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Flash Photolytic Generation of *o*-Quinone α-Phenylmethide and *o*-Quinone α-(*p*-Anisyl)methide in Aqueous Solution and Investigation of Their Reactions in that Medium. Saturation of Acid-Catalyzed Hydration

Y. Chiang, A. J. Kresge,* and Y. Zhu

Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

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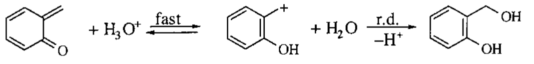
Abstract: *o*-Quinone α-phenylmethide was generated as a short-lived transient species in aqueous solution by flash photolysis of *o*-hydroxy-α-phenylbenzyl alcohol, and its rate of decay was measured in $HClO_4$ and NaOH solutions as well as in CH_3CO_2H, $H_2PO_4^-$, and HCO_3^- buffers. These data show that hydration of this quinone methide back to its benzyl alcohol precursor occurs by acid-, base-, and uncatalyzed routes. The acid-catalyzed reaction gives the solvent isotope effect $k_{H^+}/k_{D^+} = 0.34$, whose inverse nature indicates that this reaction occurs via rapid preequilibrium protonation of the quinone methide on its carbonyl oxygen atom followed by rate-determining capture of the ensuing carbocationic intermediate by water, a conclusion supported by the saturation of acid catalysis in concentrated $HClO_4$ solution. *o*-Quinone α-(*p*-anisyl)methide was also generated by flash photolysis of the corresponding benzyl alcohol and of the *p*-cyanophenol ether of this alcohol as well, and its rate of decay was measured in $HClO_4$ and NaOH solutions and in HCO_2H, CH_3CO_2H, HN_3, $CF_3CH_2NH_3^+$, imidazolium ion, $H_2PO_4^-$, $(CH_2OH)_3CNH_3^+$, $(CH_3)_3CPO_3H^-$, and HCO_3^- buffers. Acid-, base-, and uncatalyzed hydration reaction routes were again found, and solvent isotope effects as well as saturation of acid catalysis, this time in dilute $HClO_4$, confirmed a preequilibrium mechanism for the acid-catalyzed reaction. Analysis of the buffer data gave buffer-base rate constants that did not conform to the Brønsted relation, consistent with the expected nucleophilic nature of the buffer reactions.

Quinone methides are interesting reactive species with both electrophilic and nucleophilic properties that make them useful synthetic intermediates.[1] They also show pronounced biological activity and have been implicated as the ultimate cytotoxins responsible for the effects of such agents as antitumor drugs, antibiotics, and DNA alkylators.[2]

We recently showed that the parent substance, *o*-quinone methide, **1**, undergoes hydronium-ion catalyzed hydration in aqueous solution by a reaction mechanism that involves rapid equilibrium protonation of the substrate on its carbonyl oxygen atom followed by rate-determining nucleophilic capture of the ensuing carbocation, **2**, by water, eq 1.[3] In sufficiently strong acidic solutions, the position of this protonation equilibrium should shift from unprotonated to protonated quinone methide, and acid catalysis should then become saturated. We were unable to achieve such saturation with *o*-quinone methide itself, but we have now found saturation of acid catalysis with the more basic substrates *o*-quinone α-phenylmethide, **3**, and *o*-quinone α-(*p*-anisyl)methide, **4**. The additional phenyl group in **3**, and especially the *p*-anisyl group in **4**, stabilize the carbocationic intermediate of this reaction mechanism and cause saturation of hydronium-ion catalysis to occur in an accessible acidity region.



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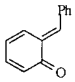

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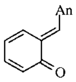

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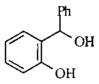

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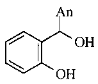

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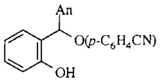

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We generated these quinone methides by photodehydration of the corresponding *o*-hydroxybenzyl alcohols, **5** and **6**; this is a well-known quinone methide forming reaction.[4] We also obtained **4** by photocleavage of the *o*-hydroxybenzyl *p*-cyanophenyl ether **7**. Because the reactions of these quinone methides were fast, we used flash photolytic techniques to monitor their progress.

Experimental Section

Materials. *o*-Hydroxy-α-phenylbenzyl alcohol (**5**) was prepared by treating salicylaldehyde with phenylmagnesium bromide,[5] and *o*-hydroxy-α-(*p*-anisyl)benzyl alcohol (**6**) was prepared by a similar reaction

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(1) For a brief review, see: Wan, P.; Barker, B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. *Can. J. Chem.* **1996**, *74*, 465−475.

(2) See for example: Peter, M. G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 555−570. Bolton, J. L.; Pisha, E.; Zhang, F.; Qiu, S. *Chem. Res. Toxicol.* **1998**, *11*, 1113−1117. Pande, P.; Shearer, J.; Yang, J.; Greenberg, W. A.; Rokita, S. E. *J. Am. Chem. Soc.* **1999**, *121*, 6773−6779.

