

ABSTRACT

Title of Document: ***N*-METHYL-4-PICOLINIUM IODIDE ESTERS AS VISIBLE LIGHT PHOTOREMOVABLE PROTECTING GROUPS FOR CARBOXYLIC ACIDS**

David Joseph Kunsberg, Master of Science, 2015

Directed By: **Professor Daniel E. Falvey, Organic Division, Department of Chemistry and Biochemistry**

Facile photorelease of carboxylic acids is performed through charge-transfer excitation of *N*-methyl-4-picolinium iodide esters. Photolysis reactions are carried out under mild, biphasic solvent conditions using a household LED lamp. Release is quantified by ¹H NMR analysis and carboxylic acid release is reported in high yields. The viability of this method for synthetic chemistry is demonstrated through a macroscale photolysis. Additionally, the potential for solvent-independent NAP ester charge-transfer photolysis is explored.

N-METHYL-4-PICOLINIUM IODIDE ESTERS AS VISIBLE LIGHT
PHOTOREMOVABLE PROTECTING GROUPS FOR CARBOXYLIC ACIDS

By

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1 Introduction

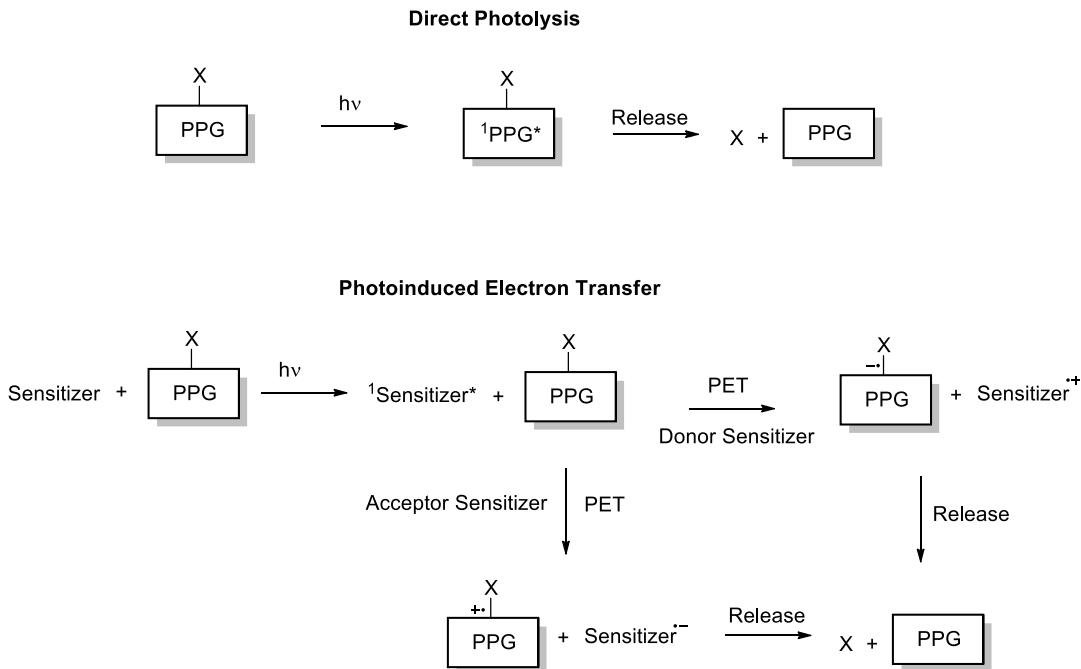
1.1 Photoremovable Protecting Groups

Photoremovable protecting groups (PPGs) are molecular species that use light as a reagent to release chemical compounds. As with traditional protecting groups, many PPGs are covalently bound to a substrate in a way that masks its reactivity. When a PPG is irradiated, it restores the bound substrate to its active form. Release by light confers spatiotemporal control, allowing for applications in organic synthesis,¹⁻³ photolithography,^{4,5} drug release,⁶⁻⁸ neurobiology,^{9,10} and optogenetics.^{11,12}

The breadth of PPG application is attributable to the advantages they provide over conventional protecting groups. Light is a traceless reagent that can be used with unparalleled spatiotemporal control. Light's intensity and direction can be finely tuned, allowing for precise photolysis conforming to a particular experiment's individual requirements. In addition, light may provide an alternate means for inducing chemical reactions that is applicable to sensitive applications such as biological systems.

Direct photolysis is the most established method in literature for PPG release, and it relies on an internal radical or rearrangement mechanism after the chromophore of a molecule is photochemically excited. In contrast, Falvey and coworkers have reported the use of a photoinduced electron transfer (PET) mechanism for PPG release.¹³ In these PET-PPGs, the substrate is bound to a non-photoactive group. Instead, the reaction is contingent upon a photochemical reduction, wherein a separate species, known as a sensitizer, is the photoactive reagent. After irradiation, the excited state sensitizer reduces the non-photoactive group and the subsequent electron transfer ultimately produces

substrate release (Scheme 1-1).



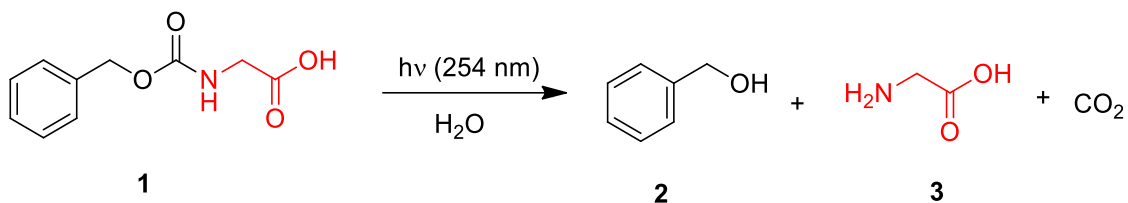
Scheme 1-1: Comparison of direct photolysis and PET mechanisms for PPGs.

For PET-PPGs, the electron transfer may be an oxidation or reduction as dictated by the relative energy levels of the sensitizer's and the PPG's Highest Occupied Molecular Orbitals (HOMOs) and Lowest Unoccupied Molecular Orbitals (LUMOs). The resulting oxidation or reduction of the PET-PPG leads to the release of caged substrate.

1.2 Direct Photolysis

Most PPGs are released through direct photolysis.¹ Here, absorption of light by a chromophore leads to the promotion of an electron from ground state to an electronically excited state. Decomposition to deprotect an organic functionality is one of several pathways the excited singlet state molecule can take. If the bond-breaking rate is competitive with other processes such as intersystem crossing, fluorescence, or internal conversion, then a portion of excited molecules see substrate release. Baltrop and

Schofield reported the first use of PPG by direct photolysis of *N*-benzyloxycarbamoyl glycine (**1**) to produce glycine (**3**) (scheme 1-2).¹⁴



Scheme 1-2. Photolysis of *N*-benzyloxycarbamoyl glycine

Several PPGs have been developed since. One of the most commonly used is the 2-nitrobenzyl chromophore, which is suitable for carboxylate and amine release.^{15,16} Other examples include the water-soluble 4-hydroxyphenacyl groups, which was developed for its benign byproducts;¹⁷⁻¹⁹ the coumarin-4-methyl group, which can be used for two-photon absorption;²⁰⁻²² fluorescein and BODIPY chromophores which allow for photorelease using visible wavelengths;^{23,24} and other groups which utilize other mechanisms of photorelease.²⁵⁻²⁸

1.3 Visible Light PPGs

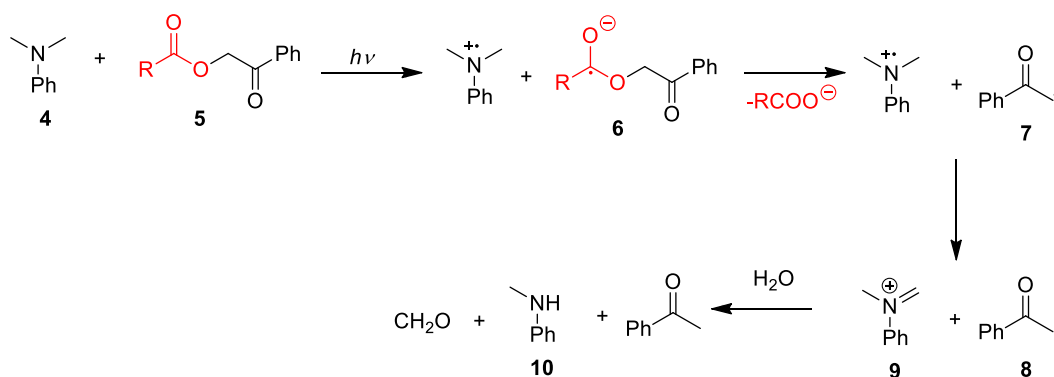
One restriction of direct photolysis PPGs is their small window for excitation, often in the UV region. Modification of a chromophore (i. e. extended conjugation for higher wavelength use) often interferes with the photophysical properties of the PPG. The resulting PPG derivative is typically less effective at achieving substrate release. Even so, visible light photoremovable protecting groups are pursued because they may be the solution to several of the drawbacks that hinder existing PPGs. In particular, UV light is

nonselective, bears greater toxicity for biological applications, and is expensive to produce relative to visible light.

Yoon and coworkers have advocated the use of visible light in synthetic reactions through photoredox catalysts.²⁹⁻³¹ These reactions take advantage of the reduced environmental impact of visible light catalysis - the improved selectivity of visible light reactions induces fewer side reactions than UV light. Macmillan and coworkers have also utilized photoredox catalysis in combination with existing organocatalysis systems in order to produce new transformations.³²⁻³⁴ Similarly, Molander *et al* have looked to expand the scope of cross coupling reactions via photoredox transmetalation.³⁵

Nicewicz and coworkers have also looked at visible light photochemistry in the context of using common LED light sources.^{36,37} These widely available light sources allow for complex photochemical reactions to be performed in non-specialized laboratories.³⁸

Through the use of a sensitizer, PET-PPGs also allow substrate release by visible light irradiation. And sensitizers can be selected for the desired excitation wavelength and solubility characteristics. Falvey *et al* have demonstrated the sensitized release of carboxylic acids, amino acids, and phosphates by phenylacyl esters as a method for PET-based photodeprotection. Photolysis of phenylacyl esters occurs in the presence of the sensitizer *N,N*-dimethylaniline (**4**) in aqueous milieu (scheme 1-3).¹³



Scheme 1-3. PET deprotection of phenacyl esters.

1.4 The N-alkylpicolinium (NAP) ester

N-alkylpicolinium (NAP) esters have also been shown to release carboxylic acids by photoinduced electron transfer.³⁹⁻⁴⁵ The NAP protecting group serves as a novel PET-PPG that does not require easily oxidized sensitizers.

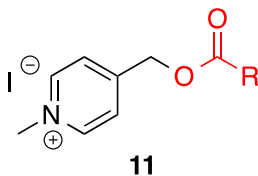
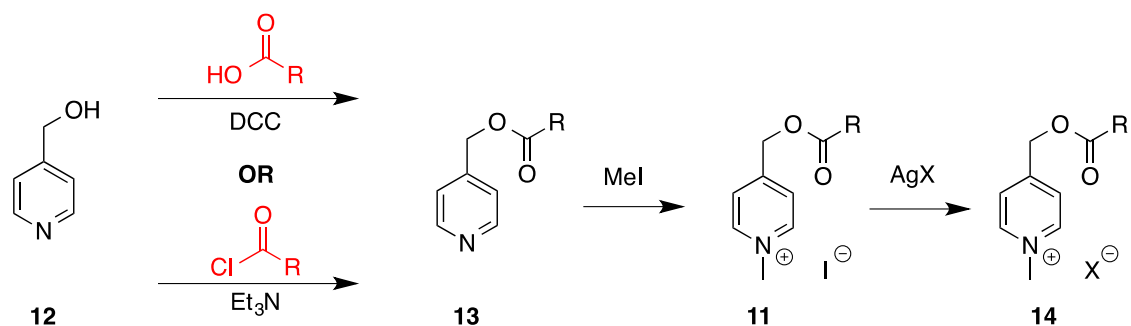


Figure 1-1. The *N*-alkylpicolinium (NAP) ester

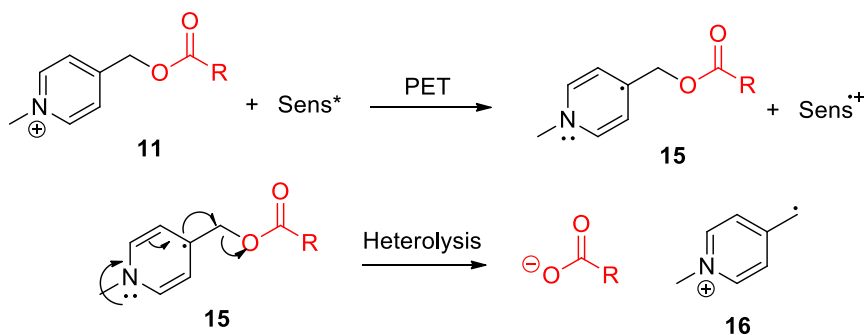
The reduction potential of the unalkylated picolyl group is very negative (-2.6 V vs SCE). Alkylation greatly increases this reduction potential (-1.1 V vs SCE), allowing for oxidation by a much wider range of sensitizers. Additionally, methylation creates an ion salt pair aiding in the solvation in more polar media. The synthesis of picolyl esters is relatively simple and is possible through two pathways (scheme 1-4).³⁹



Scheme 1-4: Synthesis of NAP-esters

Commercially obtained 4-pyridylcarbinol (**12**) can be combined with the acid chloride derivative of the desired carboxylate to produce the picolyl ester (**13**). Alternatively, the carboxylic acid can be coupled to the 4-pyridylcarbinol using dicyclohexylcarbodiimide (DCC). Both products can be alkylated using an alkyl halide, typically iodomethane, to produce the corresponding *N*-alkylpicolinium salt (**11**). The iodide counter ion can be precipitated with a silver salt to exchange counter ions (**14**).

