

## Reactive intermediates. Some chemistry of quinone methides\*

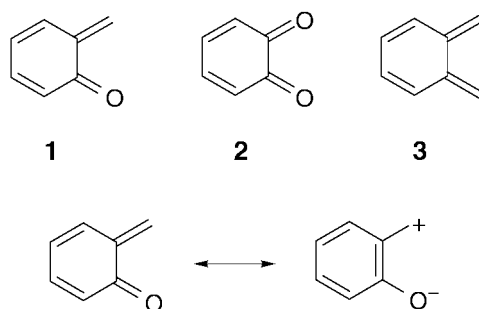
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**Abstract:** Quinone methides were produced in aqueous solution by photochemical dehydration of *o*-hydroxybenzyl alcohols (*o*-HOC<sub>6</sub>H<sub>4</sub>CHROH; R = H, C<sub>6</sub>H<sub>5</sub>, 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>), and flash photolytic techniques were used to examine their rehydration back to starting substrate as well as their interaction with bromide and thiocyanate ions. These reactions are acid-catalyzed and show inverse isotope effects ( $k_{\text{H}^+}/k_{\text{D}^+} < 1$ ), indicating that they occur through preequilibrium protonation of the quinone methide on its carbonyl carbon atom followed by rate-determining capture of the benzyl carbocations so formed by H<sub>2</sub>O, Br<sup>-</sup>, or SCN<sup>-</sup>. With some quinone methides (R = C<sub>6</sub>H<sub>5</sub> and 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>) this acid catalysis could be saturated, and analysis of the data obtained in the region of saturation for the example with R = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub> produced both the equilibrium constant for the substrate protonation step and the rate constant for the rate-determining step. Energy relationships comparing the quinone methides with their benzyl alcohol precursors are derived.

### INTRODUCTION

The parent *o*-quinone methide, **1**, is a molecule having a cyclohexadiene core with a carbonyl group and a methylene unit attached. It is related to *o*-quinone, **2**, which has two carbonyl groups, and to *o*-quinone dimethide, also known as *o*-xylylene, **3**, which has two methylene units. Unlike its relatives, however, *o*-quinone methide, with its two different functional groups, is highly polarized and therefore quite reactive. It is actually a resonance hybrid of two principal canonical forms, one of which is dipolar (Scheme 1). This gives the molecule both cationic and anionic centers, and it therefore reacts with both nucleophiles and electrophiles. Its reactions, moreover, usually 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 have been developed for their generation [1].



Scheme 1

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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. In order to provide information about these hydrations, we have begun a detailed investigation of their kinetics and mechanisms. Our study so far has focused on *o*-quinone methide itself and some of its derivatives.

### ***o*-QUINONE METHIDE**

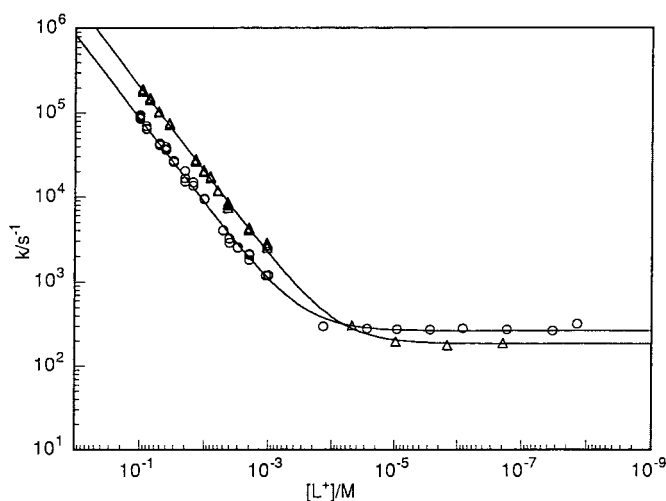
*o*-Quinone methide is quite short-lived in aqueous solution, but most of its reactions in that medium are accessible by microsecond and nanosecond flash photolytic methods. We generated this substance using a photoreaction developed by Peter Wan, which, as shown in eq. 1, produces *o*-quinone methide by dehydration of *o*-hydroxybenzyl alcohol [1,3]. Flash photolysis of this alcohol in aqueous solution generated a transient species with the strong absorbance at  $\lambda = 400$  nm that is characteristic of *o*-quinone methide [4]. Decay of this transient conformed to the first-order rate law well, and analysis of spent reaction mixtures showed only *o*-hydroxybenzyl alcohol to be present, as expected for hydration of the quinone methide back to starting substrate.



