

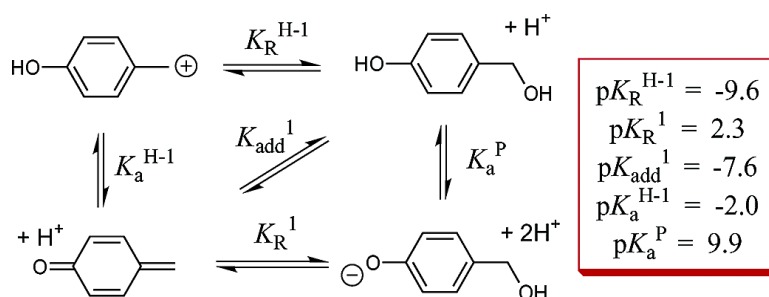
Article

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## Substituent Effects on Carbocation Stability: The $pK_R$ for $p$ -Quinone Methide

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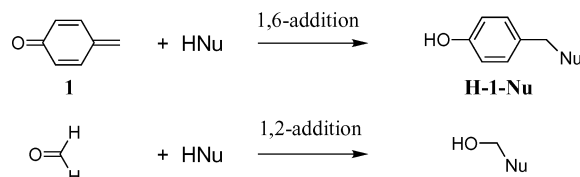
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**Abstract:** A value of  $k_H = 1.5 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$  has been determined for the generation of simple  $p$ -quinone methide by the acid-catalyzed cleavage of 4-hydroxybenzyl alcohol in water at 25 °C and  $I = 1.0$  (NaClO<sub>4</sub>). This was combined with  $k_S = 5.8 \times 10^6 \text{ s}^{-1}$  for the reverse addition of solvent water to the 4-hydroxybenzyl carbocation [J. Am. Chem. Soc. 2002, 124, 6349–6356] to give  $pK_R = -9.6$  as the Lewis acidity constant of O-protonated  $p$ -quinone methide. Values of  $pK_R = 2.3$  for the Lewis acidity constant of neutral  $p$ -quinone methide and  $pK_{\text{add}} = -7.6$  for the overall addition of solvent water to  $p$ -quinone methide to form 4-hydroxybenzyl alcohol are also reported. The thermodynamic driving force for transfer of the elements of water from formaldehyde hydrate to  $p$ -quinone methide to form formaldehyde and  $p$ -(hydroxymethyl)phenol (4-hydroxybenzyl alcohol) is determined as 6 kcal/mol. This relatively small driving force represents the balance between the much stronger chemical bonds to oxygen at the reactant formaldehyde hydrate than at the product  $p$ -(hydroxymethyl)phenol and the large stabilization of product arising from the aromatization that accompanies solvent addition to  $p$ -quinone methide. The Marcus intrinsic barrier for nucleophilic addition of solvent water to the “extended” carbonyl group at  $p$ -quinone methide is estimated to be 4.5 kcal/mol larger than that for the addition of water to the simple carbonyl group of formaldehyde. O-Alkylation of  $p$ -quinone methide to give the 4-methoxybenzyl carbocation and of formaldehyde to give a simple oxocarbenium ion results in very little change in the relative Marcus intrinsic barriers for the addition of solvent water to these electrophiles.

### Introduction

The parent  $p$ -quinone methide **1** and its relatives that contain the quinone methide functionality have long attracted the interest of discerning chemists.<sup>1–11</sup> **1** can be thought of as a formally neutral benzylic carbocation at which there is limiting resonance stabilization by electron donation from a  $p$ -oxygen anion substituent to the cationic benzylic carbon.<sup>12–14</sup> This strong interaction results in a high kinetic stability of, and large nucleophile

### Scheme 1



selectivities toward, quinone methides<sup>13,14</sup> and is responsible in part for the interesting biological activity observed for more complex quinone methides.<sup>15–20</sup> The key property that distinguishes the 1,6-addition of nucleophiles to  $p$ -quinone methides from related Michael addition reactions is the aromatization of the formal cyclohexadiene ring that accompanies this addition (Scheme 1). We are interested in evaluating the effect of this aromatic ring formation on the thermodynamic driving force for 1,6-addition of HNu to **1** through a comparison of this reaction with the related 1,2-addition of HNu to formaldehyde (Scheme 1).

The photochemical generation of simple quinone methides was first reported by Wan and co-workers.<sup>21</sup> This was followed by the determination by Kresge and co-workers of rate constants

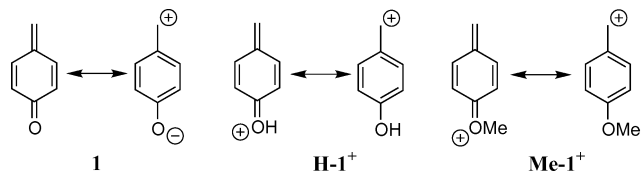
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for nucleophilic addition of solvent water to *p*-quinone methide **1**, protonated *p*-quinone methide **H-1**<sup>+</sup>, and their *o*-quinone methide counterparts, generated by laser flash photolysis.<sup>4,22–24</sup> There have also been several studies of the generation of quinone methides as intermediates of solvolysis reactions.<sup>2,5,13,14,25</sup> Kinetic data for the acid-catalyzed cleavage of 4-hydroxybenzyl alcohol **H-1-OH** would be of particular interest, because they represent the “missing link” in the experimental determination of the Lewis acidity constants for the addition of solvent water to **1** and **H-1**<sup>+</sup>. These acidity constants are required to establish the electrophilicity of simple quinone methides relative to that of other prototypical electrophiles such as the 4-methoxybenzyl carbocation **Me-1**<sup>+</sup> and the simple carbonyl compound formaldehyde.