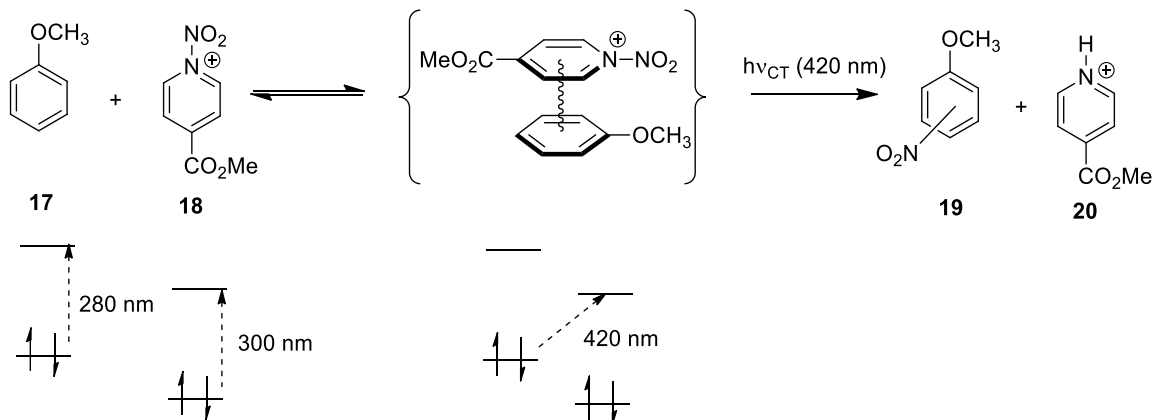
Several previous reports detail quantitative NAP ester release of carboxylic acid in the presence of an external sensitizer. Fluorescence quenching and laser flash photolysis experiments verify that the sensitizer transfers an electron to the pyridinium ring, which undergoes heterolysis to produce the 1,4-dimethyl picolinium radical (scheme 1-5).⁴²



Scheme 1-5. Proposed mechanism of NAP ester photolysis

1.5 Mulliken Charge Transfer Complex

Mulliken charge-transfer complexes provide an alternate mechanism for electron transfer. In this situation, orbital overlap between closely associated donor and acceptor molecules allows for the direct promotion of an electron from the donor HOMO to the acceptor LUMO. A charge-transfer absorption band ($h\nu_{CT}$) appears when the donor and acceptor are in close proximity and is indicative of a Mulliken complex.^{46,47} This Mulliken complex may be formed through a contact ion pair interaction or similar non-covalent binding interaction. Kochi *et al* have discussed the formation of a charge transfer complex between an *N*-nitropyridinium ester and anisole.⁴⁸ The charge transfer complex typically is in equilibrium with the solvent separated species which individually exhibit no such absorption (scheme 1-6).



Scheme 1-6. Charge-transfer nitration of anisole

Overlap of aromatic rings generates a new absorption band at 420 nm corresponding to the transfer of an electron from anisole to the pyridinium ring. The resulting anisole radical cation further reacts to transfer a nitro group from the pyridinium derivative.

1.6 NAP-Ester Iodide Charge Transfer Complex (CTC) Formation

Research during my undergraduate years primarily focused upon establishing that photolysis of NAP iodide esters can occur through charge-transfer excitation. A UV-Vis absorption band with $\lambda_{\text{max}} = 340$ was present in NAP iodide esters, and increasing $[\text{I}^-]$ amplified the intensity of this absorption band, indicative of Mulliken charge-transfer complex formation between iodide and NAP-ester (figure 1-2). Irradiation of the tail of this wavelength, which extends into the visible range (up to ~ 420 nm), is sufficient to incur carboxylic acid release. Photolysis was possible using a household LED lamp as a cheap and widely available light source. Initial rates of photolysis improved in nonpolar solvents, where NAP ester and iodide were more likely to be in contact ion pairs. This ion proximity facilitated charge-transfer complex formation. Photolysis was slow or unobserved in polar solvents where NAP ester cation and iodide anion existed as solvent separated ion pairs.

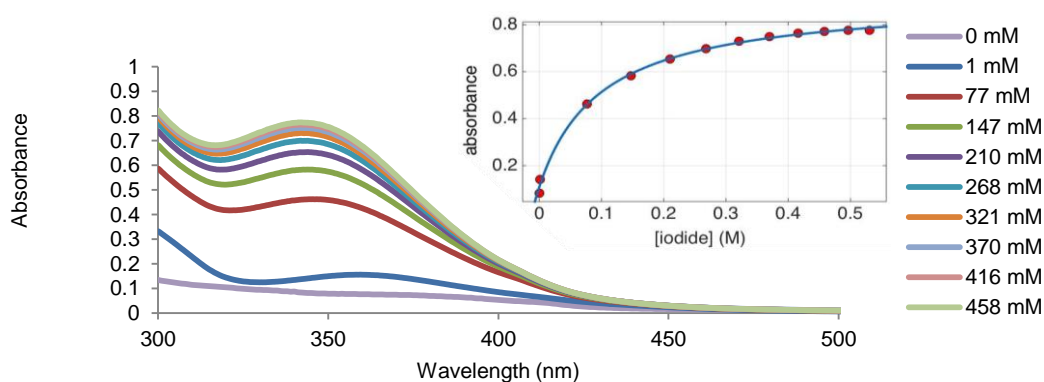


Figure 1-2. Addition of $\text{nBu}_4\text{N}^+ \text{I}^-$ to 1.0 mM 11a to form a charge-transfer complex. Inset: Increase in charge-transfer absorbance to an asymptotic binding curve. Calculated K_a of NAP-I complex formation is 11 M^{-1} .

Initial photolyses provided modest yields (*ca.* 50%) determined by HPLC and ^1H NMR.

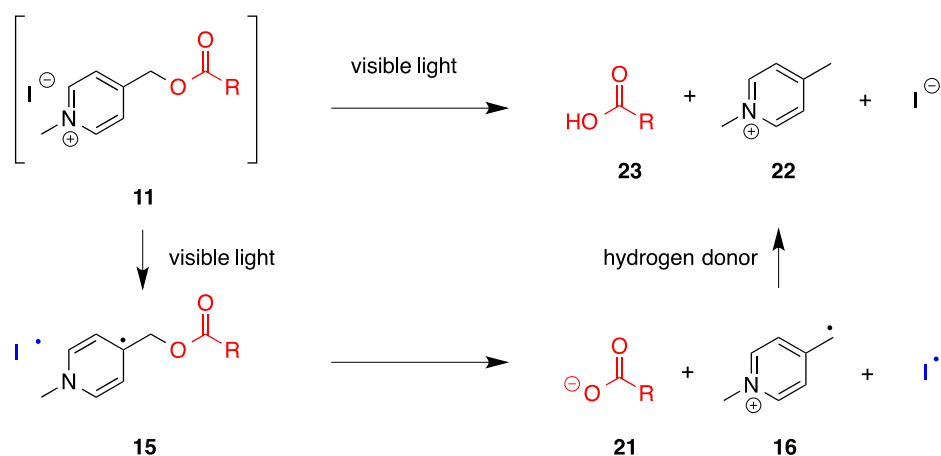
1.7 Conclusion

PPGs are a diverse group of photochemical protecting groups that have shown potential for a wide number of applications. Visible light PPGs, which do not require expensive and specialized light sources, have been of great interest to the scientific community. In the absence of an added sensitizer, The NAP iodide PET-PPG protecting group has been demonstrated to release carboxylic acids in moderate to low yields through a charge-transfer complex mechanism.

2 Photorelease of Carboxylic Acids from NAP esters using a Biphasic Solvent System

2.1 Triiodide Formation Serves as an Inner Filter of Light

A proposed mechanism for NAP ester photolysis by charge-transfer complex is provided in Scheme 2-1. After charge transfer, this mechanism follows a pathway similar to the PET-PPG mechanism in Scheme 1-4.



Scheme 2-1. Predicted mechanism of NAP-iodide ester charge transfer excitation

Previous research has determined that photolysis generates moderate yields of carboxylic acid, but the reaction does not go to completion and produced several byproducts. According to the proposed mechanism, the low yields may be explained by two related effects: First, The heterolysis of the C-O bond in **15** produces a carboxylate anion and the 1,4 dimethylpyridinium radical. The latter is a highly reactive species, which can initiate unintended radical reactions if there is not an efficient radical trapping pathway. Some of these reactions may degrade the final product and reduce overall yields. In addition, the initial electron transfer generates atomic iodine (I[•]). While this species is expected to be less reactive than radical cation **16**, it is known to generate I₃⁻ (through

combination with an additional atomic $I\cdot$ and any added I^-). I_3^- has a strong absorption band in the near UV region of the spectrum and, thus could serve as an inner filter, occluding light from the NAP ester iodide. Figure 2-1 shows UV-Vis spectra resulting from the photolysis of the 95/5 $CHCl_3/CH_3CN$ solutions of **11a** along with spectra measured from preparing varying concentrations of I_3^- in the same solvent.

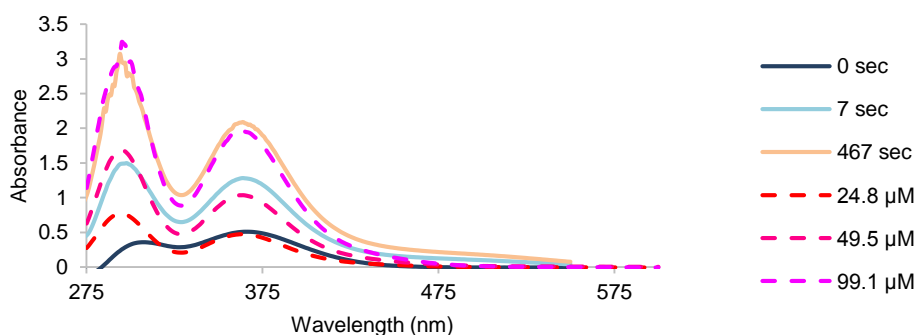


Figure 2-1. Spectra of various triiodide concentrations (dashed, legend is $[I_3^-]$) overlaid with UV-vis spectra of NAP ester photolysis spectrum (solid).

After only a few seconds of light exposure, the absorption of I_3^- begins to dominate the spectrum (a strong orange-red color is observed as the photolysis proceeds: see figure 2-2). While the formation of I_3^- conforms to the proposed mechanism, it does impede quantitative recovery of carboxylic acid yield. A reductant, such as ascorbate or starch, could serve to prevent the buildup of I_3^- at the expense of increased complexity in product separation.

2.2 Substrate Scope for NAP Iodide Esters and Quantitative Release

In order to achieve a simple method of directly isolating product from reactants, by-products and reductants, a biphasic photolysis solution is used. The NAP-ester iodide salt segregates to the organic layer, while ascorbic acid (the reductant) occupies the aqueous

layer. Irradiation of the biphasic solution with vigorous stirring ensures that any iodine formed in the organic layer that diffuses into the aqueous layer and is reduced. Additional sodium sulfate is added to the aqueous layer as a “salting out” salt to prevent migration of starting material into the aqueous layer, where the starting material is likely to dissociate into solvent separated ion pairs that do not undergo photochemical reaction.

The immiscible mixture of 250 μL water and 1.5 mL $\text{CHCl}_3/\text{CH}_3\text{CN}$ (95/5 v/v) was found to be appropriate. Solubilized in the water was 249 μmol (35.4 mg) anhydrous Na_2SO_4 and 217 μmol (38.25 mg) ascorbic acid. Figure 2-2 illustrates the visual effect of reduction of I_3^- .

