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The Hydrolysis of 4-Acyloxy-4-substituted-2,5-cyclohexadienones: Limitations of Aryloxenium Ion Chemistry

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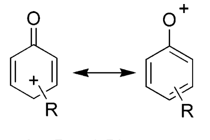
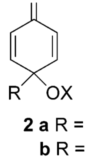
Abstract: The title compounds serve as potential precursors to aryloxenium ions, often proposed, but primarily uncharacterized intermediates in phenol oxidations. The uncatalyzed and acid-catalyzed decomposition of 4-acetoxy-4-phenyl-2,5-cyclohexadienone, **2a**, generates the quinol, **3a**. ^{18}O-Labeling studies performed in $^{18}O-H_2O$, and monitored by LC/MS and ^{13}C NMR spectroscopy that can detect ^{18}O-induced chemical shifts on ^{13}C resonances, show that **3a** was generated in both the uncatalyzed and acid-catalyzed reactions by $C_{alkyl}-O$ bond cleavage consistent with formation of an aryloxenium ion. Trapping with N_3^- and Br^- confirms that both uncatalyzed and acid-catalyzed decompositions occur by rate-limiting ionization to form the 4-biphenylyloxenium ion, **1a**. This ion has a shorter lifetime in H_2O than the corresponding nitrenium ion, **7a** (12 ns for **1a**, 300 ns for **7a** at 30 °C). Similar analyses of the product, **3b**, of acid- and base-catalyzed decomposition of 4-acetoxy-4-methyl-2,5-cyclohexadienone, **2b**, in $^{18}O-H_2O$ show that these reactions are ester hydrolyses that proceed by $C_{acyl}-O$ bond cleavage processes not involving the *p*-tolyloxenium ion, **1b**. Uncatalyzed decomposition of the more reactive 4-dichloroacetoxy-4-methyl-2,5-cyclohexadienone, **2b′**, is also an ester hydrolysis, but **2b′** undergoes a kinetically second-order reaction with N_3^- that generates an oxenium ion-like substitution product by an apparent S_N2' mechanism. Estimates based on the lifetimes of **1a**, **7a**, and the *p*-tolylnitrenium ion, **7b**, and the calculated relative stabilities of these ions toward hydration indicate that the aqueous solution lifetime of **1b** is ca. 3−5 ps. Simple 4-alkyl substituted aryloxenium ions are apparently not stable enough in aqueous solution to be competitively trapped by nonsolvent nucleophiles.

Introduction

Aryloxenium ions, **1**, have often been proposed to explain the products of the synthetically useful electrochemical and chemical oxidations of phenols[1−5] and the generation of commercially useful polymers, such as poly(2,6-dimethyl-1,4-phenylene oxide).[6,7] Despite this, surprisingly little is known of the reactivity and selectivity of these species, or even whether they have actually been generated in the cases in which they have been invoked.[1,3,5] For example, so little is known of substituent effects in these ions that prior to our investigation it was not possible to determine the relative stability of aryl- and alkyl-substituted examples, such as **1a** and **1b**, from literature data. Some examples of stable, highly delocalized **1**, such as **1c** and **1d**, have been observed or isolated,[4] but these stable species provide little insight into the reactions of transient members of this class of ions. The mechanistic studies of transient ions that do exist are not consistent with each other.[8−13] There are discrepancies in the literature concerning the regiochemistry of reaction of purported examples of **1** generated from different sources and the possible involvement of triplet ions.[2,8,10,12,13]



1 a R = 4-Ph
b R = 4-CH$_3$
c R = 2,4,6-(4'-MeOC$_6$H$_4$)
d R = 2,6-*t*-Bu-4-(4'-(Me$_2$N)C$_6$H$_4$)



2 a R = Ph, X = Ac
b R = Me, X = Ac
b' R = Me, X = Cl$_2$Ac

[†] Miami University.

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In our recent Communication, we showed that the uncatalyzed decomposition of **2a** in aqueous solution that predominates under neutral to mildly acidic conditions does generate a short-lived cation, identified as **1a**, that can be trapped by N_3^-.[13] Acid-catalyzed decomposition of **2a** also occurs, but it was not known if this reaction generates **1a** by $C_{alkyl}-O$ cleavage or if it is an acid-catalyzed ester hydrolysis that occurs with $C_{acyl}-O$ bond cleavage. Although it was clear that the uncatalyzed decomposition of **2b** was much slower than that of **2a**, it was not determined whether **1b** is formed from that uncatalyzed decomposition because acid- and base-catalyzed reactions dominated the aqueous solution chemistry of **2b**. The more reactive dichloroacetic acid ester **2b′** exhibits a predominant uncatalyzed decomposition under mildly acidic conditions that makes it possible to evaluate whether **1b** is generated from substrates of this type under any of the observed kinetic terms. In this paper, we report the results of hydrolysis of **2a**, **2b**, and **2b′** in $^{18}O-H_2O$ and nucleophilic trapping experiments on **2a** and **2b′** that demonstrate how these compounds decompose under acid- and base-catalyzed conditions, as well as under uncatalyzed conditions. The results of ab initio (HF/6-31G*//6-31G*) and DFT (pBP/DN*//HF/6-31G*) calculations that help to rationalize the experimental results are also reported. These results place some limits on the aqueous solution stability of aryloxenium ions.

Results

Kinetics of decomposition of **2a** and **2b′** at 30 °C and **2b** at 80 °C were measured in 5 vol % CH_3CN-H_2O at $\mu = 0.5$ ($NaClO_4$) in $HClO_4$ solutions (pH $<$ 3.0), or in HCO_2H/$NaHCO_2$, AcOH/AcONa, and Na_2HPO_4/NaH_2PO_4 buffers by monitoring changes in UV absorbance as a function of time. All data fit a standard first-order rate equation well. Decomposition rate constants, k_{obs}, were independent of buffer concentration in the range 0.02−0.25 M, except for the common ion rate depression previously reported for **2a**,[13] but were dependent on pH. The value of k_{obs} for **2a** in acetate buffers was extrapolated to zero buffer concentration. Figure 1 shows the pH dependence of k_{obs} for all three compounds. The rate data were fit to the rate law of eq 1, although only one compound (**2b**) exhibited all three terms of the rate law in the pH range examined (1.0−8.0). Individual rate constants for all three compounds are reported in Table 1.

$$k_{obs} = k_o + k_H[H^+] + k_{OH}[OH^-] \qquad (1)$$

The uncatalyzed term, k_o, dominates over much of the pH range examined for both **2a** and **2b′**, but it is only a minor contributor to k_{obs} for **2b**. Even at the pH (4.8) at which k_o is most important for **2b**, it accounts for <80% of k_{obs}. Previously, we showed by common ion rate depression and N_3^- trapping that the process governed by k_o for **2a** involves formation of the cation **1a**, but the mechanisms of the processes governed by k_H and k_{OH} for all compounds, as well as k_o for **2b** or **2b′**, were not examined.[13]

