

### Flash Photolytic Generation and Study of *p*-Quinone Methide in Aqueous Solution. An Estimate of Rate and Equilibrium Constants for Heterolysis of the Carbon–Bromine Bond in *p*-Hydroxybenzyl Bromide

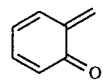
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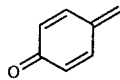
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**Abstract:** Flash photolysis of *p*-hydroxybenzyl acetate in aqueous perchloric acid solution and formic acid, acetic acid, biphosphate ion, and tris(hydroxymethyl)methylammonium ion buffers produced *p*-quinone methide as a short-lived species that underwent hydration to *p*-hydroxybenzyl alcohol in hydronium ion catalyzed ( $k_{\text{H}^+} = 5.28 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ ) and uncatalyzed ( $k_{\text{uc}} = 3.33 \text{ s}^{-1}$ ) processes. The inverse nature of the solvent isotope effect on the hydronium ion-catalyzed reaction,  $k_{\text{H}^+}/k_{\text{D}^+} = 0.41$ , indicates that this process occurs by rapid and reversible protonation of the quinone methide on its carbonyl carbon atom, followed by rate-determining capture of the *p*-hydroxybenzyl carbocation so produced by water, while the magnitude of the rate constant on the uncatalyzed process indicates that this reaction occurs by simple nucleophilic addition of water to the methylene group of the quinone methide. *p*-Quinone methide also underwent hydronium ion-catalyzed and uncatalyzed nucleophilic addition reactions with chloride ion, bromide ion, thiocyanate ion, and thiourea. The solvent isotope effects on the hydronium ion-catalyzed processes again indicate that these reactions occurred by preequilibrium mechanisms involving a *p*-hydroxybenzyl carbocation intermediate, and assignment of a diffusion-controlled value to the rate constant for reaction of this cation with thiocyanate ion led to  $K_{\text{SH}} = 110 \text{ M}$  as the acidity constant of oxygen-protonated *p*-quinone methide. In a certain perchloric acid concentration range, the bromide ion reaction became biphasic, and least-squares analysis of the kinetic data using a double-exponential function provided  $k_{\text{Br}^-} = 3.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$  as the rate constant for nucleophilic capture of the *p*-hydroxybenzyl carbocation by bromide ion,  $k_{\text{ionz}} = 8.5 \times 10^2 \text{ s}^{-1}$  for ionization of the carbon–bromine bond of *p*-hydroxybenzyl bromide, and  $K = 4.5 \times 10^5 \text{ M}^{-1}$  as the equilibrium constant for the carbocation–bromide ion combination reaction, all in aqueous solution at 25 °C. Comparisons are made of the reactivity of *p*-quinone methide with *p*-quinone  $\alpha,\alpha$ -bis(trifluoromethyl)methide as well as *p*-quinone methide with *o*-quinone methide.

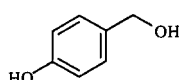
Quinone methides are short-lived reactive species with interesting chemical properties and pronounced biological activity.<sup>1</sup> We have undertaken a program of research designed to study the chemistry of these substances in aqueous solution and have already reported on our work with the parent ortho isomer **1**<sup>2</sup> and a few of its substituted analogues.<sup>3</sup> In this paper,



**1**



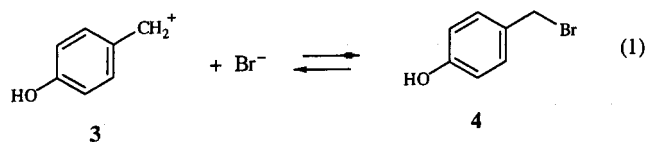
**2**



**6**

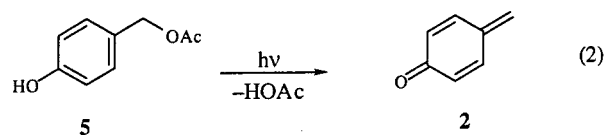
we add to that an examination of the parent para isomer **2**. Our investigation has also provided some information on the

chemistry of the *p*-hydroxybenzyl cation (**3**) through which the acid-catalyzed reactions of *p*-quinone methide occur. In par-



ticular, we have been able to provide an estimate of the rate and equilibrium constants for the reaction of this cation with bromide ion to give *p*-hydroxybenzyl bromide (**4**), eq 1.

We generated *p*-quinone methide by photolysis of *p*-hydroxybenzyl acetate (**5**), eq 2, and, because the reactions of this



(1) See, for example: Wan, P.; Barker, B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. *Can. J. Chem.* **1996**, *24*, 465–475.

(2) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2001**, *123*, 8089–8094.

(3) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2002**, *124*, 717–722.  
Chiang, Y.; Kresge, A. J.; Zhu, Y. *Photochem. Photobiol. Sci.* **2002**, *1*, 67–70.

quinone methide in the wholly aqueous solvent that we used were rapid, we employed flash photolytic methods to follow their course.

## Experimental Section

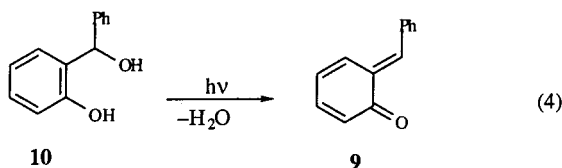
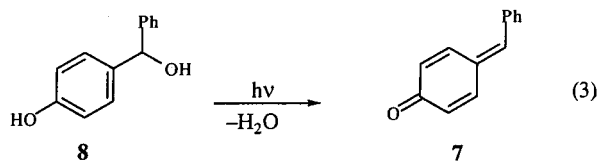
**Materials.** *p*-Hydroxybenzyl acetate (**5**) was prepared by treating *p*-hydroxybenzyl alcohol (**6**) with acetic anhydride in the presence of boron trifluoride etherate;<sup>4</sup> its <sup>1</sup>H NMR spectrum agreed with published reports.<sup>5</sup> All other materials were best available commercial grades.

