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Unraveling the Photodeprotection Mechanism of Anthraquinon-2-ylmethoxycarbonyl Caged Alcohols Using Time-Resolved Spectroscopy

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Abstract: Anthraquinone (AQ) compounds have been used as photolabile protecting groups (PPGs) to protect alcohols, ketones and carboxylic acids. However, due to the lack of direct spectroscopic information for the transient species and intermediates related with the deprotection reaction(s), the photorelease mechanism(s) of these systems are still largely unknown. In this contribution, we detail a time-resolved spectroscopic investigation using anthraquinone protected galactose (1) and adenosine (2) to investigate the photodeprotection reaction mechanism(s) of these kinds of AQ-PPGs. It was found that in THF-H₂O solvents, the ketyl radical species generated for 1 and 2was found to be a reactive intermediate that then formed a dihydroxyanthracene species. The photodeprotection then occurred with the accompaniment of a decarboxylation process. These results provide an improved understanding for how AQ-PPGs work and will help assist in the design and applications of selected anthraquinone derivatives as a PPG platform, especially in aqueous environments more relevant for use in biological systems.

Introduction

Photolabile protecting groups (PPGs) for different functional moieties have wide applications in synthetic chemistry and in the study of biology.¹²³ The more popular PPG platforms are based on arylcarbonylmethyl, coumarin-4-ylmethyl, arylmethyl and nitroaryl groups. To complement these existing platforms, there is increasing interest and continuous efforts to exploit new PPGs based on other types of functional groups.²

Anthraguinone compounds (AQs) can be very effective cancer therapy drugs. Among them, daunorubicin,³ idarubicin,⁴epirubicin,⁵ aclarubicin,⁶ pirarubicin,⁷ and valrubicin⁸ have earned clinical approval. In this research area, the photophysics and photochemistry activities of AQs have been deeply examined.⁹ A commonly studied reaction is the intermolecular hydrogen atom transfer (HAT) in a hydrogen donor like isopropanol (IPA). Previously, we performed mechanistic studies¹⁰ on an unusual and efficient photoredox reaction of AQs such as 2-(p-hydroxymethyl) phenylanthraguinone (PPAQ) and 2-hydroxyethyl anthraguinone (2-HEAQ) in aqueous solutions first discovered by Wan and coworkers.¹¹ Due to their excellent photosensitivity, AQs have been utilized as a PPG plat-form and several AQ-PPGs were developed. The first example reported by Kemp and was coworkers using (2-anthraguinonyl)-methyl to protect a carboxylic moiety.¹² Furuta and coworkers utilized anthraguinon-2-ylmethoxy-carbonyl (Agmoc) to protect some primary alcohols like galactose (1) and adenosine (2) due to their wide use in the biological areas of research such as solid-phase oligonucleotide array synthesis, nucleotide synthesis and saccharide modification. (see Scheme 1).¹³ Agmoc exhibits promising and intriguing photoreactivity that can be useful for many kinds of applications, especially to be potentially used to protect biologically related molecules.¹³ Song and coworkers developed 2-(1,2-dihydroxyethyl)-AQ to protect aldehydes and ketones,¹⁴ and used 2-(1-hydroxyethyl)-AQ as a PPG for several carboxylic acids.¹⁵ Jones

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and coworkers demonstrated that 1-alkoxy-9,10-AQ can be used to cage 4-hydroxy-2-nonenal and the photorelease gave 4-hydroxy-2-nonenal in excellent yields.¹⁶ Herrmann and coworkers employed 1-alkoxy-9,10-AQ to release fragrances like volatile aldehydes or ketones, which may have promisein body care and household applications of functional perfumery.¹⁷ Since the AQ carboxyl moiety is a photo-oxidant which may facilitate single electron oxidation from an attached arene, Floreancig and coworkers used this to develop a PPG using AQ carboxylates to release some protected carbonyl and carboxyl compounds.¹⁸

