

# Flash photolytic generation and study of *p*-quinone $\alpha$ -phenylmethide and *p*-quinone $\alpha,\alpha$ -diphenylmethide in aqueous solution<sup>†,‡</sup>

J. A. Chang, A. J. Kresge,\* H.-Q. Zhan and Y. Zhu

Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

Received 14 July 2003; revised 22 September 2003; accepted 22 September 2003

epoc

**ABSTRACT:** *p*-Quinone  $\alpha$ -phenylmethide (**7**) and *p*-quinone  $\alpha,\alpha$ -diphenylmethide (**8**) were generated by flash photolytic dehydration of *p*-hydroxy- $\alpha$ -phenylbenzyl alcohol (**9**, R<sub>1</sub> = Ph, R<sub>2</sub> = H) and *p*-hydroxy- $\alpha,\alpha$ -diphenylbenzyl alcohol (**9**, R<sub>1</sub> = R<sub>2</sub> = Ph) respectively, and rates of their decay were measured in aqueous perchloric acid and sodium hydroxide solutions and also as in acetic acid, biphosphate ion, tris(hydroxymethyl)methylammonium ion, ammonium ion and bicarbonate ion buffers. The rate profiles for the hydration of these quinone methides that these data provide show hydronium ion and hydroxide ion-catalyzed regions and also ‘uncatalyzed’ water reactions, with saturation of hydronium ion catalysis in dilute solution for the diphenyl-substituted substrate but only in concentrated acid solution for the less basic monophenyl substrate. Both substrates also give inverse hydronium ion isotope effects ( $k_{\text{H}^+}/k_{\text{D}^+} < 1$ ). These results show that the hydronium ion-catalyzed reactions occur by rapid pre-equilibrium protonation of the quinone methide on its carbonyl oxygen atom followed by rate-determining capture of the benzyl-type carbocation thus formed by water. Phenyl substitution retards the rate of hydration and also reduces the acidity constant of the quinone methide conjugate acid. The molecular basis of these substituent effects is discussed. Copyright © 2004 John Wiley & Sons, Ltd.

Additional material for this paper is available in Wiley InterScience

**KEYWORDS:** *p*-quinone  $\alpha$ -phenylmethide; *p*-quinone  $\alpha,\alpha$ -diphenylmethide; quinone methide hydration; flash photolysis; rate profiles; solvent isotope effects; reaction mechanisms

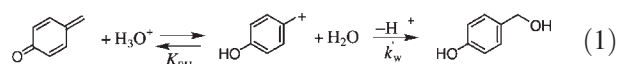
## INTRODUCTION

Quinone methides are interesting reactive species possessing both nucleophilic and electrophilic centers, which has made them useful synthetic intermediates with wide applications in organic chemistry.<sup>1</sup> Quinone methides also figure prominently in wood chemistry, playing key roles in both lignification reactions in the plant and delignification reactions in the paper mill.<sup>2</sup> But perhaps most significant of all is the pronounced activity shown by quinone methides in biological systems: they have, for example been implicated as the ultimate cytotoxins responsible for the effects of agents such as antitumor drugs, antibiotics and DNA alkylators.<sup>3</sup> 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, and how their rates depend upon quinone methide structure, we have undertaken a detailed investigation of their kinetics and reaction mechanisms.



We have already reported examination of the two parent substances, *o*-quinone methide, **1**,<sup>4</sup> and *p*-quinone methide, **2**.<sup>5</sup> These studies showed that hydration of these quinone methides occurs by hydronium ion-catalyzed, uncatalyzed and hydroxide ion-catalyzed pathways. They also revealed that hydronium ion catalysis takes place by rapid and reversible pre-equilibrium protonation of the quinone methide on its oxygen atom, followed by rate-determining hydration of the carbocation ion thus formed [Eqn (1)]:



The uncatalyzed reaction, on the other hand, occurs by simple nucleophilic attack of a water molecule on

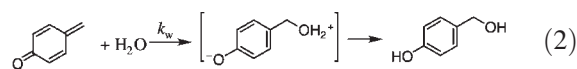
\*Correspondence to: A. J. Kresge, Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada.  
E-mail: akresge@chem.utoronto.ca

Contract/grant sponsor: Natural Sciences and Engineering Research Council of Canada.

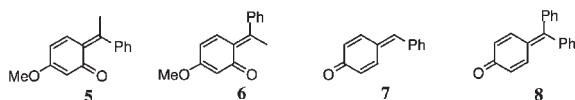
<sup>†</sup>This paper is dedicated to Professor William P. Jencks in appreciation of his seminal contributions to physical organic chemistry.

<sup>‡</sup>Selected paper part of a special issue entitled ‘Biological Applications of Physical Organic Chemistry’.

the unprotonated quinone methide, with or without simultaneous proton shuffling to avoid a zwitterionic intermediate [Eqn (2)]:

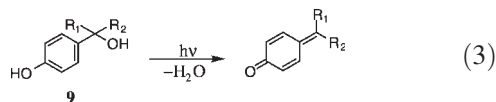


We were able also to verify the reaction mechanism of Eqn (1) for *o*-quinone  $\alpha$ -phenylmethide, **3**, and *o*-quinone  $\alpha$ -(*p*-anisyl)methide, **4**, An = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>,<sup>6</sup> and also for *cis*-, **5**, and *trans*-5-methoxy-*o*-quinone  $\alpha$ -phenylethide **6**,<sup>7</sup> by showing that acid catalysis of the hydration of these more basic substrates becomes saturated at higher acidities as the position of the pre-equilibrium step shifts from unprotonated to protonated substrate.



