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Kinetics and Mechanisms of Hydration of *o*-Quinone Methides in Aqueous Solution

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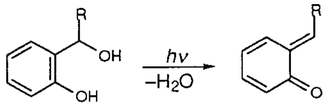
Quinone methides are interesting reactive species that show pronounced biological activity. They have, for example, been implicated as the ultimate cytotoxins responsible for the effects of such agents as antitumor drugs, antibiotics, and DNA alkylators.[1] In living systems, where water is the ubiquitous medium, this biological activity must operate against a background of wasteful quinone methide hydration reactions. We wish to report that we have now determined the kinetics and mechanisms of this hydration reaction for the parent substance, *o*-quinone methide **2**, R = H.



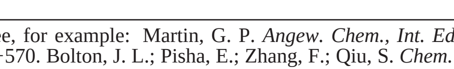
(1)

1 **2**

We generated this quinone methide by photodehydration of *o*-hydroxybenzyl alcohol, eq 1.[2] Flash photolysis of this alcohol in aqueous solution produced a short-lived transient species with the strong absorbance at $\lambda = 400$ nm that is characteristic of *o*-quinone methide.[3] Decay of this transient conformed to the first-order rate law well. Analysis of spent reaction mixtures showed only *o*-hydroxybenzyl alcohol to be present, as expected for hydration of the quinone methide back to starting material.

We made hydration rate measurements in dilute aqueous perchloric acid solution and in acetic acid and biphosphate ion buffers, all at a constant ionic strength of 0.10 M, using both H_2O and D_2O as the solvent. The measurements in buffers were made in series of solutions of constant buffer ratio but varying buffer concentration. Extrapolation of these data to zero buffer concentration gave intercepts, which, together with the perchloric acid data, were used to construct the rate profile shown in Figure 1. It may be seen that there is both an acid-catalyzed and an uncatalyzed hydration reaction. Least-squares fitting of the data using the simple rate law $k_{obs} = k_{H^+}[H^+] + k_{UC}$ gave $k_{H^+} = (8.38 \pm 0.15) \times 10^5$ M^{-1} s^{-1}, $k_{H^+}/k_{D^+} = 0.416 \pm 0.079$, and $(k_{UC})_{H_2O} = (2.61 \pm 0.10) \times 10^2$ s^{-1}, $(k_{UC})_{H_2O}/(k_{UC})_{D_2O} = 1.42 \pm 0.07$.

The inverse nature of the isotope effect on the acid-catalyzed process indicates that this reaction proceeds by a preequilibrium substrate-protonation mechanism,[4] which in this case may be formulated as rapid equilibrium protonation of the *o*-quinone methide on its carbonyl oxygen atom followed by rate-determining capture of the cation so formed by water, eq 2.



(2)

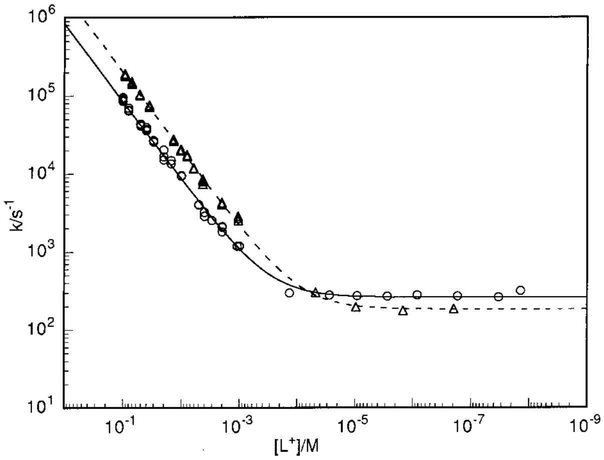
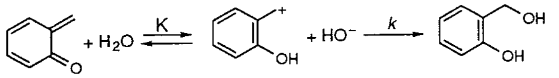
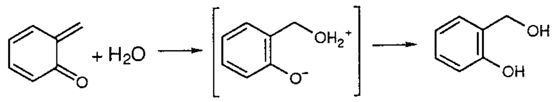


Figure 1. Rate profile for the hydration of *o*-quinone methide in H_2O (○) and D_2O (△) solution.

