelease from benzoin diethyl phosphate (Scheme 1.12). [19] According to their mechanism, two competing reaction paths of diethyl phosphate release proceed from the triplet state of the benzoin diethyl phosphate, depending on the solvent. In most solvents, reaction path (a) predominates, and forms 2-phenylbenzofuran and diethyl

phosphoric acid rapidly. In water and fluorinated alcohols, reaction path (b) dominates, and forms trifluoroethyl benzoin ether **26** as the major product.

Scheme 1.11 Mechanism proposed by Rajesh, Givens and Wirz



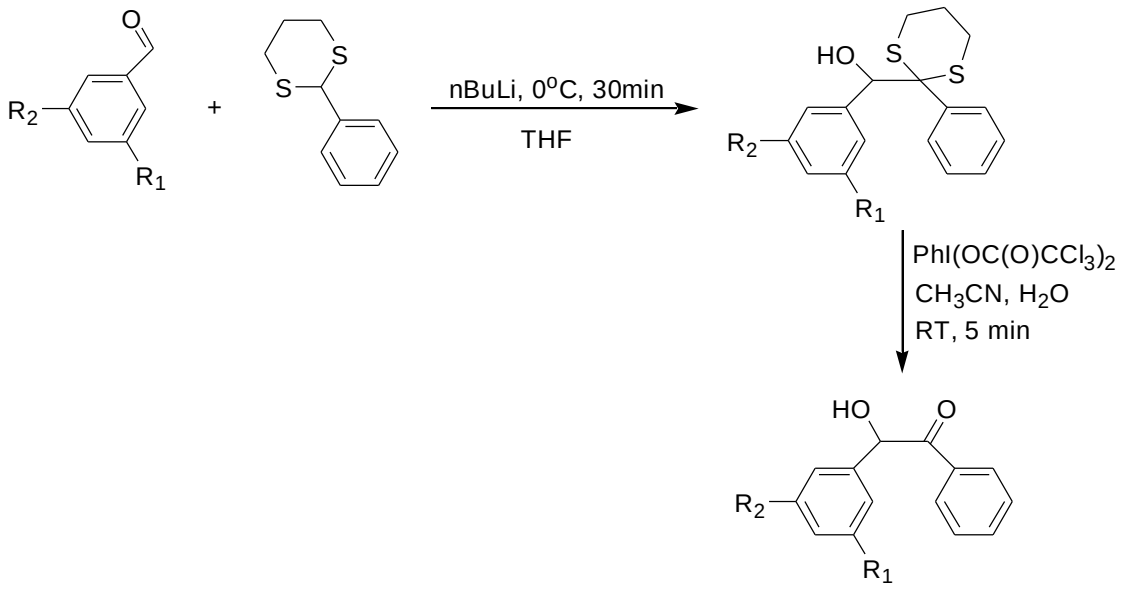
Advantages of the benzoin PRPGs include high chemical and quantum yields. The single by product benzofuran is nonpolar and inert and can be easily separated from polar or acidic components. The 3', 5'-dimethoxy benzoin esters can be cleaved by light of 366 nm. Another important advantage of the DMB group is extremely rapid photolysis, which makes benzoin cages ideal phototriggers for fast reactions.

The major drawback of the benzoin group is the additional chiral centre introduced by the benzylic carbon which makes the protection of chiral acids

problematic. Another disadvantage is that the byproduct benzofuran absorbs light and acts as an internal light filter. Also, the insolubility of benzoin caged compounds limits their biological applications. However, with the recent development of water soluble benzoin cages, these protecting groups can be used in biological systems.

Another limitation is that the 3',5'-DMB group is very light sensitive and can photorelease under normal laboratory light which makes subsequent steps problematic. To overcome this problem, safety-catch PRPGs have been developed recently based on the benzoin group. Stowell et al. have used the Corey-Seebach dithiane addition method to synthesize benzoins via the dithiane protected adduct (Scheme 1.13). [20] This allows complex protected molecules to be synthesized that can be kept photochemically inert until the dithiane moiety is converted to the parent ketone.

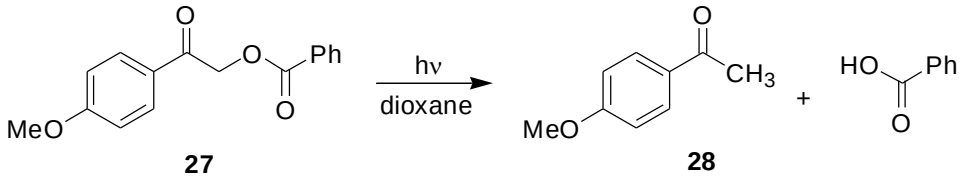
Scheme 1.12 Safety-catch benzoin protecting group



1.5 The phenacyl group

The phenacyl group was originally used as a conventional protecting group. It was introduced as a PRPG by Sheehan and Umezawa in 1973. [21] They reported that irradiation of *p*-methoxyphenacyl benzoate in dioxane or ethanol gave benzoic acid in good yield (Scheme 1.13). It was found that *p*-methoxy and 2-methyl phenacyl esters were more reactive than the unsubstituted phenacyl esters.

Scheme 1.13 Photorelease from phenacyl esters



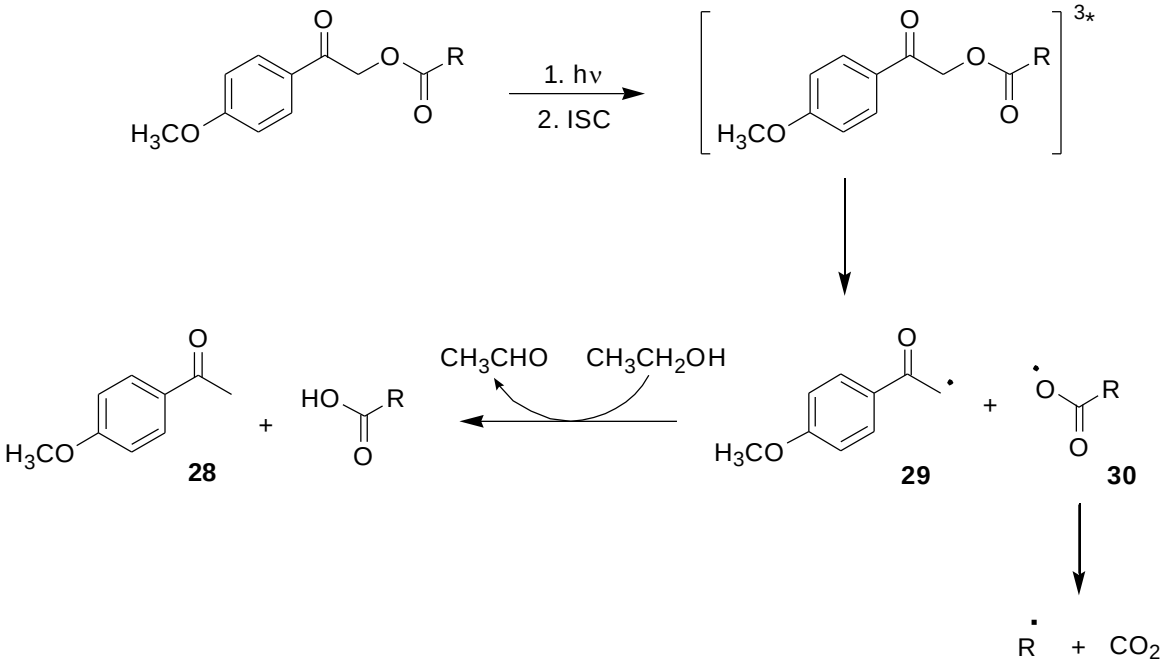
27 **28**

The *p*-methoxyphenacyl group has since then been used to protect carboxylic and amino acids, [21] phosphates [22,23] and amines. [24] Carboxylic acids and *N*-protected amino acids are protected as their phenacyl esters by reaction with phenacyl bromide in the presence of a base. [21] Amines can be protected as phenacyl urethanes. [24] These can be prepared by reaction of aryl isocyanates to α-hydroxy ketones. Phosphates are converted into phenacyl phosphates esters by the reaction of α-diazo-*p*-methoxyacetophenone with hydrogen phosphates. [23]

Deprotection of the phenacyl group can be effected by light of wavelength 300-320 nm. The presence of hydrogen atom donors was found to be necessary for deprotection. When photolysis was performed in benzene, no deprotection was observed. Good deprotection yields were obtained in solvents such as ethanol or dioxane.

Sheehan et al. proposed a mechanism involving a homolytic cleavage of the carbon-oxygen bond to give the phenacyl and acyloxy radicals **29** and **30** (Scheme 1.14). [21] They proposed that ethanol acts as a hydrogen donor, and gets dehydrogenated to acetaldehyde during the reaction. The by-product of the photorelease was *p*-methoxyacetophenone **28**. Quenching of the reaction in the presence of triplet quenchers such as benzophenone and naphthalene indicated that the reaction proceeds through a long-lived triplet state.

Scheme 1.14 Mechanism proposed by Sheehan

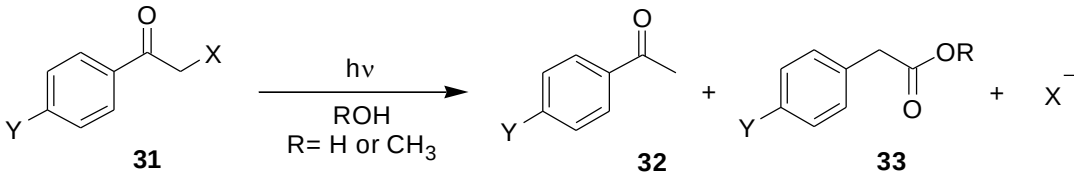


The *p*-hydroxy substituted phenacyl group was introduced by Givens and coworkers as an efficient protecting group. [25] This group has the added advantage of being water soluble and thus is compatible with biological systems. The *p*-hydroxy phenacyl group has been used to photorelease phosphates, carboxylates, amino acids,

thiols and peptides as well as several bioactive molecules such as ATP, GABA, etc owing to its fast release rate. [25-28]

Givens et al. reported that photolysis of *p*-hydroxy phenacyl protected molecules in aqueous solvents gave quantitative yields of the free substrate and *p*-hydroxyphenylacetic acid. [25] The *p*-hydroxyphenylacetic acid **33** by-product is formed as a result of a rearrangement reaction. Similar rearrangement products were also reported by Anderson for release of chlorides from *p*-methoxy or *p*-hydroxy phenacyl chlorides. [29] The rearrangement pathway was also found to dominate for *p*-methoxyphenacyl phosphates in alcoholic solvents (Scheme 1.15)

Scheme 1.15 Rearrangement product for *p*-substituted phenacyl esters.

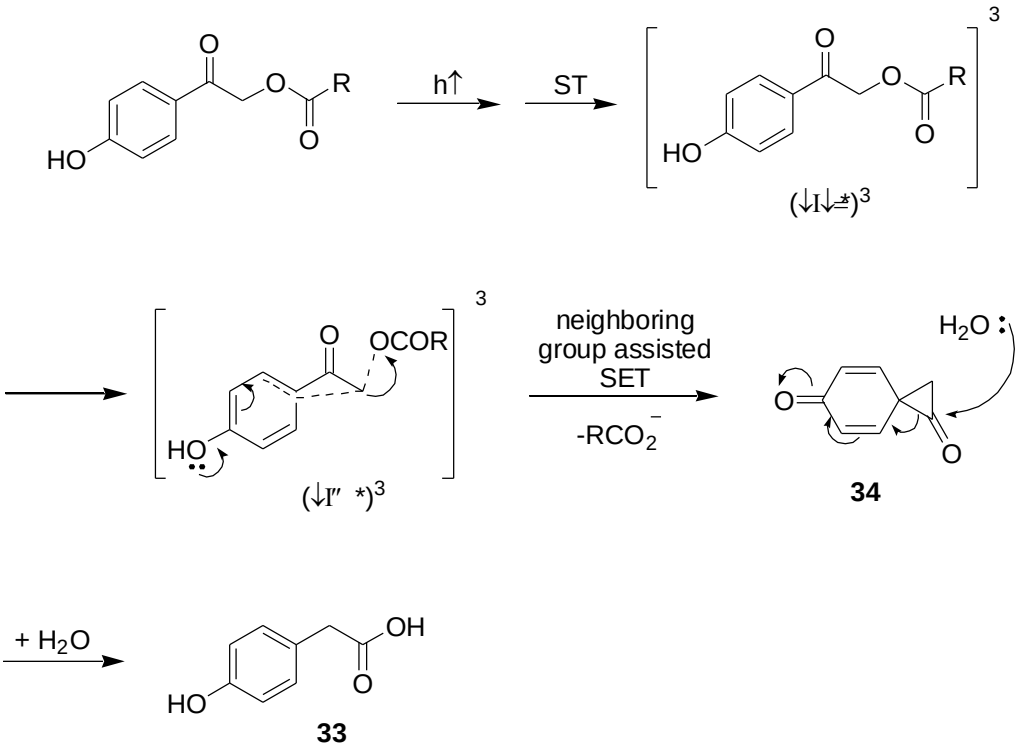


31 **32** **33**

a; Y = OCH_3; X = Cl
b; Y = OH; X = Cl
c; Y = OCH_3; X = $O_2P(OR')_2$

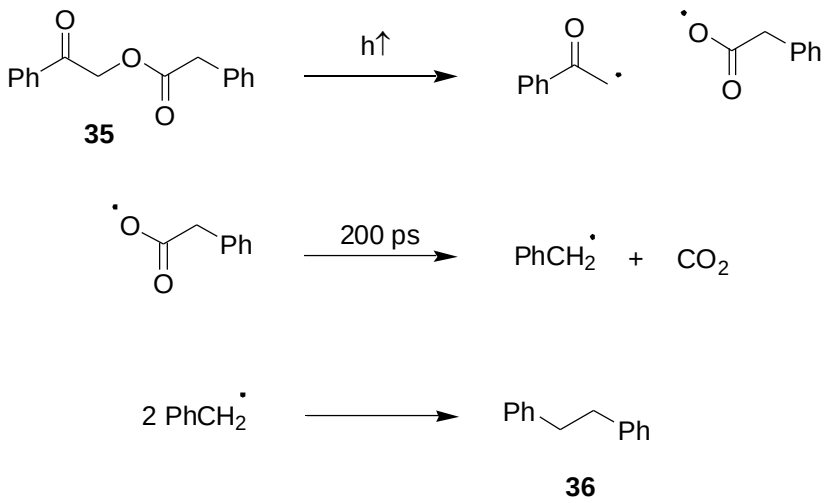
Givens and co-workers proposed a mechanism to explain the formation of the rearranged product for the *p*-hydroxyphenacyl group (Scheme 1.16). [25] Quenching studies revealed that the reaction proceeds through the triplet excited state. The mechanism proposes that the decay of the triplet excited state is synchronous with the release of the protected molecule, which takes place through a neighboring group assisted single electron transfer (SET). The resulting spirodienedione intermediate **34** can then be trapped by water or alcohol to give *p*-hydroxyphenylacetic acid.

Scheme 1.16 Mechanism proposed by Givens et al.



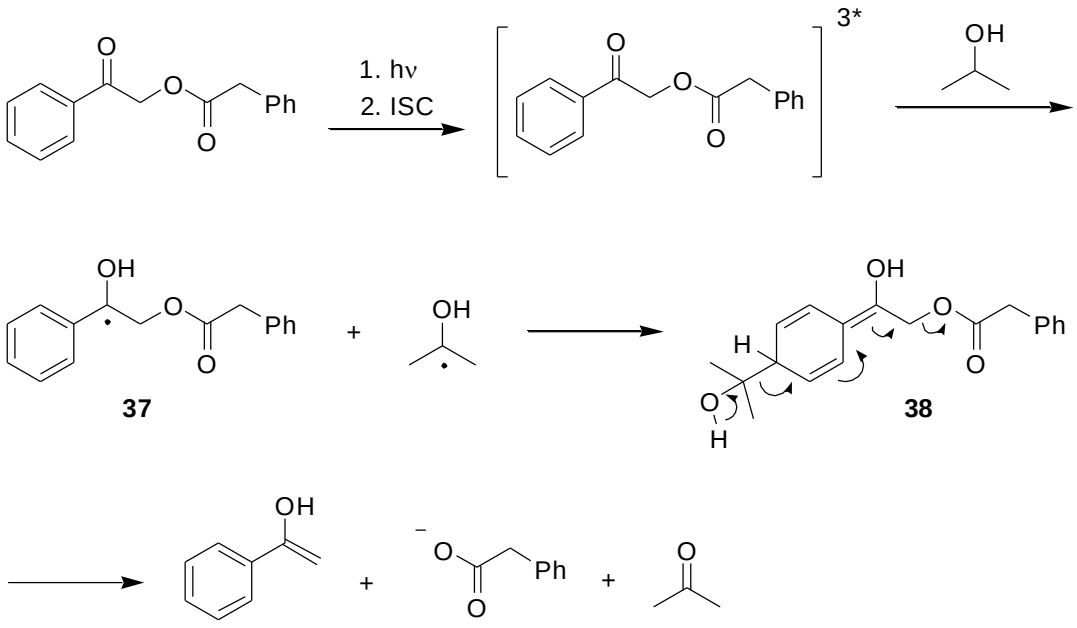
For unsubstituted phenacyl esters, the mechanism appears to be more complicated. The mechanism proposed by Givens et al. is not applicable here as these phenacyl esters lack participation by an oxygen atom in the para position as required by this mechanism. If the homolytic scission mechanism proposed by Sheehan for *p*-methoxy phenacyl esters holds good for esters with unsubstituted phenacyl groups (Scheme 1.14), then the extremely fast decarboxylation step would be competing with the H-atom abstraction step. Thus photolysis of phenacyl phenylacetate **35** was expected to give a dimerized product, bibenzyl **36**, following decarboxylation (Scheme 1.17). However, photolysis in acetonitrile gave no bibenzyl, instead high yields of acetophenone and phenylacetic acid were obtained. [30]

Scheme 1.17 Homolytic bond scission mechanism for phenacyl esters



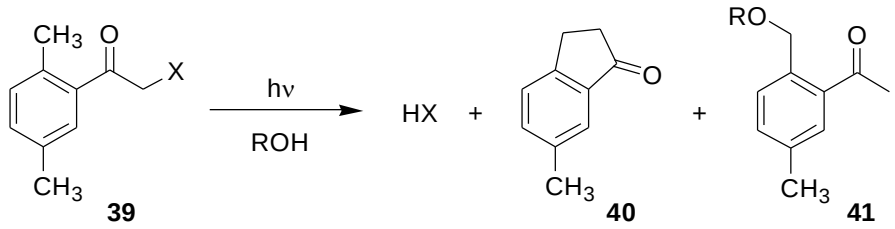
These inconsistencies led Falvey and Banerjee to propose an alternate mechanism in the presence of hydrogen donors. [30] They proposed that instead of the C-O bond scission, H-atom transfer is the initial photochemical step (Scheme 1.18). The resulting ketyl radical **37** then decays through a disproportionation reaction with the donor radical.

Scheme 1.18 Mechanism in the presence of hydrogen donors



Recently, Klan et al. have introduced the 2,5-dimethylphenacyl (DMP) group as a protecting group. [31] They have made use of the highly efficient photoenolisation reaction of *o*-alkylaryl ketones to effect release of various functional groups. They have successfully used this group to photorelease carboxylic acids, phosphates, sulfonic acids, alcohols and phenols. [31-33] Alcohols and phenols are protected as mixed carbonates while the acids and phosphates are protected as their esters. Photolysis of DMP esters results in formation of the free acid along with 6-methylindanone **40**, and in alcohol, an additional by-product, 2-(alkoxymethyl)-5-methylacetophenone **41** is observed (Scheme 1.19).

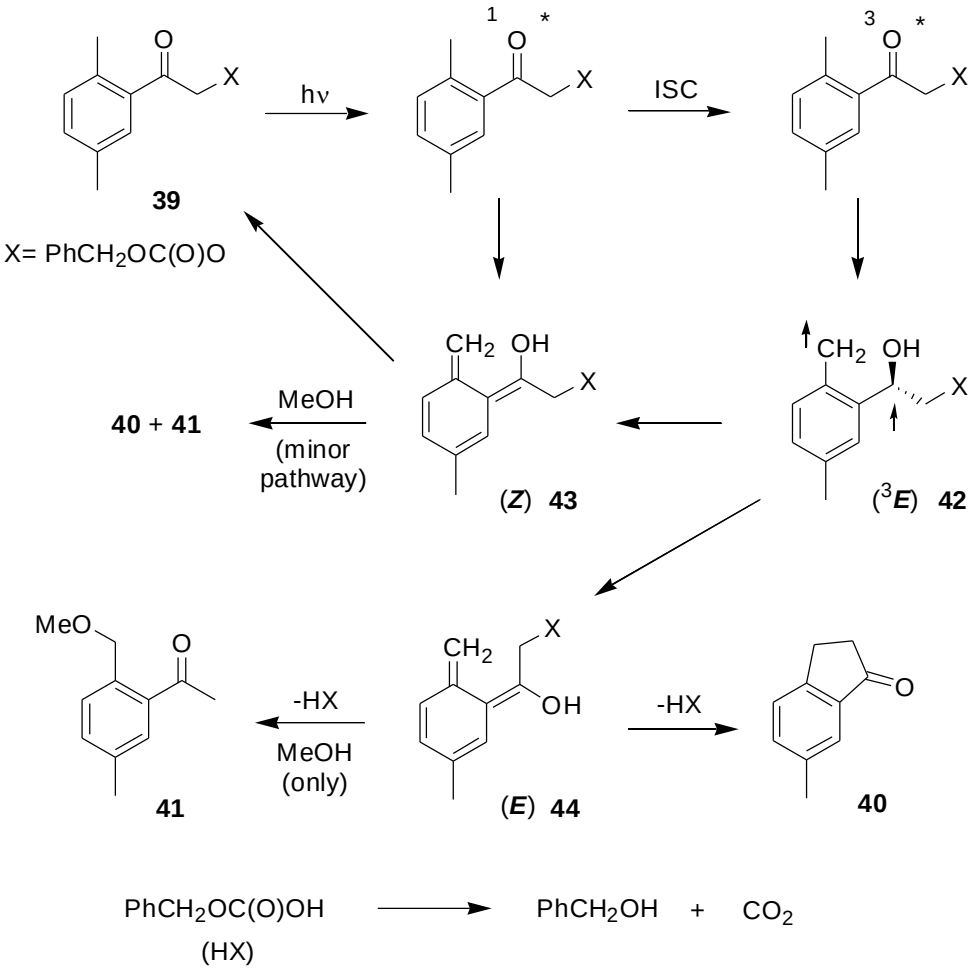
Scheme 1.19 Photorelease from 2,5-dimethylphenacyl esters



39 **40** **41**

The proposed mechanism for photorelease involves a photochemical enolization that occurs from the excited triplet state of the 2,5-dimethylphenacyl chromophore (Scheme 1.20). [33] The photoreaction is initiated by an intramolecular hydrogen abstraction to give the triplet photoenol ^3E, which then decays to ground state *E* and *Z*-photoenols. The *Z*-enol **43** undergoes rapid reketonisation in hydrocarbon solvents. The release of substrate occurs from the longer-lived *E*-enol **44** with the formation of the cyclized indanone by-product. In alcohol, addition of solvent rather than cyclization results in formation of 2-(alkoxymethyl)-5-methylacetophenone as the by-product.

Scheme 1.20 Mechanism of photorelease from the 2,5-dimethylphenacyl group

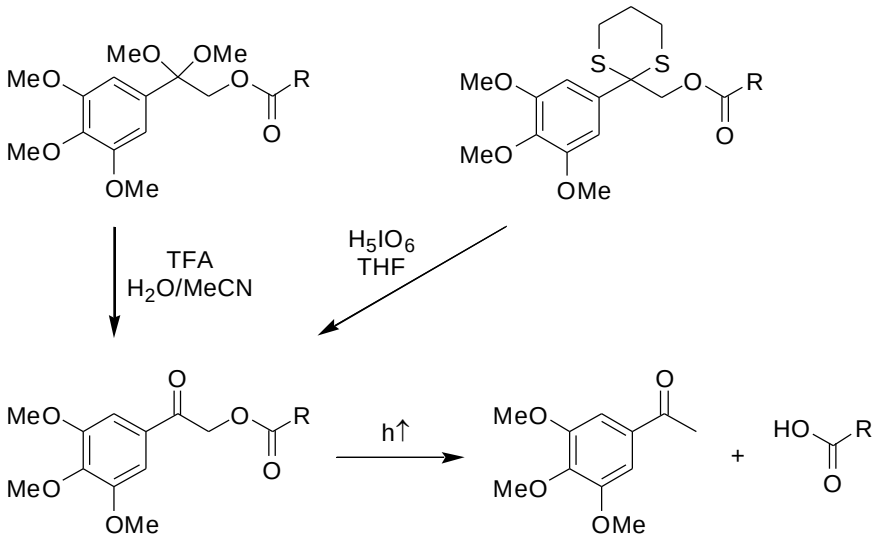


The phenacyl group has several advantages that make it a very attractive PRPG. The *p*-hydroxyphenacyl group is particularly popular for release of bioactive molecules such as ATP, GABA, peptides, etc, as it is water soluble and has a very fast release rate. The quantum yields of photorelease are high. The by-product *p*-hydroxyphenyl acetic acid is non-toxic and also has a blue-shifted UV absorption with respect to the *p*-hydroxyphenacyl protected molecule. Thus, it does not interfere with light absorption unlike the by-product from the *o*-nitrobenzyl derivatives. Also, unlike benzoin compounds, the *p*-hydroxyphenacyl group does not introduce a chiral centre in the molecule.

The major disadvantage of the phenacyl group is that it does not absorb much light above 320 nm. However, Conrad et al. have recently attempted to shift the absorption range of the *p*-hydroxyphenacyl chromophore to higher wavelengths by introducing substituents on the ring. [34] They synthesized 3,5-dimethoxy-4-hydroxyphenacyl esters of amino acids and found the molecules to absorb up to 400 nm. Unfortunately, this modification led to significantly lower quantum yields of release.

Similar to the benzoin derivatives, safety-catch protecting groups have recently been developed based on the phenacyl group. Shaginian et al. have created and used trimethoxyphenacyl based orthogonal safety-catch protecting groups in radial combinatorial chemistry. [35] They masked the ketone group of the phenacyl esters as dimethyl ketals and 1,3-dithianes which makes these molecules photoinert (Scheme 1.21). These can be converted to the photolabile ketones by treatment with aqueous acid and subsequently deprotected by light of 350 nm.

Scheme 1.21 Safety-catch protecting groups based on the trimethoxyphenacyl group



1.6 Applications of PRPGs

Photoremovable protecting groups have found various uses in diverse fields, such as photolithography, [36] time-resolved x-ray crystallography, [37] multi-step organic synthesis, [38,39] peptide synthesis [40] etc. A few of the important applications will be discussed here.

1. Photorelease of bioactive molecules

PRPGs have been extensively used to make 'caged' compounds, which are usually biological molecules with specific properties that are rendered inactive by protection with a photolabile group. The original activity can be restored upon irradiation. These phototriggers provide rapid release of the bioactive molecules in a precise and controlled fashion. Thus, they have been used to study the kinetics and mechanisms of various fast biological processes.

One important application is in the release of neurotransmitters, which are responsible for important physiological functions. Neurotransmitters bind to a receptor and cause the opening of ion channels resulting in a flow of current. When the neurotransmitters are released from their cages in a controlled manner, the resulting current can be monitored to provide information on the kinetics of the process.

A number of neurotransmitters and neurotransmitter agonists have been caged by photolabile groups, such as carbamoylcholine, γ-aminobutyric acid (GABA), glutamate, etc. and have found uses in various biological systems. For example, *p*-hydroxyphenacyl caged GABA and glutamate have been used in the study of neural processes [25] and *p*-

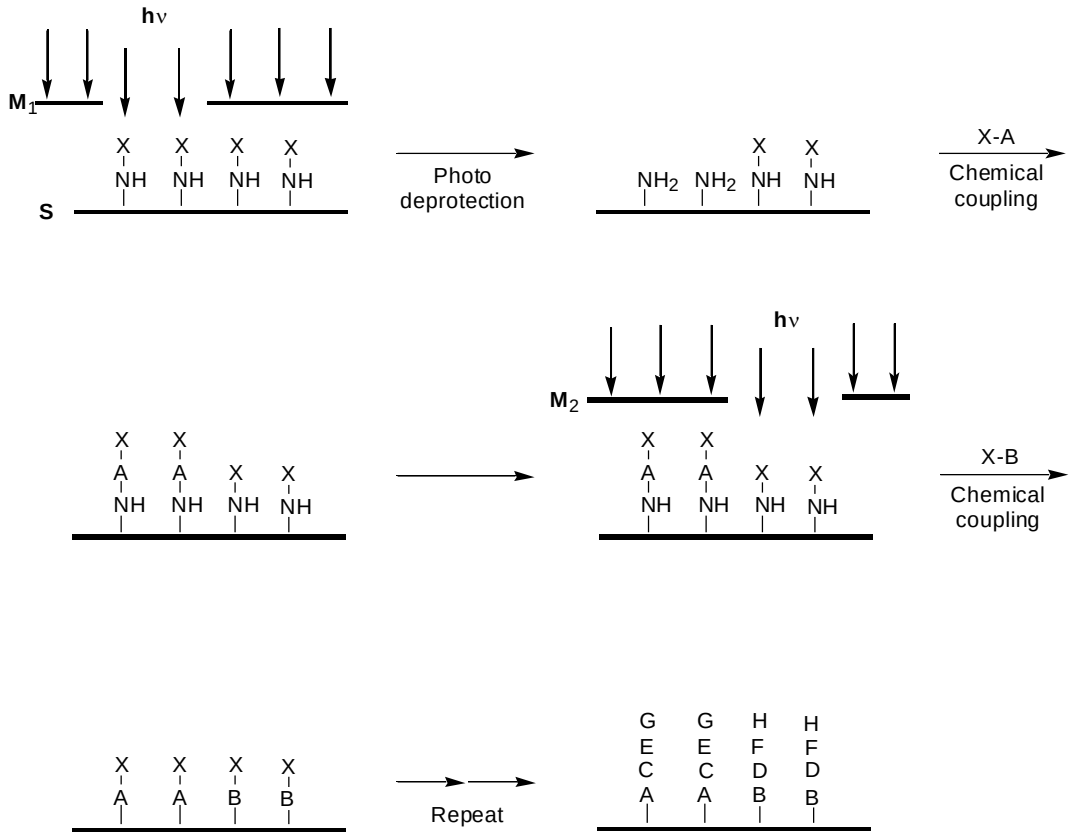
hydroxyphenacyl Bradykinin was applied to rat dorsal root ganglions, to monitor the rapid changes in Ca^{2+} concentration. [27]

Proteins and peptides have also been caged by photolabile protecting groups. For example, the *o*-nitrobenzyl group has been used to cage various useful peptides such as G-actin, neuropeptide Y (NPY) and heavy meromyosin. [10,41,42] Caged proteins have been used to study the kinetics of protein folding. Recently, the kinetics of α-helix formation (which takes place on time scales of about 0.1 μs) was investigated using a benzoin caged protein villin. [43]

2. Light-directed synthesis of molecular arrays

An interesting application of PRPGs is in light-directed, spatially addressable, parallel chemical synthesis. This technique was developed by Fodor et al. to synthesize peptides using the *o*-nitrobenzyl photolabile group. [40] In this strategy, the protected building blocks are attached to a solid support. Exposure to light occurs through a mask, and activates the selected areas by removal of the protecting group. After deprotection, the building blocks are exposed to reaction with another set of caged molecules. Reaction occurs only on the activated sites. The substrates are irradiated through a second mask that activates a different set of building blocks to reaction with another set of molecules. By varying the position of the mask and the sequence of reactants, the desired products can be synthesized (Figure 1.2). This strategy was also applied to oligonucleotide synthesis. [44,45] Recently, this strategy has been extended to light-directed assembly of nanoparticles on a solid support and applied to the preparation of nanocrystal based photonics devices. [46]

Figure 1.2 Light-direct parallel synthesis of peptides



3. Fluorescent probes

PRPGS have been used to develop fluorescent probes. It involves coupling a fluorescent dye to a photoremovable protecting group, to give a photoactivable fluorophore, whose fluorescence emission is suppressed while it is protected. The fluorescence can be regenerated by irradiation with UV light. When these molecules are attached to biomolecules of interest, they can act as photoactivable fluorescent tracers.