**Kinetics.** Rate measurements were made using a microsecond flash photolysis system that has already been described.<sup>6</sup> Initial substrate (*p*-hydroxybenzyl acetate) concentrations were of the order of  $1 \times 10^{-4}$  M, and the temperature of all reacting solutions was controlled at  $25.0 \pm 0.05$  °C. Reactions were monitored by following the decay of *p*-quinone methide absorbance at  $\lambda = 300\text{--}310$  nm. The data so obtained, for the most part, conformed to the first-order rate law well, and observed first-order rate constants were obtained by least-squares fitting of an exponential function. In some of the slower runs, however, exponential decay was followed by a small downward drift that could have been due either to instability of the monitoring light source power supply or to incursion of double-exponential behavior; in these cases, the fitting was done using a single-exponential plus linear function. In some of the runs carried out in sodium bromide solutions, this downward drift developed into a second exponential, and the data were then analyzed using a double-exponential expression.

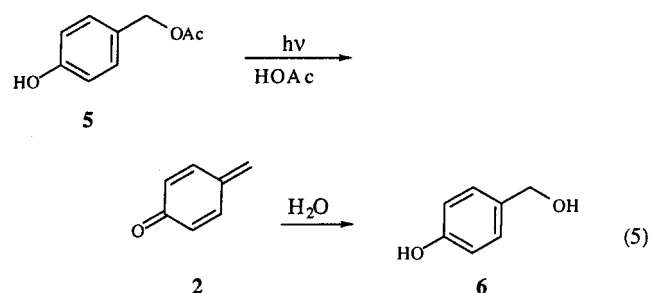
**Product Analysis.** The products formed by flash photolysis of *p*-hydroxybenzyl acetate were examined by HPLC using a Varian Vista 5500 instrument with a NovoPak C<sub>18</sub> reversed-phase column and methanol–water (50/50, v/v) as the eluent. Reaction solutions, whose temperature was controlled at  $25.0 \pm 0.05$  °C, were subjected to one flash from the microsecond system, and products were identified by comparing UV spectra and retention times with those of authentic samples. Initial *p*-hydroxybenzyl acetate concentrations were similar to those used for the kinetic measurements.

## Results

**Reaction Identification.** We<sup>2,3</sup> and others<sup>1,7</sup> have found that the corresponding *o*-hydroxybenzyl alcohols are good substrates for the photochemical generation of *o*-quinone methides. In the present work, however, we found that flash photolysis of *p*-hydroxybenzyl alcohol (**6**) failed to produce a useful transient signal. This perhaps surprising difference between ortho and para isomers is consistent with the much lower quantum yield reported for the generation of *p*-quinone  $\alpha$ -phenylmethide (**7**) from  $\alpha$ -phenyl-*p*-hydroxybenzyl alcohol (**8**), eq 3, than that for generation of *o*-quinone  $\alpha$ -phenylmethide (**9**) from  $\alpha$ -phenyl-*o*-hydroxybenzyl alcohol (**10**), eq 4;<sup>1,7</sup> quantum yields for the generation of *p*-quinone methides are also usually lower than those for the generation of *o*-quinone methides.<sup>1,7</sup>



We found further that flash photolysis of the acetic acid ester of *p*-hydroxybenzyl alcohol, **5**, did produce a good transient signal, with the strong absorbance at  $\lambda = 300$  nm expected of *p*-quinone methide. In addition, HPLC product analysis of spent reaction mixtures from flash photolysis of *p*-hydroxybenzyl acetate in 0.001 M perchloric acid as well as in acetic acid and biphosphate ion buffers showed that this substance was converted to *p*-hydroxybenzyl alcohol (**6**), as expected for the generation and subsequent hydration of *p*-quinone methide, eq 5. Further evidence that this transient species is *p*-quinone methide (**2**) comes from its chemical behavior detailed below.



**Hydration Reaction Rate Profile.** Rates of reaction of *p*-quinone methide were measured in dilute aqueous (H<sub>2</sub>O and D<sub>2</sub>O) perchloric acid solutions and in formic acid, acetic acid, biphosphate ion, and tris(hydroxymethyl)methylammonium ion buffers. The ionic strength of these solutions was maintained at 0.10 M by the addition of sodium perchlorate as needed. The data so obtained are summarized in Tables S1 and S2 (Supporting Information).<sup>8</sup>

The rate measurements in buffers were made in series of solutions of fixed buffer ratio, and therefore fixed hydronium ion concentration, but varying buffer concentration. Observed first-order rate constants proved to be linear functions of buffer concentration, and the data were therefore analyzed by least-squares fitting of the buffer dilution expression shown in eq 6.

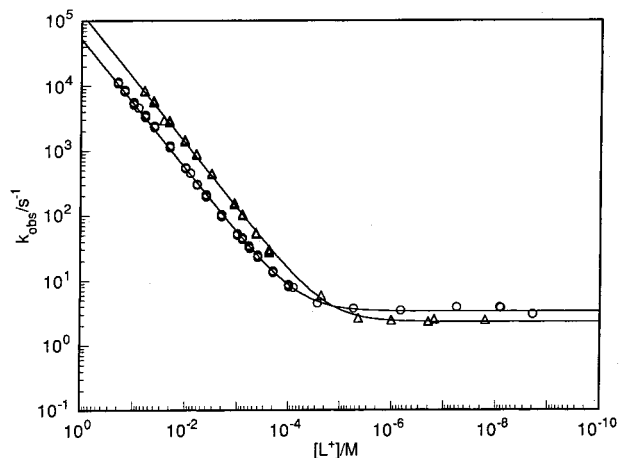
$$k_{\text{obs}} = k_{\text{int}} + k_{\text{cat}}[\text{buffer}] \quad (6)$$

The zero-buffer concentration intercepts,  $k_{\text{int}}$ , obtained in this way, together with the perchloric acid data, were then used to construct the rate profiles shown in Figure 1. Hydronium ion concentrations of the buffer solutions needed for this purpose were obtained by calculation using thermodynamic acidity constants of the buffer acids from the literature and activity coefficients recommended by Bates.<sup>9</sup>

