Photochemical & Photobiological Sciences

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Journal:	*Photochemical & Photobiological Sciences*
Manuscript ID	PP-ART-02-2020-000067.R2
Article Type:	Paper
Date Submitted by the Author:	25-Jul-2020

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Competing Pathways for Photoremovable Protecting Groups: The Effects of Solvent, Oxygen and Encapsulation

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Abstract: Extending the applications of Photoremovable Protecting Groups (PPGs) to "cage" phenols has generally met with unusually complex PPG byproducts. In this study, we demonstrate that the *p*–hydroxyphenacyl (pHP) cage for both simple and complex phenolics, including tyrosine, dispense free phenols. With the simpler unsubstituted phenols, the reaction is governed by their Brønsted Leaving Group ability. On the other hand, the byproducts of the cage vary with these phenols. For the more acidic phenols the cage byproduct follows the Favorskii rearrangement to form p-hydroxyphenylacidic acid whereas for the weaker phenols other reactions such as reduction and hydrolysis begin to emerge. When the photolysis is conducted in octa acid (OA) containers, non-Favorskii, unrearranged fragments of the cage and other byproducts arise.

Introduction

Photoremovable protecting groups (PPGs) have been employed to investigate temporal, spatial, and environmental influences on chemical and signaling events in fundamental mechanistic studies of biological processes.[1] Several groups,[2] including ours[3] have sought to pinpoint the role of specific functional groups within the multi-faceted molecular entities. The results of these investigations often serve as guidelines for molecular design for biological or

pharmaceutical agents or to identify significant molecular barriers to chemical transformations. The unraveling of mechanistic pathways in chemical and biochemical transformations has been aided by applications of PPG or "caged" initiators.[4-8] PPGs are also employed to release reagents as specific spatially-occupied, functional group initiators in chemical or biochemical processes.[9-12]

To be effective in reaching these goals, PPGs require specific attributes such as rapid, efficient release of a functional group while also forming non-perturbing residues from the protecting group or "cage" portion of the PPG. Furthermore, an ideal PPG should be versatile and adaptable for the release of, or application in the presence of, a wide variety of important functional groups. Ideally, the release reaction should occur by a common, well-understood photolysis reaction that is unperturbed by exogenous agents such as oxygen, photochemical quenchers, solvent variations, variations in pH or phase changes[1, 2, 4] *p*-Hydroxyphenacyl (pHP) has been tested as a PPG and fulfills many of the qualifications of an ideal protecting group as evidenced by a growing array of biological[1] and biochemical applications,[13-15] including neurotransmission,[13] enzyme catalysis[14, 15] and possibly drug delivery.[9, 16] While pHP has been developed for release of many familiar functional groups,[2] there remain several challenging targets that have not been thoroughly explored , e.g. amines,[3, 17] alcohols,[18] and phenols.[19-25] A factor that may distinguish these functional groups from the many successful examples cited here is their "leaving group ability", a parameter often cited in ground-state or solvolysis release reactions. The classical examples are described by Brønsted Leaving Group Ability[26] which has been explored for a few "caged" compound studies.[27] More recently, photosolvolysis reactions of caged substrates have been the subject of investigations regarding the nature of the bond breaking that occurs in the PPG excited state, thereby releasing the protected substrate from the excited protecting group.[28-33] These examinations of both the more classical and photophysical studies are coupled with theoretical analysis of the photorelease from caged substrates and are the subject of this investigation on pHP release of phenols.

Biologically significant phenols, e.g., dopamine or tyrosine[15,20-22] and phosphorylated phenols[24] have been investigated, but those efforts have generally met with difficulty or were unrewarding, primarily due to their inherently poor leaving group ability. Low yields, poor release rates, and/or competing side reactions plagued these attempts. Modifications of the PPG of choice by inserting carbonate (OCO) or carbamate (OCONH) between the PPG and a poor,

but desirable leaving group have given cleaner reactions but sidestepped only the poor yields. Low efficiencies and slower release rates[19] resulting from a slow ground-state decarboxylation to free the intended product, as well as lengthy syntheses to access the starting materials are the ongoing issues.

Modifying the PPG by adding halogens, extending the chromophore, or rearranging the key substituents frequently leads to lower release rates and efficacies or undesirable new side reactions. For example, Dore et al.[20] successfully modified their 7-hydroxyquinoline cage by incorporating Br or CN groups (e.g., 8-bromo-7-hydroxyquinolinyl (BHQ) and 8-cyano-7-hydroxyquinolinyl (CNHQ) PPG's to enhance release of tyrosine with reasonable one photon excitation (1PE) (0.32 – 0.38) and 2PE (0.61 – 0.36 GM) efficiencies at 366 or 371 nm, respectively.[20, 21] The modified PPGs are reasonably efficient for the release of tyrosine and other phenols but the reactions are frequently accompanied by fragmentation and loss of the halogen (Br).

The currently reported limitations, e.g., poor leaving groups with low efficiencies, complex product mixtures and required carbonate/carbamate linkages, that plagued previous studies on phenol release, have encouraged us to expand our investigations of pHP cages[34] to include phenols, one of which is the amino acid tyrosine. Advantages of other pHP caged functional groups vis-a-vis other PPGs, when compared by us and others,[1-4, 17, 23] suggest that extending the comparison to pHP phenol release, including their side reactions and efficiencies, are warranted and are reported here.

