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Kinetics and Mechanism of Hydration of *o*-Thioquinone Methide in Aqueous Solution. Rate-Determining Protonation of Sulfur

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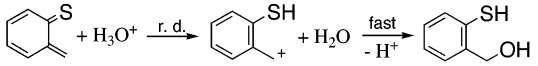
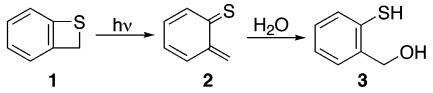


o-Thioquinone methide, **2**, was generated in aqueous solution by flash photolysis of benzothiete, **1**, and rates of hydration of this quinone methide to *o*-mercaptobenzyl alcohol, **3**, were measured in perchloric acid solutions, using H_2O and D_2O as the solvent, and also in acetic acid and tris(hydroxymethyl)methylammonium ion buffers, using H_2O as the solvent. The rate profiles constructed from these data show hydronium-ion-catalyzed and uncatalyzed hydration reaction regions, just like the rate profiles based on literature data for hydration of the oxygen analogue, *o*-quinone methide, of the presently examined substrate. Solvent isotope effects on hydronium-ion catalysis of hydration for the two substrates, however, are quite different: $k_H/k_D = 0.42$ for the oxygen quinone methide, whereas $k_H/k_D = 1.66$ for the sulfur substrate. The inverse nature ($k_H/k_D < 1$) of the isotope effect in the oxygen system indicates that this reaction occurs by a preequilibrium proton-transfer reaction mechanism, with protonation of the substrate on its oxygen atom being fast and reversible and capture of the benzyl-type carbocationic intermediate so formed being rate-determining. The normal direction ($k_H/k_D > 1$) of the isotope effect in the sulfur system, on the other hand, suggests that protonation of the substrate on its sulfur atom is in this case rate-determining, with carbocation capture a fast following step. A semiquantitative argument supporting this hypothesis is presented.

Quinone methides are interesting molecules with wide applications in organic synthesis;[1] they also play key roles in wood chemistry[2] and show pronounced biological activity.[3] In living systems where water is the ubiquitous medium, this biological activity must operate against a background of wasteful quinone methide hydration reactions. Because little appeared to be known about the kinetics and reaction mechanisms of these hydrations, we have undertaken a program of research aimed at providing some of the lacking information.

Simple quinone methides are quite short-lived in aqueous solution. They can, however, be generated and studied in that medium by using flash photolytic methods, as illustrated in eq 1 for the presently examined substrate: irradiation of benzothiete, **1**, leads to opening of the four-membered ring, which produces *o*-thioquinone methide **2**, whose hydration to *o*-mercaptobenzyl alcohol, **3**, can be monitored by following the decay of thioquinone methide UV absorbance.



(1)

Experimental Section

Materials. Benzothiete was prepared from *o*-mercaptobenzyl alcohol via benzooxathiinone.[4] All other materials were best available commercial grades.

Kinetics. Rates of hydration of *o*-thioquinone methide were measured by monitoring the decay of *o*-thioquinone methide absorbance at $\lambda = 460$ nm[5] using an eximer laser flash photolysis system operating at $\lambda = 248$ nm that has already been described.[6] The temperature of reaction mixtures at which the kinetic measurements were made was controlled

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at 25.0 ± 0.1 °C. The data so obtained conformed to the first-order rate law well, and observed first-order rate constants were obtained by least-squares fitting of a single-exponential function.

Results

It was already known, when we began the present work, that irradiation of benzothiete (**1**) causes opening of its four-membered ring, producing *o*-thioquinone methide (**2**), as shown in eq 1.[4] We verified this by observing that flash photolytic irradiation of benzothiete gives a transient species whose UV absorbance at λ = 460 nm is characteristic of *o*-thioquinone methide.[5] We also observed that this irradiation, when conducted in aqueous solution, produces *o*-mercaptobenzyl alcohol (**3**), the expected *o*-thioquinone methide hydration product (eq 1). This was shown to be so by HPLC analysis using retention times, UV spectra, and spiking with an authentic sample to identify the product.