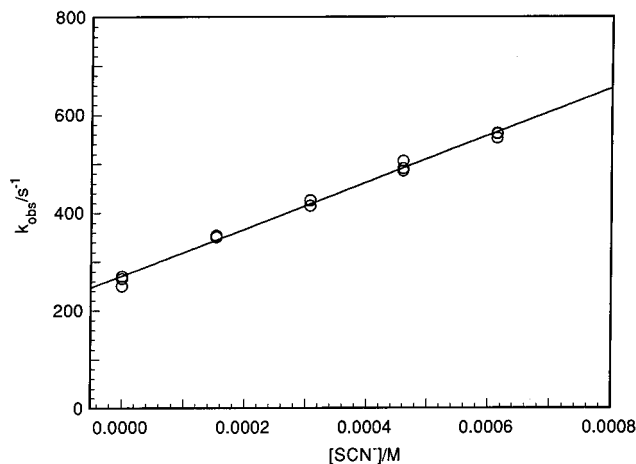
These rate profiles show acid-catalyzed and uncatalyzed portions; the data were therefore analyzed using the rate law of eq 7. Least-squares fitting gave the results  $k_{\text{H}^+} = (5.28 \pm 0.03) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ ,  $k_{\text{H}^+}/k_{\text{D}^+} = 0.409 \pm 0.005$  and  $(k_{\text{uc}})_{\text{H}_2\text{O}} = (3.33 \pm 0.08) \text{ s}^{-1}$ ,  $(k_{\text{uc}})_{\text{H}_2\text{O}}/(k_{\text{uc}})_{\text{D}_2\text{O}} = 1.46 \pm 0.07$ .

$$k_{\text{obs}} = k_{\text{uc}} + k_{\text{L}^+}[\text{L}^+] \quad (7)$$

- (4) Cottet, F.; Cottier, L.; Descote, G. *Can. J. Chem.* **1990**, *68*, 1251–1257.  
 (5) Nago, Y.; Fujita, E.; Kohno, T.; Yogi, M. *Chem. Pharm. Bull.* **1981**, *29*, 3202–3207. Allevi, P.; Ciuffreda, P.; Longo, A.; Anastasia, M. *Tetrahedron Asymmetry* **1998**, *9*, 2915–2924.  
 (6) Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000–4009.  
 (7) Diaio, L.; Yang, C.; Wan, P. *J. Am. Chem. Soc.* **1995**, *117*, 5369–5370.  
 (8) Supporting Information; see paragraph at the end of this paper regarding availability.



**Figure 1.** Rate profiles for the hydration of *p*-quinone methide in H<sub>2</sub>O (O) and D<sub>2</sub>O (Δ) solutions at 25 °C.



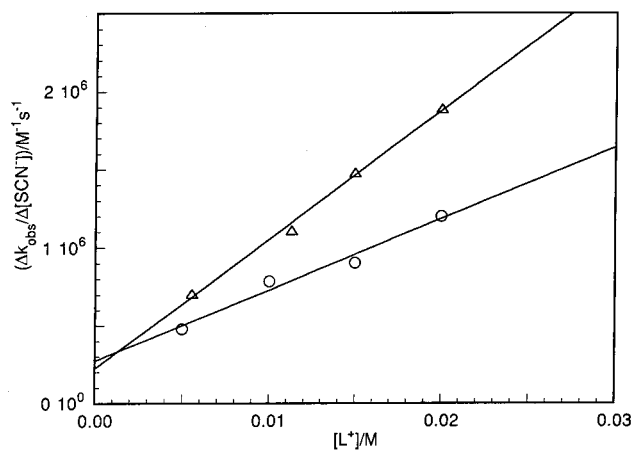
**Figure 2.** Relationship between observed rate constants and nucleophile concentration for the reaction of *p*-quinone methide with thiocyanate ion in aqueous solutions (H<sub>2</sub>O) containing 0.0050 M perchloric acid at 25 °C.

**Reaction with Nucleophiles.** The decay of *p*-quinone methide in aqueous solution was strongly accelerated by chloride, bromide, and thiocyanate ions and also by thiourea, in keeping with the nucleophilic nature of these reagents and the propensity of quinone methides to react with nucleophiles. These accelerations were also catalyzed by perchloric acid. Rate measurements were consequently made in series of solutions of fixed perchloric acid concentration but varying nucleophile concentration, using both H<sub>2</sub>O and D<sub>2</sub>O as the solvent. The ionic strength of these solutions was kept at 0.10 M by adding sodium perchlorate as required. The data so obtained are summarized in Tables S3–S6 (Supporting Information).<sup>8</sup>

As Figure 2 illustrates, observed first-order rate constants determined at fixed acid concentrations in this way increased linearly with increasing nucleophile concentration. Figure 3 shows further that the slopes of such plots,  $\Delta k_{\text{obs}}/\Delta[\text{Nuc}]$ , themselves increased linearly with increasing acidity, according to the relationship of eq 8. Linear least-squares analysis then

$$\Delta k_{\text{obs}}/\Delta[\text{Nuc}] = k_{\text{N,uc}} + k_{\text{N,L}^+}[\text{L}^+] \quad (8)$$

produced the uncatalyzed,  $k_{\text{N,uc}}$ , and acid-catalyzed,  $k_{\text{N,L}^+}$ , nucleophile rate constants listed in Table 1.



**Figure 3.** Relationship between slopes of plots such as that shown in Figure 2 and perchloric acid concentration for the reaction of *p*-quinone methide and thiocyanate ion in H<sub>2</sub>O (O) and D<sub>2</sub>O (Δ) solutions at 25 °C.

**Table 1.** Rate Constants for the Uncatalyzed  $k_{\text{N,uc}}$  and Acid-Catalyzed ( $k_{\text{N,L}^+}$ ). Reactions of *p*-Quinone Methide with Nucleophiles in Aqueous Solution at 25 °C<sup>a</sup>

nucleophile/solvent	$k_{\text{N,uc}}/\text{M}^{-1} \text{s}^{-1}$	$k_{\text{N,L}^+}/\text{M}^{-2} \text{s}^{-1}$
Cl <sup>-</sup> /H <sub>2</sub> O	$(1.10 \pm 0.16) \times 10^3$	$(5.43 \pm 0.06) \times 10^5$
Cl <sup>-</sup> /D <sub>2</sub> O	$(1.26 \pm 0.31) \times 10^3$	$(1.52 \pm 0.02) \times 10^6$
H <sub>2</sub> O/D <sub>2</sub> O:	$0.88 \pm 0.25$	$0.356 \pm 0.06$
	$(2.02 \pm 0.86) \times 10^4$	$(3.44 \pm 0.23) \times 10^6$
Br <sup>-</sup> /H <sub>2</sub> O	$(0.84 \pm 5.26) \times 10^3$	$(9.62 \pm 0.38) \times 10^6$
	-	$0.357 \pm 0.028$
SCN <sup>-</sup> /H <sub>2</sub> O	$(2.72 \pm 0.71) \times 10^5$	$(4.56 \pm 0.52) \times 10^7$
	$(2.22 \pm 0.54) \times 10^5$	$(8.29 \pm 0.38) \times 10^7$
SCN <sup>-</sup> /D <sub>2</sub> O	$1.23 \pm 0.44$	$0.550 \pm 0.068$
	$(4.82 \pm 0.45) \times 10^5$	$(3.95 \pm 0.33) \times 10^7$
thiourea/H <sub>2</sub> O	$(5.10 \pm 0.44) \times 10^5$	$(5.32 \pm 0.32) \times 10^7$
	$0.94 \pm 0.12$	$0.743 \pm 0.076$
H <sub>2</sub> O/D <sub>2</sub> O:	$3.33 \pm 0.08^b$	$(5.28 \pm 0.03) \times 10^{4c}$
	$2.29 \pm 0.10^b$	$(1.29 \pm 0.02) \times 10^{5c}$
D <sub>2</sub> O	$1.46 \pm 0.07$	$0.41 \pm 0.017$