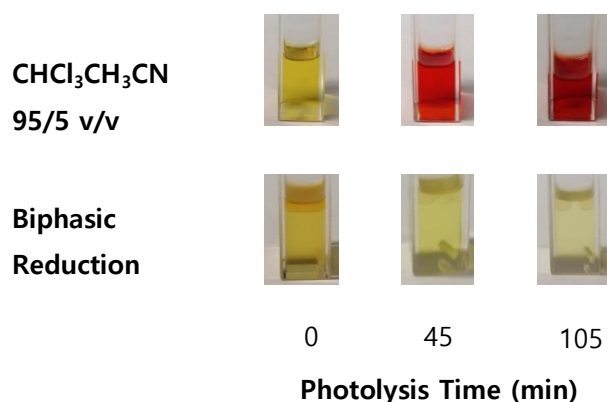
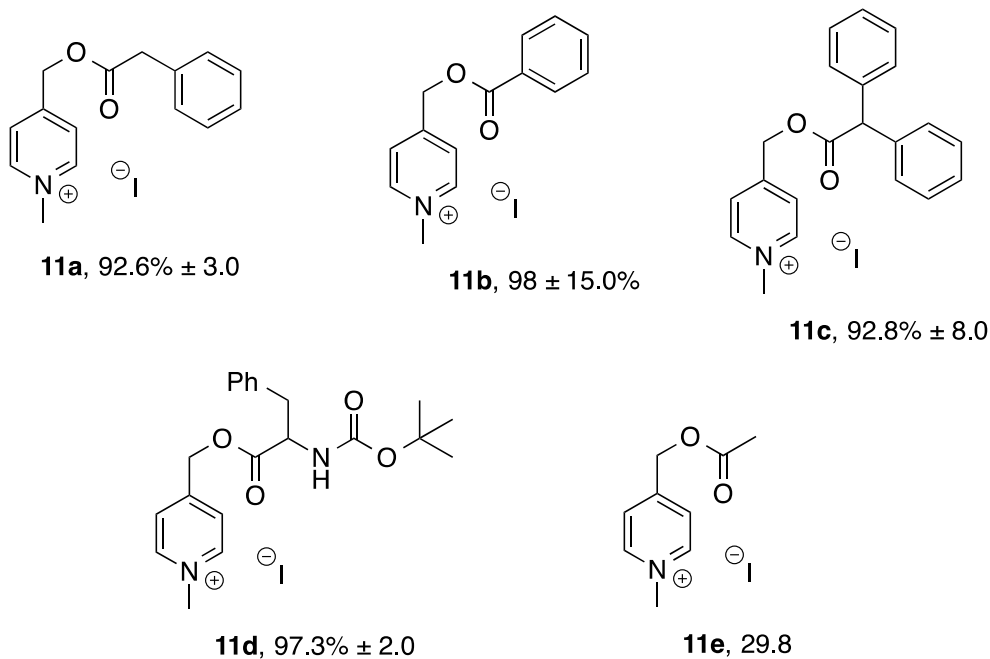
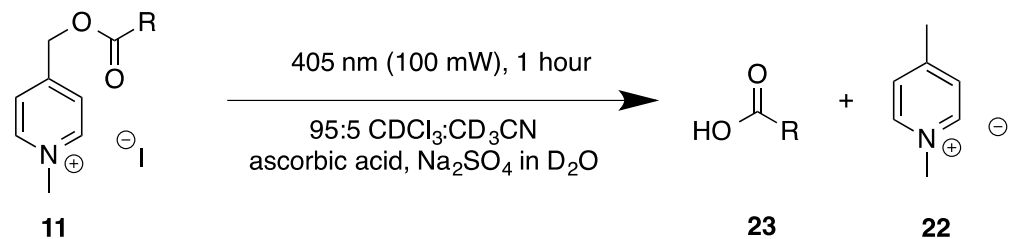


Figure 2-2 Visual changes for reduced and unreduced solutions during NAP ester photolysis. $11\text{a} = 17.1 \text{ mM}$.

Under these conditions, solutions of organic and aqueous phase were examined by ^1H NMR analysis using deuterated solvents. Esters **11a** – **11e** were found to selectively partition into the organic phase. Photolysis by 100 mW 405 nm diode laser for 1 h or the broadband output of a household LED lamp incur near quantitative release of carboxylic acids. The PPG residue, 1,4-dimethylpyridinium ion **22** and the oxidized electron donor I_3^- were found to migrate to the aqueous layer. When the reaction was performed in

deuterated solvents, the decanted organic layer was found to have high yields of carboxylic acid with no side-products or by-products detectable by ^1H NMR.



Scheme 2-2. Visible light, biphasic photolysis of NAP esters

As Scheme 2-2 shows, photorelease for several carboxylic acids is noted in high yields, except for the acetate derivative. This may be indicative of a limitation of the procedure. In the case of **11e**, the acetic acid product is partially water-soluble and efficient segregation is not achieved: Only 29.8% yield is recovered. Simple extraction of the organic layer is not sufficient to cleanly obtain all of the carboxylic acid. This is likely to

be the case for most carboxylic acids that possess high aqueous solubility in their protonated form.

2.3 Low Conversion Photolyses to Determine Additive Concentrations

To optimize the concentrations of various additives, a low conversion photolysis for 30 minutes was used. In this way, incomplete conversions could be used to analyze the relative rates of release (figure 2-3).

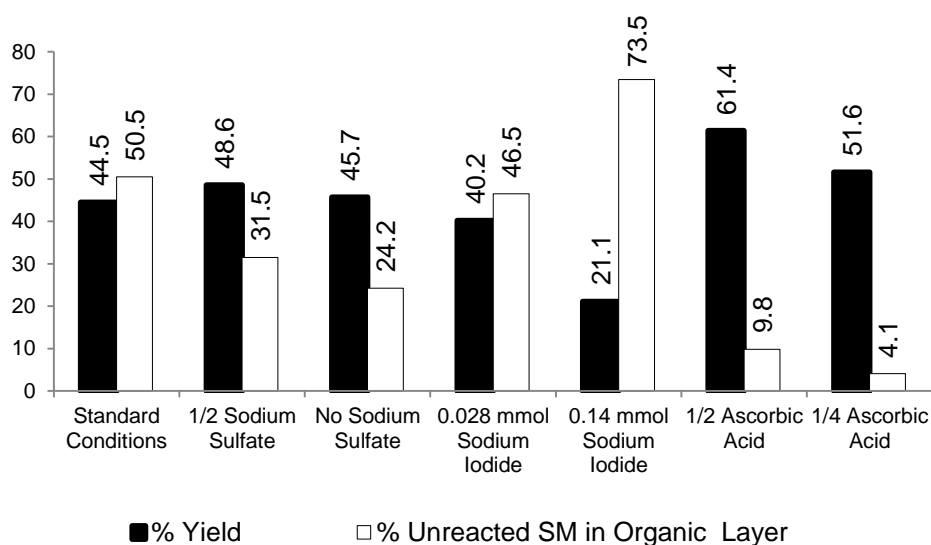


Figure 2-3. Low conversion biphasic photolyses for 11a. Standard conditions refer to a 30 min photolysis by 405 nm laser where 28 μmol NAP ester is solubilized in 1.5 mL $\text{CDCl}_3/\text{CD}_3\text{CN}$ (95/5 v/v) and 250 μL D_2O (with 249 μmol Na_2SO_4 and 217 μmol ascorbic acid).

In all cases, only phenylacetic acid and the **11a** starting material is found in the organic phase. Reduction of $[\text{Na}_2\text{SO}_4]$ has little effect on the overall rate of release. However, it does seem to affect the segregation of the starting material **11a**. Water-solubilized **11a** exists as the solvent separated NAP cation and iodide anion and no charge-transfer complexes form. In the absence of Na_2SO_4 as a salting out additive, some starting

material migrates to the aqueous layer and is photochemically inactive, limiting overall yields.

Reducing ascorbic acid concentrations appears to produce a moderate increase in substrate release rate and a reduction in mass balance. Ascorbic acid, like sodium sulfate, inhibits ester partitioning into the aqueous phase.

Additional NaI was added for the possibility that it might promote Mulliken complex formation. However, it appears that NaI does not accelerate photolysis. While there is no noticeable effect on mass balance, it appears that large concentrations of NaI inhibit photolysis. The primary influence of NaI may be through the formation of additional I_3^- , which may slow photolysis in a similar inner filter effect mentioned above (figure 2-1).

2.4 Macroscale Photolysis of 1a Using an Household LED lamp

To expand the versatility of this reaction, the use of a household LED lamp was considered. The Feit 18W PAR38 LED lamp, a typical example of LED lamps, slightly overlaps with the absorption peak of **1a** in chloroform.

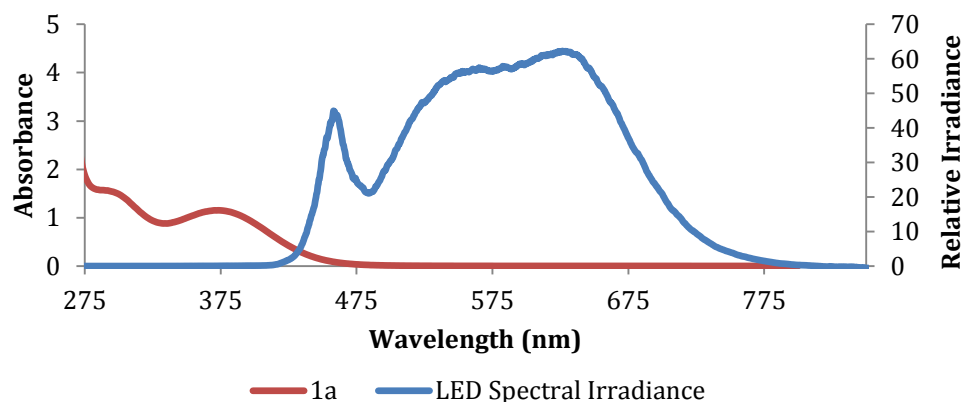


Figure 2-4. Relative irradiance of 18W PAR38 LED overlaid with 1a in $CHCl_3$.

To examine the utility of this light source for preparative scale ester deprotection, 500.1 mg (1.35 mmol) of **11a** was dissolved in 75 mL of CHCl₃/CH₃CN (95/5 v/v). 1.770 g (12.46 mmol) anhydrous Na₂SO₄ and 1.912 g (10.86 mmol) ascorbic acid were dissolved in 12.5 ml H₂O. The two layers were combined and irradiated with a Feit Electric 18 W lamp for 20 hours. The organic layer was separated from the aqueous layer and the solvent removed by rotary evaporation. The resulting crude mixture afforded 75.7% yield of phenylacetic acid after recrystallization from petroleum ether.

2.5 Conclusion

Visible light photolysis of NAP esters by charge-transfer excitation can be performed simply and catalyst-free to photorelease carboxylic acids. Photolysis and purification procedures allow this reaction to be performed outside of photochemical laboratories with minimal separation regiment. Under the conditions above, photolysis of many NAP esters could produce high yields. For individual cases, these conditions can be optimized to achieve a near-quantitative release. The byproducts of this reaction appear to be generally non-toxic (the by-product **22** is found in ranges of 5 to 25 mg/kg in coffee extract) and non-reactive, a crucial component for protecting groups to be used in biological systems.^{49,50} These characteristics suggest the provided method may be of use for synthetic chemistry, biochemistry studies, and drug release applications.

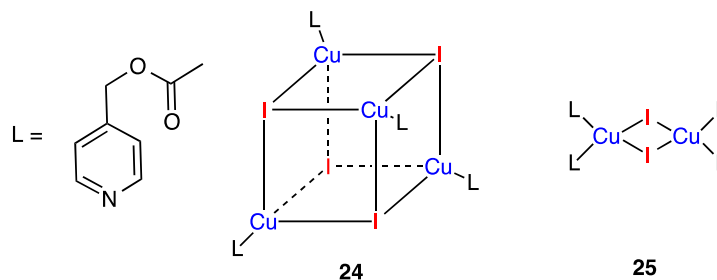
3 Pyridinium-Iodide Copper (I) Clusters for As PPGs for Carboxylic Acids

3.1 Copper (I) Iodide Scaffolding for Picolyl Esters

Charge-transfer excitation of NAP esters, as previously indicated, occurs best in nonpolar media, which serves to promote close ion pairing between NAP ester and iodide counterion. Expanding the versatility of the NAP PPG to other solvents, especially water, would overcome a constraint that impedes biological and medicinal application.

Copper (I) tetrakispyridinium tetraiodide clusters, or $\text{Cu}_4\text{I}_4(\text{py})_4$, have been well studied for their remarkable fluorescence properties.⁵¹ Of particular interest in these compounds is the association of a weak absorption band at 360 nm to a halide to ligand charge-transfer (XLCT) band.^{52,53} In theory, one could produce a picolyl ester derivative, induce a charge transfer from iodide to ligand, and obtain carboxylic acid release in a mechanism similar to that of scheme 2-1. Since it is the copper scaffold that maintains the proximity of iodide and pyridine ring, photolysis should ideally be solvent-independent.

These $\text{Cu}_4\text{I}_4\text{L}_4$ clusters, where L = pyridine, are primarily studied as the “cubane” tetranuclear isomer, **24**, though many other conformations and complexes exist. An alternative is the dinuclear complex, **25**, which forms in conditions of excess ligand. In our case, the ligand chosen is the example pyridine derivative, picolyl acetate.



Scheme 3-1: Cubane tetranuclear copper(I) picolyl acetate iodide clusters

3.2 Preliminary Results

Synthesis of the copper iodide compounds is performed with a stoichiometric amount of ligand and copper (I) iodide. CuI is prepared in saturated KI solution, and the ligand (in this case, picolyl acetate) is added dropwise into the stirred solution. After mixing, a precipitate forms. Analysis of the precipitate by X-Ray Powder Diffraction (XRD) indicates that it is polycrystalline.

