QUINONE METHIDES
Wiley Series of Reactive Intermediates in Chemistry and Biology

Steven E. Rokita, Series Editor

Quinone Methides
Edited by Steven E. Rokita
QUINONE METHIDES

Edited by

STEVEN E. ROKITA
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Most stable compounds and functional groups have benefited from numerous monographs and series devoted to their unique chemistry, and most biological materials and processes have received similar attention. Chemical and biological mechanisms have also been the subject of individual reviews and compilations. When reactive intermediates are given center stage, presentations often focus on the details and approaches of one discipline despite their common prominence in the primary literature of physical, theoretical, organic, inorganic, and biological disciplines. The *Wiley Series on Reactive Intermediates in Chemistry and Biology* is designed to supply a complementary perspective from current publications by focusing each volume on a specific reactive intermediate and endowing it with the broadest possible context and outlook. Individual volumes may serve to supplement an advanced course, sustain a special topics course, and provide a ready resource for the research community. Readers should feel equally reassured by reviews in their speciality, inspired by helpful updates in allied areas and intrigued by topics not yet familiar.

This series revels in the diversity of its perspectives and expertise. Where some books draw strength from their focused details, this series draws strength from the breadth of its presentations. The goal is to illustrate the widest possible range of literature that covers the subject of each volume. When appropriate, topics may span theoretical approaches for predicting reactivity, physical methods of analysis, strategies for generating intermediates, utility for chemical synthesis, applications in biochemistry and medicine, impact on the environmental, occurrence in biology, and more. Experimental systems used to explore these topics may be equally broad and range from simple models to complex arrays and mixtures such as those found in the final frontiers of cells, organisms, earth, and space.
Advances in chemistry and biology gain from a mutual synergy. As new methods are developed for one field, they are often rapidly adapted for application in the other. Biological transformations and pathways often inspire analogous development of new procedures in chemical synthesis, and likewise, chemical characterization and identification of transient intermediates often provide the foundation for understanding the biosynthesis and reactivity of many new biological materials. While individual chapters may draw from a single expertise, the range of contributions contained within each volume should collectively offer readers with a multidisciplinary analysis and exposure to the full range of activities in the field. As this series grows, individualized compilations may also be created through electronic access to highlight a particular approach or application across many volumes that together cover a variety of different reactive intermediates.

Interest in starting this series came easily, but the creation of each volume of this series required vision, hard work, enthusiasm, and persistence. I thank all of the contributors and editors who graciously accepted and will accept the challenge.

University of Maryland

STEVEN E. ROKITA
INTRODUCTION

The term “quinone methide” first appeared in literature in 1942 to describe the quinone analogue in which one of the carbonyl oxygens is replaced by a methylene group. Reactivity associated with such a species is typically greater than that of the parent quinone but more moderate than that of the corresponding quinodimethane in which both carbonyl oxygens are replaced by methylene groups. The single methylene substitution is still quite sufficient to create a highly transient intermediate or at least the perception of one, and this perception likely discouraged its initial study. Investigations were at first limited to polymerization and photochemistry. These topics have continued to develop and gain greater sophistication as the subtleties of quinone methides have been revealed. Despite approximately 1400 literature contributions and many reviews on quinone methides as of 2008, the current book is the first devoted to this fascinating and useful intermediate.

Most laboratories did not begin to recognize the widespread occurrence and potential applications of quinone methides until 20 years after its first report. Now, with an ever-increasing appreciation of the structural dependence of quinone methide reactivity, its use has become more frequent and diverse as illustrated by the topics covered in this volume. Their role in lignin formation was recognized as early as 1960. Soon after, the first stable quinone methide was discovered in the natural products taxodione and taxodone and offered a stark contrast to the expectation of its fleeting existence. Although the quinone methide derived from the food preservative 2,6-di-\textit{tert}-butyl-4-methylphenol was first characterized in 1963, its discovery as a product of oxidative metabolism was published 20 years later. Just prior to this, the concept of bioreductive alkylating agents was introduced to form quinone methide intermediates for treating hypoxic tumors. Both reductive and oxidative metabolisms form quinone
methides have since become a very important topic for quinone methides in drug design as well as drug safety.