<sup>a</sup> Ionic strength, 0.10 M (NaClO<sub>4</sub>). <sup>b</sup> s<sup>-1</sup>. <sup>c</sup> M<sup>-1</sup> s<sup>-1</sup>.

These rate measurements in bromide ion solutions were performed at perchloric acid concentrations in the range [HClO<sub>4</sub>] = 0.02–0.05 M where the decay of *p*-quinone methide absorbance conformed to a single-exponential rate law, followed sometimes by a slower downward drift for solutions at the lower end of this acidity range. Below [HClO<sub>4</sub>] = 0.02 M, however, this drift developed into a second exponential function. Additional rate measurements were therefore made over the concentration range [HClO<sub>4</sub>] = 0.005–0.015 M, and the data were analyzed by least-squares fitting of a double-exponential function. These results are summarized in Table S7 (Supporting Information).<sup>8</sup>

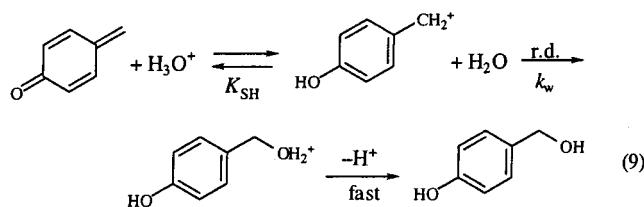
## Discussion

**Hydration.** The rate profiles of Figure 1 represent reaction of *p*-quinone methide with solvent-related species through a process that product analysis shows produces *p*-hydroxybenzyl alcohol. The inverse ( $k_{\text{H}}/k_{\text{D}} < 1$ ) nature of the solvent isotope effect on the acid-catalyzed portion of this process,  $k_{\text{H}}/k_{\text{D}}^+ = 0.41$ , implies that this reaction occurs by a preequilibrium substrate protonation mechanism,<sup>10</sup> which in this case can be formulated as rapid and reversible protonation of the quinone

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

(10) 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.

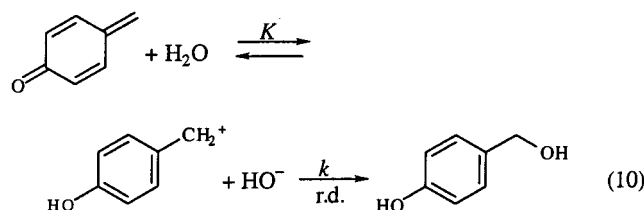
methide on its carbonyl oxygen atom, through proton transfer from the hydronium ion, followed by rate-determining capture of the ensuing carbocation by a molecule of water, eq 9. The



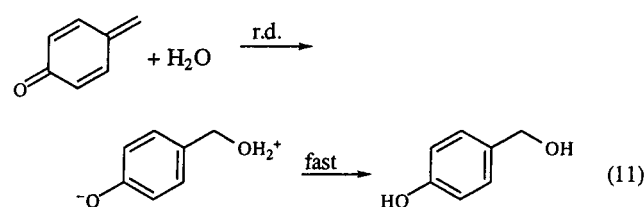
inverse nature of this isotope effect stems from the fact that positively charged O–H bonds, such as those in the hydronium ion, are looser than uncharged O–H bonds, such as those in a water molecule;<sup>11</sup> conversion of H<sub>3</sub>O<sup>+</sup> into H<sub>2</sub>O in the preequilibrium step of eq 9 then is accompanied by a tightening of O–H bonds, and that leads to an inverse isotope effect.

Such a preequilibrium process is confirmed as a general reaction mechanism for acid-catalyzed quinone methide hydration by the saturation of acid catalysis observed in the case of more basic substrates:<sup>3</sup> increasing the hydronium ion concentration in these cases shifts the position of the preequilibrium reaction from unprotonated to protonated substrate. The protonated substrates then become the reaction's initial state, and acid catalysis ceases to operate.

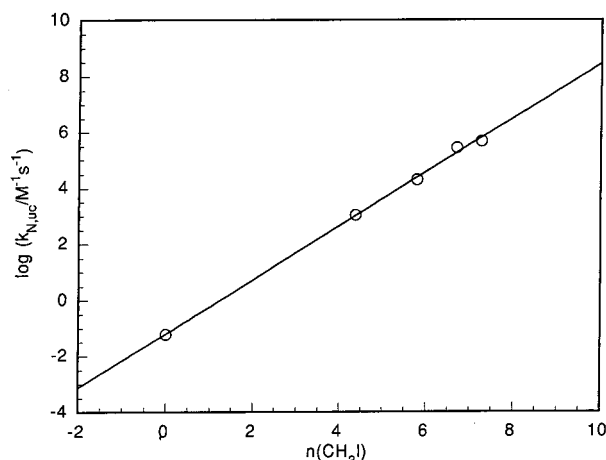
The uncatalyzed hydration reaction represented by the horizontal portions of the rate profiles of Figure 1 might occur by an analogous preequilibrium process, shown in eq 10, in



which rapid and reversible substrate protonation occurs by proton transfer from a water molecule to the quinone methide carbonyl oxygen atom, and this is then followed by rate-determining combination of the carbocation and hydroxide ion thus formed. Uncatalyzed hydration might also take place by simple rate-determining nucleophilic addition of a water molecule to the substrate's methide carbon atom, giving a zwitterionic intermediate, followed by rapid proton relocation, as shown in eq 11.