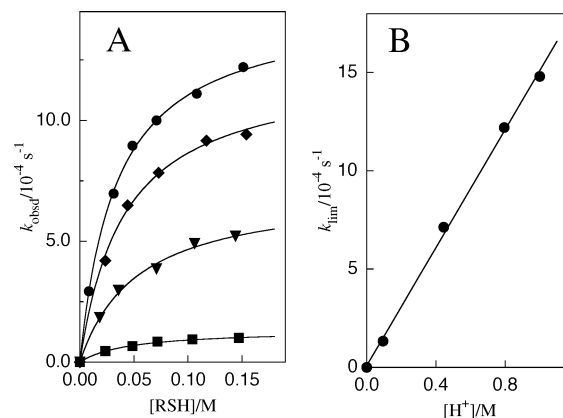
We report here the generation of the simple *p*-quinone methide **1** in dilute aqueous acid, its efficient nucleophilic trapping by the thiol group of 2-mercaptoethanol, and an analysis of the resulting kinetic data, which provides the second-order rate constant for acid-catalyzed cleavage of 4-hydroxybenzyl alcohol **H-1-OH** to give the protonated *p*-quinone methide **H-1**<sup>+</sup>. The data can be combined with kinetic data for the trapping of **H-1**<sup>+</sup> by solvent water<sup>24</sup> to obtain values of the Lewis acidity constants  $pK_R$  for both **H-1**<sup>+</sup> and **1**, along with the overall equilibrium constant for the 1,6-addition of water to the “extended” carbonyl group at **1**. A comparison with the corresponding data for the 1,2-addition of water to the simple carbonyl group at formaldehyde provides insight into the effect of formation of the aromatic ring in the product on the thermodynamic driving force for 1,6-addition of water to the *p*-quinone methide **1**.

## Experimental Section

4-Hydroxybenzyl alcohol (**H-1-OH**) was reagent grade from Aldrich and used without further purification. 2-Mercaptoethanol was Biochemica MicroSelect grade from Fluka. All other organic and inorganic chemicals were reagent grade from commercial sources and used without further purification. HPLC-grade methanol was used for all HPLC analyses. Water for kinetic studies and HPLC analyses was distilled and passed through a Milli-Q water purification system.

**Product Analysis by <sup>1</sup>H NMR.** Product characterization was carried out on a reaction mixture resulting from reaction of **H-1-OH** (7 mM) in the presence of 0.2 M perchloric acid and 0.01 M 2-mercaptoethanol in 60/40 (v/v) D<sub>2</sub>O/acetonitrile-*d*<sub>3</sub>. After one half-time (4 h), analysis by <sup>1</sup>H NMR spectroscopy at 500 MHz revealed a 1:1 mixture of the starting material and the thioether substitution product **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH**. Chemical shifts for **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH** are reported relative to HOD at 4.67 ppm: δ 7.31, 6.92 (A<sub>2</sub>B<sub>2</sub>, 4H, *J* = 8.5 Hz, C<sub>6</sub>H<sub>4</sub>); 3.82 (2H, s, ArCH<sub>2</sub>); 3.74 (2H, t, *J* = 6.5 Hz, OCH<sub>2</sub>); 2.70 (2H, t, *J* = 6.5 Hz, SCH<sub>2</sub>).

**HPLC Analyses.** HPLC analysis was carried out as described in previous work,<sup>26,27a</sup> except that peak detection was by a Waters 996



**Figure 1.** (A) Dependence of the observed first-order rate constant for acid-catalyzed nucleophilic substitution of thiol at **H-1-OH** to form **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH** on the concentration of 2-mercaptoethanol in water at 25 °C and *I* = 1.0 (NaClO<sub>4</sub>): (●) [HClO<sub>4</sub>] = 1.00 M; (◆) [HClO<sub>4</sub>] = 0.80 M; (▼) [HClO<sub>4</sub>] = 0.45 M; (■) [HClO<sub>4</sub>] = 0.094 M. Solid lines through the data were calculated using eq 1 with the values of  $k_{lim}$  (s<sup>-1</sup>) and  $k_{RSH}/k_s$  (M<sup>-1</sup>) reported in Table 1. (B) Dependence of the limiting first-order rate constant  $k_{lim}$  from Figure 1A on the concentration of perchloric acid. The slope of this correlation gives  $k_H = 1.5 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$  for acid-catalyzed cleavage of **H-1-OH** to give **H-1**<sup>+</sup> (eq 2).

diode array detector. The detection of HPLC peaks was at 273 nm, which is  $\lambda_{max}$  for **H-1-OH**. 3-(4-Methoxyphenyl)-1-propanol ( $3 \times 10^{-4}$  M) was used as an internal standard to correct the observed peak areas for small variations in the injection volume. A ratio of extinction coefficients  $\epsilon_{H-1-OH}/\epsilon_{H-1-SR} = 1$  for **H-1-OH** and **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH** at 273 nm was determined by showing that the normalized peak area for **H-1-OH** at zero time is identical, within the experimental error of  $\pm 5\%$ , with the normalized peak area for the product **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH** after  $\geq 10$  reaction half-times. The fraction of **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH** formed at time *t* during the course of the reaction,  $f_{H-1-SR}$ , was calculated as the ratio of the normalized peak areas for **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH** at time *t* and for **H-1-OH** at zero time.