In this paper, we report on the hydration reactions of *p*-quinone  $\alpha$ -phenylmethide, **7**, and *p*-quinone  $\alpha,\alpha$ -diphenylmethide, **8**. These substances together with the parent *p*-quinone methide, **2**, form a series which shows the effect of successive phenyl substitution on quinone methide reactivity.

We generated the present quinone methides, as we<sup>4-7</sup> and others<sup>1</sup> had done before, by photolytic dehydration of the corresponding substituted *p*-hydroxybenzyl alcohols, **9** [Eqn (3)]:



Most of the reactions that we studied were fairly fast, and we therefore used flash photolytic methods to determine their rates.

## EXPERIMENTAL

### Materials

*p*-Hydroxy- $\alpha$ -phenylbenzyl alcohol (**9**, R<sub>1</sub> = Ph, R<sub>2</sub> = H) was prepared by treating *p*-hydroxybenzaldehyde with phenylmagnesium bromide; its melting-point and <sup>1</sup>H NMR spectrum were consistent with literature values.<sup>8</sup> *p*-Hydroxy- $\alpha,\alpha$ -diphenylbenzyl alcohol (**9**, R<sub>1</sub> = R<sub>2</sub> = Ph) was obtained by treating methyl *p*-hydroxybenzoate with phenylmagnesium bromide; its melting-point and <sup>1</sup>H NMR spectrum also agreed with literature values.<sup>9</sup> *p*-Methoxybenzhydryl acetate was synthesized by treating *p*-methoxybenzhydrol<sup>10</sup> with acetic anhydride in the presence of pyridine;<sup>11</sup> its <sup>1</sup>H and <sup>13</sup>C NMR spectra agreed with a literature report.<sup>11</sup>

All other materials were of the best available commercial grades.

### Kinetics

Flash photolytic rate measurements were made using a microsecond conventional flash lamp system and a nanosecond eximer laser system operating at  $\lambda = 248$  nm, which have already been described.<sup>12</sup> Initial benzyl alcohol substrate concentrations were of the order of  $1 \times 10^{-5}$  M and the temperature of all reacting solutions was controlled at  $25.0 \pm 0.05$  °C. Quinone methide decay was monitored at  $\lambda = 395$  nm for *p*-quinone  $\alpha$ -phenylmethide and at  $\lambda = 415$  nm for *p*-quinone  $\alpha,\alpha$ -diphenylmethide, and *p*-methoxybenzhydryl cation decay was monitored at  $\lambda = 460$  nm. The data so obtained conformed to the first-order rate law well, and observed first-order rate constants were obtained by least-squares fitting of a single exponential function.

Rates with half-lives greater than a few seconds could not be measured in this way because the monitoring lamp power supply was not sufficiently steady. These reactions were therefore initiated by a single flash from the convention flash photolysis system and the reacting solutions were then quickly transferred to the cell compartment of a Cary 2200 spectrometer where absorbance decay measurements were made. The temperature of these reacting solutions was maintained at  $25.0 \pm 0.05$  °C. These data also conformed to the first-order rate law well, and observed first-order rate constants were again obtained by least-squares fitting of a single exponential function.

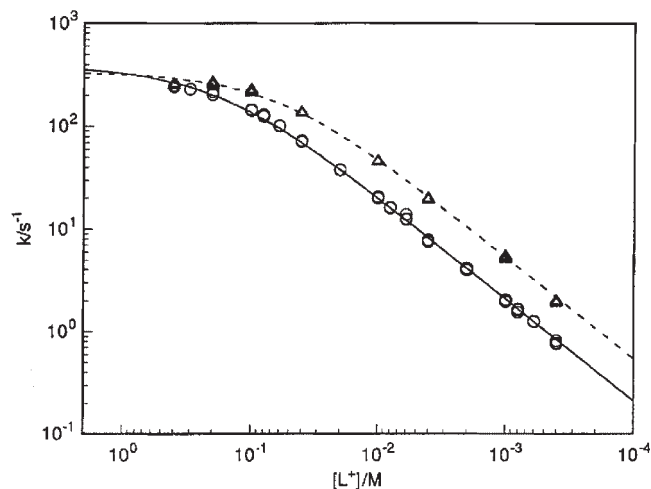
## RESULTS

### *p*-Quinone $\alpha,\alpha$ -diphenylmethide

**Perchloric acid solutions.** Rates of decay of *p*-quinone  $\alpha,\alpha$ -diphenylmethide were measured in aqueous perchloric acid solutions using both H<sub>2</sub>O and D<sub>2</sub>O as the solvent. The data so obtained are summarized in Supplementary Table S1 (available in Wiley Interscience) and are also displayed in Fig. 1.

It can be seen that reaction rates increase with increasing acid concentration at the lower end of the acidity range investigated, i.e. the reaction here is acid catalyzed. In this region, moreover, rates are slower in H<sub>2</sub>O than in D<sub>2</sub>O, i.e. the isotope effect is inverse:  $k_H/k_D < 1$ . At the higher acidity end of the range investigated, on the other hand, acid catalysis becomes saturated, and the inverse isotope effect becomes weaker and finally disappears.