Quinone methides are associated with sclerotization, the natural tanning process that stabilizes insect cuticle, as well as reactions of vitamin K and tocopherols including vitamin E. Quinone methides have also been integral to the design of many mechanism-based inactivators of enzymes, which has been adapted most recently to screen for catalytic activity within antibody libraries. Perhaps the field of organic synthesis has become the most frequent benefactor of quinone methides now that reliable methods are available for their generation and control. Of the various approaches for manipulating quinone methide reactivity, its complexation with transition metals remains the most remarkable. Finally, the reversibility of quinone methide reaction has established an excellent basis for polymer and dendrimer disassembly to the likely benefit of numerous processes in material science, biology, and medicine. My own laboratory has also been intrigued by this reversibility and in particular by its ability to extend the potential lifetime of electrophiles in biological systems.

My involvement in quinone methides arose very much by chance and was neither planned nor anticipated as typical of the serendipity associated with the pursuit of basic research. Interest has since been sustained by the intellectual challenges of this topic and the community of investigators sharing its exploration. What had once been left to the realm of physical and polymer chemists soon became the province of organic, medicinal, and theoretical chemists, biochemists, toxicologists, entomologists, biologists, and those involved in forestry and food sciences. The scientific literature is so vast that we struggle to remain current even in just the literature of our immediate disciplines, and yet innovation is often found in complementary perspectives and methodology. By assembling this collection of topics, I hope to entice readers already familiar with quinone methides to look beyond their typical focus and discover new inspiration and opportunities in allied areas. Concurrently, I hope that the range of topics and perspectives provides a comfortable entry for readers from a broad range of backgrounds and interests.

The volume has been created as a snapshot of significant activity on quinone methides and it neither attempts to cover the entire range of topics nor present comprehensive reviews on a subset of topics. A variety of excellent reviews have already been published on many of the interesting and important details. The authors of this volume embody the breadth of research involving quinone methides, and I am very much indebted to their dedication to this volume and the field in general. These authors along with many others past and present are responsible for our current understanding of quinone methides. I hope this volume will incite an even greater interest in quinone methides that in turn will merit further reviews and monographs in the future.
CONTRIBUTORS

Takuya Akiyama, Dairy Forage Research Center, USDA-Agricultural Research Service, Madison, WI, USA; and RIKEN Plant Science Center, Suehiro, Tsurumi, Yokohama, Kanagawa 230-0045, Japan

Stefan Böhmdorfer, Department of Chemistry, University of Natural Resources and Applied Life Sciences, Muthgasse 18, A-1190 Vienna, Austria

Judy L. Bolton, Department of Medicinal Chemistry and Pharmacognosy (M/C 781), College of Pharmacy, University of Illinois at Chicago, 833 S. Wood Street, Chicago, IL 60612-7231, USA

Filippo Doria, Department of Organic Chemistry, Pavia University, V. le Taramelli 10, 27100 Pavia, Italy

Rotem Erez, Department of Organic Chemistry, School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel Aviv University, Tel Aviv 69978, Israel

Mauro Freccero, Department of Organic Chemistry, Pavia University, V. le Taramelli 10, 27100 Pavia, Italy

Hoon Kim, Department of Biochemistry and Great Lakes Bioenergy Research Center, University of Wisconsin, Madison, WI, USA

Fachuang Lu, Department of Biochemistry and Great Lakes Bioenergy Research Center, University of Wisconsin, Madison, WI, USA

Matthew Lukeman, Department of Chemistry, Acadia University, Wolfville, Nova Scotia, Canada, B4P 2R6
David Milstein, Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

Stephen F. Nelsen, Department of Chemistry, University of Wisconsin, Madison, WI, USA

