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Flash Photolytic Generation of *ortho*-Quinone Methide in Aqueous Solution and Study of Its Chemistry in that Medium

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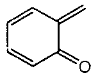
Abstract: Flash photolysis of *o*-hydroxybenzyl alcohol, *o*-hydroxybenzyl *p*-cyanophenyl ether, and (*o*-hydroxybenzyl)trimethylammonium iodide in aqueous perchloric acid and sodium hydroxide solutions, and in acetic acid and biphosphate ion buffers, produced *o*-quinone methide as a short-lived transient species that underwent hydration back to benzyl alcohol in hydrogen-ion catalyzed ($k_{\mathrm{H}^+} = 8.4 \times 10^5$ M^{-1} s^{-1}) and hydroxide-ion catalyzed ($k_{\mathrm{HO}^-} = 3.0 \times 10^4$ M^{-1} s^{-1}) reactions as well as an uncatalyzed ($k_{\mathrm{UC}} = 2.6 \times 10^2$ s^{-1}) process. The hydrogen-ion catalyzed reaction gave the solvent isotope effect $k_{\mathrm{H}^+}/k_{\mathrm{D}^+} = 0.42$, whose inverse nature indicates that this process occurs by rapid and reversible equilibrium protonation of the carbonyl oxygen atom of the quinone methide, followed by rate-determining capture of the carbocation so produced by water. The magnitude of the rate constant of the uncatalyzed reaction, on the other hand, indicates that this process occurs by simple nucleophilic addition of water to the methylene group of the quinone methide. Decay of the quinone methide is also accelerated by acetic acid buffers through both acid- and base-catalyzed pathways, and quantitative analysis of the reaction products formed in these solutions shows that this acceleration is caused by nucleophilic reactions of acetate ion rather than by acetate ion assisted hydration. Bromide and thiocyanate ions also accelerate decay of the quinone methide through both hydrogen-ion catalyzed and uncatalyzed pathways, and the inverse nature of solvent isotope effects on the hydrogen-ion catalyzed reactions shows that these reactions also occur by rapid equilibrium protonation of the quinone methide carbonyl oxygen followed by rate-determining nucleophilic capture of the ensuing carbocation. Assignment of an encounter-controlled value to the rate constant for the rate-determining step of the thiocyanate reaction leads to p$K_a = -1.7$ for the acidity constant of the carbonyl-protonated quinone methide.

Quinone methides, such as the parent *ortho* isomer **1**, are molecules having a cyclohexadiene core with a carbonyl group and a methylene unit attached. They are related to quinones, such as **2**, which have two carbonyl groups, and to quinone dimethides, such as **3**, which have two methylene units. Unlike their relatives, however, quinone methides, with their two different functional groups, are highly polarized and therefore quite reactive. They may be viewed as resonance hybrids of two principal canonical structures, one of which is dipolar (Scheme 1). This gives these molecules both cationic and anionic centers, and they therefore react with both nucleophiles and electrophiles. Their reactions, moreover, often generate an aromatic phenol ring, and this provides a considerable driving force that adds to quinone methide reactivity. Quinone methides have consequently become useful reaction intermediates with wide applications in organic synthesis, and various methods for their generation have been developed.[1]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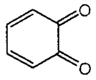
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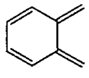
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Quinone methides also show pronounced biological activity. They have, for example, been implicated as the ultimate cytotoxins responsible for the effects of such agents as antitumor drugs, antibiotics, and DNA alkylators.[2] In living systems where water is the ubiquitous medium this biological activity must operate against a background of wasteful quinone methide hydration reactions. To provide information about these hydrations, we have begun a detailed investigation of their kinetics and reaction mechanisms. In this paper we describe the results we have obtained studying the parent *ortho* isomer, **1**, reacting in aqueous solution.[3]

Scheme 1

We generated *o*-quinone methide by photoelimination of water from *o*-hydroxybenzyl alcohol,[1,4] **4** X = H, photoelimination of *p*-cyanophenol from *o*-hydrobenzyl *p*-cyanophenyl ether, **4** X = *p*-CNC$_6$H$_4$,[5] and photoelimination of trimethylammonium hydrogen iodide from (*o*-hydroxybenzyl)trimethy-

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(1) For a brief review, see Wan, P.; Barker, B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. *Can. J. Chem.* **1996**, *74*, 465−475.

(2) See, e.g.: Peter, M. G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 555−570. Bolton, J. L.; Pisha, E.; Zhang, F.; Qiu, S. *Chem. Res. Toxicol.* **1998**, *11*, 1113−1127. Pande, P.; Shearer, J.; Yang, J.; Greenberg, W. A.; Rokita, S. E. *J. Am. Chem. Soc.* **1999**, *121*, 6773−6779.

(3) Part of this work has been published in preliminary form: Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2000**, *122*, 9854−9855.

(4) Diao, L.; Yang, C.; Wan, P. *J. Am. Chem. Soc.* **1995**, *117*, 5369−5370.