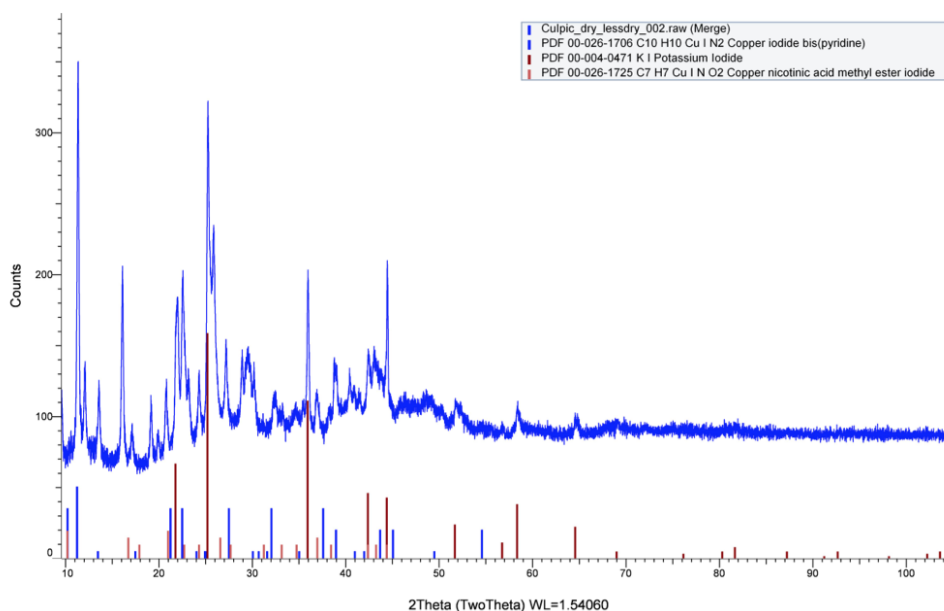


Figure 3-1: X-Ray Powder Diffraction of NAP-Cuprate Iodide

The XRD pattern shows a high similarity to both the closest literature examples of both the cubane structure (see **24**, $\text{Cu}_4\text{I}_4(\text{L})_4$, where L = nicotinic acid methyl ester), and to the water-soluble dinuclear complex (see **25**, $\text{Cu}_2\text{I}_2(\text{pyridine})_4$). It is likely that the picolyl acetate analogs of these complexes both form.

At room temperature both the tetranuclear complex $\text{Cu}_4\text{I}_4(\text{picolylacetate})_4$ and the dinuclear compound $\text{Cu}_2\text{I}_2(\text{picolylacetate})_4$ absorb at visible wavelengths and do not fluoresce. Both complexes exhibit an absorption band at $\lambda_{\text{max}} = 360$ nm in solution.

What was thought to be the dinuclear compound $\text{Cu}_2\text{I}_2(\text{picolyl acetate})_4$ (due to its similar ^1H NMR profile and different solubility) was extracted from the aqueous layer with several washes of dichloromethane, and irradiation by 100 mW 405 nm laser in CD_3CN did not release a detectable amount of acetic acid as detected by ^1H NMR. However, during photolysis, a strong dark red discoloration, similar to the production of I_3^- in Figure 2-2, was noticed. Addition of ascorbic acid returned the solution to its original yellow state, further supporting the theory of I_3^- production.

Irradiation what was thought to be the sparingly soluble $\text{Cu}_4\text{I}_4(\text{picolyl acetate})_4$ complex in deuterated acetone by 100 mW 405 nm laser does show a release of acetic acid via ^1H NMR. Irradiation by 405 mW laser initially produces a broadening of the peaks associated with the pyridyl protons of the ligand. Subsequent addition of ascorbic acid results in the appearance of sharp peaks of starting material and product. Acetic acid release is seen only upon addition of ascorbic acid (figure 3-2). The intermediate that results immediately after photolysis does not oxidize in the presence of oxygen. After addition of ascorbic acid, two new aromatic peaks, possibly associated with the methyl

pyridinium cuprate iodide structure, are clearly resolved. An additional peak at 10.2 ppm arises after photolysis and is thought to be hydrogen peroxide, suggesting a radical intermediate.⁵⁴

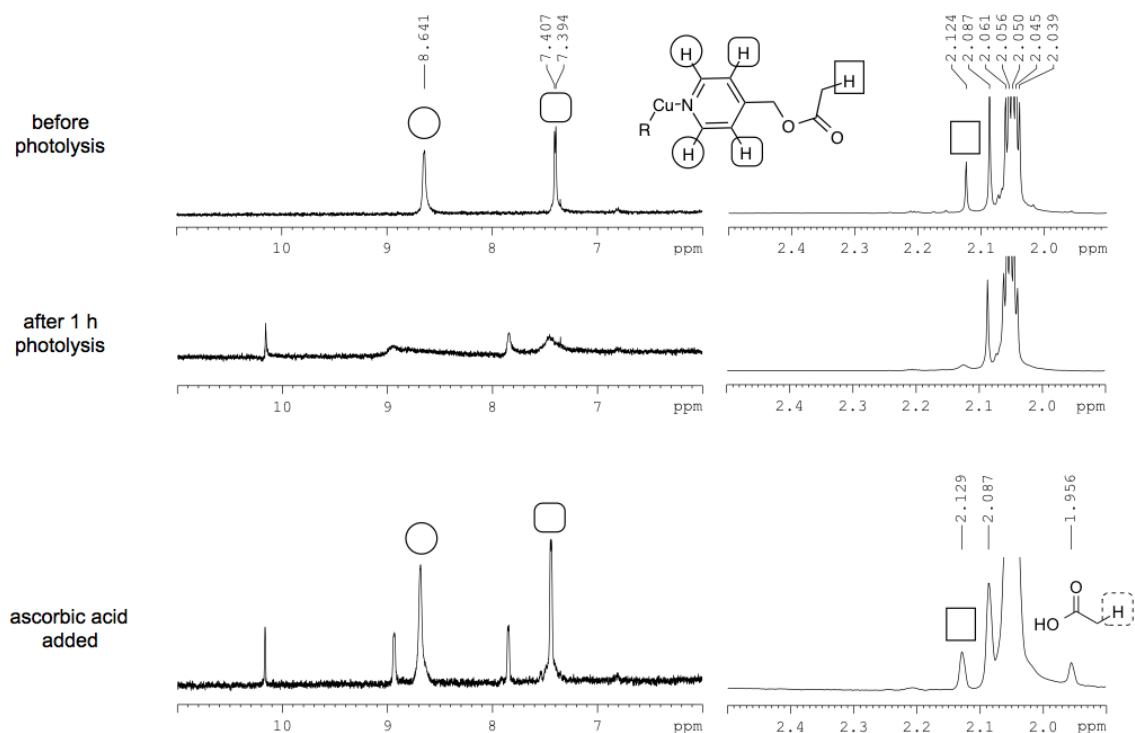


Figure 3-2: ¹H NMR analysis of Cu₄I₄(L₄) photolysis in *d*-acetone. Residual peaks at 2.087 ppm and 2.050 ppm are associated with acetone and *d*-acetone, respectively.

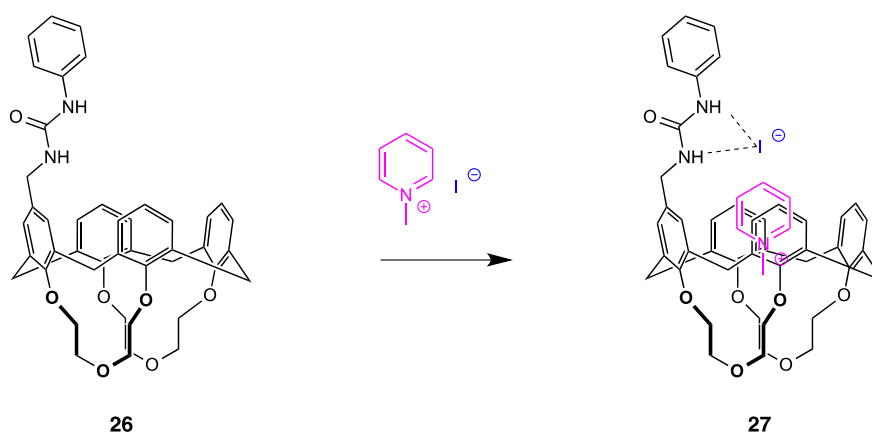
In summary, preliminary studies show promise that copper scaffolding may be a method for solvent-independent charge-transfer excitation of picolyl esters. It is important to remember that the earlier deprotection studies utilized methylated pyridinium iodides. Previously, picolyl esters have not been observed to exhibit such photodeprotection. Even so, complexation with CuI has shown evidence of (1) a photochemical reduction through the production of I₃⁻ (and transitively, atomic iodine), and (2) photochemical release of carboxylic acid substrate through the release of acetic acid. Further work should aim to

characterize the various CuI(L) complexes that form, optimize synthetic conditions to prefer each complex, and derivatize the pyridine center of the picolyl ligand to optimize aqueous solubility and yield of photorelease.

4 Conclusion and Future Work

4.1 Heteroditopic Urea-Substituted Calix[4]arenes for Solvent-Independent Carboxylate release

Ugozzoli and coworkers have demonstrated that urea Substituted calix[4]arenes can bind to N-methylpyridinium and iodide counterion simultaneously.⁵⁵ The research indicates that the mono-urea substituted calixarene is capable of recognizing and binding both ions in solution and this pair results in a notable increase in the absorbance of the charge-transfer band.



Scheme 4-1. Heteroditopic of binding *N*-methylpyridinium and iodide by urea-substituted calix[4]arene.⁵⁵

These supramolecular complexes may be able to act in an enzyme-like fashion by assisting ion pairing in polar media. A calixarene might bind to both ions in solution, bringing the two into charge-transfer complex proximity. Upon irradiation, the subsequent

neutral radical products would be unbound and diffuse into solution. The decomplexed calixarene can then bind to another NAP ester cation and iodide anion in a catalytic fashion.

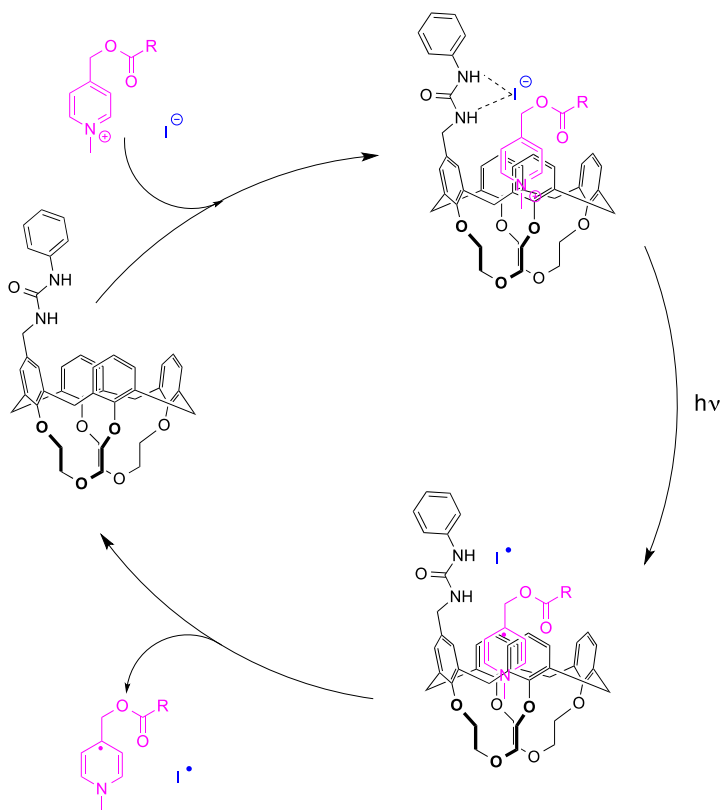


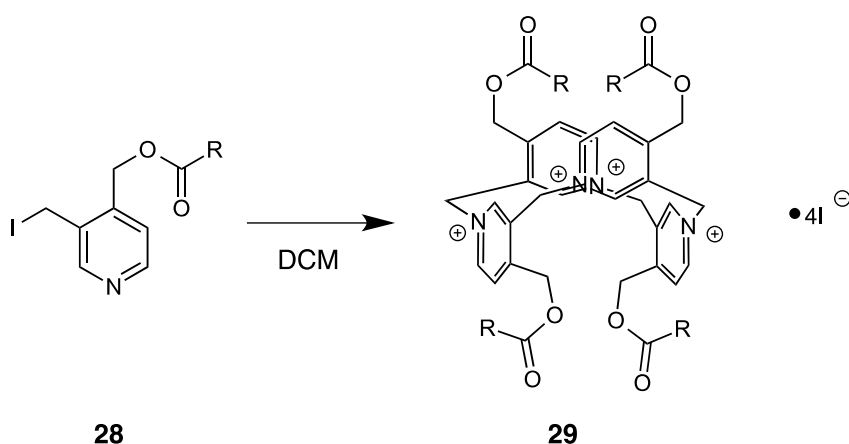
Figure 4-2: Proposed catalytic NAP ester photolysis by heteroditopic calixarene host-guest binding

Several modifications to the calixarene can be made to optimize calixarene solubility and ion binding potential. Scheme 4-1 displays the mono-substituted urea, the synthesis of which is described by Pochini and coworkers.⁵⁶ Additional substitution of urea may assist in ion binding. Mogck *et al* have described the synthesis of the di- and tetra-substituted calix[4]arene.⁵⁷

As mentioned previously, it is possible that only a catalytic amount of calixarene will be required to achieve photolysis of NAP esters in polar media. Still, many calixarenes exhibit low solubility in aqueous media. In the event that these low solubilities are not sufficient, Shinkai *et al* describe a synthesis for the sulfonate-substituted calixarene.⁵⁸

4.2 Iodide Coordination by Tetrapyridinium Macrocycle

An alternate approach to solvent-independent photolysis of NAP esters is through iodide coordination to a tetrapyridinium macrocycle. Arakawa and coworkers have examined calixpyridinium in the context of its complexation with anions.⁵⁹ In their research, they found that the macrocycle tightly binds anions, even in aqueous solution. In this context, it may be possible to synthesize the NAP-substituted calixpyridinium by a method similar to that described by Arakawa *et al* in a previous paper.⁶⁰



Scheme 4-1. NAP-substituted calixpyridinium

Synthesis of picolyl iodomethyl precursor **27** would presumably occur through synthesis of *meta*-methyl picolyl ester followed by treatment of *N*-bromosuccinimide and Sn2 substitution with iodide.