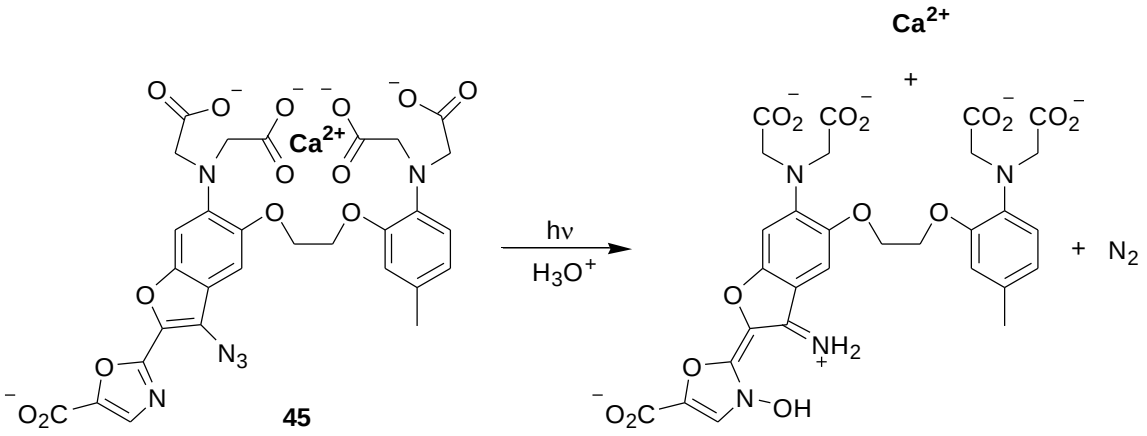
Some examples of photoactivable fluorophores are caged fluorescein, rhodamine, resorufin and 8-hydroxypyrene-1,3,6-trisulfonic acid (HPTS). [47,48] These fluorescent probes have been successfully applied in various fields. Photoactivation of these

fluorescent probes is especially useful in biological systems, as they can be used to generate the bioactive molecule *in situ*, in a mild and controlled fashion. The subsequent development or movement of the released substrate in the system can then be easily monitored. For example, caged resorufin coupled to G-actin has been used to study intracellular motility of pathogens. [49] A nitrobenzyl caged fluorescein tracer has been used to study cell lineage during the development of *Drosophilia* embryos. [50] They have also been used as calibration systems to study extent of photolysis of other caged compounds, [48] and in assays of photodamage. [51]

4. Photorelease of Ca^{2+}

An important application of PRPGs is in the photorelease of calcium. Fluctuations in intracellular concentration of free Ca^{2+} is believed to affect various physiological functions such as muscle contraction, hormone secretion and neurosynaptic transmission. Photolabile caging groups for Ca^{2+} allow the generation of rapid changes in Ca^{2+} concentration. Ca^{2+} is caged by complexation with chelator molecules that can change their affinity for Ca^{2+} upon irradiation. Caging groups have been developed based on substituted *o*-nitrobenzyl derivatives with chelating ligands whose binding to Ca^{2+} is either electronically (e.g the 'nitr' series) [52] or sterically (DM-nitrophen) [53] lowered upon irradiation with UV light. Recently Adams et al. have developed an improved caged calcium, azid-1, that releases free Ca^{2+} with unit quantum yield (Scheme 1.22). [54]

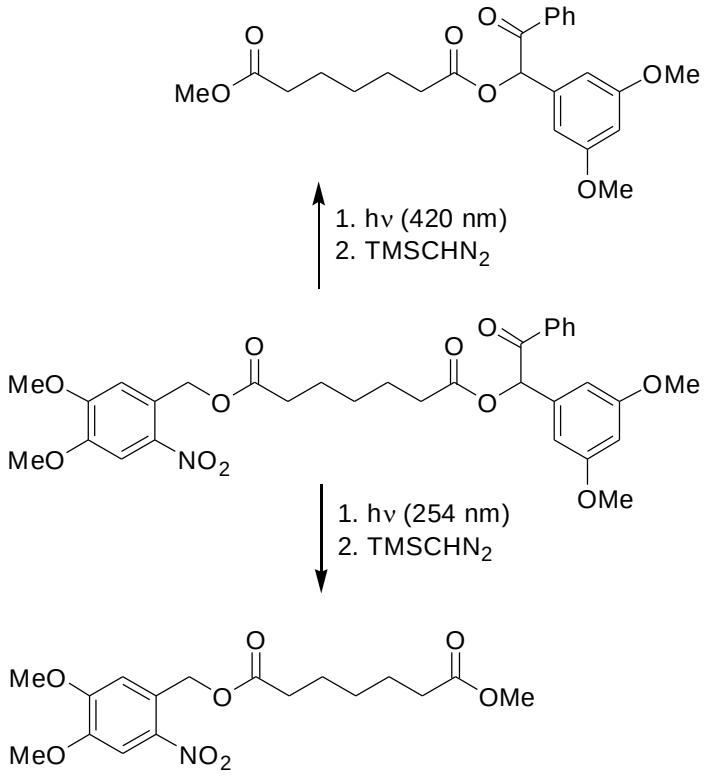
Scheme 1.22 Photorelease of Ca^{2+} from azid-1



5. Orthogonal deprotection

Recently a PRPG system has been developed by Bochet et al. that can be orthogonally deprotected using light of different wavelengths. [55-57] While chemical orthogonality has been achieved for protecting groups, wavelength orthogonality is a novel development. Wavelength orthogonality allows a set of photolabile protecting groups on the same molecule to be selectively removed by monochromatic light of different wavelengths. Bochet et al. reported that two different PRPGs, the *o*-nitroveratryl group and 3',5'-dimethoxybenzoin group were tuned to respond to a specific wavelength (420 nm and 254 nm respectively) (Scheme 1.23). The protected substrates were released in high yields from both groups.

Scheme 1.23 Wavelength orthogonal photorelease



1.7 Conclusions

Three of the most widely used PRPGs, the *o*-nitrobenzyl group, the benzoin group, and the phenacyl group were discussed in depth in the preceding sections. These groups have several advantages that make them popular in a variety of applications. The synthesis of the protected molecules is simple, and the protected molecules are stable. The photorelease occurs with high chemical and quantum yields. In the case of the *o*-nitrobenzyl group, the by-product of the photorelease is not as benign as would be desired. However, various modifications allow these byproducts to be trapped or rendered less harmful. The benzoin group offers fast release of substrate as well as harmless byproducts of photorelease. However, the poor solubility property of this group is a serious drawback as is the introduction of a chiral centre in the protected molecule.

The phenacyl group combines the advantages of these two groups while not suffering the disadvantages of poor solubility and toxic byproducts.

While these three groups satisfy several important requirements, their light absorption properties are not satisfactory. These groups all absorb light below 350 nm which involves using harsh UV light for deprotection. Some effort at increasing their absorption range has resulted in the use of light around 400 nm. However, the shift in absorption wavelengths was found to result in lower quantum yields and in certain cases, additional reaction pathways. Thus, it is a challenging task to be able to improve the light absorption properties of PRPGs without adversely affecting their ability to release the protected molecule.

A successful solution to this problem is the development of systems which have different components responsible for light absorption and chemical behaviour. This method allows for each component to be improved without affecting the other. The goal of this project is to develop a PRPG that can release free substrates efficiently using light of high wavelengths. Thus, this decoupled strategy is the basis of this project and will be discussed further in the following chapter.

Chapter 2. Photorelease by Photoinduced Electron Transfer

2.1 Introduction

As this work is concerned with the removal of protecting groups using light, a discussion of the deprotection methods and mechanisms is appropriate at this point. PRPGs can be cleaved by two different methods- direct irradiation or sensitized irradiation.

Direct irradiation involves a PRPG which is light sensitive and which upon irradiation, undergoes a chemical transformation that subsequently releases the protected substrate. In this case the light absorption and bond cleavage occur within the same molecule. Most of the widely used PRPGs, including the *o*-nitrobenzyl, benzoin and phenacyl groups use this strategy for photorelease. However, the main disadvantage of direct irradiation is that it allows for very little modification to the PRPG, as the light absorption and bond cleavage steps are coupled to each other. An attempt to improve the fragmentation reaction could adversely affect the light absorption property of the molecule and vice versa.

Sensitized irradiation utilizes an external molecule, called a sensitizer, to absorb light and transfer energy or electrons to the PRPG, which would then undergo a suitable chemical transformation and release the protected molecule. This procedure overcomes the drawbacks of the direct irradiation method. The use of a sensitizer allows light of different wavelengths to be used for deprotection, while the chemical behaviour of the protecting group remains unchanged. Thus, in a 'decoupled' PRPG system, each of the

two components can be independently altered and improved, providing more control over the deprotection step.

The major goal of this project is to develop an efficient PRPG which can be removed by light of longer wavelengths, preferably in the visible region. The sensitized irradiation method is a more desirable strategy for this purpose as it provides more control over the wavelengths used for deprotection. Hence, we have used sensitizers to carry out a photoinduced electron transfer (PET) process to photorelease the carboxylate functionality at various irradiation wavelengths. This process will be discussed in detail in the following sections, as well as our reasons for adopting it as our photorelease strategy.

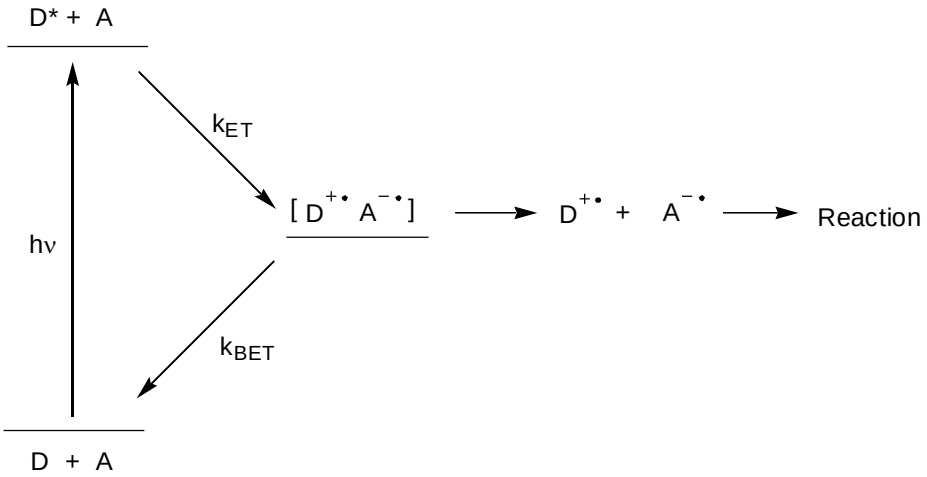
2.2 Photoinduced electron transfer

Photoinduced electron transfer (PET) is a well studied phenomenon which has been applied to various fields such as solar energy conversion, [58-60] photolithography [61,62] and molecular electronics. [63,64] PET has been recognized as a powerful tool to effect various chemical transformations and has found applications in organic synthesis. [65-67] The ability of PET to generate reactive radicals or ions in a mild and controlled fashion also makes it an attractive strategy for the release of protecting groups.

A photoinduced electron transfer (PET) process involves a donor and an acceptor molecule, one of which is capable of light absorption and promotion to its excited state. From the excited state, the molecule can either donate or accept electrons, resulting in the formation of the donor cation radical and anion radical of the acceptor. This radical ion pair can undergo solvent separation to give free radical ions or undergo a return (or back)

electron transfer (BET). This energy wasting process is efficient and competes with chemical reactions arising from the geminate ion pair or the solvent separated ions. A schematic depiction of PET is shown below (Figure 2.1). A light absorbing donor is used in this illustration, but it is also possible to initiate PET with a light absorbing acceptor.

Figure 2.1 General mechanism of PET

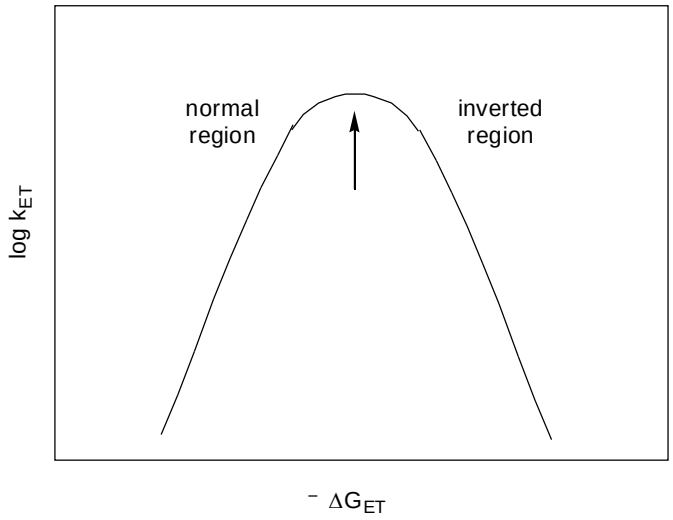


PET can occur only if the free energy change for electron transfer is exergonic. The feasibility of electron transfer from a donor to an acceptor can be predicted using the Weller equation (Equation 1). [68,69] This equation relates the free energy change for electron transfer to the oxidation potential of the donor (E_{ox}), the reduction potential of the acceptor (E_{red}), and the excited state energy of the sensitizer ($E_{o\text{-}o}$). The correction factor for desolvation and ion-pair attraction ($e^2/R\varepsilon$) is negligible in polar solvents such as acetonitrile and methanol and can be ignored for qualitative purposes.

$$\Delta G_{ET} = 23.06\,(E_{ox} - E_{red} - e^2/R\varepsilon) - E_{o\text{-}o} \qquad (1)$$

Early theoretical models of PET and its dependence on free energy change, ΔG_{ET}, were advanced by Marcus. [70-72] According to his proposed model, the rate of electron transfer is related to the free energy change ΔG_{ET} for the electron transfer process. He predicted that the rate constant for electron transfer, k_{et}, would increase with increasing reaction exergonicity until a certain value of ΔG_{ET} was reached, after which point the rate constant k_{et} would drop with increasing ΔG_{ET}. This parabolic relationship between k_{et} and ΔG_{ET} consists of two regions (Figure 2.2). In the 'normal' region, rate of electron transfer increases with reaction driving force, while in the 'inverted' region, the rate decreases with increase in driving force.

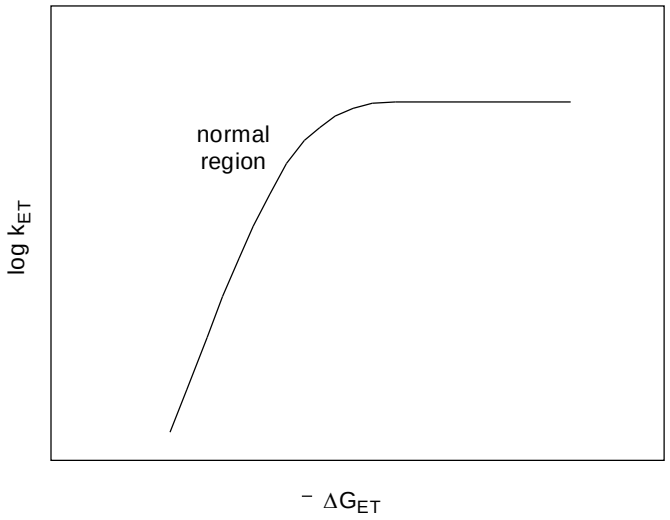
Figure 2.2 Relationship between k_{et} and ΔG_{ET} according to the Marcus theory



With the advent of laser flash photolysis (LFP), electron spin resonance (ESR) and other analytical techniques for observing transient species, various groups have attempted to study the mechanism of PET and experimental data has been obtained to test Marcus's prediction. Initial studies by Rehm and Weller on the fluorescence quenching

rate constants of various electron donors and acceptors did not entirely support the Marcus theory. [69] Fluorescence quenching rate constants are representative of the rate constant for electron transfer k_{et}, and it was observed that this quantity increased with exothermicity and ultimately reached a diffusion limit (Figure 2.3). The 'inverted' region predicted by Marcus was not observed in this case.

Figure 2.3 Observed relationship between k_{et} and ΔG_{ET} by Rehm et al [69]



Further investigation by other groups, however, indicated the existence of the 'inverted' region. The first experimental observation of the 'inverted' region was by Miller and Closs in their study of PET in rigidly linked donor-acceptor systems. [73-75] They noted that with very negative ΔG_{ET}, the rates of intramolecular electron transfer decreased. Later work by Gould and Farid on rates of back electron transfer in intermolecular cases also supported the Marcus theory. [76,77]

Recent work by Gopidas and coworkers involving hydrogen-bonded donor-acceptor pairs, [78] in conjunction with the previous experiments reveals the influence of diffusion on the rates of electron transfer. It was observed that when donors and acceptors

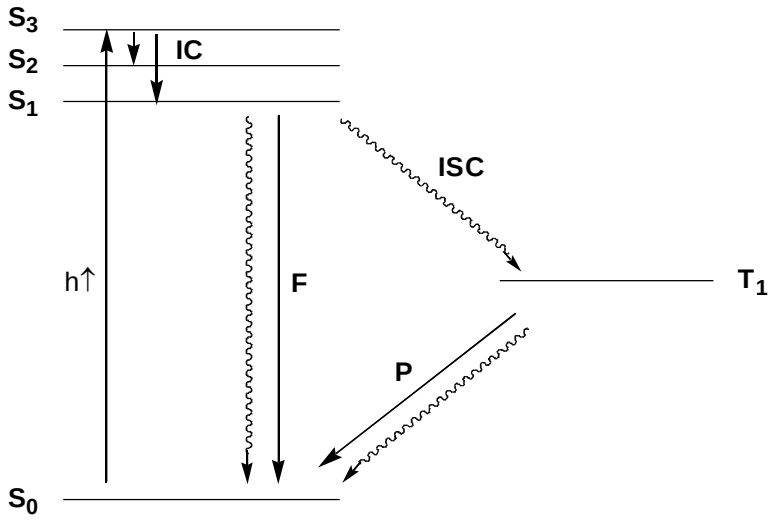
are linked either covalently or through hydrogen bonds, k_{et} showed the Marcus predicted dependence on ΔG_{ET}, and the inverted region can be observed. In intermolecular cases, diffusion separated the donors and acceptors and set a limit to the observable k_{et} thus cutting off the top of the curve in Figure 2.2.

Besides diffusion, other factors were also found to influence rates of electron transfer. Solvent polarity and viscosity play an important role as they affect the encounter probability of the donor and acceptor, and hence the probability of electron transfers as well. Also, distance between the donors and acceptors strongly affected the k_{et} and the electron transfer reactions were found to be most efficient when the donors and acceptors were less than 10 Å apart.

A key role in a photoinduced electron transfer process is played by the sensitizer. The sensitizer molecule is responsible for the light absorption step and subsequent initiation of the PET. There are various photophysical processes involved following light absorption by the sensitizer and prior to PET. These are depicted by the Jablonskii diagram (Figure 2.4).

When a sensitizer absorbs light, it gets promoted to the higher excited singlet states, from where it undergoes a non-radiative decay (IC) to the lowest excited singlet state S_1. From this state, it has several possible decay pathways. It can fluoresce or decay in a non-radiative manner to the ground state S_0, or it can undergo a spin-changing decay (ISC) to the excited triplet state T_1. The triplet state is longer lived than the singlet state and allows decay through phosphorescence or non-radiative processes to the ground state. The PET process can occur from either the S_1 or the T_1 states, depending on the sensitizer.

Figure 2.4 The Jablonskii diagram



S_0: Singlet ground state	S_1, S_2, S_3: Excited singlet states
T_1: Excited triplet state	hν: Light energy
F: Fluorescence	P: Phosphorescence
IC: Internal Conversion	ISC: Inter-System Crossing
Straight arrows: Radiative processes	Wavy arrows: Non-radiative processes

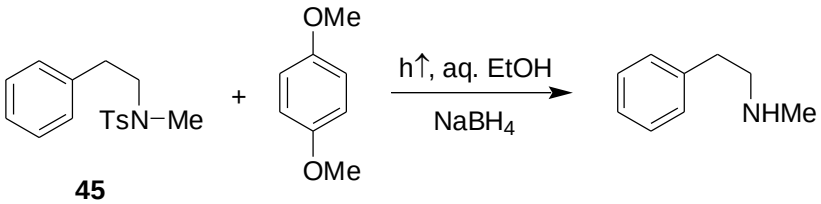
2.3 Protecting groups based on sensitized irradiation

Several researchers have used PET to bring about photorelease. However, PRPGs using a PET-based deprotection strategy are fairly recent and have not been studied as extensively as the common PRPGs (*o*-nitrobenzyl and benzoin groups) that are removable by direct irradiation. Much work still needs to be done to optimize these systems and to understand the mechanisms of photorelease. Some of the more efficient sensitized photorelease systems will be discussed here.

2.3.1 Tosyl amides and esters

The first PET-based deprotection strategy was developed by Yonemitsu et al. [79] They found that photolysis of tosylamides in the presence of electron rich compounds such as 1,4-dimethoxy benzene, and a secondary reductant, such as sodium borohydride, in protic solvents, resulted in release of the free amines (Scheme 2.1). The reaction was believed to proceed through a sulfonamide anion radical, which releases the amine and sulfinyl radical. The secondary reductant was found to be necessary in order to reduce the sulfinyl radical and the sensitizer cation radical to sulfinic acid and sensitizer respectively (Scheme 2.2).

Scheme 2.1 Photorelease of amines from tosylamides



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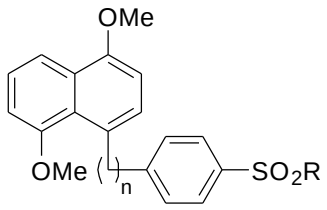
While the chemical yields for deprotection were quite high, very low quantum yields of photorelease were obtained. This was believed to be due to the low efficiency of intermolecular PET. Various sensitizers were covalently linked to the benzenesulfonamide moiety through an alkyl linker in the hope that the intramolecular photoreaction would be more efficient. [80] The most efficient photorelease was obtained with the 4-(4,8-dimethoxynaphthylmethyl) benzenesulfonyl (DNMBS) group (Figure 2.5), and the quantum yield of photorelease was as high as 0.65, as opposed to 0.069 for the intermolecular system.

Figure 2.5 The DNMBS group



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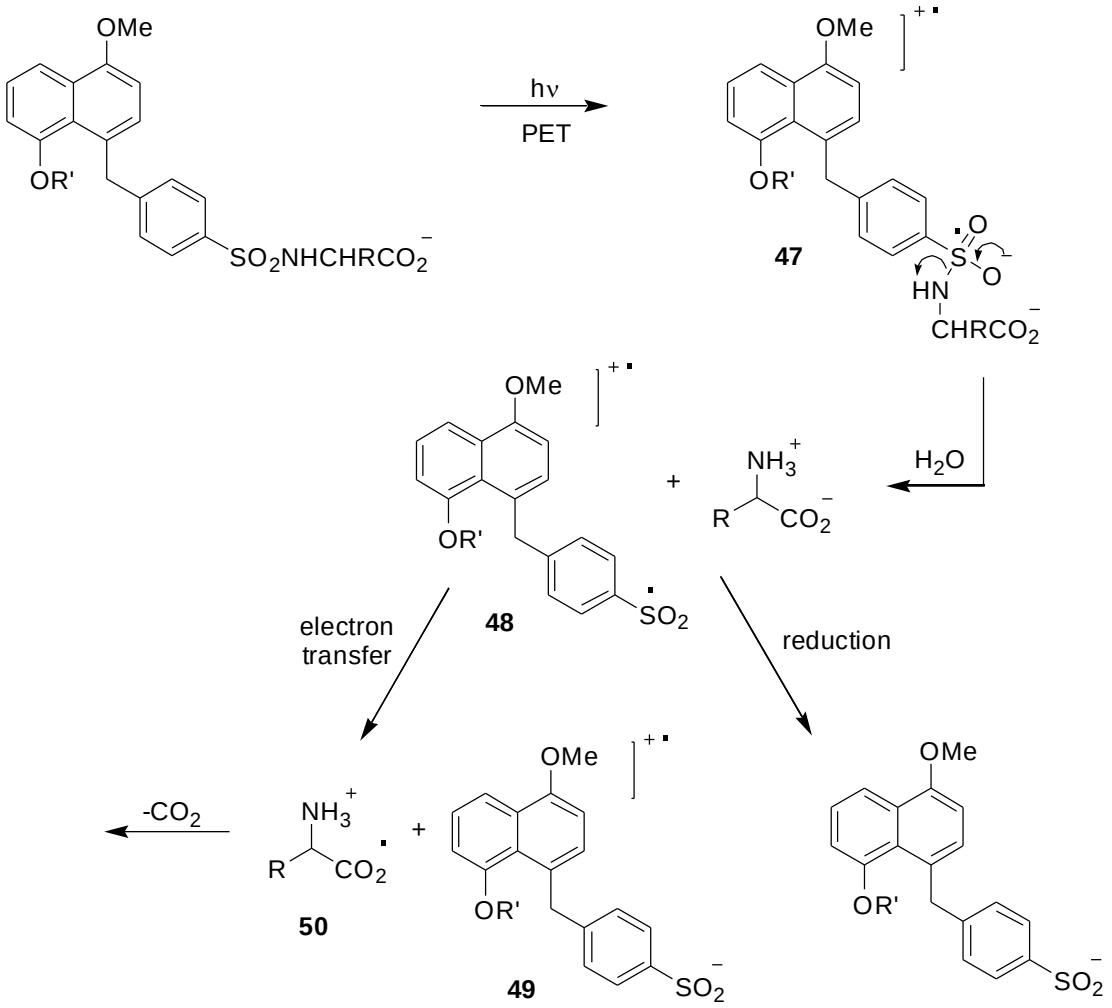
Scheme 2.2 Mechanism of photorelease of amino acids from the DNMBS group



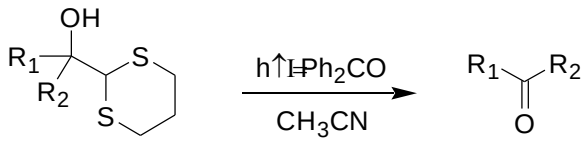
The DNMBS group has found use in the protection of various amines, amino acids, as well as the hydroxyl group. In the case of amino acids, poor chemical yields

were obtained despite good quantum yields. [81,82] To explain the low yields of the free acids, it was proposed that a secondary oxidation of the carboxylate group occurs, and causes the resulting amino acid radical **50** to undergo rapid decarboxylation (Scheme 2.2).

2.3.2 Dithianes

Kutateladze et al. have reported the photosensitized fragmentation reaction of dithiane-carbonyl adducts (Scheme 2.3). [83-85] They utilized this reaction to release ketones and aldehydes from dithianes upon photolysis with a triplet sensitizer such as benzophenone. They have applied this photorelease to the synthesis of dithiane-based photolabile scaffolds for molecular recognition, [84] and photolabile liposomes. [86]

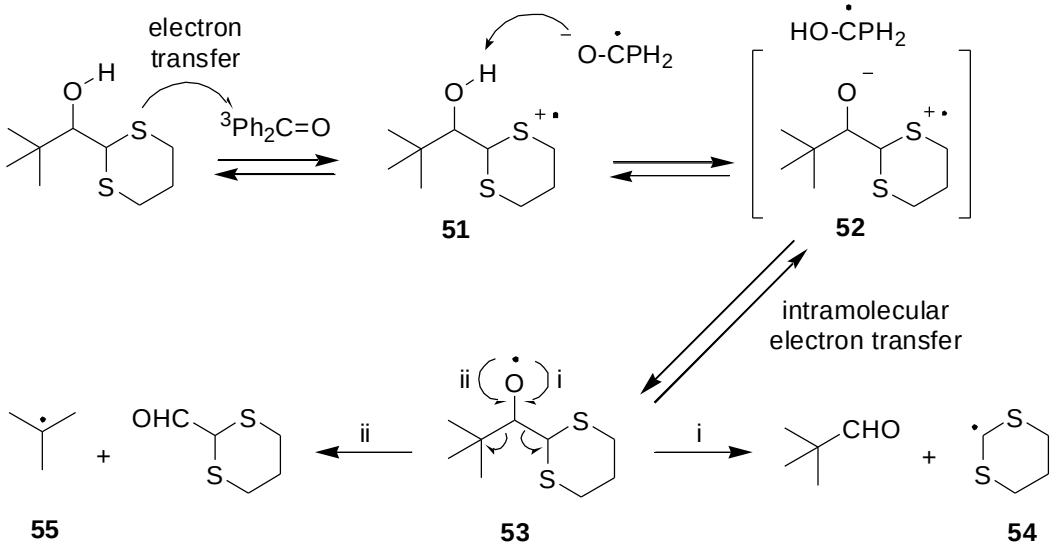
Scheme 2.3 Photorelease of ketones from dithianes



The proposed reaction mechanism involves a PET from the dithiane to the excited state oxidant, benzophenone (Scheme 2.4). [87] The anion radical of benzophenone is formed and deprotonates the hydroxyl group. The resulting zwitter-ionic intermediate **52** undergoes an intra-molecular electron transfer to give an oxy radical **53**. This radical can undergo either of two fragmentation pathways, i and ii, to give the carbonyl and a radical. The product compositions were found to depend on the stability of the released radicals. In the case of simple carbonyl compounds, pathway i predominated and the

resulting products were the released aldehyde and the dithianyl radical **54**, while branched carbonyls fragment through pathway ii to form the more stable tertiary radical **55**.

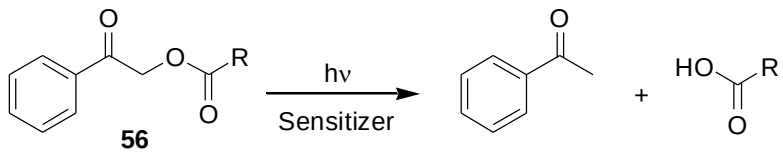
Scheme 2.4 Mechanism of photorelease from dithianes



2.3.3 The phenacyl group

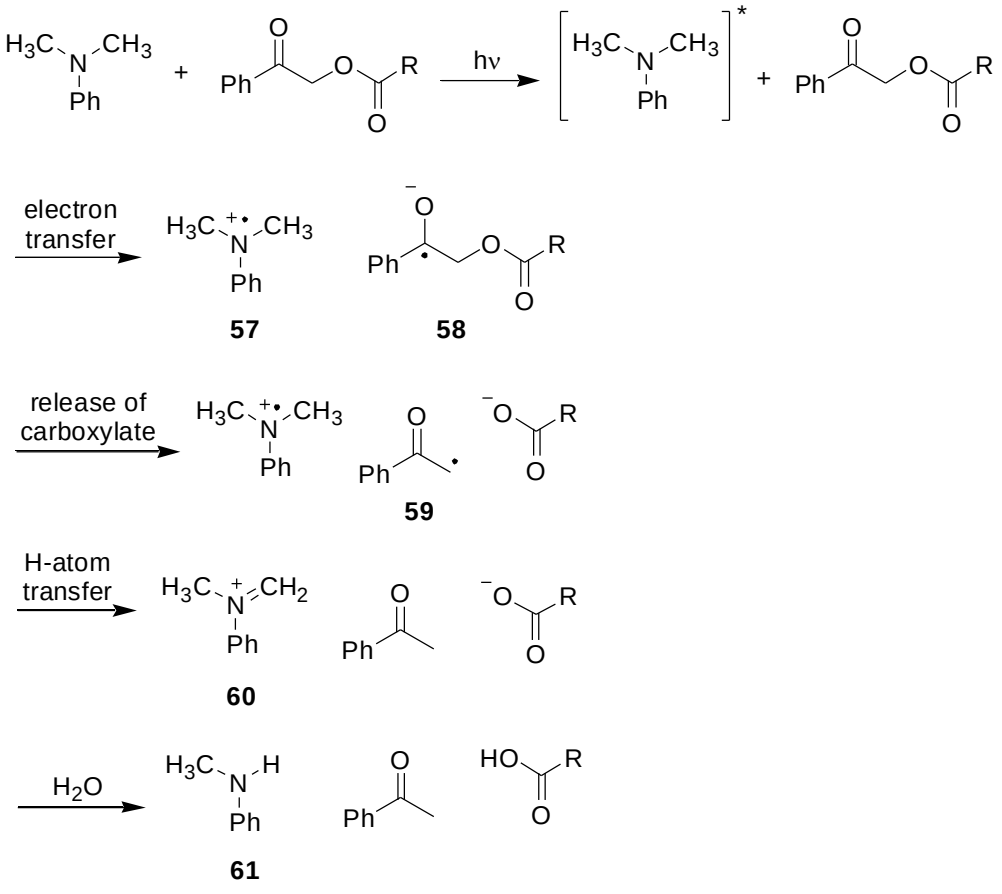
Phenacyl groups have been used to release carboxylic acids by direct irradiation as discussed in chapter 1. Recently, they have been successfully used in a PET-based strategy to release carboxylic acids, amino acids and phosphates (Scheme 2.5). The release occurred with satisfactory chemical and quantum yields. [88,89]

Scheme 2.5 Sensitized photorelease from phenacyl esters



The proposed mechanism of photorelease for the dimethylaniline (DMA) sensitized case is shown in Scheme 2.6. A PET occurs from the excited singlet state of DMA to form the DMA cation radical and the phenacyl anion radical **58** which rapidly eliminates the carboxylate anion. The resulting phenacyl radical **59** abstracts an electron from the DMA cation radical to form acetophenone and an iminium ion **60** which can be hydrolyzed to give *N*-methyl aniline **61**.

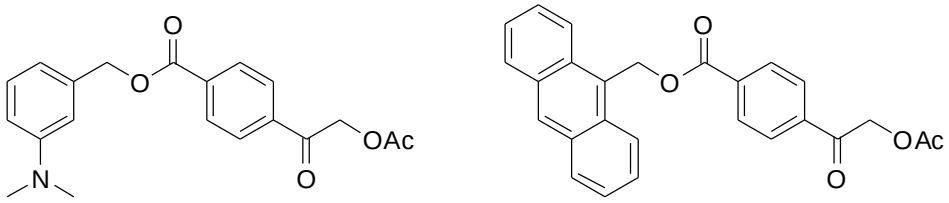
Scheme 2.6 Mechanism of DMA-sensitized photorelease from phenacyl esters



Similar to Yonemitsu's strategy, it was attempted to improve the efficiency of photorelease by covalently linking the sensitizer to the phenacyl ester. Two such linked

systems were studied, a dimethylaniline-linked phenacyl ester and the anthracene analog (Scheme 2.7). [90] In the unlinked case, both dimethylaniline and anthracene effected photorelease from the phenacyl esters. Interestingly, when these chromophores were linked to the phenacyl esters, photorelease was observed only in the case of DMA-linked esters, while with the anthracene chromophore, there was no deprotection. This was attributed to an efficient return-electron transfer process that competes with the release of free carboxylate. It was observed that the initial charge transfer pair rapidly decayed to a low lying triplet state of anthracene. Thus, from this study it is seen that in designing donor-acceptor linked systems, it is essential to have the charge-transfer state lower in energy than the triplet state of the sensitizer.

Scheme 2.7 Sensitizer-linked phenacyl esters



62 **63**

2.4. Conclusions

The sulfonamide group, particularly the DNMBS group provides an efficient PET-based method to protect the amino and hydroxyl groups. Dithianes and related adducts can be used to release the carbonyl functionality. Research in our lab has focussed on developing improved PRPGs for the carboxylate functionality, based on the phenacyl group. The phenacyl group was successfully used to release a variety of carboxylic acids by a PET-based strategy. However, this group suffers from several

drawbacks. The phenacyl group has poor solubility in aqueous systems. The deprotection wavelengths used are not as high as would be desired. Moreover, the choice of sensitizers is limited due to the low reduction potential (-2.2 V) of the phenacyl esters, as only few sensitizers can carry out an exothermic electron transfer to these groups. The low reduction potential offers yet another pitfall as it doesn't allow for protection of molecules that can be easily reduced.