(5) McClelland, R. A. *Tetrahedron* **1996**, *52*, 6823−6858.

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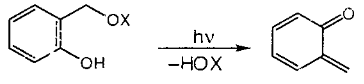
lammonium iodide, **4** OX = $(CH_3)_3N^+I^-$,[6] eq 1. Flash photolysis



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(1)

of these substrates in aqueous solution produced a transient species with the strong absorbance at $\lambda = 400$ nm that is characteristic of *o*-quinone methide.[7] Neither the lifetime of this transient species nor the amount produced was affected by the presence or absence of dissolved oxygen, which again is as expected for this transient being *o*-quinone methide.[7]

Experimental Section

Materials. *o*-hydroxybenzyl acetate was prepared by treating *o*-hydroxybenzyl alcohol with acetic anhydride in the presence of boron trifluoride etherate,[8] and (*o*-hydroxybenzyl)trimethylethylammonium iodide was synthesized by methyl iodide methylation of (*o*-hydroxybenzyl)dimethylamine,[6] itself obtained by the reaction of potassium phenolate with *N*,*N*-dimethylmethyleneammonium iodide.[9]

***o*-Hydroxybenzyl *p*-cyanophenyl ether** was prepared in a one-pot process by first converting *o*-hydroxybenzyl alcohol to *o*-hydroxybenzyl bromide, using the mild conditions of the Ph_3P/CBr_4 reagent,[10] and then immediately adding sodium *p*-cyanophenoxide. A flask containing an argon atmosphere was charged with 1.00 g *o*-hydroxybenzyl alcohol, 2.33 g triphenylphosphine, 2.95 g carbon tetrabromide, and 10 mL DMSO. This mixture was stirred at room temperature for 10 min, and 1.25 g sodium *p*-cyanophenoxide was then added, and that mixture was stirred overnight. The following day, 30 mL of water was added, the resulting mixture was extracted with two 75-mL portions of ethyl ether, and the ether extracts were washed with saturated brine and were dried over sodium sulfate. The residue remaining after removal of the ether was purified by column chromatography (silical gel with hexane eluent) to give 0.50 g (28%) of colorless crystals: mp 135−136 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 7.59 (d, $J = 8.9$ Hz, 2H), 7.32−7.25 (m, 2H), 7.07 (d, $J = 9.0$ Hz, 2H), 6.99−6.86 (m, 2H), 5.81 (s, 1H), 5.22 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ/ppm = 162.02, 154.80, 134.49, 130.52, 129.72, 122.06, 121.43, 119.44, 116.73, 116.22, 105.17, 67.84; HRMS: *m*/*e* = 225.0790 (calc), 225.0794 (obs).

All other materials were best-available commercial grades.

Product Analysis. Product analyses were conducted by HPLC using a Varian Vista 5500 instrument with a NovoPak C_{18} reverse-phase column and methanol−water (60/40 = v/v) as the eluent. Reaction solutions, containing ca.. 2×10^{-5} M substrate and ca.. 4×10^{-5} M anisole, which served as an internal standard, were subjected to a single pulse from our microsecond flash photolysis system.[11] Products were identified by comparing retention times and UV spectra with authentic samples. The temperature of all reactions was controlled at 25.0 ± 0.1 °C, and parallel analyses of unphotolyzed reaction mixtures showed that no thermal transformations occurred during the time of the photolysis experiments.

Kinetics. Rate measurements were made using microsecond[11] and nanosecond[12] ($\lambda_{exc} = 248$ nm) flash photolysis systems that have already been described.[11,12] *o*-Hydroxybenzyl alcohol was the photolysis substrate for all rate measurements except those made in sodium hydroxide solution, where (*o*-hydroxybenzyl)trimethylammonium iodide was used instead. Initial substrate concentrations were ca.. 2×10^{-4} M for the alcohol and ca.. 4×10^{-5} M for the ammonium iodide. The temperature of all reacting solutions was controlled at 25.0 ± 0.05 °C. Reactions were monitored by following the decay of quinone methide absorbance at $\lambda = 400$ nm, and observed first-order rate constants were obtained by least-squares fitting of an exponential function.

Results

Product Analysis. Analysis of spent reaction mixtures showed that only *o*-hydroxybenzyl alcohol was produced from *o*-quinone methide generated by flash photolysis of *o*-hydroxybenzyl alcohol in perchloric acid solution, as expected for clean hydration of the quinone methide back to starting material. When *o*-hydroxybenzyl *p*-cyanophenyl ether was the photolysis substrate, on the other hand, a minor amount (ca. 10%) of an additional unidentified substance was formed. In acetic acid buffers, these products were accompanied by formation of *o*-hydroxybenzyl acetate.

Because of the unknown additional product formation from *o*-hydroxybenzyl p-cyanophenyl ether, this substrate was not used for rate measurements. It was, however, employed for quantitative product analysis, where a substrate other than *o*-hydroxybenzyl alcohol was needed in order to distinguish the hydration product from unphotolyzed starting material.