(3) (a) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc*. **2000**, *122*, 9854−9855; (b) **2001**, *123*, 8089−8094.

(4) Diao, L.; Yang, C.; Wan, P. *J. Am. Chem. Soc*. **1995**, *117*, 5369−5370.

10.1021/ja0120375 CCC: $22.00

using *p*-anisylmagnesium bromide. The latter alcohol was characterized by its NMR and mass spectra. ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 8.14 (s, 1H), 7.29−6.78 (m, 8H), 5.91 (s, 1H), 3.77 (s, 3H), 3.26 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ/ppm = 160.0, 156.0, 134.7, 129.7, 128.8, 128.7, 127.3, 120.4, 117.7, 114.6, 77.1, 55.8. HRMS: *m*/*e* = 229.0865 (calc), 229.0855 (found).

o-Hydroxy-α-(*p*-anisyl)benzyl *p*-cyanophenol ether (**7**) was prepared by the one-pot process developed for the synthesis of the parent *o*-hydroxybenzyl *p*-cyanophenol ether,[3b] which involved first converting *o*-hydroxy-α-(*p*-anisyl)benzyl alcohol to the corresponding bromide, using the mild conditions of the Ph_3P/CBr_4 reagent,[6] and then immediately adding sodium *p*-cyanophenoxide. The product was purified by chromatography on silica gel with hexane and then hexane/diethyl ether (100/5) as the eluent. This gave a colorless liquid in 75% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 7.51 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.15 (m, 1H), 6.88 (m, 7H), 5.96 (s, 1H), 3.77 (s, 3H). HRMS: *m*/*e* = 331.1208 (calc), 331.1193 (found).

All other materials were best available commercial grades.

Kinetics. Rate measurements were made using microsecond[7] and nanosecond[8] (λ_{exc} = 248 nm) flash photolysis systems that have already been described.[7,8] Substrate concentrations in the reacting solutions were ca. 10^{-4} M, and the temperature of these solutions was controlled at 25.0 ± 0.05 °C. Reactions were monitored by following the decay of quinone methide absorbance at λ = ca. 400 nm. Observed first-order rate constants were calculated by least-squares fitting of a single-exponential function; in some cases, however, instrumental instability caused minor baseline drift, and a linear term was then added to the exponential fitting function.

Results and Discussion

***o*-Quinone α-Phenylmethide.** Rates of decay of *o*-quinone α-phenylmethide were measured in dilute solutions of perchloric acid in H_2O and in D_2O, in dilute solutions of sodium hydroxide in H_2O, and in dilute acetic acid, biphosphate ion, and bicarbonate ion buffers, also in H_2O. The ionic strength of the reacting solutions was maintained at 0.10 M by adding sodium perchlorate as required, and their temperature during rate measurements was maintained at 25.0 ± 0.05 °C. The data thus obtained are summarized in Tables S1−S3.[9]

Observed first-order rate constants determined in these perchloric acid solutions increased linearly with increasing acid concentration, and the data were therefore subjected to linear least-squares analysis. This gave the hydronium ion rate constant $k_{H^+} = (1.22 \pm 0.02) \times 10^6\ M^{-1}\ s^{-1}$ and the isotope effect $k_{H^+}/k_{D^+} = 0.338 \pm 0.006$. The inverse nature of this isotope effect ($k_H/k_D < 1$) provides evidence that this reaction occurs by the preequilibrium mechanism shown in eq 1.[10] This follows from the fact that the positively charged O−H bonds of the hydronium ion are looser than the uncharged O−H bonds of the water molecule formed in the preequilibrium step; the reaction therefore proceeds with a tightening up of the hydrogenic environment, and that makes the isotope effect inverse.[11]

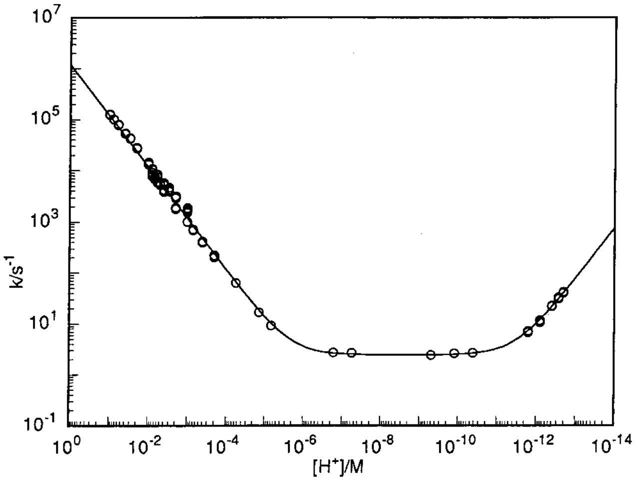


Figure 1. Rate profile for the hydration of *o*-quinone α-phenylmethide in aqueous solution at 25 °C.