These disadvantages of the phenacyl group prompted us to develop an improved PRPG having a high reduction potential, which would allow it to protect even substrates that can be readily reduced. A high reduction potential would enable the use of a wide range of sensitizers and bring us closer to our goal of using visible light sensitizers for photorelease. In the following chapters, the development of such a PRPG will be discussed.

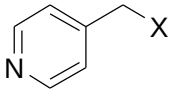
Chapter 3. *N*-Methyl Picolinium Esters: A New Class of PRPGs

3.1 Introduction

In our endeavor to develop a new and efficient PRPG for carboxylic acids, we investigated conventional protecting groups that could be modified into PRPGs. An ideal candidate would be a group that can be easily converted into the protected molecule, which should then be stable to the reaction conditions, inert in the dark, soluble in aqueous solutions, and give harmless byproducts upon photolysis. Since we intend to use PET techniques to perform an electron transfer, the protecting group should preferably be removable by reductive means.

During our search for a protecting group that satisfies these requirements, we came across the 4-picolyl group (4-pyridylmethyl) which was introduced as a conventional protecting group by Young et al. in 1968 (Figure 3.1), and has been used as a carboxyl protecting group in peptide synthesis. [91,92] Its use has also been extended to the protection of hydroxyl groups of amino acids. [93]

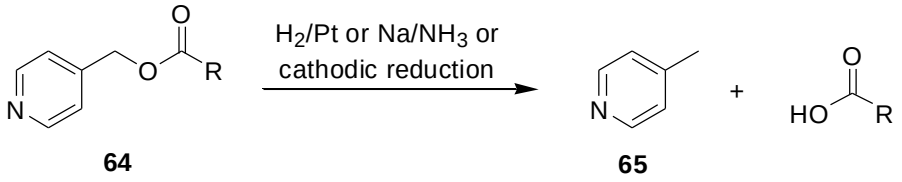
Figure 3.1 The 4-picolyl group



The picolyl group has been used as a basic handle to facilitate peptide synthesis, and is thus compatible with aqueous and biological systems. The by-product of the release (4-picoline) is non-reactive and non-toxic. Previous reports indicate that the picolyl esters can be released easily using cold alkali, catalytic hydrogenation, reducing

metals, or electrolytic reduction (Scheme 3.1). [94] The latter two reactions are particularly interesting as they indicate that the picolyl group can be removed by reduction of the group.

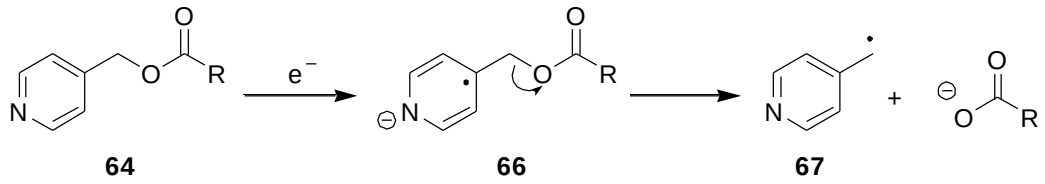
Scheme 3.1 Reductive deprotection of picolyl esters



64 **65**

The mechanism of release from picolyl esters has not been examined in detail. It is likely that reduction of the picolyl ester affords the anion radical of the ester which then undergoes bond cleavage to release the carboxylate anion and the picolyl radical (Scheme 3.2). If the release proceeds through this mechanism, then it should be possible to accomplish the analogous reaction via photochemical reduction.

Scheme 3.2 Mechanism of reductive cleavage of picolyl esters



64 **66** **67**

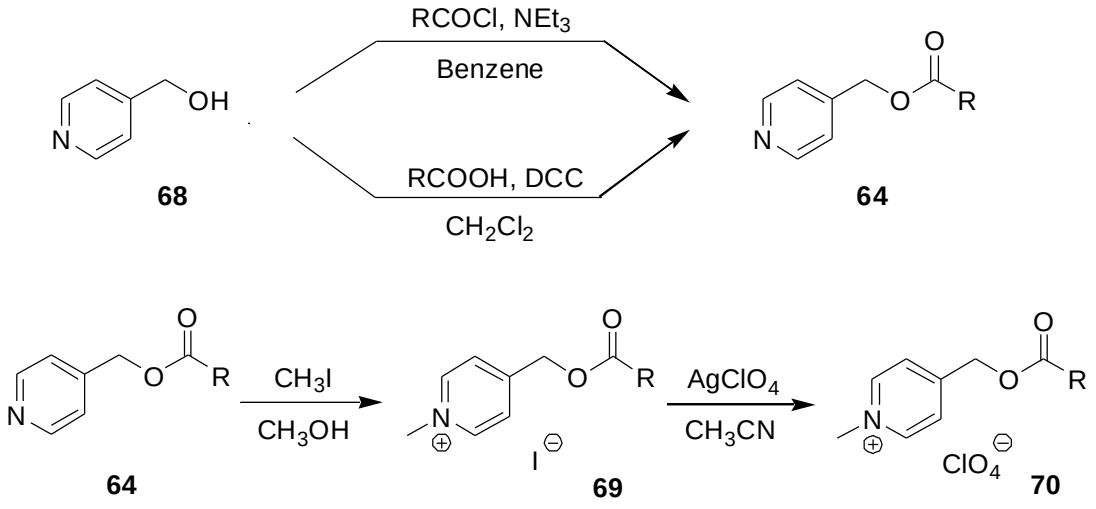
The 4-picolyl esters are clearly suitable for a PET-based photodeprotection. However, it is likely that the picolyl esters do not have high reduction potentials, as the closely related pyridine has a reduction potential of only about -2.6 V vs. SCE. [95] The reduction potentials of *N*-alkylpyridinium salts are reported to be about –1.7 V, [95] suggesting that the *N*-alkylated derivatives would be better electron acceptors. Thus, we

decided to modify the 4-picolyl esters into *N*-methyl picolinium esters in an attempt to increase the reduction potential of the group, thereby allowing for PET with a wider array of sensitizers. The *N*-methyl picolinium salts would also have improved aqueous solubility.

3.2 Synthesis of picolinium esters

The protection of carboxylic acids was achieved by converting them into their corresponding picolyl esters by simple esterification procedures. The 4-picolyl esters **64** were prepared by the reaction of 4-pyridylcarbinol **68** with acid chlorides and triethylamine in benzene, [96] or alternately by reacting the corresponding carboxylic acids with 4-pyridylcarbinol and dicyclohexylcarbodiimide (DCC) in methylene chloride (Scheme 3.3). [94]

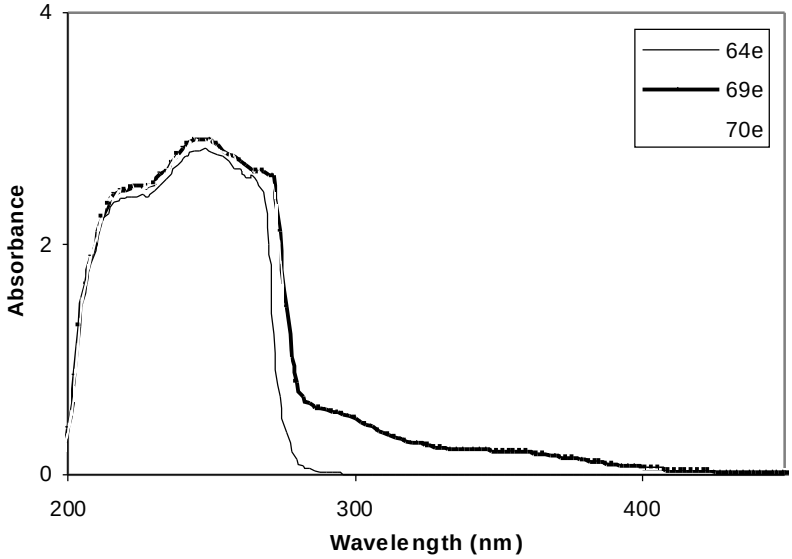
Scheme 3.3 Synthesis of picolinium esters



The picolyl esters **64** were then *N*-methylated with methyl iodide to give the corresponding iodide salts **69**. These iodide salts display a charge-transfer band around 350-400 nm, depending on the solvent. To avoid any ambiguities resulting from competing absorption by the sensitizers and the charge transfer band, the iodide counter-ion was exchanged for perchlorate, yielding **70**. A model compound lacking the carboxylate group, *N*-methyl picolinium perchlorate **71**, was also prepared by the same procedure, to study the properties of the picolinium group.

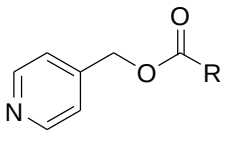
These perchlorate salts absorb below 320 nm, with some esters displaying a weak absorption tail above 320 nm (Figure 3.2). The UV spectra of the corresponding picolyl esters and picolinium iodides were also examined to ensure that these groups do not absorb light where the sensitizers are expected to absorb.

Figure 3.2 UV spectra of picolyl ester **64e**, picolinium iodide salt **69e** and picolinium perchlorate salt **70e** in acetonitrile

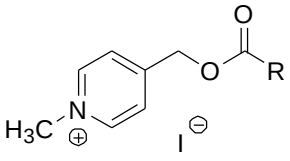


Eight examples of picolinium esters **70**, listed in Table 3.1, were prepared. The carboxylic acids were chosen with a view to demonstrate photorelease in various aliphatic as well as aromatic esters. Also, as we analyzed the photoproducts by ^{1}H NMR peak integration, it was desirable to use carboxylic acids with peaks distinct from those of the sensitizers. The syntheses proceeded with good yields as seen in Table 3.1.

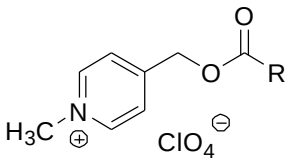
Table 3.1 Protection yields for picolinium esters



64



69



70

Ester	R	Yields %		
		64	**69**	**70**
a	CH_3	94	91	82
b	C_6H_5	60	84	51
c	$CH_2C_6H_5$	88	95	80
d	$C(CH_3)_3$	82	88	88
e	$CH(C_6H_5)_2$	83	74	92
f	$CH_2C_6H_4CH_3$	73	100	87
g	$CH_2C_6H_4Br$	71	89	64
h	$CH{=}CHC_6H_5$	98	73	78

3.3 Control experiments on picolyl and picolinium esters

Having synthesized various picolyl and picolinium esters, the next step was to determine if they could behave as photoremovable protecting groups, and release the free acids upon photolysis.

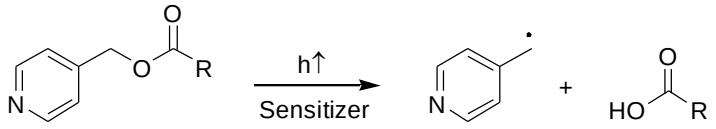
Preparative photolyses of the 4-picolyl and picolinium esters were carried out in the presence of various electron-donating sensitizers to determine if C-O bond scission would occur, releasing the corresponding carboxylic acids. Four different sensitizers, *N*, *N*, *N*', *N*' -tetramethyl benzidine (TMB), 9-methyl carbazole (9-MC), pyrene, and triphenylamine (TPA) were employed. The esters were subjected to filtered (>320nm) irradiation with the photosensitizers, using a 200 W Hg lamp. At these wavelengths, the sensitizers absorb the light but the esters do not. The photolysis solution consisted of 3.5 mM of ester and 3.5-4.0 mM of sensitizer in methanol. In each case, an identical solution was held in the dark as a control sample. The photolysis and dark control solutions were then analyzed by ^{1}H NMR and the yields of the carboxylic acids, as well as the amount of ester consumed, were determined by integration of the acid peaks relative to an internal standard. Estimated error is ± 5%.

3.3.1 Photolysis of the 4-picolyl esters

Upon irradiation, the 4-picolyl esters were found to release carboxylic acids only when TMB was used as the photosensitizer (Table 3.2). When other sensitizers such as 9-MC and pyrene were employed, no detectable conversion of the ester was observed, even upon long exposure times (up to 8 hrs). We attribute this to the fact that the picolyl group is difficult to reduce. TMB is the strongest reducing agent amongst the sensitizers that

were used, while 9-MC and pyrene have much lower oxidation potentials. Thus it appears that the picolyl esters require highly reducing photosensitizers for photodeprotection.

Table 3.2 Sensitized photofragmentation of 4-picolyl esters **64**.



64

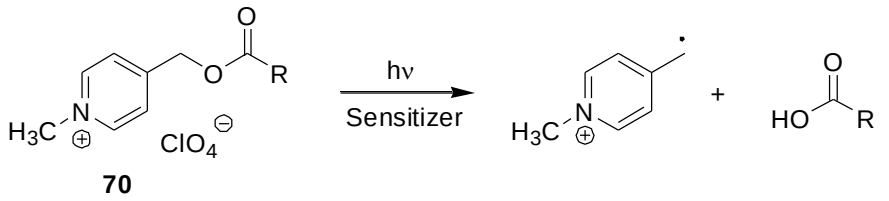
Compound	R	Sensitizer	Conditions	% acid formed	% ester consumed
64d	$C(CH_3)_3$	TMB	3h, MeOH	14	31
64e	$CH(C_6H_5)_2$	TMB	3h, MeOH	43	53
64f	$CH_2C_6H_4CH_3$	TMB	3h, MeOH	29	30

Yields were determined by ^1H NMR integration of the carboxylic acid peak relative to an internal standard. Estimated error ± 5 %

3.3.2 Photolysis of the *N*-methyl-4-picolinium esters

In contrast to the picolyl esters, it is possible to initiate the fragmentation of picolinium esters using a variety of sensitizers. As shown in Table 3.3, four different sensitizers TMB, 9-MC, pyrene, and TPA were employed with ester **70c** and in each case efficient release of the free acid was observed upon photolysis.

Table 3.3 Sensitized photofragmentation of 4-picolinium esters **70**



70

Ester	R	Sensitizer	λ_{max}	Conditions	% acid formed	% ester consumed
70c	$CH_2C_6H_5$	9-MC	350	3h, MeOH	45	41
70c	$CH_2C_6H_5$	TMB	345	3h, MeOH	92	87
70c	$CH_2C_6H_5$	Pyrene	370	3h, MeOH	84	92
70c	$CH_2C_6H_5$	TPA	305	5h, MeOH	77	79

Yields were determined by ^{1}H NMR integration of the carboxylic acid peak relative to an internal standard. Estimated error ± 5 %

3.4 Development of a new PRPG

The control preparative photolyses reveal that picolinium esters can indeed be photoreleased in good yields. In order to develop the picolinium group as a practical and efficient PRPG the following steps need to be performed:

1. Preparative photolysis on a variety of picolinium esters- to determine if the protecting group is general for a wide range of carboxylic acids, and if yields of photorelease are sensitive to other functionalities present on the substrates.
2. Determination of quantum yields of photorelease- to estimate photochemical efficiency of the protecting group

3. Investigation of photorelease mechanism- to understand the photorelease process and factors affecting it, to identify and analyze intermediates and byproducts, and to optimize the PRPG.

Through several experiments, we have demonstrated that the picolinium esters are novel and efficient PRPGs for carboxylic acids. These experiments and their results will be discussed in detail in the following sections.

3.5 Preparative photolysis on picolinium esters

Sensitized photolyses of various picolinium esters were carried out using a 200 W Hg lamp, with a 320 nm cutoff filter and 9-MC as the sensitizer. Equimolar solutions (or slight excess of sensitizer) of the ester and sensitizer (3.5-4.0 mM) in methanol were photolyzed for a fixed amount of time, and the photoproducts were analyzed by ^{1}H NMR as described before.

Control experiments were also carried out on several esters without the sensitizers, under identical photolysis conditions. In the absence of the sensitizer, irradiation of the picolinium salts afforded no photoproducts, indicating that these esters are stable to the photolysis conditions.

Under sensitized irradiation, the esters efficiently released the free carboxylic acids (Table 3.4). For the simple aryl- and alkyl-esters, **70a-f** the conversions were clean and the amount of carboxylic acid formed was the same or nearly the same as the amount of ester consumed. It was observed that the amount of ester consumed was not the same for the different esters, although the chemical yields of the carboxylic acids were

consistently quantitative. This might be due to differences in lamp intensity and/or errors due to ^{1}H NMR integration.

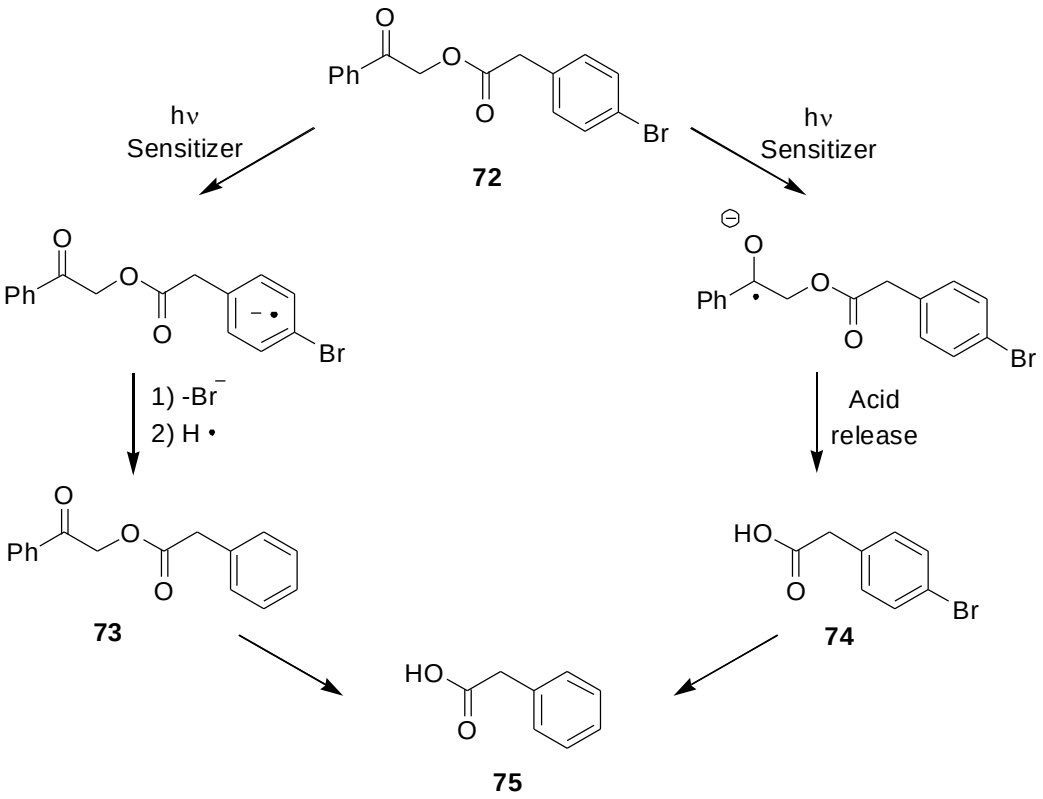
Table 3.4 Sensitized photofragmentation of *N*-methyl-4-picolinium esters

Compound	R	Sensitizer	Conditions	% acid formed	% ester consumed
70a	CH_3	9-MC	3h, MeOH	62	65
70b	C_6H_5	TMB	3h, MeOH	30	26
70c	$CH_2C_6H_5$	9-MC	3h, MeOH	45	41
70d	$C(CH_3)_3$	9-MC	3h, MeOH	43	43
70e	$CH(C_6H_5)_2$	9-MC	3h, MeOH	74	78
70f	$CH_2C_6H_4CH_3$	9-MC	3h, MeOH	21	25
70g	$CH_2C_6H_4Br$	9-MC	3h, MeOH	49	58
70h	$CH=CHC_6H_5$	9-MC	3h, MeOH	22	64

Yields were determined by ^{1}H NMR integration of the carboxylic acid peak relative to an internal standard. Estimated error ± 5 %

In the case of *N*-methyl picolinium 4-bromophenylacetate **70g**, the protected acid can be easily reduced. Previous PET studies with the corresponding phenacyl esters demonstrated the difficulties of reducing the protecting group preferentially over the aryl bromide part of the ester (aryl bromides readily expel the halide ion following one-electron reduction). [97] Phenacyl 4-bromophenylacetate yields a mixture of products upon sensitized photolysis (Scheme 3.4). [88] This is a result of competing electron transfer to the phenacyl group and the aryl bromide. Along with 4-bromophenylacetic acid **74**, the debrominated phenacyl phenylacetate **73** and phenylacetic acid **75** were also obtained.

Scheme 3.4 Competing bromide and carboxylate elimination in phenacyl bromophenylacetate



In contrast, sensitized photolysis of the corresponding picolinium ester **70g** gives only the desired product, 4-bromophenylacetic acid, in good yields. This result indicated that the picolinium group is far easier to reduce and can be used for protection of reductively labile carboxylic acids.

The cinnamate ester **70h** was studied to observe the effect of the alkene functionality on efficiency of photorelease. Alkenes, especially highly conjugated ones such as the cinnamate ester, are known to undergo several photochemical reactions, and are difficult to photodeprotect. Upon photolysis, we observed release of cinnamic acid, although in low yields and with several byproducts. At higher conversions of the ester,

the yields of the free acids were found to diminish. This may be due to the photoreactivity of the cinnamate ester or due to photoreactions of the product cinnamic acid itself, which could be undergoing secondary photochemical processes.

3.6 Quantum yields for photorelease

Quantum yield (Φ) of a photochemical reaction is a measure of the efficiency of the reaction. The quantum yield can be defined as the ratio of number of photoreactions to the number of photons absorbed by the system.

Φ = moles of given species formed or destroyed/ moles of photons absorbed (2)

The quantum yields for sensitized photorelease were determined for the picolinium esters. Solutions of the ester and an equal amount of sensitizer were irradiated by a 1000 W xenon lamp fitted with a monochromator, for different periods of time, and the rate of disappearance of the ester was determined by ^{1}H NMR. The quantum yields were found using equation 3.

$$\Phi = RP/ 0.588. I_o (1\text{-}10^{-A}) \qquad (3)$$

The parameter R is the rate of disappearance of the ester (in molecules cm^{-3} s^{-1}), P is the path length of the sample cell (1 cm), I_o is the light intensity of the lamp (in photons cm^{-2} s^{-1}), obtained from a radiometer, 0.588 is the correction factor for the radiometer obtained by ferrioxalate actinometry, [98] and A is the absorbance of the sample at the

irradiation wavelength. The quantum yields were determined for both 9-MC and TMB in methanol and acetonitrile (Table 3.5). Higher Φ values were obtained in methanol than in acetonitrile. This is possibly due to the ability of MeOH to prevent recombination of the initial fragments formed upon the C-O bond scission due to its higher polarity, as well as to scavenge the free radicals formed.

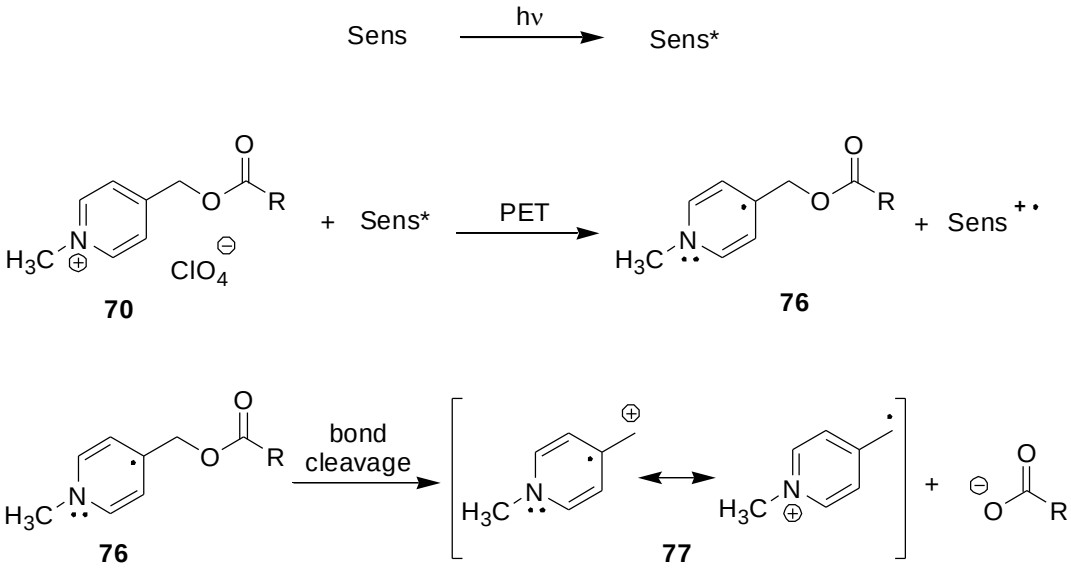
Table 3.5 Quantum yields for sensitized photolysis of esters **70**

Compound	R	Sensitizer	Solvent	Quantum yield
70c	$CH_2C_6H_5$	9-MC	MeOH	0.23
70c	$CH_2C_6H_5$	9-MC	MeCN	0.14
70c	$CH_2C_6H_5$	TMB	MeCN	0.05

3.7 Proposed mechanism for deprotection

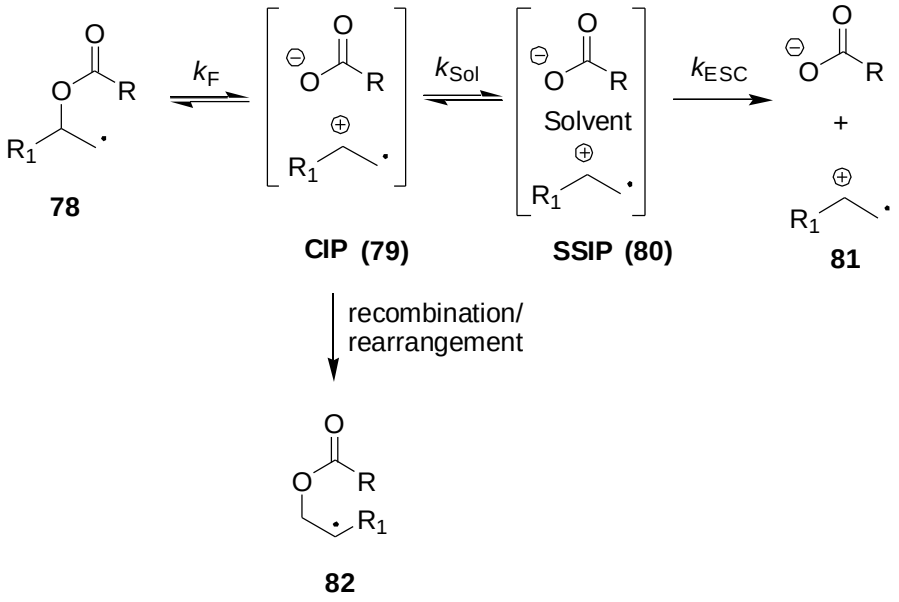
The picolinium esters release the free acids efficiently upon irradiation, as seen by the deprotection yields and quantum yields. It is essential to understand the mechanism of this photorelease in order to be able to modify or improve the system. The proposed mechanism of the photofragmentation is shown in Scheme 3.5. Upon irradiation, the photosensitizer molecule (Sens) absorbs light preferentially over the substrate and is promoted to its excited singlet state ($Sens^{*1}$). The latter transfers an electron to the picolinium ester to give the picolyl radical 7**6**. The reduced radical 7**6** subsequently releases the carboxylate anion, along with a picolylmethyl radical fragment **77**.

Scheme 3.5 Proposed mechanism for the photofragmentation reaction



Similar heterolytic cleavage reactions have been reported previously for the related β-(phosphatoxy)alkyl and β-(acyloxy)alkyl radicals. [99-101] These radicals undergo a rearrangement reaction, which proceeds through a rate-determining radical ionic fragmentation to a contact radical ion pair (CIP), which can then undergo recombination to give the rearranged product. Alternately, if polar solvents are used, there will be solvent separation followed by escape from the solvent cage to give the carboxylate anion and a positively charged radical (Scheme 3.6).

Scheme 3.6 Fragmentation/rearrangement reaction of β-(acyloxy)alkyl radicals.



Thus, our proposed deprotection mechanism has a well established precedent in the β-(acyloxy)alkyl radical fragmentation. We obtained further evidence to confirm the proposed mechanism by the following experiments:

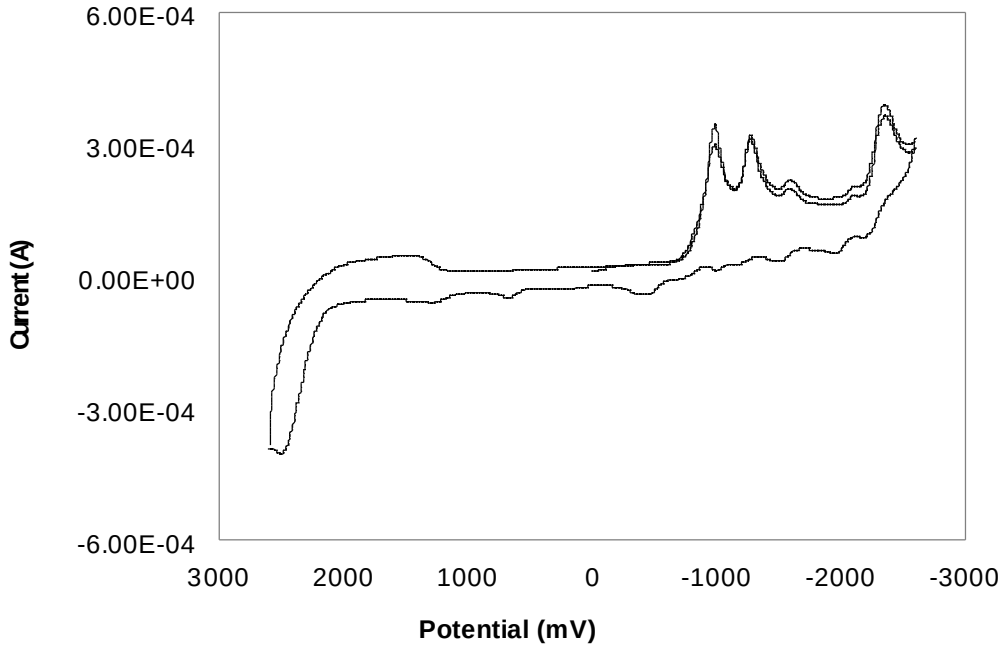
1. Cyclic voltammetry
2. Fluorescence quenching
3. Laser flash photolysis
4. Trapping of intermediates

3.7.1 Cyclic Voltammetry

It is necessary to determine the ability of the picolinium esters to accept an electron from the sensitizer, as a reductive electron transfer is the key step in the mechanism. The reduction potentials, $E_{red,}$ of the various *N*-methyl picolinium esters were

determined by cyclic voltammetry (CV) experiments (Figure 3.3). The E_{red} values were found using a reference Ag/AgCl electrode, a carbon working electrode and a platinum auxiliary electrode. A ferrocene/ferrocenium couple was used as the internal standard. In each case an irreversible reduction wave was observed with $E_{½}$ between –1050 mV to –1200 mV (Table 3.6). The $E_{½}$ values were calculated at a scan rate 100 mV/sec.

Figure 3.3 Cyclic voltammogram of *N*-methylpicolinium acetate perchlorate **70a**



The reduction potential of the model compound *N*-methyl picolinium perchlorate **71** was also determined by CV to be -1380 mV (Figure 3.4). As expected, this molecule has a reduction potential lower than the picolinium esters, since it lacks the carboxylate leaving group and the inductive effect of the oxygen of the -OCOR substituent.

Figure 3.4 Cyclic voltammogram of *N*-methylpicolinium perchlorate **71**

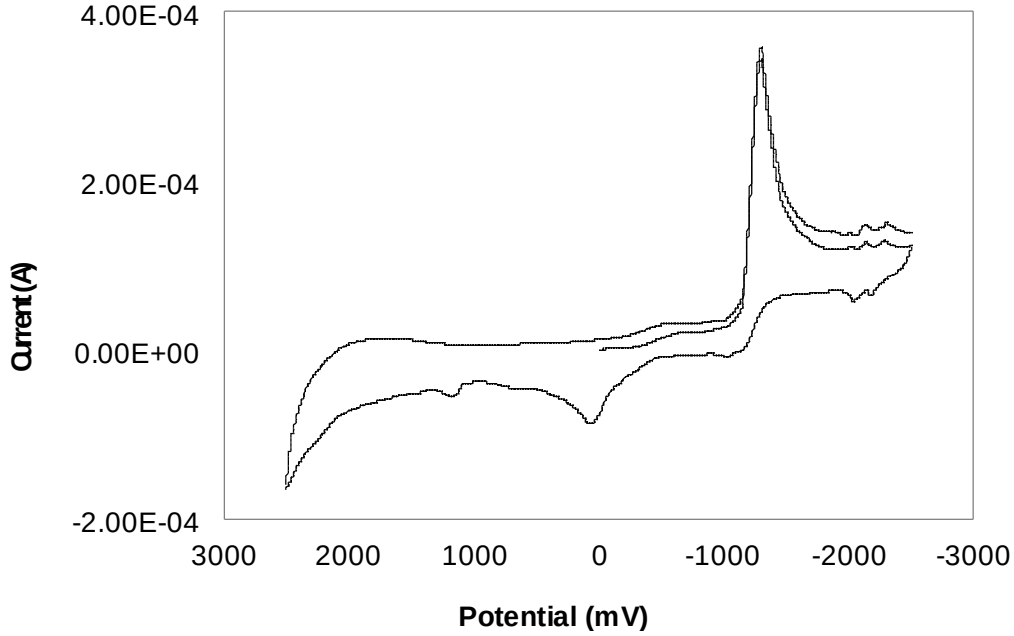


Table 3.6 Reduction potentials for *N*-methyl-4-picolinium esters.