Quantitative product analyses were carried out in acetic acid buffers using a series of solutions of fixed buffer ratio ($[HOAc]/[OAc^-] = 0.10$) and constant ionic strength (0.10 M). The data so obtained are summarized in Table S1.[13]

Kinetics, Perchloric Acid, Sodium Hydroxide, and Buffer Solutions. Rates of decay of *o*-quinone methide were measured in dilute perchloric acid solution over the concentration range $[HClO_4]$ 0.001−0.1 M and also in acetic acid and biphosphate ion buffers, using both H_2O and D_2O as the solvent. The ionic strength of these solutions was kept constant at 0.10 M by supplying sodium perchlorate as required. These results are summarized in Tables S2 and S3.[13]

The rate measurements in buffers were made in series of solutions of fixed buffer ratio, and therefore fixed hydrogen ion concentration, but varying buffer concentration. Extrapolation of these data to zero buffer concentration using the buffer dilution expression of eq 2

$$k_{obs} = k_{int} + k_{cat}\,[\mathrm{Buffer}] \qquad (2)$$

gave intercepts, k_{int}, which, together with the dilute perchloric acid solution data, were used to construct the rate profiles shown in Figure 1. Hydrogen-ion concentrations of the buffer solutions needed for this purpose were obtained by calculation, using thermodynamic acidity constants from the literature and activity coefficients recommended by Bates.[14]

Figure 1 shows that *o*-quinone methide undergoes both acid-catalyzed and uncatalyzed reactions. The data were therefore analyzed using the rate law of eq 3. Least-squares fitting provided the results $k_{H^+} = (8.41 \pm 0.12) \times 10^5$ M^{-1} s^{-1}, $k_{H^+}/k_{D^+} = 0.418 \pm 0.017$, $(k_{UC})_{H_2O} = (2.60 \pm 0.06) \times 10^2$ s^{-1}, $(k_{UC})_{H_2O}/(k_{UC})_{D_2O} = 1.42 \pm 0.06$.

$$k_{obs} = k_{UC} + k_{L^+}\,[L^+] \qquad (3)$$

These results are consistent with $k_{H^+} = 1.4 \times 10^6$ M^{-1} s^{-1} and $k_{UC} = 3.2 \times 10^2$ s^{-1} recently reported for these reactions.[6]

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(6) Modica, E.; Zanaletti, R.; Freccero, M.; Mella, M. *J. Org. Chem.* **2001**, *66*, 41−52.

(7) Barker, B.; Diao, L.; Wan, P. *J. Photochem. Photobiol. A* **1997**, *104*, 91−96.

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(12) Andraos, J.; Chiang, Y.; Huang, C. G.; Kresge, A. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1993**, *115*, 10605−10610.

(13) Supporting Information; see paragraph at the end of this paper regarding availability.

(14) Bates, R. G. *Determination of pH Theory and Practice*; Wiley: New York, 1973; p 49.

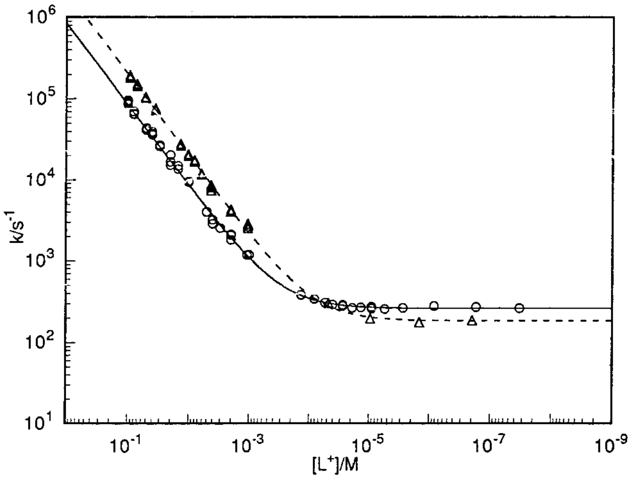

Figure 1. Rate profiles for the hydration of *o*-quinone methide in H_2O (○) and D_2O (Δ) solution at 25 °C.

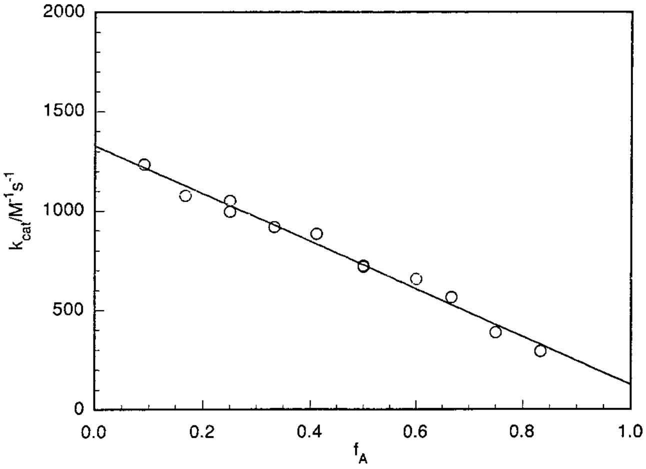

Figure 2. Separation of buffer catalysis into general acid and general base components for the reaction of *o*-quinone methide in aqueous (H_2O) acetic acid buffer solutions at 25 °C.

