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Photochemical Generation and the Reactivity of *o*-Naphthoquinone Methides in Aqueous Solutions

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Abstract: Irradiation of 3-hydroxy-2-naphthalenemethanol (**3a**) and 2-hydroxy-1-naphthalenemethanol (**4a**) results in efficient ($\Phi_{254} = 0.17$ and 0.20) dehydration and the formation of isomeric naphthoquinone methides, 2,3-naphthoquinone-3-methide (**1**) and 1,2-naphthoquinone-1-methide (**2**), respectively. In aqueous solution, naphthoquinone methides **1** and **2** undergo rapid hydration to regenerate starting materials (τ_{H2O} (**1**) = 7.4 ms and τ_{H2O} (**2**) = 4.5 ms at 25 °C). The hydration reaction is strongly catalyzed by the hydroxide ion but shows acid catalysis only at pH < 1. Reactive intermediates **1** and **2** can be intercepted by other nucleophiles, such as the azide ion (k_{N3}(**1**) $= 2.0 \times 10^4$ M^{-1} s^{-1} and k_{N3}(**2**) $= 3.0 \times 10^4$ M^{-1} s^{-1}) or thiol (k_{SH}(**1**) $= 2.2 \times 10^5$ M^{-1} s^{-1} and k_{SH}(**2**) $= 3.3 \times 10^5$ M^{-1} s^{-1}). Ethyl vinyl ether readily reacts with **1** and **2** (k_{DA}(**1**) $= 4.1 \times 10^4$ M^{-1} s^{-1} and k_{DA}(**2**) $= 6.0 \times 10^4$ M^{-1} s^{-1}) to produce Diels−Alder adducts in excellent yield. *o*-Naphthoquinone methides **1** and **2** were also generated by photolysis of 3-ethoxymethyl- (**3b**) and 1-(ethoxymethyl)-2-naphthols (**4b**), as well as from (2-hydroxy-3-naphthyl)methyl- (**3c**) and [(2-hydroxy-1-naphthyl)methyl] trimethylammonium iodides (**4c**). Laser flash photolysis of **3a**,**b** and **4a**,**b** allows the detection of short-lived ($\tau_{25°C} \sim 12$ μs) precursors of naphthoquinone methides **1** and **2**. On the basis of the precursor reactivity and the results of DFT calculations, 2H-naphthoxete structure was assigned to these species.

Introduction

o-Quinone methides (oQMs) are important intermediates in many chemical and biological processes.[1,2] These reactive species are efficient dDNA alkylating and cross-linking agents,[3] and are believed to be responsible for the cytotoxicity of antitumor antibiotics of the mitomycin C and anthracycline families.[4] The reactivity of oQMs resembles that of α,β-unsaturated ketones. The zwitterionic resonance form in the former, however, is additionally stabilized by aromatic conjugation (Scheme 1). Enhanced charge separation results in high electrophilicity of the methide carbon atom, and also makes Diels−Alder addition of electron-rich alkenes to oQMs very facile.[5]

oQMs can be conveniently generated by photochemical dehydration of *o*-hydroxybenzyl alcohols and its analogues (Scheme 1).[1a,5a−c] The loss of water from the excited state of *o*-hydroxybenzyl alcohols is very fast and the formation of oQMs is usually complete within a nanosecond laser pulse.[5a−c] The mechanism of this reaction, however, is not yet fully established. Since phenols and naphthols are very strong acids in the excited state, it is proposed that the excitation of *o*-hydroxybenzyl alcohols results in an excited state intramolecular proton transfer (ESIPT) of a phenolic proton to an oxygen atom in the benzylic position. The C−O bond heterolysis might proceed in a concerted fashion with ESIPT. On the other hand, there is some evidence that loss of water happens in the ground state after proton transfer is complete.[6] Our research

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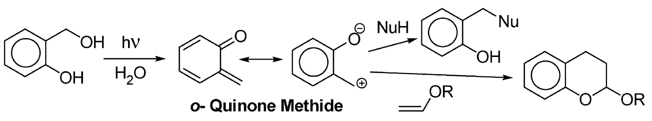
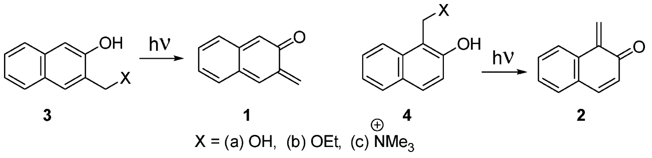
Scheme 1



Scheme 2



group uses photochemical reactions of *o*-hydroxybenzyl alcohol analogues for the development of photolabile protecting groups.[7] Since the parent *o*-hydroxybenzyl chromophore has little absorbance above 250 nm, it is hardly suitable for practical applications. The absorbance of 3-hydroxymethyl- (**3a**) and 1-hydroxymethyl-2-naphthols (**4a**, Scheme 2), on the other hand, extends beyond 350 nm (Figure 1). Additionally, we expected that higher excited state acidity of 2-naphthol[8] will facilitate ESIPT and enhance the efficiency of oQM formation. In this report, we discuss the generation and reactivity of two isomeric *o*-naphthoquinone methides (oNQM), 2,3-naphthoquinone-3-methide (**1**) and 1,2-naphthoquinone-1-methide (**2**, Scheme 2).

Results and Discussion

Three sets of precursors were employed for the generation of oNQMs **1** and **2**: 3-hydroxy-2-naphthalenemethanol (**3a**) and 2-hydroxy-1-naphthalenemethanol (**4a**); 3-ethoxymethyl- (**3b**) and 1-(ethoxymethyl)-2-naphthols (**4b**); (2-hydroxy-3-naphthyl)methyl- (**3c**) and [(2-hydroxy-1-naphthyl)methyl] trimethylammonium iodides (**4c**, Scheme 2).[9] Kinetics of the oNQM reactions was studied in aqueous solutions using a nanosecond kinetic spectrometer equipped with a pulsed Nd:YAG laser.[10] The quantitative product analysis of photolysis mixtures were conducted by HPLC using individual compounds as references. Preparative photolyses were performed in aqueous acetonitrile solutions.