Compound	R	E_{red} (V) vs. SCE
70a	CH_3	-1.09
70b	C_6H_5	-1.01
70c	$CH_2C_6H_5$	-1.08
70d	$C(CH_3)_3$	-1.11
70e	$CH(C_6H_5)_2$	-1.17
70f	$CH_2C_6H_4CH_3$	-1.15
70g	$CH_2C_6H_4Br$	-1.09
70h	$CH=CHC_6H_5$	-1.05

3.7.2 Selection of sensitizer

The sensitizer plays a vital role in a PET based deprotection strategy. Hence, selection of sensitizers is an important step. A suitable photosensitizer must satisfy the following criteria:

1. It must be stable in the ground state in the absence of light.
2. It must not react with the protected molecule in the absence of irradiation- there must not be any ground-state complexation between the sensitizer and protected molecule.
3. The sensitizer should be an excited state electron donor
4. The sensitizer must efficiently donate an electron to the protecting group, and it is essential that this step be exergonic.

The feasibility of electron transfer from the sensitizer to the picolinium moiety can be determined using the Weller equation (Equation 1). The Weller equation relates the free energy change for electron transfer to the oxidation potential of the electron-donating sensitizer (E_{ox}), the reduction potential of the picolinium ester (E_{red}), and the excited state energy of the sensitizer (E_{o-o}).

$$\Delta G_{ET} = 23.06\,(E_{ox} - E_{red} - e^2/R\varepsilon) - E_{o-o} \qquad (1)$$

The correction factor for desolvation and ion-pair attraction ($e^2/R\varepsilon$) is negligible in polar solvents such as acetonitrile and methanol and can be ignored for qualitative purposes.

$$\text{Also, } E_{ox}^* = E_{ox} - E_{o-o} / 23.06 \qquad (4)$$

where, E_{ox}^* is the excited-state oxidation potential of the sensitizer. So eqn 1 can be reduced to,

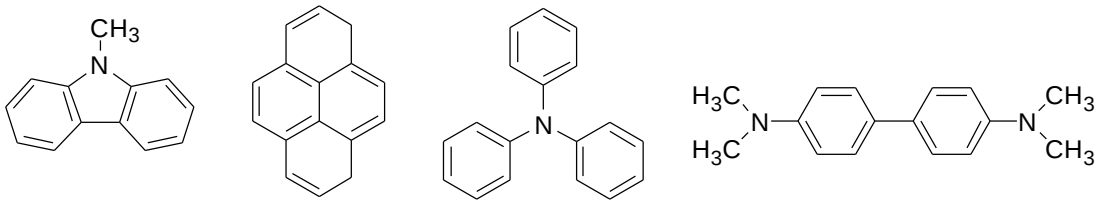
$$\Delta G_{ET} = 23.06\,(E_{ox}^{*} - E_{red}) \qquad (5)$$

The photosensitizers employed in this study are listed in Table 3.7, along with their photophysical parameters. The E_{ox}^{*} values for the sensitizers are derived from published values for the singlet-state energies ($E_{o\text{-}o}$ in kcal/mol) [95] and their ground state oxidation potentials (E_{ox} in V vs. SCE) using eq 4.

As seen from Table 3.7, TMB is the strongest excited state reductant, having an E_{ox}^{*} = -3.17 V (vs. SCE). The least effective excited state reductant is triphenylamine (TPA), which has an E_{ox}* value of –2.06 V. Pyrene and 9-methylcarbazole have intermediate values of –2.17 and –2.46 V, respectively.

Thus for the sensitizers employed in this study, ΔG_{ET} is predicted to range between -22.1 kcal/mol (in the case of Ph_3N) and –47.7 kcal/mol (in the case of TMB), using -1.1 V as the E_{red} for esters **70**. Thus, the thermodynamics of this system are favorable and consistent with our mechanism.

Figure 3.5 Photosensitizers used for reducing picolinium esters



9-MC Pyrene TPA TMB

Table 3.7 Properties of photosensitizers used in photocleavage experiments [95]

Sensitizer	E_{ox}^{*} (V)	E_{o-o} (kcal/mol)	τ (ns)	λ_{max} (nm)
N, *N*, *N*', *N*'-tetramethylbenzidine (TMB)	-3.17	83.0	9.4	350
9-methylcarbazole (9-MC)	-2.46	82.1	16.0	345
Pyrene	-2.17	76.8	190.0	370
Triphenylamine (TPA)	-2.06	70.1	17.0	305

To ensure that there is no ground-state complexation between the picolinium salts **70** and the sensitizers, we examined the UV-vis spectra of mixtures of the perchlorate salts and sensitizers. The UV spectra of the sensitizers were found to be unchanged upon addition of increasing amounts of esters **70**. No charge transfer bands were observed, and the UV spectra of sensitizers showed little change with addition of esters upto 20 mM (1-2 mM solutions of sensitizer in 3.5 mL methanol were used). Thus the chosen sensitizers do not react with the picolinium esters in the ground state.

3.7.3 Fluorescence quenching

Fluorescence quenching experiments were performed to determine if there was indeed an electron transfer from the sensitizer to the protected molecule, and if so, to observe the efficiency of the electron transfer. As seen in the proposed mechanism in Scheme 3.5, electron transfer occurs from the excited singlet-state of the sensitizer. Hence, interaction between the acceptor molecule and the excited state of the sensitizer in the form of electron transfer is expected to lower the fluorescence intensity of the

sensitizer. The fluorescence quenching rate is thus an indication of the efficiency of electron transfer from the sensitizers to the esters.

The initial fluorescence of the sensitizer was first observed. Increasing concentrations of the picolinium esters were then added to the sensitizer, and its fluorescence was seen to be efficiently quenched (Figure 3.6a). The rate of the fluorescence quenching was then determined using the Stern-Volmer equation (Eq. 6),

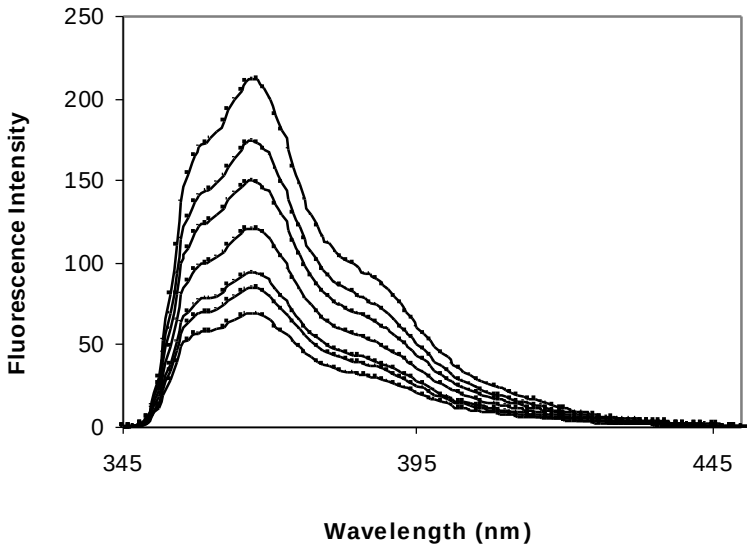
$$\Phi_o/\Phi = k_q [Q] \tau + 1 \qquad (6)$$

where, Φ_o/Φ is the ratio of fluorescence intensity without quencher (Φ_o) and with quencher (Φ), k_q is the rate constant of fluorescence quenching in M^{-1} s^{-1}, τ is the fluorescence lifetime of the sensitizer in seconds, and [Q] is the quencher concentration in mol/L. The relative fluorescence intensity (Φ_o/Φ) is plotted against quencher concentration [Q], and the slope of this plot gives the $k_q\tau$ value (Figure 3.6b). Knowing the fluorescence lifetimes τ of the sensitizers, the quenching rate constants were calculated.

The quenching rate constants are given in Table 3.8, and are seen to be near the diffusion limit (~ 1.9×10^{10} in MeCN). This indicates that there is efficient PET from the sensitizers to the picolinium esters. Thus, the fluorescence quenching experiments support our proposed mechanism.

Figure 3.6 (a) Fluorescence quenching of 9-MC by **70c (b)** Stern-Volmer plot

(a)



(b)

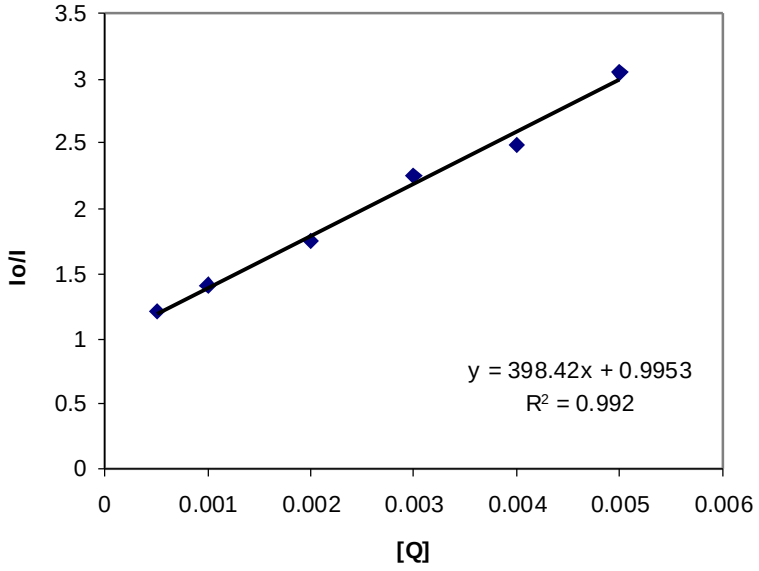


Table 3.8 Rate constants for flourescence quenching of sensitizers by picolinium esters

Compound	R	Sensitizer	k_q x 10^{10} (M^{-1} s^{-1})
70a	CH_3	9-MC	2.3
70a	CH_3	TMB	1.6
70b	C_6H_5	9-MC	2.5
70b	C_6H_5	TMB	2.9
70c	$CH_2C_6H_5$	9-MC	2.2
70d	C $(CH_3)_3$	9-MC	1.8
70e	CH $(C_6H_5)_2$	9-MC	2.4
70f	$CH_2C_6H_4CH_3$	9-MC	2.1
70g	$CH_2C_6H_4Br$	9-MC	1.8
70h	$CH=CHC_6H_5$	9-MC	1.4
64e	CH $(C_6H_5)_2$	TMB	1.6

The unalkylated esters **64** likewise quench the fluorescence of the most reactive donor, TMB (k_q =1.6 x 10^{10} M^{-1} s^{-1}). The less reactive sensitizer 9-MC is also quenched, but far less efficiently (k_q = 8.6 x 10^5 M^{-1} s^{-1}). The least reactive sensitizers, pyrene and Ph_3N show no fluorescence quenching when **64** is added. This observation is consistent with the observation of no photofragmentation of the picolyl esters using the latter sensitizers.

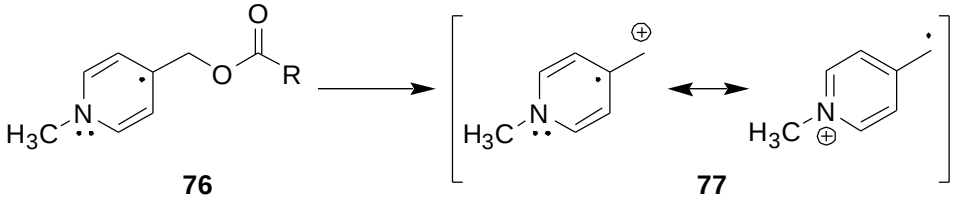
3.7.4 Laser flash photolysis (LFP) studies

Laser flash photolysis experiments were performed on the picolinium esters to observe the reactive intermediates formed during photolysis and to provide further support for the proposed mechanism. LFP involves photolyzing the substrate along with a sensitizer at the desired wavelength, and observing the UV-Vis spectra of the transient

species formed as a result of the photolysis. Irradiation of the esters was performed using light at 355 nm at which wavelength only the sensitizers absorb.

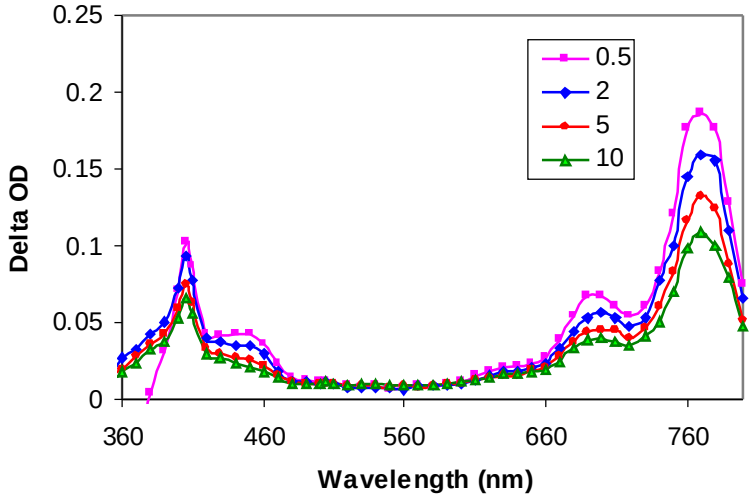
According to our mechanism, photolysis would induce an electron transfer from the sensitizer to the picolinium ester to form the initial reduced radical **76**, which would then undergo a heterolytic C-O bond cleavage, to release the free carboxylate anion, and form the radical **77**, which exists in two resonance forms. Thus, by LFP we might expect to detect the two short-lived intermediates **76** and 77 (Scheme 3.7).

Scheme 3.7. Reactive intermediates expected from photolysis of picolinium esters

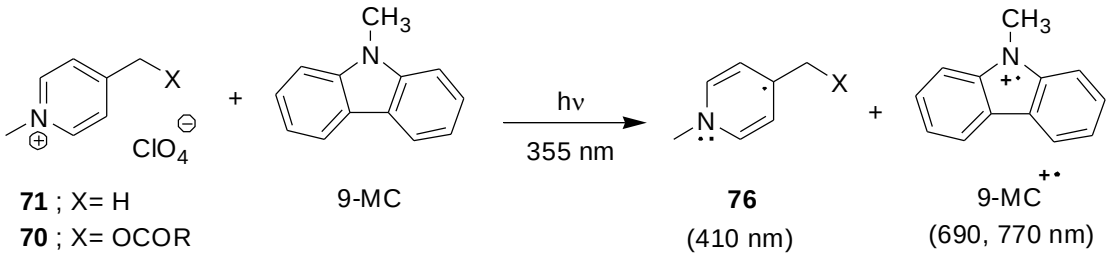


Laser flash photolysis (355 nm, 50-100 mJ/pulse, 4-8 ns) was performed on a solution of sensitizer (9-MC) and picolinium ester **70e** in dry acetonitrile. The resulting transient UV-Vis spectra obtained shows strong absorption bands at 410 nm, 690 nm and 770 nm (Figure 3.7). The latter two peaks correspond to the known absorptions for the 9-MC cation radicals (Scheme 3.8). [102] The remaining peak at 410 nm is assigned to the reduced *N*-methylpicolinium radical **76.** Several other esters were examined using the same LFP experiment and similar spectra are observed in all cases.

Figure 3.7 Transient absorption spectra from pulsed laser photolysis (355 nm, 50-100 mJ, 6 ns) of 9-MC with **70e** in N_2-purged CH_3CN.



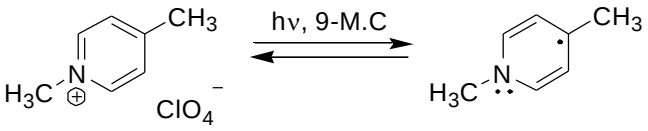
Scheme 3.8. PET from sensitizer to picolinium moiety.



The assignment of the 410 nm peak is supported by similar laser flash photolysis experiments carried out on the model compound *N*-methyl picolinium perchlorate **71.** This molecule has a similar structure as the picolinium esters, and only lacks the carboxylate leaving group. Thus it is expected to be reduced by excited state sensitizers, forming a radical similar to **76**. Similar to the esters **70**, compound **71** efficiently quenched the fluorescence of 9-MC, with a rate constant of 2.4 x 10^{10} M^{-1} s^{-1}. Preparative photolyses carried out with *N*-methyl picolinium perchlorate **71** and 9-MC

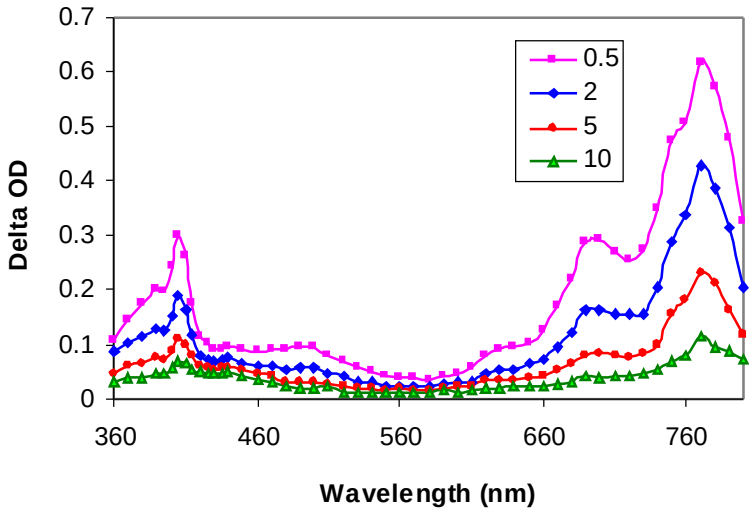
showed that there is no significant change in the solution composition over several hours of photolysis. Thus, **71** undergoes a reversible electron transfer from the sensitizer to form the *N*-methyl-4-picolyl radical **77** (Scheme 3.9).The transient absorption spectra obtained by LFP on **71** with 9-MC as sensitizer show the 9-MC cation radical peaks at 690 nm and 770 nm, and a peak at 410 nm, as seen with the esters **70** (Figure 3.8).

Scheme 3.9 Sensitized photolysis of *N*-methyl picolinium perchlorate **71**



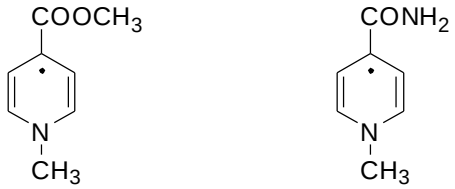
71 **77**

Figure 3.8 Transient absorption spectra from pulsed laser photolysis (355 nm, 50-100 mJ, 6 ns) of 9-MC with **71** in N_2-purged CH_3CN.



Absorption maxima of similar radicals in literature also support this assignment (Figure 3.9). The stable 1-alkyl-4-(carbomethoxy)pyridinyl **83** and 1-alkyl-4-carbamido pyridinyl **84** radicals have been reported to absorb at 400 nm. [103]

Figure 3.9 Pyridinyl radicals having similar structure and absorption as the picolyl radical **76**



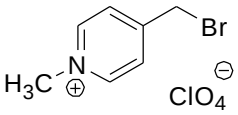
83 **84**

LFP experiments were carried out on esters **70** using the other sensitizers, TMB, pyrene and TPA as well. In all cases the observed transient signals agree with the known spectra for the cation radicals of the sensitizers. With 9-MC, pyrene and TPA, we were able to detect the expected 410 nm peak for the reduced ester. In the case of TMB, the strong absorbance of the TMB cation radical at 470 nm obscures the expected 410 nm peak for the reduced ester.

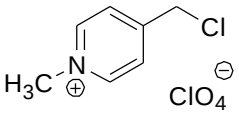
Clearly, the LFP experiment support our proposed PET mechanism, as we observe the absorption peaks for the oxidized sensitizers, and the reduced picolinium ester. However we were unable to detect the *N*-methyl-4-picolinium methyl radical **77**. To our knowledge the absorption spectrum of this radical is unknown.

We attempted to independently generate radical **77** from similar picolinium compounds. Changing the leaving group from carboxylate to halide was expected to have no effect on its release. We prepared the bromide and chloride analogues of the esters in order to change the leaving group (Figure 3.10). Irradiation of these molecules with a sensitizer is expected to release the halide leaving group and form radical **77**.

Figure 3.10 Bromide and chloride analogues of picolinium esters



85



86

LFP (266 nm, 5-15 mJ, 4-8 ns) experiments were performed on *N*-methyl-4-bromopicolinium perchlorate **85** and *N*-methyl-4-chloropicolinium perchlorate **86** with 9-MC as sensitizer. In both cases, we observed only the 410 nm peak and the absorption peaks for oxidized 9-MC, indicating that the initial electron transfer had occurred. However, no other peaks were seen that could be assigned to radical **77**. It is possible that the signal for radical **77** is obscured by absorptions of the sensitizer and/or the *N*-methyl-4-picolinium group.

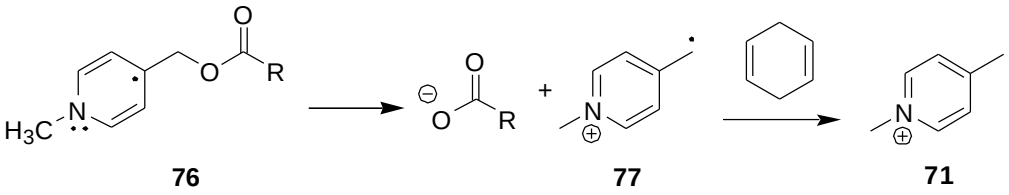
The unalkylated esters **64** were also examined using LFP. However, we were limited to using TMB as the sensitizer since the other three sensitizers are unable to reduce the ester. We observed the absorption peak corresponding to the cation radical of TMB, however, no transient peak corresponding to anion radical **66** could be detected. The anion radical of pyridine is known to have a weak absorption around 330 nm, and if radical **66** has a similar absorption, then under our LFP conditions we would be unable to observe it.

3.7.5 Trapping of *N*-methyl-4-picolinium radical 77

Since we were unable to detect the *N*-methyl-4-picolinium radical by LFP, we considered alternative experiments to verify the formation of **77**. Trapping experiments were an obvious choice, as reactive radicals such as **77** can be trapped using hydrogen atom donors. We used 1, 4-cyclohexadiene (CHD) which is a good H atom donor, having

C-H bond dissociation energy of 76.0 kcal/mol, and an oxidation potential of 1.6 V. Thus, it was anticipated that CHD would efficiently trap radical **77** as the *N*-methylpicolinium ion **71** (Scheme 3.10). This proved to be the case.

Scheme 3.10. Trapping of *N*-methyl-4-picolinium methyl radical by CHD.



76 **77** **71**

Table 3.9 Yields of acids and *N*-methyl picolinium ion in the presence of CHD.

Ester	R	Sensitizer	Conditions	% acid formed	% ester consumed	% **71** formed
70c	$CH_2C_6H_5$	9-MC	2h, MeOH	37	40	-
70c	$CH_2C_6H_5$	9-MC	2h, MeOH, CHD	86	94	76
70c	$CH_2C_6H_5$	9-MC	2h, MeCN	26	28	-
70c	$CH_2C_6H_5$	9-MC	2h, MeCN, CHD	47	46	43
70f	$CH_2C_6H_4CH_3$	9-MC	2h, MeOH	17	22	-
70f	$CH_2C_6H_4CH_3$	9-MC	2h, MeOH, CHD	44	49	38
70h	$CH{=}CHC_6H_5$	9-MC	2h, MeOH	26	38	-
70h	$CH{=}CHC_6H_5$	9-MC	2h, MeOH, CHD	42	57	43
70c	$CH_2C_6H_5$	pyrene	2h, MeOH	52	51	-
70c	$CH_2C_6H_5$	pyrene	2h, MeOH, CHD	94	99	80

Yields were determined by ^{1}H NMR integration of the carboxylic acid peak relative to an internal standard. Estimated error ± 5 %

As shown in Table 3.9, good yields of the radical product **71** are observed when CHD is included in the photolysis solutions. In the absence of CHD, the picolinium ion

71 was not detected in the ^{1}H NMR of the photolysis solutions. The fate of radical fragment **77** under these conditions is not known with certainty. The absence of a single significant by-product suggests that this radical decays through a variety of pathways.

In addition to successfully trapping the byproduct of the photorelease, the presence of CHD has other beneficial effects. We observed a significant increase in the efficiencies of the sensitized photolysis upon addition of CHD (Table 3.9). When CHD is included in the photolysis mixture, there is a 2-fold increase in the yield of free carboxylic acid and a corresponding increase in the amount of ester that is converted.

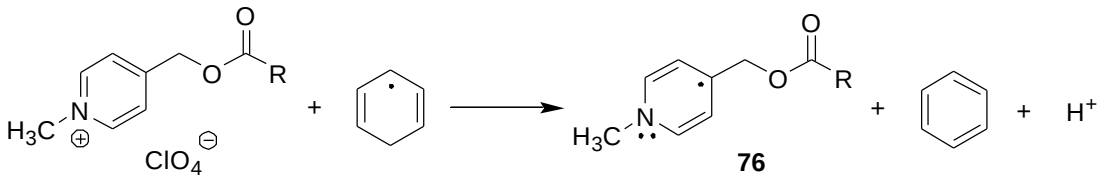
In addition to improved chemical yields, the presence of CHD also gives higher quantum yields of photorelease. In the case of ester derivative **70c**, the quantum yield for ester conversion increases from 0.23 in the absence of CHD to 0.39 when the trap is added (table 3.10).

Table 3.10 Quantum yields of photorelease with and without CHD.

Compound	Ester	Sensitizer	Conditions	Quantum yield
70c	$CH_2C_6H_5$	9-MC	MeOH	0.23
70c	$CH_2C_6H_5$	9-MC	MeOH, CHD	0.39
70c	$CH_2C_6H_5$	9-MC	MeOH / H_2O, CHD	0.36

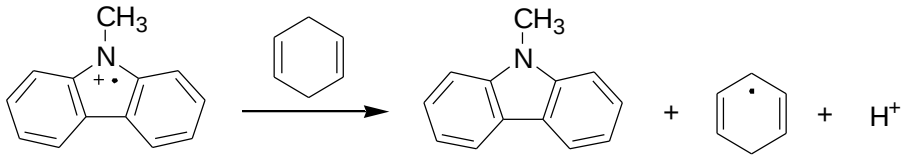
One explanation for the improved quantum yields could be a secondary, non-photochemical, chemical reduction step carried out by the 1, 4-cyclohexadienyl radical by-product of the H atom transfer reaction. It is possible that this radical reduces an unreacted *N*-methylpicolinium ester **70,** creating the same intermediate radical **76** generated in the PET step (Scheme 3.11).

Scheme 3.11 Secondary reduction by CHD radical



The presence of CHD has yet another useful effect, which is to quench the sensitizer (9-MC) cation radical (Scheme 3.12). LFP experiments were carried out on picolinium ester **70c** and 9-MC with the addition of increasing concentrations of CHD. The pseudo-first order decay of the 9-MC cation radical was calculated in each case and plotted against the CHD concentration. This provides a rate constant of 5 x 10^5 $M^{-1}s^{-1}$ for this process. Such a quenching process would prevent 9-MC cation radicals from engaging in back electron transfer with **77**. This suppression of back electron transfer would also increase the quantum yield for the PET process.

Scheme 3.12 Quenching of 9-MC cation radical by CHD

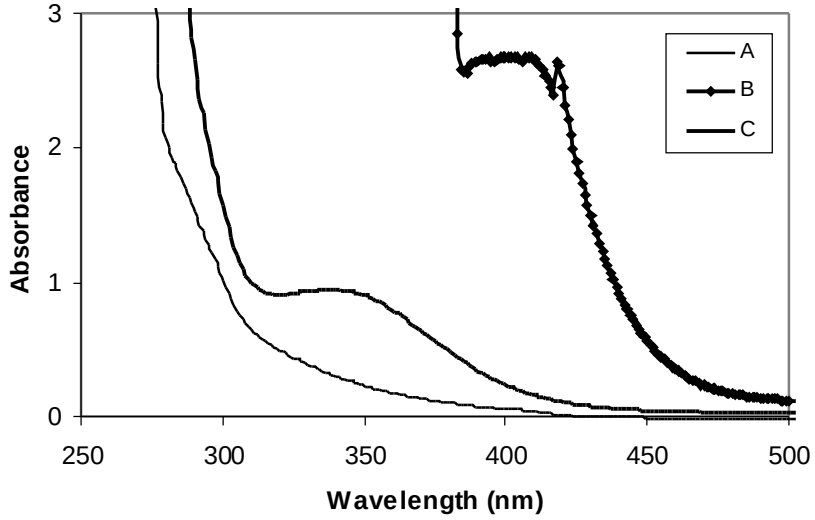


3.8 Direct photolysis of picolinium iodide salts

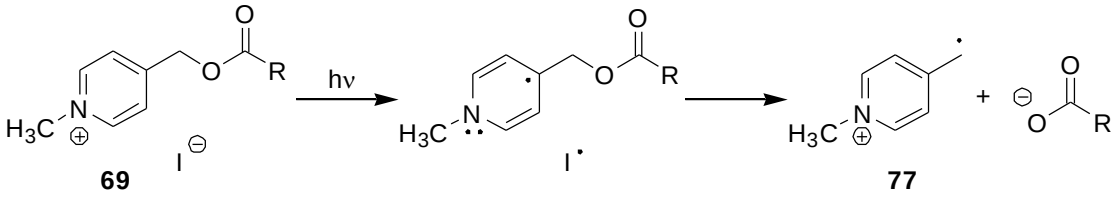
Interestingly, the picolinium esters can be removed by direct photolysis as well as by sensitized irradiation, depending on the counter-ion. While the perchlorate salts absorb only at low wavelengths (<320 nm), it was found that the iodide salts absorb between 350 and 450 nm depending on the solvent (figure 3.11). This is attributed to the charge-

transfer absorption of the picolinium/iodide ion pair. Irradiation of such charge-transfer bands creates a species that is a caged radical pair consisting of radical **76** and iodine atom (Scheme 3.13). Therefore, it is expected that photolysis of these salts would also lead to release of the carboxylate.

Figure 3.11 Steady-state UV-Vis absorption spectrum of ester **70c** in methanol (A), dichloromethane (B) and acetonitrile (C).



Scheme 3.13 Charge-transfer within the picolinium iodide salts **69**



3.8.1 Preparative photolysis of picolinium iodides

Photolysis of the *N*-methyl-4-picolinium iodides **69** in methanol (>320 nm, 200 W Hg lamp) releases the free carboxylic acids in good yields (Table 3.11). Using less polar solvents, acetonitrile (MeCN) or dichloromethane (CH_2Cl_2) allows for irradiation at higher wavelengths (figure 3.11). Entry 4 in table 3.11 was obtained by irradiation of ester **69c** in CH_2Cl_2 above 390 nm using a xenon lamp. However, in practice, the photolyses proceed more cleanly with MeOH as the solvent. This is due to the ability of MeOH to scavenge the radical intermediates resulting from the initial C-O bond scission.

The quantum yield for photorelease from the picolinium iodide salts was found using *N*-methyl picolinium benzoate to be 0.15 in methanol, comparable with the quantum yields obtained in the sensitized photolysis.

Table 3.11 Photolysis of the picolinium iodides **69**

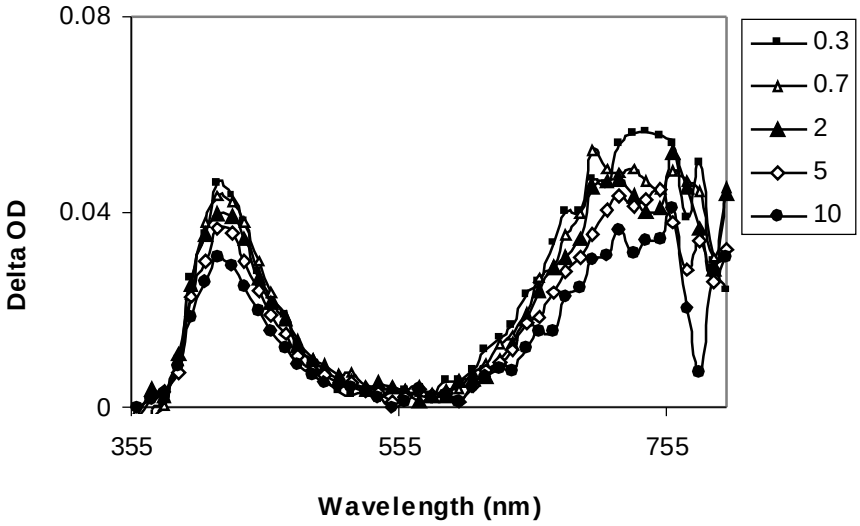
Compound	R	Conditions	% acid formed	% ester consumed
69a	CH_3	3h, MeOH [(a)]	67	74
69b	C_6H_5	3h, MeOH [(a)]	32	48
69c	$CH_2C_6H_5$	3h, MeOH [(a)]	64	92
69c	$CH_2C_6H_5$	3h, CH_2Cl_2 [(b)]	30	45
69f	$CH_2C_6H_4CH_3$	3h, MeOH [(a)]	73	90
69h	$CH{=}CHC_6H_5$	3h, MeOH [(a)]	63	71

[(a)] Irradiation by Hg lamp, >320nm cutoff filter. [(b)] Irradiation by Xe lamp, >390 nm cutoff filter. Yields were determined by ^{1}H NMR integration of the carboxylic acid peak relative to an internal standard. Estimated error ± 5 %

3.8.2 Laser flash photolysis

Laser photolysis was performed on solutions of picolinium iodides in dry acetonitrile. The transient absorption spectra show an absorption peak at 410 nm corresponding to the reduced radical **76**, as well as a peak around 750 nm (Figure 3.12). The latter absorption is probably due to the reduced iodide radical, or the triiodide radical.

Figure 3.12 Transient absorption spectra from pulsed laser photolysis of **69c**



3.9 Conclusions.

The *N*-methyl-4-picolinium group has been introduced as a new photoremovable protecting group. A variety of carboxylic acids have been protected with high yields, and the photorelease was effected through light > 320 nm. It was demonstrated that even reductively labile carboxylic acids can be released successfully.