The first of these reaction mechanisms can be ruled out because the data would require an impossibly large value of the rate constant for the rate-determining step, *k*. The rate law



**Figure 4.** Relationship between the nucleophilic reactivity parameter  $\eta_{\text{CH}_3}$  and second-order rate constants for the uncatalyzed reaction of *p*-quinone methide with nucleophiles in aqueous solution at 25 °C.

that applies to the reaction scheme of eq 10 is  $k_{\text{uc}} = kK$ , with *K*, the equilibrium constant for the first step, equal to the acidity constant of water, *K<sub>w</sub>*, divided by the acidity constant of the protonated substrate, *K<sub>SH</sub>*:  $k_{\text{uc}} = kK_{\text{w}}/K_{\text{SH}}$ . A value of *K<sub>SH</sub>* has not been determined directly, but the estimate *K<sub>SH</sub>* = 10<sup>2</sup> M can be made (vide infra). Combination of that with *K<sub>w</sub>* = 1 × 10<sup>-14</sup> M<sup>2</sup> and  $k_{\text{uc}} = 3.3 \text{ s}^{-1}$  then leads to  $k = 3 \times 10^{16} \text{ M}^{-1} \text{ s}^{-1}$ , which exceeds the encounter-controlled limit by a considerable margin.

This leaves the nucleophilic route of eq 11 as the reaction mechanism for uncatalyzed hydration of *p*-quinone methide. Support for this assignment comes from the isotope effect on this reaction,  $(k_{\text{uc}})_{\text{H}_2\text{O}}/(k_{\text{uc}})_{\text{D}_2\text{O}} = 1.46$ , which is consistent with the development of positive charge on, and the consequent weakening of, the O–H bonds of the attacking water molecule. This reaction mechanism is also consistent with the propensity of quinone methides to react with nucleophiles. A similar mechanism has been proposed for the uncatalyzed hydration of *o*-quinone methide.<sup>2</sup>

**Reaction with Nucleophiles.** The results listed in Table 1 show that the reactions of *p*-quinone methide with thiourea and chloride, bromide, and thiocyanate ions are acid catalyzed and that in most cases an uncatalyzed reaction can be detected as well. These reagents are all good nucleophiles, and it seems reasonable to conclude that the uncatalyzed reactions are processes analogous to the mechanism given for the uncatalyzed hydration reaction in eq 11, with these nucleophiles taking the place of the water molecule. This assignment is supported by Figure 4, which shows that the rate constants for these uncatalyzed reactions plus that for uncatalyzed hydration correlate well with Pearson's nucleophilic reactivity constants  $\eta_{\text{CH}_3}$ .<sup>12</sup> This assignment is also consistent with the solvent isotope effects on these reactions listed in Table 1, which, though not very precisely determined, nevertheless cluster about unity. Solvent water plays only a passive role in these reactions: there is some rearrangement of solvent shells but no serious changes in solvent O–H bond strength. Since isotope effects on solvent shells are known to be weak,<sup>11,15</sup> this mechanism would be expected to give solvent isotope effects near unity, as observed.

(11) Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncl, E., Lee, C. C., Eds.; Elsevier: New York, 1987; Chapter 4.

(12) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319–326. The value  $\eta_{\text{CH}_3} = 0.00$  for water was derived from  $\eta_{\text{CH}_3\text{Br}} = 0.00$ <sup>13</sup> for this substance and the relationship  $\eta_{\text{CH}_3} = 1.4 \eta_{\text{CH}_3\text{Br}}$ <sup>14</sup>

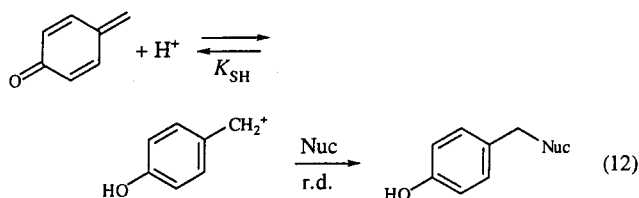
(13) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141–147.

**Table 2.** Estimated Rate Constants for the Reaction of Nucleophiles with the *p*-Hydroxybenzyl Cation in Aqueous Solution at 25 °C<sup>a</sup>

nucleophile	$k_N/10^7 \text{ M}^{-1} \text{ s}^{-1}$
H <sub>2</sub> O	0.58 <sup>b</sup>
Cl <sup>-</sup>	6.0
Br <sup>-</sup>	37
SCN	500 <sup>c</sup>
thiourea	433

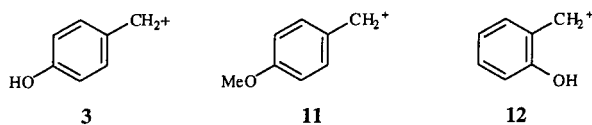
<sup>a</sup> Ionic strength, 0.10 M. <sup>b</sup> First-order rate constant in units of s<sup>-1</sup>. <sup>c</sup> Assigned value.

The isotope effects on the acid-catalyzed nucleophilic reactions, on the other hand, are all quite strongly inverse (see Table 1). This implies that acid catalysis of these nucleophile reactions occurs by a preequilibrium mechanism as shown in eq 12,



similar to that assigned above to acid-catalyzed hydration. Observed rate constants for this process are then equal to rate constants for the rate-determining nucleophile capture step,  $k_N$ , divided by the acidity constant of the quinone methide conjugate acid,  $K_{SH}$ :  $k_{\text{obs}} = k_N/K_{SH}$ .

It is likely that the reaction of thiocyanate ion with the *p*-hydroxybenzyl cation **3** in the rate-determining step of the



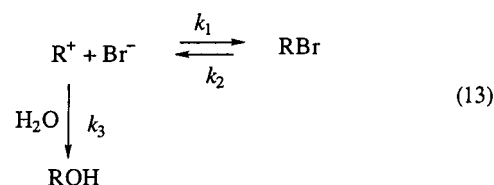
route of eq 12 is an encounter-controlled process. This cation should be of comparable stability to the *p*-methoxybenzyl cation **11**, which reacts with azide ion at the encounter-controlled limit.<sup>16</sup> Since thiocyanate ion is a stronger nucleophile than azide ion,<sup>12,13</sup> the reaction of *p*-hydroxybenzyl cation with thiocyanate ion should be an encounter-controlled reaction as well.