Liping Pettus, Department of Chemical Research and Discovery, Amgen Inc; Thousand Oaks CA 91320, USA

Thomas Pettus, Department of Chemistry and Biochemistry, University of California at Santa Barbara, Santa Barbara, CA 93106, USA

Elena Poverenov, Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

John Ralph, Department of Biochemistry and Great Lakes Bioenergy Research Center, University of Wisconsin, Madison, WI, USA; Department of Biological Systems Engineering, University of Wisconsin, Madison, WI, USA; and Dairy Forage Research Center, USDA-Agricultural Research Service, Madison, WI, USA

Michèle Reboud-Ravaux, Enzymologie Moléculaire et Fonctionnelle, FRE 2852, CNRS-Université Paris 6, T43, Institut Jacques Monod, 2 place Jussieu, 75251 Paris Cedex 05, France

Steven E. Rokita, Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 20742, USA

Thomas Rosenau, Department of Chemistry, University of Natural Resources and Applied Life Sciences, Muthgasse 18, A-1190 Vienna, Austria

Paul F. Schatz, Dairy Forage Research Center, USDA-Agricultural Research Service, Madison, WI, USA

Doron Shabat, Department of Organic Chemistry, School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel Aviv University, Tel Aviv 69978, Israel

Edward B. Skibo, Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ 85287-1604, USA

John A. Thompson, Department of Pharmaceutical Chemistry, School of Pharmacy, University of Colorado, Denver, C238-L15, 12631 E. 17th Avenue, Aurora, CO 80045, USA

Michel Wakselman, Institut Lavoisier de Versailles, UMR 8180, CNRS-Université Versailles Saint-Quentin, 45 Avenue des Etats Unis, F-78035 Versailles, France

Qibing Zhou, Department of Chemistry, Virginia Commonwealth University, 1001 West Main Street, Richmond, VA 23284-2006, USA
PHOTOCHEMICAL GENERATION AND CHARACTERIZATION OF QUINONE METHIDES

MATTHEW LUKEMAN
Department of Chemistry, Acadia University, Wolfville, Nova Scotia, Canada B4P 2R6

1.1 INTRODUCTION

Quinone methides (QMs) are reactive intermediates that are commonly encountered in many areas of chemistry and biology. Quinone methides contain a cyclohexadiene core with a carbonyl and a methylene unit attached and are related to quinones, which have two carbonyl groups, and quinone dimethides, which have two methylene groups. Quinone methides are highly polar and are much more reactive than their relatives. Ortho (1) and para (2) quinone methides are the most commonly encountered isomers, although meta-quinone methides (3), which are non-Kekulé and must be drawn as zwitterionic (3a) or biradical (3b) structures, are known as well. Both ortho- and para-quinone methides can also have zwitterionic resonance structures that give these species both cationic and anionic centers, emphasizing their polarized nature and indicating that they may react with both nucleophiles (similar to carbocations) and electrophiles (similar to phenolates). Quinone methides are much more reactive than simple enones (such as α,β-unsaturated ketones) since nucleophilic attack on a quinone methide produces an aromatic alcohol, with aromatization of the ring being a significant driving force (Scheme 1.1). Ortho-quinone methides can also readily engage in [4 + 2] cycloadditions with electron-rich dieneophiles to give chroman derivatives, again leading to rearomatization of the ring (Scheme 1.1). The reaction rates exhibited by quinone methides are highly
dependent on the substituents present; lifetimes can range from less than 1 ns to several seconds or minutes.