Reaction mechanism studies for PPGs are crucial so as to not only better understand how PPGs work under different conditions but also aid in the design of new PPGs for applications. For AQ-PPGs, although some effort has been devoted to study the photodeprotection mechanisms by using traditional steady-state methods, there appears to be little if any direct observation and characterization of the reactive intermediates and transient species from time-resolved spectroscopic investigations. Several issues are still left to be addressed. First, what is the precursor that reacts to give the photodeprotection? Second, it is noted that the different AQ-PPGs liberate the caged compounds in different solvents, like Aqmoc works well in THF-H₂O while Aqe and Aqe-diol work well in MeOH. What is the role of the solvent and its effect on the deprotection reaction of AQ-PPGs? Third, whether the photoredox reaction observed for 2-HEAQ and PPAQ will be involved in the photodeprotection of AQ-PPGs? Fourth, what is the effect of the photoreduction reaction?

In this work Aqmoc protected galactose (1) and adenosine (2) were selected to start time-resolved spectroscopy investigations for photodeprotection mechanisms of AQ-PPGs. The state-of-art time-resolved spectroscopic techniques of nanosecond transient absorption (ns-TA), femtosecond transient absorption (fs-TA) and nanosecond time-resolved resonance Raman

(ns-TR³) spectroscopies were utilized to directly probe the electronic absorption and vibrational spectra of the reactive intermediates of **1** and **2** in different solvent systems. Density functional theory (DFT) computations were also conducted to aid in the assignments and interpretation of the experimental spectra so as to improve knowledge of the reaction pathway(s) and deprotection mechanism(s) under varying conditions.



Scheme 1. The photodeprotection of 1 and 2 in THF-H₂O.^[13]

Results and Discussion

A. Time-resolved spectroscopic studies of 1 and 2 in ACN, IPA and THF

To gain representative spectra and help in the investigating of the photochemical reactions of **1** and **2** in THF-H₂O, time-resolved spectroscopic experiments were first performed for **1** and **2** in the organic solvents of acetonitrile (ACN), IPA and THF, respectively.

Ns-TA spectra for **1** and **2** in ACN are displayed in Figure S3. The spectra have absorbance features at 325, 372, 462, 620 and 670 nm and these profiles resemble those of the triplet state for other AQ containing systems.^{9d} The ns-TA spectra of **1** was compared with a DFT calculated ultraviolet-visible triplet spectrum of **1** (Figure S4) and the close resemblance implies the triplet

species is the predominant one formed after photoexcitation of **1** and **2** in ACN. Additional evidence for this triplet assignment results from ns-TR³ spectra (Figure S5), where the Raman signals at 1557, 1572, 1590 and 1616 cm⁻¹ closely resemble those for the computed triplet species Raman spectrum.

HAT is typical for aromatic ketone compounds in hydrogen donor solvents like IPA and has been studied for a number of AQ derivatives.¹⁹ The ns-TA spectra for **1** (Figure S6) and **2** (Figure S7) in IPA have characteristic absorbance features at 383 and 426 nm with a negative feature near 320 nm. A similar known negative feature near 320 nm was attributed to the fluorescence signal of the dihydroxyanthracene species, demonstrating occurrence of an HAT process of the substrate (**1** and **2**) so the transient detected at 383 and 426 nm is accordingly assigned to be a ketyl radical species.



Figure 1.(Left) Ns-TR³ spectra for **1** in IPA acquired at different delay times displayed adjacent to the spectra. (Right) Comparison of (a) the experimental 50 ns Raman spectrum to (b) the computed Raman spectrum for the **1**ketyl radical species.

The ns-TR³ experiments were performed for **1** in IPA (Figure 1). Mainly one species was probed in the ns-TR³ spectra for both **1** and **2** in IPA with Raman peaks at 1551, 1572, 1590 and 1616 cm⁻¹. Based on the ns-TA study, the experimental Raman spectrum recorded at 50 ns was selected to compare with the simulated Raman spectrum of the ketyl radical in Figure 1 (right). The good agreement between the two supports that the main photochemical reaction of **1** and **2** in IPA is the intermolecular HAT. This is consistent with our previous studies that the triplet $n\pi^*$ configuration of AQs act as the reactive species for a HAT reaction to produce a ketyl radical intermediate in IPA.¹⁰



Figure 2.(a)The fs-TA; (b) ns-TA spectra of 1 in THF.