A similar argument was made before for the reaction of thiocyanate ion with *o*-hydroxybenzyl cation **12**, generated by protonation of *o*-quinone methide, and an encounter-controlled rate constant of  $5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$  was assigned to that reaction.<sup>2</sup> Assignment of the same value to the rate constant for reaction of thiocyanate ion with *p*-hydroxybenzyl cation, coupled with the experimental result  $k_N/K_{SH} = 4.6 \times 10^7$ , leads to the estimate  $K_{SH} = 110 \text{ M}$ . This result can then be used in conjunction with the experimental rate constants  $k_N/K_{SH}$  for other nucleophiles to estimate additional values of  $k_N$ . The results so obtained are listed in Table 2.

Thiourea is a stronger nucleophile than thiocyanate ion:  $\eta_{\text{CH}_2\text{I}} = 7.27$  and 6.70, respectively.<sup>12</sup> It seems likely therefore that the reaction of *p*-hydroxybenzyl cation with thiourea is an

encounter-controlled process as well as the reaction of this cation with thiocyanate ion, and the slightly greater value of  $k_N$  for thiocyanate may be attributed to an electrostatic effect accelerating the interaction of two ions of opposite charge. The estimate  $k_N = 5.8 \times 10^6 \text{ s}^{-1}$  for the water reaction is less than  $2 \times 10^8 \text{ s}^{-1}$  estimated for the *p*-methoxybenzyl cation **11** reacting with water in a 50:50 trifluoroethanol–water solvent,<sup>16</sup> but that is consistent with the known greater cation-stabilizing ability of hydroxyl over methoxyl and the consequent lower reactivity of the hydroxyl-substituted cation.

**Double-Exponential Behavior.** Under certain conditions of perchloric acid concentration, detailed in Table S7 (Supporting Information),<sup>8</sup> the decay of *p*-quinone methide absorbance in sodium bromide solutions became biphasic and analysis of the kinetic data required use of a double-exponential expression. Such behavior has been noted before in the reaction of triphenylmethyl cation with bromide ion in a partly aqueous solvent, and it was attributed to reversible combination of the cation with bromide ion accompanied by nonreversible reaction of the cation with water, eq 13.<sup>17</sup> A similar interpretation



involving the reaction of bromide ion with the *p*-hydroxybenzyl cation may be made here.

The present experiments were done in wholly aqueous solution under conditions where the concentration of the cation was very much less than that of bromide ion. The system therefore reduces to a combination of first-order reactions, for which there is an analytical solution.<sup>18</sup> The expression for the concentration of R<sup>+</sup> as function of time is given by eq 14, with  $\gamma_1$  and  $\gamma_2$

$$[R^+] = [R^+]_0 \left\{ \frac{k_2 - \gamma_1}{\gamma_2 - \gamma_1} e^{-\gamma_1 t} - \frac{k_2 - \gamma_2}{\gamma_2 - \gamma_1} e^{-\gamma_2 t} \right\} \quad (14)$$

$$\gamma_1 = \frac{k_1 + k_2 + k_3 - \sqrt{(k_1 + k_2 + k_3)^2 - 4k_2k_3}}{2} \quad (15)$$

$$\gamma_2 = \frac{k_1 + k_2 + k_3 + \sqrt{(k_1 + k_2 + k_3)^2 - 4k_2k_3}}{2} \quad (16)$$

consisting of the individual step rate constants,  $k_1$ – $k_3$ , defined by eq 13, as shown in eqs 15 and 16. These individual step rate constants can be evaluated from the parameters obtained by least-squares fitting of the experimental data using the empirical relationship of eq 17; the expressions relating the rate constants

$$A = A_0 + A_1 e^{-\alpha t} + A_2 e^{-\beta t} \quad (17)$$

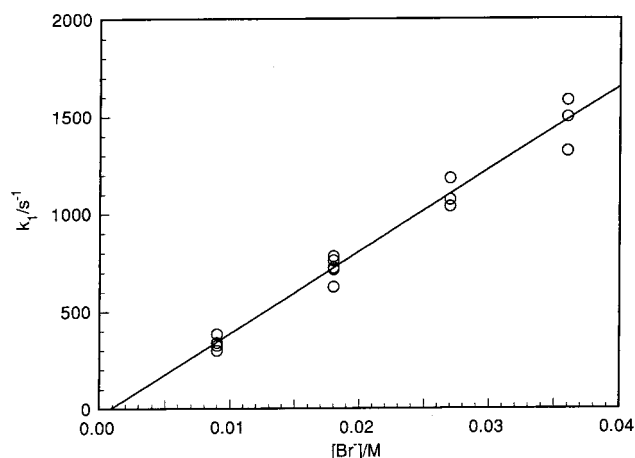
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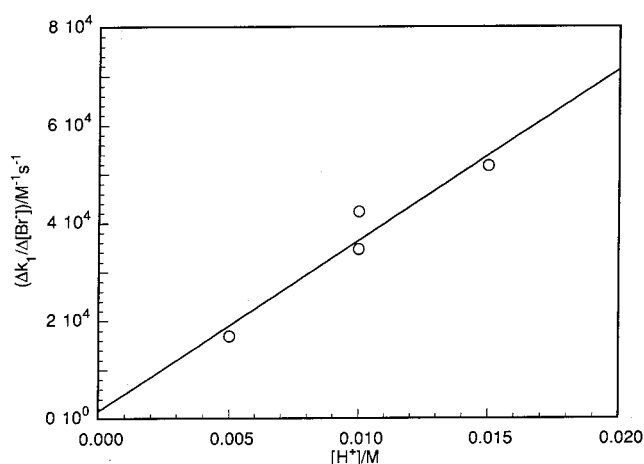
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**Figure 5.** Relationship between the rate constant  $k_1$  defined by eq 13 and bromide ion concentration at a fixed perchloric acid concentration of 0.010 M in aqueous solution at 25 °C.