A photorelease mechanism involving PET from excited state of sensitizer to picolinium ester is proposed. Results from cyclic voltammetry, fluorescence quenching, laser flash photolysis and trapping experiments support our proposed mechanism. In addition, we demonstrated that the picolinium iodides can be removed by direct irradiation.

Chapter 4. Release of Carboxylic Acids, Amino Acids and Phosphates Using Visible Light

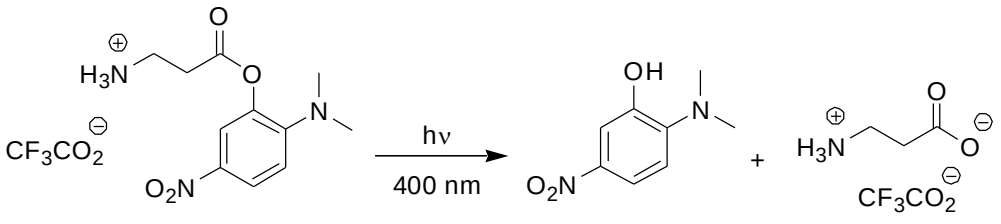
4.1 Introduction.

It has been a long standing goal of this project to use high wavelength visible light to effect photorelease. Visible light has several advantages over UV light. Visible light sources are less expensive than UV light sources. Also UV light is harmful, and requires special equipment and handling. Most organic molecules do not absorb in the visible region, so there would not be any competing absorption with the substrate. Thus visible light irradiation would prevent undesirable side reactions. In this chapter, our successful attempt to utilize visible light for photorelease of picolinium esters will be discussed.

4.2 Previous work with visible light

Several groups have recently attempted to use visible light for deprotection. For example, Banerjee et al. have introduced a new photolabile protecting group that absorbs light at 400 nm. [104] Photolysis with light around 400 nm successfully released β-alanine from the 2-(dimethylamino)-5-nitrophenyl protecting group (Scheme 4.1).

Scheme 4.1 Photorelease from the 2-(dimethylamino)-5-nitrophenyl protecting group

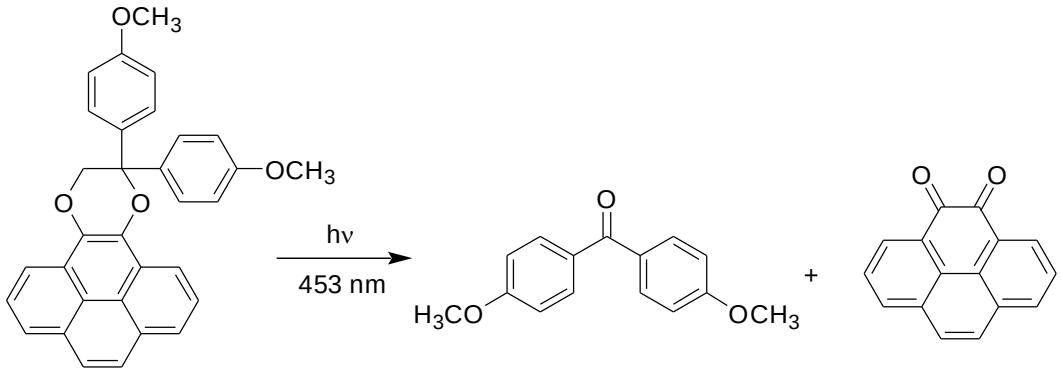


87 **88**

Givens et al have extended the absorption properties of the *p*-hydroxy phenacyl group to around 400 nm by introducing 3-methoxy or 3,5-dimethoxy substituents on the *p*-hydroxy phenacyl chromophore. [34] Bochet has used light of 420 nm for the photorelease of 2-nitroveratroyl derivatives as part of an orthogonal deprotection strategy. [56,57]

Wilson et al. have used visible light around 453 nm to unmask *ortho*-quinones from pyrene dihydrodioxins. [105] These systems undergo an autosensitized PET with UV and visible light that subsequently releases quinone (Scheme 4.2).

Scheme 4.2 Photorelease of *o*-quinone from pyrene dihydrodioxin



89 **90**

Clearly, visible light is gaining popularity as a means to effect photorelease. However these protecting groups use low wavelength visible light and direct irradiation for deprotection. We have developed a system capable of efficiently releasing carboxylic acids, amino acids and phosphates by PET using high wavelength visible light.

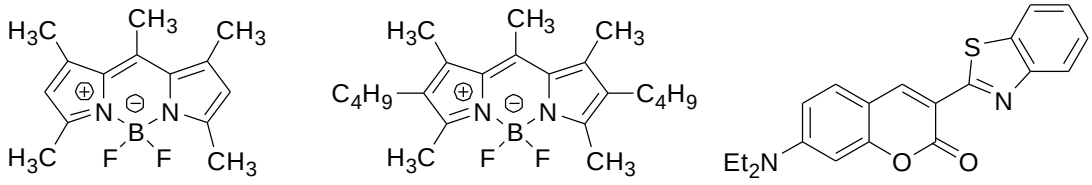
As seen previously, the picolinium esters are efficiently released with a variety of sensitizers. This allows us to use a wide range of wavelengths for deprotection. The

sensitizers used in the previous chapter had absorption wavelengths between 305 and 375 nm in the UV region. We have now attempted to use photosensitizers that absorb high-wavelength visible light, thus affording release of substrates with light of wavelength between 450-550 nm.

4.3 Visible light sensitizers

Three photosensitizers were selected that satisfied our requirements of high-wavelength absorption, exothermic electron transfer to the picolinium group, and chemical stability (Figure 4.1). These photosensitizers were originally developed as dyes for use in dye lasers and thus absorb strongly in the visible region (Figure 4.2). The two pyrromethene dyes, PM 546 and PM 597 absorb at 493 and 525 nm respectively with molar absorption coefficients ε as high as 81000 $M^{-1}cm^{-1}$. We also used a coumarin dye, Coumarin 6, which absorbs at 467 nm. The relevant photophysical parameters of these dyes are listed in Table 4.1.

Figure 4.1 Structures of sensitizer dyes PM 546, PM 597 and Coumarin 6



PM 546 **PM 597** **Coumarin 6**

Figure 4.2 UV-Vis spectra of PM 546, PM 597 and Coumarin 6

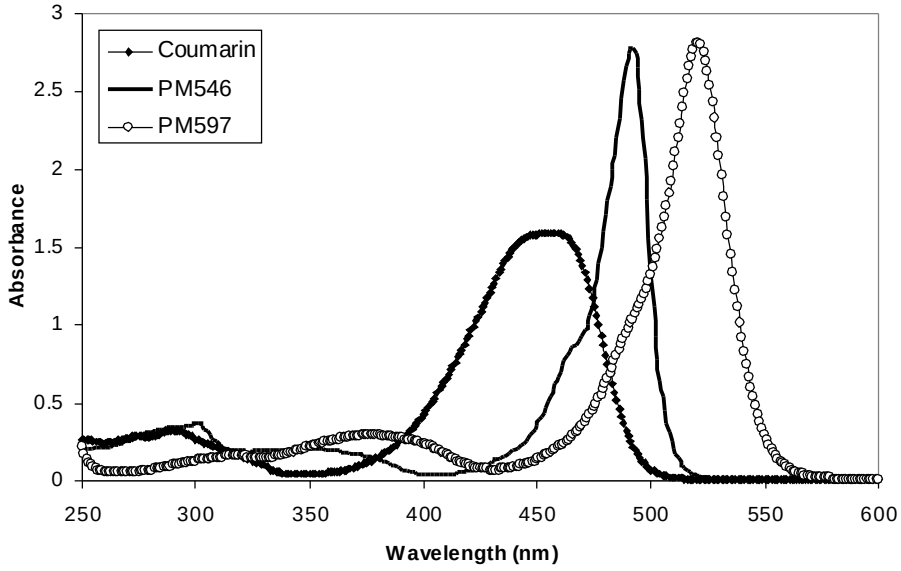


Table 4.1 Photophysical parameters of the PM dyes and Coumarin 6 [106,107]

Dye	E_{ox}	E_{o-o}	λ_{max}	ε ($M^{-1}cm^{-1}$)	τ (ns)
PM 546	1.22	2.50	493	81000	5.6
PM 597	1.01	2.32	525	68000	4.2
Coumarin 6	1.02	2.65	467	54000	3.1

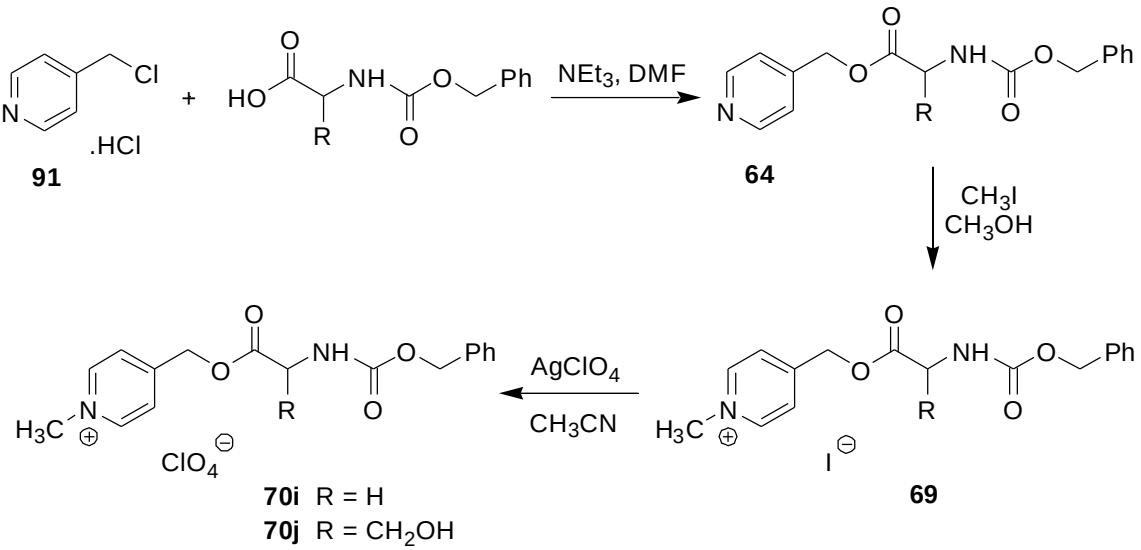
4.4 Protection of amino acids and phosphates

The picolinium group was found to release carboxylic acids efficiently as seen in the previous chapter. We have now attempted to release biological useful molecules such as amino acids and phosphates as well.

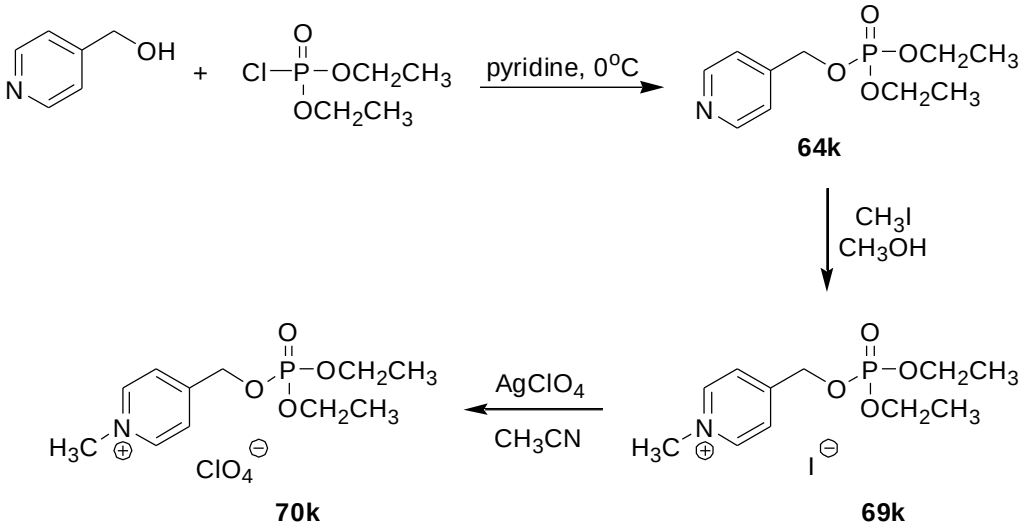
Picolinium esters of two amino acids, glycine and serine, were prepared by treating the *N*-protected amino acids with picolyl chloride hydrochloride in the presence

of triethylamine (Scheme 4.3). The picolyl ester was then methylated and converted to the perchlorate salt as previously described.

Scheme 4.3 Synthesis of picolinium esters of amino acids



Scheme 4.4 Synthesis of picolinium diethyl phosphate



Diethyl phosphate was also protected as its picolinium ester by the reaction of diethyl phosphoryl chloride on 4-pyridyl carbinol at 0 $^{\circ}$C (Scheme 4.4), followed by methylation and counter-ion exchange with silver perchlorate.

4.5 Preparative photolysis

Picolinium esters of carboxylates **70c** and **70e**, amino acids **70i** and **70j** and diethyl phosphate **70k** were photolyzed with high wavelength visible light using a 300 W tungsten lamp along with the visible light absorbing photosensitizers. The photolysis solutions consisted of an equimolar amount of ester and sensitizer dye (3.5 mM) along with 1, 4-cyclohexadiene (CHD, 1.5-1.7 M) in MeCN. The solutions were purged with N_2, irradiated with visible light for fixed periods of time and then analyzed by ^{1}H NMR spectroscopy. The percent yields of free acids were determined by ^{1}H NMR integration of the acid peaks relative to an internal standard. In each case the protected substrate was released in quantitative or nearly quantitative yield. Carboxylic acids, amino acids and diethyl phosphate were effectively released (Table 4.2).

CHD was added in order to improve the ester conversion and yields of free acids, as well as to trap the radicals formed during photolysis. As seen previously with the UV light absorbing sensitizers, the yields and conversion rates are significantly enhanced when CHD is added to the photolysis mixture. In a control experiment, ester **70c** was photolyzed with PM 546 in the absence of CHD under identical conditions and after 5 min of photolysis gave only 46 % conversion and 44 % yield which is about half of that observed when CHD is included.

Control experiments were also carried out to ensure that deprotection was effected by the visible light and not by any UV component that might be emanating from the light source. The esters were photolyzed under identical conditions with and without a 400 nm filter and the same yields were obtained in both cases within experimental error (± 5 %).

Table 4.2. Deprotection yields of picolinium esters

Dye	Ester	R	Conditions	Time (min)	% acid formed	% ester consumed
PM 546	**70c**	$CH_2C_6H_5$	MeCN, CHD	5	92	90
PM 546	**70e**	$CH(C_6H_5)_2$	MeCN, CHD	5	100	100
PM 546	**70i**	*N*-cbz-glycine	MeCN, CHD	5	77	78
PM 546	**70j**	*N*-cbz-serine	MeCN, CHD	5	100	100
PM 546	**70k**	$PO(OCH_2CH_3)_2$	MeCN, CHD	20	97	100
PM 597	**70c**	$CH_2C_6H_5$	MeCN, CHD	20	87	96
PM 597	**70e**	$CH(C_6H_5)_2$	MeCN, CHD	20	84	80
PM 597	**70i**	*N*-cbz-glycine	MeCN, CHD	20	87	87
PM 597	**70j**	*N*-cbz-serine	MeCN, CHD	20	100	100
PM 597	**70k**	$PO(OCH_2CH_3)_2$	MeCN, CHD	60	100	100
Coumarin 6	**70c**	$CH_2C_6H_5$	MeCN, CHD	20	100	100
Coumarin 6	**70e**	$CH(C_6H_5)_2$	MeCN, CHD	20	100	100
Coumarin 6	**70i**	*N*-cbz-glycine	MeCN, CHD	20	76	75
Coumarin 6	**70j**	*N*-cbz-serine	MeCN, CHD	20	97	100
Coumarin 6	**70k**	$PO(OCH_2CH_3)_2$	MeCN, CHD	60	100	100

Yields were determined by ^{1}H NMR integration of the carboxylic acid peak relative to an internal standard. Estimated error ± 5 %.

4. 6 Quantum yields

Quantum yields were determined for the three dyes using picolinium phenylacetate perchlorate **70c**. Solutions of dye and ester were photolyzed using a 1000 W xenon lamp fitted with a monochromator set to the absorption maxima of the dye with a bandwidth of 20 nm. The light intensities were measured using a radiometer calibrated by ferrioxalate actinometry. The quantum yields were found to be between 0.017 and 0.05 for the three dyes. However, the effective quantum yield, $\Phi\varepsilon$, which is the product of photochemical quantum yield Φ, and the molar absorption coefficient ε at the wavelength of irradiation, is very high for the three dyes (Table 4.3). The quantity $\Phi\varepsilon$ for the UV sensitizer 9-MC is 1.3×10^3, which is comparable to that obtained using the dyes.

Table 4.3. Quantum yields of photofragmentation of picolinium ester **70c**

Dye	Ester	Conditions	$\Phi\varepsilon$ (10^3 $M^{-1}cm^{-1}$)
PM 546	**70c**	MeCN, CHD	4.46
PM 597	**70c**	MeCN, CHD	1.70
Coumarin 6	**70c**	MeCN, CHD	0.65

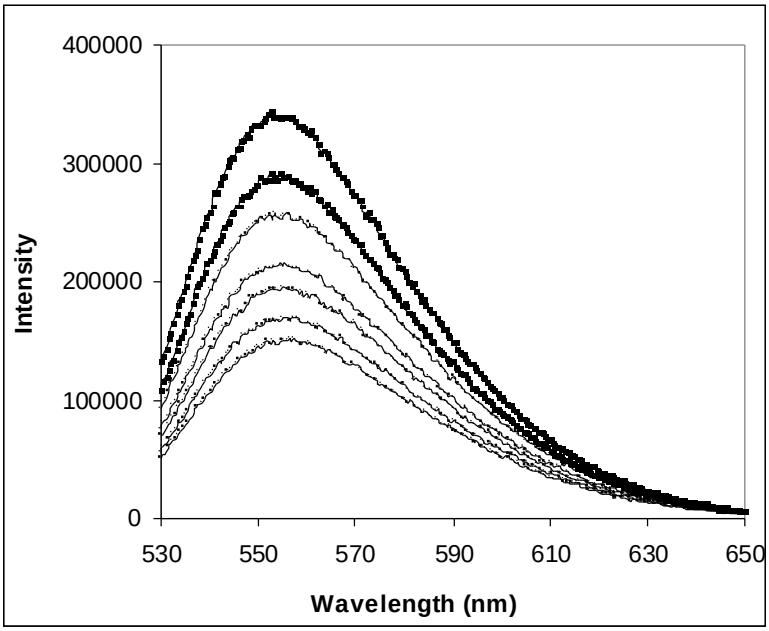
4.7 Fluorescence quenching data

The three sensitizer dyes carry out PET to the esters from their excited singlet states. To measure the efficiency of this interaction, fluorescence quenching experiments were performed on the dyes with picolinium ester **70c**. The strong fluorescence of the dyes was quenched upon addition of increasing concentrations of **70c**. Stern-Volmer analysis of the quenching data gave rate constants of 10^9 M^{-1} s^{-1} (Table 4.4) which are

near the diffusion limit. It was observed that CHD also quenches the excited state of the sensitizers, although much less efficiently than the picolinium esters.

Figure 4.3 (a) Fluorescence quenching of PM 597 by **70c (b)** Stern-Volmer plot

(a)



(b)

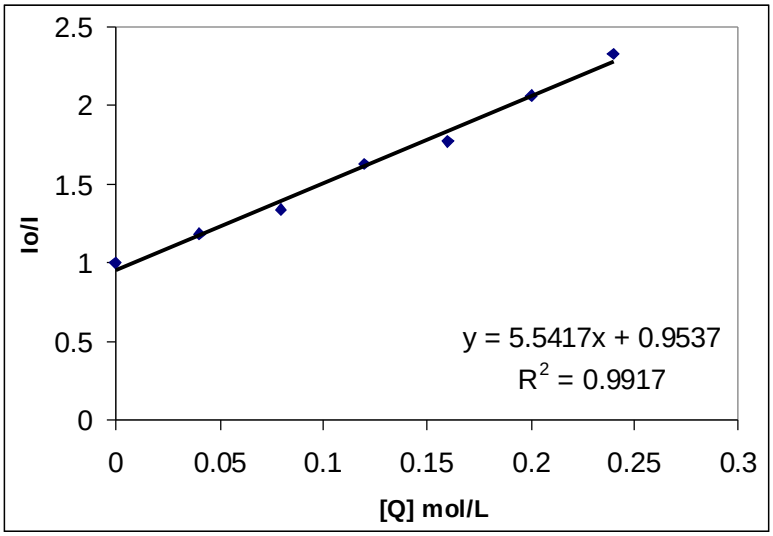


Table 4.4. Fluorescence quenching rate constants

Dye	k_q (M^{-1} s^{-1}) with	
	Ester **70c**	CHD
PM 546	2.8×10^9	1.6×10^7
PM 597	1.3×10^9	2.1×10^7
Coumarin 6	7.6×10^9	3.6×10^7

4.8 Laser flash photolysis

Laser flash photolysis experiments were performed to confirm that the PM dyes and Coumarin 6 carry out a PET to picolinium esters. The expected intermediates are the cation radicals of the dyes and the reduced picolinium radical **76** from our proposed deprotection mechanism.

Transient absorption spectra obtained by laser flash photolysis (355 nm, 10 ns, 10-20 mJ) on PM 546 and ester **70c** revealed a single absorption peak at 410 nm (Figure 4.5). Since the radical **76** also absorbs at 410 nm, we generated the cation radical of PM 546 by using a different acceptor, pyromellitic dianhydride (PMDA) and again observed an absorption peak at 410 nm as well as the previously characterized absorption peak of the PMDA anion radical at 650 nm (Figure 4.6). Thus, the 410 nm band corresponds to the PM 546 oxidized radical as well the radical **76**. Previous work on other PM dyes indicates similar absorption peaks for the dye cation radicals. LFP on PM 597 also gave similar spectra with an absorption peak at 420 nm for the dye cation radical which obscures the absorption of the radical **76**. LFP experiments on Coumarin 6 were unsuccessful, and we were not able to observe any absorption bands.

Figure 4.5 Transient absorption spectra of PM 546 with *N*-methyl-4-picolinium phenylacetate ester **70c**

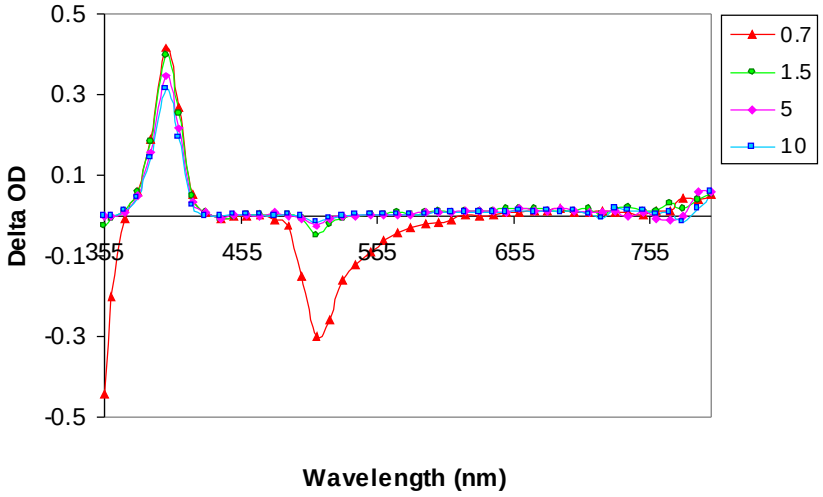
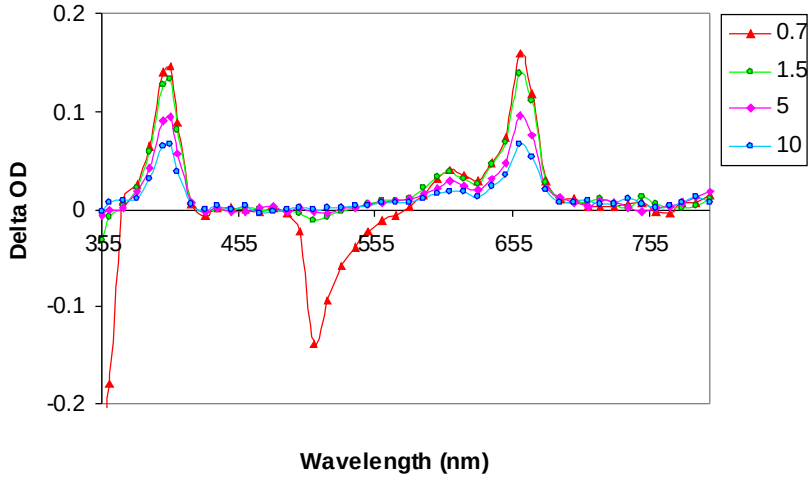


Figure 4.6 Transient absorption spectra of PM 546 with PMDA



4.9 Conclusions

We have successfully used high-wavelength visible light to release free substrates from picolinium esters. Carboxylic acids and amino acids as well as diethyl phosphate were released in quantitative yields. The reactions proceed with high effective quantum yields. Through fluorescence quenching and laser flash photolysis experiments, it is clear that this system photodeprotects through our proposed deprotection mechanism.

Chapter 5. Release of Carboxylic Acids, Amino Acids and Phosphates by Mediated Relay Electron Transfer

5.1 Introduction

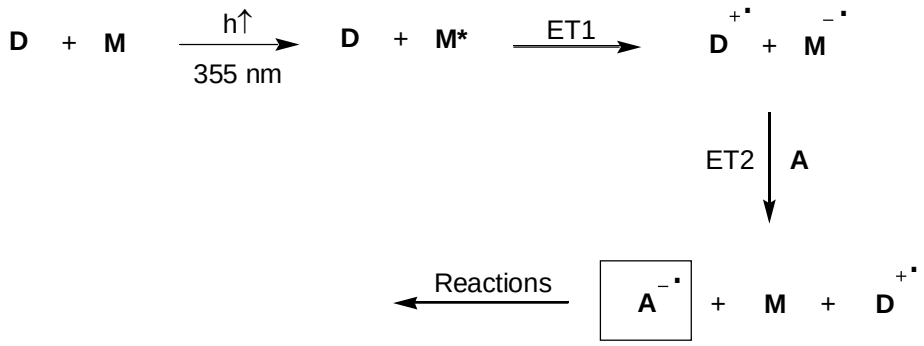
Having shown that picolinium esters can efficiently release a variety of substrates upon irradiation with both UV and visible light, we now turned our attention to optimizing this system. The picolinium esters are released with high chemical yields, however the quantum yields Φ for the photorelease are not as high as we would desire (15-25 %). Thus, our present goal is to improve the photochemical efficiency of the release process. One approach to this would be through modification of the release strategy.

While PET has proven to be an effective method for photorelease, there are some disadvantages associated with it. The quantum yields in these cases are limited by the back-electron transfer between the initial radical ion pair. Also, we have employed singlet state sensitizers until now, which have very short excited state lifetimes. This requires high effective concentrations of the picolinium esters in order to efficiently quench the excited state.

In order to reduce back-electron transfer and improve the efficiency of these reactions, we decided to use mediated electron transfer through triplet sensitizers. In a mediated or 'relay' electron transfer, the primary electron transfer (ET1) from the donor (D) to the mediator (M) is followed immediately by a second electron transfer (ET2) to the acceptor (A) (Scheme 5.1). Using mediators that undergo rapid inter-system crossing to the triplet state prevents the charge recombination pathway from occurring. Also, the

triplet excited state is quite long-lived and thus allows the sensitizer and quencher molecules to attain a close configuration within the excited state lifetime of the sensitizer.

Scheme 5.1 General scheme for a relay electron transfer based deprotection



Mediated electron transfer has received some interest in recent years. For example, acridine-9-carboxylate has been used to mediate electron transfer from vitamin A and ascorbic acid to bipyridinium salts such as methyl viologen. [108] Triplet mediated electron transfers from molecules such as acridine and anthracene have potential applications in solar-energy conversion schemes. [109-111] However to our knowledge, this strategy has not been used as a photorelease mechanism. Here, we are pleased to report the efficient release of carboxylic and amino acids from picolinium esters through a triplet mediated relay electron transfer.

5.2 Selection of suitable donors and mediators

Several mediators were used to carry out the relay electron transfer. The two most efficient triplet mediators were found to be benzophenone and xanthone and will be discussed in detail in the following sections. Anthracene and 2-benzoyl benzoic acid gave

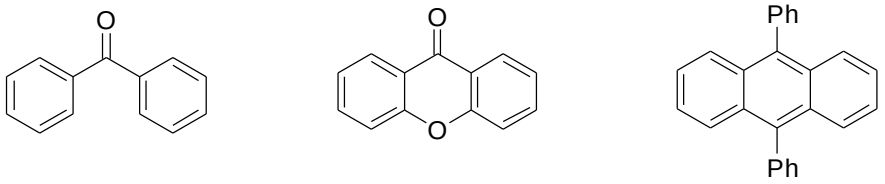
only moderate photorelease. We also compared the efficiencies of the triplet mediated electron transfer against an excited singlet state mediator, 9,10- diphenylanthracene (DPA). *N*,*N*-Dimethylaniline (DMA) was used as the donor in all the cases as it absorbs light at lower wavelengths than the mediators, and does not create complications due to competing light absorption.

The chosen mediator molecules absorb light at our wavelength of irradiation (355 nm), and from their excited state, abstract electrons from the donor DMA. The mediators have reduction potentials that are more negative than that of the picolinium esters (-1.1 V), so that the second electron transfer can be downhill.

The Weller equation (Eq 1) was used to determine that the initial electron transfer between the donor and mediator was exothermic. Values for ΔG_{ET} can be estimated using the excited-state reduction potential of the mediator (E_{red}), the oxidation potential of the donor DMA (E_{ox}), and the excited-state energy of the mediator (E_{o-o}). [95,112,113] The photophysical parameters of the mediators are given in Table 5.1.

$$\Delta G_{ET} = 23.06\,(E_{ox} - E_{red}) - E_{o-o} + 0.06 \text{ eV} \qquad (1)$$

Figure 5.1 Mediators used for relay electron transfer



Benzophenone Xanthone DPA

Table 5.1 Photophysical properties of the mediators [95,112,113]

Mediator	λ_{max} (nm)	E_{red}	$E_{o\text{-}o}$ (s)	$E_{o\text{-}o}$ (t)
Xanthone	340	-1.77	3.36	3.21
Benzophenone	384	-1.68	3.23	3.01
9,10- DPA	392	-1.94	3.16	-

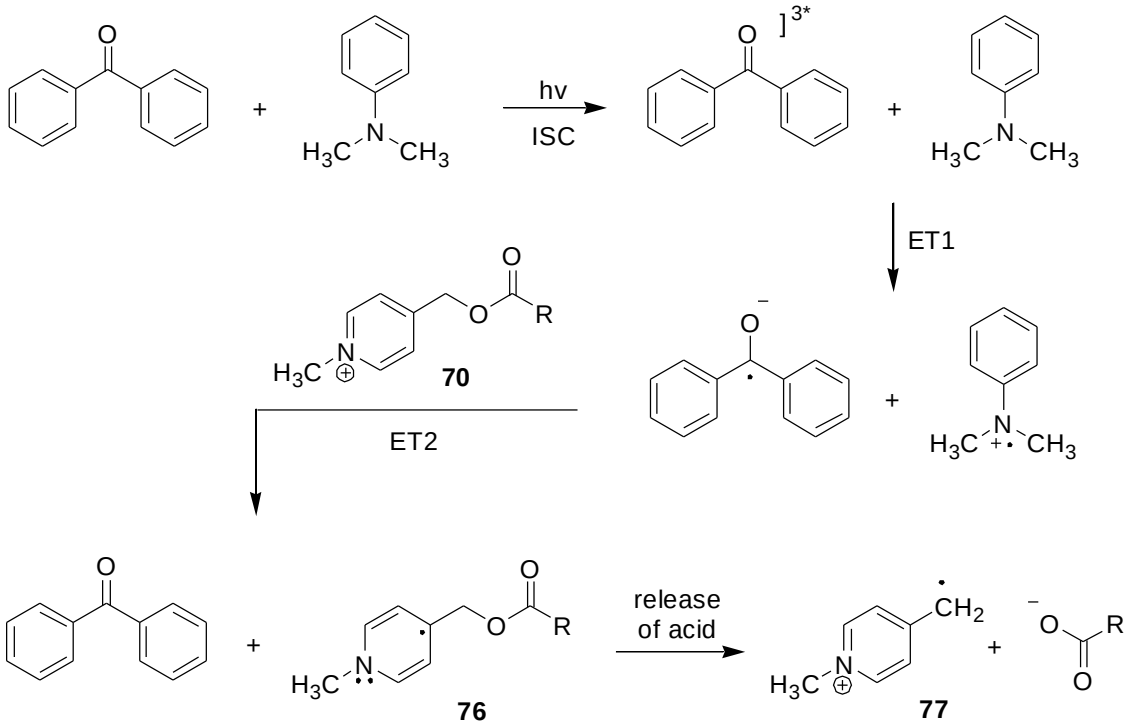
5.3 Mediated systems

The two triplet mediated systems with xanthone and benzophenone and the singlet mediated DPA system were studied through preparative photolysis, laser flash photolysis, and quantum yield experiments. These experiments demonstrate that the triplet mediated relay electron transfer strategy is a definite improvement over the direct sensitized cases.

5.3.1 Benzophenone-DMA system

The proposed mechanism of photorelease is shown in Scheme 5.1. Irradiation of benzophenone promotes it to the excited singlet state, from where it undergoes rapid intersystem crossing (ISC) to its triplet state. The triplet state of benzophenone can then abstract an electron from DMA (ET1), to generate the radical ion pair. The anion radical of benzophenone then transfers an electron to the picolinium ester **70** (ET2). The reduced picolinium ester **76** undergoes a C-O bond fragmentation to release the carboxylate anion and the picolinium radical **77**. Abstraction of H from solvent or the cation radical of DMA gives the acid and *N*-methyl picolinium ion **71**.

