Quinone Methide Intermediates from the Photolysis of Hydroxybenzyl Alcohols in Aqueous Solution

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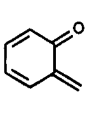
o- and *p*-quinone methides (QMs, **1** and **2**, respectively) are intermediates of relevance in a variety of areas. *o*-QMs are widely used in organic synthesis, in particular for carrying out "reverse electron demand" Diels–Alder [4 + 2] cycloadditions with electron rich alkenes, to give chroman derivatives.[1] *p*-QMs have also been used in synthesis,[2] notably by Angle and co-workers.[2a,b] Although little quantitative reactivity data are available, *o*- and *p*-QMs are known to be powerful electrophiles[3] and are believed to have widespread occurrence as intermediates in biochemical transformations. For example, the mode of action of some important anticancer drugs and the biological toxicity of some chemicals have been explained in terms of the electrophilic character of QMs.[4] *p*-QMs are also relevant intermediates in lignin chemistry.[5] *m*-QMs (**3**), of which several forms may be envisioned including the non-Kekulé form **3c**, are less widely known. A *m*-naphthoquinone methide as well as the parent **3** have received considerable theoretical and experimental study.[6] Most of the methods reported to date for generating *o*- and *p*-QMs involve high-temperature thermolysis and/or use of highly derivatized or structurally complex precursors.[1–3,6,7] Although isolated reports of the photogeneration of *o*-QMs have appeared,[8] we now report a simple and general method for photogenerating all three isomers of QM (**1**–**3**).

The method involves photolysis of readily available hydroxy-substituted benzyl alcohols **4**–**10** in aqueous solution. We[8a,b] and others[8e,j] have suggested the possibility that photolysis of *o*-hydroxybenzyl alcohols[8a,b,e] or their methyl ethers[8j] leads to the corresponding *o*-QM. We now offer compelling evidence that *o*-QMs are indeed formed as intermediates from *o*-hydroxybenzyl alcohol precursors with high quantum efficiency.



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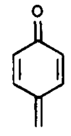

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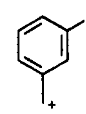

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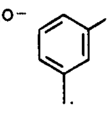

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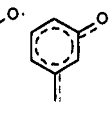
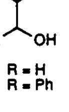
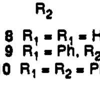


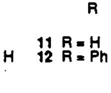
3c



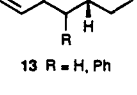
6 R = H
7 R = Ph



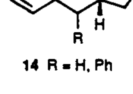
8 R₁ = R₁ = H
9 R₁ = Ph, R₂ = H
10 R₁ = R₂ = Ph



11 R = H
12 R = Ph

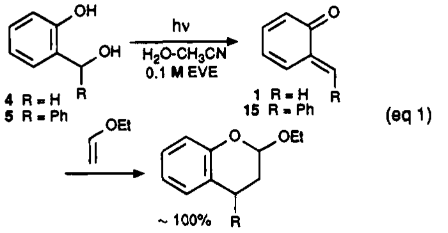


13 R = H, Ph



14 R = H, Ph

Photolysis of **4** and **5** (10^{-3} M; Rayonet photoreactor; 254 nm; ~15 °C; argon) in 1:1 MeOH–H_2O gave the corresponding methyl ethers cleanly in low-conversion experiments (<20%), with $\Phi = 0.23$ and 0.46, respectively. The corresponding methoxy derivatives of **4** and **5** (i.e., **11** and **12**) reacted with much lower efficiency ($\Phi < 0.1$). Photolysis of **4** and **5** in 1:1 H_2O–CH_3CN with 0.1 M ethyl vinyl ether (EVE) gave the corresponding [4 + 2] cycloaddition products (regioselectively) in quantitative yield (eq 1). High-field ^{1}H NMR showed that the adduct from **5** is predominantly (>90%) the *trans* diastereomer. Photolysis in the presence of dihydropyran or dihydrofuran gave the corresponding chroman adducts **13** and **14** (>90%), with preference for the *trans* diastereomer when **5** was used. The isolation of these chroman systems is consistent with formation of *o*-QM intermediates on photolysis of **4** and **5**.