**Figure 6.** Relationship between slopes of plots such as that shown in Figure 5 and perchloric acid concentration.

to these empirical parameters are given by eqs 18–20.

$$k_2 = \frac{A_1\beta + A_2\alpha}{A_1 + A_2}$$

$$k_3 = ab/k_2 \quad (19)$$

$$k_1 = \alpha + \beta - k_2 - k_3 \quad (20)$$

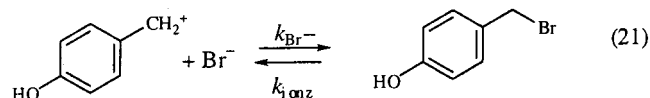
Double-exponential rate measurements were made in series of solutions of fixed perchloric acid concentration ( $[\text{HClO}_4] = 0.005, 0.01, \text{ and } 0.015 \text{ M}$ ) but varying bromide ion concentration ( $[\text{Br}^-] = 0.01\text{--}0.04 \text{ M}$ ). The values of  $k_1$ ,  $k_2$ , and  $k_3$  obtained from these measurements through the use of the relationships of eqs 17–20 are listed in Table S7 (Supporting Information).<sup>8</sup>

As is illustrated in Figure 5, the rate constant  $k_1$  determined at a given constant acidity increased regularly in a linear fashion with increasing bromide ion concentration, as expected for the *p*-hydroxybenzyl cation plus bromide ion combination reaction. Figure 6 illustrates further that the slopes of plots such as that shown in Figure 5 themselves increased with increasing acid concentration, again as expected inasmuch as the *p*-hydroxybenzyl cation is produced from *p*-quinone methide by an acid-catalyzed reaction. The slope of the plot shown in Figure 6 is

the third-order rate constant for nucleophilic capture of the *p*-hydroxybenzyl cation by bromide ion; it is gratifying that its value,  $k_{\text{Br}^-}/K_{\text{SH}} = (3.49 \pm 0.69) \times 10^6 \text{ M}^{-2} \text{ s}^{-1}$ , agrees well with that,  $k_{\text{Br}^-}/K_{\text{SH}} = (3.44 \pm 0.23) \times 10^6 \text{ M}^{-2} \text{ s}^{-1}$ , determined under single-exponential decay conditions (vide supra). This good agreement lends credence to this treatment of the double-exponential data.

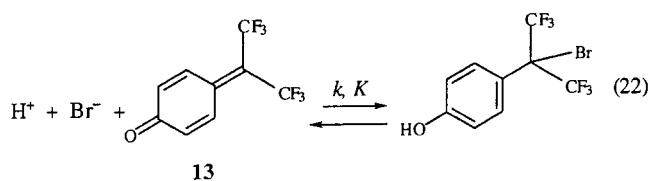
Further support for this method of analysis comes from the behavior of  $k_2$  and  $k_3$ . The rate constant  $k_2$  proved to be independent of both bromide ion and perchloric acid concentrations, as expected for the simple ionization of *p*-hydroxybenzyl bromide. Its best value,  $k_2 = (8.45 \pm 0.27) \times 10^2 \text{ s}^{-1}$ , was therefore determined as the simple average of all of the (85) individual values obtained. The rate constant  $k_3$ , on the other hand, though independent of bromide ion concentration, did increase linearly with increasing perchloric acid concentration. This is consistent with  $k_3$  being the rate constant for hydration of the *p*-hydroxybenzyl cation, a process that does require the acid-induced generation of this cation but does not involve bromide ion. Linear least-squares analysis of the relationship between  $k_3$  and acid concentration produced the acid-catalyzed hydration rate constant,  $k_{\text{H}^+} = (2.92 \pm 1.29) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ , which is not inconsistent with  $k_{\text{H}^+} = (5.28 \pm 0.03) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$  obtained from the hydration rate profile.

These double-exponential rate measurements were made by monitoring the decay of *p*-quinone methide, and conversion of the results into rate constants referred to the *p*-hydroxybenzyl cation as the initial state requires application of the equilibrium constant  $K_{\text{SH}}$  relating the cation to the quinone methide. Use of the value  $K_{\text{SH}} = 110 \text{ M}$  estimated above from the thiocyanate ion reaction then gives  $k_{\text{Br}^-} = (3.49 \times 10^6)(1.10 \times 10^2) = 3.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$  as the rate constant for the reaction of the *p*-hydroxybenzyl cation with bromide ion, eq 21. This result may



be combined with  $k_2 (= k_{\text{ionz}})$  to give  $K = k_{\text{Br}^-}/k_{\text{ionz}} = 4.5 \times 10^5 \text{ M}^{-1}$  as the equilibrium constant for this reaction. This result shows that un-ionized *p*-hydroxybenzyl bromide is much more stable than *p*-hydroxybenzyl cation and bromide ion. The un-ionized bromide, however, does not persist in aqueous solution because ionization followed by capture of the cation so formed by water provides a facile route to the still more stable *p*-hydroxybenzyl alcohol hydration product.

**Comparison of *p*-Quinone Methide with *p*-Quinone  $\alpha,\alpha$ -Bis(trifluoromethyl)methide.** The results obtained here for the acid-catalyzed addition of bromide ion to *p*-quinone methide provide a striking contrast with those reported for the corresponding reaction of *p*-quinone  $\alpha,\alpha$ -bis(trifluoromethyl)methide (13), eq 22.<sup>19</sup> The mechanisms of these two reactions are not the same: the hydronium ion isotope effect on the reaction of



**Table 3.** Comparison of the Acid-Catalyzed Reaction of Bromide Ion with *p*-Quinone Methide, **2**, and with *p*-Quinone  $\alpha$ ,  $\alpha$ -Bis(trifluoromethyl)methide, **13**

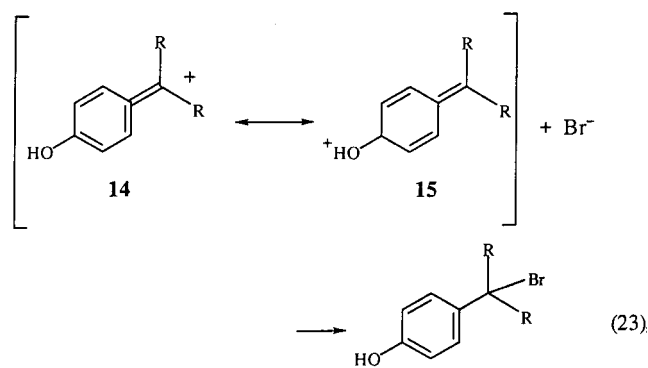
	<b>2</b> <sup>a</sup>	<b>13</b> <sup>b</sup>
$K/M^{-2}$	$4.1 \times 10^3$	$6.4 \times 10^4$
$\Delta G^\circ/\text{kcal mol}^{-1}$	-4.9	-6.6
$k/M^{-2} \text{ s}^{-1}$	$3.4 \times 10^6$	3.7
$\Delta G^\ddagger/\text{kcal mol}^{-1}$	8.5	16.7
$\Delta G_o^\ddagger/\text{kcal mol}^{-1}$	10.9	19.8

<sup>a</sup> Aqueous solution, 25 °C, ionic strength = 0.10 M (NaClO<sub>4</sub>). <sup>b</sup> Data from ref 19; 50:50 (*v/v*) trifluoroethanol/water, 25 °C, ionic strength = 0.50 (NaClO<sub>4</sub>).

the fluorinated substrate is unity rather than inverse,<sup>19</sup> which indicates that proton transfer and bromide ion capture here are concerted and not stepwise as in the reaction of the unfluorinated substrate, eq 12. The hypothetical stepwise reaction of the fluorinated substrate, because it does not occur, must therefore be slower than the observed concerted reaction, and the rate constant observed can consequently serve as an upper limit for that of the stepwise reaction.