The rate measurements in buffers were made in series of solutions of constant buffer ratio, and therefore constant hydronium ion concentration, but varying total buffer concentration. Observed first-order rate constants increased linearly with increasing buffer concentration, and the data were therefore analyzed by least-squares fitting of the buffer dilution expression shown in eq 2. The buffer-independent intercepts, k_o, obtained in this way were then combined with the rate constants

$$k_{obs} = k_o + k_{buff}[\text{Buffer}] \tag{2}$$

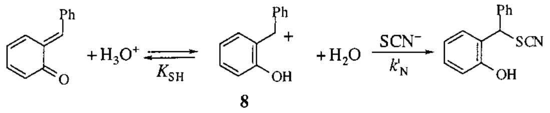
determined in the perchloric acid and sodium hydroxide solutions to construct the rate profile shown in Figure 1. Hydronium ion concentrations of the buffer solutions needed for this purpose were obtained by calculation, using literature pK_a values of the buffer acids and activity coefficients recommended by Bates.[12]

This rate profile shows both acid- and base-catalyzed limbs as well as a central uncatalyzed portion. It therefore conforms to the simple rate law shown in eq 3, and least-squares fitting

$$k_{obs} = k_{H^+}[H^+] + k_{uc} + k_{HO^-}[HO^-] \tag{3}$$

of this expression gave $k_{H^+} = (1.18 \pm 0.02) \times 10^6\ M^{-1}\ s^{-1}$, $k_{uc} = 2.43 \pm 0.17\ s^{-1}$, and $k_{HO^-} = (4.71 \pm 0.20) \times 10^2\ M^{-1}\ s^{-1}$.

The rate of *o*-quinone α-phenylmethide decay was found to be strongly accelerated by thiocyanate ion in a process that was also acid-catalyzed. This reaction may be formulated as an analogue, eq 4, of that shown in eq 1, in which the much more nucleophilic thiocyanate ion takes the place of a water molecule.



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(4)

Rates of this reaction were measured in series of aqueous (H_2O) solutions of constant perchloric acid concentration but varying sodium thiocyanate concentration. The data thus obtained are summarized in Table S4.[9]

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(5) Becker, H.-D.; Bremholt, T. *Tetrahedron Lett.* **1973**, 197−200.

(6) Wagner, A.; Heitz, M.-P.; Moskowski, C. *Tetrahedron Lett.* **1989**, *30*, 557−558. Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801−811.

(7) Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000−4009.

(8) Andraos, J.; Chiang, Y.; Huang, C. G.; Kresge, A. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1993**, *115*, 10605−10610.

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

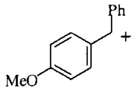
(10) Keeffe, J. R.; Kresge, A. J. In *Investigation of Rates and Mechanisms of Reactions*; Bernasconi, C. F., Ed.; Wiley: New York, 1986; pp 761−766.

(11) Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: New York, 1987; Vol. 7, pp 220−226.

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

Observed first-order rate constants measured in these solutions increased linearly with increasing thiocyanate ion concentration, and the data were therefore subjected to linear least-squares analysis. The $\Delta k_{obs}/\Delta[SCN^-]$ gradients obtained in this way also increased linearly with increasing perchloric acid concentration, and further linear least-squares analysis produced the relationship $\Delta k_{obs}/\Delta[SCN^-] = (3.00 \pm 0.28) \times 10^5 + (1.06 \pm 0.10) \times 10^9 [HClO_4]$. The nonacid-catalyzed intercept of this relationship is the rate constant, k_N, for reaction of thiocyanate ion with unprotonated quinone methide, and the coefficient of $[HClO_4]$ is the rate constant, k'_N/K_{SH}, for reaction of thiocyanate ion with the protonated quinone methide through the *o*-hydroxydiphenylmethyl cationic intermediate, **8**, of eq 4.

It is likely that the cation-capture step of eq 4, with rate constant k'_N, is an encounter-controlled process. This follows from the fact that the capture of the *p*-methoxydiphenylmethyl cation, **9**, whose reactivity toward nucleophiles may be expected to be similar to that of *o*-hydroxydiphenylmethyl cation, **8**, by azide ion, whose strength as a nucleophile is less than that of the thiocyanate ion used here,[13] is an encounter-controlled process.[14] Giving k'_N the encounter-controlled value of 5×10^9 $M^{-1}\ s^{-1}$ in the expression $k'_N/K_{SH} = (1.06) \times 10^9\ M^{-2}\ s^{-1}$ then leads to $K_{SH} = 4.7$ M, $pK_{SH} = -0.67$, as an estimate of the acidity constant of carbonyl-oxygen protonated *o*-quinone α-phenylmethide.