Quinone methides have been shown to be important intermediates in chemical synthesis,1,2 in lignin biosynthesis,3 and in the activity of antitumor and antibiotic agents.4 They react with many biologically relevant nucleophiles including alcohols,1 thiols,5–7 nucleic acids,8–10 proteins,6,11 and phosphodiesters.12 The reaction of nucleophiles with ortho- and para-quinone methides is pH dependent and can occur via either acid-catalyzed or uncatalyzed pathways.13–17 The electron transfer chemistry that is typical of the related quinones does not appear to play a role in the nucleophilic reactivity of QMs.18

Much attention has been devoted to the development of methods to generate quinone methides photochemically,1,19–20 since this provides temporal and spatial control over their formation (and subsequent reaction). In addition, the ability to photogenerate quinone methides enables their study using time-resolved absorption techniques (such as nanosecond laser flash photolysis (LFP)).21 This chapter covers the most important methods for the photogeneration of ortho-, meta-, and para-quinone methides. In addition, spectral and reactivity data are discussed for quinone methides that are characterized by LFP.

1.2 QUINONE METHIDES FROM BENZYLIC PHOTOELIMINATION

1.2.1 Photoelimination of Fluoride

Seiler and Wirz carried out one of the earliest systematic studies of the photochemistry of phenols containing benzylic subsitutents.22,23 They examined the photochemistry
of 11 trifluoromethyl-substituted phenols and naphthols and found that all isomers underwent photohydrolysis in neutral or basic aqueous solution to give the corresponding hydroxybenzoic acid, some with efficiencies as high as $\Phi = 0.8$ (Scheme 1.2). A detailed mechanistic investigation led them to propose a common reaction mechanism for all 11 isomers: C–F bond heterolysis takes place from the singlet excited state of the phenolate, generated by either direct excitation of the ground-state phenolate (at $pH > pK_a$) or following excited-state proton transfer (ESPT) of the excited phenol (at $pH < pK_a$) (Scheme 1.2). Ejection of the fluoride gives an $\alpha,\alpha$-difluoroquinone methide as the first formed ground-state intermediate. Because the mechanism is common to all 11 reactive starting materials, this reaction can be considered a source of ortho-, meta-, and para-quinone methides, as well as a variety of naphthoquinone methides. The authors were able to detect one such naphthoquinone methide (4) using LFP and found that it absorbs light strongly in the 500–550 nm region and decays with a lifetime of 5 $\mu$s in phosphate buffer (pH 6.8). Although this work demonstrated for the first time that quinone methides can be efficiently photogenerated from phenols containing suitable benzylic substituents, the generality of this reaction would not be recognized until many years later.

### 1.2.2 Photodehydration

Phenols containing benzyl alcohol side groups are much more accessible than the trifluoromethyl derivatives studied by Wirz, and their photochemistry has been studied extensively, beginning in the 1970s. Hamai and Kokubun$^{24,25}$ observed that solutions of 5 and 6 in hexane became highly colored when exposed to UV light due to their conversion to the corresponding $\alpha,\alpha$-diphenylquinone methides (ortho-fuchsons) 7 and 8 (Eq. 1.1). The mechanism of this reaction was not investigated, although the ortho arrangement of the phenol and the benzylic alcohol would permit excited-state
intramolecular proton transfer (ESIPT) from the phenol OH to the benzyl alcohol via a six-membered transition state, facilitating the departure of the molecule of water. Methoxyfuchsone 8 was detected by UV–Vis spectroscopy and showed broad absorption bands at \(~340\) and \(420\) nm, which tailed off at \(600\) nm.

The photochemistry of the related para-hydroxytriphenylmethanols was first examined by Gomberg in 1913. White powdered samples of 9 became yellow in color following exposure to sunlight, which was proposed to be due to dehydration to fuchsone 12 (Eq. 1.2). The photoreaction was revisited in the late 1970s by Lewis and coworkers, who introduced related derivatives 10 and 11 to the study, which also undergo photodehydration to give the corresponding fuchsones 13 and 14 in the solid state. While direct ESIPT between the phenol and benzyl alcohol within a given molecule is not possible in the solid state due to the large distance between these groups, X-ray crystal structures revealed that each phenolic OH is aligned with the benzyl alcohol moiety of an adjacent molecule. One possible pathway for this reaction, then, is excited-state proton transfer (ESPT) from an excited phenol to the benzyl alcohol of its neighbor, thus facilitating the dehydration reaction.