We measured rates of *o*-thioquinone methide hydration in perchloric acid solutions over the concentration range $[HClO_4] = 0.001-4.56$ M using H_2O as the solvent and over the concentration range $[DClO_4] = 0.001-1.14$ M using D_2O as the solvent. Some rate measurements were also made in acetic acid and tris(hydroxymethyl)methylammonium ion buffers using H_2O as the solvent. These data are summarized in Tables S1 and S2 (Supporting Information).[7]

The rates of reaction at perchloric acid concentrations greater than 0.10 M increased more rapidly than in direct proportion to acid concentration, and the data were therefore analyzed by the Cox−Yates method using the X_0 acidity function,[8] with X_0 in D_2O equal to X_0 in H_2O at the same molar acid concentration.[9] Fitting of the data was done using the expression given as eq 2, in which $[L_3O^+]$ and X_0 are independent variables and k_{uc} and k_L are rate constants for the uncatalyzed and hydronium-ion-catalyzed reactions, respectively. Least squares analysis produced $(k_{uc})_H = (1.19 \pm 0.01) \times 10^5$ s^{-1}, $(k_{uc})_H/(k_{uc})_D = 1.21 \pm 0.01$, and $k_H = (7.04 \pm 0.16) \times 10^4$ M^{-1} s^{-1}, $k_H/k_D = 1.66 \pm 0.15$.

$$k_{obs} = k_{uc} + k_L[L_3O^+]10^{mX_0} \quad (2)$$

The rate measurements in buffers were carried out using a series of solutions of constant buffer ratio and constant ionic strength (0.10 M), and therefore constant hydronium ion concentration, but varying total buffer concentration. The data within a given series proved to be linearly proportional to buffer concentration, and the data were therefore analyzed using the buffer dilution expression shown as eq 3, in which k_{buff} is the buffer catalytic coefficient and k_{int} is the zero-buffer-concentration intercept. These zero-concentration intercepts, together with the data obtained from measurements in perchloric acid solutions, were used to construct rate profiles for the *o*-thioquinone methide hydration reaction (vide infra); values of $[H^+]$ needed for this purpose were obtained by calculation, using acidity constants for the buffer acids from the literature and activity coefficients recommended by Bates.[10]

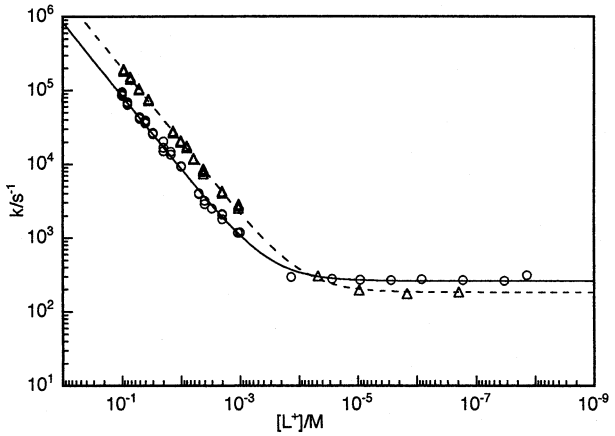
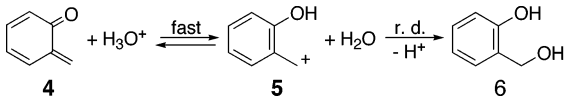


FIGURE 1. Rate profiles for the hydration of *o*-quinone methide in H_2O, O, and D_2O, △, solution at 25 °C.

$$k_{obs} = k_{int} + k_{buff}[buffer] \quad (3)$$

Discussion

The rate profiles displayed in Figure 1 are based upon rate measurements we made in a previous study of the hydration of *o*-quinone methide,[11] which is the oxygen analogue of the presently examined *o*-thioquinone methide. It may be seen that the hydronium-ion-catalyzed portion of that reaction occurs more rapidly in D_2O solution than in H_2O solution. This gives the isotope effect $k_H/k_D = 0.42$,[11] whose inverse nature, $k_H/k_D < 1$, is classic evidence for a preequilibrium substrate-protonation reaction mechanism,[12] 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 by water of the benzyl-type carbocation so formed (eq 4). 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.[13] Conversion of H_3O^+ into H_2O in the equilibrium step of eq 4 then leads to a tightening of the hydrogenic environment of the species involved, producing an inverse isotope effect.