Properties and Reactivity of oNQM Precursors. UV spectra of 3-hydroxy-2-naphthalenemethanol (**3a**) and 2-hydroxy-1-naphthalenemethanol (**4a**) are expectedly similar and resemble the spectrum of 2-naphthol (Figure 1). In aqueous solution, UV spectra of compounds **3a** and **4a** contain two major absorption bands above 210 nm: at $\lambda_{max} = 275$ nm (**3a**, log $\varepsilon = 4.06$), 277 nm (**4a**, log $\varepsilon = 4.06$), and at $\lambda_{max} = 324$ nm (**3a**, log $\varepsilon = 3.70$ and **4a**, log $\varepsilon = 3.83$). Both bands show pronounced vibrational structure. Both diols **3a** and **4a** show strong fluorescence. Their emission spectra in aqueous solutions are almost identical and contain two major bands at 360 and 423 nm (Figure 2). 2-Hydroxy-1-naphthalemethanol (**4a**), however, shows somewhat higher fluorescence efficiency ($\Phi_{Fl} = 0.30 \pm 0.01$) than **3a** ($\Phi_{Fl} = 0.230 \pm 0.002$).[10] Upon 266 nm laser pulse excitation the fluorescence intensity of these compounds rapidly decays with the time constant of $\tau_{FL} \sim 7$ ns (**3a**) and 8 ns (**4a**). While the spectra and fluorescent quantum yields of **3a** and **4a** are similar to those of 2-naphthol ($\Phi_{Fl} = 0.27$),[11] fluorescence lifetimes are somewhat shorter than for 2-naphthol ($\tau_{FL} \sim 11$ ns).[12] This observation apparently indicates that a new pathway for the excited state decay is opened for **3a** and **4a**. Spectral properties of oNQM precursors **3b**,**c** and **4b**,**c** are similar to those of the parent diols.

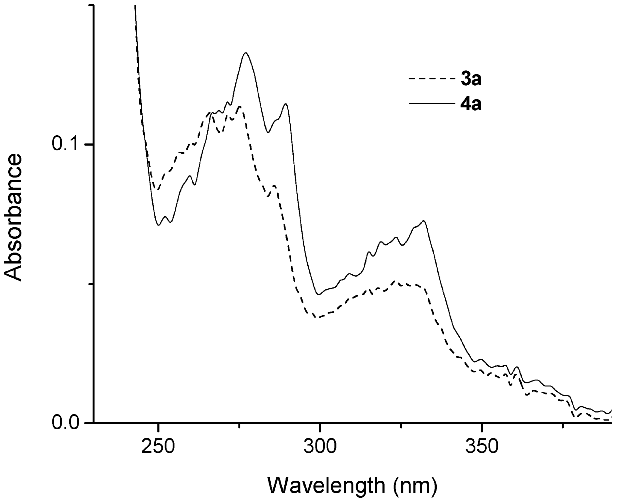


Figure 1. UV-spectra of ca. 10^{-5} M aqueous solutions of **3a** (dashed line) and **4a** (solid line).

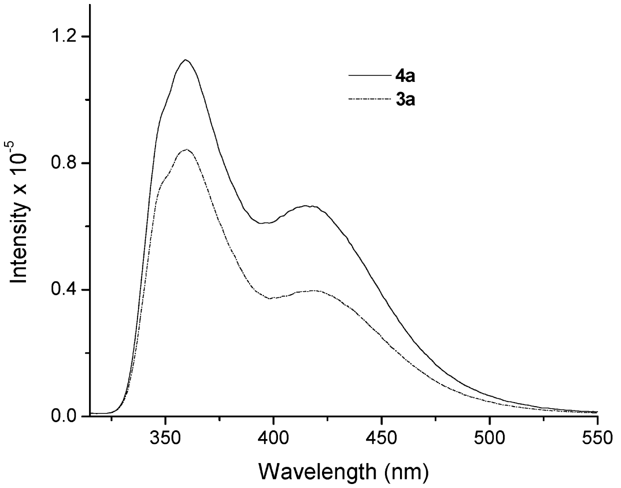


Figure 2. Emission spectra at $\lambda_{ex} = 305$ nm of ca. 10^{-5} M aqueous solutions of **3a** (dashed line) and **4a** (solid line).

The ground-state acidities of 3-hydroxy-2-naphthalenemethanol (**3a**) p$K_a = 9.01$ and 2-hydroxy-1-naphthalene-methanol (**4a**) p$K_a = 8.93$ were determined by spectrophotometric titration in aqueous solution at 25 ± 0.1 °C (Figure 3).[10] These values are about 0.5 units lower than the pK_a of 2-naphthol (9.5−9.6).[13] The enhanced acidity of **3a** and **4a** can be apparently explained

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(9) Preparation of the precursors **3a**−**c** and **4a**−**c** is described in the Supporting Information.

(10) See Supporting Information for details.