4.3 Conclusion

Through my undergraduate work, the dependence of charge-transfer complex formation on ion pairing was demonstrated. My graduate work has endeavored to expand these results and to meet the following goals:

- 1) Quantify NAP ester photorelease through a biphasic mixture.
- 2) Demonstrate facile isolation and separation of nonpolar carboxylic acids through biphasic segregation.
- 3) Demonstrate that commercially available visible light household LED lamps are sufficient to incur photolysis.
- 4) Perform NAP ester release on a synthesis-scale experiment.
- 5) Observe a photochemical reduction in cuprate iodide-picolyl complexes.

Ideally, a mechanism for solvent-independent NAP ester photolysis for visible light carboxylate release can be achieved. As discussed previously, several leads are being pursued: Scaffolding by cuprate salts, host-guest interactions with diheterotopic calixarenes, and formation of a pyridinium macrocycle.

The results of this research indicate a method for carboxylic acid photorelease that does not require expensive photochemistry equipment. Simple methods for deprotection and isolation without expensive light sources or photocatalysts allow for application beyond the organic chemistry laboratory. This non-invasive means of

carboxylate release may find applications in organic chemistry, biochemistry, and microbiology.

5 Experimental

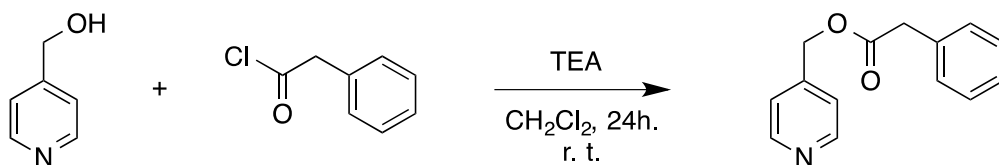
5.1 General Procedures

Unless stated otherwise all reagents were purchased from commercial sources and used without any further purification. Solvents used were of HPLC grade. All ^1H and ^{13}C NMR were obtained using a Bruker 400 MHz spectrometer. Chemical shifts (δ) are referenced to solvent peaks of chloroform (7.27 ppm) or acetonitrile (1.94 ppm). UV-VIS spectra were collected using a Shimadzu UV-1800 Spectrophotometer using a 1 cm four-sided quartz cuvette. Infrared spectroscopy was collected using a Thermo Nicolet IR-200 Attenuated Total Reflectance Fourier Transform Infrared Spectrometer. Room light photolyses were performed with a Feit Electric PAR38 18 W LED lamp. Laser photolyses were performed using a 100 mW Laserglow Technologies 405 nm laser. Powder X-Ray diffraction was performed using a Bruker C2 Discover with a 2D detector.

5.2 Synthesis of NAP-Esters

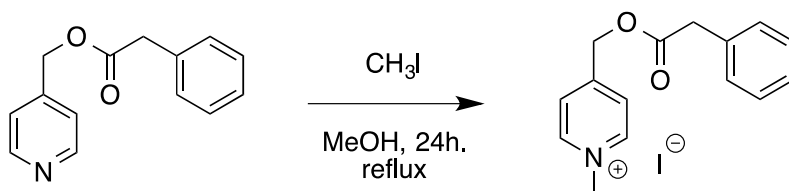
NAP-esters **11a**, **11b**, **11c**, and **11e** were used as previously prepared or synthesized based on reported procedures by Sundararajan et al.⁶¹

Synthesis of 4-Picolyl Phenylacetate



The unmethylated precursor to **11a** was synthesized with minor improvements on a method developed by Sundararajan et al.⁵⁴ To a solution of 4-pyridyl carbinol (583.8 mg, 5.35 mmol) in 6.0 mL of dichloromethane, triethylamine (1.30 mL, 9.31 mmol) is added. A solution of phenylacetyl chloride (7.53 mmol) in 2.3 mL of dichloromethane is added dropwise. The reaction mixture was stirred at room temperature for 24 hours. Two separatory washes of 10.0 mL of H₂O are performed and the organic layer extracted. An additional wash is performed using 10.0 mL of H₂O with saturated sodium bicarbonate to remove excess carboxylic acid. The product is dried with magnesium sulfate before vacuum evaporation. The product is a dark red oil and coincides with previously reported characterization. ¹H NMR (CD₃CN): δ 3.74 (s, 2H), 5.13 (s, 2H), 7.23-7.34 (m, 7H), 8.50-8.52 (m, 2H). Yield was determined by weight (1.0959g, 87.2%).

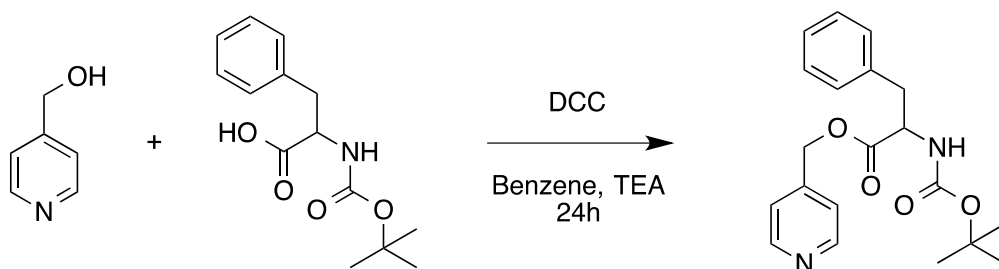
***N*-Methyl-4-Picolinium Phenylacetate Iodide (**11a**)**



Synthesis of **11a** was performed using 0.25 mL methyl iodide (3.95 mmol), which is added slowly to 600.0 mg of picolyl phenylacetate (2.64 mmol) dissolved in 3.0 mL CH₃OH. The reaction mixture is refluxed for 24 hours. After the reaction, the solvent is removed by reduced pressure and the product is recrystallized from hot methanol and

ethyl acetate. The product is a brown solid and coincides with previously reported characterization. $^1\text{H NMR}$ (CD_3CN) δ 3.83 (s, 2H), 4.28 (s, 3H), 5.37 (s, 2H), 7.36-7.30 (m, 5H), 7.88 (d, $J=6.2$, 2H), 8.62 (d, $J=6.2$, 2H). A melting point of 110-112 $^\circ\text{C}$ was consistent with literature reports.¹ Yield was determined by weight (0.7027g, 72.1%).

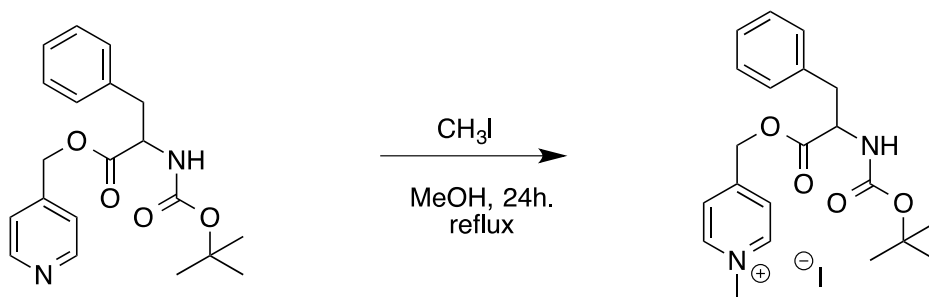
4-Picolyl Boc-Phenylalanine



The unmethylated precursor to **11a** was synthesized by DCC coupling. In a 100 mL roundbottom flask, 0.8914 g (3.36 mmol) *N*-(tert-butoxycarbonyl)-L-phenylalanine and 0.3082 g (2.82 mmol) 4-pyridylcarbinol were dissolved in 15.0 mL benzene. 0.7104g (3.44 mmol) *N,N'*-Dicyclohexylcarbodiimide (DCC) was subsequently dissolved in the reaction mixture. 5 mL of triethylamine was added to the reaction and the mixture was stirred at room temperature for 24 hours. A white precipitate (presumably dicyclohexylurea) was removed by vacuum filtration and the mother liquors were extracted. These were placed under reduced pressure. The resulting yellow oil was dissolved in 25.0 mL dichloromethane and washed twice with 25.0 mL saturated sodium bicarbonate. This was followed by several washes with 25.0 mL of H_2O until the washes were neutral. The product is dried with magnesium sulfate before solvent removal by vacuum evaporation. The crude product was purified using flash column chromatography (EtOAc:hexanes, 80:20), and obtained as a white crystal. Yield was determined by weight

(0.9359g, 93.0%). Mp 89-91 °C; IR (ATR FTIR) 1749 cm⁻¹ (s, Ester C=O Stretch), 1702 cm⁻¹ (s, Amide C=O Stretch); ¹H NMR (CD₃CN) δ 1.25-1.39 (s, 9H), 2.97 (dd, J=13.8, 9.0, 1H), 3.13 (dd, J=14.0, 5.6, 1H), 4.45 (q, J=8.0, 1H), 5.14 (s, 2H), 5.72 (d, J=7.2, 1H), 7.19-7.30 (m, 5H), 7.29 (d, J= 7.6, 2H), 8.54 (d, J=6.0, 2H); ¹³C NMR (CD₃CN) δ 28.5, 38.1, 56.3, 65.6, 80.2, 122.8, 127.9, 129.5, 130.3, 138.1, 146.0, 150.9, 159.5, 172.9; HRMS (ESI+) calcd 3567.1808, found 357.1828.

N-Methyl-4-Picolinium Boc-Phenylalanine Iodide (11d)



In a 25 mL roundbottom flask, 550.3 mg (1.54 mmol) 4-Picolyl Boc-Phenylalanine was dissolved in 5.0 mL methanol. 0.220 mL (502 mg, 3.53 mmol) methyl iodide was added to the reaction dropwise. The reaction was wrapped in aluminum foil to reduce light exposure and stirred under reflux for 24 hours. After reaction, the solvent is removed under reduced pressure. The product is a yellow solid. The product was not purified further, as it appeared pure by ¹H NMR. Yield was determined by weight (0.5237g 68.1%). Mp 80-84 °C IR; (ATR FTIR) 1745 cm⁻¹ (s, Ester C=O Stretch), 1699 cm⁻¹ (s, Amide C=O Stretch); ¹H NMR (CD₃CN) δ 1.23-139 (s, 9H), 3.05 (dd, J=14.0, 9.4, 1H), 3.17 (dd, J=14.0, 6.0, 1H), 4.31 (s, 3H), 4.50 (q, J=6.4, 1H), 5.38 (d, J=8, 2H), 5.85 (d, J=7.2, 1H), 7.23-7.32 (m, 5H), 7.87 (d, J=5.6, 2H), 8.69 (d, J=6.0, 2H); ¹³C NMR (CD₃CN) δ 28.5, 37.9, 49.0, 56.3, 64.6, 80.31, 126.0, 127.9, 129.5, 130.3, 138.0, 146.1, 156.1, 157.0, 172.7;

HRMS (ESI+) calcd 371.1965, found 371.1984.

5.3 Charge-Transfer Complex UV-Vis Experiments

Effect of iodide ion on absorption maximum (Figure 1-1)

19.9 mg of **1a** was dissolved in 20.0 mL of acetonitrile (1.0 mM). 1.0 mL of this solution was sampled by UV-Vis. 295.7 mg of tetrabutylammonium iodide was dissolved in 0.5 mL of acetonitrile (1.6 M). 50.0 μ L of this solution was added to the previously sampled **1a** solution (final concentration: 80 mM tetrabutylammonium iodide). An addition of 50.0 μ L of 1.6 M tetrabutylammonium iodide solution was performed between UV-Vis sampling until there was no noticeable increase in absorbance. The absorbance at 345 nm was plotted against iodide concentration and a curve fitted to equation 1:

$$A_{CTC} = \frac{K_a[I][NAP_{total}]\epsilon_{CTC}b}{1 + K_a[I]} \quad (1)$$

Where K_a is the binding constant of the charge-transfer complex, ϵ_{CTC} is the molar absorptivity of the charge transfer complex, b is the spectrophotometer path length of 1 cm, and $[I]$ is the concentration of iodide. This is derived from Beer's law:

$$A_{CTC} = \epsilon_{CTC}[NAP \cdot I]b \quad (2)$$

Where $[NAP \cdot I]$ is the concentration of charge-transfer complex and is derived from the following equations:

$$[NAP \bullet I] = K_a [NAP_{uncomplexed}] [I] \quad (3)$$

$$[NAP_{total}] - [NAP \bullet I] = [NAP_{uncomplexed}] \quad (4)$$

$$[NAP \bullet I] = K_a [NAP_{total}] [I] - K_a [NAP \bullet I] [I] \quad (5)$$

$$[NAP \bullet I] = \frac{K_a [NAP_{total}] [I]}{1 + K_a [I]} \quad (6)$$

Effect of solvent polarity on absorption maximum

14.3 mg of **1a** was dissolved in 2.5 mL of acetonitrile (5.2 mM). 400 μ L of this solution was added to various solvent mixtures of chloroform and acetonitrile to prepare 2.0 mL of each concentration (i.e. 400 μ L of 2.6 mM *N*-methyl picolinium phenylacetate in acetonitrile + 800 μ L acetonitrile + 400 μ L chloroform = “25% CHCl₃ by volume” solution). The final concentration of **1a** in each solution was 1.3 mM). UV-Vis spectra were collected for all samples.