4 **5** 6 (4)

This reaction mechanism is supported by saturation of hydronium-ion catalysis in the case of more basic substrates such as *o*-quinone α-phenylmethide, **7**, or

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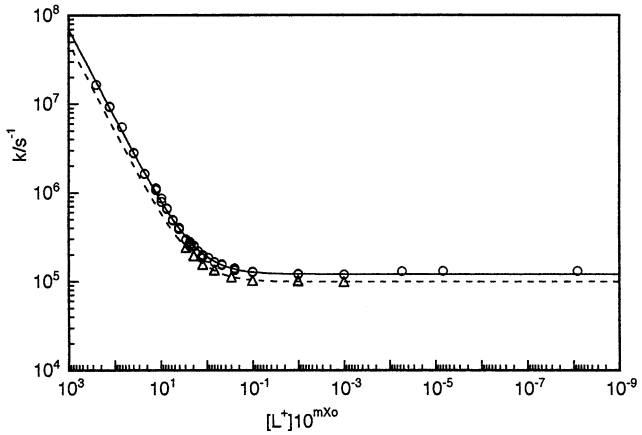
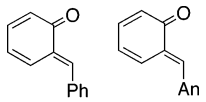


FIGURE 2. Rate profiles for the hydration of *o*-thioquinone methide in H_2O, O, and D_2O, △, solution at 25 °C.

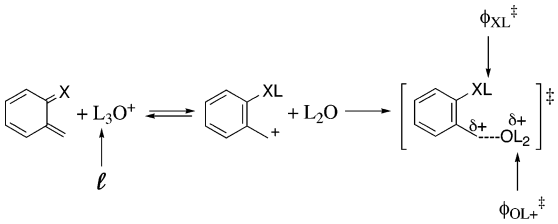
o-quinone α-(*p*-anisyl)methide, **8**.[14] With these substrates, as the hydronium ion concentration increases, the position of the preequilibrium shifts over to protonated substrate; protonated substrate then becomes the reaction's initial state, further substrate protonation is no longer necessary, and acid catalysis disappears.



7 **8**

Figure 2 shows rate profiles for the hydration of the sulfur analogue, *o*-thioquinone methide, constructed using presently measured rate constants. It may be seen that the shape of these profiles is similar to those of the oxygen analogue shown in Figure 1: both have hydronium-ion-catalyzed and uncatalyzed regions. There is, however, an important difference: whereas the isotope effect on hydronium-ion catalysis in the oxygen system was inverse, that for the sulfur system is in the normal direction: $k_H/k_D = 1.66$. This suggests that the hydronium-ion-catalyzed hydration of *o*-thioquinone methide is not occurring by a preequilibrium proton-transfer reaction mechanism.

This suggestion is reinforced by an estimate of the isotope effect on such a (hypothetical) preequilibrium reaction of the thioquinone substrate that can be made using fractionation factor theory.[13] This theory formulates solvent isotope effects as the product of fractionation factors for all exchangeable hydrogens in the reaction's initial state, ϕ^{IS}, divided by a similar product of fractionation factors for all exchangeable hydrogens in the reaction's transition state, $\phi^{‡}$: $k_H/k_D = \Pi\phi_I^{IS}/\Pi\phi_j^{‡}$. Equation 5, in which exchangeable hydrogens are designated by the symbol "L", shows that the initial state of a quinone methide hydration reaction occurring by a preequilibrium proton-transfer mechanism has exchangeable hydrogens in its hydronium ion, with fractionation factor *l*,[15] and that the transition state has exchangeable hydrogens taking on positive charge in its attacking water molecule, with fractionation factor $\phi_{OL+}^{‡}$, plus exchangeable hydrogens in its uncharged X−L bond, with fractionationfactor $\phi_{XL}^{‡}$.