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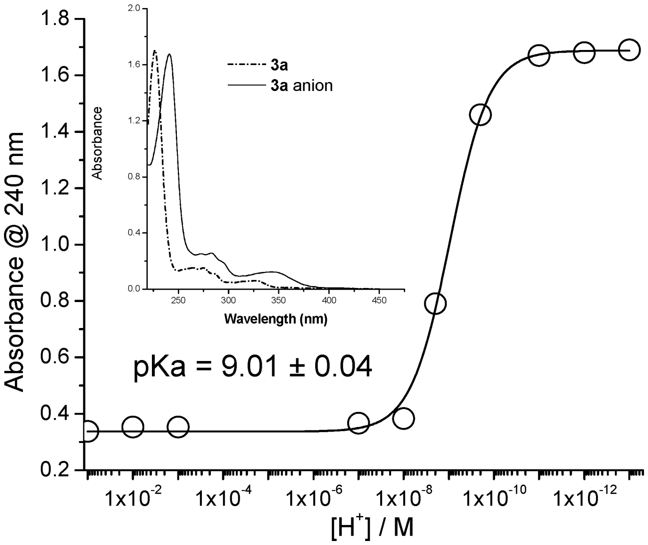
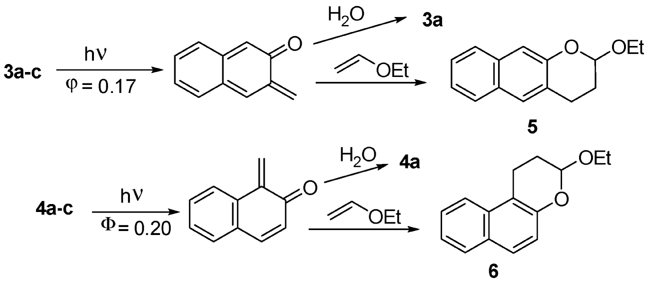


Figure 3. Spectrophotometric titration of diol **3a**. The inset shows spectra of **3a** and its anion (dashed line).

Scheme 3



by the formation of an anion-stabilizing intramolecular hydrogen bond between negatively charged phenolate oxygen and a benzylic hydroxy group.

The 254 or 300 nm irradiation of aqueous solutions of oNQM precursors **3a** and **4a** did not produce detectable amounts of new products, apparently because the formation of oNQM **1** and **2** is followed by the rapid and efficient rehydration to yield starting materials (*vide infra*). Photolysis of the aqueous solutions of ethyl ethers **3b** and **4b**, on the other hand, results in rapid consumption of the substrates and the formation of **3a** and **4a**, respectively (Scheme 3). The quantum yield for the photoelimination of ethanol from **3b** and **4b** at 254 nm was determined using ferrioxalate actinometry:[10] $\Phi_{3b} = 0.17 \pm 0.02$ and $\Phi_{4b} = 0.20 \pm 0.01$. Chemical yields of **3a** and **4a** are almost quantitative at low conversions, but are somewhat reduced at longer irradiation times, apparently due to secondary photochemical processes (Table 1). No new photoproducts were detected by HPLC or isolated by flash chromatography, however, even after prolonged photolysis of **3a**,**b**. This observation suggests that the secondary photoproducts are most likely oNQM oligomers,[14] which were trapped in the column.

Table 1. Yields of the Hydration Product (**3a**, **4a**) and Ethyl Vinyl Ether Adduct (**5**, **6**)

QM precursor	yield of hydration product/% (conversion)[a,b]	yield of ethyl vinyl ether adduct/% (conversion)[a,c–e]
3b	95 ± 1 (11%) 76 ± 1 (56%)	96 ± 1 (91%)
3c	95 ± 1 (11%) 76 ± 3 (68%)	89 ± 1 (99%)
4b	95 ± 4 (13%) 76 ± 3 (53%)	95 ± 1 (91%)
4c	96 ± 1 (11%) 70 ± 3 (61%)	87 ± 1 (99%)

[a] λ_{irr} = 254 or 300 nm. [b] Ca. 6×10^{-4} M in water. [c] Ca. 3×10^{-4} M solutions of the substrate. [d] Ca. 0.03 M ethyl vinyl ether. [e] In 50% $CH_3CN_{aq.}$.

Quinone methides are known to undergo very efficient hetero Diels–Alder reactions with electron-rich alkenes.[5] The 254 or 300 nm irradiation of naphthols **3a** and **4a** in aqueous acetonitrile in the presence of ethyl vinyl ether resulted in the formation of adducts **5** and **6** in 87% isolated yields.[10] The former products were also formed when 355 nm monochromatic radiation[15] was used for photolysis of **3a** and **4b**; conversion, however, was rather slow due to a week substrate absorbance at this wavelength (Figure 1). HPLC analysis shows near quantitative formation of vinyl ether adducts in photolyses of alternative precursors **3b**,**c** and **4b**,**c**, even at high conversions (Table 1). Interestingly, 2-ethoxybenzochromans **5** and **6** are photochemically stable and show virtually no decomposition even after prolonged irradiation at 254 or 300 nm. It is also important to note that adducts **5** and **6** are formed almost quantitatively in the photolyses of ethyl ethers **3b** and **4b** even at low conversion (Table 1). The quantitative formation of Diels–Alder adducts despite the presence of more than a 1000-fold excess (33 M versus 0.03 M) of a nucleophilic solvent indicates that addition of ethyl vinyl ether to oNQMs is at least 2 orders of magnitude faster than a hydration reaction. Direct rate measurements (*vide infra*) enabled us to quantify this rate difference.

Formation and Reactivity of 2,3-Naphthoquinone-3-methide (1) and 1,2-Naphthoquinone-1-methide (2). Substrate concentrations in aqueous solutions for kinetic measurements were of the order of 10^{-5} M, and the temperature of these solutions was controlled at 25 ± 0.1 °C. Excitation of naphthols **3a** and **4a** with 4 ns 266 nm pulses of a Nd:YAG laser under these conditions results in the formation of short-lived transients ($\tau = 12-13$ μs) with λ_{max} at 370 nm, which rapidly decay to yield new intermediates with λ_{max} at 330 nm and broad absorption extending to 430 nm (Figure 4). The latter transients then decay at somewhat slower rate ($\tau = 4-8$ ms).

Upon laser pulsed excitation, both naphthols **3a** and **4a** produce a burst of bright fluorescence covering the region from 320 to 500 nm (Figure 2). This intense emission saturates the detector and produces significant artifacts when measurements are made within this spectral region. Hence, the formation and decay of the both reactions were monitored at 310 nm, where the fluorescence interference was negligible.