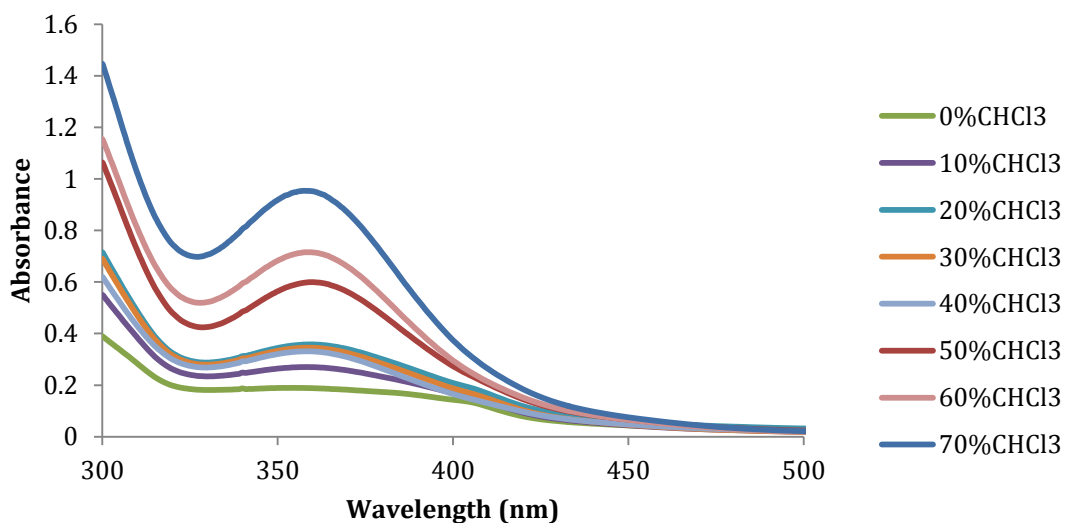


Figure 5-1: Increasing absorption maximum of NAP-phenylacetate (1a) in decreasing solvent polarities by addition of chloroform to acetonitrile

Relative Irradiance of 18W PAR38 LED lamp (Figure 2-4)

The spectral output of the Feit Electric PAR38 18W LED lamp was compared to the charge-transfer band to determine overlap. The spectral irradiance was measured using a Ocean Optics USB-2000 Fiber Optic Spectrometer. It is calibrated to an Ocean Optics LS-1 3100K Color Temperature Tungsten Halogen Light Source.

5.4 Deprotection Photolyses

Quantification of Release By NMR (Scheme 2-2)

Prior to irradiation, samples of 28 μmol **1** were solubilized in 1.5mL 95%:5% CDCl_3 : CD_3CN . 1.0 μL (0.76 mg, 4.7 μmol) Hexamethyldisiloxane (HMDS) was added as an internal standard. After an initial ^1H NMR, the solution is placed into a 1-dram borosilicate glass vial. 249 μmol (35.4 mg) anhydrous Na_2SO_4 and 217 μmol (38.25 mg) ascorbic acid was dissolved into 250 μL of D_2O is added to the organic solution to form a biphasic mixture. The mixture is placed in front of a 100 mW 405 nm laser and stirred for one hour. After irradiation, the organic layer is removed and immediately examined by ^1H NMR. Yield of carboxylic acid is determined by the integrations of alpha-carboxylate protons, which usually have a ~ 0.2 ppm shift between ester and carboxylate. The yield is evaluated by integration of the alpha-carboxylate protons, subtracted from any pre-existing carboxylic acid peaks, and divided by the integration of initial NAP-ester alpha-carboxylate protons present in solution. HMDS serves as an internal standard from the organic phase, and does not noticeably migrate into the aqueous layer (determined by ^1H NMR of the aqueous layer). In Figure 3, this procedure is referred to as “standard

conditions”.

Low Conversion Conditions for Biphasic photolysis (Figure 2-3)

1.5mL 95%:5% CDCl₃:CD₃CN and 250 μ L D₂O biphasic solutions containing **11a**, Na₂SO₄, Ascorbic Acid, and NaI were constructed according to Table 5-1.

Table 5-1. Optimization Conditions for Biphasic Photolysis

Entry	11a (mmol)	Na ₂ SO ₄ (mmol)	Ascorbic Acid (mmol)	NaI (mmol)	Temp.	% Yield 23a	% Unreacted 11a
1	0.028	0.249	0.217	0	rt	44.5	50.5
2	0.028	0.125	0.217	0	rt	48.6	31.5
3	0.028	0	0.217	0	rt	45.7	24.2
4	0.028	0.249	0.217	0.028	rt	40.2	46.5
5	0.028	0.249	0.217	0.14	rt	21.1	73.5
6	0.028	0.249	0.108	0	rt	61.4	9.8
7	0.028	0.249	0.054	0	rt	51.6	4.1

1.0 μ L (0.76 mg, 4.7 μ mol) Hexamethyldisiloxane (HMDS) was added as an internal standard. After initial NMR processing, the solution is placed into a 1-dram borosilicate glass vial. The mixture is placed in front of a 100 mW 405 nm laser and stirred for 30 minutes. The organic layer is removed and examined by ¹H NMR. The yield is evaluated by integration of the alpha protons, subtracted from any pre-existing carboxylic acid, and divided by the amount of initial NAP-ester present in solution. The unreacted starting material is derived from the remaining integration of starting material ester peaks.

Macroscale Photolysis of **11a**

500.1 mg (1.35 mmol) of **11a** was dissolved in 75 mL of 95%:5% CHCl₃:CH₃CN. 1.770 g (12.46 mmol) anhydrous Na₂SO₄ and 1.912 g (10.86 mmol) ascorbic acid were dissolved in 12.5 ml H₂O. The two layers were combined and irradiated with a Feit Electric 18 W lamp for 20 hours. The organic layer was separated from the aqueous layer and the solvent removed by rotary evaporation. The resulting crude mixture afforded 75.7% yield of phenylacetic acid after recrystallization from petroleum ether (mp. 76–77 °C, lit 77 °C).⁶²

NMR Timecourse of NAP-Acetate without reduction

10.0 mg **11e** was dissolved in 2.0 mL of 95%:5% CDCl₃:CD₃CN (17.1 mM). Using a Feit Electric 18 W lamp, the solution was irradiated and sampled at 15 minute intervals. The solution was directly analyzed by ¹H NMR between these 15 minute intervals, during

which the solution was covered with aluminum foil to reduce unwanted light exposure.

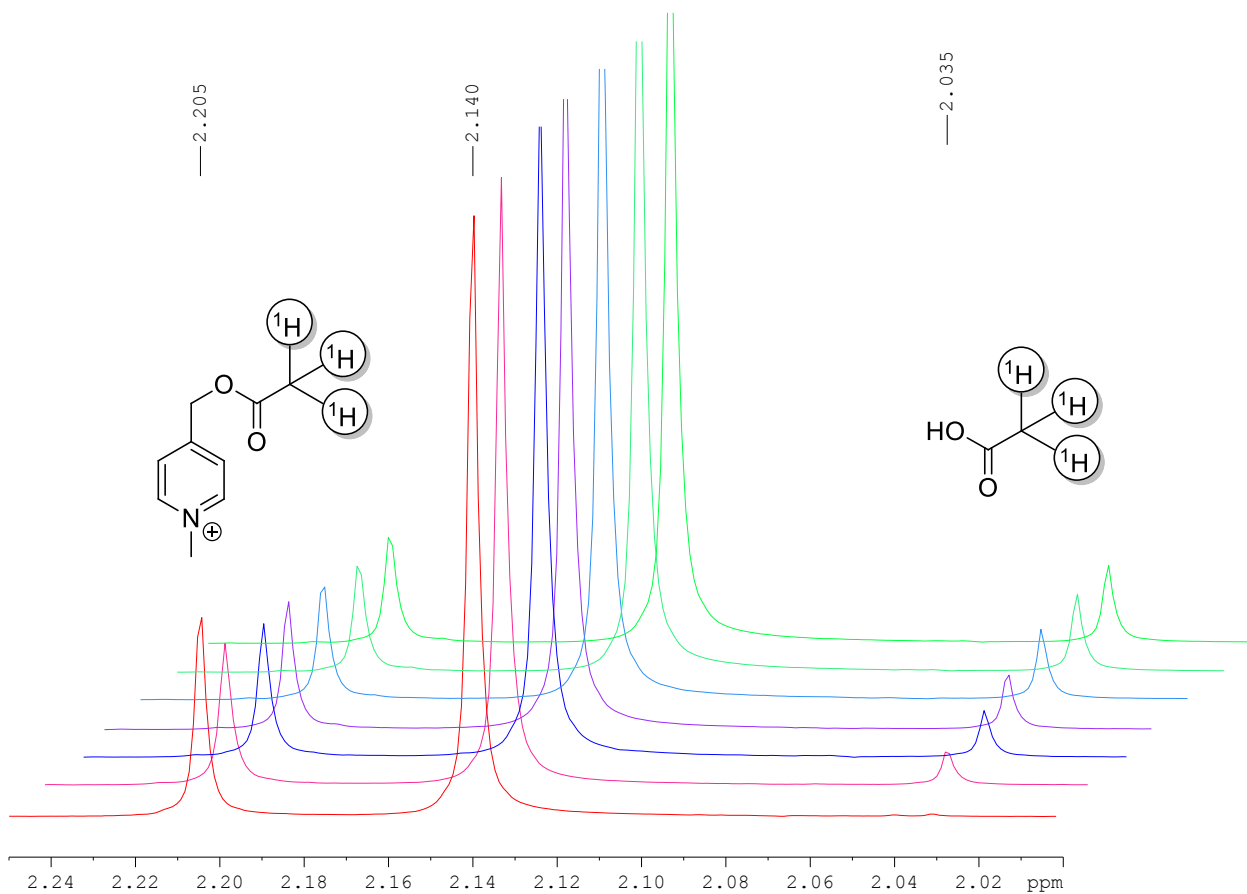


Figure 5-2 Time course photolysis of NAP-acetate 11e. The peak at *ca.* 2.14 ppm is a solvent associated peak (HOD). Scans are at 15 min. intervals, from *t* = 0 (red line) to *t* = 90 minutes (green line)

As indicated figure 5-2, the photolysis produces the expected product acetic acid (*ca.* 2.03 ppm). A reduction of the corresponding NMR peak of the in the aliphatic α -carbonyl protons (*ca.* 2.20 ppm) of the NAP acetate indicates depletion of starting material. The peak at 2.14 ppm is associated with water impurities. The photolysis achieves a moderate yield *ca.* 39%.

HPLC Time Course of NAP-Phenylacetic acid without reduction

High Performance Liquid Chromatography (HPLC) was performed using a Shimadzu Prominence pump system equipped with a 4.6 x 150 mm Zorbax SB-Aq reversed-phase column and UV-Vis detector. HPLC determination of free acid was performed using an isocratic elution method. A 3/1 sodium sulfate buffer (100 mM Na₂SO₄ – reduced to pH 2.51 by methanesulfonic acid)/acetonitrile solvent mixture afforded resolution of produced phenylacetic acid, monitored at 254 nm (1ml/min). Elution of phenylacetic acid occurred between 6.25-7.75 min (20 μL sample injection, 60 μL injection loop).

9.43 mg **11a** was dissolved in 1.5 mL of 95%:5% CHCl₃:CH₃CN (17.0 mM). Using a Feit Electric 18 W lamp, the solution was irradiated at 15 minute intervals. The solution was directly analyzed by HPLC between time intervals. Yields were calculated by the final concentration of free acid produced.