(eq 1)

Nanosecond laser flash photolysis (LFP; 266 nm; YAG laser; <35 mJ; 20 °C) of flowing solutions of **5** in 1:1 H_2O–CH_3CN (pH 7) gave a long-lived and strongly absorbing species (λ_{max} = 345, 450 nm; τ = 5–10 s)[9] (Figure 1) which was unaffected by oxygen but whose lifetime was shortened by addition of ethanolamine (as nucleophile) or EVE, with decay rates independent of λ. LFP of **5** in 100% CH_3CN gave much weaker signals; LFP of **11** and **12** in 1:1 H_2O–CH_3CN failed to give any signal.[10] For **5**, addition of H_2O to CH_3CN resulted in an increase in signal intensity. LFP in acidic pH resulted in diminishing signal intensity, with complete loss of signal below

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(1) Some representative and leading references: (a) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651. (b) Boger, D. L.; Weinreb, S. N. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. (c) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; Wiley: New York, 1990. (d) Chambers, J. D.; Crawford, J.; Williams, H. W. R.; Dufresne, C.; Scheigetz, J.; Bernstein, M. A.; Lau, C. K. *Can. J. Chem.* **1992**, *70*, 1717.

(2) (a) Angle, S. R.; Arnaiz, D. O.; Boyce, J. P.; Frutos, R. P.; Louie, M. S.; Mattson-Arnaiz, H. L.; Rainier, J. D.; Turnbull, K. D.; Yang, W. *J. Org. Chem.* **1994**, *59*, 6322. (b) Angle, S. R.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5937. (c) Roper, J. M.; Everly, C. R. *J. Org. Chem.* **1988**, *53*, 2639. (d) Scanner, M. A.; Stansberry, M.; Weigelt, C.; Michne, W. F. *Tetrahedron Lett.* **1992**, 5287.

(3) (a) Turner, A. B. *Q. Rev.* **1964**, *28*, 347. (b) Wagner, H.-U.; Gompper, R. In *The Chemistry of the Quinonoid Compounds*; Patai, S., Ed.; Wiley: New York, 1974; Part 2. (c) Grünanger, P. In *Houben-Weyl Methoden der Organischen Chemie*; Müller, E., Bayer, O., Eds.; G. Thieme Verlag: Stuttgard, 1979; Vol. VII/3b, pp 395–521. (d) Karabelas, K.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 5372.

(4) (a) Boger, D. L.; Nishi, T.; Teegarden, B. R. *J. Org. Chem.* **1994**, *59*, 4943. (b) Chatterjee, M.; Rokita, S. E. *J. Am. Chem. Soc.* **1994**, *116*, 1690. (c) Skibo, E. B. *J. Org. Chem.* **1992**, *57*, 5874. (d) Nicolaou, K. C.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 8908. (e) Bolton, J. L.; Sevestre, H.; Ibe, B. O.; Thompson, J. A. *Chem. Res. Toxicol.* **1990**, *3*, 65.

(5) (a) Shevchenko, S. M.; Apushkinskii, A. G. *Russ. Chem. Rev.* **1992**, *61*, 105. (b) Leary, G. J. *Wood Sci. Technol.* **1980**, *14*, 21.

(6) (a) Goodman, J. L.; Khan, M. I. *J. Am. Chem. Soc.* **1994**, *116*, 10342. (b) Goodman, J. L.; Peters, K. S.; Lahti, P. M.; Berson, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 276. (c) Rule, M.; Matlin, A. R.; Hilinski, E. F.; Dougherty, D. A.; Berson, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 5098. (d) Rule, M.; Matlin, A. R.; Seeger, D. E.; Hilinski, E. F.; Dougherty, D. A., Berson, J. A. *Tetrahedron* **1982**, *38*, 787.

(7) Representative examples: (a) Katritzky, A. R.; Lan, X. *Synthesis* **1992**, 761. (b) Letulle, M.; Guenot, P.; Ripoll, J.-L. *Tetrahedron Lett.* **1991**, *32*, 2013. (c) Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1990**, *112*, 5341. (d) Loubinoux, B.; Miazimbakana, J.; Gerardin, P. *Tetrahedron Lett.* **1989**, *30*, 1939. (e) Talley, J. J. *J. Org. Chem.* **1985**, *50*, 1695. (f) Arduini, A.; Bosi, A.; Pochini, A.; Ungaro, R. *Tetrahedron* **1985**, *41*, 3095. (g) Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3672. (h) Casnati, G.; Pochini, A.; Terenghi, M. G.; Ungaro, R. *J. Org. Chem.* **1983**, *48*, 3783.