We made hydration rate measurements at 25 °C in dilute aqueous perchloric acid solutions and in acetic acid and biphosphate ion buffers, all at a constant ionic strength of 0.10 M, using both H<sub>2</sub>O and D<sub>2</sub>O as the solvent. The buffer solutions gave pronounced buffer catalysis, but extrapolation of the data to zero buffer concentration provided intercepts, which, together with the perchloric acid data, were used to construct the rate profiles shown in Fig. 1.

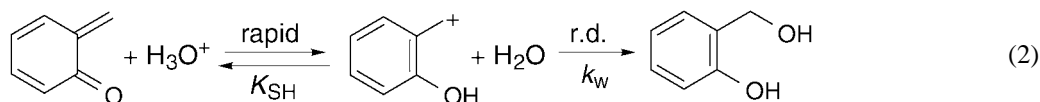
It may be seen that there are both acid-catalyzed and uncatalyzed hydration reactions, and that, whereas the acid-catalyzed process is faster in D<sub>2</sub>O than in H<sub>2</sub>O,  $k_{\text{H}^+}/k_{\text{D}^+} = 0.42 \pm 0.08$ , the opposite is true of the uncatalyzed reaction,  $(k_{\text{UC}})_{\text{H}_2\text{O}}/(k_{\text{UC}})_{\text{D}_2\text{O}} = 1.42 \pm 0.07$ .

The inverse isotope effect ( $k_{\text{H}}/k_{\text{D}} < 1$ ) on the acid-catalyzed process indicates that this reaction proceeds by a preequilibrium substrate-protonation mechanism [5], which in this case may be formu-

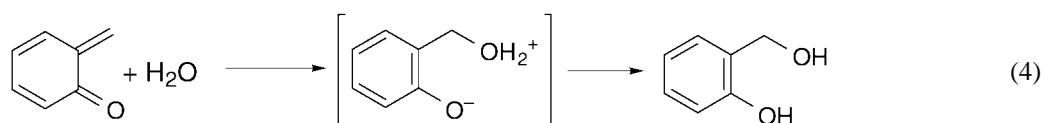
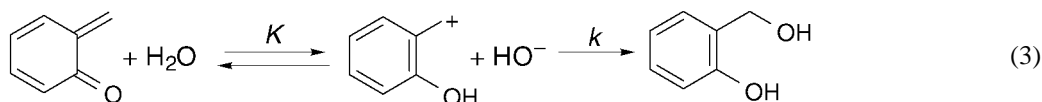


**Fig. 1** Rate profiles for the hydration of *o*-quinone methide in H<sub>2</sub>O (○) and D<sub>2</sub>O (△) solution.

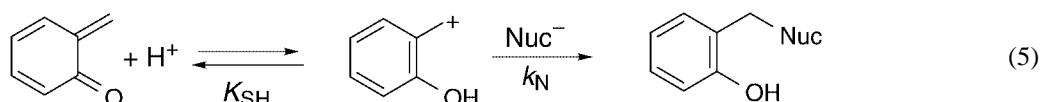
lated as rapid equilibrium protonation of *o*-quinone methide on its carbonyl oxygen atom followed by rate-determining capture of the cation so formed by water, eq. 2. The inverse nature of this isotope effect stems from the fact that positively charged O–H bonds, such as those in the hydronium ion, are looser than uncharged O–H bonds, such as those in a water molecule [6]. Conversion of  $\text{H}_3\text{O}^+$  into  $\text{H}_2\text{O}$  in the equilibrium step of eq. 2 then leads to a tightening of the hydrogenic environment of the species involved, and that produces an inverse isotope effect.