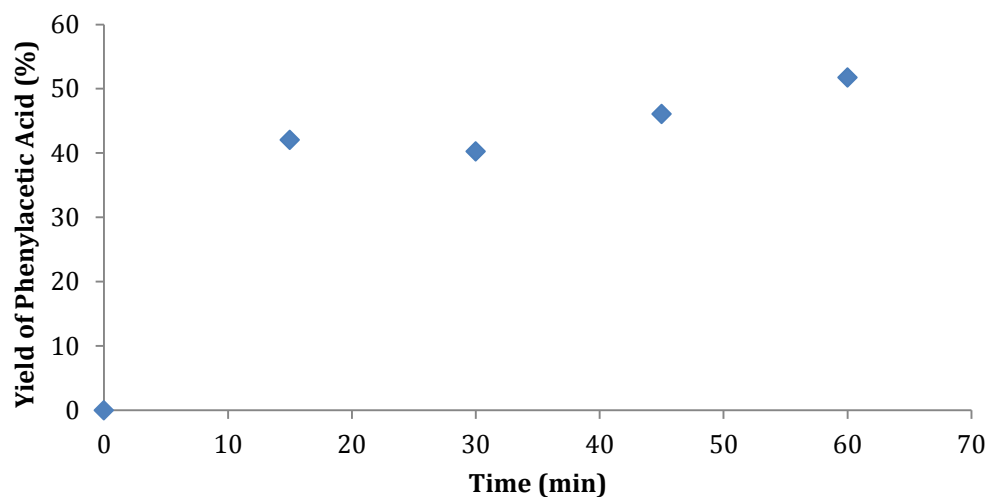


Figure 5-3 HPLC time course of NAP-phenylacetic acid (11a) photolysis. [NAP-phenylacetate iodide] = 17.1 mM

As a common trend in the unreduced reactions, production of carboxylic acid slows drastically after a moderate yield is obtained, even in the continued presence of starting material. This photolysis reaches a yield of 51% phenylacetic acid release in only 1 hour.

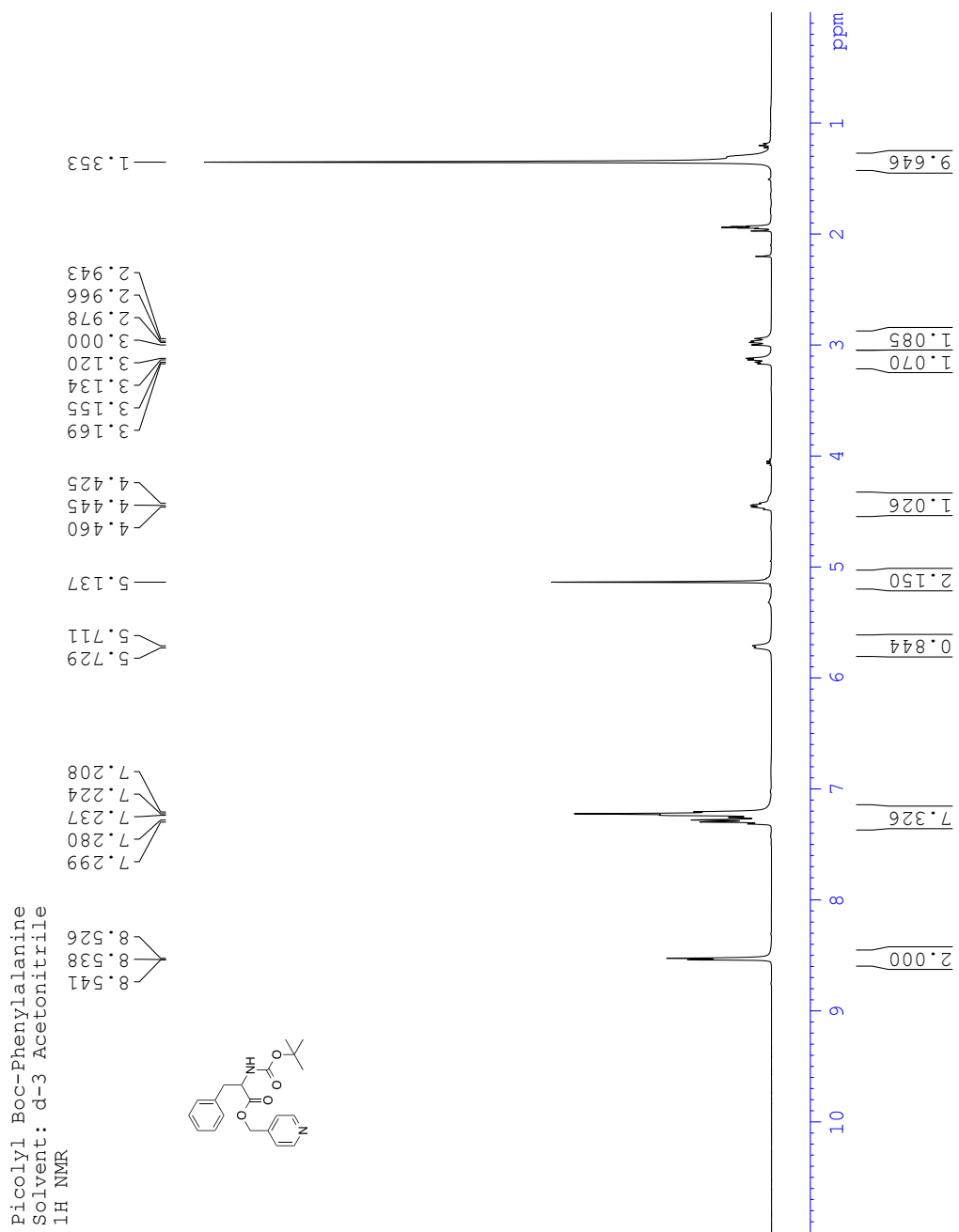
Triiodide UV-vis and photolysis time course by UV-vis (Figure 2-1)

To examine the spectrum of I_3^- , 42.8 mg (166.7 μmol) I_2 and 61.6 mg (166.7 μmol) Tetrabutylammonium Iodide were combined in 1 mL of 95%:5% CHCl_3 : CH_3CN . A literature value of $698 \pm 10 \text{ M}$ for the equilibrium constant of triiodide formation was used.⁶³ The solution was diluted to the indicated concentrations using the same solvent and examine by UV-Vis. To compare, 9.43 mg **1a** was dissolved in 1.5 mL of 95%:5% CHCl_3 : CH_3CN (17.0 mM). Using a Feit Electric 18 W lamp, the solution was irradiated for brief periods of time, and the UV-Vis spectrum subsequently recorded. The resulting spectra indicated similar UV-Vis profiles between concentrations of triiodide and later stages of unreduced photolysis. Figure 2-2 demonstrates the visual change that occurs in unreduced photolysis. No such color change is noted in reduced photolyses.

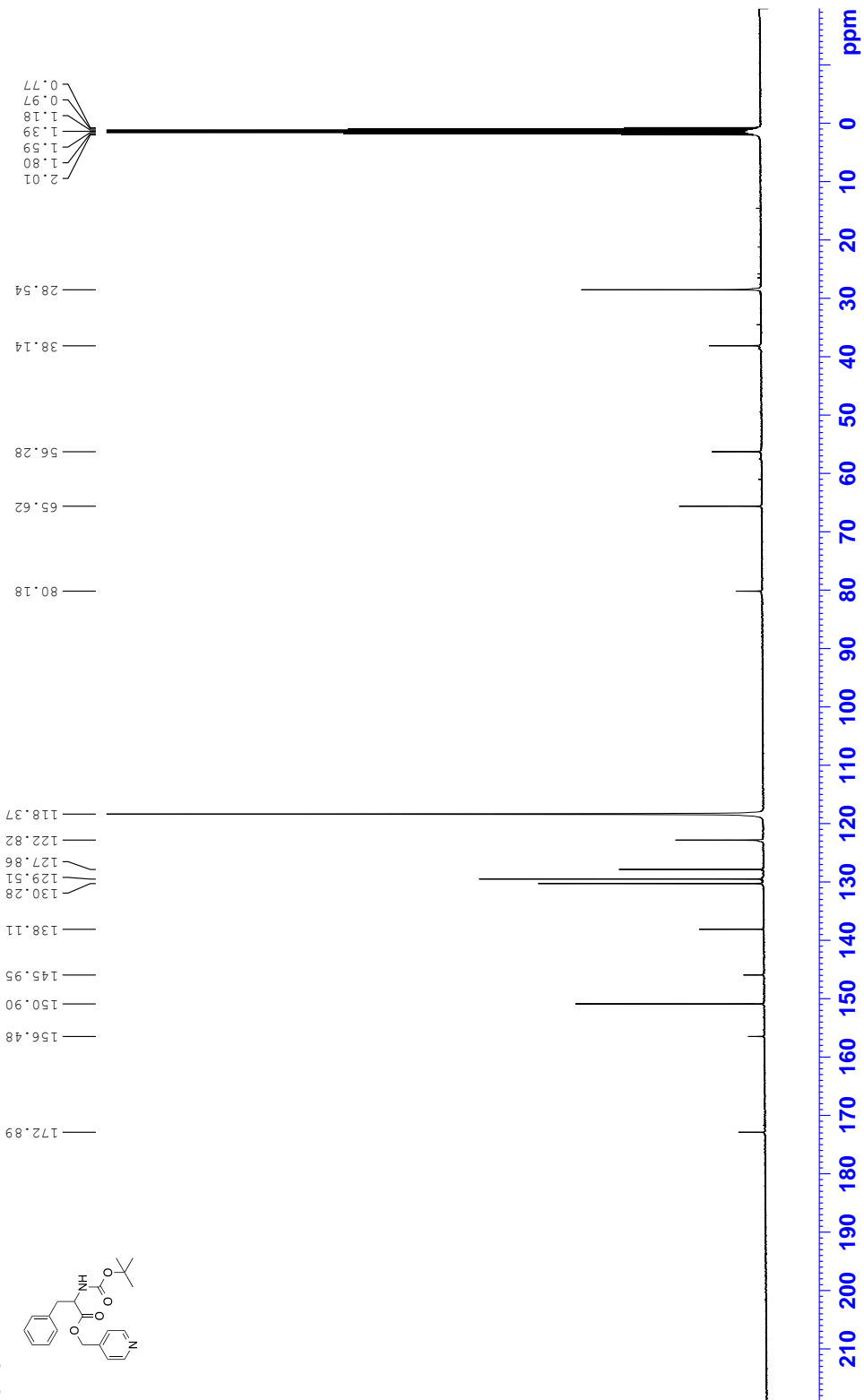
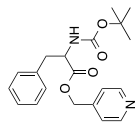
5.5 Additional Characterization Data

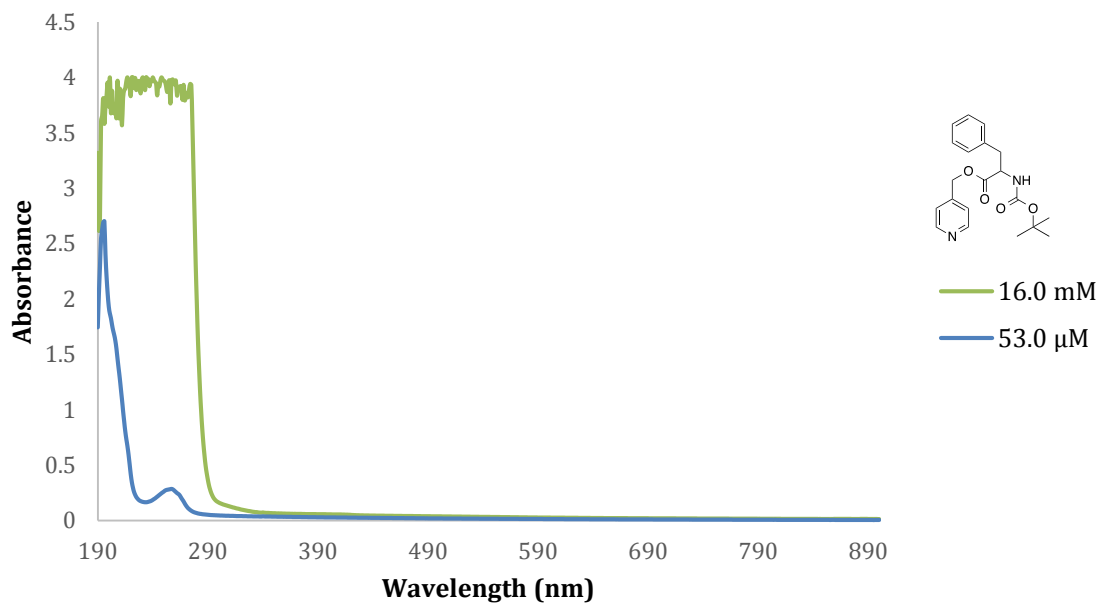
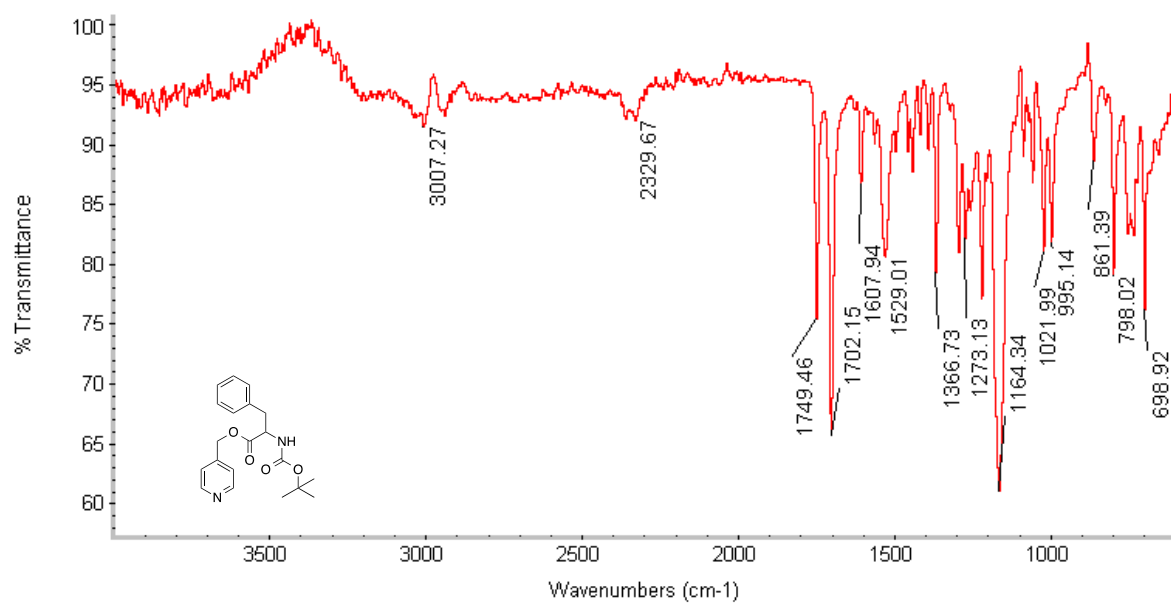
All NMR spectra were performed using CD₃CN. UV-Vis data were collected using CH₃CN as the solvent.