Since the rates of the rise and the decay of oNQM absorbance were sufficiently different (*vide infra*), these processes were recorded in separate experiments using different time scales and signal amplifications. The observed first-order rate constants were obtained by fitting experimental data separately to single exponential functions (Figure 5).[10] Decay of the intermediate generated in the photolysis of **3a** is relatively slow in aqueous solution ($k_{obs} = 135 \pm 7$ s^{-1} at pH = 7.0), but is strongly

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(15) Frequency tripled output of Nd:YAG laser.

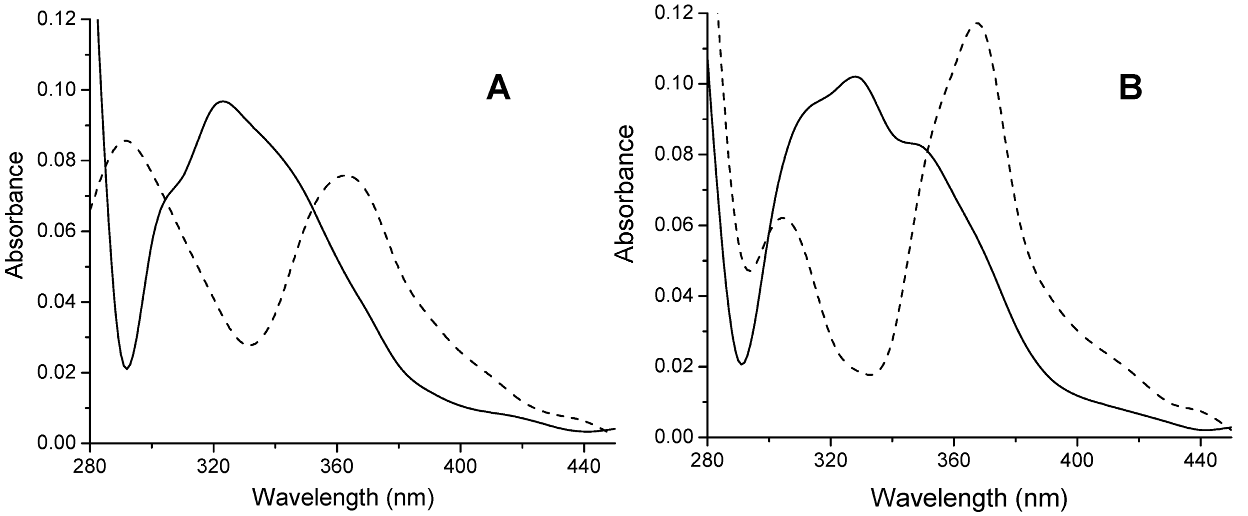

Figure 4. Transient spectra of obtained 1 μs (dashed line) and 1 ms (solid line) after the laser pulse in photolysis of ca. 0.01 mM aqueous solutions of **3a** (A) and **4a** (B) at pH = 7.0.

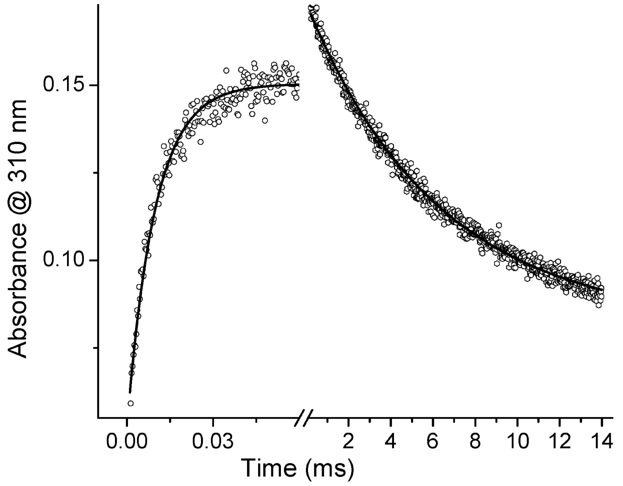

Figure 5. Formation and decay of 2,3-naphtho-quinone-3-methide (**1**) in the photolysis of ca. 0.01 mM aqueous solution of **3a** at pH = 7.0.

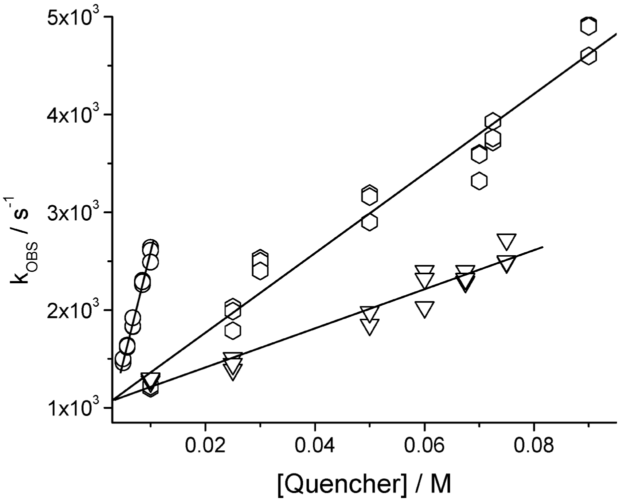

Figure 6. Quenching of oNQM **1** by ethyl vinyl ether (hexagons); sodium azide (triangles); and thioethanolamine hydrochloride (circles) in aqueous solutions at pH = 7.0.