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This estimate of K_{SH} may be combined with the rate constant k_{H^+} ($= 1.18 \times 10^6\ M^{-1}\ s^{-1}$; vide supra) of the simple rate law of eq 3, which in terms of the mechanism of eq 1 is equal to k'_w/K_{SH}, to give $k'_w = 5.6 \times 10^6\ s^{-1}$ as the rate constant for capture of the *o*-hydroxydiphenylmethyl cation, **8**, by water. This result is consistent with $k = 2 \times 10^6\ s^{-1}$ determined for the capture by water of the *p*-methoxydiphenylmethyl cation, **9**,[14,15] which is the closest analogue to the present system for which such a rate constant has been reported.

Some measurements of the rate of *o*-quinone α-phenylmethide decay were also made in concentrated perchloric acid solutions over the concentration range $[HClO_4] = 0.23-3.7$ M at variable ionic strengths equal to the acid concentrations. These data are summarized in Table S5[9] and are displayed in Figure 2.

This figure shows that acid catalysis of this reaction levels off and becomes saturated at $[HClO_4] =$ ca. 2.5 M. Such saturation is, of course, as expected for the preequilibrium reaction mechanism of eq 1, and it provides strong additional support for this reaction scheme. Figure 2 also shows that above $[HClO_4] =$ ca. 2.5 M, rate constants begin to drop. This, also, is consistent with expectation, for perchlorate ion is known to inhibit the rate of reaction of large delocalized carbocations with water, an effect that has been attributed to carbocation-perchlorate ion ion-pair formation.[16]

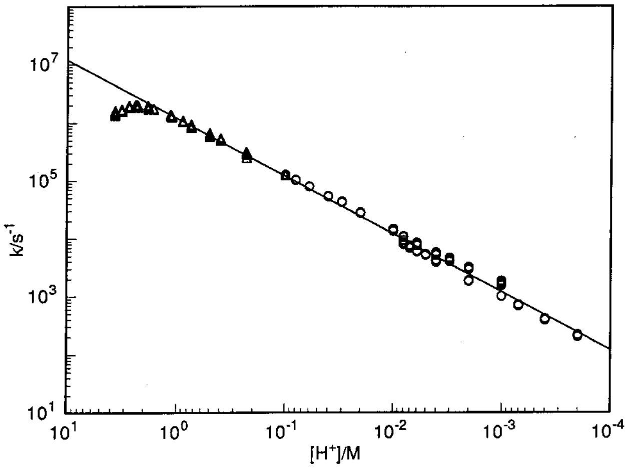

Figure 2. Comparison of rate constants for the hydration of *o*-quinone α-phenylmethide measured in dilute (O) and concentrated (Δ) perchloric acid solutions at 25 °C.

Quantitative analysis of these data obtained in concentrated perchloric acid is complicated by the need to use acidity functions to represent the acid strength of the concentrated solutions employed. To avoid this complication, we turned to the more basic substrate *o*-quinone α-(*p*-anisyl)methide, whose acid-catalyzed hydration becomes saturated in dilute solution where acidity function treatments need not be employed.

***o*-Quinone α-(*p*-Anisyl)methide.** Rates of decay of *o*-quinone α-(*p*-anisyl)methide were measured in dilute perchloric acid solutions in H_2O and in D_2O, in dilute sodium hydroxide solutions in H_2O and in formic acid, hydrazoic acid, acetic acid, trifluorethylammonium ion, imidazolium ion, biphosphate ion, tris-(hydroxymethyl)methylammonium ion, *tert*-butylhydrogen phosphonium ion, and bicarbonate ion buffers, all in H_2O. The ionic strength of the sodium hydroxide and buffer solutions, as well as the perchloric acid solutions up to an acid concentration of 0.10 M, was maintained at 0.10 M, whereas those of the perchloric acid solutions above 0.10 M (up to 0.37 M in H_2O and 0.29 M in D_2O) were equal to the acid concentration. All of the rate measurements were made at 25.0 ± 0.05 °C. The data thus obtained are summarized in Tables S6−S8.[9]

Most of these rate measurements were made using *o*-hydroxy-α-(*p*-anisyl)benzyl alcohol as the flash photolysis substrate, but in some of the perchloric acid solutions *o*-hydroxy-α-(*p*-anisyl)-benzyl *p*-cyanophenyl ether was used as well. Exactly equivalent results were obtained with the two substrates.

The rate measurements in buffers were again made in series of solutions of constant buffer ratio, and therefore constant hydronium ion concentration, but varying buffer concentration, and the data were again analyzed by least-squares fitting of eq 2. Buffer catalysis was very strong in the hydrazoic acid, trifluoroethylammonium ion, and imidazolium ion buffers, and the buffer-independent intercepts, k_o, of the buffer dilution plots for these buffers were consequently very small and poorly defined; they were therefore not used for rate profile construction. The intercepts of the other buffer solutions, however, were well determined, and they were therefore combined with the perchloric acid and sodium hydroxide data to give the rate profile shown in Figure 3.

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(13) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141−147. Pearson, R. G. In *Advances in Linear Free Energy Relationships*; Chapman, N. B., Shorter, J., Eds.; Plenum: New York, 1972; Chapter 6.