The decay of *o*-quinone methide in acetic acid buffers showed pronounced buffer catalysis, and buffer catalytic coefficients, k_{cat} eq 2, were well determined. These catalytic coefficients were separated into their general acid, k_{HA}, and general base, k_B, components with the aid of the relationship shown in eq 4,

$$k_{cat} = k_B + (k_{HA} - k_B)f_A \tag{4}$$

where f_A is the fraction of buffer present in the acid form. Figure 2 shows that the data obtained conform to this relationship well. Least-squares analysis gave $k_{HA} = (1.25 \pm 0.29) \times 10^2$ M^{-1} s^{-1}, $k_{HA}/k_{DA} = 1.35 \pm 0.83$, $k_B = (1.33 \pm 0.02) \times 10^3$ M^{-1} s^{-1}, $(k_B)_{H_2O}/(k_B)_{D_2O} = 1.17 \pm 0.06$.

In biphosphate ion buffers, on the other hand, buffer catalysis was weak and reliable values of k_{cat} in these solutions were not obtained. The zero-concentration intercepts, k_{int}, for these buffers, however, were well-determined.

Some rate measurements of *o*-quinone methide decay were also made in concentrated perchloric acid solutions over the concentration range $[HClO_4] = 0.2-4.5$ M. No additional inert electrolyte was added to these solutions, and their ionic strength was therefore equal to perchloric acid concentration. These data are summarized in Table S4.[13]

Rate measurements were also attempted in sodium hydroxide solutions using *o*-hydroxybenzyl alcohol as the photolysis substrate, but the decay of *o*-quinone methide absorbance in these solutions no longer gave good first-order kinetics. We believe that this was so because first-order hydration was accompanied by an additional second-order reaction of the quinone methide with some unphotolyzed *o*-hydroxybenzyl alcohol substrate, which was present in these solutions in its highly nucleophilic phenoxide-ion form. Such an additional reaction would produce oligomeric products, whose formation from *o*-quinone methide in basic solutions has been observed.[15]

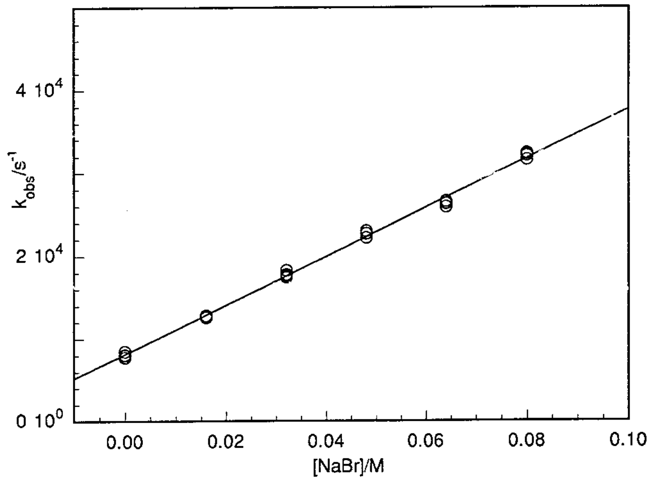

Figure 3. Relationship between observed rate constants and bromide ion concentration for the reaction of *o*-quinone methide in aqueous solution (H_2O) containing 0.020 M perchloric acid at 25 °C.

We found, however, that use of (*o*-hydroxybenzyl)trimethylammonium iodide as the photolysis substrate in sodium hydroxide solutions gave good first-order kinetic behavior. Rates of this reaction were therefore measured over the concentration range [NaOH] = 0.001−0.1 M at a constant ionic strength of 0.10 M ($NaClO_4$). The data so obtained are summarized in Table S5.[13]

Observed first-order rate constants determined in these sodium hydroxide solutions increased linearly with increasing sodium hydroxide concentration, and linear least-squares analysis gave the hydroxide-ion rate constant $k_{HO^-} = (2.95 \pm 0.04) \times 10^4$ M^{-1} s^{-1}. This result is consistent with $k_{HO^-} = 6.3 \times 10^4$ M^{-1} s^{-1} recently reported for this reaction.[6]

Kinetics, Bromide and Thiocyanate Ion Solutions. The decay of *o*-quinone methide in aqueous solution was strongly accelerated by bromide and thiocyanate ions, in keeping with the proclivity of quinone methides to react with nucleophiles. These accelerations were also catalyzed by acids. As Figure 3 illustrates, the rate of the bromide ion reaction at a fixed acidity increased linearly with bromide ion concentration, and Figure 4 shows that second-order bromide-ion rate constants, obtained as slopes of plots such as that of Figure 3, themselves increased linearly with hydrogen ion concentration. Similar behavior was observed with thiocyanate ion.