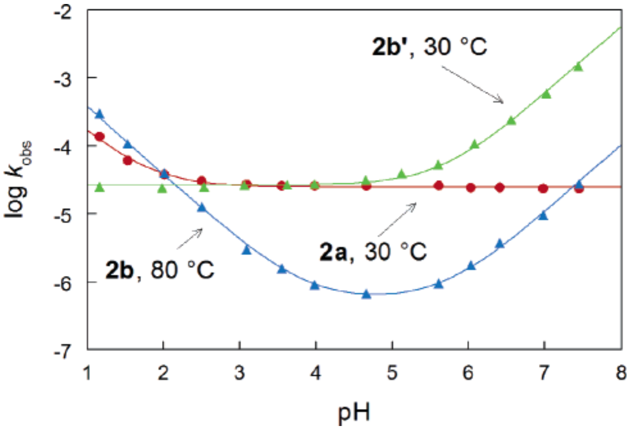

Figure 1. Log k_{obs} versus pH for **2a**, **2b**, and **2b′**. Data were fit to eq 1 by least-squares procedures.

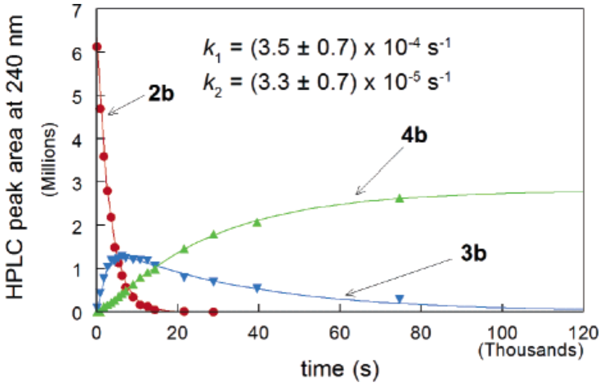

Figure 2. Decomposition of **2b** at pH 1.0 and 80 °C monitored by HPLC. Data for **3b** and **4b** were fit to a consecutive first-order rate equation.

Table 1. Rate Constants for the Decomposition of **2a** and **2b′** at 30 °C and **2b** at 80 °C from Least-Squares Fits to Equation 1

ester	k_o (s^{-1})	k_H (M^{-1} s^{-1})	k_{OH} (M^{-1} s^{-1})
2a	$(2.50 \pm 0.05) \times 10^{-5}$	$(1.45 \pm 0.08) \times 10^{-3}$	
2b	$(5.4 \pm 0.5) \times 10^{-7}$	$(3.8 \pm 0.2) \times 10^{-3}$	104 ± 6
2b′	$(2.66 \pm 0.08) \times 10^{-5}$		5790 ± 260

HPLC examination of the reactions at pH 1.0, 4.6, and 7.0 showed that for all cases, in the absence of any nucleophile other than H_2O, the only products observed were the corresponding quinols **3a** or **3b**. The HPLC data showed that **2a**,**b** and **2b′** disappeared and **3a**,**b** were generated in a first-order manner with rate constants equivalent, within experimental error, to k_{obs} measured by UV methods. In one case (**2b** at pH 1.0 and 80 °C), the HPLC data (Figure 2) showed slow subsequent rearrangement of **3b** into **4b** that was identified by comparison of the isolated compound to an authentic sample. The overall process was governed by two rate constants (k_1 and k_2 of Figure 2). The larger rate constant, k_1, was equivalent, within experimental error, to k_{obs} measured by UV methods for **2b** at the same pH. The smaller rate constant, k_2, was equivalent to the rate constant obtained for the rearrangement of authentic **3b** at the same pH. The dienone−phenol rearrangement of **3b** into

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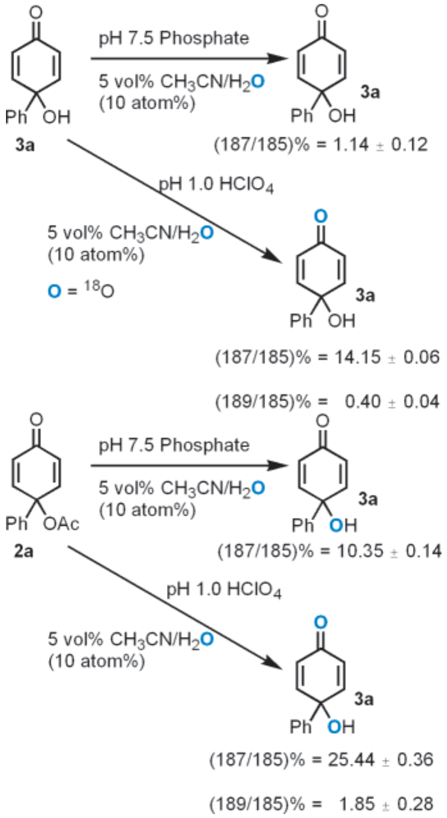
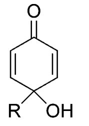
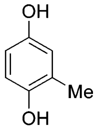
Scheme 1



4b in concentrated $HClO_4$ solution ($H_o < -2.2$) has been reported previously.[14] At pH 1.0 and 30 °C, rearrangement of **3a** and **3b** was sufficiently slow that it was not noticeable during the course of our experiments.



3 a R = Ph
b R = Me



4b

Mass spectral analysis of the ^{18}O content of **3a**,**b** generated during the hydrolysis of the esters **2a**, **2b**, and **2b′** in $^{18}O-H_2O$ can show whether the quinols are generated by processes involving $C_{alkyl}-O$ or $C_{acyl}-O$ bond cleavage in the esters. Analysis is complicated by ^{18}O exchange into the carbonyl-O of **3a**,**b**, but the two labeling sites can be distinguished by the ^{18}O-induced upfield chemical shift on the ^{13}C NMR signal of carbon bonded to the ^{18}O.[15,16]

The results of the LC/MS analysis of **3a** obtained from the hydrolysis of **2a** in 10 atom % $^{18}O-H_2O$ in pH 1.0 $HClO_4$ and pH 7.5 0.02 M phosphate buffer at 30 °C for one half-life of the hydrolysis reaction of **2a** (5060 s at pH 1.0, 29 400 s at pH 7.5) and of **3a** incubated in the same solutions for the same length of time as controls are summarized in Scheme 1. Paired control and experimental runs at the same pH were performed with the same aqueous solutions on consecutive days. The best ionization conditions for **3a** were found to be negative ion ESI, so peaks at *m/e* 185 ($(M - 1)^-$), 187 ($(M + 1)^-$), and 189 ($(M + 3)^-$) were analyzed. Results of triplicate injections for each experiment are shown in Scheme 1. The control experiments show that ^{18}O is incorporated into the carbonyl-O of **3a** at pH 1.0, but not at pH 7.5. The observed (187/185)% for **3a** incubated in unlabeled H_2O at pH 7.5 is 1.10 ± 0.02, which is equivalent, within experimental error, to (187/185)% observed for **3a** incubated in the $^{18}O-H_2O$ at pH 7.5.