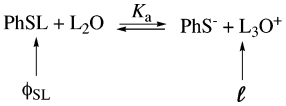


(5)

Two of these three sets of exchangeable hydrogens, those in the initial state hydronium ion and those in the transition state attacking water molecule, occur in bonds to the same kind of atom (oxygen) in the sulfur system (eq 5, X = S) as in the oxygen system (eq 5, X = O), and their fractionation factors will therefore cancel in a ratio of sulfur system to oxygen system isotope effects. This ratio of isotope effects thus reduces to the simple expression involving only fractionation factors for the S−H and O−H bonds in the reaction's transition state, as shown in eq 6.

$$(k_H/k_D)_S/(k_H/k_D)_O = \phi_{OL}^{‡}/\phi_{SL}^{‡} \qquad (6)$$

Hydrogenic fractionation factors are based upon a scale that assigns a value of unity to factors for uncharged O−H bonds, and we may therefore take $\phi_{OL}^{‡} = 1.00$. The transition state S−H bond in the X = S version of eq 5 is fully formed and uncharged. It is therefore not unlike the S−H bond in thiophenol, and a value of $\phi_{SL}^{‡}$ may consequently be estimated from the known solvent isotope effect on the acid ionization of thiophenol (eq 7).



(7)

The fractionation factor expression for an equilibrium process such as this is analogous to that for the rate process given above, with final state fractionation factors replacing transition state values: $(K_a)_H/(K_a)_D = \phi_{SL}/l^3$. Use of $l = 0.69$[13] and $(K_a)_H/(K_a)_D = 2.2$[16] then leads to ϕ_{SL} $(= \phi_{SL}^{‡}) = 0.72$. This result is consistent with $\phi_{SL} = 0.83$ and 0.65 determined for cysteine and 2-mercaptoethanesulfonate, respectively.[17]

We have measured seven solvent isotope effects for oxygen quinone methides hydrating by the preequilibrium proton-transfer reaction mechanism.[11,14,18] Use of the average of these values, $k_H/k_D = 0.39 \pm 0.03$, plus $\phi_{OL}^{‡} = 1.00$ and $\phi_{SL}^{‡} = 0.72$ in eq 6 then leads to $(k_H/k_D)_S = 0.54$ as an estimate of the solvent isotope effect for *o*-thioquinone methide hydrating by a (hypothetical) preequilibrium proton-transfer reaction mechanism. This estimate is quite different from the measured value $k_H/$

(14) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2002**, *124*, 717−722.

(15) Symbol "*l*", rather than "ϕ" with an appropriate subscript and/or superscript, is commonly used for the fractionation factor of the hydronium ion.

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(17) Jarret, R. M.; Saunders, M. *J. Am. Chem. Soc.* **1985**, *107*, 2648−2654.

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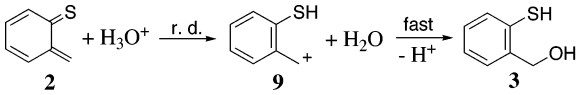
$k_D = 1.66$, certainly different enough to add good support to the idea that the hydronium-ion-catalyzed hydratioin of *o*-thioquinone methide does not occur by a preequilibrium proton-transfer reaction mechanism

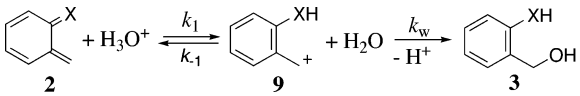
Our working hypothesis is that proton transfer to sulfur is rate-determining in the hydronium-ion catalyzed hydration of *o*-thioquinone methide and that this step is then followed by rapid capture of the benzyl-type carbocation thus formed, **9**, by a water molecule (eq 8).