**Kinetic Studies.** Kinetic studies were carried out in 0.1–1.0 M aqueous perchloric acid in the presence of 0.01–0.15 M 2-mercaptoethanol at 25 °C and *I* = 1.0 (NaClO<sub>4</sub>). The concentration of thiol was determined directly before each kinetic run using Ellman’s reagent [5,5’-dithiobis-(2-nitrobenzoic acid)].<sup>28</sup> The reactions were initiated by making a 100-fold dilution of a 0.03 M (in the case of faster reactions with  $\tau_{1/2} \leq 25$  min) or a 0.3 M (in the case of slower reactions with  $\tau_{1/2} > 25$  min) solution of **H-1-OH** in acetonitrile into the reaction mixture. The reactions were monitored by withdrawal of an aliquot (100  $\mu$ L) of the reaction mixture at various times, which was neutralized with 2 M sodium acetate before analysis by HPLC.

The observed first-order rate constants  $k_{obsd}$  (s<sup>-1</sup>) for reactions with  $\tau_{1/2} \leq 25$  min were determined from the disappearance of **H-1-OH** and the formation of **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH** as the slopes of semilogarithmic plots of reaction progress against time which covered at least 2.5 half-times. The observed first-order rate constants  $k_{obsd}$  (s<sup>-1</sup>) for reactions with  $\tau_{1/2} > 25$  min were determined by the method of initial rates as the slopes of linear plots of the fraction of **H-1-OH** converted to **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH** against time,  $f_{H-1-SR}$ , that covered no more than 5% of the total reaction ( $f_{H-1-SR} \leq 0.05$ ).

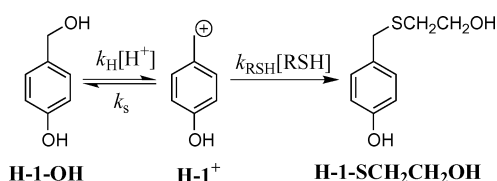
## Results

In dilute aqueous acid in the presence of 2-mercaptoethanol, 4-hydroxybenzyl alcohol **H-1-OH** undergoes clean nucleophilic substitution to give the thioether **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH**, which was characterized by <sup>1</sup>H NMR spectroscopy.

Figure 1A shows the dependence of the observed first-order rate constant  $k_{obsd}$  (s<sup>-1</sup>) for the conversion of **H-1-OH** to **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH** in the presence of various concentrations of

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Scheme 2



**Table 1.** Parameters Derived from Kinetic Analysis of the Acid-Catalyzed Conversion of **H-1-OH** to Give **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH** in Water (Scheme 2)<sup>a</sup>

[H <sup>+</sup> ]/M <sup>b</sup>	<i>k</i> <sub>lim</sub> (s <sup>-1</sup> ) <sup>c</sup>	<i>k</i> <sub>RSH</sub> / <i>k</i> <sub>s</sub> (M <sup>-1</sup> ) <sup>d</sup>
0.094	1.34 × 10 <sup>-4</sup>	22
0.445	7.13 × 10 <sup>-4</sup>	19
0.800	1.22 × 10 <sup>-3</sup>	24
1.000	1.48 × 10 <sup>-3</sup>	29

*k*<sub>H</sub> = 1.5 × 10<sup>-3</sup> M<sup>-1</sup> s<sup>-1</sup> <sup>e</sup>

<sup>a</sup> In the presence of 0.01–0.15 M 2-mercaptoethanol at 25 °C and *I* = 1.0 (NaClO<sub>4</sub>). <sup>b</sup> Concentration of perchloric acid. <sup>c</sup> Limiting first-order rate constant for acid-catalyzed reaction of **H-1-OH** in the presence of relatively high concentrations of 2-mercaptoethanol (eq 1). <sup>d</sup> Observed rate constant ratio for partitioning of the reaction intermediate between nucleophilic addition of 2-mercaptoethanol and solvent water. <sup>e</sup> Second-order rate constant for acid-catalyzed cleavage of **H-1-OH** to give **H-1<sup>+</sup>**, determined as the slope of the plot of *k*<sub>lim</sub> against [H<sup>+</sup>] shown in Figure 1B (eq 2).

perchloric acid on the concentration of 2-mercaptoethanol (RSH) at 25 °C and *I* = 1.0 (NaClO<sub>4</sub>). The least-squares fit of the data to eq 1 (solid lines), derived for the mechanism shown in Scheme 2, provided the values of the following parameters that are reported in Table 1:

$$k_{\text{obsd}} = \left( \frac{k_{\text{lim}}[\text{RSH}]}{[\text{RSH}] + k_s/k_{\text{RSH}}} \right) \quad (1)$$

$$k_{\text{lim}} = k_{\text{H}}[\text{H}^+] \quad (2)$$

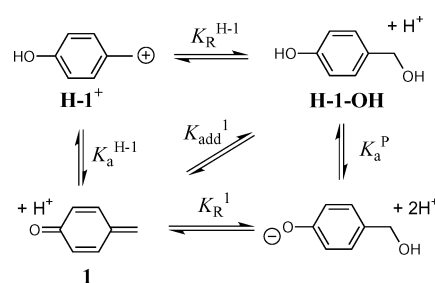
(1) Values of the limiting first-order rate constant *k*<sub>lim</sub> (s<sup>-1</sup>) for acid-catalyzed reaction of **H-1-OH** in the presence of relatively high concentrations of thiol. Figure 1B shows the dependence of the values of *k*<sub>lim</sub> (s<sup>-1</sup>) on the concentration of perchloric acid. The slope of this correlation gives the second-order rate constant *k*<sub>H</sub> = 1.5 × 10<sup>-3</sup> M<sup>-1</sup> s<sup>-1</sup> for acid-catalyzed cleavage of **H-1-OH** to give **H-1<sup>+</sup>** (eq 2, derived for Scheme 2).

(2) Values of the rate constant ratio *k*<sub>RSH</sub>/*k*<sub>s</sub> (M<sup>-1</sup>) for partitioning of the 4-hydroxybenzyl carbocation intermediate **H-1<sup>+</sup>** between nucleophilic addition of 2-mercaptoethanol and solvent water.