Experimental

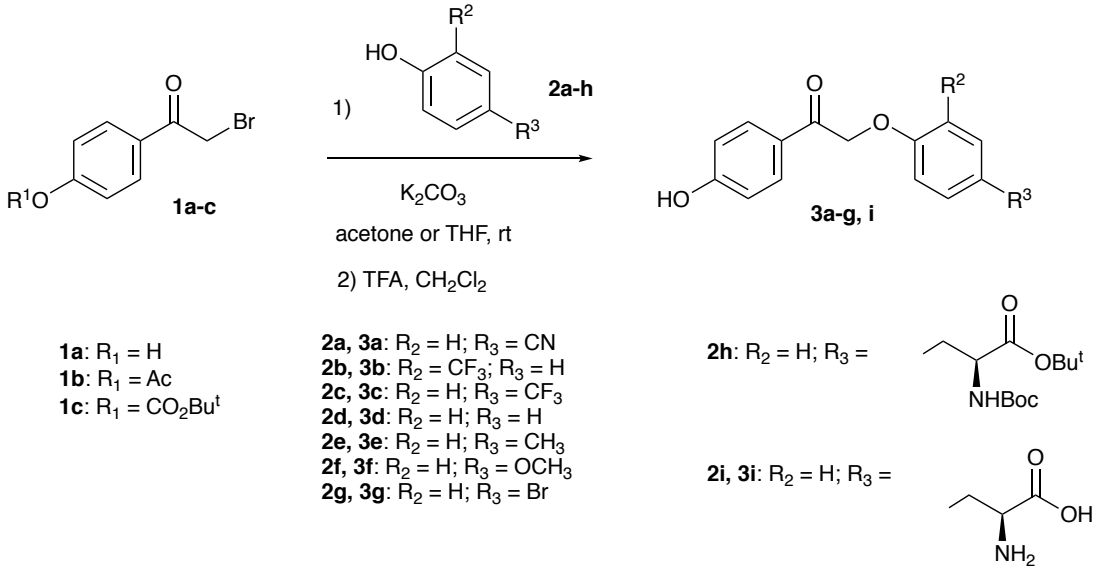
Detailed adopted methods for the synthesis of reactants, procedure used for irradiation, of analysis of photoproducts and measurements of quantum yields and instruments used for analyses are provided in the Supporting Information section.

Results

Synthesis

A series of seven representative pHP phenyl ethers (**3a** – **f**)[26] and pHP tyrosyl-O ether (**3i**) were synthesized by Williamson alkylation of substituted phenols **2a-h** by 2'-bromo-4-hydroxyacetophenone **1a** (Scheme 1). Occasionally, it was necessary to protect the phenolic

moiety (**2c**, **h** and **i**) in the pHP bromide with acetyl (**1b**), or in the tyrosyl series, *t*-butoxycarbonyl (Boc) to also protect the amino acid function in **1c**.[27] Upon completion of the alkylation step, the protecting groups were removed by treating the crude reaction mixtures with trifluoroacetic acid (TFA).



Scheme 1. Synthesis of *p*-hydroxyphenacyl phenyl ethers **3a** – **g**, **i**. For details, see SI.

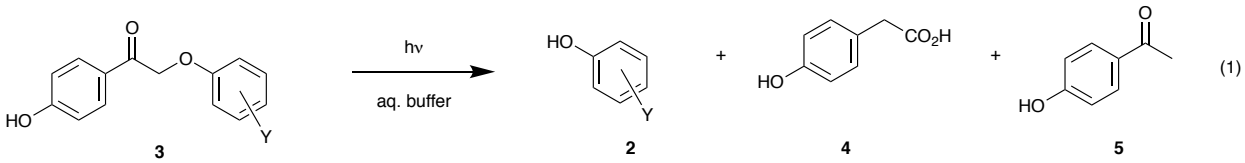
To explore the photochemistry and limitations of the phenol as a leaving group, we evaluated the following variables: (a) the effects of varying substituents and their phenolic pK_a's on the reaction and products, (b) the effects of quenchers, the solvent pH, and supramolecular encapsulation by the cavitand octa acid, and (c) the role of oxygen on the photochemistry.

(a) Substituent Effects by the Phenol Leaving Group on the Photochemistry

Earlier studies on the relationship between pK_a and rates[28, 29] or efficiencies[16] have reported linear Brønsted dependence for a large range of acid leaving groups, including pHP esters.[25, 35-42] Accordingly, a series of pHP phenyl ethers arranged based on increasing pK_a of the leaving group's conjugate acid, were irradiated in D_2O-acetonitrile-d_3 solutions at 300 nm for 1 hr and respective NMR yields were obtained as shown in Table 1. All electron-deficient phenols **2a-c** were released cleanly and very efficiently with nearly quantitative yields; however, for the less

acidic substrates, yields of phenol were low, and so were yields of the Favorskii rearrangement product **4**. Furthermore, reactions were accompanied by increasing amounts of the reduction byproduct **5**, suggesting a growing diversion from the established photo-Favorskii pathway (Table 1, eq 1). For bromo-substituted analog **3g** a plethora of radical-derived products was obtained; therefore, this derivative was not pursued further.

Table 1. Yields of Mono-Substituted Phenols and Cage Byproducts in Photolysis of pHP Caged Phenyl Ethers[a]



Substituent Y in 3	Recovered 3 (%)	Released 2 (%)[a]	Favorskii Product 4 (%)	Reduction Product 5 (%)
p-CN (**3a**)	n/o[b]	98	94	n/o
o-CF_3 (**3b**)	n/o	99	90	n/o
p-CF_3 (**3c**)	n/o	98	90	n/o
H (**3d**)	26	30	26	3.5
p-CH_3 (**3e**)	35	25	n/o	~ 10
p-OCH_3 (**3f**)	27	37	n/o	15

[a]Determined by ^{1}H NMR of crude reaction mixtures using DMF as the internal standard, after 1h photolysis at 300 nm in a 1:3 mixture of D_2O/CD_3CN buffered at pH range 5-7. [b]n/o = not observed.

As evident from Table 2 and Figure 1A, the decrease of phenol yield with increasing pK_a was reflected by the decrease in the appearance quantum yields for **2a** – **2f** (Φ_{phenol}), in accord with the Brønsted Leaving Group relationship employed for ground state S_N1 reactions. This correlation has been observed in a few other photochemical cage release reactions.[1, 23] This trend, however, was not observed for the pHP ether disappearance quantum yield (Φ_{dis}, Table 2; Figure