For both ions, rate measurements were consequently made in series of solutions of constant hydrogen ion concentration but varying nucleophile concentration, using both H_2O and D_2O as the solvent. Perchloric acid or biphosphate ion buffers were employed to keep hydrogen ion concentrations constant, and the ionic strength was maintained at 0.10 M by adding sodium perchlorate as required. The results are summarized in Tables S6-S9.[13]

Least-squares analysis of the data obtained in perchloric acid solutions gave $k = (2.10 \pm 0.05) \times 10^7$ M^{-2} s^{-1} and k_{H_2O}/k_{D_2O}

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(15) Wan, P.; Hennig, D. *J. Chem. Soc., Chem. Commun.* **1987**, 939−941.

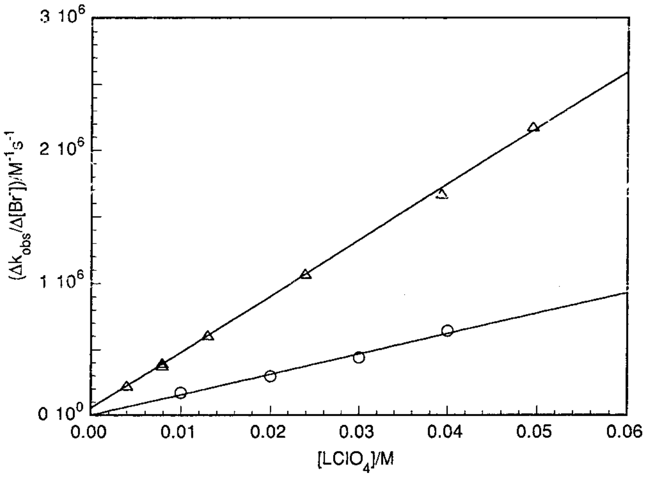


Figure 4. Relationship between bromide-ion rate constants and perchloric acid concentration for the reaction of *o*-quinone methide in H_2O (○) and D_2O (Δ) solution at 25 °C.

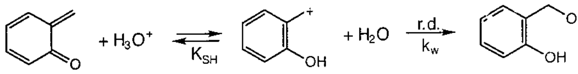
$= 0.495 \pm 0.010$ for the acid-catalyzed bromide-ion reaction and $k = (9.56 \pm 0.76) \times 10^7$ M^{-2} s^{-1} and $k_{H_2O}/k_{D_2O} = 0.607 \pm 0.059$ for its thiocyanate-ion counterpart.

As Figure 4 illustrates, the zero-hydrogen-ionic concentration intercepts of the ($\Delta k_{obs}/\Delta$[Nuc]) versus [L^+] plots for bromide ion were essentially zero, and a bromide-ion reaction not catalyzed by perchloric acid could not be detected. Such an uncatalyzed reaction could also not be seen in the much less acidic biphosphate buffers: observed rate constants determined in these solutions did not increase with increasing bromide ion concentration but rather varied randomly about an average value consistent with the rate of a reaction in biphosphate buffers with no added bromide ion. Although an uncatalyzed bromide-ion reaction could not be observed, an upper limit for its rate constant could be estimated by assuming that a 10% bromide-ion-induced increase in rate in the biphosphate-ion buffers would have been detected. The result is $k_{Br^-} < (3.25) \times 10^2$ M^{-1} s^{-1}.

In contrast to this behavior of bromide ion, the zero-hydrogen-ion concentration intercepts of the ($\Delta k_{obs}/\Delta$[Nuc]) versus [L^+] plots for thiocyanate ion were finite and well-determined, giving $k = (1.24 \pm 0.05) \times 10^7$ M^{-1} s^{-1} and $k_{H_2O}/k_{D_2O} = 1.20 \pm 0.07$ for the not acid-catalyzed portion of the thiocyanate reaction. This uncatalyzed reaction was also apparent in biphosphate ion buffers, where observed rate constants increased linearly with increasing thiocyanate ion concentration. Least-squares analysis gave $k = (1.28 \pm 0.04) \times 10^7$ M^{-1} s^{-1} and $k_{H_2O}/k_{D_2O} = 1.08 \pm 0.04$, in good agreement with the determination of these quantities as the [L^+] plot intercepts.

Discussion

Mechanisms of the Hydration Reactions. The rate profiles of Figure 1 pertain to decay of *o*-quinone methide through reaction with solvent-related species, where product analysis shows that hydration to *o*-hydroxybenzyl alcohol is the only process occurring. The inverse isotope effect on the acid-catalyzed portion of this process, $k_{H^+}/k_{D^+} = 0.42$, implies that this reaction occurs by a preequilibrium substrate-protonation mechanism,[16] which in this case may be formulated as rapid equilibrium protonation of the quinone methide on its carbonyl oxygen atom followed by rate-determining capture of the cation so formed by water, eq 5. The inverse nature of this isotope effect stems from the fact that positively charged O−H bonds, such as those in the hydronium ion, are looser than uncharged O−H bonds, such as those in a water molecule.[17] Conversion of H_3O^+ into H_2O in the equilibrium step of eq 5 then leads to a tightening of the hydrogenic environment of the species involved, and that produces an inverse isotope effect.