## Discussion

**Reaction Mechanism.** In acidic aqueous solution in the presence of 2-mercaptoethanol (RSH), 4-hydroxybenzyl alcohol **H-1-OH** undergoes clean acid-catalyzed conversion to the thioether **H-1-SCH<sub>2</sub>CH<sub>2</sub>OH**. The data in Figure 1A show that there is a change in the kinetic order of the reaction with respect to the concentration of the thiol RSH as the concentration of RSH is increased. The reaction is first-order in [RSH] when the concentration of RSH is low but changes to zero-order at high [RSH]. This shows that the specific-acid-catalyzed nucleophilic substitution reaction of **H-1-OH** follows the two-step D<sub>N</sub> + A<sub>N</sub> mechanism<sup>29</sup> shown in Scheme 2, with a change from rate-determining addition of thiol to the carbocation intermediate **H-1<sup>+</sup>** at low [RSH] (*k*<sub>s</sub> ≫ *k*<sub>RSH</sub>[RSH]) to rate-

Scheme 3



determining acid-catalyzed cleavage of **H-1-OH**, *k*<sub>lim</sub> = *k*<sub>H</sub>[H<sup>+</sup>], at high [RSH] (*k*<sub>RSH</sub>[RSH] ≫ *k*<sub>s</sub>).

The appearance of the plots in Figure 1A is determined by two parameters. (1) The limiting first-order rate constant *k*<sub>lim</sub> = *k*<sub>H</sub>[H<sup>+</sup>] for reaction at high [RSH], where the acid-catalyzed cleavage of **H-1-OH** to give the 4-hydroxybenzyl carbocation intermediate **H-1<sup>+</sup>** (protonated *p*-quinone methide) is rate-determining for the overall nucleophilic substitution. (2) The rate constant ratio *k*<sub>RSH</sub>/*k*<sub>s</sub> (M<sup>-1</sup>) for partitioning of the carbocation **H-1<sup>+</sup>** (protonated *p*-quinone methide) between nucleophilic addition of thiol and solvent water (Scheme 2). The values of *k*<sub>RSH</sub>/*k*<sub>s</sub> (M<sup>-1</sup>) determined for partitioning of **H-1<sup>+</sup>** between nucleophilic addition of 2-mercaptoethanol and solvent water range from 22 M<sup>-1</sup> at [H<sup>+</sup>] = 0.094 M, to 29 M<sup>-1</sup> at [H<sup>+</sup>] = 1.0 M (Table 1). The reaction of solvent water with the *p*-quinone methide **1** at these acidities is acid catalyzed and occurs by nucleophilic attack of water on the protonated quinone methide **H-1<sup>+</sup>**.<sup>24</sup> Therefore, the observation that the values of *k*<sub>RSH</sub>/*k*<sub>s</sub> (M<sup>-1</sup>) are nearly independent of [H<sup>+</sup>] shows that the reaction of thiol (*k*<sub>RSH</sub>, M<sup>-1</sup> s<sup>-1</sup>) occurs by the same mechanism (Scheme 2). The small increase in *k*<sub>RSH</sub>/*k*<sub>s</sub> (M<sup>-1</sup>) observed at high [H<sup>+</sup>] may reflect a medium effect on the reactivity of solvent water and/or thiol.

The partitioning ratio *k*<sub>RSH</sub>/*k*<sub>s</sub> ≈ 20 M<sup>-1</sup> can be combined with the value of *k*<sub>s</sub> = 5.8 × 10<sup>6</sup> s<sup>-1</sup> for the nucleophilic addition of solvent water to **H-1<sup>+</sup>**<sup>24</sup> to give *k*<sub>RSH</sub> ≈ 1.2 × 10<sup>8</sup> M<sup>-1</sup> s<sup>-1</sup> as the second-order rate constant for nucleophilic addition of 2-mercaptoethanol to **H-1<sup>+</sup>**. A ca. 10-fold larger value of *k*<sub>RSH</sub> = 1.5 × 10<sup>9</sup> M<sup>-1</sup> s<sup>-1</sup> has been reported for nucleophilic addition of 1-propanethiol to the 1-(4-methoxyphenyl)ethyl carbocation in 50/50 (v/v) trifluoroethanol/water.<sup>27b</sup> Similarly, the value of *k*<sub>s</sub> = 5 × 10<sup>7</sup> s<sup>-1</sup> for addition of a solvent of 50/50 (v/v) trifluoroethanol/water to the 1-(4-methoxyphenyl)ethyl carbocation<sup>27a</sup> is 9-fold larger than *k*<sub>s</sub> = 5.8 × 10<sup>6</sup> s<sup>-1</sup> for addition of solvent water to **H-1<sup>+</sup>**.<sup>24</sup>

**Rate and Equilibrium Constants for Formation and Reaction of *p*-Quinone Methide.** The second-order rate constant *k*<sub>H</sub> (M<sup>-1</sup> s<sup>-1</sup>) for the specific-acid-catalyzed cleavage of **H-1-OH** to give the protonated *p*-quinone methide **H-1<sup>+</sup>** completes the thermodynamic cycles for the reactions of *p*-quinone methide **1** shown in Scheme 3. This rate constant can be combined with other rate and equilibrium constants from Scheme 3 to give the following:

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 (27) (a) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361–1372. (b) Calculated from the rate constant ratio *k*<sub>RSH</sub>/*k*<sub>s</sub> = 3.3 for addition of azide ion and 1-propanethiol and *k*<sub>az</sub> = 5 × 10<sup>9</sup> M<sup>-1</sup> s<sup>-1</sup> for the diffusion-limited reaction of azide ion with unstable carbocations (ref 27a).  
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(1) A value of  $pK_R^{H-1} = -\log(k_s/k_H) = -9.6 \pm 0.1$ <sup>30</sup> for the Lewis acidity constant of **H-1**<sup>+</sup> can be calculated from  $k_H = 1.5 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$  for acid-catalyzed cleavage of **H-1-OH** (this work) and  $k_s = 5.8 \times 10^6 \text{ s}^{-1}$  for the reverse nucleophilic addition of solvent water to **H-1**<sup>+</sup>.<sup>24</sup>

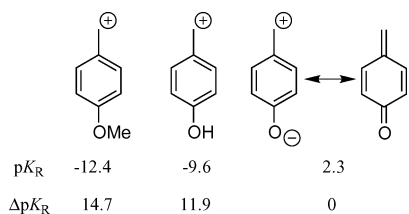
(2) A value of  $pK_{\text{add}}^1 = -7.6 \pm 0.1$ <sup>30</sup> for the overall 1,6-addition of the elements of water to **1** to give **H-1-OH** can be calculated from the values of  $pK_R^{H-1} = -9.6$  and  $pK_a^{H-1} = -2.0$  for deprotonation of the phenolic oxygen of **H-1**<sup>+</sup>,<sup>24</sup> according to eq 3.

(3) A value of  $pK_R^1 = 2.3 \pm 0.1$ <sup>30</sup> for the Lewis acidity constant of **1** can be calculated from the values of  $pK_{\text{add}}^1 = -7.6$  and  $pK_a^P = 9.9$ <sup>31a</sup> for deprotonation of the phenolic oxygen of **H-1-OH**, according to eq 4.

$$pK_{\text{add}}^1 = pK_R^{H-1} - pK_a^{H-1} \quad (3)$$

$$pK_R^1 = pK_{\text{add}}^1 + pK_a^P \quad (4)$$

Chart 1



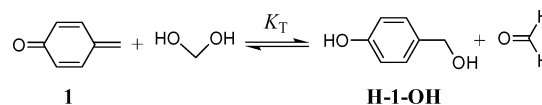
These data show that the neutralization of partial negative charge at the quinone oxygen of **1** by O-protonation to give **H-1**<sup>+</sup> destabilizes the cationic center by 16 kcal/mol (Chart 1). By comparison, a value of  $pK_R = -12.4$  has been determined as the Lewis acidity constant of the 4-methoxybenzyl carbocation **Me-1**<sup>+</sup>,<sup>33</sup> so that O-methylation of **1** to give **Me-1**<sup>+</sup> results in an even larger 20 kcal/mol destabilization of the electrophilic center toward addition of solvent water (Chart 1).

The effect of a methyl for hydrogen substitution on the Brønsted acidity of nitrogen or oxygen acids is generally small for acid–base reactions in water. For example, the  $pK_a$ s of water and methanol are similar, and only small changes in the acidity of the ammonium ion are observed as three of the four hydrogens are replaced by methyl groups.<sup>34</sup> By comparison, the methyl for hydrogen substitution at **H-1**<sup>+</sup> to give **Me-1**<sup>+</sup> occurs at a site distant from the Lewis-acid-type addition of water to

these benzylic carbocations. We attribute the greater Lewis acidity of **Me-1**<sup>+</sup> compared to **H-1**<sup>+</sup> to the formation of a relatively strong hydrogen bond between solvent water and the acidic phenolic proton of **H-1**<sup>+</sup> ( $pK_a^{H-1} = -2.0$ ),<sup>24</sup> in which there is partial proton transfer from the hydrogen bond donor **H-1**<sup>+</sup> to the hydrogen bond acceptor water.<sup>35</sup> This increases both the formal negative charge density at the phenolic oxygen of **H-1**<sup>+</sup>, relative to that at the methoxy oxygen of **Me-1**<sup>+</sup>, and the stabilization of the cationic center through the formal delocalization of this charge (Chart 1).

**Comparison of 1,2- and 1,6-Addition.** The *p*-quinone methide **1** is in one sense an extended carbonyl group at which a cyclohexadiene/phenyl ring has been “inserted” between the carbonyl oxygen and the methylene group of formaldehyde. The localization of opposite charges at the 1- and 6-positions of **1** (see Chart 1) is favored relative to this localization of charge at the 1- and 2-positions of formaldehyde by the compensating gain in aromaticity of the phenyl ring (Chart 1). Similarly, the 1,6-addition of HNu to **1** is favored relative to 1,2-addition to formaldehyde by the greater aromaticity of the product *p*-(hydroxymethyl)phenol **H-1-OH** than of the reactant **1** (Scheme 4).

Scheme 4



The net effect of this cyclohexadiene/phenyl ring insertion at the carbonyl group is an increase in the overall equilibrium constant for the addition of solvent water, from  $K_{\text{add}}^F = 2.3 \times 10^3$  for hydration of formaldehyde,<sup>36</sup> to  $K_{\text{add}}^1 = 4.0 \times 10^7$  for hydration of the *p*-quinone methide **1** (this work, Table 2), so that  $K_T = K_{\text{add}}^1/K_{\text{add}}^F = 1.7 \times 10^4$  for transfer of the elements of water from formaldehyde hydrate to **1** (Scheme 4). The relatively small driving force of 6 kcal/mol for this transfer of water from  $\text{CH}_2(\text{OH})_2$  to **1** represents the balance between much larger opposing effects:

(1) The ca. 31 kcal greater stability of the reactant formaldehyde hydrate than of the product *p*-(hydroxymethyl)phenol **H-1-OH** due to the stronger single bonds to oxygen. This is a result of the 15 kcal/mol stabilizing interactions between the geminal oxygens at  $\text{CH}_2(\text{OH})_2$ ,<sup>37</sup> and the weakening of the phenolic O–H bond at **H-1-OH** due to the ca. 16 kcal/mol stabilization of the alkoxy radical by the aromatic ring.<sup>38</sup>

(2) The even larger ca.  $(31 + 6) = 37$  kcal/mol driving force associated with the larger formal aromatic stabilization of the six-membered ring at the product **H-1-OH** than at the reactant **1**. It is interesting that this effect is very similar to the total aromatic stabilization of a phenyl ring, which has been estimated to lie between 30 and 36 kcal/mol.<sup>39</sup> It might be argued that any formal contribution of an aromatic zwitterionic valence

(30) Quoted errors are standard errors that were calculated as described in Supporting Information.