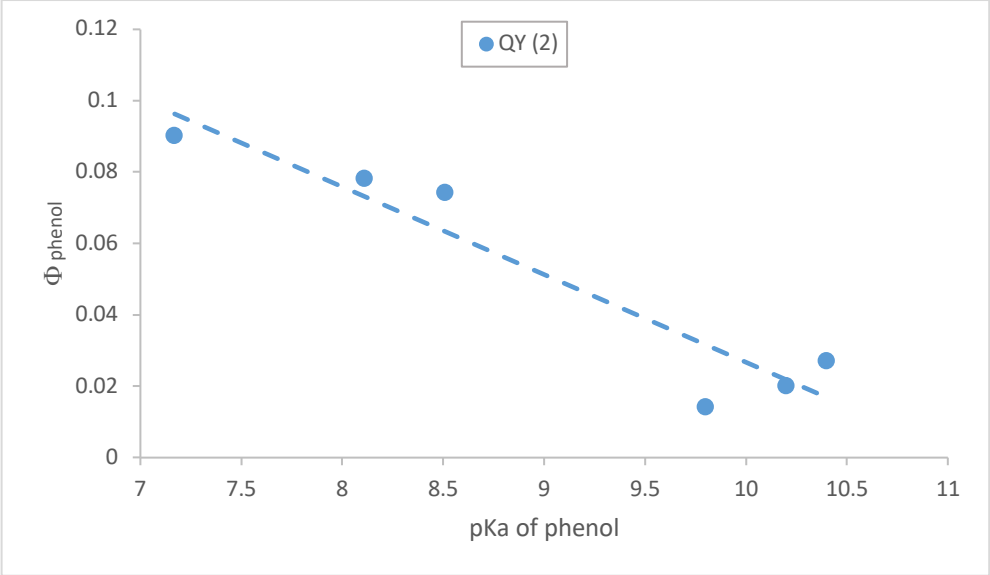
1B). More than two products, as well as unknown isomers, were formed in photolysis reactions of **3d-f**. While phenol appearance QYs for **2d-f** fit in the trend (Figure 1A), the disappearance of **3d-f** is complicated by multiple pathways reaction takes (Figure 1B).

Table 2. Quantum Yields for pHP Phenol Ether **3a-f** Disappearance (Φ_{dis}) and Phenol **2a–f** Appearance (Φ_{phenol}) as a Function of Phenol's pK_a at the pH Range 5-7.

pHP Phenyl Ether **3**	pKa of **2**[43]	Φ_{dis} of **3**	Φ_{phenol} of **2**
p-CN (**3a**)[a]	7.17	0.11	0.09
o-CF_3 (**3b**)	8.11	0.085	0.078
p-CF_3 (**3c**)	8.51	0.093	0.074
H (**3d**)[a]	9.8	0.029	0.014
Tyrosine (**3i**)[b]	10.07	0.1	0.085
p-CH_3 (**3e**)	10.2	0.121	0.02
p-OCH_3 (**3f**)	10.4	0.13	0.027

[a] See refs. [24,25]
[b] Tyrosine not included in the Brønsted correlation. Its pK_a is influenced by contribution of the amino acid moiety.

(A)



(B)

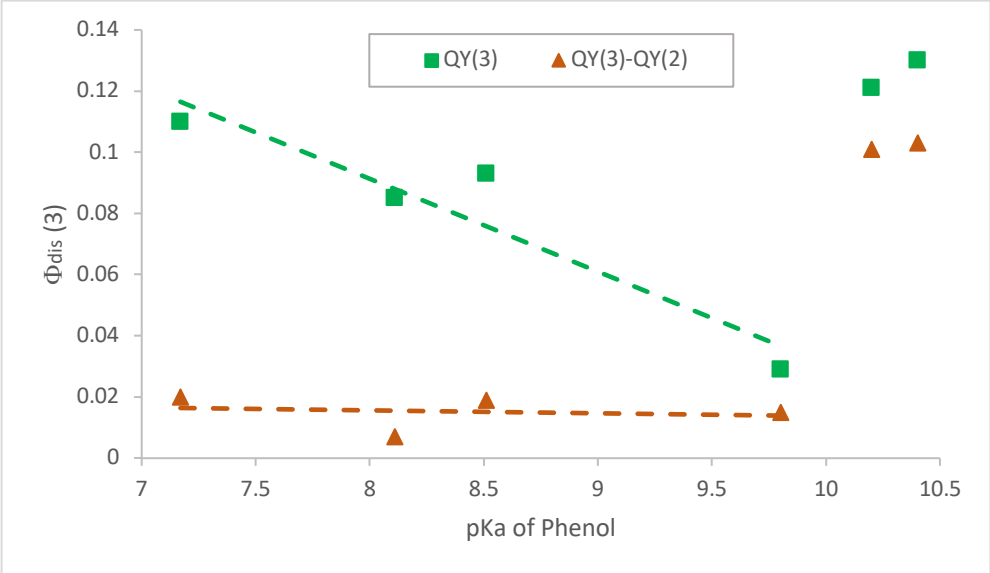


Figure 1. The effect of pK_a of the phenol leaving group on quantum yields at pH 5-7. **A.** Appearance quantum yield of phenol release versus its pK_a. **B**. Disappearance quantum yield of pHP phenyl ether vs phenol pK_a (green). For the weakly acidic phenols **3e,f** (pKa > 10), significant amounts of new by-products emerge alongside the released phenol, which is illustrated by the difference $\Phi_{diss}(3)$-$\Phi(2)$ (orange). Note that this graph does not detail the

complexity of the mixture of pHP phenyl ether isomers resulting from photolysis of **3e,f**, as it is beyond the scope of this paper.

(b) Effects of Quencher, pH, and Supramolecular Encapsulation by Octa Acid on the Photochemistry

The photorelease of phenols **2a** – **f** occurs through the triplet excited state[1] as demonstrated by methyl sorbate quenching[21] in accord with our earlier studies.[2, 28, 29, 35] Photolysis of **3a** at 300 nm gave Stern-Volmer quenching ($K_{sv} = 10^6$ M^{-1}) and a typical triplet lifetime of $\tau^3 = 4.2$ ns (see SI for details), in accord with triplet lifetimes obtained for pHP phosphate release. [2, 23]

Two of the pHP phenyl ethers (**3c** and **3f**) that represented the two extremes in pHP disappearance and product diversity were chosen for encapsulation within an octa acid capsule, i.e., @$(OA)_2$, as the host: **3c**@$(OA)_2$ and **3f**@$(OA)_2$. The phenol and byproduct yields were determined after 1 hr photolyses of their conjugate bases at $\lambda \geq 300$ nm in borate buffer (pH 8.7) within OA. When **3c**@$(OA)_2$ was irradiated, the pHP caging chromophore was primarily converted to the Favorskii rearrangement product **4**. ^{1}H NMR absorptions were assigned to *p*-trifluoromethylphenol (**2c**) as the major product and small amounts of *p*-hydroxyacetophenone (**5**), a reduction product, along with a few other minor, unidentified products. For **3f**@$(OA)_2$, however, a more extended irradiation was required resulting in the expected decreased yield of phenol **2f** along with a dramatic increase of the side products. The photoreactions were monitored by LC-DAD-MS, which provided quantitative assessment of **2**, **4**, and **5** (Table 3, Figures 2 and 3; also see SI figures S10-12 for details).