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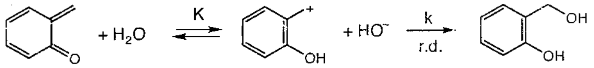
At sufficiently high acidities, the position of the equilibrium preceding the rate-determining step of the mechanism of eq 5 will shift from unprotonated to protonated substrate, and acid catalysis of the quinone methide hydration reaction will become saturated. Figure 5 shows that such saturation was not achieved up to perchloric acid concentrations of 4.5 M, where rates reached the fast-reaction limit of our flash photolysis system. In concentrated acids, in fact, hydration rates, rather than saturating, increased more rapidly than in proportion to acid concentration. This is often the case in concentrated acid solutions, where reactions frequently follow acidity functions rather than acid concentration. Although saturation of acid catalysis was not achieved in this case, it was realized in related studies with other more basic quinone methide substrates and will be reported separately.

The isotope effect on the uncatalyzed *o*-quinone methide hydration reaction is less mechanistically diagnostic. It does not serve to distinguish between an analogue of the acid-catalyzed reaction mechanism, involving rapid equilibrium substrate protonation by proton transfer from a water molecule followed by cation capture by the hydroxide ion so formed, eq 6, or simple nucleophilic attack of water on the quinone methide methylene group, with or without simultaneous proton transfer to avoid a zwitterionic intermediate, eq 7. The first of these uncatalyzed reaction mechanisms can be ruled out, however, on the basis of the fact that it would require an impossibly large value of the rate constant for its slow step, k. The rate law that applies to the scheme of eq 6 is $k_{UC} = k\,K$, with K, the equilibrium constant of the first step, equal to the ionization constant of water, K_w, divided by the acidity constant of the protonated substrate, K_{SH}. The value of K_{SH} is not known, but the fact that the rate profile of Figure 5 shows no saturation of acid catalysis up to the highest acid concentration used, [H^+] = 4.5 M, indicates that K_{SH} must be greater than this, that is, $K_{SH} > 4.5$ M. The observed value of k_{UC} is 2.6×10^2 s^{-1}, and combination of that with $K_w = 10^{-14}$ M^{-2} and $K_{SH} > 4.5$ M then leads to $k > 1.2 \times 10^{17}$ M^{-1} s^{-1}, which exceeds the encounter-controlled limit of $k \cong 1 \times 10^{10}$ M^{-1} s^{-1} by a considerable margin.



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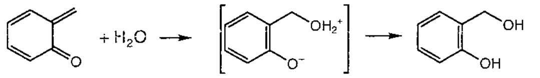

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Mechanisms of the Reactions Promoted by Acetic Acid Buffers. Rates of decay of *o*-quinone methide were appreciably accelerated by acetic acid buffers, with a somewhat stronger acceleration by the buffer base than by the buffer acid (cf Figure 2). *o*-Hydroxybenzyl acetate was formed in these solutions as

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[16] Keeffe, J.R.; Kresge, A. J. In *Investigation of Rates and Mechanisms of Reactions*; Bernasconi, C. F., Ed.; Wiley: New York, 1986; pp 747−790.

[17] Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E.; Lee, C. C., Eds.; Elsevier: New York, 1987; Chapter 4.

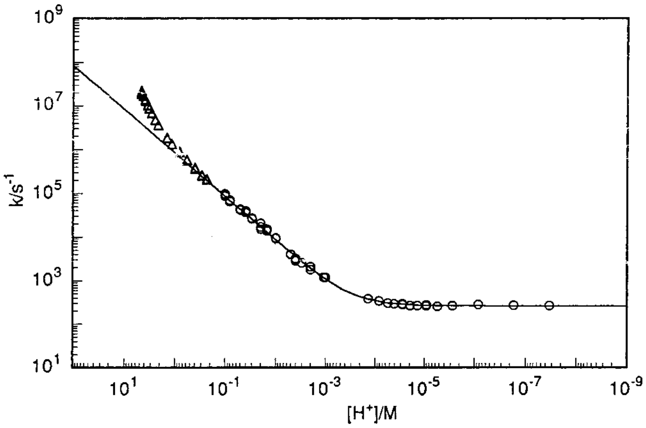
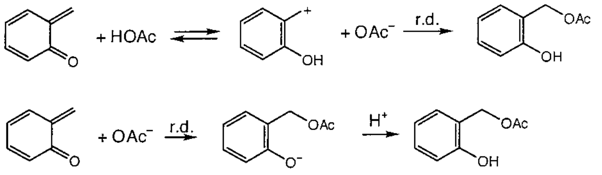


Figure 5. Comparison of rates of hydration of *o*-quinone methide in concentrated (Δ) and dilute (○) aqueous perchloric acid solution at 25 °C.

well, and this suggests that the buffer reactions occur by mechanisms that are analogues of those established for *o*-quinone methide hydration, eqs 5 and 7, with acetate ion rather than water playing the nucleophilic role. The acid-catalyzed buffer reaction would then involve rapid equilibrium protonation of the quinone methide on its carbonyl oxygen atom, followed by rate-determining nucleophilic capture of the ensuing cation by acetate ion, eq 8, whereas the base-catalyzed buffer reaction would consist of simple rate-determining nucleophilic attack of acetate ion on the methide group of unprotonated *o*-quinone methide, eq 9.