(31) (a) Calculated from  $pK_a = 10.0$  for phenol (ref 34),  $\sigma = 0.03$  for the *p*- $\text{CH}_2\text{-OMe}$  substituent (ref 32, p 66), and  $\rho = 2.2$  for ionization of ring-substituted phenols (ref 32, p 162). (b) Calculated from  $pK_a = -3.0$  for protonated 4-methoxybenzyl alcohol, the difference in the values of  $\sigma_n = -0.5$  and  $-0.13$  for the 4- $\text{O}^-$  and 4-MeO substituents (ref 32, p 72), respectively, and  $\rho = 1.1$  for ionization of ring-substituted acetophenone hydrates (Stewart, R.; Linden, R. V. D. *Can. J. Chem.* **1960**, *38*, 399–406) or ring-substituted benzylammonium ions (Blackwell, L. F.; Fischer, A.; Miller, I. J.; Topsom, R. D.; Vaughan, J. J. *J. Chem. Soc.* **1964**, 3588–3591). The value of  $pK_a = -3.0$  for protonated 4-methoxybenzyl alcohol was calculated from  $pK_a = -2.05$  for  $\text{MeOH}_2^+$  (Perdoncin, G.; Scorrano, G. *J. Am. Chem. Soc.* **1977**, *99*, 6983–6986),  $\sigma_1 = 0.11$  for the 4-MeOC<sub>6</sub>H<sub>4</sub> substituent (Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119–251), and  $\rho_1 = 8.75$  (footnote 9 of ref 42) for ionization of alcohols of structure R<sup>1</sup>R<sup>2</sup>CHOH. (c) Calculated as described for the  $pK_a$  for protonated 4-methoxybenzyl alcohol in ref 31b, using the values of  $\sigma_1 = 0.28$  and  $-0.01$  for the EtO and Et substituents, respectively.

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(37) Benson, S. W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 812–819.

(38) The bond dissociation energy  $D(\text{RO}-\text{H})$  for the O–H bond of methanol is 16 kcal/mol larger than that for the O–H bond of phenol [calculated from  $D(\text{RO}-\text{H}) = \Delta_f H^\circ(\text{H}^\cdot) + \Delta_f H^\circ(\text{RO}^\cdot) - \Delta_f H^\circ(\text{ROH})$ ; standard heats of formation  $\Delta_f H^\circ$  are from NIST Standard Reference Database Number 69, July 2001 Release (<http://webbook.nist.gov/chemistry/>)].

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**Table 2.** Rate and Equilibrium Constants and Marcus Intrinsic Barriers for Addition of Solvent Water to **1** and Formaldehyde and to Their O-Alkylated Analogues **Me-1<sup>+</sup>** and **2** (Scheme 5)<sup>a</sup>

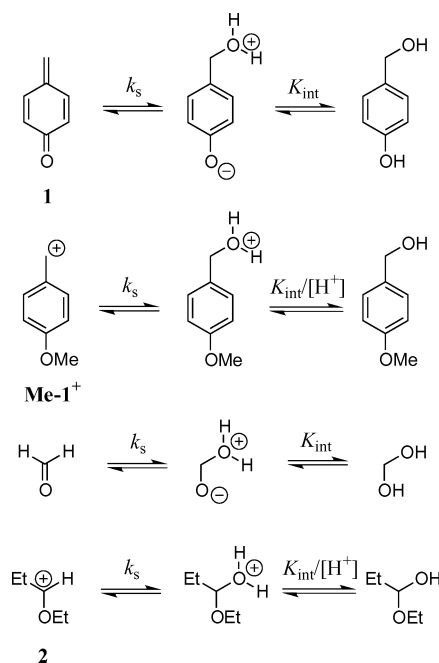
electrophile	$k_s/s^{-1}$ <sup>b</sup>	$K_{add}$ <sup>c</sup>	$K_{int}$ <sup>d</sup>	$K_Z$ <sup>e</sup>	$\Delta \log K_Z$ <sup>f</sup>	$\Lambda$ <sup>g</sup>
<b>1</b>	3.3 <sup>h</sup>	$4.0 \times 10^7$	$3.2 \times 10^{12}$ <sup>i</sup>	$1.3 \times 10^{-5}$	14.2	13.2 ± 0.8
<b>Me-1<sup>+</sup></b>	$2.5 \times 10^8$ <sup>j</sup>	$2.3 \times 10^{12}$ M <sup>k</sup>	$1.0 \times 10^3$ M <sup>k</sup>	$2.3 \times 10^9$		11.5 ± 0.6
H <sub>2</sub> CO	10 <sup>l</sup>	$2.3 \times 10^3$ <sup>l</sup>	$4.0 \times 10^{12}$ <sup>m</sup>	$5.8 \times 10^{-10}$	14.6	8.7 ± 1.2
<b>2</b>	$2 \times 10^{10}$ <sup>n</sup>	$5.4 \times 10^9$ M <sup>o</sup>	$2.5 \times 10^4$ M <sup>p</sup>	$2.2 \times 10^5$		6.6 ± 0.8