Peter Wan was the first to investigate the photochemistry of hydroxybenzyl alcohols in a systematic way, and his work has established the foundation of our current understanding of their behavior. His work in this area began in 1986 when he investigated the photochemistry of ortho- and meta-hydroxybenzyl alcohol (15 and 16, respectively), along with several methoxybenzyl alcohols. When irradiated in aqueous methanol, both 15 and 16 underwent conversion to the corresponding hydroxybenzyl ethers 17 and 18, presumably via ortho- and meta-quinone methides 1 and 3, although these were not detected in this work (Eq. 1.3). The reaction quantum yield for ortho derivative 15 was found to be much higher than that of the meta isomer. A mechanism was suggested that accounts for this difference: for 15, excitation
initiates an ESIPT from the phenol to the benzyl alcohol, which is facilitated by the presence of a hydrogen bond between these groups in the ground state, which loses water to give the quinone methide (Scheme 1.3). This intramolecular hydrogen bond is not present in the ground state for meta isomer 16, and so this mechanism is not available to it leading to its lower efficiency. It was demonstrated in a subsequent paper that ortho-quinone methide 1 can also be photogenerated from 15 in alkaline solution, indicating that the phenolic OH is not necessarily a requirement for these reactions to take place. Wan and coworkers were later successful in detecting quinone methide 1 generated by photolysis of 15 using LFP. A broad absorption centered at 400 nm was obtained, although the spectrum was partially obscured by the simultaneous photogeneration of the phenoxy radical of 15, which absorbs in the same region.

Almost a decade later, Wan greatly expanded his investigation into the photochemistry of hydroxybenzyl alcohols by examining 15 and 16 in more detail and adding derivatives 19–23. All hydroxybenzyl alcohols examined gave quinone methides on irradiation in aqueous solution, as evidenced by their trapping either as $4 + 2$ cycloaddition chroman adducts with dienophiles (for ortho-quinone methides) or as their methyl ethers (via nucleophilic attack by solvent). The quantum yields observed for the ortho derivatives 15 and 19 were the highest, followed by the meta derivatives 16, 20, and 21, and with para derivatives 22 and 23 reacting with the lowest efficiency (Table 1.1). Several of these derivatives were examined by LFP in an

| Table 1.1 Quantum Yields of Photomethanolysis for Selected Hydroxybenzyl Alcohol Substrates |
|---------------------------------|-------|
| Substrate          | $\Phi_R$ (in 1:1 CH$_3$OH–H$_2$O) |
| 15                | 0.23  |
| 16                | 0.12  |
| 19                | 0.46  |
| 20                | 0.23  |
| 22                | 0.007 |
| 23                | 0.1   |
attempt to detect the suspected quinone methide intermediates. All of the \(\alpha\)-phenyl derivatives (19–21, 23) gave strongly absorbing transients in aqueous acetonitrile in the 300–600 nm region that showed quenching behavior characteristic of quinone methides. The spectra for the mono-\(\alpha\)-phenyl quinone methides 24 (from 19), 25 (from 20), and 26 (from 23) are shown in Fig. 1.1. Ortho- and para-quinone methides 24 and 26 were very long lived in aqueous acetonitrile, showing lifetimes longer than 5 s, while meta-quinone methide 25 decayed significantly faster with a lifetime of \(~30\) ns in the same solvent system, suggesting that its reactivity might be more closely related to that of benzylic cations.

\[
\begin{align*}
&\text{OH} \quad \text{Ph} \\
&\text{OH} \\
&\text{19} \\
&\text{HO} \quad \text{Ph} \\
&\text{20} R_1 = \text{H}, R_2 = \text{Ph} \\
&\text{21} R_1 = \text{Ph}, R_2 = \text{Ph} \\
&\text{22} R = \text{H} \\
&\text{23} R = \text{Ph} \\
&\text{OH} \\
&\text{24} o\text{-QM} \\
&\text{25} m\text{-QM} \\
&\text{26} p\text{-QM} \\
\end{align*}
\]