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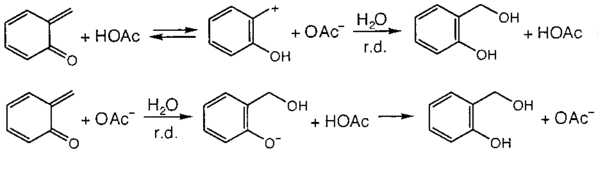
These reaction mechanisms, however, might also be accompanied by additional mechanisms in which acetate ion, rather than serving as a nucleophile, operates as a general base assisting attack of water on the protonated substrate, eq 10, or on the unprotonated substrate, eq 11.



(10)

(11)

The products of these two sets of reactions are different: those of eqs 8 and 9 give *o*-hydroxybenzyl acetate, whereas those of eqs 10 and 11 give *o*-hydroxybenzyl alcohol. The incursion or absence of the additional reaction mechanisms of eqs 10 and 11 may consequently be determined by performing a quantitative product analysis. To avoid difficulties introduced by the simultaneous operation of both buffer acid and buffer base catalysis, we carried out this analysis using buffers with a buffer ratio of [HOAc]/[OAc$^-$] = 0.10; in these very basic buffers, buffer acid catalysis makes a negligibly small rate contribution and essentially all of the buffer reaction occurs by the basic route. The product data were analyzed using eq 12,

$$\frac{[\mathrm{BzOAc}]}{[\mathrm{BzOH}]} = \frac{\omega[\mathrm{Buffer}]}{(1-\omega)[\mathrm{Buffer}] + k_{\mathrm{int}}/k_{\mathrm{cat}}} \tag{12}$$

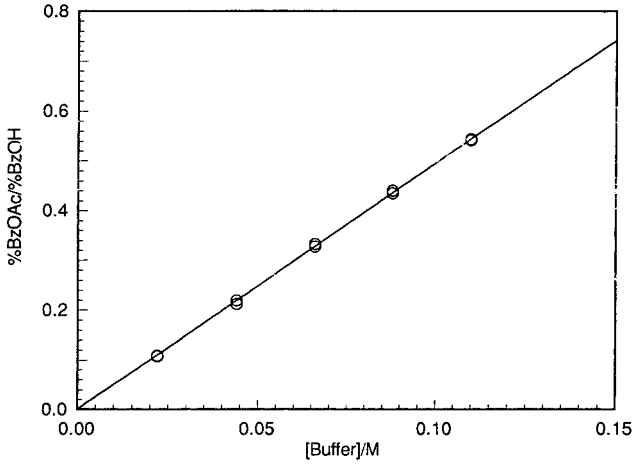


Figure 6. Ratio of products formed by reaction of *o*-quinone methide in aqueous (H_2O) acetic acid buffers, [HOAc]/[OAc$^-$] = 0.10, at 25 °C plotted according to eq 12.

where ratios of *o*-hydroxybenzylacetate to *o*-hydroxybenzyl alcohol concentrations, [BzOAc]/[BzOH], are related to buffer concentration through the parameter ω, which is the fraction of the buffer catalyzed reaction that gives acetate product, plus the term $k_{\mathrm{int}}/k_{\mathrm{cat}}$, which is the ratio of buffer-uncatalyzed to buffer-catalyzed rate constants at the buffer ratio under examination (see eq 2). Figure 6 shows that the experimental data conform to this relationship well. Least-squares analysis of two separate series of determinations gave results whose weighted averages are $\omega = 1.00 \pm 0.02$ and $k_{\mathrm{int}}/k_{\mathrm{cat}} = 0.198 \pm 0.007$ M; the latter agrees well with $k_{\mathrm{int}}/k_{\mathrm{cat}} = 0.214 \pm 0.006$ derived from the buffer dilution kinetics plot at [HOAc]/[OAc$^-$] = 0.10.

The unit value of ω obtained in this way indicates that all of the buffer-base-accelerated decay of *o*-quinone methide occurs by the nucleophilic pathway of eq 9 and that none of this acceleration take place by the general base-assisted hydration reaction of eq 11. This result also makes it quite likely that the buffer-acid-accelerated decay is a wholly nucleophilic reaction as well and that the preequilibrium protonation followed by a general base-assisted hydration scheme of eq 10 is not operating at all. This is because such general base assistance is known to become progressively less important as the species undergoing reaction becomes more electrophilic,[18] and of course the benzyl cation intermediate of eq 10 is much more electrophilic than the neutral quinone methide of eq 11.