(14) McClelland, R. A.; Kanagasabapathy, V. M.; Steenken, S. *J. Am. Chem. Soc.* **1988**, *110*, 6913−6914.

(15) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 3966−3972.

(16) See: (a) Crugeiras, J.; Maskill, H. *Can. J. Chem.* **1999**, *77*, 530−536; (b) *J. Chem. Soc., Perkin Trans. 2* **2000**, 441−445 and references therein.

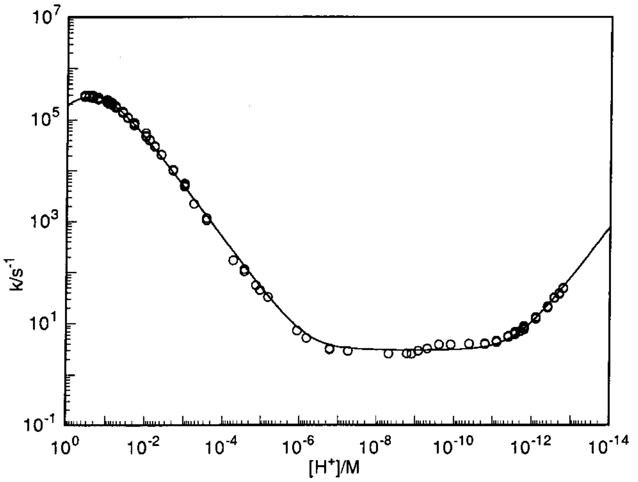
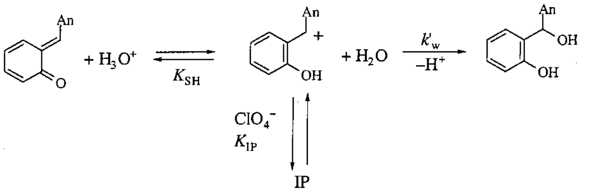


Figure 3. Rate profile for the hydration of *o*-quinone α-(*p*-anisyl)methide in dilute aqueous solution at 25 °C.

This figure shows that saturation of acid catalysis for reaction of this substrate occurs in the dilute acid region just above $[HClO_4] = 0.1$ M; the data may therefore be analyzed without recourse to an acidity function. Saturation of acid catalysis implies, of course, that the preequilibrium reaction mechanism of eq 1 is operating, but this scheme must now be modified to include reduction of the concentration of the reactive carbocation intermediate by ion pair formation, as shown in eq 5.



(5)

The simple rate law of eq 3 must also be modified to include an ion-pair formation constant, K_{IP}, as well as explicit inclusion of the acidity constant of the O−H bond of the carbocation intermediate, K_{SH}, and the rate constant for reaction of this intermediate with water, k'_w. The result is shown as eq 6. Least-squares fitting of this expression gave $k'_w = (5.22 \pm 0.30) \times 10^5$ s^{-1}, $K_{SH} = (1.09 \pm 0.07) \times 10^{-1}$ M, $K_{IP} = (1.69 \pm 0.35)$ M^{-1}, $k_{uc} = (3.03 \pm 0.07)$ s^{-1}, and $k_{HO^-} = (4.82 \pm 0.11) \times 10^2$ M^{-1} s^{-1}. The value of k'_w obtained is consistent with $k = 1.3 \times 10^5$ s^{-1} for the reaction of the di-(*p*-anisyl)methyl cation

$$k_{obs} = \frac{k'_W[H^+]}{K_{SH} + [H^+](1 + K_{IP}[H^+])} + k_{uc} + k_{HO^-}[HO^-] \quad (6)$$

with water,[15] which is the closest analogue of the present system for which such a rate constant has been reported, and the value of K_{IP} obtained here agrees well with $K_{IP} = 1.45$ M^{-1} determined for ion pair formation between perchlorate ion and the di-(*p*-anisyl)phenylmethyl cation.[16a] The value obtained for the acidity constant K_{SH}, as well as $pK_{SH} = -0.67$ estimated above for *o*-quinone α-phenylmethide, however, make these carbonyl-oxygen protonated quinone methides much weaker acids than carbonyl-protonated simple ketones,[17] but protonation of the quinone methides generates an aromatic phenol ring, and that makes these substances much stronger bases and their conjugate acids correspondingly less acidic.