The isotope effect on the uncatalyzed reaction is less diagnostic. It does not serve to distinguish between preequilibrium substrate protonation by proton transfer from water followed by cation capture by hydroxide ion, eq. 3, or simple nucleophilic attack of water on the quinone methide methylene group, with or without simultaneous proton transfer to avoid a zwitterionic 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 its slow step,  $k$ . The rate law that applies to the scheme of eq. 3 is  $k_{\text{UC}} = kK$ , with  $K$ , the equilibrium constant of the first step, equal to the ionization constant of water,  $K_{\text{w}}$ , divided by the acidity constant of the protonated substrate,  $K_{\text{SH}}$ . The numerical value of  $K_{\text{SH}}$  is not known, but the fact that the rate profile of Fig. 1 shows no saturation of acid catalysis up to the highest acid concentration used,  $[\text{H}^+] = 0.10 \text{ M}$ , indicates that  $K_{\text{SH}}$  must be greater than this, i.e.,  $K_{\text{SH}} > 0.10 \text{ M}$ . The observed value of  $k_{\text{UC}}$  is  $2.6 \times 10^2 \text{ s}^{-1}$ , and use of this and  $K_{\text{w}} = 1 \times 10^{-14} \text{ M}^{-2}$  plus  $K_{\text{SH}} > 0.10 \text{ M}$  in the rate law then leads to  $k > 2.6 \times 10^{15} \text{ M}^{-1} \text{ s}^{-1}$ , which far exceeds the encounter-controlled limit of  $k \cong 1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ .



Benzyl carbocations such as that formed by oxygen-protonation of *o*-quinone methide (eq. 2) should be captured by other nucleophiles in addition to water, and this proved to be the case. We found that rates of decay of *o*-quinone methide at fixed hydronium ion concentrations were strongly accelerated by added bromide and thiocyanate ions, and that these accelerations increased with increasing  $[\text{H}^+]$ . Comparison of the acidity dependence of these accelerations in  $\text{H}_2\text{O}$  with those in  $\text{D}_2\text{O}$  gave the solvent isotope effects  $k_{\text{H}^+}/k_{\text{D}^+} = 0.49 \pm 0.01$  for the bromide ion reaction and  $k_{\text{H}^+}/k_{\text{D}^+} = 0.54 \pm 0.07$  for the thiocyanate ion reaction. The inverse direction of these isotope effects confirms that these reactions occur by preequilibrium carbocation formation (eq. 5) just like the hydration process.



It seems likely that the reaction of the *o*-hydroxybenzyl carbocation with thiocyanate ion (eq. 5,  $\text{Nuc} = \text{SCN}^-$ ) is an encounter-controlled process. The reactivity of this carbocation should be similar to that of the *p*-methoxybenzyl cation, whose capture by azide ion is encounter-controlled [7], and since thiocyanate ion is a better nucleophile than azide ion [8], the reactions of thiocyanate with these carbocations should be encounter-controlled as well. Use of the encounter-controlled rate constant  $k_{\text{N}} = 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$  and the value of the observed rate constant for thiocyanate,  $k_{\text{obs}} = (9.6 \pm 0.8) \times 10^7$

$\text{M}^{-2} \text{s}^{-1}$ , in the rate law for the process of eq. 5,  $k_{\text{obs}} = k_{\text{N}}/K_{\text{SH}}$ , then leads to an estimate of the protonated *o*-quinone methide acidity constant,  $K_{\text{SH}} = 52 \text{ M}$ ,  $\text{p}K_{\text{SH}} = -1.72$ .

In sufficiently strong acidic solutions, the position of equilibrium protonation of *o*-quinone methide should shift from unprotonated to protonated species, and acid catalysis of the reactions of this substance will then become saturated. Suitable analysis of rate data obtained in the region of change-over from catalysis to no catalysis can then be used to determine  $K_{\text{SH}}$  directly. We consequently make hydration rate measurements in concentrated perchloric acid solutions up to  $[\text{HClO}_4] = 4.5 \text{ M}$ , where observed rate constants reached the limit of our flash photolysis system ( $k = 2 \times 10^7 \text{ s}^{-1}$ ), but, as Fig. 2 shows, no saturation of acid catalysis occurred. Rates of hydration, in fact, began to increase faster than in direct proportion to acid concentration, as might have been expected, for many reactions follow acidity functions rather than acid concentration in concentrated acid solutions.

We then switched our quest for saturation of acid catalysis to modification of the substrate through introduction of substituents designed to stabilize the benzyl carbocation intermediate. This would have the effect of retarding its capture by nucleophiles and perhaps thereby inducing saturation at slower, more accessible reaction rates.