These phenomena are consequences of the operation of the pre-equilibrium protonation reaction mechanism shown as Eqn (1). At low acidities, the position of the pre-equilibrium step is over on the side of unprotonated substrate, and protonation, i.e. acid catalysis, is required to convert unprotonated substrate into product. The pre-equilibrium step, moreover, transforms the relatively loose 'non-reacting' O—H bonds of the hydronium ion into tighter O—H bonds of a water molecule.<sup>13</sup> There is



**Figure 1.** Rates of hydration of *p*-quinone  $\alpha,\alpha$ -diphenylmethide in H<sub>2</sub>O (○) and D<sub>2</sub>O (Δ) solutions of perchloric acid at 25 °C

therefore a tightening up of isotopically substituted bonds, and an inverse isotope effect results. At high acidities, on the other hand, the position of the pre-equilibrium shifts to protonated substrate, and this then becomes the reaction's initial state; substrate protonation is now no longer required to convert this initial state into product and acid catalysis becomes saturated. The initial state now also contains a water molecule rather than a hydronium ion and tightening up of loose hydronium ion O—H bonds no longer takes place; the inverse isotope effect consequently disappears.

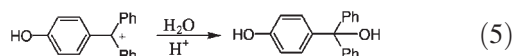
The rate law that applies to this reaction mechanism is as follows:

$$k_{\text{obs}} = k'_w [\text{H}^+] / (K_{\text{SH}} + [\text{H}^+]) \quad (4)$$

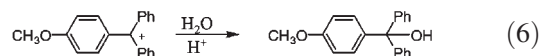
with the rate constant for carbocation ion capture,  $k'_w$ , and the substrate conjugate acid ionization constant,  $K_{\text{SH}}$ , as defined by Eqn (1). Least-squares fitting of this expression gave  $k'_w = (3.87 \pm 0.09) \times 10^2 \text{ s}^{-1}$  and  $K_{\text{SH}} = (1.84 \pm 0.05) \times 10^{-1} \text{ M}$ ,  $\text{p}K_{\text{SH}} = 0.74 \pm 0.01$ , plus the isotope effects ( $k'_{\text{wH}_2\text{O}}/k'_{\text{wD}_2\text{O}} = 1.14 \pm 0.04$  and  $K_{\text{SH}}/K_{\text{SD}} = 2.95 \pm 0.13$ ).

At low acidities where  $[\text{H}^+] \ll K_{\text{SH}}$ , Eqn (4) reduces to  $k_{\text{obs}} = (k'_w/K_{\text{SH}})[\text{H}^+]$ , which shows that the hydronium ion catalytic coefficient, defined as  $k_{\text{H}^+} = \Delta k_{\text{obs}}/\Delta[\text{H}^+]$ , is equal to  $k'_w/K_{\text{SH}}$ . Use of the least-squares results given above for  $k'_w$  and  $K_{\text{SH}}$  then provides  $k_{\text{H}^+} = (2.11 \pm 0.08) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$  and the inverse isotope effect  $k_{\text{H}^+}/k_{\text{D}^+} = 0.387 \pm 0.022$ .

The rate constant determined here,  $k'_w = 3.9 \times 10^2 \text{ s}^{-1}$ , for capture of the *p*-hydroxyphenyldiphenylmethyl cation by water in aqueous solution:



is nicely consistent with  $k = 1 \times 10^3 \text{ s}^{-1}$  determined for the analogous reaction of *p*-methoxyphenyldiphenylmethyl cation with water:<sup>14</sup>



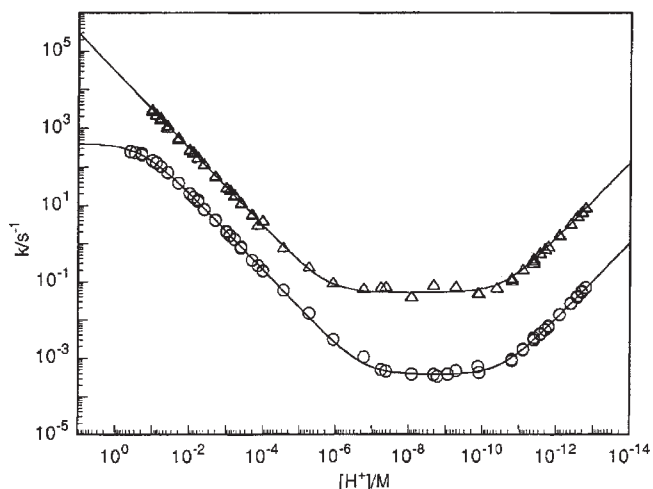
and the recent report that a *p*-hydroxyphenyl group is about twice as good at stabilizing aryl substituted cations as a *p*-methoxyphenyl group.<sup>15</sup> The isotope effect on the ionization of the substrate conjugate acid determined here,  $K_{\text{SH}}/K_{\text{SD}} = 3.0$ , is also consistent with solvent isotope effects on the ionization of other oxygen acids of similar acid strength, e.g.  $K_{\text{H}}/K_{\text{D}} = 2.8$  for the ionization of picric acid.<sup>16</sup>

**Rate profile.** Rates of reaction of *p*-quinone  $\alpha,\alpha$ -diphenylmethide were also measured in aqueous sodium hydroxide solutions and in acetic acid, biphosphate ion, tris(hydroxymethyl)methylammonium ion, ammonium ion and bicarbonate ion buffers. The data so obtained are summarized in Supplementary Tables S2 and S3.