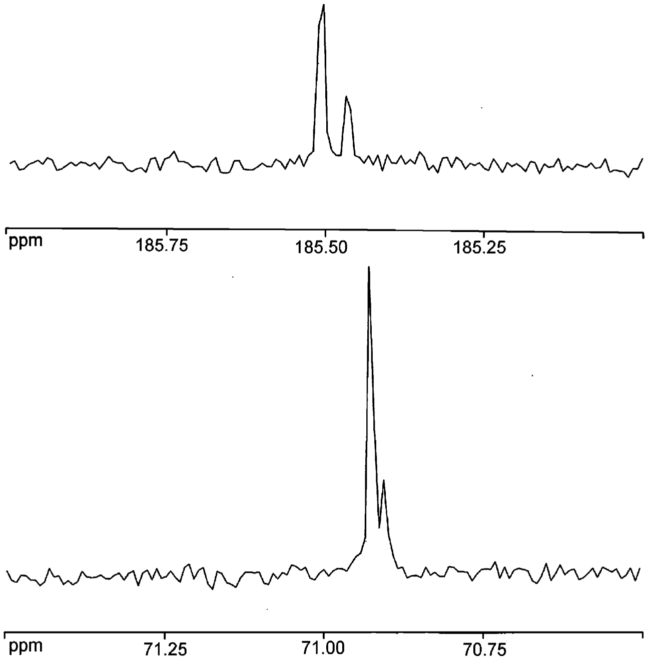


Figure 3. Portions of the ^{13}C NMR spectrum of **3a** generated by decomposition of **2a** in 25 atom % $^{18}O-H_2O$ at pH 1.0. The upper region contains the carbonyl-C resonance; the lower region contains the hydroxyl-C resonance.

MS analysis of **3a** obtained from the hydrolysis of **2a** in $^{18}O-H_2O$ shows that ^{18}O has been incorporated into the hydroxyl-O at pH 7.5, and into both hydroxyl-O and carbonyl-O at pH 1.0. The latter conclusion is supported not only by the large value of (187/185)% observed at pH 1.0 but also by the unusually large value of (189/185)% measured at this pH. This value is only (0.40 ± 0.04)% in the corresponding control experiment. Both conclusions were confirmed by ^{13}C NMR results from hydrolysis of **2a** in 25 atom % $^{18}O-H_2O$. The product **3a** was extracted into CH_2Cl_2 after 10 half-lives of the reaction, and ^{13}C NMR spectra were measured at 125.8 MHz in CD_2Cl_2. In the pH 1.0 experiment, upfield satellites were observed for both the carbonyl-C (42 ppb upfield, 37% of the integrated intensity of the main peak at 185.510 ppm) and the hydroxyl-C (21 ppb upfield, 34% of the integrated intensity of the main peak at 70.926 ppm) (Figure 3). In pH 7.5 phosphate buffer, an upfield satellite was observed for the hydroxyl-C (21 ppb upfield, 35% of the intensity of the main peak). A small peak, ca. 5% of the intensity of the main peak, was observed 42 ppb upfield of the carbonyl-C with long-term signal averaging. Due to its small magnitude, this peak cannot be unequivocally identified as an ^{18}O satellite, but it does place an upper limit on the amount of exchange occurring into the carbonyl position at neutral pH. Such a small amount of ^{18}O incorporation would not have been noted in the MS experiment that was run at smaller atom % ^{18}O and for only one half-life of the hydrolysis reaction. No

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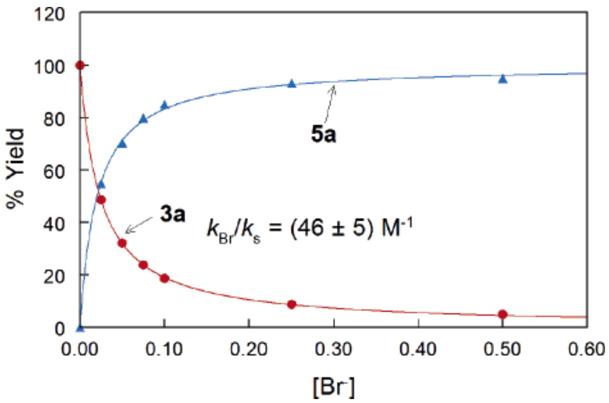


Figure 4. Trapping out of **3a** by Br^- to generate **5a** during the decomposition of **2a** at pH 1.0. The ratio k_{Br}/k_s was calculated from a least-squares fit of the data to the "azide clock" formulas.[18]

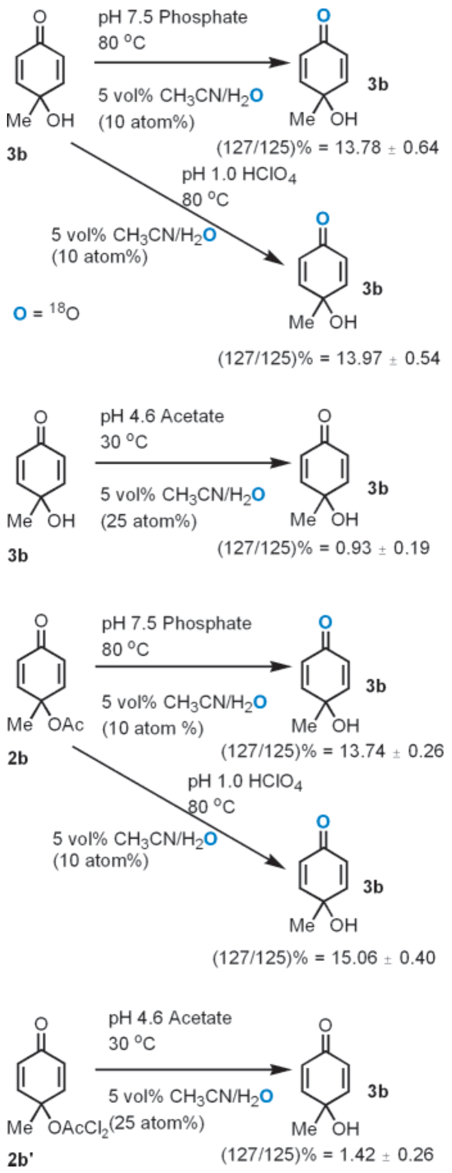
^{18}O-related satellites were observed in any other ^{13}C resonances of **3a** at either pH, and no satellites were observed in control experiments in which **3a** was generated from **2b** in H_2O with normal isotopic abundance.