The isotope effect on the uncatalyzed process is less diagnostic and does not serve to distinguish between preequilibrium substrate protonation followed by cation capture by hydroxide ion, eq 3,



(3)



(4)

or simple nucleophilic attack of water on the quinone methide methylene group, with or without simultaneous proton transfer to avoid a zwitterion intermediate, eq 4. 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 for the rate constant of the slow step, *k*. The rate law that applies to the scheme of eq 3 is shown as eq 5,

$$k_{UC} = kK = kK_w/K_{SH} \qquad (5)$$

in which *K*, the equilibrium constant for the first step, is equal to the ionization constant of water, K_w, divided by the acidity constant of the protonated substrate, K_{SH}. The numerical value of K_{SH} is not known but the fact that the rate profile of Figure 1 shows no saturation of acid catalysis up to the highest acid concentration used, $[H^+] = 0.10$ M, indicates that K_{SH} must be greater than this value, i.e., $K_{SH} > 0.10$ M. Rearrangement of eq 5 to $k = k_{UC}K_{SH}/K_w$ and insertion of $k_{UC} = 2.6 \times 10^2$ s^{-1}, $K_{SH} > 0.10$ M, and $K_w = 10^{-14}$ M^2 then leads to $k > 2.6 \times 10^{15}$ M^{-1} s^{-1}, which far exceeds the encounter controlled limit of $k \cong 1 \times 10^{10}$ M^{-1} s^{-1}.

To determine whether acid catalysis could be saturated by going to more concentrated perchloric acid solutions, we made rate measurements up to 4.5 M, where observed rate constants reached the limit of our flash photolysis system ($k = 2 \times 10^7$ s^{-1}), but no saturation occurred. We then modified our substrate by adding substituents designed to stabilize the cationic intermediate formed by protonation of *o*-quinone methide, and we found saturation of acid catalysis for the phenyl derivative (**2**, R = C_6H_5) at 2.5 M perchloric acid and also for the *p*-anisyl derivative (**2**, R = 4-$MeOC_6H_4$) at 0.1 M perchloric acid. Analysis of the data for

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(1) See, for example: Martin, G. P. *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.

(2) Diao, L.; Yang, C.; Wan, P. *J. Am. Chem. Soc.* **1995**, *117*, 5369−5370. Wan, P.; Barker, B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. *Can. J. Chem.* **1996**, *74*, 465−475.

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

(4) Keeffe, J. R.; Kresge, A. J. In *Investigation of Rates and Mechanisms of Reactions*; Bernasconi, C. F., Ed.; Wiley-Interscience: New York, 1986; pp 747−790.

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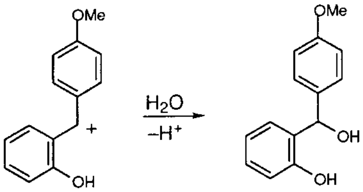
the phenyl derivative is complicated by the need to use acidity functions in the concentrated acid solutions employed. Analysis of the data for the anisyl derivative, on the other hand, is free of such complication, and least-squares fitting[5] gave $K_{SH} = (8.21 \pm 0.21) \times 10^{-2}$ M and $K_{SH}/K_{SD} = 3.62 \pm 0.10$ for the acidity constant of the oxygen-protonated quinone methide, **3**, and $k = (4.62 \pm 0.13) \times 10^5$ s^{-1} and $k_{H_2O}/k_{D_2O} = 1.32 \pm 0.04$ for the rate constant of the rate-determining step in which the protonated quinone methide is captured by reaction with water at its benzylic carbon atom, eq 6. This rate constant is consistent with $k = 1.0 \times 10^5$ s^{-1} determined for the reaction of the di(*p*-anisyl)methyl cation with water in a 4:1 water−acetonitrile solvent,[7] which is the closest analogue to the present system for which such a rate constant has been measured. The isotope effect on the acidity constant is also consistent with the fact that oxygen acids usually show solvent isotope effects of this magnitude on their acid dissociation,[8] and the isotope effect on k is consistent as well with the slight weakening of the O−H bonds of the attaching water molecule as it takes on positive charge.[9]



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(6)

Our observation of continuing acid catalysis of *o*-quinone methide hydration well up into the concentrated acid region is at variance with a report that flash photolytic generation of the phenyl derivative, **2** (R = C_6H_5), in acidic solutions gave a signal that decreased in intensity with increasing acidity and was lost completely at acidities greater than pH 1.[2] This difference suggests that the hypothesis advanced on the basis of this signal loss, viz. that photolytic generation of quinone methides from *o*-hydroxybenzyl alcohols occurs through excited-state phenolic hydroxyl group ionization, should be reexamined.

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[5] The rate law used is $k_{obs} = k[H^+]/(K_{SH} + [H^+]) + S[H^+]$, in which a linear term, $S[H^+]$, is added to take into account the pronounced inhibition of carbocation hydration reactions by perchlorate ion.[6]

[6] See: Crugeiras, J.; Maskill, H. *Can. J. Chem.* **1999**, *77*, 530−536 and references therein.

[7] McClelland, R. A.; Kanagasabapathy, V. M.; Steenken, S. *J. Am. Chem. Soc.* **1988**, *110*, 6913−6914.

[8] Laughton, P. M.; Robertson, R. E. In *Solute−Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; M. Dekker: New York, 1969; Chapter 7.

[9] 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; Vol. 7, Chapter 4.