The measurements in buffers were made using series of solutions of constant buffer ratio and constant ionic strength (0.10 M), and therefore constant hydronium ion concentration, but varying total buffer concentration. The data were analyzed by least-squares fitting of the buffer dilution expression

$$k_{\text{obs}} = k_{\text{int}} + k_{\text{buff}}[\text{buffer}] \quad (7)$$

Buffer catalysis was found to be either very weak or non-existent, and buffer catalytic coefficients,  $k_{\text{buff}}$ , could consequently not be well determined. Zero buffer concentration intercepts,  $k_{\text{int}}$ , on the other hand, could be determined well. These, together with the rate constants measured in perchloric acid and sodium hydroxide solutions, are displayed as the lower rate profile of Fig. 2.



**Figure 2.** Rate profiles for the hydration of *p*-quinone  $\alpha,\alpha$ -diphenylmethide (○) and *p*-quinone  $\alpha$ -phenylmethide (Δ) in aqueous solution at 25 °C

Hydronium ion concentrations of the buffer solutions needed for this purpose were obtained by calculation using buffer acid ionization constants from the literature and activity coefficients recommended by Bates.<sup>17</sup>

It can be seen that these additional data have added an uncatalyzed water reaction and a hydroxide ion-catalyzed process to the rate profile of Fig. 1. The rate law that now applies is therefore that of Eqn (4) with uncatalyzed and hydroxide ion catalyzed terms added:

$$k = k'_w[H^+]/(K_{SH} + [H^+]) + k_w + k_{HO^-}[HO^-] \quad (8)$$

Least-squares fitting of this expression gave  $k'_w = (3.92 \pm 0.14) \times 10^2 \text{ s}^{-1}$ ,  $K_{SH} = (1.89 \pm 0.08) \times 10^{-1} \text{ M}$ ,  $k_w = (3.69 \pm 0.11) \times 10^{-4} \text{ s}^{-1}$  and  $k_{HO^-} = (6.48 \pm 0.10) \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ . The first two of these values are nicely consistent with the results obtained by fitting Eqn (4). Weighted averages of the two determinations give  $k'_w = (3.89 \pm 0.08) \times 10^2 \text{ s}^{-1}$  and  $K_{SH} = (1.85 \pm 0.04) \times 10^{-1} \text{ M}$ ,  $pK_{SH} = 0.73 \pm 0.01$ .

### *p*-Quinone $\alpha$ -phenylmethide

**Rate profile.** Rates of decay of *p*-quinone  $\alpha$ -phenylmethide were measured in dilute aqueous perchloric acid solutions, again using both H<sub>2</sub>O and D<sub>2</sub>O as the solvent, as well as in sodium hydroxide solutions and also in acetic acid, biphosphate anion, tris(hydroxymethyl)methylammonium ion, ammonium ion and bicarbonate ion buffers. These data are summarized in Supplementary Tables S4–S6.

The measurements in buffers were again made in series of solutions of constant buffer ratio and constant ionic strength (0.10 M) but varying total buffer concentration, and the data were again analyzed by least-squares fitting of Eqn (7). Buffer catalysis was now still weak although somewhat stronger than that found for *p*-quinone  $\alpha, \alpha$ -diphenylmethide. This is consistent with the expectation that the buffer base serves as a nucleophile reacting directly with the quinone methidesubstituted methylene group, which is less crowded in the monophenyl than in the diphenyl substrate.

The zero buffer concentration intercepts obtained in this way, together with the rate constants determined in perchloric acid and sodium hydroxide solutions, were used to construct the upper rate profile shown in Fig. 2. This rate profile has the same general shape as that obtained for *p*-quinone  $\alpha, \alpha$ -diphenylmethide (Fig. 2, lower profile), except that it lacks saturation of acid catalysis. The present quinone methide nevertheless does react by the preequilibrium protonation mechanism of Eqn (1), as shown by its inverse hydronium ion isotope effect: observed rate constants in dilute DClO<sub>4</sub>–D<sub>2</sub>O solution are linear functions of acid concentration, just as they are in dilute HClO<sub>4</sub>–H<sub>2</sub>O solutions, and linear least-squares analysis gives  $k_{H^+} = (2.92 \pm 0.03) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$  and  $k_{H^+}/k_{D^+} = 0.408 \pm 0.011$ .

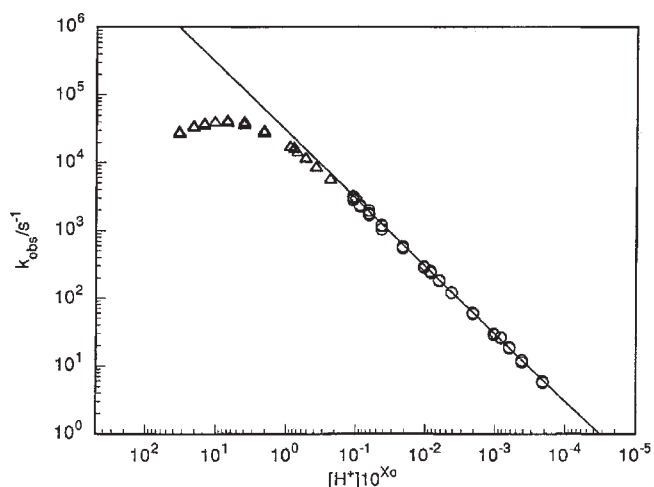
This lack of saturation of acid catalysis, coupled with a pre-equilibrium protonation reaction mechanism, means that hydronium ion concentrations have not yet reached the level where they are comparable to the value of the substrate acidity constant  $K_{SH}$ , and this requires that the condition  $[H^+] \ll K_{SH}$  be imposed upon the rate law Eqn (8). The result is the rate law