The ^{18}O data for the reaction run in pH 7.5 phosphate buffer support our previous conclusion, based on common ion rate depression and N_3^- trapping, that **2a** decomposes via $C_{alkyl}-O$ bond cleavage into **1a** under conditions in which k_o is the dominant rate term.[13] The ^{18}O data indicate that at pH 1.0, where $k_H[H^+]$ accounts for 85% of k_{obs}, $C_{alkyl}-O$ bond cleavage also occurs. The ^{18}O results are consistent with generation of **1a** by the acid-catalyzed pathway, but they cannot rule out some other process that leads to $C_{alkyl}-O$ bond cleavage without generation of **1a**.

Trapping of the cation by N_3^- cannot be done at pH 1.0, but other potential nucleophiles, such as Br^-, are not protonated under these conditions. We found that Br^- does trap out **3a** to form the substitution product **5a**, identified by comparison to an authentic sample (Figure 4).[17] At high $[Br^-]$, the yield of **3a** asymptotes to 0%, indicating that $C_{acyl}-O$ bond cleavage does not compete significantly with the dominant $C_{alkyl}-O$ bond cleavage process. Trapping occurs without rate acceleration: k_{obs} at pH 1.00 in 0.5 M ClO_4^- is $(1.81 \pm 0.07) \times 10^{-4}$ s^{-1}, and at pH 1.00 in 0.5 M Br^-, conditions in which ca. 95% of **3a** has been trapped out, k_{obs} is $(1.38 \pm 0.05) \times 10^{-4}$ s^{-1}. This indicates that the trapping occurs on an intermediate generated after the rate-limiting step of the reaction. Application of the "azide-clock" formulas[18] to the data of Figure 4 provides a value of the ratio of the second-order rate constant for trapping of the intermediate by Br^- and the pseudo-first-order rate constant for trapping by the aqueous solvent, k_{Br}/k_s, of (46 ± 5) M^{-1}. Trapping by Br^- at pH 7.5 occurs without rate acceleration of the hydrolysis of **2a** to yield the same product, **5a**, with the same trapping efficiency, indicating that the same intermediate, **1a**, is generated and trapped by Br^- at both pH.

Results of ^{18}O-labeling experiments performed on **2b** at 80 °C at pH 1.0 in $HClO_4$ solution and at pH 7.5 in 0.02 M phosphate buffer, and on **2b′** at 30 °C at pH 4.6 in 0.02 M acetate buffer, are summarized in Scheme 2. The experiments on **2b** and the corresponding control experiments on **3b** were performed in 10 atom % $^{18}O-H_2O$. The experiment on **2b′** and the corresponding control experiment were performed in 25 atom % $^{18}O-H_2O$. In all cases, reactions were run for one half-life of the hydrolysis reaction of **2b** or **2b′** (2300 s at pH 1.0, 22 200 s at pH 4.6, and 25 000 s at pH 7.5) with experimental runs and the corresponding controls performed with the same aqueous solutions on consecutive days. Ionization conditions used for **3b** were positive ion ESI, so peaks at *m*/*e* 125 ($(M + 1)^+$) and 127 ($(M + 3)^+$) were monitored. Results of triplicate injections for each experiment are reported in Scheme 2. At 80 °C at both pH 1.0 and 7.5, the carbonyl-O of **3b** undergoes apparently complete exchange with $^{18}O-H_2O$, but no significant exchange occurs at 30 °C at pH 4.6. The observed value of (127/125)% for **3b** incubated in unlabeled H_2O at pH 4.6 is (0.40 ± 0.10)%. The experimental data at pH 4.6 and 7.5 are indistinguishable from the data for the corresponding controls at the 95% confidence level, but the experimental result for (127/125)% at pH 1.0 is different from the control at the 95% confidence level, but not at the 99% confidence level. If the result from the control experiment represents complete exchange of ^{18}O into the carbonyl-O, the small excess incorporation in the hydrolysis experiment indicates that $C_{alkyl}-O$ bond cleavage

Scheme 2



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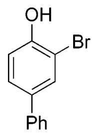
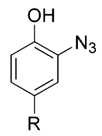
may occur to the extent of 8 ± 5% of the overall reaction under acidic conditions. The predominant, if not exclusive, mode of reaction under all three pH conditions is $C_{acyl}{-}O$ bond cleavage. This is particularly true for **2b′** at pH 4.6, where k_o is the dominant kinetic term since these data were collected in 25 atom % $^{18}O{-}H_2O$. This would have made it possible to detect as little as 3% $C_{alkyl}{-}O$ bond cleavage ((127/125)% ca. 1.0% greater than the control). A (127/125)% of ca. 1.9% compared to the control of 0.9% would have been a statistically significant difference at the 95% confidence level within the observed reproducibility of these experiments.

^{13}C NMR experiments confirmed that at pH 7.5 the carbonyl-C of **3b** generated from decomposition of **2b** in 10 atom % $^{18}O{-}H_2O$ showed an ^{18}O-induced satellite. The satellite was observed in $CDCl_3$ at 49 ppb upfield from the main carbonyl-C resonance at 185.323 ppm. The satellite had an integrated intensity 9% of that of the main peak. No other resonances of **3b** generated in this manner exhibited observable upfield satellites. The NMR experiment was not attempted at pH 4.6 because of the lack of significant labeling observed by MS. The NMR analysis at pH 1.0 is complicated by the dienone–phenol rearrangement of **3b**. It is possible to stop the reaction at a point where this rearrangement has not become extensive, but >90% of **2b** has reacted. For an experiment run in 25 atom % $^{18}O{-}H_2O$, a prominent ^{18}O satellite of the carbonyl-C resonance is observed, but no ^{18}O satellite can be detected for the hydroxyl-C after 24 h of signal averaging. If its chemical shift difference is similar to that observed for the hydroxyl-C of **3a** (ca. 20 ppb), it would have been possible to detect a signal about 2–3% of the magnitude of the main hydroxyl-C peak of **3b**. This establishes an upper limit of ca. 6–9% reaction by $C_{alkyl}{-}O$ bond cleavage at pH 1.0.