Table 2. Second-Order Rates of oNQMs **1** and **2** Reactions with Various Trapping Agents

QM precursor	NaN_3 k/M^{-1} s^{-1}	$HSCH_2CH_2NH_3 \cdot HCl$ k/M^{-1} s^{-1}	$CH_2{=}CH{-}O{-}C_2H_5$ k/M^{-1} s^{-1}
3a	$(2.00 \pm 0.11) \times 10^4$	$(2.24 \pm 0.06) \times 10^5$	$(4.07 \pm 0.19) \times 10^4$
3c	$(2.04 \pm 0.46) \times 10^4$	$(2.22 \pm 0.05) \times 10^5$	$(4.26 \pm 0.13) \times 10^4$
4a	$(3.00 \pm 0.25) \times 10^4$	$(3.34 \pm 0.28) \times 10^5$	$(6.05 \pm 0.34) \times 10^4$
4c	$(2.75 \pm 0.05) \times 10^4$	$(3.30 \pm 0.86) \times 10^5$	$(6.01 \pm 0.42) \times 10^4$

affected by the addition of reactive nucleophiles or electron-rich dienophiles (Figure 6, Table 2).[10] Thus, the azide ion ($k_{N3} = 2.00 \times 10^4$ M^{-1} s^{-1}) and thiolethanolamine hydrochloride ($k_{SH} = 2.24 \times 10^5$ M^{-1} s^{-1}) efficiently trap the intermediate. The rate of decay is also linearly proportional to the concentration of ethyl vinyl ether ($k_{EVE} = 4.07 \times 10^4$ M^{-1} s^{-1}). Since the product studies indicated that the photolysis of 2-naphthol derivatives **3a**–**c** in the presence of ethyl vinyl ether ultimately produces 2-ethoxybenzochroman **5**, this observation enables us to identify the intermediate as 2,3-naphthoquinone-3-methide (**1**, Scheme 3). The second order rate constants of oNQM **1** reactions with various trapping agents are summarized in Table 2. It is interesting to note that UV absorbance of oNQMs is blue-sifted from that of the parent oQM (Scheme 1).[1a,b,5b] This observation is consisitent with previous reports on a binaphthol analogue.[3e,f]

o-Hydroxybenzyl trimethylammonium salts are also known to generate oQMs upon irradiation.[16] To explore the alternative source of oNQM, we have studied the photochemistry of (2-hydroxy-3-naphthyl)methyltrimethylammonium iodide (**3c**). As mentioned earlier, preparative photolysis of **3c** in the presence of ethyl vinyl ether allows for trapping of oNQM **1** as Diels–Alder adduct **5** in 89% preparative yield (Table 1). Laser flash excitation of **3c** at 266 nm generates a reactive intermediate, whose spectral properties and reactivity are identical to oNQM **1** (Table 2). It is interesting to note that the formation of **1** in the photolysis of ammonium precursor **3c** is complete within the duration of a laser pulse (ca. 6 ns) and no kinetic precursors to oNQM **1** were observed in this case.

In aqueous solutions, in the absence of nucleophiles or dienophiles, naphthoquinone methide **1** undergoes hydration to

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[16] Modica, E.; Zanaletti, R.; Freccero, M.; Mella, M. *J. Org. Chem.* **2001**, *66*, 41.

yield 3-hydroxy-2-naphthalenemethanol (**3a**), as evident from the results of preparative photolyses of **3b** and **3c** (Table 1, Scheme 3).

Flash photolysis of 2-hydroxy-1-naphthalenemethanol (**4a**) enabled us to observe the formation and decay of the isomeric 1,2-naphthoquinone-1-methide (**2**, Scheme 3). The reactivity of oNQM **2** is very similar to that of **1**, although the rate of hydration in aqueous solution was somewhat higher ($k_{\mathrm{obs}} = 224 \pm 6$ s^{-1}, pH = 7.0). oNQM **2** is also about 25−30% more reactive toward nucleophiles (NaN_3 and thioethanolamine HCl), as well as ethyl vinyl ether (Table 2). oNQM **2** was also generated from [(2-hydroxy-1-naphthyl)methyl] trimethylammonium iodides (**4c**, Table 2). The rate of reaction of oNQMs **1** and **2** with thiols (Table 2) is similar to that of the parent *o*-quinone methide with 2-mercaptoethanol ($k_{SH} = 1.9 \times 10^5$ M^{-1} s^{-1}).[16]

Kinetics of Hydration of *o*-Naphthoquinone Methides in Perchloric acid, Base, and Buffer Solutions. Rates of the hydration of oNQM **1** and **2** were determined in dilute aqueous solutions of perchloric acid and sodium hydroxide, as well as in biphosphate ion and bicarbonate ion buffers. The ionic strength of these solutions was kept constant at 0.1 M by adding sodium perchlorate as required, except for the measurements conducted at pH < 1. Kinetic data obtained in perchloric acid solutions and in buffers obeyed the first-order rate law well, and observed pseudo-first-order rate constants were determined by least-squares fitting to a single exponential function. In aqueous sodium hydroxide solutions, reactions of oNQMs **1** and **2** generated from precursors **3a** and **4a** showed complex kinetic behavior. The rate of the reaction did not fit the exponential law well and was dependent on the substrate concentration. We believe that this phenomenon is most likely due to the reaction of oNQMs with the deprotonated form of the substrate (**3a** or **4a**). Similar complex behavior was previously observed in photolyses of *o*-hydroxybenzyl alcohol.[17] Photolyses of (2-hydroxy-3-naphthyl)methyl- (**3c**) and [(2-hydroxy-1-naphthyl)-methyl] trimethylammonium iodides (**4c**) in basic solutions, on the other hand, produce clean pseudo-first-order kinetics. Therefore, hydration of oNQMs **1** and **2** in sodium hydroxide solutions was studied using precursors **3c** and **4c**. Rate measurements in buffered solutions were performed in series of solutions of varying buffer concentration but constant buffer ratio. The observed rates were then extrapolated to a zero buffer concentration. While no appreciable buffer catalysis was observed, the zero-concentration intercepts were well-determined. The buffer-independent rate constants, together with observed rate constants determined in perchloric acid and sodium hydroxide solutions, are shown as the rate profile in Figure 7.