<sup>a</sup> In water at 25 °C. <sup>b</sup> First-order rate constant for addition of solvent water to the electrophile. <sup>c</sup> Overall equilibrium constant for addition of solvent water to give the neutral alcohol product. These are dimensionless quantities for **1** and H<sub>2</sub>CO but have units of M for **Me-1<sup>+</sup>** and **2** for which the addition of water generates a proton. <sup>d</sup> Equilibrium constant for the proton-transfer reaction that converts the initial ionic solvent adduct to the final neutral alcohol product. These are dimensionless quantities for **1** and H<sub>2</sub>CO but have units of M for **Me-1<sup>+</sup>** and **2**. <sup>e</sup> Equilibrium constant for addition of solvent water to the electrophile to give the ionic solvent adduct, calculated using the relationship  $K_Z = K_{add}/K_{int}$ . <sup>f</sup> Difference in  $\log K_Z$  for **Me-1<sup>+</sup>** and **1** or **2** and H<sub>2</sub>CO. <sup>g</sup> Marcus intrinsic barrier for addition of solvent water to the electrophile, calculated from the values of  $k_s$  and  $K_Z$  using eq 5. Quoted errors are standard errors that were calculated as described in Supporting Information. <sup>h</sup> Data from ref 24. <sup>i</sup> Calculated from the values of  $K_1 = 10^{2.6}$  for deprotonation of <sup>-</sup>OC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>OH<sub>2</sub><sup>+</sup> [ref 31b] and  $K_2 = 10^{-9.9}$  for deprotonation of the phenolic oxygen of HOCH<sub>2</sub>CH<sub>2</sub>OH [ref 31a] using the relationship  $K_Z = K_1/K_2$ . Data from ref 33. <sup>k</sup> From the estimated value of  $pK_a = -3.0$  for protonated 4-methoxybenzyl alcohol (ref 31b). <sup>l</sup> Data from ref 36a. <sup>m</sup> Calculated from the values of  $K_1 = 10^{-0.7}$  for deprotonation of <sup>-</sup>OCH<sub>2</sub>OH<sub>2</sub><sup>+</sup> (ref 36a) and  $K_2 = 10^{-13.3}$  for deprotonation of HOCH<sub>2</sub>OH (ref 36a) using the relationship  $K_Z = K_1/K_2$ . <sup>n</sup> Data from ref 46. <sup>o</sup> Calculated using the relationship  $K_{add} = (k_s/k_H)$  with  $k_s = 2 \times 10^{10}$  s<sup>-1</sup> (ref 46) and the estimated value of  $k_H = 3.7$  M<sup>-1</sup> s<sup>-1</sup> for the acid-catalyzed cleavage of propionaldehyde ethyl hemiacetal to give the oxocarbenium ion **2**. This value of  $k_H$  was estimated from  $k_H = 1.63$  M<sup>-1</sup> s<sup>-1</sup> for the acid-catalyzed hydrolysis of acetaldehyde diethyl acetal (ref 47) and the 2.3-fold faster acid-catalyzed cleavage of 1-(4-methoxyphenyl)ethyl alcohol than of the corresponding ethyl ether in 50/50 (v/v) trifluoroethanol/water (footnote 22 of ref 14). <sup>p</sup> From the estimated value of  $pK_a = -4.4$  for protonated propionaldehyde ethyl hemiacetal (ref 31c).

bond resonance form to the structure of **1** (Chart 1) should reduce the driving force for formation of **H-1-OH** associated with the formation of an aromatic ring. We therefore suggest that the stabilization of **1** toward the addition of water by the development of “aromatic” character is roughly offset by a compensating destabilization of **1** due to weakening of the C=O  $\pi$ -bond [there is no such bond at the formal zwitterion] relative to that at formaldehyde. Thus, the *apparent* effect of aromatization on the thermodynamic driving force for the isodesmic reaction shown in Scheme 4 is approximately equal to the full aromatic stabilization of the product **H-1-OH**.

**Intrinsic Reaction Barriers.** The kinetic barriers to organic reactions depend on both the thermodynamic driving force to the reaction and the “intrinsic” barrier to the reaction in the absence of any driving force ( $\Delta G_o = 0$ ).<sup>40,41</sup> Thus, the determination of both the thermodynamic driving force  $\Delta G_o$  and the Marcus intrinsic barrier  $\Lambda$  is critical to the development of explanations for why different reactions proceed at different rates. There have been relatively few quantitative determinations of the intrinsic barriers for organic reactions.<sup>12,42</sup> We are interested in characterizing these barriers for a large body of simple organic reactions, to develop an understanding of their origin through the application of simple chemical principles and, perhaps, through computational studies by others aimed at reproducing the experimental intrinsic reaction barriers.<sup>43</sup>

Table 2 summarizes the rate and equilibrium constants and estimated Marcus intrinsic barriers  $\Lambda$  for the nucleophilic addition of solvent water to the series of simple electrophiles shown in Scheme 5. These values of  $\Lambda$  were determined from the rate constants  $k_s$  (s<sup>-1</sup>) for the addition of solvent water and the equilibrium constants  $K_Z$  for formation of the initial ionic solvent adduct (Scheme 5), using the Marcus equation derived at 298 K (eq 5). The values of  $K_Z$  were calculated from  $K_{add}$  for the overall addition of solvent water to the electrophile to form the neutral alcohol adduct and  $K_{int}$  for conversion of the initial ionic solvent adduct to the neutral alcohol product (estimated as described in the footnotes to Table 2), using the

**Scheme 5**

relationship  $K_Z = K_{add}/K_{int}$  (Scheme 5).