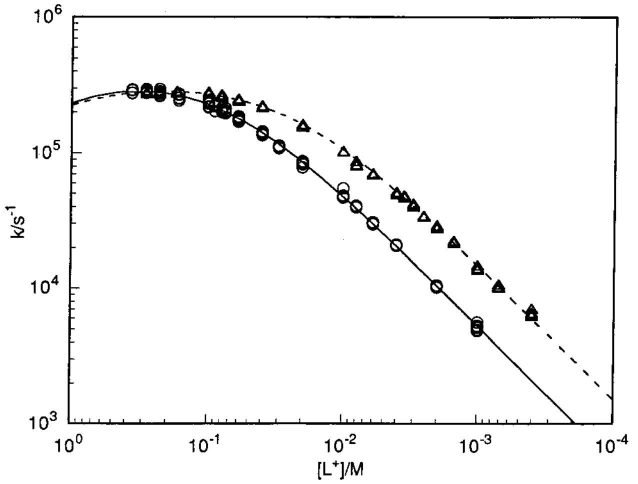


Figure 4. Comparison of rates of hydration of *o*-quinone α-(*p*-anisyl)methide in H_2O (O) and D_2O (Δ) solutions of perchloric acid at 25 °C.

Additional support for a preequilibrium reaction mechanism comes from the solvent isotope effects provided by the rate measurements made in D_2O solutions of perchloric acid. These rate measurements are compared with their H_2O counterparts in Figure 4. It may be seen that at low acidities the reaction is faster in D_2O than in H_2O which gives an inverse isotope effect, $k_{H^+}/k_{D^+} = 0.351 \pm 0.013$, that is characteristic of a preequilibrium mechanism. At higher acidities, however, saturation of acid catalysis occurs earlier in D_2O than in H_2O, and a crossover takes place, with the reaction becoming slightly faster in H_2O than in D_2O at the highest acidities investigated. Quantitative analysis of the data using the first term only of the rate law of eq 6 gives the isotope effects $K_{SH}/K_{SD} = 3.49 \pm 0.10$, $(k'_w)_{H_2O}/(k'_w)_{D_2O} = 1.22 \pm 0.03$, and $(K_{IP})_{H_2O}/(K_{IP})_{D_2O} = 1.44 \pm 0.30$. The first of these results is a typical value for the equilibrium ionization of an oxygen acid;[18] the solvent isotope effect on the ionization of acetic acid, for example, is $K_H/K_D = 3.3$.[19] Such isotope effects are produced by the conversion of the relatively tight uncharged O−H bonds of the acid and a water molecule into the somewhat looser, positively charged O−H bonds of a hydronium ion. The isotope effect on k'_w, the rate constant for capture of the carbocation intermediate by a water molecule, is also as expected, for the capturing water molecule in this process is taking on positive charge, and its O−H bonds are consequently being loosened; this loosening, however, is only slightly developed in the early transition state of this quite fast reaction, and the magnitude of this isotope effect is small. The isotope effect on the ion-pair formation constant, K_{IP}, is essentially unity, and that is also consistent with the nature of this process, which requires only some rearrangement of the solvent shells of the ions involved without large changes in solvent O−H bond strength; isotope effects on solvation shells are known to be small.[20]

Some measurements of the decay of *o*-quinone α-(*p*-anisyl)methide in aqueous (H_2O) thiocyanate ion solutions at fixed

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(17) Bagno, A.; Scorrano, G.; More O'Ferrall, R. A. *Rev. Chem. Intermed.* **1987**, *7*, 313−352.

(18) Laughton, P. M.; Robertson, R. E. In *Solute−Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; Dekker: New York, 1969; Chapter 7.

(19) Gary, R.; Bates, R. G.; Robinson, R. A. *J. Phys. Chem.* **1965**, *69*, 2750−2753. Gold, V.; Lowe, B. M. *J. Chem. Soc. A* **1968**, 1923−1932.

(20) Albery, W. J. In *Proton-Transfer Reactions*; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; pp 282−283.

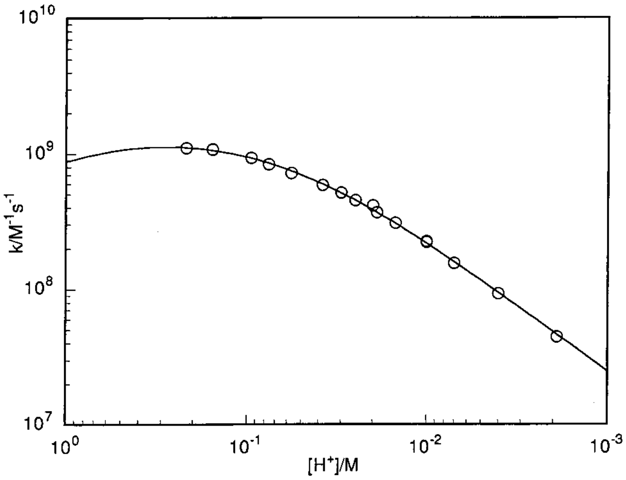


Figure 5. Rate profile for the reaction of *o*-quinone α-(*p*-anisyl)methide with thiocyanate ion in aqueous (H_2O) perchloric acid solutions at 25 °C.