### SUBSTITUTED *o*-QUINONE METHIDES

As Fig. 3 shows, we achieved saturation of acid catalysis of *o*-quinone methide hydration with the  $\alpha$ -phenyl derivative, **4**, which we generated by flash photolysis of the corresponding benzyl alcohol, eq. 6.

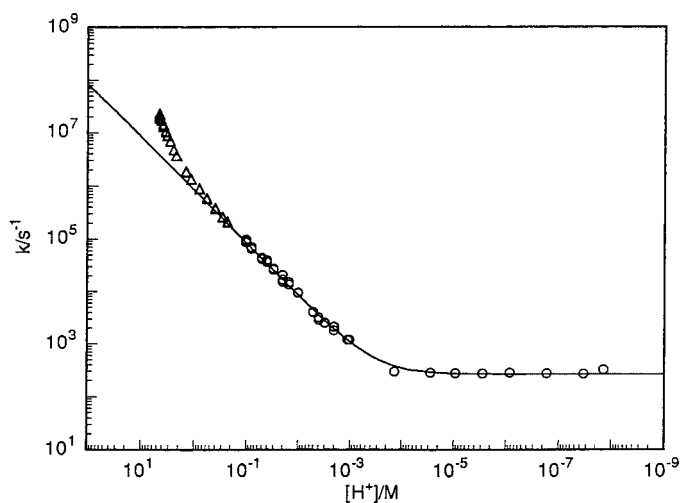
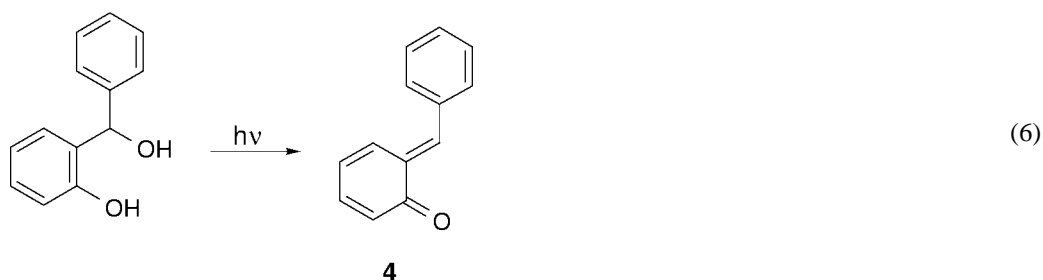
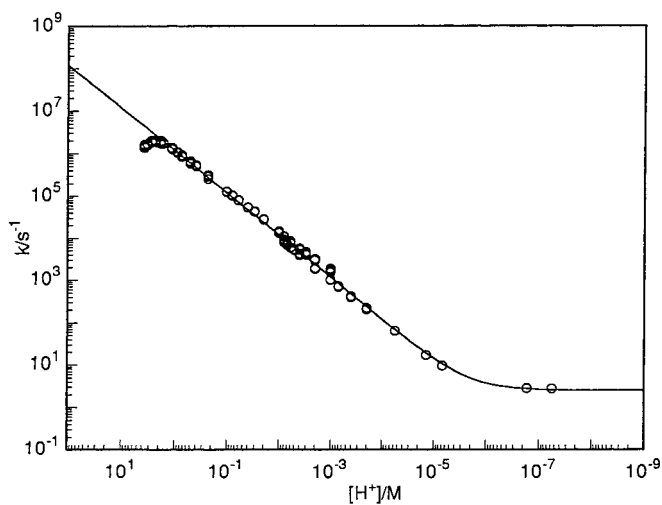


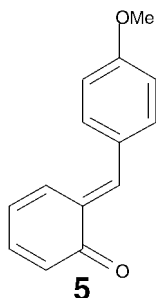
Fig. 2 Comparison of rates of hydration of *o*-quinone methide in concentrated and dilute acid solution.