It is interesting to note that quantum yield of oNQM generation rapidly decreases at $[\mathrm{H}^+] > 0.1$ M and no oNQM signal is observed at $[\mathrm{HClO_4}] > 1$ M (see inset in Figure 7). Since photochemical dehydration of *o*-hydroxybenzyl alcohol and its analogues, such as **3a**, proceeds via deprotonation of the phenolic hydroxyl in the excited state, this phenomenon enables us to evaluate the excited state acidity of 3-hydroxy-2-naphthalenemethanol (**3a**). The inflection point on the sigmoid titration curve (inset in Figure 7) corresponds to $\mathrm{p}K_\mathrm{a}^* = 0.77 \pm 0.04$. This makes **3a*** 100 times more acidic than 2-naphthol in the exited state ($\mathrm{p}K_\mathrm{a} \sim 2.8$).[13] Similar acidifying effect of the *o*-hydroxymethyl substituent was also reported for *o*-hydroxybenzyl alcohol $\mathrm{p}K_\mathrm{a}^* \sim 2.5$[5c] versus phenol $\mathrm{p}K_\mathrm{a}^* \sim 3.6$.[18] The nature of this effect is probably the same as in the ground state (*vide supra*): stabilization of an anion by intramolecular hydrogen bond between negatively charged phenolate oxygen and a benzylic hydroxy group.

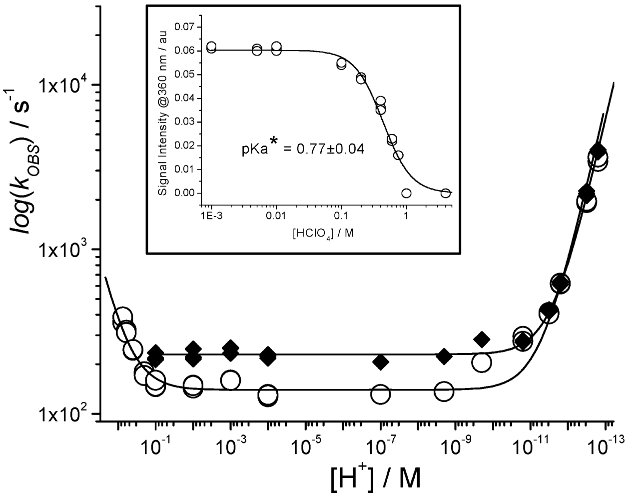

Figure 7. Rate profile for the hydration of oNQM **1** (empty circles) and **2** (filed squares) in aqueous solution at 25 °C. Inset illustrates the dependence of the signal intensity of oNQM **1** on perchloric acid concentration.

The rate of hydration of oNQMs **1** and **2** is independent of the acidity of aqueous solutions in the range from pH 1 to 8 resulting in a broad horizontal region in the rate profile (Figure 7). The observed rate constants on this plateau are $k_{\mathrm{H_2O}} = 145 \pm 12$ s^{-1} for oNQM **1** and $k_{\mathrm{H_2O}} = 229 \pm 14$ s^{-1} for oNQM **2**. These values are very similar to uncatalyzed hydration of the parent oQM ($k_{\mathrm{H_2O}} = 260$ s^{-1}).[19] Also, these values are in excellent agreement with those obtained from flash photolysis of **3a** and **4a** at pH 7.[7b] The rate of hydration of the parent oQM, however, showed pronounced specific acid catalysis ($k_{\mathrm{H+}} = 8.4 \times 10^5$ M^{-1} s^{-1}),[5b,18] which was assigned to the rapid pre-equilibrium protonation of the oQM, which produces a more reactive *o*-hydroxybenzyl cation. The acid catalysis of the hydration of oNQM **1** is much weaker ($k_{\mathrm{H+}} = 299 \pm 11$ M^{-1} s^{-1}) and becomes prominent only at pH < 1. We were not able to study H^+-catalyzed hydration of an isomeric oNQM **2** because its precursors **4a−c** are unstable in acidic solutions at $[\mathrm{H}^+] > 0.1$ M. Weaker acid catalysis of oNQMs **1** and **2** hydration can apparently be explained by the lower basicity of naphthoquinone methides versus oQMs (compare, for example, 2-naphthol, $\mathrm{p}K_\mathrm{a} = 9.5-9.6$[13] and phenol $\mathrm{p}K_\mathrm{a} = 10.0$[20]). In addition, the reactivity of protonated oNQMs is potentially lower due to an increased delocalization of the positive charge.

The hydration of oNQMs **1** and **2** is strongly catalyzed by the hydroxide-ion, as illustrated by the upward slope of the rate profile at pH > 10. The rate constant for hydroxide-ion catalyzed hydration is $k_{\mathrm{OH}} = (3.30 \pm 0.03) \times 10^4$ M^{-1} s^{-1} for oNQM **1** and $k_{\mathrm{OH}} = (3.74 \pm 0.04) \times 10^4$ M^{-1} s^{-1} for NQM **2**. The reactivities of oNQMs **1** and **2** toward nucleophilic attack by the hydroxide-ion are very similar to the parent *o*-quinonemethide ($k_{\mathrm{OH}} = 3.0 \times 10^4$ M^{-1} s^{-1}). The rate profile of Figure 7 is readily understood in terms of this reaction scheme (Scheme 4).

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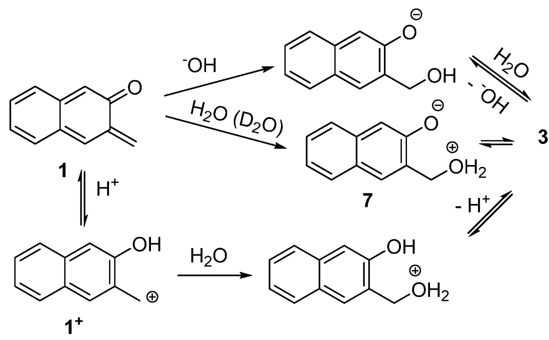
(20) Bordwell pK_a tables: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.