Table 1. Rate Constants for the Reaction of *o*-Quinone α-(*p*-Anisyl)methide and Its Conjugate Acid with Nucleophiles in Aqueous Solution at 25 °C

nucleophile	pK_a(HNuc)	$k_N/M^{-1}\,s^{-1\,a}$	$k'_N/M^{-1}\,s^{-1\,b}$
H_2O	−1.74	0.0546	9410
SCN^-	−1.28		1.64×10^9
HCO_2^-	3.75		3.58×10^6
N_3^-	4.65	1.35×10^6	9.97×10^8
$CH_3CO_2^-$	4.76		3.84×10^6
$CF_3CH_2NH_2$	5.59	4740	2.64×10^7
imidazole	6.99	833	2.52×10^7
HPO_4^{2-}	7.20	8.37	7.96×10^6
$(CH_2OH)_3CNH_2$	8.07	851	6.86×10^8
$(CH_3)_3CPO_3^{2-}$	8.71	11.0	5.14×10^7
CO_3^{2-}	10.33	86.4	7.93×10^9

[a] Rate constant for reaction of the unprotonated quinone methide. [b] Rate constant for reaction of the protonated quinone methide.

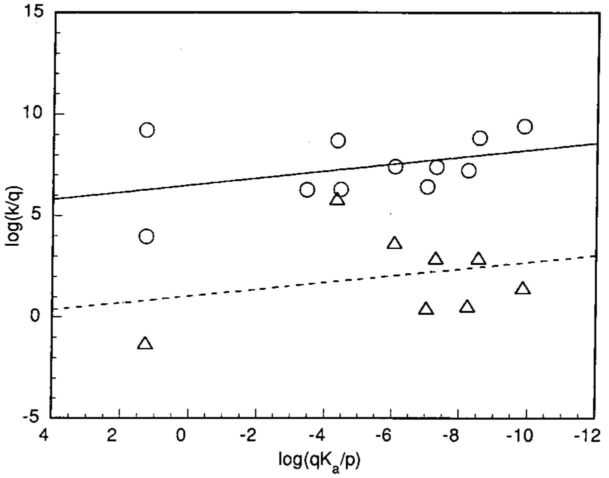


Figure 6. Brønsted type plots for the reaction of nucleophiles with *o*-quinone α-(*p*-anisyl)methide (Δ) and its conjugate acid (O) in aqueous solution at 25 °C.

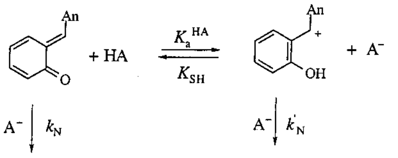
perchloric acid concentrations were also made. These data are summarized in Table S9.[9] Observed first-order rate constants determined at constant acidity increased linearly with increasing thiocyanate ion concentration, and the data were therefore subjected to linear least-squares analysis. The second-order thiocyanate ion rate constants obtained in this way are displayed in Figure 5.[21]

This figure shows that the thiocyanate reaction is acid-catalyzed at low acid concentrations but that this catalysis becomes saturated at higher acidities. This behavior is similar to that of the hydration reaction (see Figure 4) and implies that this reaction also occurs by a preequilibrium mechanism involving rapid protonation of the quinone methide followed by thiocyanate capture of the carbocation thus formed. The data were therefore analyzed by an analogue of the method used for acid-catalyzed hydration, by least-squares fitting of the first term of the rate expression of eq 6 with k'_{SCN} substituted for k'_w. This gave the results $k'_{SCN} = (1.64 \pm 0.99) \times 10^9\ M^{-1}\ s^{-1}$, $K_{SH} = (6.55 \pm 0.47) \times 10^{-2}$ M, and $K_{IP} = (8.13 \pm 4.07) \times 10^{-1}\ M^{-1}$. These values of K_{SH} and K_{IP} are consistent with the results obtained by analysis of the hydration reaction rate profile (vide supra); the weighted average of the two sets of results gives $K_{SH} = (7.78 \pm 0.40) \times 10^{-2}$ M, $pK_a = 1.11 \pm 0.02$, and $K_{IP} = 1.32 \pm 0.27\ M^{-1}$ as the best values of these constants.

Analysis of the rate data for decay of *o*-quinone α-(*p*-anisyl)-methide in buffer solutions using eq 2 produced rate constants for reaction through the buffer species, k_{buff}, in addition to the zero-buffer concentration intercepts, k_o. These buffer rate constants were separated into their buffer acid, k_{HA}, and buffer base, k_B, components by least-squares fitting of eq 7, in which f_A is the fraction of buffer present in the acid form.

$$k_{buff} = k_B + (k_{HA} - k_B)f_A \qquad (7)$$

These buffer reactions may be formulated as shown in eq 8, where the unprotonated and protonated quinone methides react with the buffer base acting as a nucleophile, with rate constants k_N and k'_N, respectively. This formulation leads to the relationship $k_B = k_N$, and values of k_N obtained in this way are listed in Table 1. The scheme of eq 8 also leads to the further relationship $k_{HA} = k'_N K_a^{HA}/K_{SH}$, from which k'_N may be evaluated using the known values of K_a^{HA}, the acidity constant of the buffer acid, and K_{SH}, the acidity constant of the protonated quinone methide. Values of k'_N obtained in this way are also listed in Table 1.