(c) Effect of O_2 (Oxygen) in pHP Photochemistry

Prompted by our earlier studies of the effect of oxygen on the reactions of the 7-diethylaminocoumarin-4-methyl (DEA) cage photochemistry[37] we turned our attention to the effect of O_2 on the pHP release of phenols in the photolysis reaction of **3c**@$(OA)_2$ and **3f**@$(OA)_2$.

The LC-DAD-MS analyses of the photolysis mixtures are shown in Figures 2 and 3. The blue traces are for decaging under normal, aerated conditions described above that indicate the

relative yields of the respective phenols **2**, the rearranged **4** along with the minor, but measurable amounts of **5**.

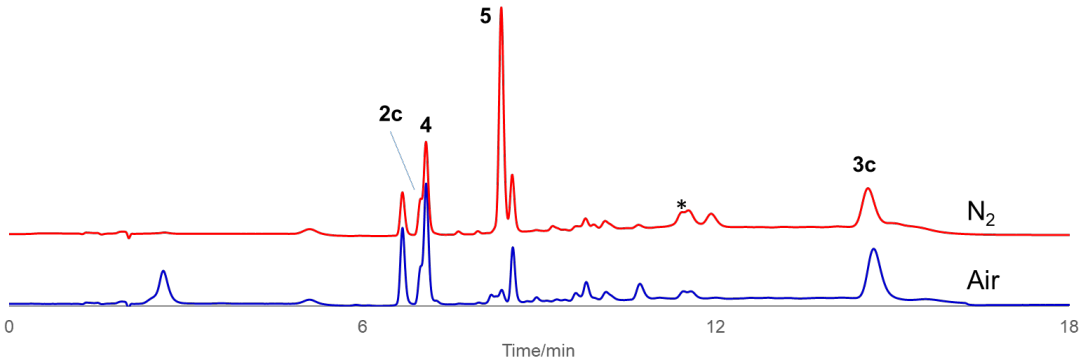


Figure 2. Effect of O_2 on photolysis of **3c**@$(OA)_2$. LC-DAD profiles (280 nm) from irradiation of **3c**@$(OA)_2$ complexes at $\lambda > 300$ nm in air (blue trace) and after N_2 purging (red trace). Solutions of complexes were prepared in aqueous borate buffer (pH 8.7) at 1:2 stoichiometry (200 μM OA:100 μM of **3c**). An asterisk denotes two photoproducts that are isomeric with the caged ether, **3c**.

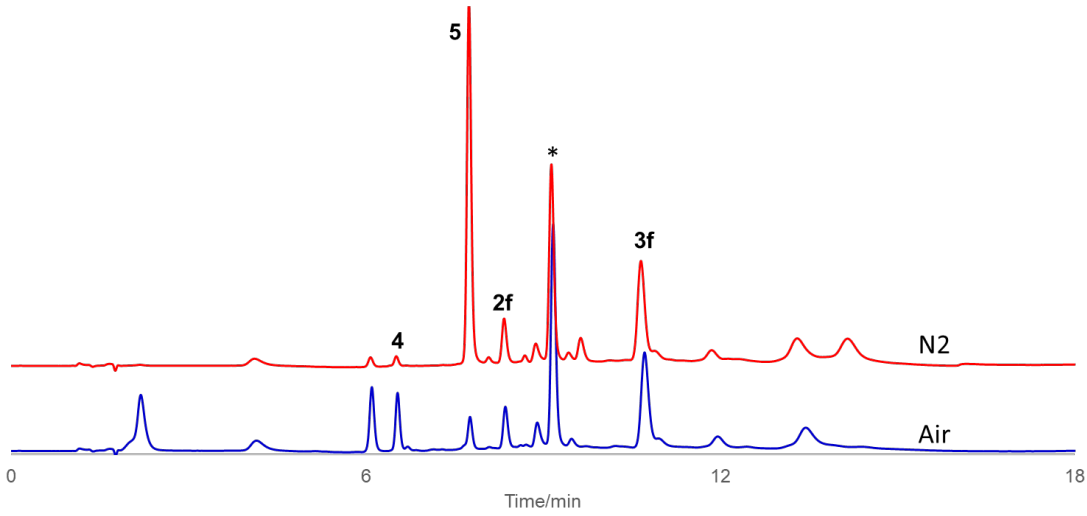


Figure 3. Effect of O_2 on photolysis of **3f**@$(OA)_2$. LC-DAD profiles (280 nm) from irradiation of **3f**@$(OA)_2$ complexes at $\lambda > 300$ nm in air (blue trace) and after N_2 purging (red trace). The prominent peak at 10 min marked with an asterisk and the smaller adjacent peak are unidentified isomers of **3f** (See SI for details).

When the photoreactions are conducted after N_2 purging, the LC-DAD-MS analyses show a significant increase in formation of the reduction product **5** shown by the red traces in Figures 2 and 3. Table 3 depicts the 10-fold increase in reduction product **5** for both **3c**@$(OA)_2$ and **3f**@$(OA)_2$, and decrease in the major Favorskii byproduct **4**, particularly dramatic in the case of **3f**@$(OA)_2$. The cage-release reaction of the two phenols from both encapsulated pHP phenyl ethers progressed unperturbed in the presence or absence of O_2.