(8) (a) Wan, P.; Chak, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1751. (b) Wan, P.; Hennig, D. *J. Chem. Soc., Chem. Commun.* **1987**, 939. (c) Uchida, M.; Irie, M. *Chem. Lett.* **1991**, 2159. (d) Kalanderopoulos, P.; Yates, K. *J. Am. Chem. Soc.* **1986**, *108*, 6290. (e) Hamai, S.; Kokubun, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2085. (f) Padwa, A.; Lee, G. A. *J. Chem. Soc., Chem. Commun.* **1972**, 795. (g) Chapman, O. L.; McIntosh, C. L. *J. Chem. Soc., Chem. Commun.* **1971**, 383. (h) Lenoble, C.; Becker, R. S. *J. Photochem.* **1986**, *33*, 187. (i) Climent, M. J.; Garcia, H.; Miranda, M. A.; Primo, J. *Tetrahedron* **1987**, *43*, 999. (j) Padwa, A.; Dehm, D.; Oine, T.; Lee, G. A. *J. Am. Chem. Soc.* **1975**, *97*, 1837. (k) Oude-Alink, B. A. M.; Chan, A. W. K.; Gutsche, C. D. *J. Org. Chem.* **1973**, *38*, 1993.

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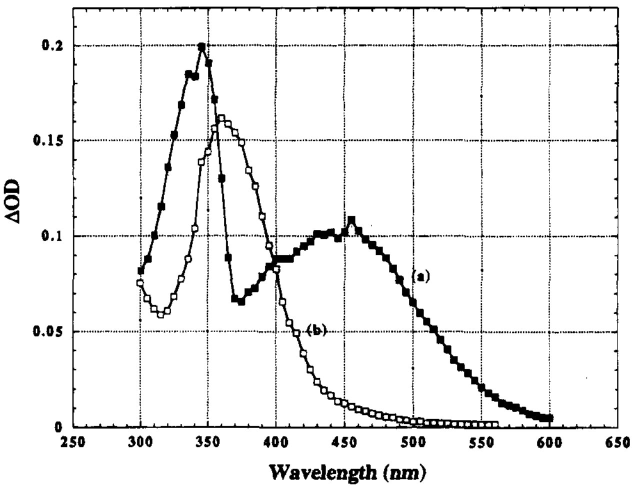
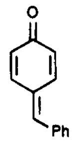


Figure 1. Spectra observed on LFP of **5** and **7** in 1:1 H_2O-CH_3CN. Spectrum a is assigned to *o*-QM **15**, and spectrum b is assigned to *p*-QM **16**.

pH 1. A plot of signal intensity vs pH showed a sigmoid pH titration curve (inflection point at pH ≈ 2.5) indicating that the dissociated phenol (in S_1)[11] is required for reaction. We assign the spectrum obtained from **5** (Figure 1) as that of *o*-QM **15**. LFP of **4** also gave a long-lived species (λ_{max} = 380 nm), but the spectrum was much weaker and not as well-defined.

We proceeded to examine the photochemical behavior of **6–10**, not expecting significant reactivity from these systems. However, LFP of **7** in 100% H_2O also gave a strong and long-lived transient (Figure 1; τ > 5 s) which was unaffected by oxygen but quenchable with ethanolamine. Photolysis of **6** and **7** in 1:1 $MeOH-H_2O$ gave the corresponding methyl ethers but with lower quantum yields compared to the ortho isomers (Φ ≈ 0.007 and 0.1, respectively).[13] We assign the transient spectrum obtained from **7** (Figure 1) as *p*-QM **16**.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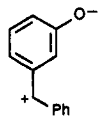
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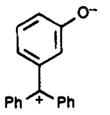
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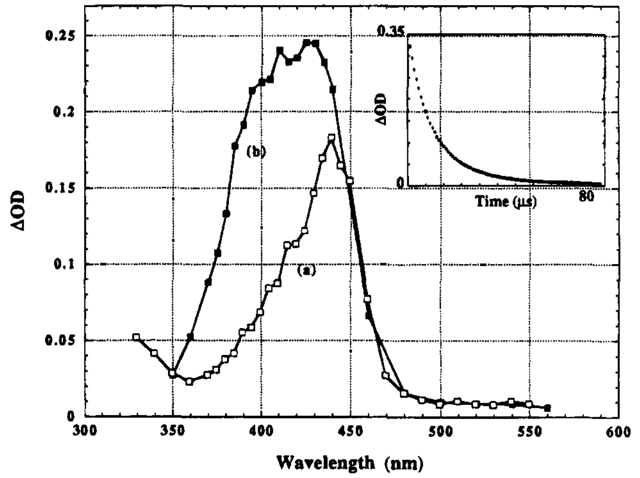

Figure 2. Transient spectra observed on LFP of **9** (H_2O-CH_3CN 1:1) and **10** (100% H_2O). Spectrum a is assigned as *m*-QM **17**, and spectrum b is assigned as *m*-QM **18**. Inset: Clean first-order decay of **18** (λ = 430 nm; 100% H_2O; pH 7; 20 °C), with a lifetime of 10 µs.