$$k = k_{H^+}[H^+] + k_w + k_{HO^-}[HO^-] \quad (9)$$

with  $k_{H^+} = k'_w/K_{SH}$ . Least-squares fitting of this expression gave  $k_{H^+} = (2.97 \pm 0.04) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ ,  $k_w = (5.12 \pm 0.20) \times 10^{-2} \text{ s}^{-1}$  and  $k_{HO^-} = (8.20 \pm 0.15) \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$ . This value of  $k_{H^+}$  is nicely consistent with  $k_{H^+} = (2.92 \pm 0.03) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$  obtained above in the isotope effect determination. The weighted average of the two values is  $k_{H^+} = (2.94 \pm 0.02) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ .

**Concentrated perchloric acid solutions.** In an attempt to detect saturation of acid catalysis, which was not apparent from the dilute perchloric acid data ( $[HClO_4] \leq 0.1 \text{ M}$ ) represented by the upper rate profile of Fig. 2, rates of decay of *p*-quinone  $\alpha$ -phenylmethide were also measured in concentrated perchloric acid solutions up to 3.6 M. These data are summarized in Supplementary Table S7. They, together with the results obtained in dilute perchloric acid solutions, are also displayed in Fig. 3, which uses the  $X_0$  excess acidity scale<sup>18</sup> in its abscissa to account for the increased effective acidity of the concentrated acid solutions.

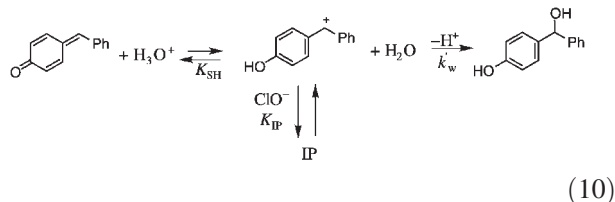
The line drawn in Fig. 3 is based on the dilute solution data, where observed rate constants are linearly related to acid concentration. Saturation of acid catalysis in the concentrated acid solutions is clearly visible. Observed rate constants, however, do not simply level off to a constant value as expected for simple saturation; instead,



**Figure 3.** Rates of hydration of *p*-quinone  $\alpha$ -phenylmethide in dilute (○) and concentrated (Δ) perchloric acid solutions, illustrating saturation of acid catalysis and inhibition by ion-pair formation



they reach a maximum value and then decrease. This decrease is produced by the known ability of perchlorate ions to inhibit the rates of reaction of large delocalized carbocations with water, an effect that has been attributed to carbocation–perchlorate ion ion-pair formation.<sup>19</sup> This complication requires modification of the simple pre-equilibrium protonation reaction scheme of Eqn (1) by inclusion of an ion-pair formation equilibrium:



The simple rate law of Eqn (4) must also be modified to include this ion-pair equilibrium, and also to include the activity of water, which decreases significantly over the range of acid concentrations used, in contrast to the situation in dilute solution where water activity remained constant. In addition, the increased effective acidity of concentrated acid solutions must be taken into account by including the excess acidity function  $X_0$  and an acidity function slope parameter  $m$ .

The resulting expression:

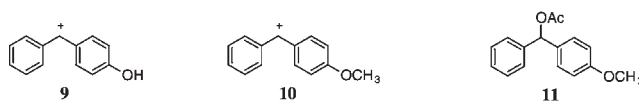
$$k_{\text{obs}} = \frac{k'_w ([\text{H}^+] 10^{mX_0}) A_{\text{H}_2\text{O}}}{K_{\text{SH}} + ([\text{H}^+] 10^{mX_0}) (1 + K_{\text{IP}} [\text{ClO}_4^-])} \quad (11)$$

contains three independent variables:  $[\text{H}^+]$  ( $= [\text{ClO}_4^-]$ ),  $X_0$  and  $A_{\text{H}_2\text{O}}$ , and four parameters to be determined:  $k'_w$ ,  $K_{\text{SH}}$ ,  $K_{\text{IP}}$  and  $m$ . We attempted to evaluate these four parameters by least-squares fitting using GraFit Software,<sup>20</sup> but we were unable to obtain a unique solution that did not vary with changes in the initial guesses of these parameters, which were needed as input for the calculation. A similar difficulty was encountered when the number of parameters to be determined was reduced from four to three by fitting of a modified form of Eqn (11) that incorporated the value of  $k'_w/K_{\text{SH}}$  ( $= k_{\text{H}^+}$ ) determined in dilute acid solutions. Despite the fact that we could not analyze our data quantitatively, the concentrated acid rate measurements are nevertheless qualitatively consistent with saturation of acid catalysis and ion pair formation.