Although **2b′** appears to react entirely by an ester hydrolysis pathway under conditions in which k_o is the dominant rate term, it is possible to generate an oxenium-like substitution product from this ester. At pH 4.6 in the presence of N_3^-, the product **6b** is generated in an $[N_3^-]$-dependent manner (Figure 5A). This product is formed in a kinetically second-order process (Figure 5B), so it is clearly not generated from trapping an oxenium ion generated in a rate-limiting step. The yield of the substitution product correlates well with the observed kinetics; the ratio k_{az}/k_o derived from the kinetics and the product yield data are in good agreement with each other. An analogous product, **6a**, was obtained from N_3^- trapping experiments on **2a**, but in this case, the reaction was kinetically first-order and the product was derived from **1a** generated during rate-limiting decomposition of **2a**.[13]



5a



6 a R = Ph
b R = Me

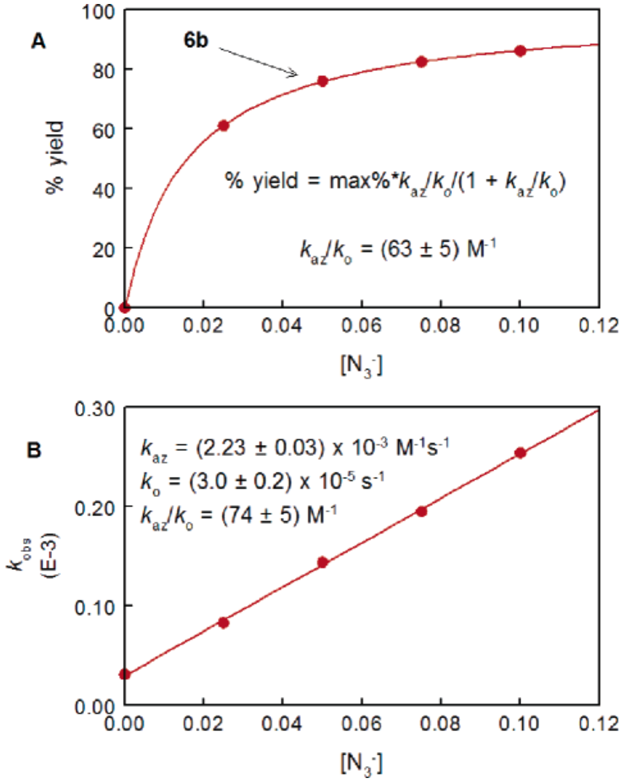
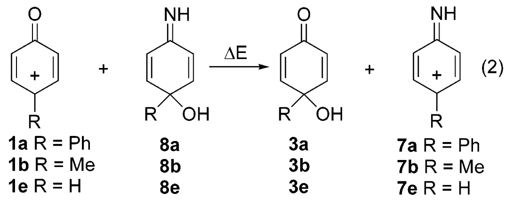


Figure 5. (A) Yield of **6b** as a function of $[N_3^-]$ during the decomposition of **2b′** at pH 4.6. (B) Rate constants for decomposition of **2b′** as a function of $[N_3^-]$ at pH 4.6.

Calculations have been carried out on **1a**, **1b**, and the unsubstituted phenyloxenium ion **1e**, on the corresponding quinols **3a**, **3b**, and **3e**, as well as on the corresponding nitrenium species **7a**, **7b**, and **7e**, and iminoquinols **8a**, **8b**, and **8e**. The iminoquinols are known to be the initial major or exclusive hydration products of the nitrenium ions, and **3a** is the only product of hydration of **1a**.[13,19,20] Geometries were optimized at the HF/6-31G* level, and these were used to compute energies at the density functional level (pBP/DN*//HF/6-31G*).[21] A full frequency analysis at the pBP/DN* level was used to obtain zero-point energies, enthalpies, and entropies. Optimized geometries are provided in the Supporting Information. Comparisons of the geometries, vibrational frequencies, and other properties of the oxenium species and the corresponding nitrenium and carbenium ions will be presented elsewhere.[22] Here, we are primarily concerned with the stabilities of the oxenium and nitrenium species **1** and **7** relative to each other and to their hydration products **3** and **8**. The energetics of the isodesmic eqs 2 and 3 were calculated at three levels of theory: (1) HF/6-31G*, (2) pBP/DN*//HF/6-31G* with ZPE corrections, and (3) pBP/DN*//HF/6-31G* with ZPE corrections and thermodynamic corrections at 298.15 °C.



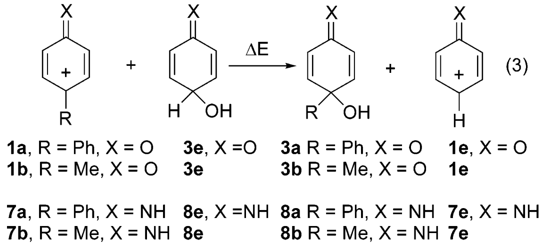


Table 2. Energetics of Isodesmic Reactions of Equations 2 and 3 at HF and DFT Levels

eq	first cmpd in eq	Δ*E* (kcal/mol) HF/6-31G*	Δ*E* (kcal/mol) pBP/DN*, ZPE	Δ*E* (kcal/mol) pBP/DN*, ZPE, thermo
2	**1a**	−12.2	−12.3	−11.0
2	**1b**	−18.9	−19.2	−18.4
2	**1e**	−21.3	−19.8	−19.3
3	**1a**	25.9	28.2	29.0
3	**1b**	10.6	9.5	10.3
3	**7a**	16.7	20.8	20.6
3	**7b**	8.2	9.0	9.4

Comparisons of the reaction energies in Table 2 show that, in general, inclusion of electron correlation, ZPE corrections, and thermodynamic quantities make little difference to the results. The isodesmic reaction of eq 2 compares the stabilities of the oxenium ions with the corresponding nitrenium ions relative to the respective hydration products. All oxenium ions are less stable than the corresponding nitrenium species, but the 4-phenyl substituent of **1a** stabilizes it to the reaction of eq 2 by ca. 7 kcal/mol relative to the 4-methyl substituted **1b** and ca. 8 kcal/mol relative to the unsubstituted **1e**. The calculated results for **1a** and **7a** are in accord with the experimentally estimated lifetimes of the two ions in aqueous solution at 30 °C (12 ns for **1a** and 300 ns for **7a**).[13,23] The *p*-tolyloxenium ion, **1b**, is calculated to be ca. 19 kcal/mol less stable to hydration than **7b**, which has a lifetime of only ca. 0.8 ns at 20 °C.[20] The isodesmic reactions of eq 3 compare the hydration stabilities of the substituted oxenium ions **1a** and **1b** to the unsubstituted ion **1e** and the similar hydration stabilities of **7a** and **7b** relative to the unsubstituted nitrenium ion **7e**. The energetics of this reaction were previously calculated at the HF/6-31G*//HF/3-21G* level for a series of nitrenium ions including **7a** and **7b**. The Δ*E* calculated at that level for **7a** (19.3 kcal/mol) and **7b** (8.1 kcal/mol) are comparable to the values shown in Table 2.[24] The results show that the 4-phenyl substituent stabilizes **7a** relative to the 4-methyl substituted **7b** by ca. 11 kcal/mol. The effect of the 4-phenyl substituent on the stabilization of **1a** relative to **1b** is significantly larger at ca. 19 kcal/mol.