Figure 2 presents the fs-TA and ns-TA spectra for **1** in THF. To be concise, only the fs-TA spectra recorded at a later delay time region are presented. The first species at 372 and 462 nm decayed to form a new intermediate that absorbs at 380 and 426 nm with an isosbestic feature near 405 nm. Based on the time-resolved spectroscopic studies in ACN and IPA, the first species is the triplet species and the second is the ketyl radical species of **1**. For the ns-TA spectra recorded in THF, a ketyl radical species was also probed for **1** and **2** (Figure S8). That is, the HAT takes place for **1** and **2** in THF. On the other hand, it is noted that in THF the triplet

species was still observable with its typical signal at 462 nm for both **1** and **2** while the bleaching band observed in IPA was absent for **1** and was less intense for **2**.



Figure 3. Ns-TR³ results of (a) **1** and (b) **2** in THF obtained with different time delays displayed adjacent to the spectra.

The ns-TR³ spectra for **1** and **2** in THF are displayed in Figure3. The spectra have Raman peaks at 1551, 1557, 1572, 1590 and 1616 cm⁻¹ and therefore is proposed to gain combined contributions from the triplet and the ketyl radical species. It can be concluded that the HAT reaction takes place for both **1** and **2** in THF but that it occurred with a slower rate compared to that seen in IPA. This is reasonable as the HAT process for the substrates from the 3° C –H bond of IPA is easier to take place than that from the 2° C-H of THF.

B. Time-resolved spectroscopic studies of 1 and 2 in THF/H₂O and THF/KMOPS

After clarifying the photophysical and photochemical reactions of **1** and **2** in organic solvents, we now focus on the photochemical reactions of Aqmoc-PPG in THF-H₂O, where photodeprotection was found to take place.¹³ Photolysis experiments were performed for **1** and **2** in THF-H₂O and the products were isolated by thick layer chromatography. It was determined that the predominant product after photolysis is 2-methylAQ (Figure S9). This is consistent with the studies by Kemp and coworkers on AQ protected carbonic acids that the predominant deprotection product is 2-methylAQ. It is noted that the major deprotection byproduct of **1** was anthraquinon-2-ylmethanol tetrahydrofuranyl ether as reported earlier by Furuta. This is not surprising because THF is known to be easily oxidized and the ether product could be formed from 2-methylAQ by several pathways.





Figure 4.Shown are the fs-TA (a, b, c and d) and ns-TA (e and f) results for 1 in THF-H₂O (1:1).

Figure 4 presents ns-TA and fs-TA results observed of **1** in THF-H₂O. The very early changes seen within 1 ps (Figure 4a) are attributed to an internal conversion transformation of S_n to S_1 . Then, S_1 decayed with the production of the triplet having the specific absorption features near 382 and 452 nm (see Figure 4b, 4c). Finally, the triplet species reacts to produce a ketyl radical species (Figure 4d). This is similar to the transformations observed for **1** in pure THF solvent. In the subsequent times revealed by the ns-TA spectra (Figure 4e and Figure 4f), the observation of an isobestic point at 410 nm for both **1** and **2** suggests a kinetic transformation from the ketyl radical species (382 and 426 nm) to another transient species having its typical absorbance at

505 nm, that was not seen in the organic solvent systems we studied and this species is denoted as IM1. It is noted that the radical anion species of some AQ compounds absorbs in the 500-620 nm region.^[20] To discern whether IM1 is the radical anion intermediate of an AQ species, the ns-TA experiment was performed for **1** in the electron donor solvent dimethylsulfoxide (DMSO) (Figure S10). The spectra profile in Figure S10 resembles well with the spectrum of the reported radical anion species of an AQ compound,⁹ while the spectrum was distinctly different from that observed in THF-H₂O, suggesting that IM1 is not the radical anion species of an AQ species. After 2 μ s, IM1 decayed and a second new species (denoted as IM2) that has a shoulder band at 370 and 400 nm, and a band at 400 nm formed around 16 μ s.