2 **9** **3** (8)

The difference between this mechanism and the preequilibrium scheme that operates in the case of oxygen quinone methides is consistent with the well-known fact that proton transfers to and from sulfur are slower than those involving oxygen.[19] It is also consistent with the poorer ability of an ortho SH group than an ortho OH group at stabilizing the positive charge of the benzyl-type carbocation intermediate in these quinone methide hydration reactions, as evidenced, for example, by the resonance substituent constants of these groups: $R^+(SH) = -0.33$ and $R^+(OH) = -1.25$.[20] Each of these differences operates in a way to slow the reverse of the proton-transfer step and accelerate the subsequent carbocation capture step, thus changing the preequilibrium reaction mechanism observed for the oxygen quinone methide into a rate-determining proton-transfer scheme for the sulfur quinone methide.

This conclusion can be supported further by the following approximate quantitative argument. Whether the generalized reaction of eq 9 occurs by a preequilibrium mechanism or by a rate-determining proton-transfer scheme depends on the relative magnitudes of the rate constants k_{-1} and k_w: if $k_{-1} > k_w$, the mechanism is preequilibrium proton transfer, and if $k_{-1} < k_w$, the mechanism is rate-determining proton transfer.



2 **9** **3** (9)

In the oxygen quinone methide case, k_{-1} refers to a downhill oxygen-to-oxygen proton transfer reaction that would normally be a diffusion-controlled process with a rate constant equal to the rotational correlation time of the solvent water, 10^{11} s^{-1}.[21] In the present case, however, k_{-1} will be less than this because the reaction converts an aromatic benzene ring into a cyclohexadiene structure, giving up some of the benzene resonance energy and adding to the small diffusional reaction barrier. But k_{-1} cannot be less than k_w, which has been estimated at $k_w = 4 \times 10^7$ s^{-1},[11] because the oxygen quinone methide reacts by a preequilibrium mechanism with $k_{-1} > k_w$. A reasonable estimate might therefore be $k_{-1} = 1 \times 10^9$ s^{-1}. The value of k_{-1} for the sulfur system will be less than this because proton transfer to and from sulfur is slower than that to and from oxygen,[19] and a not unreasonable estimate of this retardation might be the factor 10^2 by which downhill proton removal from the S−H bond of 2-mercaptoethanol is slower than the anticipated diffusion-controlled reaction of the corresponding oxygen system.[19a] This puts k_{-1} for the sulfur quinone methide at $k_{-1} = (1 \times 10^9)(10^{-2}) = 1 \times 10^7$ s^{-1}. It was noted above that an ortho SH group is less effective than an ortho OH group at stabilizing the positive charge of the benzyl-type carbocation intermediate in these quinone methide hydration reactions. This will make the sulfur system carbocation more reactive than that in the oxygen system, pushing k_w for the sulfur quinone methide above the value, $k_w = 4 \times 10^7$ s^{-1},[11] estimated for the oxygen quinone methide. The net result is to change the oxygen system inequality $k_{-1} > k_w$ into the different inequality $k_{-1} < k_w$ for the sulfur system and thus change the preequilibrium reaction mechanism into a rate-determining proton transfer reaction scheme.

Although we have been able to make a plausible case for a reaction mechanism in which proton transfer to sulfur is rate-determining and subsequent capture of the benzyl-type cation is a fast following step, we cannot, on the basis of the evidence we have so far, rule out a concerted reaction scheme in which proton transfer and cation capture occur in the sane reaction step. We do favor the stepwise mechanism, however, and we are using that as a working hypothesis to guide further studies, because it is a simple variant of the preequilibrium reaction mechanism that is firmly established for oxygen quinone methide systems.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support of this work.

Supporting Information Available: Tables S1 and S2 of rate data. This material is available free of charge via the Internet at http://pubs.acs.org.

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