Scheme 5.2 Proposed mechanism of photorelease in the mediated system

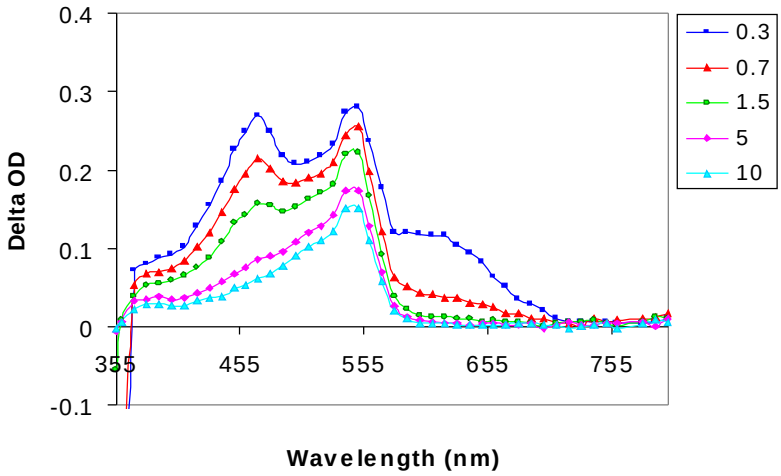


Laser flash photolysis was carried out on the donor- mediator solutions to observe the intermediates formed due to electron transfer. Irradiation of a solution of benzophenone with an excess of DMA at 355 nm produced the cation radical of DMA, which has a known absorption at 470 nm, and also an absorption peak at 630 nm which corresponds to the benzophenone anion radical (Figure 5.2a). [102] The benzophenone ketyl was also observed at 550 nm. Clearly, the initial electron transfer between the donor and excited-state mediator takes place. It is expected that addition of picolinium ester would quench the absorption peak of the benzophenone anion radical following a relay electron transfer. This is in fact what we observed (Figure 5.2b). Upon addition of picolinium

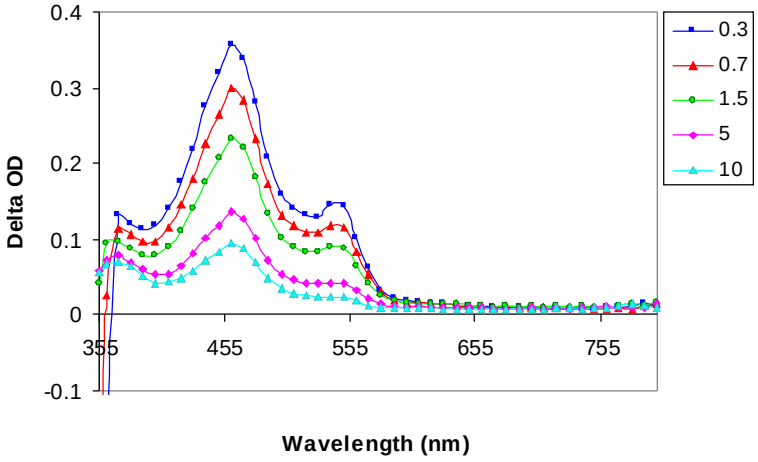
ester, only the absorption peaks for DMA cation radical and the benzophenone ketyl are seen.

Figure 5.2 Transient absorption spectra from pulsed photolysis (355 nm, 50-100 mJ, 6 ns) of (**a**) Benzophenone and DMA and (**b**) Benzophenone, DMA and ester **70e** in N_2-purged MeOH

(a)



(b)



The rate constant for quenching of the anion radical of benzophenone by picolinium ester was obtained by adding increasing concentrations of the quencher to a solution of mediator and DMA. The observed rate of decay of the anion radical was plotted against the quencher concentration, and the quenching rate constant was determined from the slope of the plot (Figure 5.3). The benzophenone anion radical was found to be quenched at a diffusion limited rate (1×10^{10}), indicating efficient electron transfer from oxidized benzophenone to the picolinium ester. The ketyl radical was also quenched, however the quenching is much slower (3×10^{8}) (Figure 5.4).

Figure 5.3 Quenching of benzophenone anion radical (at 630 nm) by picolinium ester

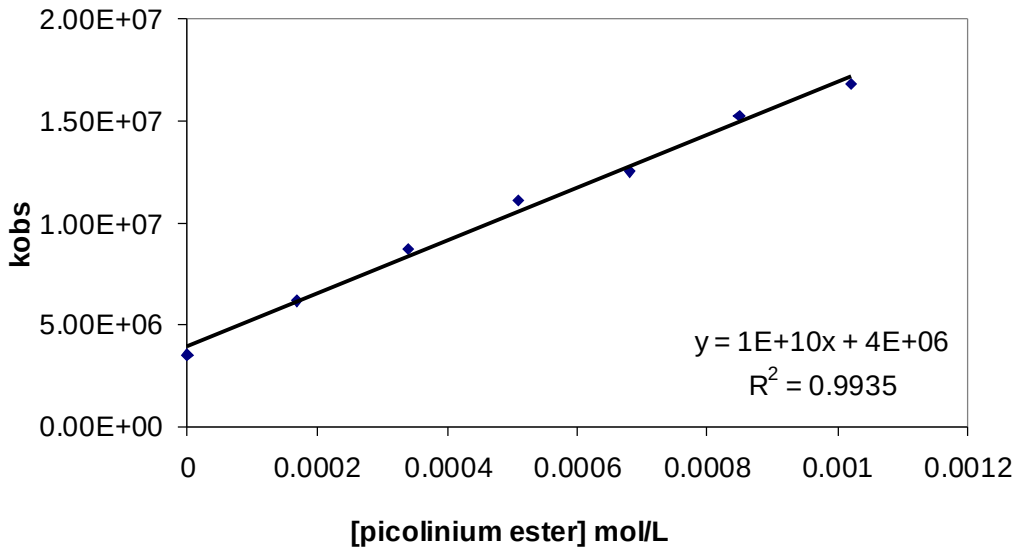
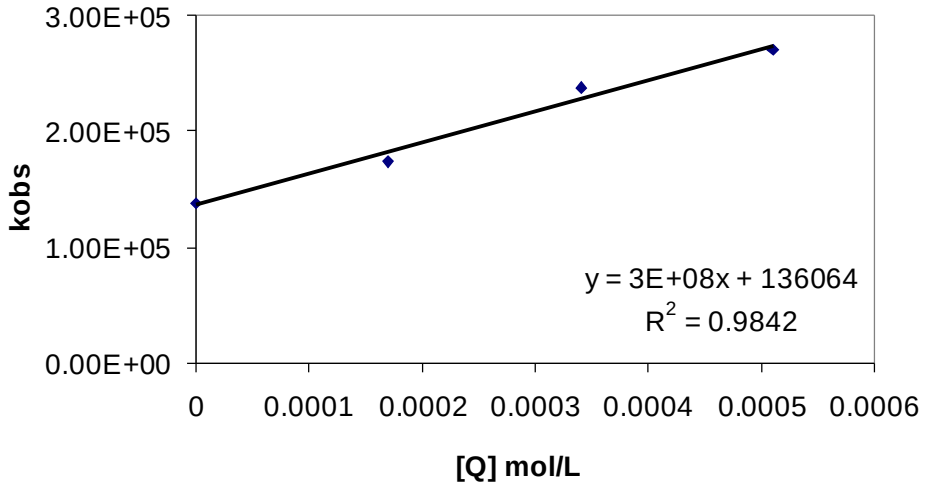


Figure 5.4 Quenching of benzophenone ketyl radical (at 560 nm) by picolinium ester



Preparative photolyses were carried out to observe release of free acids. Methanol solutions of benzophenone, DMA and picolinium esters were irradiated by UV light (>325 nm) using a 300 W mercury lamp. The photolysis solution was 2.5-3.0 mL of 2 mM benzophenone, 4 mM ester and 10-15 mM DMA in methanol. Ester conversions and product yields were obtained by ^{1}H NMR and the estimated error is ± 5%. In all cases quantitative or nearly quantitative yields of the free acids were obtained (Table 5.2). The byproduct of the photorelease is the *N*-methyl picolinium ion **71** which is formed in the same amounts as the free acids. The observation of the picolinium fragment **71** supports our proposed photorelease mechanism.

Table 5.2. Photorelease of *N*-methyl picolinium esters in the benzophenone–DMA system.

Donor	Acceptor	Ester	Conditions	% acid formed	% ester consumed
DMA	Benzophenone	**70c**	2h, MeOH	94	94
DMA	Benzophenone	**70e**	2h, MeOH	84	88
DMA	Benzophenone	**70f**	2h, MeOH	78	80
DMA	Benzophenone	**70i**	2h, MeOH	97	97
DMA	Benzophenone	**70j**	2h, MeOH	100	100

Yields were determined by ^{1}H NMR integration of the carboxylic acid peak relative to an internal standard. Estimated error ± 5 %

Control experiments were carried out to determine if any direct electron transfer occurs between the mediator and picolinium ester. In the absence of DMA, there is very little deprotection with the mediator. This slight photorelease is probably due to electron transfer from the ketyl radical of benzophenone. This was supported by LFP studies. The absorption peak of the benzophenone ketyl radical at 550 nm gets quenched, albeit slowly, on addition of increasing amounts of picolinium ester. The contribution of the benzophenone ketyl radical towards reducing the picolinium esters could be a reason for the high efficiency of this system.

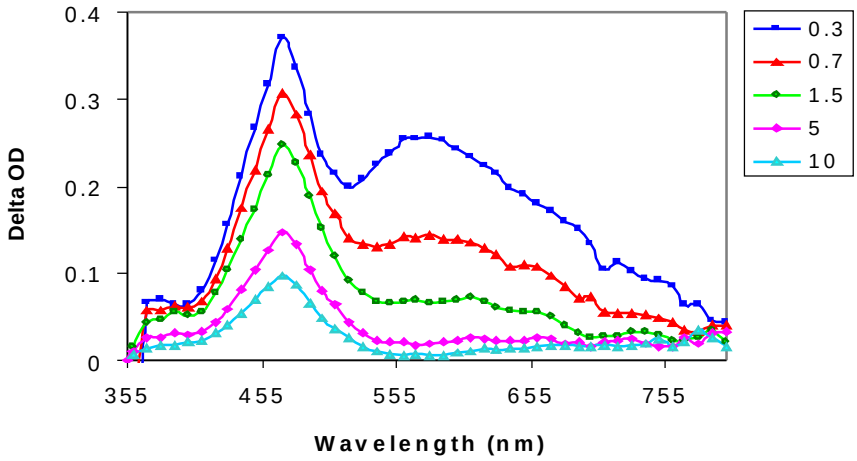
5.3.2 Xanthone-DMA system

The xanthone mediated photorelease is expected to proceed through the same mechanism as the benzophenone system. Laser flash photolysis was carried out on a solution of xanthone and DMA in methanol. Electron transfer was evident by the cation radical of DMA at 470 nm, and the appearance of a peak at 560 nm, which is due to the

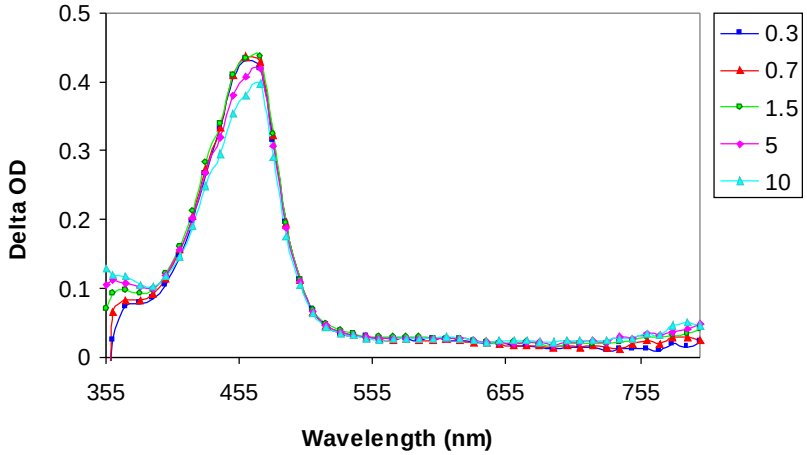
xanthone anion radical (Figure 5.5a). [114] Addition of picolinium ester quenched the peak at 560 nm and only the absorption of the DMA cation radical was observed as expected (Figure 5.5b).

Figure 5.5 Transient absorption spectra from pulsed photolysis (355 nm, 50-100 mJ, 6 ns) of (a) Xanthone and DMA (b) Xanthone, DMA and **70e** in N_2-purged MeOH.

(a)



(b)



The rate constant for quenching of the xanthone anion radical by picolinium ester was determined in the same manner as for benzophenone (Figure 5.6). The quenching rate constant was again found to be near the diffusion limit (9×10^9).

Figure 5.6 Quenching of xanthone anion radical (at 560 nm) by picolinium ester

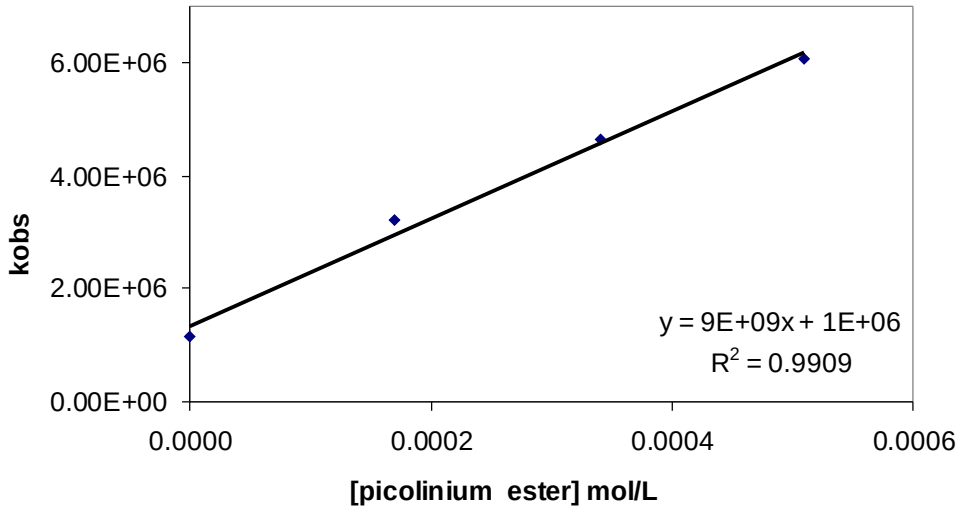


Table 5.3 Photorelease of *N*-methyl picolinium esters in the xanthone-DMA system

Donor	Acceptor	Ester	Conditions	% acid formed	% ester consumed
DMA	Xanthone	**70c**	3h, MeOH	62	62
DMA	Xanthone	**70e**	3h, MeOH	86	84
DMA	Xanthone	**70f**	3h, MeOH	73	80
DMA	Xanthone	**70i**	3h, MeOH	88	88
DMA	Xanthone	**70j**	3h, MeOH	100	100

Yields were determined by ^{1}H NMR integration of the carboxylic acid peak relative to an internal standard. Estimated error ± 5 %

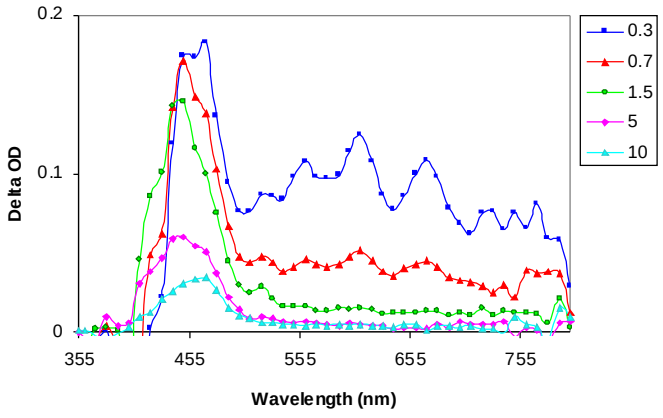
Preparative photolysis of solutions of xanthone, DMA and several picolinium esters in methanol was carried out and the free acids were obtained in nearly quantitative yields (Table 5.3). Control experiments in the absence of DMA yielded slight deprotection. Again, this could be due to electron transfer from the ketyl radical of xanthone.

5.3.3 Diphenylanthracene-DMA system

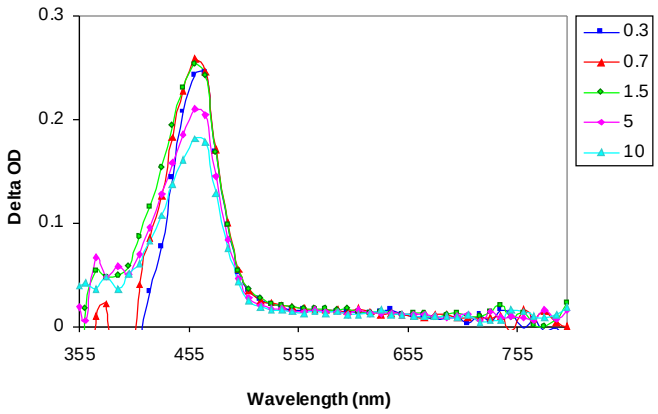
The singlet state mediator DPA was also investigated for its ability to carry out relay electron transfer. Laser photolysis carried out on DPA with DMA shows the formation of the DMA cation radical and the absorption peaks of the DPA anion radical at 560, 610 and 670 nm (Figure 5.7a), [102] and subsequent quenching of the DPA anion radicals upon addition of picolinium ester (Figure 5.7b).

Figure 5.7 Transient absorption spectra from pulsed photolysis (355nm, 50-100mJ, 6ns) of (**a)** 9, 10-DPA and DMA and (**b**) 9, 10- DPA, DMA and **70e** in N_2-purged MeOH

(a)



(b)



Preparative photolysis was performed with DPA as the mediator. Methanol/acetonitrile (1:1) solutions of DPA, DMA and picolinium esters were irradiated with the output of a 300 W Hg lamp with a 320 nm cutoff filter. The free acids were released in mostly quantitative yields, similar to the triplet mediated cases (Table 5.4).

Table 5.4 Photorelease of *N*-methyl picolinium esters in the 9, 10- DPA-DMA system.

Donor	Acceptor	Ester	Conditions	% acid formed	% ester consumed
DMA	9, 10-DPA	**70c**	3h	98	100
DMA	9, 10-DPA	**70e**	3h	100	100
DMA	9, 10-DPA	**70f**	3h	81	85
DMA	9, 10-DPA	**70i**	3h	100	100
DMA	9, 10-DPA	**70j**	3h	94	100

Yields were determined by ^{1}H NMR integration of the carboxylic acid peak relative to an internal standard. Estimated error ± 5 %

5.4 Quantum yields

The quantum yields were determined by irradiating a solution of mediator, DMA and picolinium esters with a 1000 W xenon lamp, fitted with a monochromator set to the

absorption maxima of the mediator and a bandwidth of 10 nm. The quantum yields for the mediated systems were found to be significantly greater than the direct sensitized cases. The quantum yield for photofragmentation of picolinium esters by direct sensitization with 9-methyl carbazole was determined earlier to be 0.23 under similar conditions. Also, the quantum yield of the mediated DPA-DMA system was found to be only 0.17, which is much lower than the quantum yields observed for the two triplet mediated systems. Evidently, the triplet-mediated electron transfer proceeds more efficiently than direct sensitization or singlet-mediated electron transfer (Table 5.5).

Table 5.5 Quantum yields for photofragmentation of *N*-methyl-4-picolinium esters

Donor	Mediator	Ester	Conditions	Quantum yield
DMA	Benzophenone	**70e**	MeOH	0.51
DMA	Xanthone	**70c**	MeOH	0.39
DMA	DPA	**70c**	MeOH/MeCN	0.17

5.5 Conclusions

Mediated electron transfer can be used to effectively photorelease carboxylic and amino acids from *N*-methyl-4-picolinium esters. This strategy allows for a wide range of excitation wavelengths as different mediators can be used. The relay electron transfer method also considerably improves the quantum efficiency by lowering the back electron transfer.

Chapter 6. Linked Systems

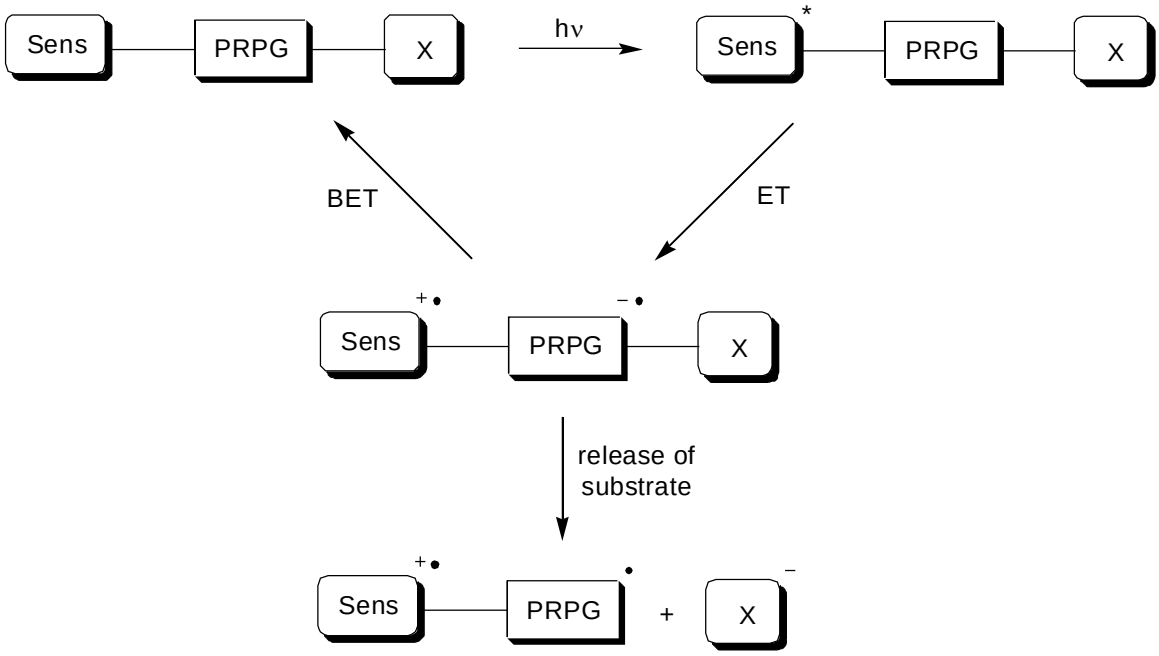
6.1 Introduction

We have seen that the picolinium esters efficiently release the free substrates through direct sensitized as well as triplet mediated electron transfer. Linked donor-acceptor systems are expected to perform more efficiently, as the donor and acceptor molecules are in close contact and electron transfer is not slowed down by the separation between the interacting molecules. Thus in order to further improve the efficiency of the picolinium PRPG, we synthesized and studied covalently linked picolinium esters based on the direct sensitized systems as well as the triplet mediated systems.

6.1 Linked direct sensitization systems

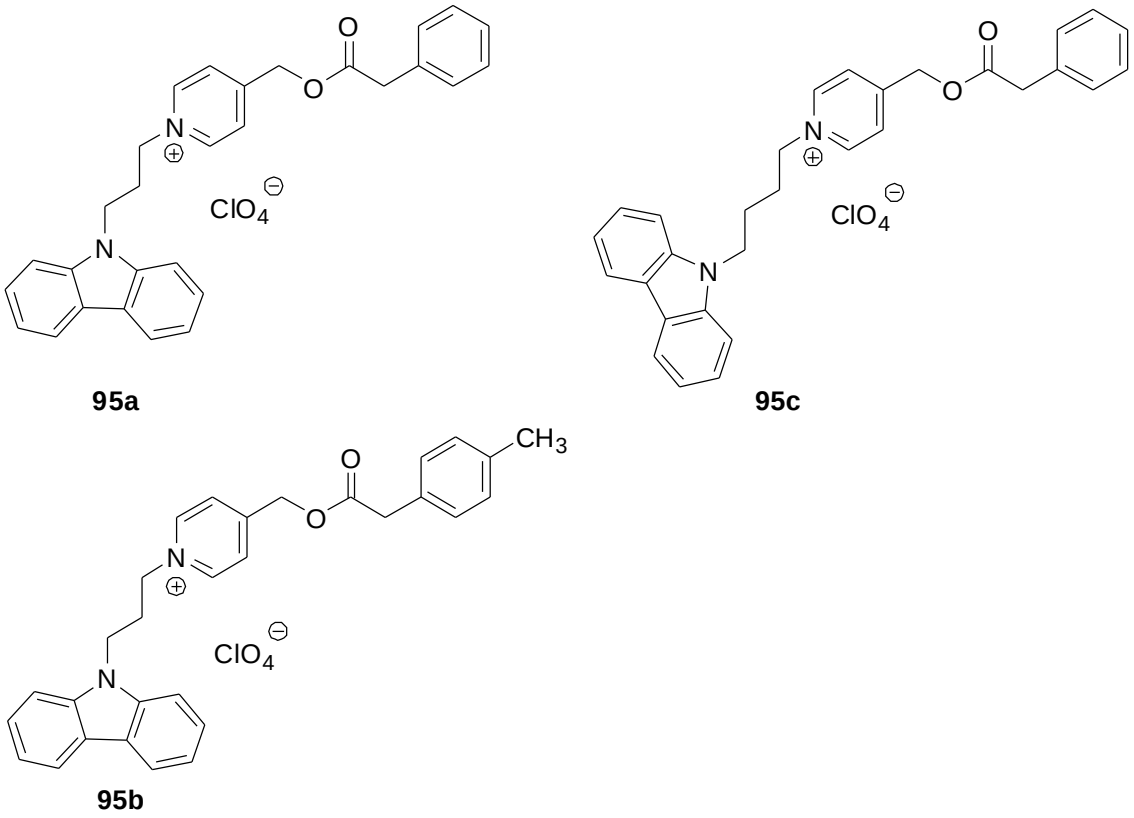
A linked system was designed based on the general scheme for electron transfer in a covalently tied donor and acceptor, depicted in Figure 6.1. It involves tethering the electron donating sensitizer molecule to the protecting group, which in turn is attached to the substrate to be released. Irradiation promotes the sensitizer to its excited state. As the excited sensitizer is tethered to the quencher, the electron transfer to the protecting group will be rapid. The radical ion pair can either decay through BET or release of substrate.

Figure 6.1 General scheme of a donor-acceptor linked system



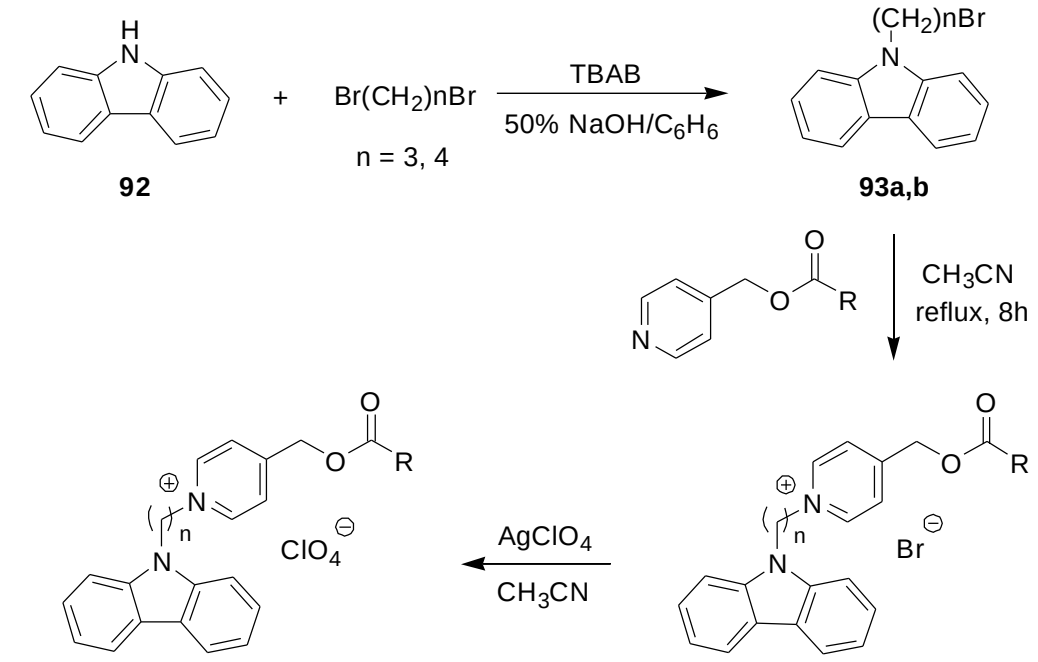
The photosensitizer, 9-methyl carbazole (9-MC) has been successfully used previously to carry out PET triggered photorelease of picolinium esters. Hence, carbazole was chosen as the sensitizer to be linked to picolyl esters. The linker between the sensitizer and ester is an essential component, as it can affect the rate of electron transfer and BET. Previous work with linked systems utilized carbonyl or alkyl linkers. We chose the latter as it involves simple synthetic transformations, and BET can be controlled through adjustment of the alkyl chain length. Two propylcarbazole linked esters (**95a** and **95b**) and one butylcarbazole linked ester (**95c**) were prepared (Figure 6.2).

Figure 6.2 Carbazole-linked picolinium esters



The synthesis of the carbazole linked picolinium esters involves a straightforward three step procedure (Scheme 6.1). In the first step, carbazole is attached to a linker bromopropyl or bromobutyl chain by the reaction of carbazole with a dibromoalkane in the presence of a phase transfer catalyst such as tetrabutyl ammonium bromide (TBAB). [115] The bromopropyl/ bromobutyl carbazole was then reacted with picolyl esters to form linked picolinium bromide salts which were then subjected to counter-ion exchange with $AgClO_4$ to give the corresponding perchlorate salts.

Scheme 6.1 Synthesis of carbazole linked picolinium esters.



95a R = $CH_2C_6H_5$; n = 3
95b R = $CH_2C_6H_4CH_3$; n = 3
95c R = $CH_2C_6H_5$; n = 4

As carbazole is an excited singlet state sensitizer, fluorescence quenching experiments were carried out to determine interaction between the donor and acceptor moieties. As expected, the linked esters showed no fluorescence behaviour due to intramolecular quenching by the picolinium moiety. However, when preparative photolyses were carried out on the linked esters, very little or no photorelease was observed. Laser flash photolysis on the carbazole linked systems showed no absorption peaks corresponding to the carbazole cation radical or the reduced picolinium radical, as was previously observed in the unlinked case.

Clearly there is PET between the carbazole moiety and the picolyl group when they are linked, as indicated by the absence of fluorescence in the linked esters. It is likely that the back electron transfer process or charge recombination is faster and more efficient than bond fragmentation (Scheme 6.2). Linking donors and acceptors is known to increase the rates of both forward and back electron transfer processes. Another possible reason for the fast return electron transfer could be the planar geometry of the molecule with only the carboxylate moiety twisted out of the plane.

Scheme 6.2 Reversible electron transfer upon photolysis of carbazole linked esters

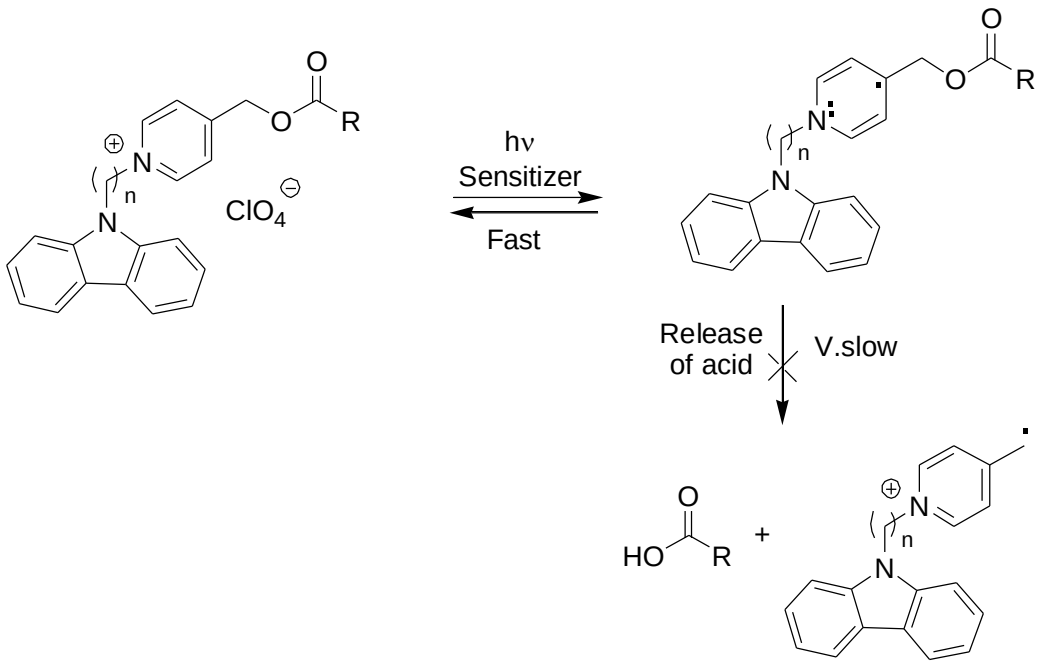
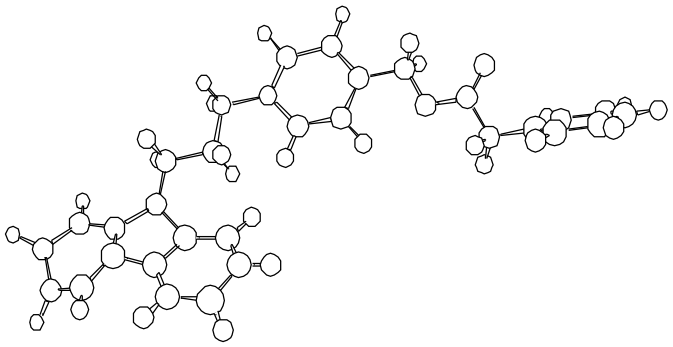


Figure 6.3 Molecular model of carbazole-linked ester

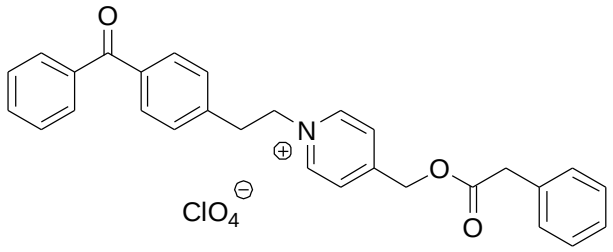


6.3 Linked mediator systems

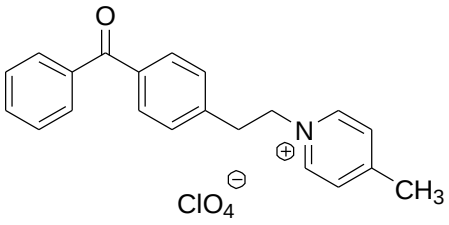
The carbazole linked esters were unsuccessful in bringing about photorelease due to a dominant back electron transfer process. As seen in the previous chapter, mediated electron transfer using triplet sensitizers can be employed to suppress back electron transfer and improve the efficiency of photorelease. Hence, we reasoned that a linked system involving a triplet mediated electron transfer would provide better photorelease than the carbazole linked systems.