Table 3. Relative Yields (%) of Reduction product **5** vs Favorskii product **4** after Irradiation of **3c**@$(OA)_2$ and **3f**@$(OA)_2$ in Air Equilibrated and N_2 Purged Solutions

Irradiation Conditions[a]	**3c converted**	**2c**	**4**	**5**[b]	**3f converted**	**2f**	**4**	**5**[b]
OA, air equilibrated	89	25	79	2	89	31	29	3
OA N_2 purged	93	24	59	22	89	32	6	33

[a] Concentration of the pHP ethers were 100 μM. Concentration of OA was 200 μM. Conversions and yields of products after 45 min irradiation (λ > 300 nm). Yield calculations were based on calibration curves obtained for absorbance coefficients for products **4** and **5**. [b] Trace amounts (1-4%) of 2,4'-dihydroxyacetophenone, the hydrolysis product, was also detected along with reduction product **5** and other unidentified, side products. The amount of hydrolysis product did not change significantly upon change of conditions (air/N_2).

Discussion

The results presented herein complement earlier investigations on photorelease of phenols by us and other groups,[1, 2, 18, 19, 23, 26] by providing a quantifiable, monotonic series of pK_a gradients to probe the nature of the bond-breaking process in the excited state.[26, 36-39] Furthermore, this series systemically tests a few poor leaving groups that might explore alternate pathways at the reactivity limits.

Scheme 1 illustrates the synthetic approach to the series of pHP-substituted phenol ethers. Since pHP itself is a weakly acidic phenol (pK_a 7.9), synthesis requires protection of the OH

group, especially for phenols with a higher pK_a, e.g. tyrosine, as shown in Scheme 1 and detailed in SI. The mechanism and environmental factors influencing the photorelease of pHP phenols were investigated through the following fundamental studies: (a) the effect of increasing phenol pK_a vis-a-vis quantum yield and rate constant, i.e., Brønsted behavior, (b) the mechanism for the pHP phenol release, (c) the supramolecular encapsulation and O_2 environmental effects on product distribution and chromophore degradation.

(a) Brønsted Behavior

The photorelease of phenols in aqueous acetonitrile solvents were quantitatively assayed for pHP phenyl ethers **3a** – **3f** (Table 2). As expected, these leaving groups were less efficient when compared with our previous studies using leaving groups with lower pK_a's as defined by Brønsted Leaving Group measures for solvolysis reactions.[1,2] Thus, **3a** through **3f** appearance quantum efficiencies were determined and were substantially lower than those reported for sulfonate, phosphate and carboxylate leaving groups.[2] For example, the unsubstituted phenol **3d** and most acidic member **3a** had lower rates of release in accord with the expected Brønsted Behavior, as shown in Figure 4 and Table 4.

Table 4: The Triplet State Quantum Efficiencies and Rate constants for Disappearance (log k_r) for pHP Sulfonate, Phosphate, Carboxylates,[25] Fluoride,[17] and for pHP Phenol and *p*-Cyanophenol Ethers.[25]

pHP Caged Leaving Groups	Φ_{dis}[a]	**LG pK_a**	**Log (k)**
Mesylate (**6**)	0.932	1.54	9.7
Tosylate (**7**)	1.04	0.44	10
Diethyl phosphate (**8**)	0.40	0.71	9.06
Fluoride (**9**)	0.84	3.17	9.3
p-CF_3 Benzoate (**10**)	0.288	3.69	8.51
Formate (**11**)	0.94	3.75	9.15
p-OCH_3 benzoate (**12**)	0.288	4.09	8.54

Benzoate (**13**)	0.316	4.21	8.44
GABA (**14**)	0.21	4.26	8.78
p-CN Phenoxy (**3a**)	0.11	7.17	7.88
ATP (**15**)	0.38	7.4	9.8
Phenoxy (**3d**)	0.03	10.02	7.02

[a] Determined in aqueous acetonitrile solutions at pH 5.8-7.3

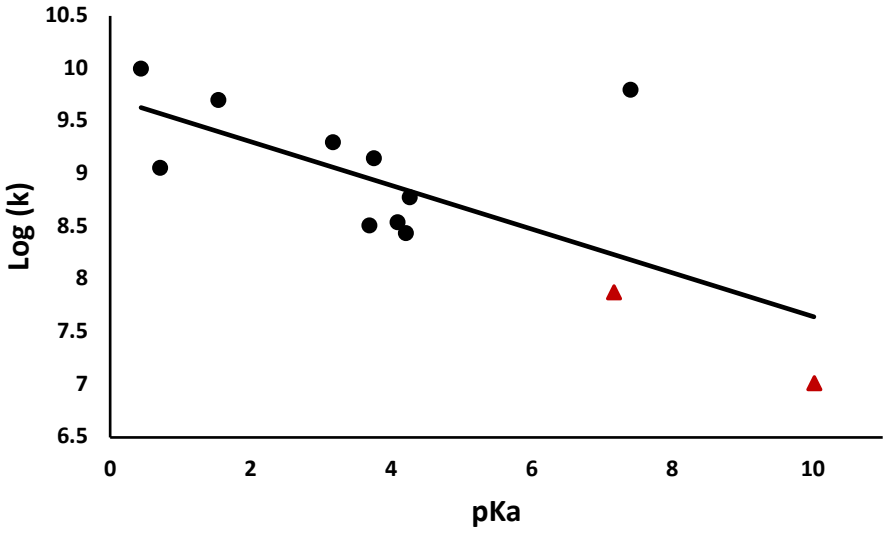


Figure 4. The Brønsted Linear Free Energy Relationship applied to rates of release from pHP derivatives versus the pK_a of the leaving group acid including pHP phenyl ethers **3a** and **3d** (red). The pK_a's of the leaving group conjugate acids are plotted versus the log k_r'sfor the rates of photorelease from the pHP triplet excited states. The values for log k_r and pK_a are given in Table 4. A 95% confidence interval for the fit includes **3a** and **3d** (this work) and pHP fluoride (**9**). The slope of the fit is -0.18 + 0.06 ($p < 0.05$l; Pearson Coefficient R2 = 0.49).

Particularly intriguing, however, were the changes in the cage product composition. As seen from Table 1 and Figure 5, the yields of phenol and the mass balance of the reactions drop dramatically as the pK_a's of the departing phenol increases. It is noteworthy that the photoproduct of the cage, i.e., the Favorskii rearranged acid **4**, gives way to a new reduction product **5** when the pK_a of the leaving phenol is above 9.8. That change in the byproducts,

however, does not alter the trend in the efficiencies of either the disappearance of the ethers or the appearance of the phenol versus the increase in the leaving group pK_a (Table 3).