\(\Delta \text{OD vs. Wavelength (nm)}\)

**FIGURE 1.1** Absorption spectra of 24 (○), 25 (▲), and 26 (□) obtained by LFP of hydroxybenzyl alcohols 19, 20, and 23, respectively, in aqueous acetonitrile. **Source:** Data taken with permission from Ref. [31].
Wan’s group showed that the observed photodehydration of hydroxybenzyl alcohols can be extended to several other chromophores as well, giving rise to many new types of quinone methides. For example, he has shown that a variety of biphenyl quinone methides can be photogenerated from the appropriate biaryl hydroxybenzyl alcohols.\textsuperscript{32,33} Isomeric biaryls 27–29 each have the benzylic moiety on the ring that does not contain the phenol, yet all were found to efficiently give rise to the corresponding quinone methides (30–32) (Eqs. 1.4–1.6). Quinone methides 31 and 32 were detected via LFP and showed absorption maxima of 570 and 525 nm, respectively (in 100% water, Table 1.2). Quinone methide 30 was too short lived to be detected by LFP, but was implicated by formation of product 33 that would arise from electrocyclic ring closure of 30 (Eq. 1.4).

![Diagram](image)

This concept was then extended to bulkier biaryl systems containing naphthalene rings.\textsuperscript{34,35} Biaryls 34–36 were all observed to undergo photochemically

### TABLE 1.2 Absorption and Lifetime (1/k) Data for Selected Quinone Methides

<table>
<thead>
<tr>
<th>Quinone Methide</th>
<th>Solvent</th>
<th>( \lambda_{\text{max}} ) (nm)</th>
<th>( \tau )</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>Aq. CH(_3)CN</td>
<td>350, 460</td>
<td>&gt;5 s</td>
</tr>
<tr>
<td>25</td>
<td>Aq. CH(_3)CN</td>
<td>445</td>
<td>30 ns</td>
</tr>
<tr>
<td>26</td>
<td>Aq. CH(_3)CN</td>
<td>360</td>
<td>&gt;5 s</td>
</tr>
<tr>
<td>31</td>
<td>H(_2)O</td>
<td>570</td>
<td>400 ns</td>
</tr>
<tr>
<td>32</td>
<td>H(_2)O</td>
<td>525</td>
<td>67 ( \mu )s</td>
</tr>
<tr>
<td>42</td>
<td>Cyclohexane</td>
<td>560</td>
<td>5 ( \mu )s</td>
</tr>
<tr>
<td>43</td>
<td>Aq. CH(_3)CN</td>
<td>360, 580</td>
<td>230 ( \mu )s</td>
</tr>
<tr>
<td>44</td>
<td>TFE</td>
<td>420</td>
<td>8.5 ( \mu )s</td>
</tr>
<tr>
<td>45</td>
<td>Aq. CH(_3)CN</td>
<td>330, 425, 700</td>
<td>30 ( \mu )s</td>
</tr>
<tr>
<td>48</td>
<td>Aq. CH(_3)CN</td>
<td>450</td>
<td>5–10 s</td>
</tr>
<tr>
<td>52</td>
<td>Aq. CH(_3)CN</td>
<td>410, 700</td>
<td>34 ( \mu )s</td>
</tr>
</tbody>
</table>
induced dehydration and cyclization to go from the highly twisted biaryl starting materials to the (more) planar diarylpyrans 37–39 via biaryl quinone methides 40–42 (Eqs. [1.7–1.9]). These quinone methides were not detectable by LFP in aqueous acetonitrile, presumably because electrocyclic ring closure is very rapid since it regenerates two aromatic rings in all cases (and might relieve some steric congestion). However, Burnham and Schuster36 observed a transient absorption ranging from 520 to 620 nm and centered at 560 nm, with a lifetime of 5.02 µs when examining 36 by LFP in cyclohexane. They assign the absorption to quinone methide 42. Under the different experimental conditions of Burnham and Schuster, it is possible that some of the intermediate exists as the transoid form 42b, which cannot readily cyclize to 39 and hence would be expected to persist for longer periods of time.