We designed a linked system using benzophenone as the mediator since we obtained the most efficient deprotection from benzophenone in the unlinked cases. After the initial electron transfer from DMA, the relay electron transfer from the reduced benzophenone molecule to the picolinium moiety should proceed fast, followed by bond cleavage to release the free acid.

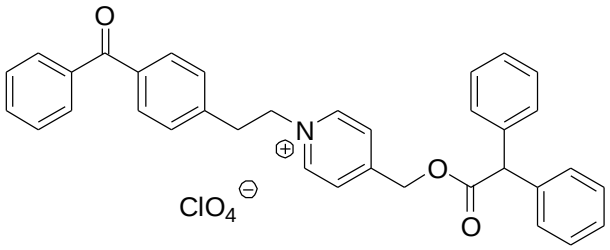
Figure 6.4 The mediator linked picolinium esters



98a



99

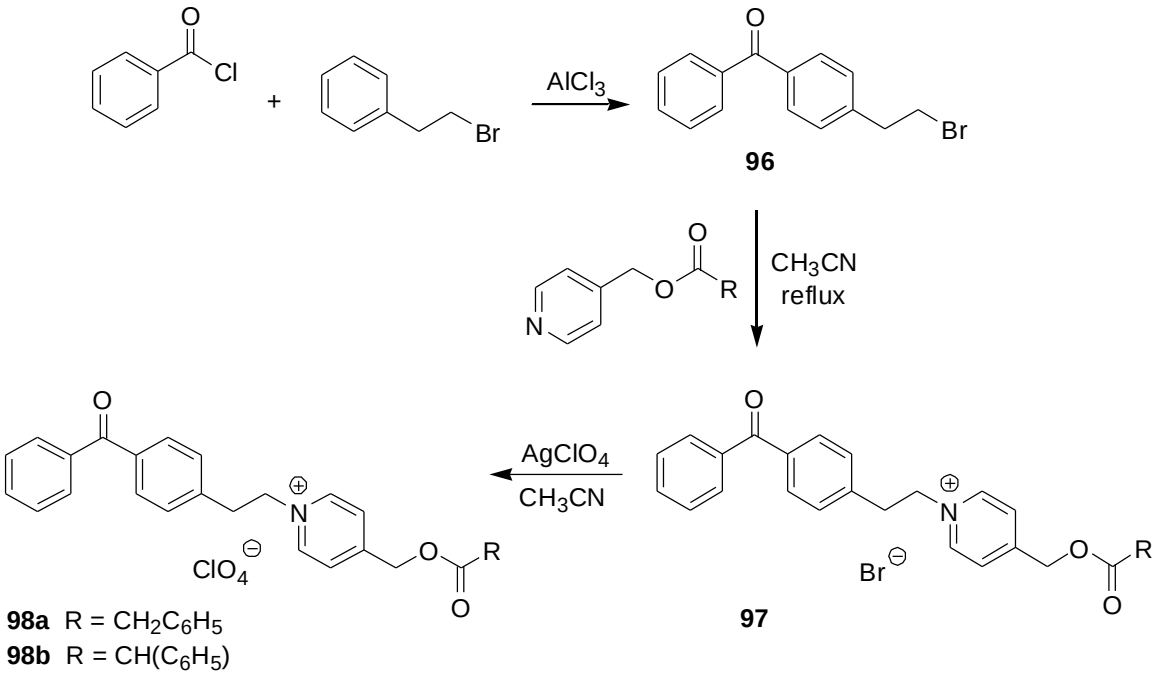


98b

The synthesis of the linked system (Scheme 6.3) involves a Friedel-Crafts reaction to form 4-bromoethyl benzophenone **16**, which is then coupled with picolyl ester to give the linked picolinium bromide salt. Counter-ion exchange is carried out to replace the bromide with the perchlorate ion and eliminate any charge-transfer absorption bands.

Two benzophenone-linked esters were prepared by the above procedure, ethylbenzophenone picoliniumphenylacetate perchlorate **98a** and ethylbenzophenone picoliniumdiphenylacetate perchlorate **98b**. In addition, a model linked system was also prepared, ethylbenzophenonepicolinium perchlorate **99** which lacks the carboxylic acid leaving group (Figure 6.4).

Scheme 6.3 Synthesis of benzophenone-linked systems



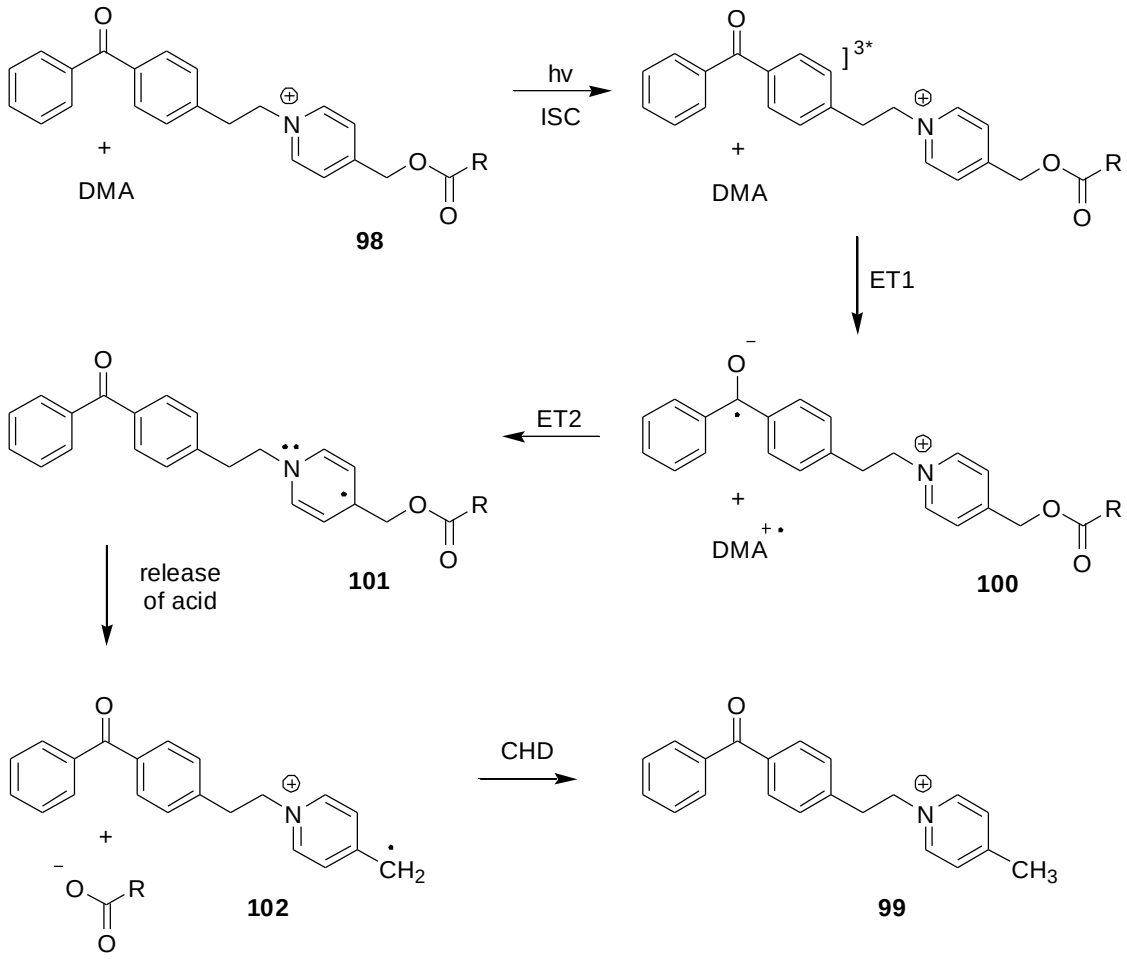
Preparative photolyses of the linked esters with DMA give the free carboxylic acids in nearly quantitative yields (Table 6.1). Upon addition of CHD, the intermediate radical **102** is trapped to give the model compound **99** in quantitative yields. The quantum yield was determined for **98a** in methanol and found to be 0.72.

Table 6.1 Deprotection yields for benzophenone-linked system

Donor	Linked ester	Conditions	% acid formed	% ester consumed	% ion **99** formed
DMA	**98a**	2h, MeOH	70	76	-
DMA	**98b**	2h, MeOH	63	62	-
DMA	**98a**	2h, MeOH, CHD	41	46	40

Yields were determined by ^{1}H NMR integration of the carboxylic acid peak relative to an internal standard. Estimated error ± 5 %

Scheme 6.4 Proposed photorelease mechanism for linked mediated systems



LFP experiments on the linked systems were expected to show only the absorption peak of DMA cation radical at 470 nm as the relay electron transfer to the linked picolinium ester would quench the anion radical of the acceptor. This was in fact what was observed (Figure 6.5).

Figure 6.5 Transient absorption spectra from pulsed photolysis (355 nm, 50-100 mJ, 6 ns) of **98a** and DMA in N_2-purged MeOH

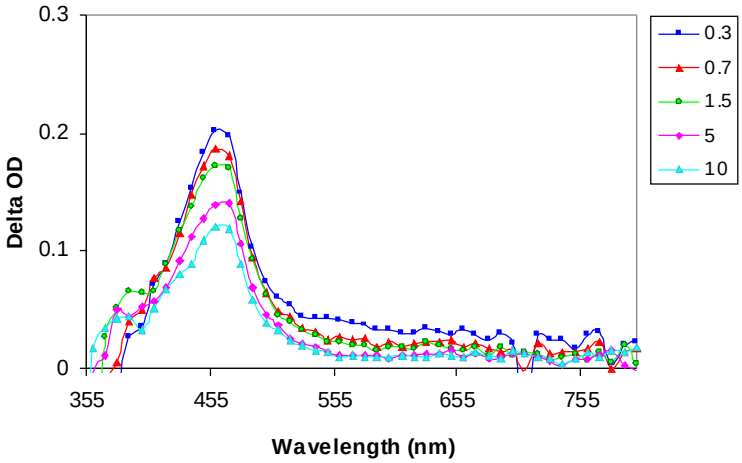
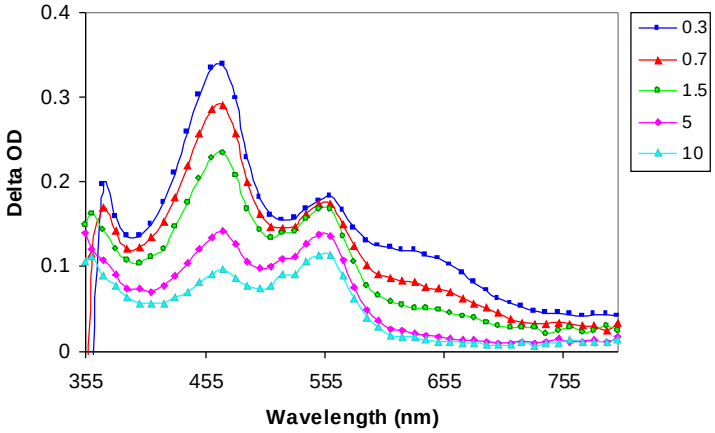


Figure 6.6 Transient absorption spectra from pulsed photolysis of **99** and DMA in N_2-purged MeOH

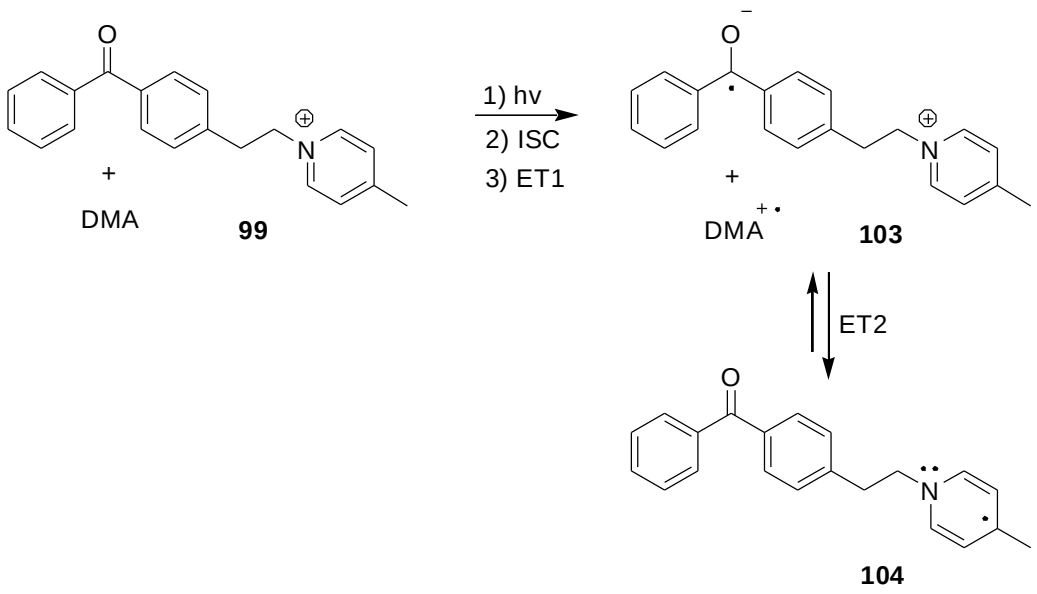


However, laser flash photolysis on the model compound **99** showed weak quenching of the anion radical of benzophenone (Figure 6.6). We observed similar

behaviour of **71** in the unlinked case. It is seen that in both the linked and unlinked systems, the absence of the carboxylate leaving group results in poor interaction of the picolinium group with the reduced acceptor.

There are two possible reasons for this: (1) the reduction potential of the unsubstituted picolinium group is lower than that of the picolinium esters (-1.4 V for **71** vs. -1.1 V for picolinium esters **70**), as it lacks the inductive effect of the carboxylate group. So it is more difficult to reduce. (2) The reduced radical of **99** probably undergoes back electron transfer and exists in equilibrium with the reduced mediator **103** (Scheme 6.5).

Scheme 6.5 Photolysis of benzophenone-linked picolinium ion **99**



6.4 Conclusions

Back electron transfer plays an important role in a PET-triggered release mechanism. Covalently linking the carbazole sensitizer to picolinium esters was a

fruitless effort as the back electron transfer was faster than the release step. A solution to this problem was found by using linked mediated systems. Picolinium esters covalently linked to a triplet mediator, benzophenone, released the free acids efficiently with a high quantum yield.

Chapter 7. Conclusions

Photoremovable protecting groups (PRPGs) are fast gaining in popularity due to the selectivity and control they provide over the deprotection step. They offer a milder alternative to conventional protecting groups removable by chemical means. Various PRPGs have been developed for different functionalites and applications. Some of the common protecting groups were discussed in detail in the previous chapters. While these groups offer several advantages, they also suffer from some serious drawbacks, such as harmful or reactive photoproducts, slow release rates, and low wavelength light absorption. This latter property requires the use of harmful UV light, which results in the competing absorption of the protected substrate leading to undesired side reactions. Attempts to increase the absorption properties of these PRPGs resulted in lower quantum yields and several undesirable reaction pathways.

Thus, it is necessary to separate the light absorption step from the chemical fragmentation step in order to be able to improve each property without adversely affecting the other. This can be achieved by using a sensitized strategy involving a photoinduced electron transfer (PET). This strategy has been successfully employed to release carboxylic acids from phenacyl esters. However, the phenacyl group suffers from several drawbacks such as poor solubility and low reduction potential (-2.2 V) which allows only a few sensitizers to carry out an exothermic electron transfer to these groups. The low reduction potential also prevents protection of molecules that can be easily reduced.

These disadvantages of the phenacyl group indicate the need for an improved PRPG having a high reduction potential, which would allow it to protect even substrates that can be readily reduced. It is also desirable to have a PRPG that can be released through visible light.

The four major goals set for this project were the following:

(1) to design a new and improved PRPG based on PET that could release a variety of carboxylic acids, including acids that can be easily reduced, as well as biologically useful molecules such as amino acids and phosphates

(2) to use high wavelength visible light to effect photorelease

(3) to use a triplet mediated electron transfer strategy to improve efficiency of the system by suppressing back electron transfer

(4) to release carboxylic acids from covalently linked systems.

We developed a new PRPG based on the 4-picolyl group, by modifying it into the *N*-methyl-4-picolinium group. A variety of carboxylic acids were protected as their *N*-methyl-4-picolinium esters through simple synthetic procedures. Sensitized photolysis of these esters afforded the free carboxylic acids in high chemical and quantum yields. Two *N*-protected amino acids and diethyl phosphate were also successfully released from their picolinium esters.

The *N*-methyl-4-picolinium group offers several advantages over the phenacyl protecting group. The considerably higher reduction potential of the picolinium esters allows for protection of acids that are easily reduced. The high reduction potential also widens the choice of sensitizers. We were able to employ several sensitizers having different absorption wavelengths. Four photosensitizers, TMB, 9-MC, pyrene and TPA,

absorbing UV light between 305-375 nm, efficiently brought about deprotection of the free acids. Three visible light sensitizers, PM 546, PM 597 and Coumarin 6, were also used to effect photorelease at high wavelength visible light between 450-525 nm.

A PET based mechanism has been proposed for the photorelease. Various experiments such as cyclic voltammetry, fluorescence quenching and laser flash photolysis support our proposed mechanism. Trapping studies successfully afforded the expected byproduct according to our photorelease mechanism, providing further evidence in its favor.

In an attempt to further improve the efficiency of the photorelease, a triplet mediated relay electron transfer was employed as the release strategy. A mediated system is expected to suffer less of back electron transfer, an energy wasting process, and thus provide higher quantum yields for the photorelease. Two triplet mediators, xanthone and benzophenone were employed as well as a singlet mediator, DPA. The two triplet mediators are highly efficient in releasing the picolinium group, while the singlet mediator is not much of an improvement over the direct sensitized cases.

Covalently linked sensitizer-PRPG systems are expected to perform better than the intermolecular systems due to more efficient electron transfer between the donor and acceptor. With this in mind, we synthesized and studied several carbazole linked picolinium esters. While we observed efficient fluorescence quenching of the sensitizer indicating electron transfer, photolysis of the esters did not afford release of the free acids. Thus, we conclude that these systems undergo an efficient back electron transfer process.

The triplet mediated systems are less prone to back electron transfer, thus a mediator linked system was designed. Two benzophenone linked picolinium esters were synthesized and photolyzed with DMA as the donor. In both cases, we observe rapid release of the free acids. The quantum yield is also significantly greater than in the unlinked case.

Chapter 8. Experimental Section

8.1 General procedures.

All ^{1}H and ^{13}C NMR were obtained using a Bruker 400 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Deuterated CD_3CN or CD_3OD were used for all NMR experiments. Acetonitrile was distilled from calcium hydride under nitrogen atmosphere. Ultraviolet-visible spectra were recorded on a Perkin-Elmer Lambda 2S spectrophotometer.

8.2 General photochemical experiments

8.2.1 Cyclic voltammetry experiments.

All electrochemical experiments were performed using a voltammetry analyzer with $[Bu_4N][PF_6]$ as the supporting electrolyte. The electrodes used were a carbon working, platinum auxiliary, and Ag/AgCl reference. Ferrocene was used as the internal standard. The CV data were taken in spectroscopic grade anhydrous MeCN after N_2 purging the samples for 15 min. The ferrocene/ferrocenium couple was found around 590 mV and the typical scan speed was 100 mV/sec.

8.2.2 Fluorescence quenching experiments.

Fluorescence quenching experiments were performed using a luminescence spectrometer. Samples in MeCN solvent were placed in 1 cm quartz cuvettes, sealed with rubber septums and purged with N_2 for 10-15 min. Sample concentrations were prepared such that the optical densities at the excitation wavelength were about 0.1-0.4.

8.2.3 Fluorescence lifetime measurement.

Fluorescence lifetimes were determined by measuring the fluorescence decay on a nanoflash fluorescence apparatus. Samples in MeCN solvent were placed in 1 cm quartz cuvettes, sealed with rubber septums and purged with N_2 for 10-15 min. Sample concentrations were prepared such that the optical densities at the excitation wavelength were about 0.1-0.4. The fluorescence lifetime of the sensitizer TPA was determined by this procedure.

8.2.4 Deprotection photolysis.

For the direct sensitization deprotection (UV sensitizers): A solution of 4-10 mg of the picolinium ester and an equal amount or slight excess of sensitizer was prepared in about 5 mL of CH_3OH (3.5-4.0 mM of ester and 3.5-4.0 mM of sensitizer). Half of the solution was used as dark control and the remaining half was purged with N_2 for 15 min, and irradiated using a 200 W Hg lamp with continuous stirring for about 3 h. A pyrex filter was used to cut-off light below 325 nm to ensure light absorption by the sensitizer alone. The solutions were then evaporated and redissolved in CD_3OD with hexamethyldisiloxane (HMDS) as the internal standard and ^1H NMR spectra were obtained. The percent yields were determined by ^1H NMR integration of the carboxylic acid peaks (alpha protons in both protected and free acids) relative to the internal standard. The estimated error is ± 5%.

For the triplet mediated deprotection: A solution of 4-10 mg of the picolinium ester and an equal amount or slight excess of mediator was prepared in about 5 mL of

CH_3OH (2-3 mM of mediator, 4.0 mM of ester and 10-15 mM of DMA). The remaining procedure is the same as above.

For the direct sensitization linked systems: A solution of 4-10 mg of the carbazole linked picolinium ester was prepared in about 5 mL of CH_3OH (3.5-4.0 mM of ester). The remaining procedure is the same as above.

For the mediated linked systems: A solution of 4-10 mg of the benzophenone-linked ester and an excess of donor was prepared in about 5 mL of CH_3OH (2-3 mM of mediator-linked ester and 10-15 mM of DMA). The remaining procedure is the same as above.

For the direct sensitization deprotection (with visible light sensitizers): A solution of 4-10 mg of the picolinium ester and an equal amount or slight excess of sensitizer was prepared in about 5 mL of CH_3CN (3.5-4.0 mM of ester and 3.5-4.0 mM of sensitizer). The light source was a 300 W tungsten lamp. The photolysis and analysis was performed in the same manner as above.

8.2.5 Laser flash photolysis.

Laser flash photolysis experiments were performed using an Nd:YAG laser as the pump beam source. The laser used was a Continuum Surelite II-10 capable of 266 or 355 nm pulses between 4-6 ns duration. A LeCroy 350 MHz digital oscilloscope was used to observe the waveforms. The samples were prepared such that the absorbances were between 1.5 and 2.0 at the excitation wavelength, 355 nm. The samples were placed in 1 cm quartz cuvettes and N_2 (or O_2) purged for 15 min, and stirred continuously during the photolysis.

8.2.6 Quantum yield determination.

The solutions were photolyzed by the output of a 1000 W Hg-Xe lamp after passing through a spectral energy monochromator set to the absorption maxima of the sensitizers with a 10 nm bandwidth. Solutions of ester and sensitizer/mediator (8 mM ester, solution OD at λ_{max} about 0.1-0.3) were placed in a 1 cm quartz cuvette and purged with N_2 for 15 min. The samples were irradiated for different times and the amount of ester converted was determined by ^{1}H NMR integration. Light intensities were measured by a radiometer calibrated by ferrioxalate actinometry.

8.3 Synthesis and characterization of picolinium esters

General procedures for the synthesis of esters 64a-k

Method 1. Esters **64a-d** and **64h** were prepared using the procedure of Abele et al. [96] To a solution of 4- pyridyl carbinol (3.45 g, 31.6 mmol) in 40 mL of benzene, triethylamine (7.97 mL, 56.8 mmol) is added. A solution of the corresponding acyl chloride (50.5 mmol) in 15 mL of benzene is added dropwise. The reaction mixture is stirred at room temperature for 16 h. About 30 mL of H_2O is added and the organic layer is separated, dried over $MgSO_4$, and concentrated in vacuo to give the ester. The properties and characterization data of the individual esters are described following the general synthesis methods.

Method 2. Esters **64e, 64f,** and **64g** were prepared using the procedure of Camble et al. [94] *N*, *N*'-Dicyclohexylcarbodiimide (DCC) (3.40 g, 16.4 mmol) is added to a solution of the

carboxylic acid (16.4 mmol) and 4- pyridyl carbinol (1.62 g, 14.8 mmol) in 50 mL of dichloromethane. The reaction mixture is stirred at room temperature for about 24 h, and checked by TLC for disappearance of starting material. The urea precipitate is filtered and the filtrate is washed with $NaHCO_3$ (2 x 25 mL) and H_2O (2 x 10 mL). The organic layers are collected and dried over $MgSO_4$ and the solvent is evaporated to give the ester. The properties and characterization data of the individual esters are described following the general synthesis methods.

Method 3. Esters **64i** and **64j** were prepared using the procedure of Camble et al. [94] A solution of *N*-benzyloxycarbonyl-L-glycine or *N*-benzyloxycarbonyl-L-serine (10 mmoles), 4-picolyl chloride hydrochloride (1.6 g, 10 mmoles), and triethylamine (2.1 g, 20 mmoles) in dimethylformamide (30 mL) was heated at 90° C for 3 h, till TLC showed absence of 4-picolyl chloride. The solvent was distilled off, and 30 mL of ethyl acetate was added to the residue. The solution was washed with sat. $NaHCO_3$ (3 x 10 mL), water (2 x 10 mL) and brine (10 mL) and then dried over $MgSO_4$. After evaporation of the solvent, the dark brown solid was recrystallized twice from ether to give the ester. The properties and characterization data of the individual esters are described following the general synthesis methods.

Method 4. Ester **64k** was prepared using a modified procedure of Givens et al. [116,117] To a solution of 4-pyridyl methanol (2.2 g, 20.2 mmol) in 8 mL of pyridine maintained at -2 °C diethyl phosphoryl chloride (6.4 mL, 41.6 mmol) was added dropwise. The solution was stirred at -2 °C for 2 hrs and then stirred at room temperature for 12-16 hrs. About 50

mL of water was added to the reaction mixture and the pH of the solution was raised to 8.5 by adding base. The mixture was extracted with dichloromethane (3 x 30 mL). The organic layers were collected and washed with water (2 x 30 mL), and then dried over $MgSO_4$. The solvent was evaporated and the product dried under reduced pressure to give the ester. The properties and characterization data of the ester are described following the general synthesis methods.

General procedure for the synthesis of methylated esters (69a-k)

About 0.02 mol of the corresponding picolyl ester was dissolved in 15 mL of CH_3OH, and methyl iodide (4.26 g, 0.03 mol) was added slowly. The reaction mixture was refluxed at 70-75 ºC for 8 h. The solvent was removed under reduced pressure and the residue was recrystallized from hot methanol or ethanol.

General procedure for Counter –Ion Exchange (70a-k)

The picolyl methiodide (5 mmol) is dissolved in the minimum amount of acetonitrile. A solution of silver perchlorate (1.04 g, 5 mmol) in acetonitrile is added and the reaction mixture is stirred overnight at room temperature. The yellow AgI precipitate is filtered off and the filtrate is concentrated *in vacuo* and recrystallized from hot ethanol.

Picolyl Acetate (64a).

Compound **64a** was prepared by the above general procedure, method 1, from acetyl chloride. The product is a dark brown liquid (4.64 g, 94 %). The product was not purified further, as it appeared pure by ^1H NMR. IR (CCl_4) 3036 (m), 2935 (s), 1735 (s), 1603

(m); LRMS (FAB) 152 ($(M+H)^+$, 6), 151 (41), 109 (100), 92 (26), 80 (29), 65 (21). ^1H NMR data was consistent with the data previously reported by Abele et al. [96]

Picolyl Benzoate (64b).

Compound **64b** is prepared using the general method 1 described above, using benzoyl chloride. The product was purified by flash column chromatography (EtOAc: hexanes, 60:40) and obtained as a dark-brown liquid (4.01 g, 60%). TLC R_f = 0.30 (EtOAc: hexanes, 60:40); ^1H NMR (CD_3CN): δ 5.36 (s, 2H), 7.39 (d, *J*= 6.0, 2H), 7.52 (t, *J*=7.4, 2H), 7.64 (d, *J*=7.4, 1H), 8.08-8.06 (m, 2H), 8.57-8.56 (m, 2H); ^{13}C (CD_3CN): δ 65.4, 122.8, 129.6, 130.4, 130.7, 134.3, 146.3, 150.9, 166.7; LRMS (FAB) 214 ($(M+H)^+$, 100), 154 (94), 136 (71), 105 (40), 77 (25); HRMS (FAB) calcd for $C_{13}H_{12}NO_2$ 214.0868 $(M+H)^+$, found 214.0871.

Picolyl Phenylacetate (64c).

Compound **64c** is prepared using the general method 1 using phenylacetyl chloride. The product is a thick dark brown liquid (6.33 g, 87%). The product was not purified further, as it appeared pure by ^1H NMR. IR (CCl_4) 3036 (m), 2942 (s), 1747 (s), 1603 (m); ^1H NMR (CD_3CN): δ 3.74 (s, 2H), 5.13 (s, 2H), 7.34-7.23 (m, 7H), 8.52-8.50 (m, 2H); ^{13}C NMR (CD_3CN): δ 41.4, 65.1, 122.7, 128.0, 129.4, 130.3, 135.2, 146.5, 150.5, 171.9; MS (EI) 227 (60), 91 (100), 41 (35); HRMS (FAB) calcd for $C_{14}H_{13}NO_2$ 227.0946 $(M)^+$, found 227.0943.

Picolyl Trimethylacetate (64d)

Compound **64d** is prepared using the general method 1 using trimethylacetyl chloride. The product is a dark brown liquid (5.06 g, 82 %). ^{1}H NMR (CD_3CN): δ 1.22 (s, 9H), 5.10 (s, 2H), 7.29-7.27 (m, 2H), 8.54 (d, *J*=6.0, 2H); ^{13}C NMR (CD_3CN): δ 26.5, 39.4, 64.8, 122.4, 146.9, 150.6, 178.5; LRMS (FAB) 194 ($(M+H)^+$, 100), 57 (30); DCI 193 (36), 92 (22), 85 (20), 57 (100); HRMS (FAB) calcd for $C_{11}H_{15}NO_2$ 193.1103 $(M)^+$, found 193.1101.

Picolyl Diphenylacetate (64e)

Compound **64e** is prepared using the general method 2 using diphenylacetic acid. The product is a brown semisolid, which upon recrystallization from hot ethanol yielded a white solid (7.84 g, 83%). Mp 130-134 ºC; ^{1}H NMR (CD_3CN): δ 5.18 (s, 2H), 5.22 (s, 1H), 7.16 (d, *J*=5.4, 2H), 7.36-7.28 (m, 10H), 8.48 (d, *J*=5.4, 2H); ^{13}C NMR (CD_3CN) δ 51.2, 57.3, 65.6, 122.6, 128.2, 129.5, 139.8, 145.9, 150.7, 172.9; LRMS (FAB) 304 ($(M+H)^+$, 100), 154 (40), 136 (31); HRMS (FAB) calcd for $C_{20}H_{18}NO_2$ 304.1338 $(M+H)^+$, found 304.1349.

Picolyl *p*-Tolylacetate (64f)

Compound **64f** is prepared using the general method 2 using *p*-tolylacetic acid. The product is a light brown semisolid (5.24g, 73%). The product was not purified further, as it appeared pure by ^{1}H NMR. ^{1}H NMR (CD_3CN): δ 2.30 (s, 3H), 3.68 (s, 2H), 5.11 (s, 2H), 7.23-7.11 (m, 6H), 8.52-8.51 (m, 2H); ^{13}C NMR (CD_3CN) δ 21.0, 40.1, 65.1, 122.9,

130.0, 130.2, 132.1, 137.6, 146.3, 150.7, 172.2; LRMS (FAB) 242 ($(M+H)^+$, 100); HRMS (FAB) calcd for $C_{15}H_{16}NO_2$ 242.1181 $(M+H)^+$, found 242.1185.

Picolyl Bromophenylacetate (64g)

Compound **64g** is prepared using the general method 2 using 4-bromophenylacetic acid. The product is a brown liquid (3.25g, 71%). The product was not purified further, as it appeared pure by ^{1}H NMR. ^{1}H NMR (CD_3CN): δ 3.72 (s, 2H), 5.13 (s, 2H), 7.21-7.24 (m, 4H), 7.48-7.50 (m, 2H), 8.52-8.53 (m, 2H); ^{13}C NMR (CD_3CN): δ 40.1, 65.3, 121.4, 122.6, 132.3, 132.4, 134.5, 146.1, 150.8, 171.6; LRMS (FAB) 306 ($(M+H)^+$, 100); DEI 305 (60), 169 (100), 92 (40); HRMS (FAB) calcd for $C_{14}H_{13}NO_2Br$ 306.0130 $(M)^+$, found 306.0135, calcd for $C_{14}H_{13}NO_2Br$ 308.0109 $(M)^+$, found 308.0117.

