Quinone methide intermediates in organic photochemistry*

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Abstract: Quinone methides are widely encountered reactive intermediates in the chemistry of phenols and related compounds. This paper summarizes our recent progress in uncovering new and general photochemical methods for forming quinone methides of various structural types in aqueous solution. Their mechanism of formation and subsequent chemistry are also discussed. New examples of excited-state intramolecular proton transfer (ESIPT) have been uncovered in these studies. We have also discovered that appropriately designed biphenyls and terphenyls display photochemistry that is best rationalized by highly polarized and planar excited states of these ring systems, which can efficiently lead to the corresponding *extended* quinone methides.

INTRODUCTION

Quinone methides (QMs; **1** and **2**) are widely occurring reactive intermediates in the chemistry of phenols and related compounds [1–3]. They are believed to be fundamental intermediates in the bioformation of lignin as well as critical intermediates in the mechanism of action of many anticancer drugs [1–3]. QMs are structurally related to benzoquinones with one of the carbonyl oxygens replaced by a methylene group. This structural change makes them much more reactive, particularly with respect to nucleophiles as the QM is now quite polarized: simple nucleophilic attack at the methylene carbon returns them to aromatic phenols, gaining an aromatic system in turn. Formal [4+2] cycloaddition chemistry of *o*-QMs with electron-rich alkenes provides access to chroman derivatives [1]. In thermal chemistry, the *ortho* and *para*-QMs (**1** and **2**) are the most common isomers although the *meta*-QM (**3**)—which is an example of a non-Kekulé molecule—has generated theoretical interest [4]. More examples of *meta*-QMs (and related non-Kekulé molecules) are now accessible via photochemical routes to be disclosed below. Our work on QM photogeneration is centered on using phenol derivatives as substrates. It is well-known that phenols are much more acidic in S_1 ($pK_a \approx 4$) than in S_0 ($pK_a \approx 10$). Moreover, it is known that water is sufficiently polar to mediate the dissociation of excited-state phenols during the lifetime of the singlet state (which is typically in the 1–10 ns range for these aromatics).
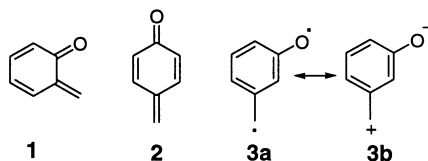

1 **2** **3a** **3b**

Dissociation of the phenolic proton in S_1 leads to an excited-state phenolate ion (adiabatic deprotonation). Such excited-state phenolates have their negative charge strongly delocalized into the aromatic system. It is this electron donation that provides the driving force for subsequent chemistry such as heterolytic cleavage of a benzylic C–OH bond required for QM formation. Zimmerman's "*ortho-meta effect*" [5] in the photosolvolytic chemistry of substituted benzylic substrates controls the relative reactivity of the various isomers; it is the anticipated enhanced reactivity of the *meta*-isomers that naturally leads to the efficient formation of non-Kekulé isomers.

PARENT QUINONE METHIDES

Previous workers such as Wirz and others [6] have shown that photolysis of phenols with labile benzylic substituents and other benzenoid derivatives leads to QMs. Based on our work on the photosolvolysis of methoxy-substituted benzyl alcohols and related compounds, we hypothesized that the corresponding hydroxy-substituted benzyl alcohols (phenols) could react to give QMs that would offer an explanation for their high photosolvolytic reactivity [7]. Indeed, photolysis of all the isomeric phenols **4**–**6** gave the corresponding QMs, via formal loss of water [7,8]. Photolysis of **4** in the presence of ethyl vinyl ether or dihydropyran gave the corresponding [4+2] chroman adducts (**7** and **8**, respectively) in high yield consistent with efficient photogeneration of an *ortho*-QM. Nanosecond laser flash photolysis (LFP) showed formation of strong transients (λ_{max} = 350–450 nm) identifiable as the corresponding QMs. The *o*- and *p*-QMs were very long-lived (lifetime > 1 ms) while the *m*-QM **9** had a much shorter lifetime of 30 ns, consistent with its non-Kekulé structure. This method appears to be general as many derivatives have now been shown to react this way. Moreover, the starting materials are readily available preparatively, via simple $NaBH_4$ reduction of the corresponding ketones or via a Grignard reaction.
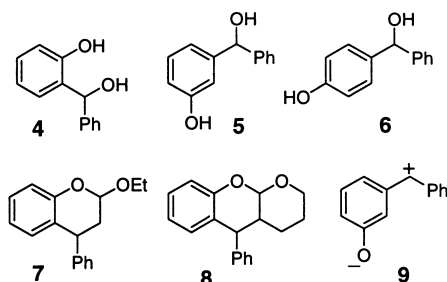