**Fig. 3** Rate profile for the hydration of *o*-quinone  $\alpha$ -phenylmethide in H<sub>2</sub>O solution.

Acid catalysis with this substrate leveled off at  $[\text{HClO}_4] = 2.5 \text{ M}$ , and, beyond this point, rate constants actually began to drop. This is consistent with the known inhibitory effect of perchlorate ion on the rate of reaction of large delocalized carbocations with water [9]. In dilute acid solution, hydration of this substrate gave the solvent isotope effect  $k_{\text{H}^+}/k_{\text{D}^+} = 0.33 \pm 0.01$ , whose inverse nature confirms a preequilibrium protonation mechanism for this reaction.

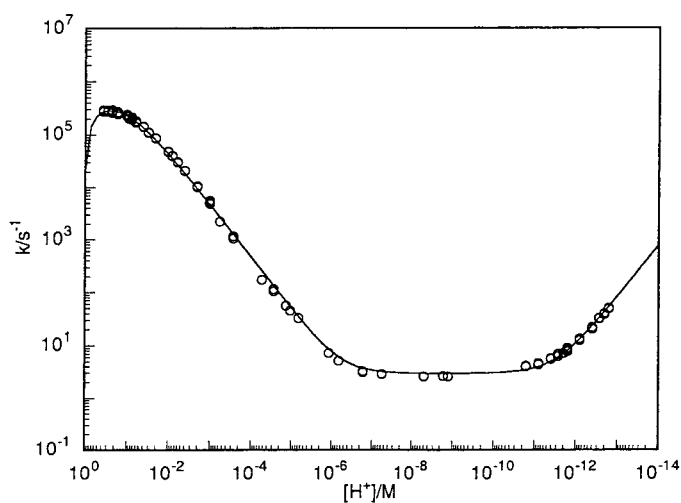
Detailed analysis of rate data obtained in concentrated acid solutions is complicated by the need to use acidity functions. In order to avoid this complication, we examined *o*-quinone  $\alpha$ -(*p*-anisyl)methide, **5**, whose oxygen-protonated benzyl cation product is stabilized further by the *p*-methoxy group. We generated this quinone methide, as we did previous substrates, by flash photolysis of the corresponding benzyl alcohol.



As Fig. 4 shows, a saturation of acid catalysis of hydration of this substrate begins to occur at  $[\text{HClO}_4] \cong 0.1 \text{ M}$ . Again, rates of reaction began to drop at higher acidities, in keeping with the expected inhibitory effect of perchlorate ion. With this substrate, we could also make hydration rate measurements well into the basic region. That was not possible with the parent *o*-quinone methide itself because of a complicating, very fast reaction of that more reactive substrate with phenoxide ions, produced by ionization of regenerated plus initially unphotolyzed *o*-hydroxybenzyl alcohol [10].

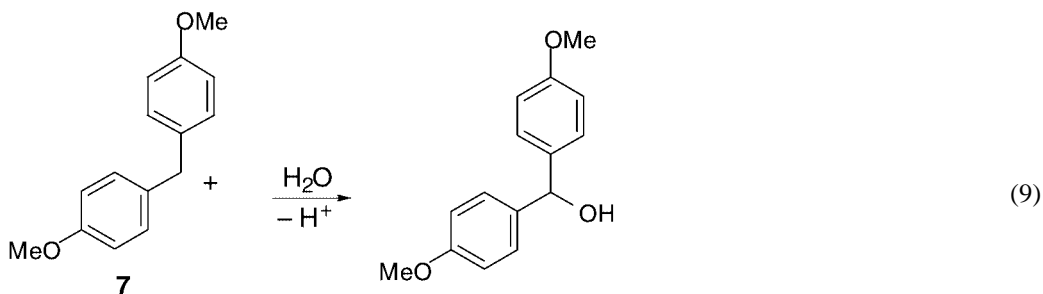
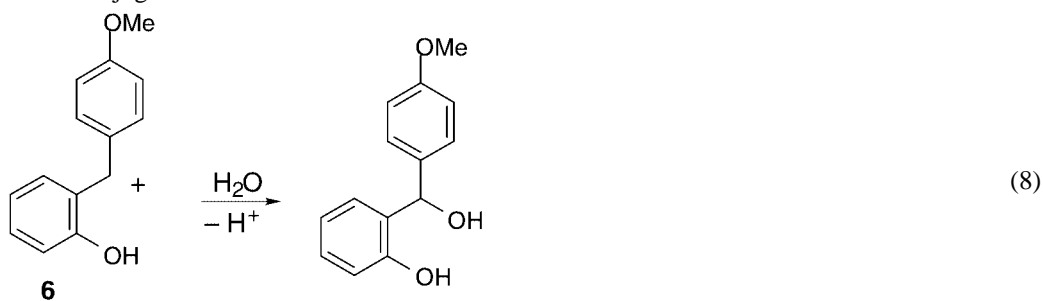
The high-acidity portion of this rate profile, determined in perchloric acid solutions over the concentration range  $[\text{HClO}_4] = 0.001\text{--}0.4 \text{ M}$ , was analyzed using the rate law shown in eq. 7. The last term of this rate law accounts for the