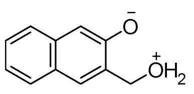
Scheme 4



The base-catalyzed portion of the rate profiles apparently corresponds to the rate-limiting attack of the hydroxide ion on the methide carbon of oNQMs **1** and **2**. The observed weak acid catalysis at $[H^+] > 0.1$ M should be assigned, as in case of the parent oQM,[5b,18] to the rapid pre-equilibrium protonation of the oNQM, which produces the more reactive cation $\mathbf{1}^+$ (Scheme 4). The uncatalyzed portion at pH < 9 has two possible interpretations, the first of which is reversible protonation of the oNQM by water, followed by cation capture by the hydroxide ion so formed. This mechanism can be ruled out on the basis of the very weak specific acid catalysis of hydration. The more probable mechanism of the uncatalyzed reaction is simple nucleophilic attack of water on the oNQM methylene group, with or without simultaneous proton transfer to avoid a zwitterionic intermediate (**7**, Scheme 4). Rates of hydration of oNQMs **1** and **2** were also measured in D_2O solutions of deuterated hydrochloric acid in the range of concentrations from 0.001 to 0.1 M. As in the case of H_2O, no acid catalysis was observed in this range of acidities, but the reaction was appreciably slower, producing solvent kinetic isotope effect in the normal direction ($k_{H_2O}/k_{D_2O} = 1.85 \pm 0.14$ for **1** and $k_{H_2O}/k_{D_2O} = 1.42 \pm 0.07$ for **2**). The nature of this isotope effect stems from the fact that positively charged O−H bonds, such as those in the intermediate **7** (Scheme 4), are looser than uncharged O−H bonds, such as those in a water molecule.[21] Conversion of H_2O into ROH_2^+ leads to a loosening of the hydrogenic environment of the species involved, and that produces an isotope effect in normal direction.

The rate of hydration of oNQM **1** generated from ammonium precursor **3c** in neutral conditions and in 0.1−0.001 M perchloric acid matches the results obtained using **3a** within the uncertainty limits ($k_{H_2O} = 132 \pm 10$ M^{-1} s^{-1}). [(2-Hydroxy-1-naphthyl)methyl] trimethyl ammonium iodide (**4c**) is unstable in aqueous solutions at pH < 4; therefore, the rate measurements were performed in a biphosphate buffer at pH = 7.0 to give $k_{H_2O} = 201 \pm 6$ M^{-1} s^{-1}. This value is similar to the rate of hydration of **2** obtained in laser flash photolysis of diol **4a**.

Nature of the oNQM Precursor. While the formation of oNQMs **1** and **2** in the flash photolysis of ammonium precursors **3c** and **4c** happens within the duration of a laser pulse, irradiation of 3-hydroxy-2-naphthalenemethanol (**3a**) and 2-hydroxy-1-naphthalenemethanol (**4a**), as well as their ethoxy derivatives **3b** and **4b**, allows for the detection of a kinetic precursor to oNQMs. Thus, the formation of oNQM **1** in aqueous solution proceeds with the observed rate of $k_{obs} = (8.03 \pm 0.04) \times 10^4$ s^{-1} (Figure 5) and $k_{obs} = (8.10 \pm 0.07) \times 10^4$ s^{-1} for oNQM **2**. In agreement with previously reported data,[5b] we did not observe kinetic precursors to the parent *o*-quinone methide in the laser flash photolysis of *o*-hydroxybenzyl alcohol. The rate of oNQMs formation is independent of pH of the solution and is not affected by the presence of the azide ion, thiolethanolamine hydrochloride, or ethyl vinyl ether. The fluorescence lifetime of **3a** ($\tau \sim 7$ ns, *vide supra*) is much shorter than the rise time of oNQM **1**, indicating that the latter species is not formed directly from the singlet excited state of **3a**. The spectrum of **3a** and **4a** fluorescence is essentially identical to that of 2-naphtol, suggesting that no significant structural changes occur at the singlet excited state surface. Since saturation of the solution with oxygen or addition of increased 1,3-cyclohexadiene do not quench the first transient, we can conclude that triple excited state of **3a** is not involved in the formation of oNQM **1**. The zwitterionic structure **7** can be also excluded from consideration because proton transfer between electronegative atoms in aqueous solution proceeds at least at the diffusion-controlled rate limit. In addition, the rate of decay of **7** should be dependent on the acidity of solution, which is not observed.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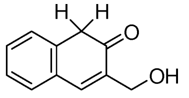
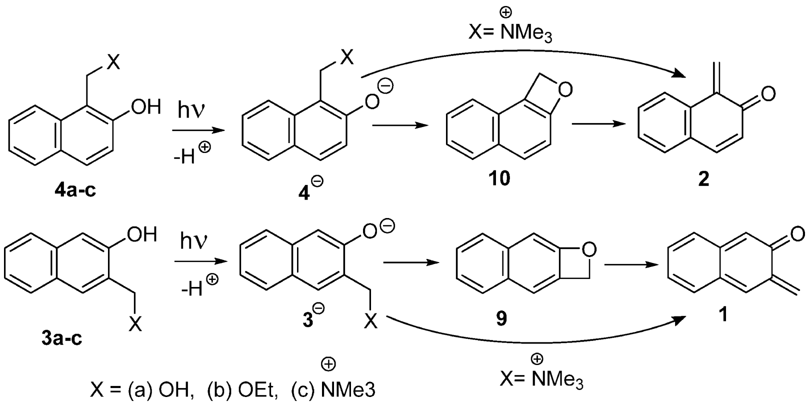

8

Excited state proton transfer from the phenolic oxygen to the aromatic carbon in the singlet excited state is well-documented

Scheme 5



for phenols and naphthols.[22] Such carbon protonation leading to keto-intermediate **8** or its isomers should result in incorporation of deuterium in hydration products when photolysis is conducted in deuterated solvents. GC-MS analysis of the products formed after prolonged irradiation of diols **3a** and **4a** in D_2O showed no deuterium enrichment in the aromatic rings. This observation enables us to rule out participation of **8** or isomeric structures. It has been shown, on the other hand, that *o*-quinone methides might reversibly isomerize to benzoxete derivatives, which are stable only at cryogenic temperatures.[23] A similar ring-opening reaction is actually used for the generation of thio-*o*-quinone methides from benzothietes.[24] In addition, thermolysis of thio-analogues of diols **3a** and **4a** produce the corresponding isomeric naphthothietes.[23a] We believe that in our case, oxetanes **9** and **10** are the likely precursors of *o*-naphthoquinone methides **1** and **2** (Scheme 5).