Strongly absorbing transients were also observed on LFP of meta isomers **9** and **10** in aqueous solution (Figure 2). Their lifetimes (first-order decays) were significantly shorter than transients observed for the ortho and para isomers (τ = 30 ns (1:1 H_2O-CH_3CN) and 10 µs (100% H_2O), pH 7, 20 °C, for the transients from **9** and **10**, respectively). These transients were insensitive to oxygen and quenchable by ethanolamine. The λ_{max} and band shape of these spectra are essentially identical to those of the corresponding diarylmethyl and triarylmethyl cations reported by McClelland et al.[14] Although they did not photogenerate the appropriate *m*-hydroxy-substituted cations, the lifetimes of those that were reported are informative. For example, diarylmethyl cations without strongly stabilizing substituents have lifetimes of less than 10 ns in aqueous solution and are not detectable by standard nanosecond LFP; τ was estimated to be 1 and 6 ns for the diphenylmethyl and the (*p*-methylphenyl)phenylmethyl cations, respectively.[14] The lifetimes of the parent trityl (triphenylmethyl) cation and the (*m*-methoxyphenyl)diphenylmethyl cation were measured to be 7 and 6 µs, respectively. Clearly, the transients observed from **9** and **10** are arylmethyl carbocations, but their lifetimes are too long to be simply the corresponding *m*-hydroxy-substituted species. The rationale is as follows. The deprotonated hydroxy group (O^-) is an electron-donating group on the benzene ring, at either a meta or para position ($\sigma_m = -0.47$; $\sigma_p = -0.81$),[15] unlike the hydroxy group itself, which is electron withdrawing at the meta position ($\sigma_m = +0.12$).[15] If the transient from **9** were simply the (*m*-hydroxyphenyl)phenylmethyl carbocation, its expected lifetime in aqueous solution, using data from McClelland et al.,[14] would be *less* than 1 ns! Its much longer observed lifetime is consistent with the hydroxyl group having deprotonated. We thus assign these transients (Figure 2) as *m*-QMs **17** and **18**, from **9** and **10**, respectively. Corroborating data that carbocations are indeed formed comes from the photolysis of **8–10** in 1:1 $MeOH-H_2O$, which gave high yields of the corresponding methyl ethers, with quantum yields which were only fractionally lower than those measured for the corresponding ortho isomers (Φ = 0.12 and 0.23 for **8** and **9**, respectively).

In summary, we have shown that all of the isomers of QM can be photogenerated readily, with high efficiency for the ortho and meta isomers, by photolysis of the corresponding hydroxybenzyl alcohols in aqueous solution. The method appears sufficiently general for the photogeneration of a wide variety of these intermediates. In addition, it is possible to characterize all three QM isomers spectrophotometrically, and we have shown that *m*-QMs exist as singlet ground states (zwitterions) in aqueous solution.[16]

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[9] LFP is unnecessary in these experiments. We later used a Rayonet reactor turned on for a brief period of time to produce the visually observable orange-red transient. Its lifetime was then measured with a standard spectrophotometer.

[10] These two observations also apply to LFP studies of the para and meta isomers (for the corresponding compounds) studied in this work, supporting the notion that a general mechanism operates for these compounds, regardless of position of hydroxy substitution.

[11] Singlet state reactivity for these and related types of photosolvolyses is now well established.[8a,12]

[12] Wan, P.; Shukla, D. *Chem. Rev.* **1993**, *93*, 571.

[13] Dark control reactions were carried out on a routine basis in all experiments and showed no significant thermal solvolysis for any of the compounds studied in this work except for **7**, which gave some residual thermal solvolysis if the solutions used had traces of acid. However, this does not interfere with the LFP studies for this compound.

[14] McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 3966.

[15] Murov, S. L.; Carmichael, I.; Hug, G. L. *Handbook of Photochemistry*, 2nd ed.; Marcel Dekker: New York, 1993; p 345.

[16] The photochemical method for QM formation described in this work opens the way for studying the reactivity of these intermediates in aqueous solution as a function of pH, for which little data is presently available. These studies are in progress and will be reported in due course.