$$k_{\text{obs}} = k_{\text{w}}[\text{H}^+]/(K_{\text{SH}} + [\text{H}^+]) - \text{S}[\text{ClO}_4^-] \quad (7)$$



**Fig. 4** Rate profile for the hydration of *o*-quinone  $\alpha$ -(*p*-anisyl)methide in H<sub>2</sub>O solution.

inhibitory effect of perchlorate ion, and the other symbols are as defined by eq. 2. Least squares fitting produced the results  $k_w = (4.6 \pm 0.1) \times 10^5 \text{ s}^{-1}$  and  $K_{\text{SH}} = (8.2 \pm 0.2) \times 10^{-2} \text{ M}$ ,  $\text{p}K_{\text{SH}} = 1.09 \pm 0.01$ . The rate constant  $k_w$  refers to capture of the (2-hydroxy-4'-methoxy)diphenylmethyl cation, **6**, by water, eq. 8; its value is consistent with  $k = 1.0 \times 10^5 \text{ s}^{-1}$  for the analogous reaction of the (4,4'-dimethoxy)diphenylmethyl cation, **7** [11], eq. 9, which is the closest analog of the present system for which such a rate constant has been measured. The value obtained for the acidity constant  $K_{\text{SH}}$ , on the other hand, makes the carbonyl-oxygen protonated quinone methide a much weaker acid, by 4–5 orders of magnitude, than carbonyl-protonated simple ketones [12]. Protonation of the quinone methide, however, generates an aromatic phenol ring, and this makes the quinone methide a considerably stronger base and its conjugate acid a much weaker acid.



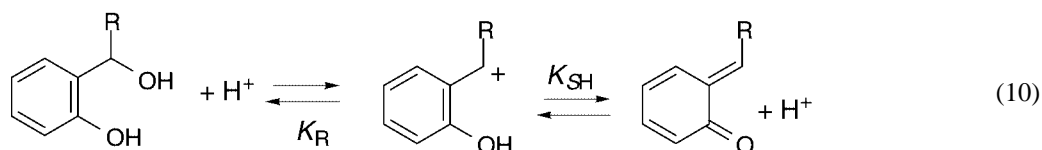
Measurements of hydration of *o*-quinone  $\alpha$ -(*p*-anisyl)methide were also made in D<sub>2</sub>O solutions of perchloric acid, and analysis of these data produced results, which, when compared with their H<sub>2</sub>O

counterparts, gave the isotope effects  $K_{SH}/K_{SD} = 3.6 \pm 0.1$  and  $(k_w)_{H_2O}/(k_w)_{D_2O} = 1.32 \pm 0.04$ . The first of these isotope effects agrees well with solvent isotope effects on the ionization of other oxygen acids, which generally fall in the range  $K_H/K_D = 3-4$  [13]. The normal direction ( $K_H/K_D > 1$ ) of these isotope effects stems from the fact that acid ionization involves conversion of a water molecule, with its relatively tight uncharged O–H bonds, into a hydronium ion, whose positively charged O–H bonds are looser. The isotope effect on the rate constant for capture of the carbocation by water,  $k_w$ , is also consistent with expectation, for the capturing water molecule is taking on positive charge, and initially tight, uncharged O–H bonds are being converted into looser charged ones. This produces an isotope effect in the normal direction, although one of only modest magnitude because the bonding changes involved are only partly realized in the early transition state of this fast reaction [14].