**Thiocyanate ion solutions.** Several of the quinone methides that we examined before also, like the present substrate, did not show saturation of acid-catalyzed hydration in dilute acid solution where we could analyze the data quantitatively.<sup>4,5</sup> We were nonetheless able to obtain estimates of the substrate conjugate acid ionization constants,  $K_{\text{SH}}$ , for these systems by determining the acid-catalyzed rate constants for reaction of these quinone methides with thiocyanate ion. This rate constant is equal to  $k'_{\text{SCN}}/K_{\text{SH}}$ , where  $k'_{\text{SCN}}$  is the bimolecular rate

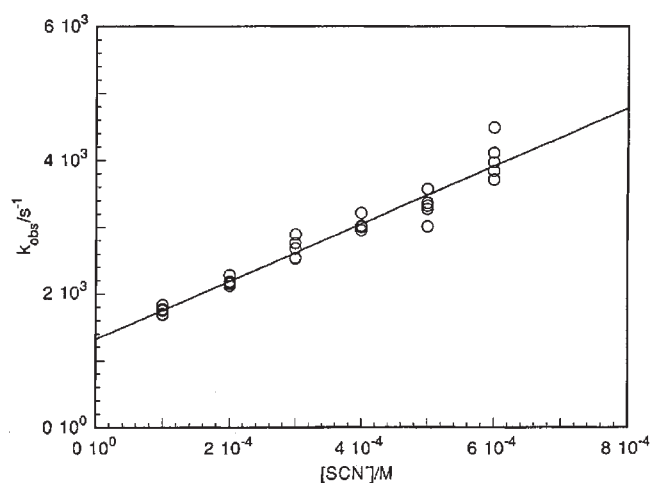
constant for capture of the carbocationic quinone methide conjugate acid by thiocyanate ion. On the reasonable assumption that this carbocation capture is an encounter-controlled process, the encounter-controlled rate constant  $k = 5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$  could then be assigned to  $k'_{\text{SCN}}$  and  $K_{\text{SH}}$  could be evaluated.

Protonation of the present quinone methide produces a carbocation, **9**, that is more stable than those to which this method of estimating  $K_{\text{SH}}$  was previously applied,<sup>4,5</sup> and its capture by thiocyanate ion is consequently not an encounter-controlled process (see below). An estimate of  $k'_{\text{SCN}}$  for **9** may nevertheless still be made by measuring the rate constant for capture of its methoxy-substituted analog, **10**, by thiocyanate ion and then applying the factor of two by which hydroxy-substituted cations have recently been shown to be more stable than their methoxy-substituted analogs.<sup>15</sup>

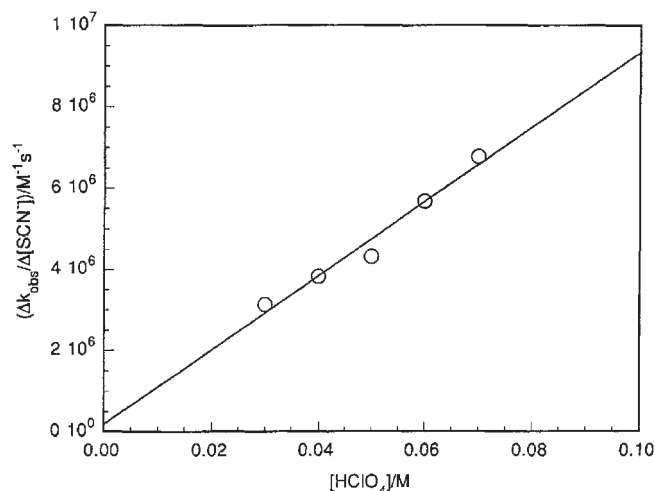


The rate of capture of carbocation **9** by thiocyanate ion was determined by measuring rates of decay of *p*-quinone  $\alpha$ -phenylmethide in series of dilute aqueous sodium thiocyanate solutions at fixed perchloric acid concentrations. These data are summarized in Supplementary Table S8.

Observed first-order rate constants obtained in this way proved to be linear functions of thiocyanate concentration, as is illustrated in Fig. 4. The gradients of these relationships,  $\Delta k_{\text{obs}}/\Delta [\text{SCN}^-]$ , were in turn linear functions of acid concentration, as shown in Fig. 5, and the gradient of that relationship then provided the rate constant  $k'_{\text{SCN}}/K_{\text{SH}} = (9.15 \pm 0.95) \times 10^7 \text{ M}^{-2} \text{ s}^{-1}$ .



**Figure 4.** Relationship between thiocyanate ion concentration and observed rate constants for the decay of *p*-quinone  $\alpha$ -phenylmethide in aqueous 0.05 M perchloric acid solutions at 25 °C



**Figure 5.** Relationship between perchloric acid concentration and slopes of plots such as that shown in Fig. 4

The methoxy-substituted carbocation **10** was generated by flash photolysis of the corresponding benzhydryl acetate **11**,<sup>21</sup> and rates of its decay were measured in dilute sodium thiocyanate solutions. These data are summarized in Supplementary Table S9. Observed first-order rate constants obtained in this way proved to be linear functions of thiocyanate ion concentration, giving the rate constant  $k = (2.81 \pm 0.03) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$  for capture of the methoxy-substituted carbocation **10** by thiocyanate ion.

Combination of this result with the factor of two by which hydroxy-substituted carbocations have been shown to be more stable than their methoxy-substituted analogs<sup>15</sup> leads to  $k'_{\text{SCN}} = 1.4 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$  as an estimate of the rate constant for capture of the hydroxy-substituted carbocation **9** by thiocyanate ion. Use of this estimate with the relationship  $k'_{\text{SCN}}/K_{\text{SH}} = 9.15 \times 10^7 \text{ M}^{-2} \text{ s}^{-1}$  then gives  $K_{\text{SH}} = 15 \text{ M}$  as the acidity constant of oxygen-protonated *p*-quinone  $\alpha$ -phenylmethide. (This value of  $K_{\text{SH}}$  can be no more than a rough estimate because the factor by which hydroxy-substituted carbocations are less reactive than their methoxy-substituted analogs can be expected to vary from system to system, and the factor of two used here is itself only a rough approximation).