4-Picolyl Boc-Phenylalanine

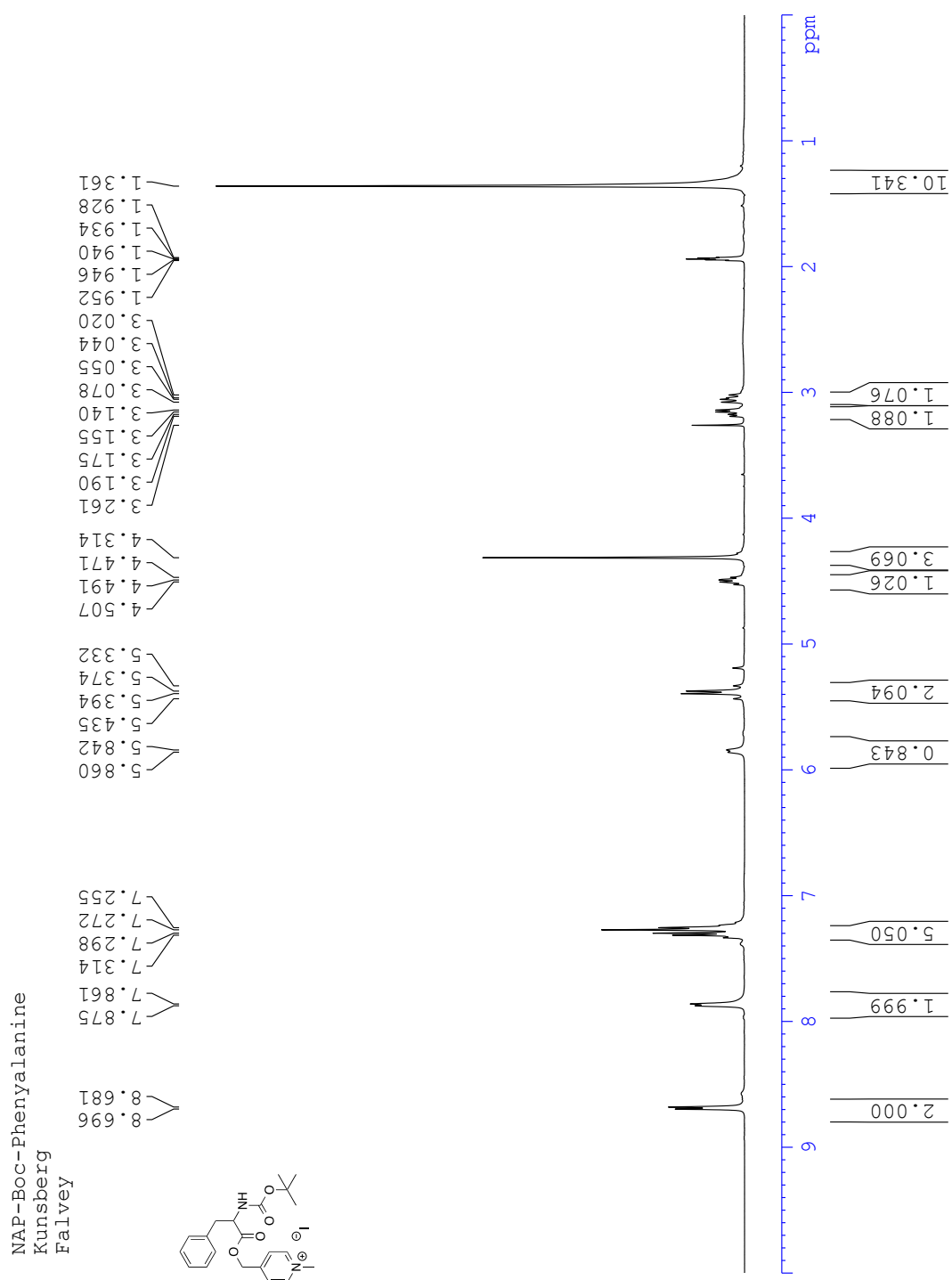


Picolyl Boc-Phenylalanine
Solvent: d-3 Acetonitrile
C13

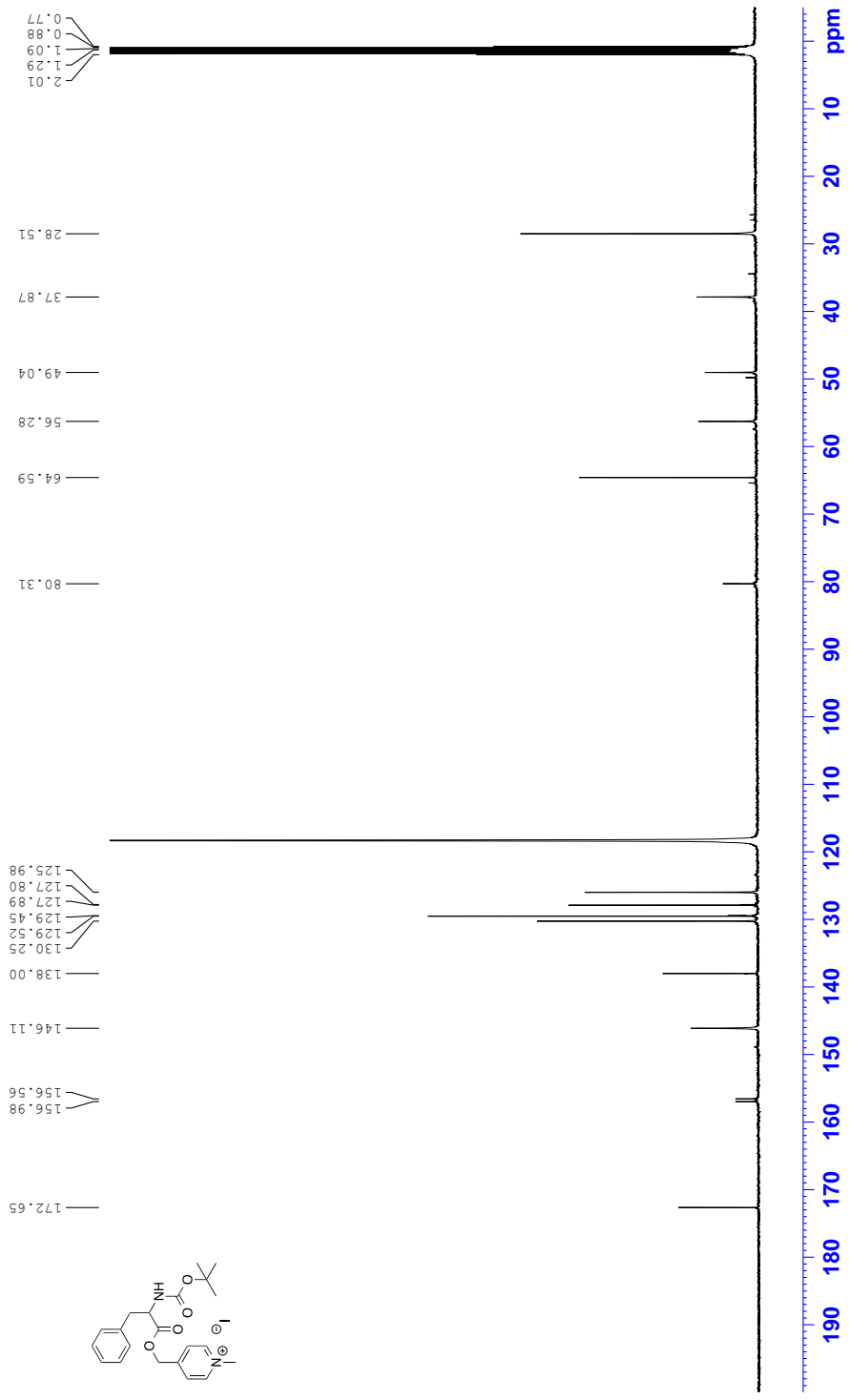


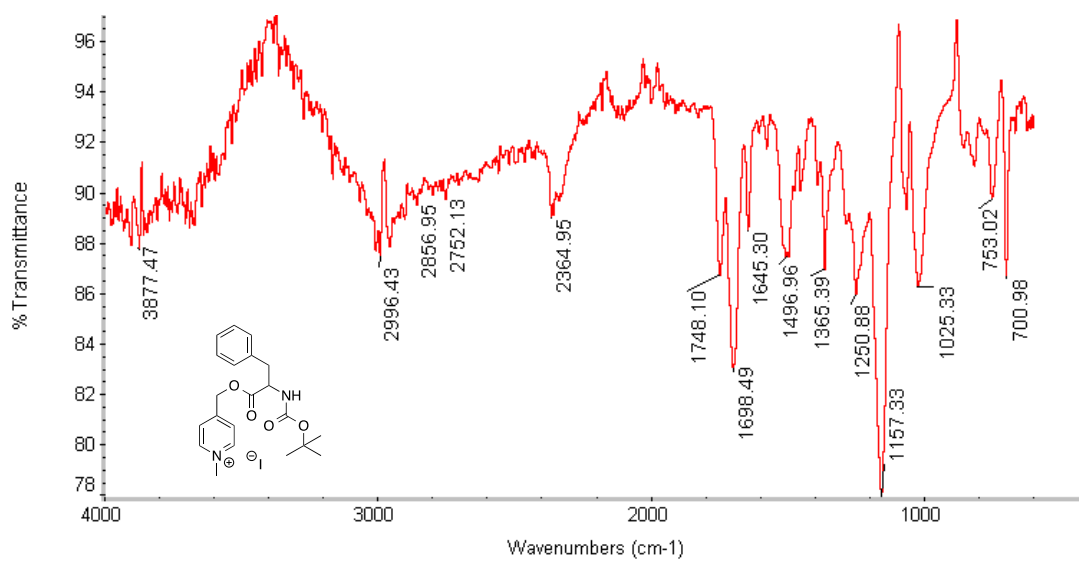
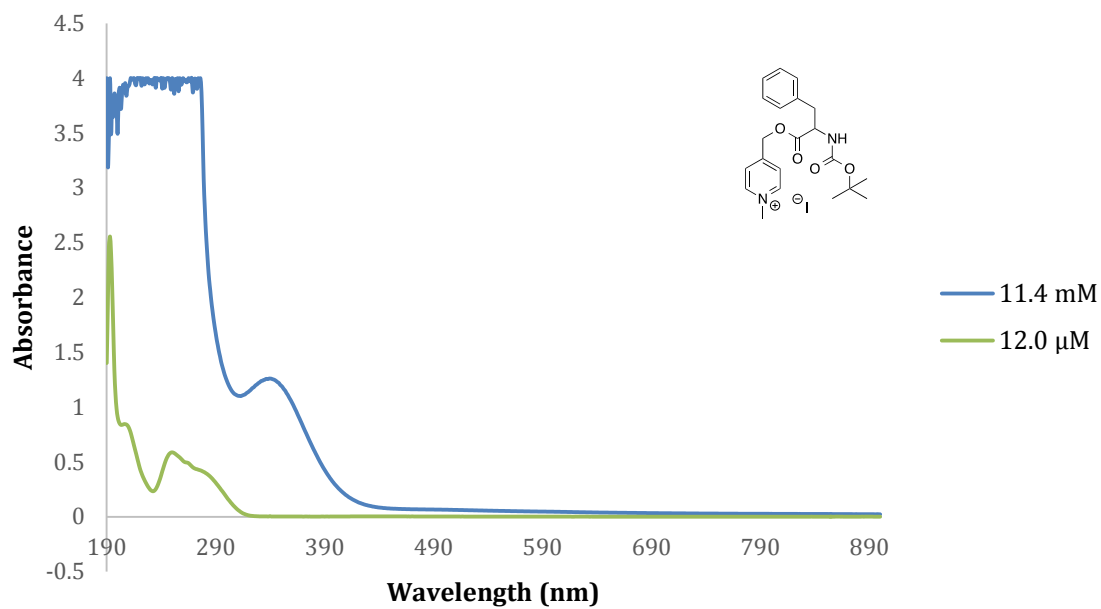


N-Methyl-4-Picolinium Boc-Phenylalanine Iodide (1d)



NAP-Boc-Phenylalanine
Kunsberg
Falvey





6 References

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