Since the final product analysis suggested that the deprotection occurs more efficiently for **2** in a THF-KMOPS solutions (with quantum yields up to 98%), ns-TA spectra of **1** and **2** were also obtained in THF-KMOPS (Figure 5). Upon 266 nm irradiation, IM1 was produced and then transferred to IM2 faster and more efficiently as compared to the analogous species seen in THF-H₂O. In addition, a third species (IM3) was observed at 330 nm for**1** and **2**that coexisted with IM1 in THF-H₂O and THF-KMOPS. To assist in the identification of the three intermediates IM1, IM2 and IM3, ns-TR³ experiments were performed for **1** and **2** in THF-H₂O and THF-KMOPS, and these results are respectively shown in Figure 6 and Figure S11.



Figure 6.Thens-TR³ results obtained for **2** in (a) THF-H₂O (1:1) and (b) THF-KMOPS (1:1) solutions recorded at varying time delays displayed adjacent to the spectra.

In THF-H₂O, the ns-TR³ spectral profile of the first species (Figure 6a) exhibits an apparent similarity with that of a ketyl radical species (see the comparison of the spectra observed in IPA

and THF-H₂O in Figure S12). It was shown earlier that the HAT reaction for **1** and **2** can take place between the substrates and the solvent THF with the generation of the ketyl radical species. At 10 μ s, a new transient emerged with diagnostic Raman features at 1585 and 1612 cm⁻¹ along with a weak while still noticeable feature at 1635 cm⁻¹.

For the ns-TR³ results for **2** in THF-KMOPS (Figure 6b) the species having Raman peaks at 1585, 1612 and 1635 cm⁻¹ was produced earlier at around 100 ns and completely formed by 300 ns (indicated by the blue line) and appears to be produced more efficiently with more intense Raman signals accompanying the decay of the ketyl radical species. On one hand, as the deprotection of **2** occurs more efficiently in a THF-KMOPS solution,^[13] the preceding behavior suggests that IM1 is formed from the decay of ketyl radical species and IM1 that has specific electronic absorption bands at 372 and 505 nm and vibrational peaks at 1585, 1612 and 1635 cm⁻¹ could be produced from the photodeprotection reaction. On the other hand, the predominant product after photolysis for **1** and **2** is 2-methyl AQ.



Figure 7. (Left) Comparison of (a) the ns-TA spectrum of **2** obtained in THF-H₂O at 2 μ s to the (b) calculated xylylidene species of 2-methylAQ (utilizing a 1.0 scale factor with a 2500 cm⁻¹ half-width) with its structure shown in the figure, and comparison of (d) the ns-TA spectrum of **2** in THF-KMOPS recorded at 2 μ s to (c) the UV-vis spectra of 2-methyl AQ acquired in THF-H₂O and (e) computed ultraviolet-visible spectrum of triplet couple-reaction product between the ketyl radical and THF (using a 1.1 scale factor with a 1400 cm⁻¹half-width)with its structure shown in the figure. (Right) Comparison of (black) the ns-TR³ spectrum of **2** in THF-KMOPS at 10 μ s to (red) the computed Raman spectrum for the xylylideneform for 2-methyl AQ.

We compared the experimental ns-TA spectra of the species IM1 recorded for 2 in THF-H₂O at 2 µs with an UV-vis spectrum of an authentic sample of 2-methyl AQ in THF-H₂O and a calculated one for its xylylidene form (Figure 7, Left), and compared the experimental resonance Raman spectrum for the intermediate IM1 at 10 µs was respectively correlated with the computed ones for 2-methyl AQ (Figure S13) and its xylylidene species (Figure 7, Right). It is found the ns-TA spectra have joint inputs due to the two species, that is, the absorbance at 372 and 505 nm (IM1) are from a more conjugated xylylidene structure of 2-methylAQ and the 330 nm (IM3) band gains a contribution from 2-methyIAQ. This assignment is consistent with the ns-TA study on naphthoquinone by Wirz and coworkers showing the quinone form absorbs in the lower wavelength region while its corresponding enol has a specific absorption at longer wavelength from 500 nm.²¹To make the assignment of the species IM2 generated at late delay time with a shoulder band spectrum (372, 400 and 500 nm), TD-DFT calculations were performed for several possible species and the experiment spectrum is more similar to the simulated ultraviolet-visible spectrum for the triplet of the couple-reaction product between the ketyl radical of 2-methylAQ and THF (see its chemical structure in Figure 7e). The ns-TR³