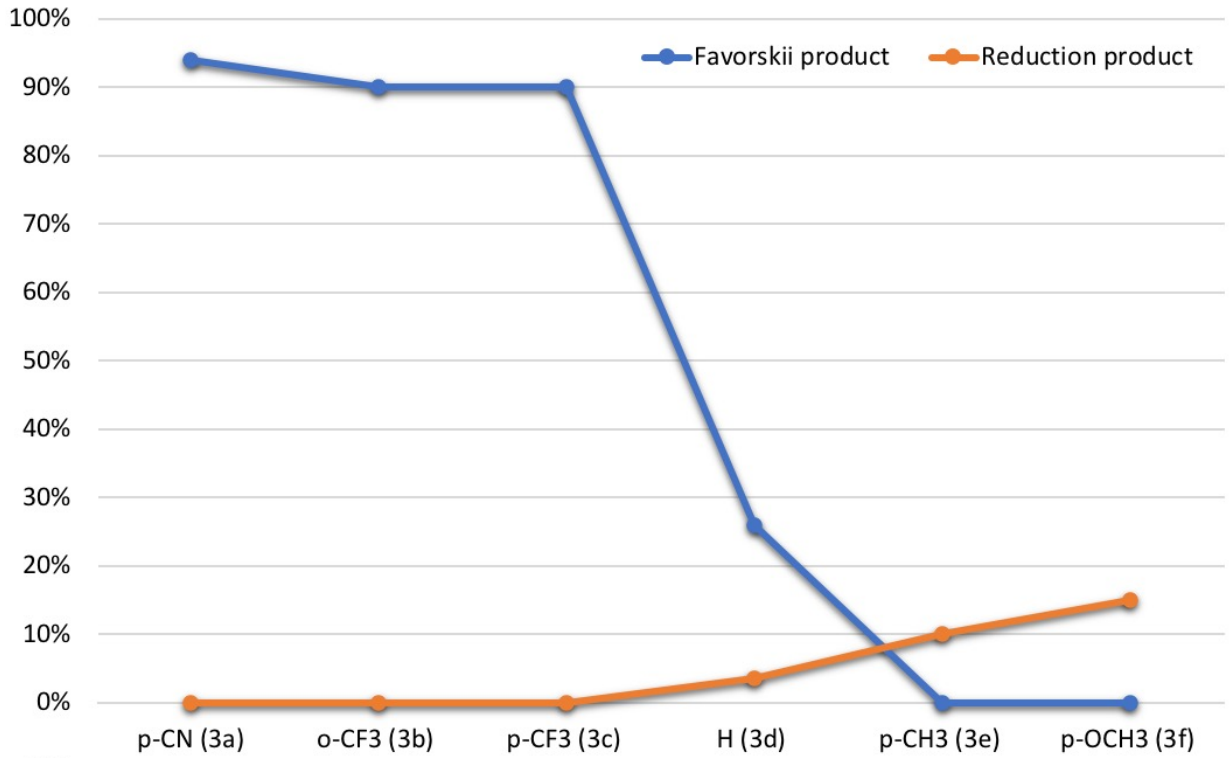
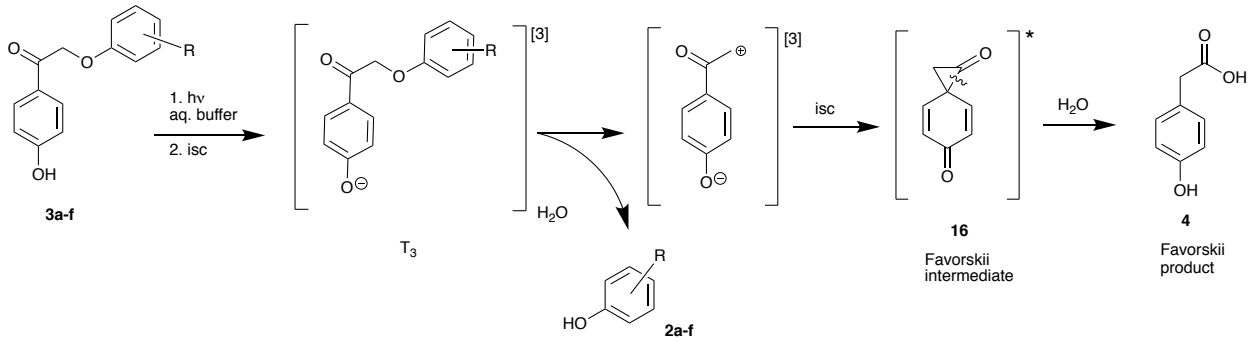


Figure 5. Percent of Favorskii **4** (blue) and reduction **5** (orange) products from the pHP phenyl ether photolysis vs phenol pK_a. Note that additional byproducts are not accounted for **3d-3f**.

(b) The Mechanism for the pHP release of Phenols and Formation of the Favorskii Product

There have been several previous studies on the mechanism for the pHP esters such as phosphates, mesylates, and carboxylates.[35,44-46] A similar mechanism is depicted in Scheme 2 for the release of phenols **2a-f**, and is based solely on the appearance efficiencies and rates shown (Table 2, Figure 1A).



Scheme 2. Mechanism for pHP release of phenols.[45-47]

The initial events, excitation to the pHP singlet, then efficient intersystem crossing yields the reactive triplet state, the conjugate base of the pHP triplet.[47] Rapid cleavage of the pHP-ether bond ($10^9 s^{-1}$) yields the ion pair in accord with our earlier studies on pHP photorelease.[2,45-47] The rate of release of the phenol is linearly dependent on its pK_a, following the Brønsted prediction (Table 2, Figure 1A),[25] and occurs within a few nanoseconds.[45-48] The pHP portion, the protecting group fragment, forms the intermediate dienedione **16**. The primary reaction of **16** is the formation of *p*-hydroxyphenylacetic acid (Favorskii product **4**).[16,34,45-48]

The larger disappearance efficiencies observed for **3d, 3e** and **3f**, however, contrast sharply with the appearance of the phenols (See Figure 1B). They continue to follow the Brønsted correlation as shown in Table 2 and Figure 1. However, these products signaled a competing mechanism for the appearance of two new isomers of the starting pHP protected ethers **3e** and **3f**. These two products have not been fully characterized, nor are their properties part of our Brønsted behavior study.