Decay of this quinone methide, just like that of the parent unsubstituted substrate, was strongly accelerated by thiocyanate ion. This acceleration was again catalyzed by perchloric acid, but in this case the catalysis, though proportional to acid concentration at low  $[HClO_4]$ , became saturated at higher acidities. This behavior is similar to saturation of acid catalysis of the hydration reaction noted above, and analysis of the data using an analog of the rate law of eq. 7 produced an acidity constant,  $K_{SH} = (6.7 \pm 0.5) \times 10^{-2}$  M, consistent with that determined by the hydrolysis reaction,  $K_{SH} = (8.2 \pm 0.2) \times 10^{-2}$  M. Saturation of acid catalysis, of course, confirms a preequilibrium protonation mechanism for this reaction.

## ENERGETICS

The carbocations formed here by quinone methide protonation can also be generated by reaction of the corresponding benzyl alcohols with concentrated acids, and the equilibrium constants for these reactions referred to dilute solution standard states ( $K_R$  values) may be evaluated using acidity function methods. Combination of  $K_R$  values with protonated quinone methide acidity constants,  $K_{SH}$  (eq. 10), then provides equilibrium constants joining the benzyl alcohols with the quinone methides, which in turn affords a measure of the energy difference between a formally fully formed aromatic ring and the quinone methide structure.



We determined  $K_R$  for the (2-hydroxy-4'-methoxy)diphenylmethyl cation by monitoring the strong absorbance of this ion, at  $\lambda = 508$  nm in concentrated perchloric acid solutions. The conventional way of treating such data is to convert absorbances into log I values, where I is the ratio of concentrations of protonated to unprotonated forms of the substrate, and then use an acidity function to extrapolate log I linearly down to dilute solution. This method, however, requires good knowledge of the limiting absorbances of the unprotonated and fully protonated forms of the substrate, since these are used as known parameters in the calculation of each value of I. Values of I, moreover, are less reliable the farther they are from unity [15], and measurements should either be confined to a region not too far distant from  $I = 1$ , or log I values should be weighted appropriately.

These difficulties can be avoided by obtaining  $K_R$  through nonlinear least-squares fitting using a titration curve expression such as that shown in eq. 11. In this kind of analysis, the limiting absorbances  $A_{R^+}$  and  $A_{ROH}$  are treated as

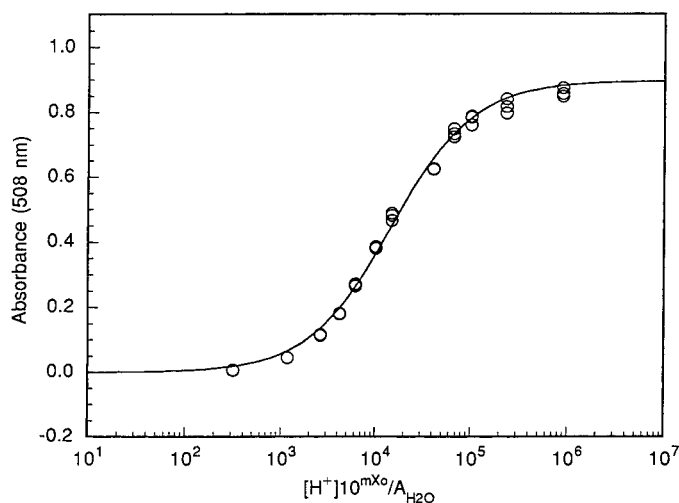
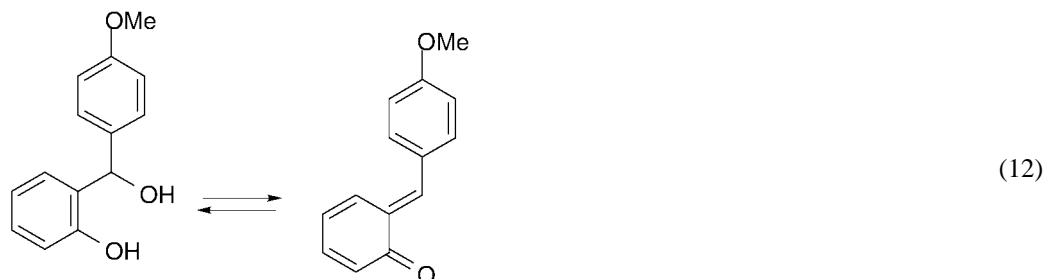
$$A = \frac{A_{R^+} ([H^+] 10^{mX_o} / a_{H_2O}) + A_{ROH} K_R}{K_R + ([H^+] 10^{mX_o} / a_{H_2O})} \quad (11)$$

disposable parameters whose values are determined by the fit, and absorbances of solutions in which the substrate is only partly protonated,  $A$  are used directly without calculating  $I$ . Since all values of  $A$  are likely to have the same uncertainty [16], no weighting of points is required.