(8)

Justification for formulating the buffer processes as nucleophilic reactions of the buffer bases comes from the poor Brønsted relations that the data give. It is well known that basic strength is only one of the factors that governs nucleophilic reactivity,[23] and nucleophilic reactions of bases of such widely different types as the present set give notoriously poor Brønsted plots.[24] Figure 6 shows that this is easily the case for the present data; both k_N and k'_N give plots that are essentially scatter diagrams, with undefined Brønsted exponents, $\beta = 0.17 \pm 0.25$

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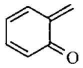
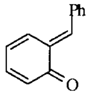
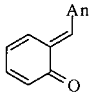
(21) Minor corrections for small extents of conversion of thiocyanate ion to its unreactive protonated form at the highest acid concentrations employed were made using the recently determined ionization constant of isothiocyanic acid, $pK_a = -1.28$.[22]

(22) Chiang, Y.; Kresge, A. J. *Can. J. Chem.* **2000**, *78*, 1627−1628.

(23) See for example: Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; pp 78−111.

(24) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 1778−1786.

Table 2. Comparison of Quinone Methide Reactivity[a]

substrate	k_{H^+}/M^{-1} s^{-1}	pK_{SH}/M	k'_w/s^{-1}
	8.4×10^{-5}	-1.72	4.4×10^{7}
	1.18×10^{6}	-0.67	5.6×10^{6}
	6.7×10^{6}	1.11	5.2×10^{5}

[a] In aqueous solution at 25 °C.

and 0.17 ± 0.13, and poor correlation coefficients, $r = 0.260$ and 0.398.

Substituent Effects on Quinone Methide Reactivity. Data that allow the overall rate constant for acid-catalyzed hydration of quinone methides, k_{H^+}, to be broken down into its constituent parts, that is, into the acidity constant of the carbocationic intermediate, K_{SH}, and the rate constant for capture of this intermediate by water, k'_w, are now available for three quinone methides. The values that result, listed in Table 2, show that introduction of an α-phenyl substituent and then replacement of that by a *p*-anisyl group produce a steady increase in pK_{SH} and thus an increase in substrate basicity. This is as expected, inasmuch as these substituents stabilize the positive charge of the carbocationic intermediate, and *p*-anisyl is better at positive charge stabilization than is phenyl. This increasing carbocation stability also leads to a steadily diminishing rate of capture of the carbocation by water, again as expected. The overall rate constant, however, changes in the opposite, perhaps unexpected, direction. This is because the overall rate constant is equal to the ratio of k'_w to K_{SH}, $k_{H^+} = k'_w/K_{SH}$, and the substituent effect on K_{SH} is stronger than that on k'_w, causing the two rate constants to change in opposite directions. The stronger substituent effect on K_{SH} than on k'_w is, of course, a consequence of the fact that the equilibrium process represented by K_{SH} involves a full unit change in substrate positive charge, whereas the kinetic process represented by k'_w involves only a fractional, and therefore somewhat smaller, change in this charge.

Mechanism of the Quinone Methide Generating Photoreaction. It has been reported[1,4] that the transient absorbance signal given by *o*-quinone α-phenylmethide, generated by flash photolysis of *o*-hydroxy-α-phenylbenzyl alcohol in aqueous solution, decreased in intensity with increasing solvent acidity until it was lost completely below pH = 1. A plot of this signal intensity versus pH, moreover, was found to be sigmoid in shape with an inflection point at pH = ca. 2.5. On the basis of this, a mechanism for the photoreaction was proposed that involved excitation of the benzyl alcohol photochemical substrate followed by ionization of its phenolic group, whose excited-state pK_a was judged to be ca. 2.5. Suppression of this requisite excited-state ionization at low pH was then taken to be the reason for signal loss.

Our observation of continuing acid-catalyzed hydration of *o*-quinone α-phenylmethide well up into the concentrated acid region is at variance with this earlier report. In a series of flash photolysis experiments, moreover, in which we took care to keep the laser power and the concentration of the *o*-hydroxy-α-phenylbenzyl alcohol photochemical substrate constant, we observed much the same initial intensity of the transient signal over the acidity range neutral solution to 1 M perchloric acid.

We suspect that the source of this difference between the previous and the present studies is the failure by the previous investigators to recognize that the hydration reaction is acid-catalyzed. They could then quite easily have used a time frame throughout their work that was appropriate for the quite slow reaction at neutral pH but too slow to catch all of the much faster reactions at acidic pH's. The evidence requiring a reaction mechanism involving quinone methide generation via excited-state phenolic group ionization should therefore be discounted.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support of this work. This paper is dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

Supporting Information Available: Tables S1−S9 of rate data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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