It has been noted previously that π-donor substituents considerably stabilize nitrenium ions compared to the corresponding carbenium ions.[19,20,23−25] These calculations indicate that aryloxenium ions are even more sensitive to π-donor stabilization than are nitrenium ions. This is consistent with greater localization of the positive charge at the 4-position of the ring of the oxenium ion caused by the more electronegative oxygen.[13,25]

Scheme 3

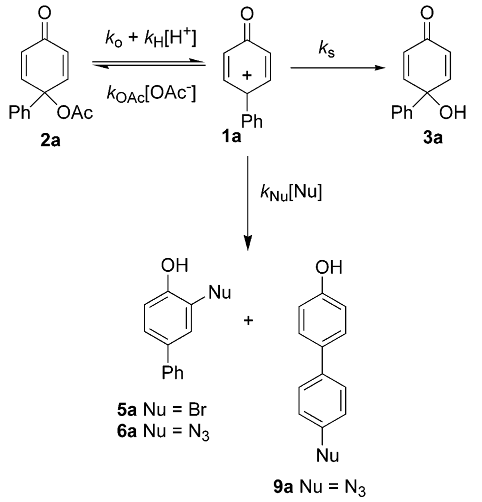


Table 3. Rate Constant Ratios and Estimated Rate Constants for Reaction of Nucleophiles with **1a** at 30 °C

nucleophile	k_{Nu}/k_s (M^{-1})	k_{Nu} (M^{-1} s^{-1})
N_3^-	77 ± 5[a]	6.5 × 10^9 [b]
Br^-	46 ± 5	3.9 × 10^9
OAc^-	3.3 ± 0.2[a]	2.8 × 10^8
H_2O		(8.4 × 10^7 s^{-1})[c]

[a] From ref 13. [b] Assumed diffusion limit based on observed k_{az} for **7a**; see ref 13. [c] This is k_s, the pseudo-first-order rate constant for reaction with solvent.

Discussion

The ^{18}O-labeling results and nucleophilic trapping experiments performed under neutral and acidic conditions for **2a** and the common ion rate depression observed for this compound are readily interpreted in terms of the mechanism of Scheme 3. Both of the processes governed by k_o and k_H generate the same reactive intermediate, identified as the oxenium ion **1a**. The regiochemistry of reaction with **1a** differs for the nucleophiles examined (Br^-, N_3^-, OAc^-, H_2O) and is not completely understood at this time. The regiochemistry of reaction with H_2O was also previously observed for similarly substituted nitrenium ions.[19,20] An analogous product may initially be formed with other nucleophiles, but these products would be expected to decompose rapidly by loss of the leaving group.[20] The common ion rate depression observed for **2a** in acetate buffers requires that OAc^- reacts at the same position as H_2O. The unusual product **9a** (18% of the isolated N_3^- adducts of **2a**) is thought to arise because of the significant amount of charge delocalization that occurs into the distal ring of **1a** that is calculated to be coplanar with the proximal ring.[13] Analogous products were not observed from reaction with H_2O or Br^-. Samples of both of these products analogous to **9a** are available, so it is possible on the basis of HPLC data to set upper limits of 1 and 2%, respectively, for the yields of 4,4′-dihydroxybiphenyl and 4′-bromo-4-hydroxybiphenyl under conditions in which the yields of **3a** or **5a**, respectively, are maximized.

The rate constant ratios, k_{Nu}/k_s, obtained from nucleophilic trapping experiments and common ion rate depression measurements on **1a** are gathered in Table 3. Rate constants, k_{az}, for reaction of nitrenium ions with N_3^- with k_{az}/k_s as large as 10^5 M^{-1} are diffusion limited, so it is likely that k_{az} for **1a** is also diffusion limited.[23,26] The estimated value for k_{az} in Table 3 is

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(20) (a) Novak, M.; Kahley, M. J.; Lin, J.; Kennedy, S. A.; Swanegan, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 11626−11627. (b) Novak, M.; Kahley, M. J.; Lin, J.; Kennedy, S. A.; James, T. G. *J. Org. Chem.* **1995**, *60*, 8294−8304.

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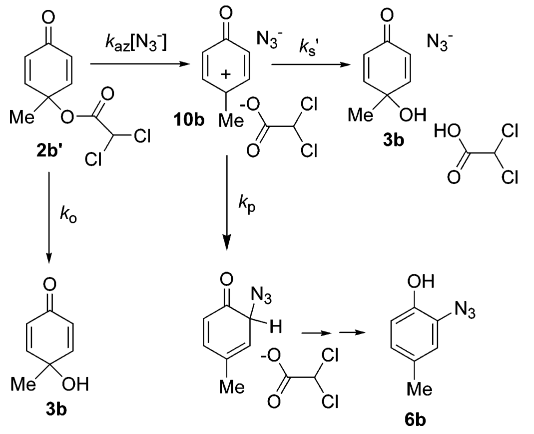
Scheme 4



the observed value of k_{az} for **7a** at 20 °C corrected to 30 °C.[13] All other rate constants in Table 3 are estimated based on the observed rate constant ratios and on the assumption that k_{az} is diffusion limited for **1a**. The rate constant for reaction with Br^-, k_{Br}, is also large, but about a factor of 2 below the diffusion limit. The estimated lifetime of **1a** at 30 °C in aqueous solution, $1/k_s$, is 12 ns. This is considerably shorter than the lifetime of **7a** of 300 ns extrapolated to 30 °C from data obtained at 20 °C.[13,23] The lifetimes are in accord with the relative stabilities of **1a** and **7a** toward hydration calculated from the isodesmic reaction of eq 2 (Table 2).