Additional support for this mechanism comes from the fact that excitation of trimethylammonium derivatives **3c** and **4c** directly produces corresponding oNQMs, bypassing intermediates **9** and **10**. Dissociation of the highly acidic excited states of 2-naphthol derivatives **3** and **4** produce anions **3**$^-$ and **4**$^-$ (Scheme 5). When "**X**" is a good leaving group, such as trimethylamine, these anions might form oNQMs directly. In the case of poor leaving groups, such as hydroxyl or alkoxyl, an intramolecular S_N2 reaction produces oxetenes **9** or **10**. Ring-opening of the latter to give oNQMs **1** and **2** is an electrocyclic reaction and, therefore, is not sensitive to acid/base catalysis or the presence of reactive nucleophiles.

Theoretical Analysis. To gain a better understanding of the difference in the kinetics of the formation of oNQMs and the parent *o*-quinonemethide **12** (Scheme 6), we conducted computational comparison of these two reactions. The ring-opening of naphthoxete **9** is much slower than a decay of an excited state of **3a** (*vide supra*) and is, apparently, a thermal reaction. We have analyzed the reactivity and relative stability of oxetenes **9** and **11** at the B3LYP/6-311++G(d,p)//B3LYP/6-31++G(d,p) and MP2/6-31++G(d,p)//FC-MP2/6-31++G(d,p) levels of theory. The geometries of transition states **9**‡ and **11**‡ (Scheme 6) were also optimized by open-shell UB3LYP/6-31++G(d,p) calculations. The latter, however, converged to the same structures and energies as closed-shell calculations. The optimized geometries of structures **1**, **9**, **9**‡, **11**, **11**‡, **12**, as well as the details of theoretical procedures, are provided in the Supporting Information file.[10] The relative electronic energies of isomeric oxetenes and *o*-quinonemethides, ring-opening transition states (**9**‡ and **11**‡), and C−O distances are shown in Table 3.

Scheme 6

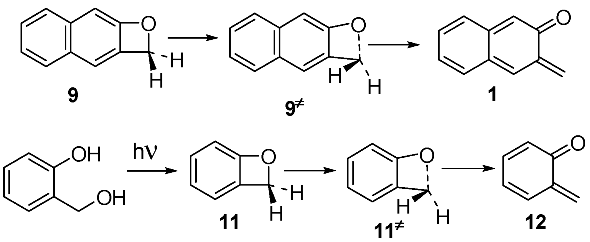


Table 3. Relative Electronic Energies and C−O Distances for Oxetanes **9** and **11**, *o*-Quinonemethides **1** and **12**, and Transition States **9**‡ and **11**‡

	ΔE (kcal/mol)[a]		
	B3LYP/6-311++G(d,p)	MP2/6-31++G(d,p)	C−O distance (Å)
9	0.0	0.0	1.49
9‡	31.2	35.0	2.10
1	0.2	4.8	2.81
11	0.0	0.0	1.49
11‡	26.6	31.3	2.06
12	−13.2	−7.4	2.82

[a] ZPVE, corrected energy; electronic energy of **9** was used as a reference for oNQM system, and **11** - for oQM system.

Calculation results shown in Table 3 illustrate the striking difference between benzene and naphthalene-derived systems. The parent oQM (**12**) is substantially more stable than its potential precursor benzoxete (**11**). The electronic energy of oNQM **1**, on the other hand, is close to (DFT) or even higher than that of naphthoxete (**9**). The energies of transition states **9**‡ and **11**‡ are rather high in the gas phase but can be significantly reduced in polar solvents capable of hydrogen bonding. However, both DFT and MP2 methods predict that the barrier for the ring-opening of **11** to yield **12** is about 4 kcal/mol lower than for opening of **9** to **1**. A higher relative energy and lower activation barrier for the electrocyclic ring-opening of **11** suggests that these species are thermally unstable and decay within a duration of laser pulse if formed in the photolysis of o-hydroxybenzyl alcohol.

Conclusions

The isomeric 2,3-naphthoquinone-3-methide (**1**) and 1,2-naphthoquinone-1-methide (**2**) are predictably very reactive species and undergo efficient hydration in aqueous solutions to form 3-hydroxy-2-naphthalenemethanol (**3a**) and 2-hydroxy-1-naphthalenemethanol (**4a**), respectively. These *o*-naphthoquinone methides react even faster with good nucleophiles, such as thiols and the azide ion. What is surprising is that the reactivity of regioisomers **1** and **2** is quite similar, despite vastly different electronic structures. In fact, the rate of the addition of various nucleophiles to *o*-naphthoquinone methides is close to that of the parent *o*-quinone methide. The only significant difference from the parent system is the much weaker acid catalysis of the hydration reaction, apparently due to the lower basicity of oNQMs versus oQM. The hetero-Diels−Alder reaction of oNQM **1** and **2** with ethyl vinyl ether is very facile and produces high yield of 2-ethoxybenzochromans, even in aqueous solution. These adducts are photochemically stable and might be employed for photochemically induced cross-linking or ligation. From a practical point of view, the generation of reactive *o*-quinone methides by photolysis of 2-hydroxynaphthalene methanols is more convenient than from *o*-hydroxybenzylalcohols because 350 nm light can be employed.

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Another interesting feature of the photochemistry of **3a** and **4a** is the observation of a kinetic precursor to oNQMs. On the basis of the analysis of the reactivity of these species and the results of DFT calculations, we have assigned the naphthoxete structure to these transients.

Acknowledgment. Authors thank the National Science Foundation (CHE-0449478), and donors of the ACS Petroleum Research Fund (434444-AC4) for the support of this project.

Supporting Information Available: Experimental details; synthetic procedures for the preparation of compounds **3a**−**c** and **4a**−**c**; details of kinetic measurements; Cartesian coordinates of DFT-optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

JA9031924