Wan’s group investigated a number of phenyl-substituted hydroxybiphenylbenzyl alcohols in the hope that the α-phenyl quinone methides photogenerated from them might show enhanced absorption and lifetimes, and thus be easier to characterize by LFP.37,38 They were successfully able to photogenerate and characterize quinone
methides 43–45 by LFP, and their absorption maxima and lifetimes (in 50% v/v aqueous acetonitrile) are presented in Table 1.2.

Hydroxy-9-fluorenols 46 and 47 have been similarly shown to undergo photodehydration in aqueous solution to give the corresponding fluorenylquinone methides 48 and 49 (Eqs. 1.10 and 1.11). 49 was very reactive and not observable by LFP (presumably because its reaction regenerates two aromatic rings); however 48 was much more persistent, having a lifetime in the 5–10 s range, and was observable using a conventional UV–Vis spectrometer ($\lambda_{\text{max}} = 450 \text{ nm}$). Formation of 48 was further confirmed by the isolation of its $4 + 2$ cycloaddition products with ethyl vinyl ether (EVE).

Wan also studied hydroxybenzyl alcohols based on the naphthalene chromophore. 50 Naphthols 50 and 51 were both examined for their ability to photogenerate naphthoquinone methides 52 and 53, respectively (Eqs. 1.12 and 1.13). While 50 underwent very efficient photosolvolysis, presumably via naphthoquinone methide 52, 51 was essentially unreactive when exposed to light. The inability of 51 to photogenerate 53 is a rare example where the generality of the photodehydration of benzyl alcohols fails. LFP of 50 yielded a very strong visible absorption ($\lambda_{\text{max}} = 410$ and 700 nm) that decayed in aqueous acetonitrile with a lifetime of 34 μs (Fig. 1.2). This transient was assigned to naphthoquinone methide 52 due in part to its efficient quenching when the nucleophilic ethanolamine was added.
Through these works, Wan has conclusively demonstrated that the photodehydration of hydroxybenzyl alcohols is a general reaction, and a wide variety of quinone methides can be photogenerated and detected using this method. Quinone methide photogeneration via this method has been shown to have importance in the photochemistry of Vitamin B$_6$\textsuperscript{41,42} and in model lignins.\textsuperscript{43}

### 1.2.3 Photoelimination of Quaternary Ammonium Salts

Saito and coworkers showed that a variety of ortho-quinone methides can be photogenerated from the Mannich bases of phenols and naphthols.\textsuperscript{44} For example, irradiation of 54 gives ortho-quinone methide 55, as evidenced by the isolation of the cycloaddition trapping product 56 (Eq. 1.14). Although quantum yields were not reported, the yields of quinone methides appeared to be much higher from the Mannich bases than from the analogous benzyl alcohols. The proposed mechanism involves initial adiabatic ESIPT from the phenol OH to the nitrogen to generate the singlet excited dialkylammonium zwitterion, which then undergoes loss of the neutral amine to generate the ortho-quinone methide (Scheme 1.4). Direct excitation of the ground-state phenolate did not lead to quinone methide formation, presumably because the nitrogen needs to be protonated by the phenolic OH prior to its departure.

\[
\text{Ph} \text{OH} \text{NMe}_2 \xrightarrow{h\nu} \text{Ph} \text{O} \xrightarrow{EVE} \text{Ph} \text{OEt} 
\]

In one example described in the paper,\textsuperscript{44} irradiation of biphenol 57 in the presence of EVE gives the bisquinone methide–EVE adduct 58 in 22% yield (Eq. 1.15). The