It should be emphasized that the Brønsted driven release of the phenoxides may be too rapid to include a radical cleavage, the disproportionation process proposed by Peters.[28] In that case, radical coupling processes were critical for determining Marcus behavior as demonstrated in the earlier work of Pincock.[39,40] However, the pHP release reaction bypasses a competing radical coupling opportunity of the radical pair formation step, which is fundamental for evaluating Marcus behavior from the radical versus ionic pathways. Furthermore, our earlier studies had established that bond cleavage from the triplet is not reversible[44,48] by the absence of isotope scrambling (O^{18} vs. O^{16}) in labeled carboxylate esters.[49,50] It is also supported by the

observation that diastereomeric centers of chiral pHP analogs are not compromised during photorelease of carboxylates.[44]

The formation of new products for **3d, 3e** and **3f** may point to an additional reaction pathway for leaving groups with higher pK_as. To investigate, relaxed scan calculations of the C-O bond length between the pHP and the leaving group were done on the triplet surface using UB3LYP/6-31G+(d,p) and the SOMOs were visualized at the optimized geometry, the transition state, and at longer bond lengths (See SI for details). The better leaving group (*p*-cyanophenol) has both SOMOs located on the pHP at the transition state as well as at longer bond lengths, indicating that the pHP retains triplet character and the phenol has singlet character and is leaving as a phenoxide. However, in the transition state of the very poor leaving group (*p*-methoxyphenol) one SOMO is primarily localized on the pHP while the other is localized on the phenol, which holds true at longer bond lengths as well. These results indicate that pHP ethers with poor leaving groups may react via homolysis.

Since **5** comprises of less than 10% of cage byproduct under standard pHP photolysis conditions (non-OA, air equilibrated solutions) even for the poorest leaving groups such as **3d, 3e,** and **3f**, we conclude that the mechanism in Scheme 2 best represents pHP phenol (**3a-3c**) release, similar to all other leaving groups shown in Table 4.[35,45,46]

(c) Supramolecular Encapsulation and O_2 Environmental Effects on Product Distribution

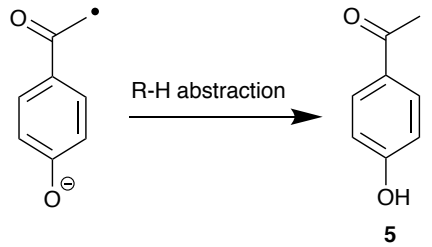
To shed more light on the observed change in the reaction course, we turned our attention to another method to probe the photorelease process, i.e., the supramolecular encasement of the caged derivative, which had recently given promising results for a number of caged compounds,[37] including pHP esters.[4,5,6,37] In those studies,[5] the release from the pHP esters was very efficient and free of extraneous side reactions, in contrast to more complicated product arrays found with three other PPG's examined.[6,37]

OA complexes of pHP phenyl ethers **3c** and **3f** were photolyzed in aqueous buffer (pH 8.7) to release phenols **2c** and **2f**, respectively, along with byproducts of the cage, **4** and **5** (*vide supra*).[5] At this pH, photolysis occurs from the pHP conjugate base (See SI Figures S10-S12), and reveals an even greater decrease in the yield of Favorskii product **4**. Photolysis of **3c**@OA_2, with its very good leaving group, produces **2c** and byproduct **4**, whereas **3f**@OA_2, bearing a very

poor leaving group, shows very little **4** in the resulting solutions. When purged with nitrogen, **4** becomes a minor component of the reaction mixture. Yet, in both cases the pHP chromophore disappearance occurs with nearly the same efficiency (Figures 2 and 3 and Table 3). This suggests that the bond cleavage continues to be sensitive to the leaving group's pK_a(See SI for details).[28,29]

Evidently, the presence of oxygen quenches the formation of the reduction product, *p*-hydroxylacetophenone **5**,[35] decreasing the ratio of the reduction or radical pathway to the ionic pathway for the cage fragment, without affecting the phenol release (Scheme 3). In aerated aqueous media, the deprotonation of pHP is facilitated resulting in **16** (Scheme 2).[1,3,45,46,48] Thus, when O_2 is absent, more reduction occurs whereas in its presence, solvolysis product **6** dominates. H-Atom abstraction controls the product distribution in nitrogen-purged reactions, leading primarily to the reduction product **5** (*vide supra*),[5] established in the earlier studies on the closely related caged *p*-methoxyphenacyl analogs[51] first pioneered by Sheehan and Umezawa[52] and later extensively reexamined by Phillips.[21,53-57]

Here, the hydrogen atom source for the reduction appears to be OA since, when it is present in excess, more reduction products result (see SI for details). Evidence for the reduction pathway was also found when the photolysis of pHP phenols was carried out in anhydrous acetonitrile. Mixtures of several new products were formed, along with reduction product **5**, confirming our earlier studies on the critical influence of water on the pHP release reactions (See SI for details).



5

Scheme 3. Reduction pathway leading to formation of **5**.

A recent study by Phillips and Dore[20,21,55] on phenol and ester release from 7-hydroxy quinolinylmethyl cation ($DEACM^+$), a singlet reaction, and our work on 7-methoxycoumaryl-4-methyl caged acids[7] demonstrated a similar oxygen effect during phenol release in OA.

The triplet state release from pHP phenyl ethers compares favorably with that of the coumarin protected esters which occur from their singlet excited state, i.e., 4-methylcoumaryl phosphates and carboxylates, reported by us[1, 2] and by Schmidt, Bendig, et al.[36, 42, 58]

There are several significant differences when comparing the triplet pHP cage, with the singlet coumaryl-4-methyl cages. For example, the relative rates of release for both coumarylmethyl and pHP series are very similar, whereas, quantum efficiencies can be nearly an order of magnitude or more lower for coumarylmethyl cages. However, the coumaryl series requires lower, milder excitation energy accompanied by fluorescence. That both of these chromophores are governed by Brønsted Leaving Group Behavior, they display predictable photorelease reactivity.