Another general method uncovered for QM photogeneration is via formal excited-state intramolecular proton transfer (ESIPT) in hydroxy-substituted styrenes in aqueous solution [9]. Kalanderopoulos and Yates [10] were the first to show that *o*-hydroxystyrenes **10** photohydrated efficiently to the corresponding Markovnikov alcohol, via ESIPT, to generate an intermediate that had a QM structure. We have now shown [11] that QMs are indeed formed (by LFP) and that the ESIPT does not appear to be assisted by solvent water. Moreover, the method is *general* for all the isomeric hydroxystyrenes (e.g., **11** and **12**) [9]. That is, photolysis of **11** or **12** resulted in efficient photohydration, via observable QMs (LFP), whereas the corresponding methoxy compounds were much less reactive, if at all. Additionally, based on fluorescence quenching data and water-concentration effect on LFP signal, we proposed that the formal ESIPT for the *meta* isomer **13** occurred via mediation of three water molecules, to give **14** within the laser pulse. This is a new type of solvent-assisted formal ESIPT, between *meta* positions on a benzene ring, and is in good accord with Zimmerman's "*ortho-meta effect*" [5] described above. Additional derivatives of **13** have now been studied and shown to react in a similar way. In other work on benzenoid-type systems, we have shown that photolysis (in aqueous solution) of pyridoxine (vitamin B_6), which has the requisite functionality for QM photogeneration; indeed, forms the corresponding QM, as evidenced by trapping with ethyl vinyl ether, methanol, and LFP studies [12].
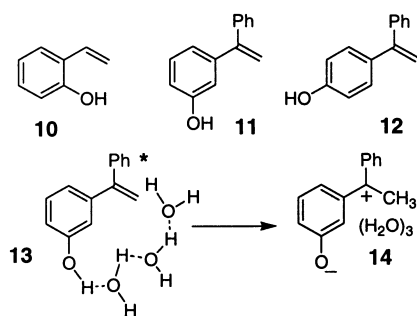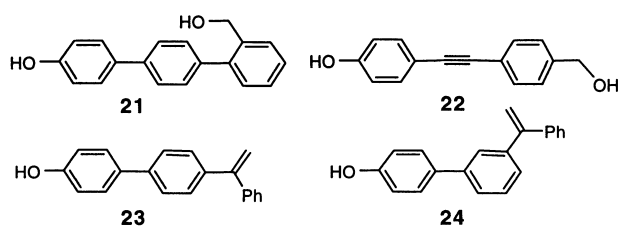
The biological impact of QM formation on exposure of pyridoxine to UV light remains to be investigated.

BIARYL AND TERPHENYL QUINONE METHIDES

Our first hint that biaryl-type QMs can be photogenerated in a general fashion was provided by our study of the photocycloaddition of 2-(2′-hydroxyphenyl)benzyl alcohol [13]. This study has now been extended [14] to a variety of biaryl substrates including a 1,1′-bisnaphthalene **15** which on photolysis gave the ring closed pyran **17** via the proposed naphthoquinone methide **16**. The reaction is photochromic: **15** does not absorb above 350 nm, whereas **16** has a λ_{max} = 355 nm. The photostationary state between **15** and **17** can be altered by changing the excitation wavelength. QM **16** was not observable by LFP, presumably due to the fast electrocyclic ring closure pathway open to this species, to give **17**. We have now studied biphenyl derivatives with the required functionalities for QM photogeneration but in which the QMs cannot undergo electrocyclic ring closure [15]. These biaryl alcohols do indeed give rise to long-wavelength transients that are assignable to biphenyl QMs. For example, LFP studies of biphenyl alcohol **18** gave a broadly absorbing transient with λ_{max} = 570 nm (τ = 0.40 μs) assigned to biphenyl QM **19**. Consistent with this assignment was the fact that methyl ether **20** was isolated in high yield when photolyzed in 1:1 H_2O–MeOH (Φ = 0.24).
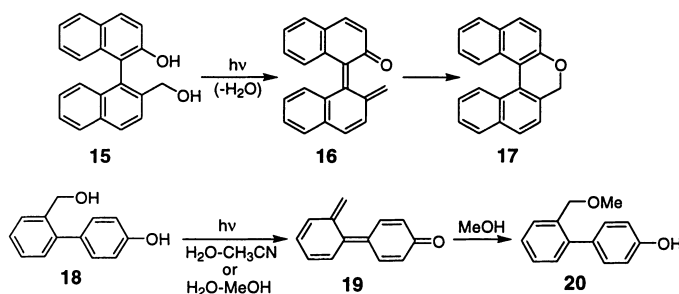