Unlike **2a**, **2b** and **2b′** decompose predominately by ester hydrolysis pathways involving $C_{acyl}-O$ bond cleavage under all pH conditions examined. The calculations suggest that this may be due to the instability of **1b** in an aqueous environment. Since the oxenium ion pathway is energetically unfavorable for **2b** and **2b′**, these esters react predominately by an alternative pathway that does not involve **1b**. The calculated stability toward hydration of **1b** provides a way to estimate the lifetime of **1b**, provided that log k_s correlates with these calculated stabilities. There is evidence that this is the case for nitrenium ions.[24] Log k_s for a series of 18 nitrenium ions with widely varying structure correlates with ΔE of eq 3 (all relative to **7e**) calculated at the HF6-31G*//3-21G level with slope -0.19 ± 0.02 ($r^2 = 0.89$).[24] If a similar correlation holds for the oxenium ions, the calculated value of $1/k_s$ for **1b** based on the lifetime of **1a** and the calculated values for the hydration stabilities of **1a** and **1b** relative to **1e** (eq 3) is 3 ps. An estimate based on the isodesmic reactions of eq 2 and the lifetimes of **1a**, **7a**, and **7b** provides a similar value for the lifetime of **1b** of 5 ps. Simple 4-alkyl substituted aryloxenium ions are unlikely to be generated in aqueous solution as trappable intermediates in diffusional equilibrium with nonsolvent nucleophiles. Although **1b** is apparently not formed to a significant extent from **2b** or **2b′** in H_2O in the absence of other nucleophiles, **2b′** can be induced to undergo bimolecular substitution reactions that generate oxenium-like products. Since N_3^- clearly accelerates the decomposition of **2b′**, the reaction of **2b′** with N_3^- must occur by a preassociation process. Two mechanisms are possible: a fully concerted S_N2' process, or a stepwise process involving N_3^- trapping of an intermediate ion sandwich, **10b**, that is generated by N_3^--assisted ionization (Scheme 4). It has been argued that concerted S_N2' mechanisms do not occur,[27] and energetic conditions that must be met for a concerted transition state involving multiple bond-making/bond-breaking events are stringent.[28] Nevertheless, if the intermediate is too short-lived to exist as an intermediate (lifetime $<10^{-13}$ s), the concerted mechanism is enforced.[29] This may be the case for **10b**. Isolation experiments for **6b** at high $[N_3^-]$ show that the yield of **3b** becomes vanishingly small. The results indicate that k_s' is at least 50-fold smaller than k_p for **10b**. If k_s' is of the same magnitude as the estimated k_s for **1b**, it is ca. $(2-3) \times 10^{11}$ s^{-1}, and k_p is at least 10^{13} s^{-1}. This, in turn, suggests that **10b** is not an intermediate at all, but a transition state. The error limits on the estimated value of k_s' are large, probably an order of magnitude or more, so we cannot preclude the possibility that **10b** is an intermediate with a very short lifetime. An upper limit of the lifetime of **10b** and similar species of ca. 10^{-10} to 10^{-11} s is enforced by the rate of diffusional separation of ion pair intermediates in aqueous solution, so k_p must be at least ca. 10^{11} s^{-1} if the reaction does occur through this species.[30]

Conclusion

An aryloxenium ion stabilized by a π-donor substituent at the 4-position appears to be stable enough in an aqueous environment to be readily generated and to have sufficient lifetime to react with some selectivity with nonsolvent nucleophiles. A σ-donor, such as a 4-methyl substituent, is far less effective at stabilizing the ion; **1b** cannot be generated under conditions in which **1a** is readily formed, and the calculations indicate that even if this species could be formed in a nucleophilic solvent, such as H_2O or MeOH, it would be far too reactive with the solvent to be effectively trapped by nonsolvent nucleophiles. An apparent oxenium ion nucleophilic substitution product can be generated from a precursor to the 4-methyl ion, but this product is generated by a kinetically second-order process that has the characteristics of an S_N2' reaction. We will continue to delineate substituent effects on the stability/reactivity of these ions and will make efforts to generate sufficiently stable examples by laser flash photolysis methods.

Experimental Section

Synthesis: The syntheses of **2a,b** and **3a,b** were described previously.[13] A sample of 2-bromo-4-phenylphenol (**5a**) was obtained from a previously published procedure.[17] Methylhydroquinone (**4b**), 4′-bromo-4-hydroxybiphenyl, and 4,4′-dihydroxybiphenyl were commercially available.

4-Dichloroacetoxy-4-methyl-2,5-cyclohexadienone (2b′): A 0.54 g sample of *p*-cresol (5 mmol) was dissolved in 40 mL of dichloroacetic acid, and the resulting solution was stirred vigorously as 1.77 g (5.5 mmol) of phenyliodonium diacetate (PIDA) in 40 mL of dichloroacetic acid was added in a dropwise fashion over a period of ca. 8 h. After completion of addition, the solution was diluted with 150 mL of CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), followed by brine (1 × 50 mL). The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under vacuum. The crude

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product was triturated with hot hexanes (4 × 5 mL). After evaporation of the hexanes, the residue was subjected to chromatography on a chromatatron (2 mm silica gel, 75/25 hexanes/EtOAc) to yield 150−200 mg (13−17%) of a yellowish waxy solid that was sufficiently pure for most purposes. A cleaner sample could be obtained by recrystallization from hexanes or by vacuum sublimation (−5 °C coldfinger, 40 °C bath): mp 69−71 °C; IR 3022, 1749, 1665, 1629, 1272, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (3H, s), 5.92 (1H, s), 6.33 (2H, d(AB), $J = 10.2$ Hz), 6.92 (2H, d(AB), $J = 10.2$ Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 25.8, 64.1, 77.2, 129.3, 146.4, 162.7, 184.3; LC/MS (ESI positive) *m/e* 235 (100%) ($(^{35}Cl_2M + H)^+$), 237 (70%) ($(^{35}Cl^{37}ClM + H)^+$), 239 (10%) ($(^{37}Cl_2M + H)^+$); high-resolution MS (ES, positive), $C_9H_8{}^{35}Cl_2O_3Na$ (M + Na) requires *m/e* 256.9748, found 256.9752, $C_9H_8{}^{35}Cl^{37}ClO_3Na$ requires *m/e* 258.9718, found 258.9717.

2-Azido-4-methylphenol (6b): A 70 mg (0.30 mmol) sample of **2b′** was dissolved in 1 mL of CH_3CN and added in 200 μL portions at 20 min intervals to 100 mL of a 0.5 M NaN_3, 0.25 M $HClO_4$ buffer (1/1 NaN_3/HN_3, pH 4.6) in 5 vol % CH_3CN-H_2O incubated at 30 °C. The reaction mixture was extracted (4 × 50 mL) with CH_2Cl_2 after the disappearance of **2b′** was confirmed by HPLC (ca. 3 h after the last addition). After drying over Na_2SO_4, the CH_2Cl_2 extract was evaporated to dryness under vacuum, and the residue was subjected to vacuum sublimation (−15 °C coldfinger, 30 °C bath) to provide 23 mg (51%) of the off-white azide adduct: mp 42.5−44 °C; IR (thin film) 3415, 2120, 1600, 1510, 1305 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.33 (3H, s), 5.22 (1H, s), 6.82 (1H, d, $J = 8.2$ Hz), 6.89 (1H, dd, $J = 1.3$, 8.2 Hz), 6.95 (1H, d, $J = 1.2$ Hz); ^{13}C NMR (125.8 MHz, CD_2Cl_2) δ 20.3, 115.5, 118.8, 125.5, 126.5, 130.9, 145.1; LC/MS (ESI, negative) *m/e* 148 $(M - H)^-$ (weak), (ESI positive) *m/e* 122 $(M-N_2 + H)^+$; high-resolution MS (ES, positive) $C_7H_7N_3ONa$ (M + Na) requires *m/e* 172.0487, found 172.0484.