Conclusions

Caged pHP phenols including tyrosine have been synthesized and their photochemistry examined. Upon photolysis the phenols are released in modest to good yields, but with poor quantum yields. Our investigations confirm the mechanism for release of phenols in accord with several earlier studies. The subsequent chemistry of the triplet intermediate is heterolysis releasing the phenol. The efficiency of these reactions is strongly influenced by their environment.

It is not clear at what stage or under what conditions **16** partitions toward Favorskii closure eventually forming the rearrangement product, phenylacetic acid.[45, 48] For the more strongly acidic phenols **2a** – **2d,** the pHP protected phenol is easily released and does so according to the same predictable Brønsted leaving group behavior previously observed for a large array of leaving group acids. This same consistent predictable release behavior continues even with weakly acidic phenols, **2e** and **2f** with progressively less efficiency as predicted by Brønsted analysis. This lower reactivity supports our initial Brønsted-governed mechanism for this leaving group, in accord with most caged pHP photorelease reactions.

We also discovered that, especially for the poorer leaving groups, the effects of solvent, presence of oxygen, confinement, pK_a and multiplicity influence the chemistry of the PPG and the released product. In fact, new products in addition to the phenols are formed and are increasingly apparent as the phenolic leaving group's pK_a increases for **3c** through **3f**. Future

studies will be necessary to pursue the change in reactions and mechanism for these "poorer" leaving groups.

Electronic Supplementary Information

Experimental procedures, ^{1}H NMR, UV and ESI-MS spectra for all new compounds. Irradiation procedures, ^{1}H NMR titration spectra of host-guest complexes, progress of photoreactions as monitored by ^{1}H NMR, LC-DAD-MS.

Conflicts of interest

The authors declare no competing financial interest.

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Acknowledgements

The Kansas University Endowment Association (RSG and JP), the National Institutes of Health (RSG) and National Science Foundation (VR, RSG) are acknowledged for their generous financial support. JPDS thanks Portuguese national funds from FCT – Foundation

for Science and Technology through project UID/Multi/04326/2019, and from the operational programs CRESC Algarve 2020 and COMPETE 2020 through project EMBRC.PT ALG-01-0145-FEDER-022121.

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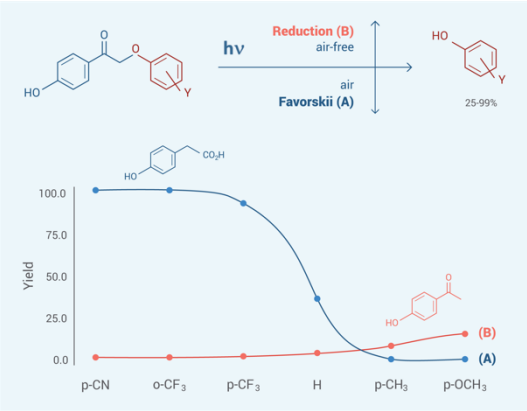

Photolysis of p-hydroxyphenacyloxy arenes releases free phenols in good yields governed by their pKa. At high pKa, new byproducts (B vs A) reveal a change in reaction mechanism.

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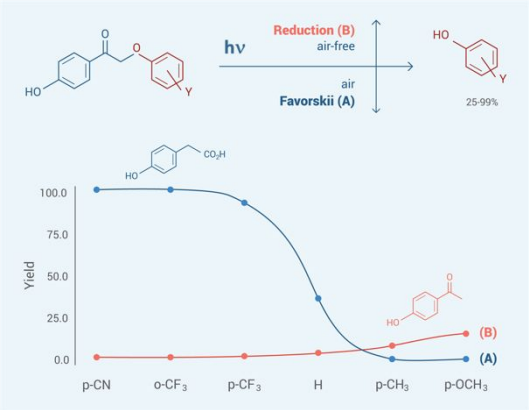

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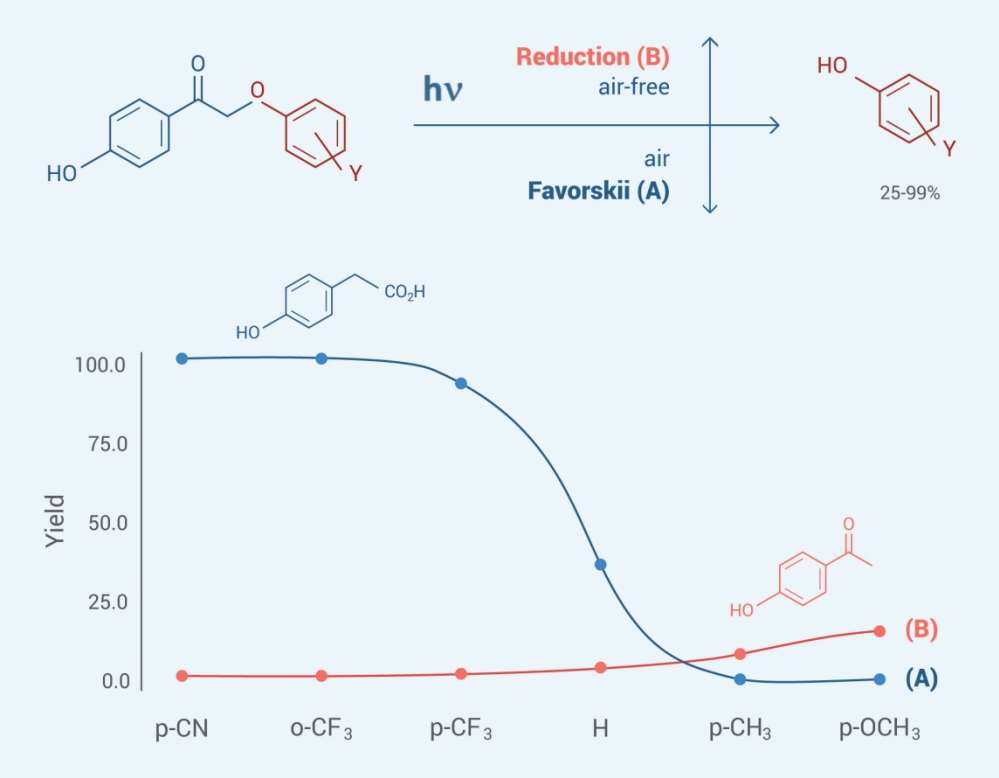

TOC graphic

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