results for the species (1585, 1612 cm and 1635 cm⁻¹) seen subsequent to the decay of the ketyl radical resembles more with the xylylidene species while it is different from 2-methylAQ and the couple-reaction product. This could be due to the fact that 2-methylAQ has a strong 330 nm absorbance so it is not easy to be observed under our ns-TR³ experimental condition using the probe wavelength of 368.9 nm. The absence of signal from the couple-reaction product in ns-TR³ could be accounted for by the ns-TA experiments being done for the sample solutions stored in a quartz cell, which allows for the detection of the byproduct, while the ns-TR³ experiments use a flowing system which makes sure the species are generated from fresh sample solutions with little build-up of photoproducts in the bulk solution.

After generation of dihydroxyanthracene species, the cleavage process was proposed to be accompanied by a decarboxylation, which resembles the cleavage of 2-nitrobenzyl carbonate esters,²² coumarin esters,²³ N-methylpicolinium carbamates²⁴ and thiochromone S,S-dioxide esters.²⁵As suggested by the ns-TA and ns-TR³ results, the photodeprotection takes place during the nanosecond time region and thus the singlet excited state reaction pathway is therefore excluded. We first simulated this reaction on the excited triplet surface using DFT calculations and these results are presented in Figure 8 and suggest the triplet dihydroxyanthracene overcomes a barrier of 10.05 kcal/mol to release the protected alcohol as well as undergoes a decarboxylation process. We also simulated the deprotection via the ground state surface (Figure S14), while the endothermic product and the energy barrier of 24.17 kcal/mol excluded this pathway.



Figure 8. Profile of the reaction energy derived by (U)B3LYP/6-311G** computations for the photodeprotection of **1** via triplet surface accompanied by the decarboxylation process with assistance of two H₂O molecules.

Combing these DFT computational results to final product analysis data and the time-resolved spectroscopic data, a photorelease reaction mechanism is proposed for the Aqmoc caged alcohol compounds (Scheme 2). Briefly, the caged AQs are excited to S_n and undergo an efficient ISC process to produce the triplet species, which starts the photorelease reaction. Then, a process occurs that generates the ketyl radical species and that then further formed the dihydroxyanthracene species, which undergoes the deprotection reaction along with a decarboxylation.



Scheme 2. The proposed photodeprotection mechanism of alcohols from Aqmoc-PPG in aqueous solutions. ^a

^a Letters below the structures are the corresponding labels used in the text. And the absorbance for the transient species detected from fs-TA and/or ns-TA spectra, and the Raman bands from ns-TR³ are given.

Conclusions

To conclude, the investigation here found that in THF-H₂O solvents, the ketyl radical species of is active intermediate deprotection. After and on the way to the dihydroxyanthraceneintermediate was formed from the ketyl radical, the deprotection of alcohols from the AQ-PPGs 1 and 2 occurred with the accompaniment of a decarboxylation. The release of the protected alcohol as well as the carbon dioxide might have potential applications as a probe and maybe useful in the photodynamic therapy area for suitably designed molecules.

Even though the ketyl radical species can be efficiently produced for **1** and **2** in IPA, no photorelease was observed for the two Aqmoc-PPG compounds under this solvent system. That is because the recombination reaction between the ketyl radical species and IPA radical

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competed effectively relative to the photodeprotection of **1** and **2**. This is also the case for the experimental fact that the photodeprotection product was detected for 1 and 2 in THF-H₂O while not in pure THF. In addition, the photodeprotection occurs more efficiently in a THF-KMOPS solution than in THF-H₂O for both1 and2. This is because the buffered solution facilitates the decarboxylation reaction as observed for ketoprofen PPGs.^[26] We note that studies on AQ-PPGs using the Age and Age-diol platforms that do not contain the ether group were reported to release the carbonyl group efficiently in methanol and the use of a buffered aqueous solution is not required which supports that the decarboxylation is likely involved in the Agmoc-PPG deprotection as well. It is noted that the photorelease occurs more efficiently for 2 than 1 under analogous experimental conditions (in both THF-H₂O and THF-KMOPS). This can be accounted for by the adenosine moiety in 2 being a more effective leaving moiety compared to that of galactose in 1, resulting from the less basic character of adenosine as the leaving group than galactose which makes it is easier to accept electrons and facilitate its cleavage, also the two electron-withdrawing hydroxyl groups attached can stabilize the O⁻ of the adenosine after cleavage.