Using successive Suzuki-type coupling methodology, we have embarked on the synthesis of a variety of other biaryl and terphenyl derivatives which are capable of giving rise to QMs on photolysis. The high reactivity displayed by biaryls and biphenyls studied to date is no doubt due to the tendency for the excited states of these species to planarize. This is readily rationalized by examination of HOMO and LUMO coefficients for the π systems of these molecules. When substituted with a highly electron donating group such as a phenolate ion, one can expect the excited state to be both planar *and* highly polarized. These are requisite for the kind of chemistry required for forming QMs. We have synthesized terphenyl alcohol **21** and related compounds and shown that it undergoes photosolvolytic chemistry consistent with a terphenyl QM intermediate [16]. However, we have been unable to detect any transients assignable to QMs, suggesting that terphenyl QMs are too short-lived for detection by nanosec-

ond LFP. The lifetime of the biphenyl QM **19** was 0.40 μs in water. Extending this biphenyl QM to the terphenyl analog should reduce its lifetime (i.e., more reactive), perhaps by an order of magnitude or more. Such a reduction in lifetime (to less than 40 ns) would make such species undetectable by our laser system. We have also investigated using an "alkyne spacer" in place of the middle benzene ring in the terphenyl system, to see if charge transfer can be induced through the alkyne moiety. However, photolysis of **22** (in 1:1 H_2O–MeOH) gave only products derived from photoprotonation of the alkyne moiety. This seems to eliminate the use of such spacers although it may work for more reactive systems that we have not yet studied or uncovered.

Extension of the new type of formal ESIPT in the hydroxystyrenes described above to biphenyl versions has now been achieved [17]. Thus, biphenylalkenes **23** and **24** have been successfully synthesized, along with a variety of related compounds such as the corresponding methoxy analogs and simple nonsubstituted systems, to test for reactivity via QMs and perhaps long range formal ESIPT. Both **23** and **24** were found to photohydrate efficiently and to be more reactive than the corresponding methoxy analog. The fluorescence emission of both was found to be highly sensitive to water content suggesting operation of a formal ESIPT process in the photohydration mechanism. LFP studies in aqueous solution gave a transient assignable to a biphenyl QM for **23** but no signals were observed for **24** consistent with a much shorter-lived QM species for this isomer (which would give rise to a non-Kekulé QM derivative).

We have recently discovered that a simple biphenyl derivative, 2-phenylphenol (**25**) can undergo ESIPT, to generate a QM intermediate [18]. Photolysis of **25** (after deuterium exchange of the phenolic proton in D_2O–CH_3CN) gave almost exclusively deuterium incorporation at the 2-position on the other benzene ring (to give **27**; $\Phi \approx 0.02$), with a minor amount of incorporation at the 4-position (also on the other benzene ring). Only incorporation to the 2-position (to give **27**) was observed on photolysis in neat MeOD and in the solid state (after exchange of the phenol OH to OD prior to photolysis). A similar reaction was observed for 2,2′-di-hydroxybiphenyl but not with 3-phenyl-phenol, 4-phenylphenol or any of the methoxy analogs of the above compounds. A plot of % deuterium incorporation at the 2-(*ortho*) and 4-(*para*) positions (measured globally by ^{1}H (360 MHz) NMR) versus D_2O content in CH_3CN is shown in Fig. 1. The very fast increase in yield for exchange at the 2-position is consistent with exchange of the phenol OH with added D_2O. Once all such protons have been exchanged to OD, the yield of deuterium incorporation at the 2-position remains constant with increasing D_2O content. Deuterium incorporation at the 4-position, however, appears to require the presence of water. These observations are consistent with a mechanism in which the exchange at the 2-position involves ESIPT, from the phenol to the alkene carbon at the 2-position, to generate QM **26**. This is the first example of an ESIPT involving proton transfer to an aromatic ring carbon and opens up exploring such types of reactions in related compounds.
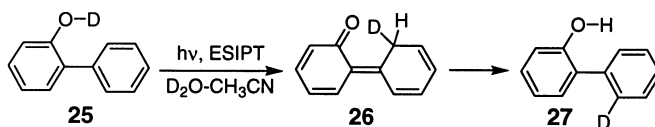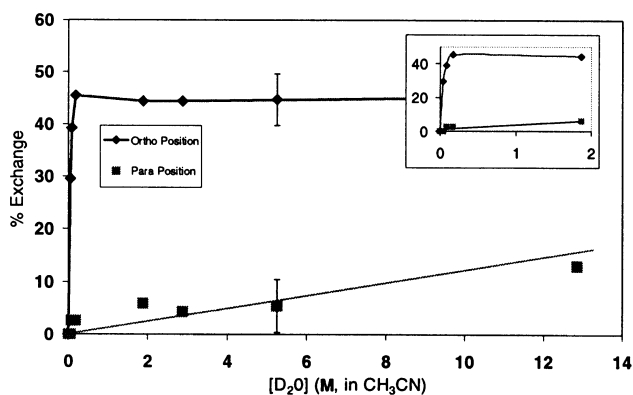
Fig. 1 Plot of % deuterium incorporation in 2-phenylphenol (**25**, unexchanged ArOH compound) vs. D_2O content (inset: expanded region at low D_2O concentration).

ACKNOWLEDGMENTS

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