The data assembled in Table 3 show that the driving forces of the two reactions, as measured by the equilibrium constants,  $K$ , are closely similar: the corresponding free energies of reaction,  $\Delta G^\circ$ , differ by only 1.7 kcal mol<sup>-1</sup>. The rate constants  $k$ , on the other hand, are quite different and give free energies of activation,  $\Delta G^\ddagger$ , that differ by 8.2 cal mol<sup>-1</sup>. These quantities may be converted into intrinsic barriers,  $\Delta G_o^\ddagger$ , which measure intrinsic kinetic reactivity free of any thermodynamic drive or impediment,<sup>20</sup> through the application of Marcus rate theory.<sup>21</sup> The results give an intrinsic barrier difference of 8.9 kcal mol<sup>-1</sup>, which, because  $\Delta G_o^\ddagger$  for the fluorinated system is a lower limit, shows that intrinsic barriers for stepwise reactions of the two substrates must differ by more than this amount.

This strong difference in intrinsic kinetic reactivity can be understood in terms of an interplay of electrical effects that operate in the rate-determining bromide ion capture step of these reactions, eq 23.<sup>19,22</sup> The positive charge of the carbocation in



the initial state of this reaction step will be stabilized by delocalization into the aromatic ring and onto the *p*-hydroxy group. As carbon–bromine covalent bond formation occurs in the transition state of this reaction, this resonance stabilization

**Table 4.** Comparison of *o*- and *p*-Quinone Methides<sup>a</sup>

quantity	<i>o</i> -isomer	<i>p</i> -isomer	<i>o/p</i>
$k_{uc}/\text{s}^{-1}$	$2.6 \times 10^2$	3.3	78
$K_{SH}/M$	$5.2 \times 10^1$	$1.1 \times 10^2$	0.47
$k_w/\text{s}^{-1}$	$4.4 \times 10^7$	$5.8 \times 10^6$	7.6
$k_{Br^-}/M^{-1} \text{ s}^{-1}$	$1.1 \times 10^9$	$3.7 \times 10^8$	2.9
$k_{H^+}/M^{-1} \text{ s}^{-1}$	$8.4 \times 10^5$	$5.3 \times 10^4$	16

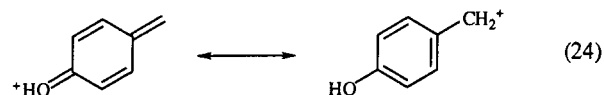
<sup>a</sup> Aqueous solution; 25 °C; ionic strength, 0.10 M.

will be lost, and that loss will run ahead of covalent bond formation,<sup>23</sup> creating an imbalance that will lower kinetic reactivity and augment the intrinsic barrier.<sup>24</sup> Because trifluoromethyl groups are strongly electron-withdrawing, they will destabilize the canonical resonance form of the carbocation with positive charge on the benzyl carbon atom **14**, decreasing its contribution and increasing the contribution of the delocalized forms represented by **15**. The fluorinated cation will therefore have more resonance stabilization to be lost, will suffer from more imbalance in its transition state, and will be the more intrinsically slow reactant.

**Comparison of *o*- and *p*-Quinone Methide.** Some of the measurements made here on *p*-quinone methide have also been carried out on *o*-quinone methide,<sup>2</sup> and it is of interest to compare the results obtained for the two systems. The relevant data are summarized in Table 4.

It may be seen that the rate of uncatalyzed hydration, measured by the rate constant  $k_{uc}$ , is nearly 80 times greater for *o*-quinone methide than for *p*-quinone methide. This undoubtedly is a reflection of the greater stability of *p*-quinoid over *o*-quinoid structures, as evidenced for example by the well-known greater stability of *p*-benzoquinone over *o*-benzoquinone.<sup>25</sup>

The protonation of *o*-quinone methide on its carbonyl oxygen atom also takes place more readily than the corresponding reaction for the para isomer, as shown by the weaker acidity of *o*-quinone methide over *p*-quinone methide. The ratio of the basic strengths, however, ( $1/0.47 = 2.1$ ) is considerably less than the ratio of the uncatalyzed hydration rate constants (78). This suggests that a considerable portion of the unprotonated quinone methide stability difference is maintained in the conjugate acids, i.e., that the protonated substrates have retained considerable quinone methide character. This is consistent with the known strong cation-stabilizing ability of the hydroxyl group and the consequent expected importance of the quinoid canonical form in the resonance hybrid structure of the quinone methide conjugate acid, as illustrated for the para isomer by the scheme of eq 24.



The importance of the quinoid form may also be seen in the greater reactivity toward capture by nucleophiles of the cation derived from *o*-quinone methide than that of the cation derived from *p*-quinone methide. It is significant also that this reactivity

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difference is greater in the slower hydration reaction ( $o/p = 7.6$ ) than in the more rapid bromide ion reaction ( $o/p = 2.9$ ), consistent with the expected greater selectivity of the slower process.

The rate constant  $k_{H^+}$  is of course a complex quantity being made up of  $k_w$  and  $K_{SH}$ :  $k_{H^+} = k_w/K_{SH}$ . Its  $o/p$  ratio therefore contains a contribution of  $o/p = 7.6$  given by  $k_w$  and a contribution of  $1/0.47 = 2.1$  given by  $K_{SH}$ .

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**Supporting Information Available:** Tables of rate data. This material is available free of charge via the Internet at <http://pubs.acs.org>. See any current masthead page for ordering information and Web access instructions.

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