The key intermediates related with photoredox reactions and photohydration reactions were not detected during the photodeprotection process for **1** and **2**,suggesting that the photodeprotection will not be effected by the photoredox process or the photohydration process.It is noted that photoredox and photohydration of AQs are respectively triggered by proton coupled electron transfer (PCET) and proton transfer (PT) via $\pi\pi^*$ configuration of the triplet states, while photodeprotection starts from HAT via $n\pi^*$ triplet in neutral aqueous conditions. The PCET, PT and HAT are general topics in photochemical and photobiological areas, therefore, this work supplies important information on the solvent-related configuration-controlled photochemical reactions of aromatic carbonyls.

Experimental Section

1 and **2** were made by utilizing procedures detailed in the literature¹³ and the synthesis route were shown in Scheme S1 and Scheme S2, respectively. For characterization of the samples prepared please see the ¹H NMR spectra displayed in Figure S1 and Figure S2.

A femtosecond regenerative amplified Ti:sapphire laser seeded by output from a 120 fs oscillator was utilized to do the fs-TA measurements. Around 5% of the generated amplified 800 nm output was used to prepare (using a CaF_2 crystal) the 320 nm to 700 nm whitelight continuum probe laser beam. One part of the probe passed through the sample (flowing through a 2 mm pathlength cuvette) that was also excited by a 267 nm pump beam. Ns-TA experiments were done with a commercial laser flash photolysis system employing 266 nm laser photoexcitation and a Xenon lamp probe. Sample solutions were prepared to have an absorbance of 1 at 266 nm and then utilized in the fs-TA and ns-TA measurements. Deionized water and spectroscopic quality acetonitrile (ACN) were utilized to prepare samples for the experiments in this study.

Ns-TR³ measurements were done with experimental methods and a system that used 266 nm pump photoexcitation and a 368.9 nm probe derived from the fourth harmonic (266 nm) of one Nd:YAG laser and the second harmonic (532 nm) second anti-Stokes hydrogen Raman-shifted laser line (368.9 nm) from a second Nd:YAG laser and a pulse delay generator

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was used to control the relative time delay between the two lasers. The pump pulse excited the sample to initiate the photochemical reactions and the probe pulse interrogated the sample and the transient species for the reaction of interest. Deionized water and spectroscopic quality acetonitrile (ACN) were utilized to prepare samples for the experiments in this study.

The DFT computations (B3LYP method with 6-311+G^{**} basis set) were performed to find structures for the ground state, triplet state, the RC, TS, and PC and the connecting reaction energy pathways Frequency computations (employing the same method and basis set) were performed to deduce the geometries were at local minima (no imaginary frequency). TD-B3LYP/6-311+G^{**} calculations were utilized to estimate the UV-vis spectra. The effect of solvent polarity was estimated by utilizing the integral equation formalism polarizable continuum model (IEFPCM) in ACN (ε = 35.688) on the gas-phase structures for the non-electrostatic terms and the radii us employed in the universal solvation model (SMD) developed by Truhlar and co-workers.²⁷ All of the preceding calculations utilized the Gaussian 03 program.²⁸

Supporting Information The synthetic route of compounds with the ¹H NMR spectra reactant and photoproduct species discussed in the text; fs-TA, ns-TA and ns-TR³ spectra for some of the interested intermediate species; DFT calculated electronic and Raman spectra, RC, TS and PC optimized geometries and the reaction energy pathway and Cartesian coordinates and energies for all calculated structures discussed in the text (PDF).

Keywords: Anthraquinone, Photolabile protecting groups, Time-resolved spectroscopy, DFT calculations

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