This assignment of reaction mechanisms is supported by the solvent isotope effects determined for these buffer-assisted reactions. The rate-determining step of the buffer-base nucleophilic pathway of eq 9 does not involve proton transfer, and the effect of changing H_2O to D_2O on the reorganization of the solvent shells of the species involved is expected to be small.[17] The solvent isotope effect on such a mechanism should therefore be small, consistent with the near-unit value observed: $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}} = 1.17$. The buffer-acid nucleophilic pathway of eq 8 does require proton transfer in its preequilibrium step, but the solvent isotope effect here is again expected to be close to unity because the equilibrium constant for this step consists of the ratio of acidity constants of acetic acid and protonated quinone methide, whose isotope effects will largely offset one another.[17] Reorganization of the solvent shells in the rate-determining step of this reaction will again contribute only a weak effect, and the overall isotope effect will once more be expected to be

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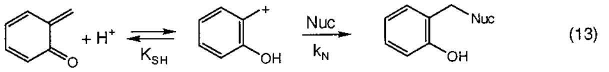
(18) Ta−Shma, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 8040−8050. Richard, J. P.; Toteva, M. M.; Crugeiras, J. *J. Am. Chem. Soc.* **2000**, *122*, 1664−1674.

close to unity, consistent with the value observed, $k_{HA}/k_{DA} = 1.35$. The buffer-assisted hydration pathways of eqs 10 and 11, on the other hand, do involve proton transfer, and these reactions may be expected to show solvent isotope effects significantly greater than unity.

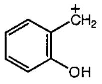
Mechanisms of the Bromide and Thiocyanate Ion Reactions. Both bromide ion and thiocyanate ion accelerate the decay of *o*-quinone methide strongly. Both accelerations, moreover, show acid-catalysis in perchloric acid solutions, and both give inverse hydrogen-ion isotope effects: $k_{H^+}/k_{D^+} = 0.49$ for bromide ion and $k_{H^+}/k_{D^+} = 0.61$ for thiocyanate ion. The inverse nature of these isotope effects implies that these accelerations occur through preequilibrium substrate protonation, just like acid-catalyzed *o*-quinone methide hydration (eq 5), and an analogous reaction mechanism may be assigned, with the stronger nucleophiles Br^- and SCN^- replacing water in the rate-determining cation-capture step, eq 13.



(13)

The thiocyanate ion also accelerated *o*-quinone methide decay by a process that was not acid-catalyzed. This reaction gave the near-unit solvent isotope effect $k_{H_2O}/k_{D_2O} = 1.14$, which is consistent with simple nucleophilic attack of SCN^- on the methylene group of unprotonated *o*-quinone methide in a process analogous to the uncatalyzed hydration reaction (eq 7). A similar bromide-ion-promoted acceleration not catalyzed by acid could not be detected.

It seems likely that the reaction of thiocyanate ion with the *o*-hydroxybenzyl cation, **5**, by the route of eq 13 is an encounter-controlled process. This cation should be less stable and therefore more reactive than the *p*-methoxyphenylethyl cation, **6**, and of similar stability and reactivity as the *p*-methoxybenzyl cation, **7**, both of which react with azide ion in a 50:50 trifluoroethanol−water solvent at the encounter-controlled limit.[19] Since thiocyanate ion is a better nucleophile than azide ion, as measured by both the Swain−Scott[20] and Pearson[21] parameters, the reaction of *o*-hydroxybenzyl cation with thiocyanate ion should be an encounter-controlled process as well.



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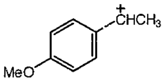

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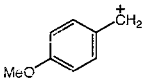

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On this basis, an encounter-controlled rate constant of $k_{Nuc} = 5 \times 10^9\ M^{-1}\ s^{-1}$ may be assigned to the rate-determining step of the reaction of eq 13 for the case Nuc = SCN^-. Combination of that with the observed rate constant $k_{Nuc}/K_{SH} = 9.6 \times 10^7\ M^{-2}\ s^{-1}$ then leads to the estimate $K_{SH} = 52$ M, $pK_{SH} = -1.7$, for the acidity constant of oxygen-protonated *o*-quinone methide.

This result may in turn be combined with the rate constant for acid-catalyzed hydration of *o*-quinone methide, $k_{H^+} = k_w/K_{SH} = 8.4 \times 10^5\ M^{-1}\ s^{-1}$ to give $k_w = 4 \times 10^7\ s^{-1}$ for the capture of the *o*-hydroxybenzyl cation by water in wholly aqueous solution. This estimate is consistent with $k_w = 2 \times 10^8\ s^{-1}$ determined for reaction of the *p*-methoxybenzyl cation, **7**, with water in 50:50 trifluroethanol:water.[19b] The value of K_{SH} itself, however, is considerably less than acidity constants of oxygen-protonated simple carbonyl compounds,[22] but ionization of oxygen-protonated *o*-quinone methide converts an aromatic ring into a quinone methide structure with a concomitant loss of some aromatic stabilization, and the weaker acidity of the quinone methide conjugate acid is understandable on that basis; an even lower acidity constant has recently been found for an oxygen-protonated quinone methide in a naphthoquinone system.[23]

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Supporting Information Available: Tables of product yields and rate data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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