$$\log k_s = \frac{1}{1.36} \left\{ 17.44 - \Lambda \left( 1 - \frac{1.36 \log K_Z}{4\Lambda} \right)^2 \right\} \quad (5)$$

O-Methylation of **1** to give **Me-1<sup>+</sup>** results in a 19 kcal/mol increase in the driving force for addition of solvent water to give the initial ionic solvent adduct ( $\Delta \log K_Z = 14.2$ ) and a small 1.7 kcal/mol decrease in the Marcus intrinsic barrier  $\Lambda$  to the reaction (Table 2). This is consistent with the notion that the intrinsic barrier to carbocation–nucleophile combination is sensitive to changes in the thermodynamic driving force resulting from changes in electron donation from substituents that are distant from the cationic center. There will be a “weaker” donation of electrons from the *p*-oxygen at **Me-1<sup>+</sup>** than at **1**, because electron donation from oxygen at **Me-1<sup>+</sup>** has the effect of increasing the formal positive charge density at the electronegative oxygen. The combination of O- and  $\alpha$ -ethylation of formaldehyde to give the simple oxocarbenium ion **2**

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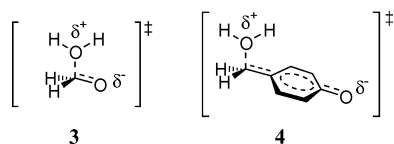
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results in a 20 kcal/mol increase in the driving force for addition of solvent water ( $\Delta \log K_z = 14.6$ ) and a small 2.1 kcal/mol decrease in the Marcus intrinsic barrier  $\Lambda$  to the reaction (Table 2).<sup>44</sup>

Despite the 6 kcal/mol greater thermodynamic driving force for the addition of solvent water to the extended carbonyl group at **1** than to the simple carbonyl compound formaldehyde, these reactions have almost identical rate constants of  $k_s = 3.3$  and  $10 \text{ s}^{-1}$ , respectively (Table 2). This corresponds to a 4.5 kcal/mol larger Marcus intrinsic barrier for addition of solvent water to **1** ( $\Lambda = 13.2 \text{ kcal/mol}$ ) than to formaldehyde ( $\Lambda = 8.7 \text{ kcal/mol}$ ), which shows that 1,6-addition to a *p*-quinone methide is *intrinsically* 2000-fold slower than 1,2-addition to a carbonyl group (Table 2). There is a very similar difference of 4.9 kcal/mol in the intrinsic barriers for addition of solvent water to **Me-1**<sup>+</sup> ( $\Lambda = 11.5 \text{ kcal/mol}$ ) and the simple oxocarbenium ion **2** ( $\Lambda = 6.6 \text{ kcal/mol}$ ). We conclude that alkylation of the carbonyl groups at **1** and formaldehyde to give **Me-1**<sup>+</sup> and a simple oxocarbenium ion, respectively, results in very little change in the relative Marcus intrinsic barriers for the addition of solvent water to these electrophiles.<sup>44</sup> This provides strong evidence that O-alkylation, a dramatic structural modification, has only a small effect on the steepness of the curvature of the reaction coordinate profile for nucleophile addition, which is the primary determinant of the magnitude of  $\Lambda$  for simple organic reactions.<sup>12,45</sup>



By comparison, the 4.5 kcal/mol difference in the intrinsic barriers for addition of solvent water to **1** and formaldehyde is almost as large as the 6 kcal/mol difference in the thermodynamic driving force for these reactions (Table 2). The intrinsic barriers for the addition of water to formaldehyde and to **1** represent the balance in the transition state between the stabilization that results from the formation of a partial bond

between the incoming nucleophile water and the electrophilic carbon and the development of unfavorable (destabilizing) interactions that accompanies this partial bond formation. The latter include the development of positive charge at the oxygen of the water nucleophile, partial cleavage of the C=O double bond of the carbonyl group at formaldehyde (see **3**), and the much more extensive electronic reorganization that occurs at the extended  $\pi$ -system at **1** (see **4**), which is the ultimate cause of the ca. 5 kcal/mol larger intrinsic barrier for 1,6- than for 1,2-addition of water. The deeper relationship between the changes in bonding that occur on proceeding from reactant to the transition state for these two reactions might be better understood through theoretical and/or computational studies designed to model these intrinsic barriers.

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**Supporting Information Available:** Discussion of the uncertainties and standard errors in the values of  $\text{p}K_R^1$ ,  $\text{p}K_R^{\text{H}^{-1}}$ , and  $\text{p}K_{\text{add}}^1$  (Scheme 3) and in the rate and equilibrium constants and Marcus intrinsic barriers reported in Table 2. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(44) O-methylation of formaldehyde gives the highly unstable methoxymethyl carbocation which undergoes addition of solvent water with  $k_s \geq 5 \times 10^{12} \text{ s}^{-1}$  (ref 46) so that there is little or no chemical barrier to this reaction. Therefore, to assess the effect of O-alkylation of formaldehyde on the intrinsic barrier for the addition of water, we use **2** as a prototypical simple oxocarbenium ion. We have estimated values of  $K_z = 2.4 \times 10^6 \text{ M}$  and  $\Lambda = 10.4 \text{ kcal/mol}$  for addition of solvent water to the 1-(4-methoxyphenyl)-ethyl carbocation to give the initial ionic solvent adduct, using the methodology described in this paper. Comparison of these quantities with those for **Me-1**<sup>+</sup> (Table 2) shows that the presence of the  $\alpha$ -alkyl group at **2** is expected to result in a decrease in the thermodynamic driving force for the addition of solvent water of ca. 4 kcal/mol, but that it should have very little effect on the Marcus intrinsic barrier for this reaction.

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