Kinetics and Product Studies: Reactions were performed in 5 vol % CH_3CN-H_2O, $\mu = 0.5$ ($NaClO_4$) at 30 °C for **2a** and **2b′**, and at 80 °C for **2b**. The pH was maintained with $HClO_4$ solutions (pH < 3.0), or with $HCO_2H/NaHCO_2$, AcOH/AcONa, and Na_2HPO_4/NaH_2PO_4 buffers. All pH values were measured at ambient (24−26 °C) temperature and are uncorrected. Detailed procedures utilized for the kinetics studies of **2a** and **2b** have been published.[13] For **2b′**, reactions were initiated by injection of 15 μL of a ca. 0.02 M CH_3CN solution of **2b′** into 3 mL of the reaction solution incubated at 30 °C for 15−20 min prior to initiation. Kinetics were monitored by changes in UV absorption at 220, 236, 240, and 250 nm. Absorbance changes were fit to a standard first-order rate equation. Product studies were performed in pH 1.0, 4.6, and 7.0 solutions by HPLC analysis of the kinetics solutions after 7−10 half-lives of the hydrolysis reactions. At these pH values, reactions were also monitored as a function of time by HPLC. HPLC conditions include the following: 20 μL injections, Novapak 8 mm × 100 mm C-18 radial compression column with 4 μ particle size, 60/40 CH_3CN/H_2O eluent, 0.5 mL/min flow rate, UV detection at 240 nm, or a 4.7 mm × 250 mm C-18 column, 60/40 $MeOH/H_2O$ or 50/50 $MeOH/H_2O$ eluent, 1.0 mL/min flow rate, UV detection at 240 nm. Product yield data for **3a**, **5a**, and **6b** as a function of $[Br^-]$ or $[N_3^-]$ were fit to eqs 4 and 5, where $[Nu] = [Br^-]$ or $[N_3^-]$.[18]

$$\mathbf{3a}\% = \max\% \, (1/(1 + k_{Nu}[Nu]/k_s)) \qquad (4)$$

$$\mathbf{5a}\% \text{ or } \mathbf{6b}\% = \max\% \, ((k_{Nu}[Nu]/k_s)/(1 + k_{Nu}[Nu]/k_s)) \qquad (5)$$

The parameter max% is a least-squares adjustable parameter. In all of the fits reported here, it is 97−102%

^{18}O-Labeling Studies: Solutions (pH 1.0 $HClO_4$, pH 4.6 0.02 M $OAc^-/HOAc$, pH 7.5 0.02 M $HPO_4{}^{-2}/H_2PO_4{}^-$) were identical to those used for kinetics, except that they were made to nominally contain 10 or 25 atom % $^{18}O-H_2O$. This was accomplished by appropriate dilution of commercially available 10 and 95 atom % $^{18}O-H_2O$.

A 2 μL injection of a 0.05 M solution of **3a** or a 0.10 M solution of **2a** in CH_3CN was made into 200 μL of an aqueous 10 atom % ^{18}O solution incubated at 30 °C for 15 min prior to injection. The resulting solution was incubated at 30 °C for one half-life (5060 s at pH 1.0, 29 400 s at pH 7.5), cooled in an ice water bath, and analyzed by LC/MS using triplicate injections. LC conditions: 2 mm × 50 mm C-18 column, 30/70 CH_3CN/H_2O, 0.2 mL/min, 10 μL injection, retention time for **3a** ca. 2.8 min. MS conditions: negative ion-ESI scanned from *m/e* 183−191 in profile mode.

Similarly, 2 μL of a 0.15 M solution of **3b** or a 0.30 M solution of **2b** in CH_3CN was injected into 200 μL of the aqueous 10 atom % ^{18}O solution preincubated at 80 °C. The solution was incubated at 80 °C for one half-life (2300 s at pH 1.0, 25 000 s at pH 7.5), cooled to room temperature, and analyzed by LC/MS using triplicate injections. LC conditions: 2 mm × 50 mm C-18 column, 17/83 $MeOH/H_2O$, 0.2 mL/min, 10 μL injection, retention time for **3b** ca. 2.4 min. MS conditions: positive ion-ESI scanned from *m/e* 123−130 in profile mode.

A 2 μL solution of a 0.04 M solution of **3b** or a 0.08 M solution of **2b′** in CH_3CN was injected into 200 μL of a 25 atom % pH 4.6 acetate buffer preincubated at 30 °C. After one half-life (22 200 s), the reaction mixture was cooled in an ice−water bath and analyzed by LC/MS using triplicate injections. LC conditions: 4.6 mm × 250 mm C-18 column, 60/40 $H_2O/MeOH$ (0.1% HOAc), 1 mL/min, 20 μL injection, retention time for **3b** ca. 4.2 min. MS conditions: positive ion-ESI.

For ^{13}C NMR analysis, 2 mL of 10 or 25 atom % $^{18}O-H_2O$ pH 1.0 and 7.5 solutions were prepared. For **2b**, 200 μL of a 0.25 M solution of the ester in CH_3CN was injected into the aqueous solution preincubated at 80 °C. For **2a**, the 0.25 M 200 μL stock solution of the ester was injected in 20 μL increments at one half-life intervals into the aqueous solution preincubated at 30 °C. The reaction mixtures were monitored by HPLC, and at appropriate reaction times, the mixtures were cooled in an ice−water bath; the acidic solutions were neutralized with Na_2HPO_4, and the solutions were extracted with CH_2Cl_2 (4 × 2 mL). The extracts were dried over Na_2SO_4 and evaporated to dryness under vacuum. The residue was dissolved in 750 μL of CD_2Cl_2 or $CDCl_3$. The resulting solutions were analyzed by ^{13}C NMR at 125.8 MHz. Acquisition and processing parameters were standard, except that the line broadening parameter was set at 0.25 Hz. Data acquisition was continued until ^{18}O satellites clearly emerged. Control experiments were run in normal isotopic abundance aqueous solutions.

Calculations: Calculations were performed with MAC Spartan Pro Version 1 and Spartan Version 5.[31] Geometries were optimized at the HF/6-31G* level, and frequency analyses were performed to verify that the geometries corresponded to true stationary points. These geometries were used to obtain energies at the perturbative Becke−Perdew density functional level pBP/DN*//HF/6-31G*.[21] A full frequency analysis at the pBP/DN* level was used to obtain zero-point energies, and enthalpies and entropies at 298.15 °C.

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Supporting Information Available: Rate constants for the decomposition of **2b′** and selected rate constants for the decomposition of **2a** in the presence and absence of Br^-, HF/6-31G* geometries of the ions **1** and **7**, and the hydration products **3** and **8**, ^{1}H and ^{13}C NMR spectra of **2b′** and **6b**, and COSY NMR spectrum of **6b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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