This result, together with  $k_{\text{H}^+} (= k'_{\text{w}}/K_{\text{SH}}) = 2.94 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$  for reaction of *p*-quinone  $\alpha$ -phenylmethide in dilute perchloric acid solutions (see above) then gives  $k'_{\text{w}} = 4.4 \times 10^5 \text{ s}^{-1}$  as the rate constant for reaction of the hydroxy-substituted carbocation **9** with water. This is consistent with  $k = 2 \times 10^6 \text{ s}^{-1}$  reported for the reaction of the corresponding methoxy substituted carbocation **10** with water in a mixed acetonitrile–water solvent,<sup>21</sup> and it provides another comparison showing hydroxy-substituted carbocations to be slightly less reactive than their methoxy-substituted counterparts.

**Table 1.** Effect of  $\alpha$ -phenyl substitution on *p*-quinone methide reactivity<sup>a</sup>

| Quantity                                       | Number of phenyl substituents |                      |                      |
|------------------------------------------------|-------------------------------|----------------------|----------------------|
|                                                | None <sup>b</sup>             | One                  | Two                  |
| $k_{\text{w}}(\text{s}^{-1})$                  | $3.3 \times 10^0$             | $5.1 \times 10^{-2}$ | $3.7 \times 10^{-4}$ |
| $k_{\text{HO}^-}(\text{s}^{-1})$               | —                             | $8.2 \times 10^1$    | $6.5 \times 10^{-1}$ |
| $k_{\text{H}^+}(\text{M}^{-1} \text{ s}^{-1})$ | $5.3 \times 10^4$             | $2.9 \times 10^4$    | $2.1 \times 10^3$    |
| $K_{\text{SH}}(\text{M})$                      | $1.1 \times 10^2$             | $1.5 \times 10^1$    | $1.9 \times 10^{-1}$ |
| $k'_{\text{w}}(\text{s}^{-1})$                 | $5.8 \times 10^6$             | $4.4 \times 10^5$    | $3.9 \times 10^2$    |

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

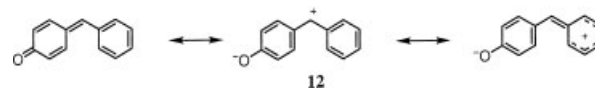
<sup>b</sup> From Ref. 5.

## DISCUSSION

The data in Table 1 show that introduction of phenyl substituents on to the  $\alpha$ -carbon atom of the methylene group of *p*-quinone methide retards the rate of its uncatalyzed reaction with water,  $k_{\text{w}}$ , and also retards the rate of its reaction with hydroxide ion,  $k_{\text{HO}^-}$ . This must be the result, at least in part, of a steric effect produced by the nucleophilic role that water and hydroxide ion play in these reactions: they add directly to the quinone methide methylene group carbon atom, which is a reaction site that becomes increasingly crowded with successive  $\alpha$ -phenyl substitution. This steric effect is apparent as well in the weak buffer catalysis of these quinone methide reactions noted above.

An additional factor that contributes to this phenyl group rate retardation arises from the stabilization that  $\alpha$ -phenyl substituents provide to the benzylic carbocation resonance form of the quinone methide, **12**, by positive charge delocalization, as shown in Scheme 1. This positive charge is being neutralized in these reactions, and such delocalization is consequently less strong in the reactions' transition states than in their initial states. As a result, the initial states are stabilized more strongly than are the transition states, and that increases the free energy difference between initial states and transition states, raising the free energy of activation and lowering the reaction rate.

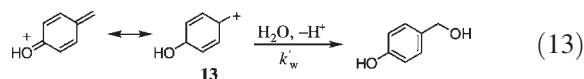
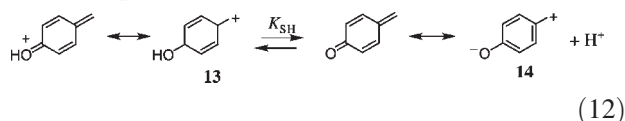
The catalytic coefficients,  $k_{\text{H}^+}$ , for hydronium ion-catalyzed addition of water to these quinone methides also decrease as  $\alpha$ -phenyl groups are added, but the change now is considerably less than for  $k_{\text{w}}$  or  $k_{\text{HO}^-}$ . This is because  $k_{\text{H}^+}$  is a composite constant equal to the specific rate of reaction of the quinone methide conjugate acid with water,  $k'_{\text{w}}$ , divided by the conjugate acid ionization constant,  $K_{\text{SH}}$ :  $k_{\text{H}^+} = k'_{\text{w}}/K_{\text{SH}}$ . Both  $k'_{\text{w}}$  and  $K_{\text{SH}}$  diminish as phenyl groups are added, but  $k'_{\text{w}}$



**Scheme 1**

decreases somewhat more strongly than  $K_{SH}$ , and the result is a moderate drop in  $k_{H^+}$  with phenyl group introduction.