The activity of water,  $a_{\text{H}_2\text{O}}$ , appears in eq. 11 because acid ionization of carbocations involves incorporation of a molecule of water. In the present work, water activities were expressed in mole fraction units, and the  $X_0$  function [17] was used to express acidity because this appears to be the best scale currently available for referring measurements to dilute solution [18]. The quantity  $m$  in eq. 11 corresponds to the slope of an  $X_0$  vs.  $\log I$  plot.

As Fig. 5 illustrates, absorbance data measured for the ionization of (2-hydroxy-4'-methoxy)diphenylmethyl cation in perchloric acid solution over the concentration range  $[\text{HClO}_4] = 5\text{--}11\text{ M}$  conforms to the expression of eq. 11 well. Two separate determinations produced consistent results, whose weighted average gave  $K_{\text{R}} = (1.46 \pm 0.29) \times 10^4\text{ M}$ ,  $\text{p}K_{\text{R}} = -4.16 \pm 0.09$ .

Combination of this result with  $K_{\text{SH}}$  for this system gives  $K = (5.6 \pm 1.1) \times 10^{-6}$  as the equilibrium constant relating *o*-quinone  $\alpha$ -(*p*-anisyl)methide to (2-hydroxy-4'-methoxy)diphenylmethanol, eq. 12 which puts the quinone methide some  $7.2\text{ kcal mol}^{-1}$  above the alcohol. This is considerably less than the resonance energy of  $36\text{ kcal mol}^{-1}$  commonly attributed to benzene. It was pointed out above, however, that *o*-quinone methide is a resonance hybrid that includes as one of its canonical structures a dipolar form which already contains a formally intact benzene ring (Scheme 1). The fact that the energy difference for the change of eq. 12 falls far short of the resonance energy of benzene indicates that the quinone methide derives a fair measure of stability from the benzene-type resonance of the dipolar form, and that this form makes a substantial contribution to the structure of *o*-quinone methide.



**Fig. 5** Titration curve for the acid ionization of (2-hydroxy-4'-methoxy)diphenylmethyl carbocation in aqueous ( $\text{H}_2\text{O}$ ) perchloric acid solution.



The example of eq. 12, of course, contains a *p*-anisyl ring, which must also lower the energy of the quinone methide relative to that of the alcohol by delocalizing the positive charge of the dipolar form. It would be of interest in this connection to make a similar comparison of alcohol and quinone methide for the parent unsubstituted *o*-quinone methide itself. Unfortunately, the required  $K_R$  value for 2-hydroxyphenylmethyl cation is not available. An estimate, however, can be made by extrapolating the difference between  $pK_R = 0.8$  for *tris*-(*p*-anisyl)methyl cation [18] and  $pK_R = -5.1$  for *bis*-(*p*-anisyl)methyl cation [19] to obtain  $pK_R = -11.0$  for *p*-anisylmethyl cation, and then assuming that a *p*-methoxy group is equivalent to an *o*-hydroxy group. Using this result and  $pK_{SH} = -1.7$  estimated as described above, then leads to  $5.2 \times 10^{-10}$  for the equilibrium constant relating *o*-quinone methide to *o*-hydroxybenzyl alcohol, eq. 13. This corresponds to an energy difference of  $12.7 \text{ kcal mol}^{-1}$ , which is considerably greater than the  $7.2 \text{ kcal mol}^{-1}$  obtained for the system of eq. 12, as expected.



### MECHANISM OF THE PHOTOREACTION

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  $\alpha$ -phenyl derivative (4) in acidic solutions gave a signal that decreased in intensity with increasing acidity and was lost completely at acidities greater than  $\text{pH} = 1$  [1,3]. 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.

### ACKNOWLEDGMENT

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