Picolyl Cinnamate (64h).

Compound **64h** is prepared using the general method 1 using cinnamoyl chloride. The product is a thick brown liquid (7.48 g, 98%). The product was not purified further, as it appeared pure by ^{1}H NMR. IR (CCl_4) 3062 (m), 3027 (m), 2951 (s), 1712 (s), 1635 (m), 1603 (m); ^{1}H NMR (CD_3CN): δ 5.25 (s, 2H), 6.61 (d, *J*=16, 1H), 7.35-7.43 (m, 5H), 7.63-7.65 (m, 2H), 7.76 (d, *J*=16, 1H), 8.56-8.57 (m, 2H); ^{13}C NMR (CD_3CN): δ 52.2, 64.9, 122.8, 129.1, 129.9, 131.5, 135.1, 146.3, 147.1, 150.2, 167.0; LRMS (FAB) 240 ($(M+H)^+$, 100), 131 (37); HRMS (FAB) calcd for $C_{15}H_{14}NO_2$ 240.1025 $(M+H)^+$, found 240.1035.

Picolyl Glycinate (64i).

Compound **64i** is prepared using the general method 3 using *N*-benzyloxycarbonyl glycine. The product is a pale pink solid after recrystallizing twice from ether (1.6 g, 53%). Mp 70-72 ºC (lit [94] 71.5-73.5); ^{1}H NMR (CD_3CN): δ 3.93 (d, *J*=6.2, 2H), 5.08 (s, 2H), 5.16 (s, 2H), 7.36-7.28 (m, 7H), 8.54 (d, *J*=6.2, 2H); ^{13}C NMR (CD_3CN): 43.2, 65.3, 67.1, 122.7, 128.4, 128.8, 129.8, 149.7, 150.4, 157.5, 170.9; LRMS (FAB) 301 ($(M+H)^+$, 100), 119 (50); HRMS (FAB) calcd for $C_{16}H_{16}N_2O_4$ 301.1188 $(M+H)^+$, found 301.1176.

Picolyl Serinate (64j).

Compound **64j** is prepared using the general method 3 using *N*-benzyloxycarbonyl serine. The product is a pale peach solid after recrystallizing twice from ether (0.95 g, 29%). Mp 130-132 ºC; ^{1}H NMR (CD_3CN): δ 3.80 (dd, *J*=4.2, 6.4, 1H), 3.90 (dd, *J*=4.2, 6.4, 1H), 4.39-4.37 (m, 1H), 5.09 (s, 2H), 5.19 (d, *J*=5.4, 2H), 7.36-7.28 (m, 7H), 8.53 (d, *J*=5.4, 2H); ^{13}C NMR (CD_3CN): 57.3, 62.6, 65.5, 67.1, 122.4, 128.6, 128.8, 129.3, 137.9, 145.9, 150.7, 157.1, 171.4; LRMS (DEI) 330 (M^+, 20), 223 (7), 181 (6); HRMS (FAB) calcd for $C_{17}H_{18}N_2O_5$ 330.1216, found 330.1214.

Picolyl Diethylphosphate (64k).

Compound **64k** is prepared using the general method 4 described above. The product is a dark brown thick liquid (2.8 g, 64%). The product was not purified further, as it appeared pure by ^{1}H NMR. ^{1}H NMR (CD_3CN): δ 1.29-1.25 (m, 6H), 4.09-4.05 (m, 4H), 5.04 (d, *J*=8.0, 2H), 7.33 (d, *J*=5.8, 2H)), 8.56 (d, *J*=5.8, 2H); ^{13}C NMR (CD_3CN): 16.2, 62.7,

64.8, 67.5, 122.4, 150.7; LRMS (FAB) 217 (M^+, 100), 108 (55); HRMS (FAB) calcd for $C_8H_{12}NPO_4$ 217.0504, found 217.0508.

***N*-Methyl Picolinium Acetate Iodide (69a).**

Compound **69a** was prepared by the general methylation procedure described above. The product was a brown solid (4.81 g, 91%). Recrystallization from hot methanol yielded pale orange crystals. Mp 140-142 ºC; IR (nujol) 2965 (s), 2905 (m), 2851 (m), 1743 (s), 1638 (m), 1464 (s); ^{1}H NMR (CD_3CN) δ 2.16 (s, 3H), 4.28 (s, 3H), 5.34 (s, 2H), 7.93 (d, *J*=6.4, 2H), 8.62 (d, *J*=6.4, 2H); ^{13}C NMR (CD_3CN) δ 20.7, 48.8, 63.8, 125.8, 146.0, 157.4, 171.0; LRMS (FAB) 166 (12), 122 (100); HRMS (FAB) calcd for $C_9H_{12}NO_2$ 166.0868, found 166.0872.

***N*-Methyl Picolinium Benzoate Iodide (69b).**

Compound **69b** was prepared by the same methylation procedure as above, and is a dark brown liquid (2.98 g, 84%). ^{1}H NMR (CD_3CN) δ 4.28 (s, 3H), 5.60 (s, 2H), 7.56 (t, *J*= 7.6, 2H), 7.71-7.68 (m, 1H), 8.03 (d, *J*=6.4, 2H), 8.13-8.11 (m, 2H), 8.62 (d, *J*=6.4, 2H); LRMS (FAB) 228 ($(M)^+$, 17), 133 (28), 89 (50), 45 (50); HRMS (FAB) calcd for $C_{14}H_{14}NO_2$ 228.1025, found 228.1027.

***N*-Methyl Picolinium Phenylacetate Iodide (69c).**

Compound **69c** was prepared as above, and is a dark brown liquid (7.03 g, 95%). ^{1}H NMR (CD_3CN) δ 3.83 (s, 2H), 4.28 (s, 3H), 5.37 (d, 2H), 7.36-7.30 (m, 5H), 7.88 (d, *J*=6.2, 2H), 8.62 (d, *J*=6.2, 2H); ^{13}C NMR (CD_3CN) δ 40.9, 48.8, 64.1, 125.7, 128.0,

129.3, 130.3, 134.7, 146.0, 157.1, 171.8; LRMS (FAB) 242 (20), 133 (24), 89 (30), 45 (30); HRMS (FAB) calcd for $C_{16}H_{16}NO_2$ 242.1181, found 242.1169.

***N*-Methyl Picolinium Trimethylacetate Iodide (69d).**

Compound **69d** was methylated by the above general methylation procedure, and is a thick dark brown liquid (4.30g, 88%). ^{1}H NMR (CD_3CN) δ 1.26 (s, 9H), 4.27 (s, 3H), 5.33 (s, 2H), 7.90 (d, *J*=6.2, 2H), 8.60 (d, *J*=6.2, 2H); ^{13}C NMR (CD_3CN) δ 30.8, 39.4, 48.8, 64.0, 125.9, 146.0, 157.8, 178.2; LRMS (FAB) 208 ($(M)^+$, 40), 166 (23), 122 (70); HRMS (FAB) calcd for $C_{12}H_{18}NO_2$ 208.1338, found 208.1331.

***N*-Methyl Picolinium Diphenylacetate Iodide (69e).**

Compound **69e** is a dark yellow solid, which upon recrystallization from hot methanol yielded yellow crystals (3.17g, 74%). Mp 130-134 ºC; ^{1}H NMR (CD_3CN) δ 4.23 (s, 3H), 5.32 (s, 1H), 5.42 (s, 2H), 7.37-7.29 (m, 10H), 7.77 (d, *J*=6.4, 2H), 8.54 (d, *J*=6.4, 2H); ^{13}C NMR (CD_3CN) δ 48.9, 57.0, 64.6, 126.0, 128.4, 129.5, 129.6, 139.4, 146.0, 157.0, 172.6; LRMS (FAB) 318 ($(M)^+$, 100), 107 (17); HRMS (FAB) calcd for $C_{21}H_{20}NO_2$ 318.1494, found 318.1503.

***N*-Methyl Picolinium *p*-Tolylacetate Iodide (69f).**

Compound **69f** is a dark orange semisolid (7.66g, 100%). ^{1}H NMR (CD_3CN) δ 2.31 (s, 3H), 3.77 (s, 2H), 4.28 (s, 3H), 5.36 (s, 2H), 7.15-7.21 (m, 4H), 7.87 (d, *J*=6.2, 2H), 8.63 (d, *J*=6.2, 2H); ^{13}C NMR (CD_3CN) δ 20.9, 40.6, 48.9, 64.2, 125.8, 130.0, 130.2, 131.7,

137.7, 146.0, 157.2, 172.0; LRMS (FAB) 256 ($(M)^+$, 100); HRMS (FAB) calcd for $C_{16}H_{18}NO_2$ 256.1338 $(M)^+$, found 256.1340.

***N*-Methyl Picolinium Bromophenylacetate Iodide (69g).**

Compound **69g** is a dark brown solid after recrystallization from hot methanol (2.78g, 89%). Mp 110-114 ºC; ^{1}H NMR (CD_3CN) δ 3.80 (s, 2H), 4.25 (s, 3H), 5.36 (s, 2H), 7.25 (d, *J*=8.4, 2H), 7.52 (d, *J*=8.4, 2H), 7.87 (d, *J*=6.0, 2H), 8.57 (d, *J*=6.0, 2H); ^{13}C NMR (CD_3CN) δ 40.3, 48.9, 64.3, 121.5, 125.9, 132.4, 132.5, 134.2, 146.0, 157.2, 171.4; LRMS (FAB) 320 ($(M)^+$, 55), 122 (25), 108 (100), 94 (20); HRMS (FAB) calcd for $C_{15}H_{15}NO_2Br$ 320.0286 $(M)^+$, found 320.0302, calcd for $C_{15}H_{15}NO_2Br$ 322.0266 $(M)^+$, found 322.0271.

***N*-Methyl Picolinium Cinnamate Iodide (69h).**

Compound **69c** was obtained as pale yellow crystals after recrystallization from hot methanol (3.06 g, 73%). Mp 104-106 ºC; IR (nujol) 2955 (s), 2916 (m), 1712 (s), 1631 (s), 1465 (m); ^{1}H NMR (CD_3CN) δ 4.26 (s, 3H), 5.48 (s, 2H), 6.67 (d, *J*=16, 1H), 7.45-7.46 (m, 3H), 7.67-7.68 (m, 2H), 7.83 (d, *J*=16, 1H), 7.98 (d, *J*=6.0, 2H), 8.58 (d, *J*=6.0, 2H); ^{13}C NMR (CD_3CN) δ 48.8, 64.0, 117.6, 125.9, 129.2, 129.9, 131.7, 134.9, 146.0, 146.9, 157.9, 166.6; LRMS (FAB) 254 (6), 177 (9), 133 (11), 89 (11), 45 (11); HRMS (FAB) calcd for $C_{16}H_{16}NO_2$ 254.1181, found 254.1183.

***N*-Methyl Picolinium Acetate Perchlorate (70a).**

Compound **70a** was obtained as a pale yellow solid (1.09 g, 82%). Shiny, pale cream-colored crystals were formed upon recrystallization from hot ethanol. Mp 128-132 ºC; IR (nujol) 3067 (m), 2959 (m), 1747 (s), 1646 (m); ^{1}H NMR (CD_3CN) δ 2.16 (s, 3H), 4.26 (s, 3H), 5.33 (s, 2H), 7.92 (d, *J*=5.8, 2H), 8.58 (d, *J*=5.8, 2H); ^{13}C NMR (CD_3CN) δ 20.8, 48.7, 63.9, 125.9, 146.1, 157.6, 171.0; LRMS (FAB) 166($(M)^+$, 100); HRMS (FAB) calcd for $C_9H_{12}NO_2$ 166.0868 $(M)^+$, found 166.0876.

***N*-Methyl Picolinium Benzoate Perchlorate (70b).**

Compound **70b** was obtained as pale cream-colored crystals upon upon recrystallization from hot ethanol (0.33 g, 51 %). Mp 146-150 ºC; IR (nujol) 3071 (m), 2939 (m), 2897 (m), 1716 (s), 1646 (m), 1460 (s); ^{1}H NMR (CD_3CN) δ 4.27 (s, 3H), 5.60 (s, 2H), 7.56 (t, *J*=7.4, 2H), 7.69 (d, *J*=7.4, 1H), 8.02 (d, *J*=6.2, 2H), 8.13-8.11 (m, 2H), 8.58 (d, *J*=6.2, 2H); ^{13}C NMR (CD_3CN) δ 48.7, 64.5, 126.2, 129.6, 129.9, 130.4, 134.7, 146.0, 157.3, 166.3; LRMS (FAB) 228 ($(M)^+$, 100), 122 (10), 108 (25); HRMS (FAB) calcd for $C_{14}H_{14}NO_2$ 228.1025, found 228.1022.

***N*-Methyl Picolinium Phenylacetate Perchlorate (70c).**

Compound **70c** was obtained as a thick brown liquid. About 20 ml of CH_3OH was added and the solution was stirred vigorously. A thick precipitate was formed. Filtration and drying of the precipitate yielded a cream-colored solid (2.27 g, 80 %). Mp 98-100 ºC; IR (nujol) 3060 (m), 2924 (m), 1735 (s), 1646 (m), 1095 (s); ^{1}H NMR (CD_3CN) δ 3.82 (s, 2H), 4.24 (s, 3H), 5.36 (s, 2H), 7.36-7.33 (m, 5H), 7.85 (d, *J*=6.0, 2H), 8.53 (d, *J*=6.0,

2H); ^{13}C NMR (CD_3CN) δ 41.1, 48.8, 64.2, 146.0, 157.4, 171.8, 125.9, 128.1, 129.4, 130.4, 134.8; MS (EI) 241 ($(M-1)^+$, 20), 136 (30), 122 (88), 91 (100); LRMS (FAB) 242 ($(M+H)^+$, 100), 152 (25), 108 (21), 45 (33); HRMS (FAB) calcd for $C_{15}H_{16}NO_2$ 242.1181, found 242.1181.

***N*-Methyl Trimethylacetate Perchlorate (70d).**

Compound **70d** was obtained as a pale yellow solid after recrystallization from hot ethanol (2.72 g, 88%). Mp 54-56 ºC; ^{1}H NMR (CD_3CN) δ 1.26 (s, 9H), 4.25 (s, 3H), 5.32 (s, 2H), 7.89 (d, *J*=6.2, 2H), 8.54 (d, *J*=6.2, 2H); ^{13}C NMR (CD_3CN) δ 27.2, 30.8, 39.4, 48.8, 64.0, 125.9, 146.0, 157.8, 178.2; LRMS (FAB) 208 ($(M)^+$, 100), 107 (13), 93 (11); HRMS (FAB) calcd for $C_{12}H_{18}NO_2$ 208.1338, found 208.1339.

***N*-Methyl Picolinium Diphenylacetate Perchlorate (70e).**

Compound **70e** was obtained as a white solid upon recrystallization from hot ethanol (2.70g, 88%). ^{1}H NMR (CD_3CN) δ 4.23 (s, 3H), 5.31 (s, 1H), 5.41 (s, 2H), 7.37-7.35 (m, 10H), 7.76 (d, *J*=6.6, 2H), 8.51 (d, *J*=6.6, 2H); ^{13}C NMR (CD_3CN) δ 48.8, 57.0, 64.6, 126.0, 128.4, 129.5, 129.6, 139.4, 146.0, 157.0, 172.6; LRMS (FAB) 318 ($(M)^+$, 100); HRMS (FAB) calcd for $C_{21}H_{20}NO_2$ 318.1494, found 318.1508.

***N*-Methyl Picolinium *p*-Tolylacetate Perchlorate (70f).**

Compound **70f** was obtained as a yellow sticky semisolid (3.07g, 86%). ^{1}H NMR (CD_3CN) δ 2.31 (s, 3H), 3.77 (s, 2H), 4.25 (s, 3H), 5.35 (s, 2H), 7.17-7.19 (m, 4H), 7.85 (d, *J*=6.4, 2H), 8.56 (d, *J*=6.4, 2H); ^{13}C NMR (CD_3CN) δ 20.9, 40.6, 48.7, 64.1, 125.8,

130.0, 130.2, 131.7, 137.8, 145.9, 157.3, 172.0; LRMS (FAB) 256 ($(M)^+$, 100), 122 (27), 107 (77); HRMS (FAB) calcd for $C_{16}H_{18}NO_2$ 256.1338 $(M)^+$, found 256.1346.

***N*-Methyl Bromophenylacetate Perchlorate (70g).**

Compound **70g** was obtained as a pale yellow solid after recrystallization from hot ethanol (1.09 g, 64%). Mp 74-78 ºC; ^{1}H NMR (CD_3CN) δ 3.80 (s, 2H), 4.24 (s, 3H), 5.36 (s, 2H), 7.24-7.26 (m, 2H), 7.50-7.53 (m, 2H), 7.86 (d, *J*=6.4, 2H), 8.54 (d, *J*=6.4, 2H); ^{13}C NMR (CD_3CN) δ 40.3, 48.8, 64.3, 121.5, 125.9, 132.4, 132.5, 134.2, 146.0, 157.2, 171.4; LRMS (FAB) 320 ($(M)^+$, 100); HRMS (FAB) calcd for $C_{15}H_{15}NO_2Br$ 320.0286 $(M)^+$, found 320.0275, calcd for $C_{15}H_{15}NO_2Br$ 322.0266 $(M)^+$, found 322.0278.

***N*-Methyl Picolinium Cinnamate Perchlorate (70h).**

About 2.5 mmol of the ester was combined with silver perchlorate to afford pale cream-colored crystals (0.69 g, 78 %). Mp 132-134 ºC; IR (nujol) 2963 (m), 2866 (m), 1708 (s), 1642 (m), 1460 (s); ^{1}H NMR (CD_3CN) δ 4.26 (s, 3H), 5.48 (s, 2H), 6.67 (d, *J*=16.4, 1H), 7.45-7.46 (m, 3H), 7.66-7.69 (m, 2H), 7.83 (d, *J*=16, 1H), 7.97 (d, *J*=6.2, 2H), 8.57 (d, *J*=6.2, 2H); ^{13}C NMR (CD_3CN) δ 48.4, 63.6, 117.3, 125.7, 128.8, 129.6, 131.3, 134.6, 146.7, 147.7, 157.3, 166.2; LRMS (FAB) 254 ($(M)^+$, 100); DCI 254 (5), 148 (20), 122 (88), 91(15), 77 (17); HRMS (FAB) calcd for $C_{16}H_{16}NO_2$ 254.1181, found 254.1192.

***N*-Methyl Picolinium Glycinate Perchlorate (70i).**

Compound **70i** was prepared by the same method as above. The product was a brown solid (1.85 g, 90%). Recrystallization from hot methanol yielded pale peach colored

solid. Mp 62-64 ºC; ^{1}H NMR (CD_3CN) δ 4.01 (d, *J*=6.4, 2H), 4.24 (s, 3H), 5.09 (s, 2H), 5.40 (s, 2H), 6.16 (s, 1H), 7.36-7.30 (m, 5H), 7.90 (d, *J*=6.4, 2H), 8.54 (d, *J*=6.4, 2H); ^{13}C NMR (CD_3CN) δ 43.1, 48.9, 64.5, 67.8, 125.7, 128.3, 128.7, 129.2, 137.7, 145.3, 156.6, 157.4, 170.7; LRMS (FAB) 315 ($(M)^+$, 100), 119 (20), 85 (20); HRMS (FAB) calcd for $C_{17}H_{19}N_2O_4$ 315.1345, found 315.1356.

***N*-Methyl Picolinium Serinate Perchlorate (70j).**

Compound **70j** was obtained as a brown solid. Recrystallization from hot methanol yielded pale orange solid (0.99 g, 71%). Mp 108-110 ºC; ^{1}H NMR (CD_3CN) δ 3.89 (dd, *J*=4.6, 6.4, 1H), 3.99 (dd, *J*=4.6, 6.4, 1H), 4.31-4.29 (m, 1H), 5.12 (s, 2H), 5.52 (s, 2H), 7.37-7.27 (m, 5H), 8.04 (d, *J*=6.2, 2H), 8.82 (d, *J*=6.2, 2H); ^{13}C NMR (CD_3CN): 48.7, 57.2, 62.6, 64.5, 67.2, 125.7, 128.5, 128.8, 129.3, 137.8, 145.9, 156.9, 157.1, 171.1; LRMS (FAB) 345 (M^+, 100), 152 (20), 85 (45); HRMS (FAB) calcd for $C_{18}H_{21}N_2O_5$ 345.1450, found 345.1465.

***N*-Methyl Picolinium Diethylphosphate Perchlorate (70k).**

Compound **70k** is a thick pale yellow liquid (1.21 g, 65%). ^{1}H NMR (CD_3CN) δ 1.32-1.26 (m, 6H), 4.15-4.02 (m, 4H), 4.28 (s, 3H), 5.30 (d, *J*=8.0, 2H), 7.95 (d, *J*=6.4, 2H), 8.59 (d, *J*=6.4, 2H); ^{13}C NMR (CD_3CN) δ 16.3, 48.9, 64.5, 65.4, 73.2, 125.6, 146.0; LRMS (FAB) 260 (M^+, 100), 154 (38), 122 (27), 107 (25); HRMS (FAB) calcd for $C_{11}H_{19}NPO_4$ 260.1052, found 260.1040.

***N*-Methyl Picolinium Perchlorate (71).**

Compound **71** was prepared from *N*-methyl picolinium iodide (Aldrich) by the counter-ion exchange procedure described above and obtained as white crystals after recrystallization from hot ethanol (0.64 g, 61 %). Mp 132-134 ºC; IR (nujol) 2957 (m), 2854 (m), 1646 (m), 1460 (s), 1095 (s); ^{1}H NMR (CD_3CN) δ 2.60 (s, 3H), 4.20 (s, 3H), 7.78 (d, *J*=6.2, 2H), 8.42 (d, *J*=6.2, 2H); ^{13}C NMR (CD_3CN) δ 21.9, 48.2, 129.2, 145.0, 160.3; LRMS (FAB) 108 ($(M)^+$, 85), 45 (85); HRMS (FAB) calcd for $C_7H_{10}N$ 108.0813, found 108.0809.

Preparation of *N*-Bromoalkyl Carbazoles 93a and 93b [115]

To a mixture of tetrabutylammonium bromide TBAB (0.40 g, 1.25 mmol), and aqueous 50% sodium hydroxide (100 mL), was added a solution of carbazole (5.0 g, 30 mmol) and the alkyl dibromide (90 mmol) in benzene (100 mL). The mixture was stirred at room temperature overnight and then poured into water. The organic components were extracted into dichloromethane (3 x 25 mL). The organic phase was washed with water and dried over magnesium sulfate. After removal of solvent, the residue was purified by column chromatography. The elution of the third band in the column by a mixture of dichloromethane /hexane (1:5) gave the bromoalkyl carbazole.

***N*-Bromopropyl Carbazole (93a)**

The product is a white needle-like solid (3.7 g, 42 %). Mp 148-150 ºC; ^{1}H NMR (CD_3CN) δ 2.46-2.40 (m, 2H), 3.38 (t, *J*=6.4, 2H), 4.49 (t, *J*=6.4, 2H), 7.26-7.22 (m, 2H), 7.49-7.44 (m, 4H), 8.09 (d, *J*=8.0, 2H); LRMS (FAB) 289 ($(M)^+$, 60), 287 ($(M)^+$, 45), 180

(100), 167 (35); HRMS (FAB) calcd for $C_{15}H_{14}NBr$ 287.0310, found 287.0313. ^1H NMR data is consistent with the data previously reported. [115]

***N*-Bromobutyl Carbazole (93b)**

The product is a white needle-like solid (4.2 g, 46 %). Mp 104-106 ºC (lit. [118] 107 ºC); ^1H NMR (CD_3CN) δ 1.94-1.86 (m, 2H), 2.07-2.02 (m, 2H), 3.38-3.34 (m, 2H), 4.36- 4.30 (m, 2H), 7.24-7.20 (m, 2H), 7.39 (d, *J*=8.0, 2H), 7.47-7.43 (m, 2H), 8.09 (d, *J*=8.0, 2H); LRMS (FAB) 303 ($(M)^+$, 70), 301 ($(M)^+$, 65), 180 (70), 135 (70), 119 (70); HRMS (FAB) calcd for $C_{16}H_{16}NBr$ 303.0446, found 303.0449 and 301.0466, found 301.0454. ^1H NMR data was consistent with the data previously reported. [115]

Synthesis of carbazole linked esters 95a, 95b and 95c

A solution of equal number of moles of *N*-propyl or butyl carbazole and the appropriate picolyl ester in MeCN (40 mL) was refluxed at 85°C for 8-10 h. The solvent was evaporated and the residue was dried under vacuum. About 2-5 mmoles of the dark brown thick liquid was then dissolved in 30 mL MeCN, and an equal number of moles of $AgClO_4$ in 5 mL MeCN was added slowly. The reaction was stirred at room temperature overnight. The AgI precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was recrystallized from hot EtOH.

***N*-Propyl Carbazole Picolinium Phenylacetate Perchlorate 95a**

Compound **95a** was prepared by the reaction of *N*-bromopropyl carbazole with picolyl phenylacetate and obtained as a dark brown liquid. Recrystallization from hot ethanol

yielded a light brown solid (1.86 g, 73 %). Mp 156-158 ºC; ^{1}H NMR (CD_3CN) δ 2.62-2.58 (m, 2H), 3.80 (s, 2H), 4.55-4.49 (m, 4H), 5.21 (s, 2H), 7.24-7.20 (m, 2H), 7.37-7.31 (m, 5H), 7.50-7.43 (m, 6H), 8.03 (d, *J*=7.6, 2H), 8.21 (d, *J*=6.4, 2H); ^{13}C NMR (CD_3CN) δ 29.9, 41.1, 40.6, 60.1, 63.9, 78.6, 109.9, 120.3, 121.2, 123.6, 125.3, 126.9, 128.1, 129.5, 130.4, 140.7, 144.1, 157.2, 171.7; LRMS (FAB) 435 ($(M)^+$, 55), 180 (100), 45 (85); HRMS (FAB) calcd for $C_{29}H_{27}N_2O_2$ 435.2073, found 435.2057.

***N*-Propyl Carbazole Picolinium Tolylacetate Perchlorate (95b)**

Compound **95b** was prepared by the reaction of *N*-bromopropyl carbazole with picolyl tolylacetate and obtained as pale yellow solid after recrystallization from hot ethanol (1.02 g, 92 %). Mp 76-78 ºC; ^{1}H NMR (CD3CN) δ 2.31 (s, 3H), 2.62-2.58 (m, 2H), 3.75 (s, 2H), 4.56-4.50 (m, 4H), 5.20 (s, 2H), 7.23-7.18 (m, 6H), 7.50-7.42 (m, 6H), 8.03 (d, *J*=7.6, 2H), 8.21 (d, *J*=6.8, 2H); ^{13}C NMR (CD_3CN) δ 21.0, 29.9, 40.6, 60.1, 63.9, 78.5, 109.9, 120.2, 121.2, 123.6, 125.3, 126.9, 130.1, 130.2, 131.7, 137.9, 140.7, 144.0, 157.2, 171.8; LRMS (FAB) 449 ($(M)^+$, 100), 180 (38), 119 (26), 85 (18); HRMS (FAB) calcd for $C_{30}H_{29}N_2O_2$ 449.2229, found 449.2214.

***N*-Butyl Carbazole Picolinium Phenylacetate Perchlorate (95c)**

Compound **95c** was prepared by the reaction of *N*-bromobutyl carbazole with picolyl phenylacetate and obtained as a dark brown liquid. Recrystallization from hot methanol yielded cream colored solid (0.90 g, 91 %). Mp 118-120 ºC; ^{1}H NMR (CD_3CN) δ 1.90-1.87 (m, 4H), 3.81 (s, 2H), 4.41-4.36 (m, 4H), 5.31 (s, 2H), 7.23-7.20 (m, 2H), 7.35-7.31 (m, 5H), 7.48-7.45 (m, 4H), 7.75 (d, *J*=6.4, 2H), 8.11 (d, *J*=8.0, 2H), 8.41 (d, *J*=6.4, 2H);

^{13}C NMR (CD_3CN) δ 25.9, 29.2, 41.0, 42.7, 61.8, 64.1, 78.6, 109.9, 119.8, 121.1, 123.4, 126.1, 126.7, 128.1, 129.4, 130.3, 141.1, 144.8, 157.7, 171.7; LRMS (FAB) 449 ($(M)^+$, 65), 315 (70), 180 (100), 85 (55); HRMS (FAB) calcd for $C_{30}H_{29}N_2O_2$ 449.2229, found 449.2228.

Preparation of 4-(2-Bromoethyl) Benzophenone [119] (96)

Aluminium chloride (6.35g, 48 mmol) and benzoyl chloride (12.15 g, 86 mmol) were heated at 50°C for 30 min under nitrogen atmosphere. To the mixture at 50°C, 2-bromoethylbenzene (8.04 g, 43 mmol) was added dropwise over 30 min. The reaction mixture was stirred at 60°C for 6 h and then poured into a crushed ice-1N hydrochloric acid mixture (500 g, 100 mL), followed by vigorous stirring to completely destroy the complex. After the addition of 150 mL of dichloromethane, the organic layer was washed with 1N hydrochloric acid, water, sat. $NaHCO_3$, and brine (3 x 20 mL each). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in 1 L of hexane and cooled in a refrigerator. Pale yellow crystals were formed, and collected by filtration (3.86 g, 31 %). Mp 48-50ºC (lit [119] 48-49ºC); ^{1}H NMR (CD_3CN) δ 3.26 (t, *J*=7.2, 2H), 3.71 (t, *J*=7.0, 2H), 7.41 (d, *J*=8.0, 2H), 7.52 (t, *J*=7.6, 2H), 7.63 (t, *J*=7.2, 1H), 7.75-7.72 (m, 4H); LRMS (FAB) 289 (M^+, 42), 245 (22), 105 (100), 77 (40); HRMS (FAB) calcd for $C_{15}H_{13}OBr$ 289.0228, found 289.0225, 291.0208, found 291.0224.

Preparation of Ethyl Benzophenone linked picolinium esters (98a and 98b) and 99

A solution of 4-(2-bromoethyl) benzophenone (1.3 g, 4.5 mmoles) and picolyl ester (4.5 mmoles) or 4-picoline (for **99**) in MeCN (40 mL) was refluxed at 85°C for 8-10 h. The solvent was evaporated and the residue was dried under vacuum. About 2.0 mmoles of the dark brown thick liquid was then dissolved in 30 mL MeCN, and an equimolar solution of $AgClO_4$ in 5 mL MeCN was added slowly. The reaction was stirred at room temperature overnight. The AgI precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was recrystallized from hot EtOH.

Ethyl Benzophenone Picolinium Phenylacetate Perchlorate (98a)

Compound **98a** was prepared from picolyl phenylacetate and obtained as a pale brown solid (2.26 g, 100%). Mp 248-250 ºC; ^{1}H NMR (CD_3CN) δ 3.35 (t, *J*=7.2, 2H), 3.81 (s, 2H), 4.76 (t, *J*=7.2, 2H), 5.35 (s, 2H), 7.32-7.26 (m, 7H), 7.54 (t, *J*=7.6, 2H), 7.75-7.68 (m, 5H), 7.82 (d, *J*=6.6, 2H), 8.48 (d, *J*=6.6, 2H); ^{13}C NMR (CD_3CN) δ 37.3, 41.0, 62.7, 64.2, 126.1, 128.1, 129.3, 129.5, 129.9, 130.4, 130.6, 131.3, 133.5, 134.8, 137.5, 138.3, 141.4, 145.1, 158.2, 171.8, 196.7; LRMS (FAB) 436 (M^+, 16), 154 (26), 138 (26), 89 (26), 77 (23); HRMS (FAB) calcd for $C_{29}H_{26}NO_3$ 436.1913, found 436.1897.

Ethyl Benzophenone Picolinium Diphenylacetate Perchlorate (98b)

Compound **98b** was prepared from picolyl diphenylacetate and obtained as a pale cream solid (1.27 g, 100%). Mp 78-80 ºC; ^{1}H NMR (CD_3CN) δ 3.34 (t, *J*=7.0, 2H), 4.75 (t, *J*=7.0, 2H), 5.29 (s, 1H), 5.40 (s, 2H), 7.35-7.23 (m, 12H), 7.53 (t, *J*=7.0, 2H), 7.74-7.67 (m, 7H), 8.42 (d, *J*=7.0, 2H); ^{13}C NMR (CD_3CN) δ 37.3, 57.0, 62.7, 64.6, 126.2, 128.4,

129.3, 129.4, 129.6, 129.8, 130.6, 131.3, 133.5, 137.5, 138.3, 139.4, 141.4, 145.1, 157.8, 172.5, 196.7; LRMS (FAB) 512 (M^+, 100), 304 (26), 167 (27), 119 (42), 85 (36); HRMS (FAB) calcd for $C_{35}H_{30}NO_3$ 512.2226, found 512.2245.

Ethyl Benzophenone Picolinium Perchlorate (99)

Compound **99** was prepared from 4-picoline and obtained as a pale cream colored flaky solid (3.72 g, 99%). Mp 108-110 ºC; ^{1}H NMR (CD_3OD) δ 2.65 (s, 3H), 3.42 (t, *J*=7.0, 2H), 4.86 (t, *J*=7.0, 2H), 7.34 (d, *J*=8.0, 2H), 7.52 (t, *J*=7.2, 2H), 7.75-7.70 (m, 5H), 7.87 (d, *J*=6.4, 2H), 8.66 (d, *J*=6.4, 2H); ^{13}C NMR (CD_3CN) δ 22.1, 37.3, 62.2, 129.3, 129.5, 129.8, 130.6, 131.3, 133.4, 137.4, 138.3, 141.6, 144.2, 161.2, 196.7; LRMS (FAB) 302 (M^+, 100), 245 (57), 198 (87), 105 (82); HRMS (FAB) calcd for $C_{21}H_{20}NO$ 302.1545, found 302.1530.

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