It is interesting that phenyl group substitution has a considerably stronger effect on  $k'_w$  than on  $K_{SH}$ . The reactions represented by these constants:



both have initial states containing protonated quinone methide, whose resonance forms include the benzyl cation structure, **13**, that is stabilized by  $\alpha$ -phenyl substituents. In the neutral quinone methide product of the acid ionization reaction of Eqn (12), a similar although less important charge-separated benzyl-cationic resonance form, **14**, contributes to the quinone methide structure, and its stabilization by phenyl groups partly offsets the effect of phenyl group stabilization of the reaction's initial state. The net result is a greater phenyl group stabilization of the reaction's initial state than of its final state, and that raises the free energy of reaction and diminishes  $K_{SH}$ .

In the hydration reaction of Eqn (13), the benzylic cationic charge of resonance form **13** is removed. This change, however, is only partly accomplished at the reaction's transition state, and it is not clear whether the resultant decrease in phenyl group stabilization of benzylic positive charge is larger or smaller than that experienced by the acid ionization reaction of Eqn (12), and whether the phenyl group effect from this source on  $k'_w$  is consequently stronger or weaker than that on  $K_{SH}$ . Phenyl substitution, however, has a powerful retarding steric effect on the velocity of the rate process,  $k'_w$ , similar to that noted above on the rate constant of the uncatalyzed water reaction,  $k_w$ , which has no counterpart in the acid ionization reaction. This steric effect apparently overwhelms any influence phenyl substitution has on benzyl cationic resonance forms, and that makes the phenyl group effect on  $k'_w$  stronger than that on  $K_{SH}$ .

## Supplementary material

Tables S1–S9 containing rate data are available in Wiley Interscience.

## Acknowledgment

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

## REFERENCES

- Wan P, Barker B, Diao L, Fischer M, Shi Y, Yang C. *Can. J. Chem.* 1996; **74**: 465–475.
- Sipila J, Brunow G. *Bull. Liaison Groupe Polyphenols* 1992; **16**: 140–143; Gratzl JS, Chen C-L. In *Lignin: Historical, Biological, and Materials Perspectives*, Glasser WA, Northey RA, Schultz TP (eds). ACS Symposium Series 742. American Chemical Society: Washington, DC, 2000; 392–421.
- Peter MG. *Angew. Chem., Int. Ed. Engl.* 1989; **28**: 555–570; Bolton JL, Pisha E, Zhang F, Qiu S. *Chem. Res. Toxicol.* 1998; **11**: 1113–1127; Veldhuyzen WF, Shalloo AJ, Jones RA, Rokita SE. *J. Am. Chem. Soc.* 2001; **123**: 11126–11132.
- Chiang Y, Kresge AJ, Zhu Y. *J. Am. Chem. Soc.* 2000; **122**: 9854–9855; 2001; **123**: 8089–8094.
- Chiang Y, Kresge AJ, Zhu Y. *J. Am. Chem. Soc.* 2002; **124**: 6349–6356.
- Chiang Y, Kresge AJ, Zhu Y. *J. Am. Chem. Soc.* 2002; **124**: 717–722.
- Chiang Y, Kresge AJ, Zhu Y. *Photochem. Photobiol. Sci.* 2002; **1**: 67–70.
- Goldstein AS, Gelb MH. *Tetrahedron Lett.* 2000; **41**: 2797–2800.
- Lewis TW, Curtin DY, Paul IC. *J. Am. Chem. Soc.* 1979; **101**: 5717–5725.
- Inoue A, Kitagawa K, Shinokuko H, Oshima K. *J. Org. Chem.* 2001; **66**: 4333–4339.
- Van Pham T, McClelland RA. *Can. J. Chem.* 2001; **79**: 1887–1897.
- Chiang Y, Hojatti M, Keffe JR, Kresge AJ, Schepp NP, Wirz J. *J. Am. Chem. Soc.* 1987; **109**: 4000–4009; Andraos J, Chiang Y, Huang C-G, Kresge AJ, Scaiano JC. *J. Am. Chem. Soc.* 1993; **115**: 10605–10610.
- Kresge AJ, More O'Ferrall RA, Powell MF. In *Isotopes in Organic Chemistry*, vol. 7, Buncl E, Lee CC (eds). Elsevier: New York, 1987; Chapt. 4.
- Diffenbach RA, Sano K, Taft RW. *J. Am. Chem. Soc.* 1966; **88**: 4747–4749.
- McClelland RA, Moriarty MA. *J. Chem. Soc., Perkin Trans. 2* 2001; 2235–2236.
- Laughton PM, Robertson RE. In *Solute–Solvent Interactions*, Coetzee JF, Ritchie CD (eds). Marcel Dekker: New York, 1969; Chapt. 7.
- Bates RG. *Determination of pH: Theory and Practice*. Wiley–Interscience: New York, 1973; 49.
- Cox RA. *Adv. Phys. Org. Chem.* 2000; **35**: 1–66; Cox RA, Yates K. *Can. J. Chem.* 1981; **59**: 2116–2124.
- Crueiras J, Maskill H. *Can. J. Chem.* 1999; **77**: 530–536; *J. Chem. Soc., Perkin Trans. 2* 2000; 441–445, and references cited therein.
- Leatherbarrow RJ. *GraFit Version 3.09b*. Erithacus Software: Staines, UK, 1996.
- McClelland RA, Kanagasabapathy VM, Banait NS, Steenken S. *J. Am. Chem. Soc.* 1989; **111**: 3966–3972.