B16 Triacetate: ^{1}H NMR δ 0.82 (3 H, s, 14-H), 1.20 (3 H, d, J = 6.6 Hz, 14′-H), 2.08, 2.08, 2.14 (3 H each, s, CH_3COO), 2.20–2.32 (1 H, m, 3β-H), 2.30 (3 H, d, J = 1.1 Hz, 12′-H), 2.48 (1 H, dd, J = 8.3 and 15.6 Hz, 3α-H), 2.83, 3.12 (1 H each, AB pattern, J_{AB} = 4.0 Hz, 13-H), 3.73 (1 H, d, J = 5.2 Hz, 11-H), 3.65, 3.87 (1 H each, d of AB pattern, J = 4.4 and 9.6 Hz, 5′-H), 3.82–3.91 (2 H, m, 2-H and 6′-H), 3.87, 4.59 (1 H each, AB pattern, J_{AB} = 12.7 Hz, 15-H), 4.48 (2 H, br s, 16-H), 5.2 (1 H, dq, $J_{6',13'}$ = 2.7 Hz and $J_{13',14'}$ = 6.6 Hz, 13′-H), 5.27 (1 H, t, J = 4.4 Hz, 4′-H), 5.75 (1 H, d, J = 5.2 Hz, 10-H), 5.76 (1 H, d, J = 11.2 Hz, 10′-H), ~5.89 (1 H, dd, $J_{6',7'}$ = 3.0 Hz and $J_{7',8'}$ = 15.3 Hz, 7′-H), 5.91 (1 H, br s, 2′-H), 6.54 (1 H, dd, $J_{8',9'} = J_{9',10'}$ = 11.2 Hz, 9′-H), 7.41 (1 H, dd, J = 15.3 and 11.2 Hz, 8′-H).

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Facile Aryl Ether Hydrolysis: Kinetics and Mechanism of 9-Anthryl Ether Cleavage in Aqueous Solution

Michael F. Powell

Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, California 94304

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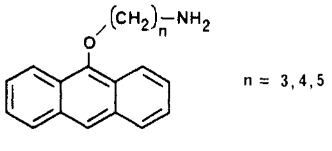
The hydrolysis rates of anthryl ether, 4-(9-anthroxy)butylamine (1), have been determined in aqueous solution from pH 1 to 12 and 25 to 80 °C, wherein it was found that this ether reacted significantly faster than other aryl ethers. The observed rate constants varied with pH according to eq 1 and values for k_{H^+}, k_0, k_N, and K_a

$$k_{obs} = (k_{H^+}[H^+] + k_0)[H^+]/(K_a + [H^+]) + k_N K_a/(K_a + [H^+]) \quad (1)$$

have been evaluated. At low pH, hydrolysis of 1 is characterized by general acid catalysis with carboxylic acid buffers ($\alpha = 0.61 \pm 0.06$) and a solvent isotope effect of 1.85 ± 0.09 at 25 °C. Further, the product deuterium isotope effect for reaction of 1 and H^+ is ~3 and, when the reaction is carried out in ^{18}O water, the anthrone reaction product contains exclusively ^{18}O. These observations show unequivocally that acid hydrolysis occurs by rate-determining proton transfer to the 10-position of the anthracene moiety, followed by rapid reaction of water at the 9-position of the oxonium ion intermediate. The acid-catalyzed hydrolysis of 1 was thus found to resemble vinyl ether hydrolysis (i.e., an A-S_E2 mechanism) instead of an A-2 mechanism shown by most other aryl ethers, such as anisole.

As part of our research into DMARD's (Disease-Modifying Anti-Rheumatic Drugs), we studied the aqueous hydrolysis of anthryl ether 1 (n = 4) and its 3- and 5-methylene analogues (shown below) and found them to be significantly more reactive than most other aryl ethers.



1 [n = 4]

In acidic solution anthryl ether 1 degraded ~10^8 times faster than anisole or other phenyl ethers—a rate enhancement shown only by activated ethers such as vinyl ethers.[1-5] This huge disparity in reaction rates is not due to a substituent effect but to a change in reaction mechanism. Vinyl ethers, for example, react by rate-determining carbon protonation followed by rapid attack of water on the oxonium intermediate,[6-8] whereas aryl ethers are thought to hydrolyze in strong acids by preequilibrium protonation of oxygen followed by rate-determining S_N2 nucleophilic displacement. It is unknown whether the enhanced reactivity of anthryl ethers can be explained by a C-protonation hydrolysis mechanism since, even though aryl alkyl ethers readily undergo ring protonation and hydrogen isotope exchange in superacid media,[9,10] hydrolysis of aryl alkyl ethers by rate-determining carbon protonation is uncommon. 9-Anthryl ethers, however, may be good candidates for showing this unusual behavior. Should protonation occur at the 10-position of the anthryl moiety, benzo group formation will stabilize the anthryl oxonium intermediate and thus compensate for the loss of the anthryl 14 π-electron aromaticity.

Despite the fact that the 9-anthroxy moiety is used routinely as a useful hydroxyl-protecting group which may be cleaved only by singlet oxygen[11,12] and that the anthryl ether group is present in several investigational DMARD's,[13] surprisingly little is known about the hydrolysis of 9-anthryl ethers. To shed some light on the aqueous chemistry of anthryl ethers, the acid, neutral, and base catalyzed hydrolysis reactions of 1 were investigated by determination of reaction products, rate constants, and isotope effects.

Results and Discussion

General. Under anaerobic reaction conditions, hydrolysis of anthryl ether 1 obeyed first-order kinetics and afforded anthrone (2) as the primary reaction product from pH 1 to 12. In the presence of oxygen, however, varying

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(14) Harned, H. S.; Owen, B. B. *The Physical Chemistry of Electrolyte Solutions*; Reinhold: New York, 1943.

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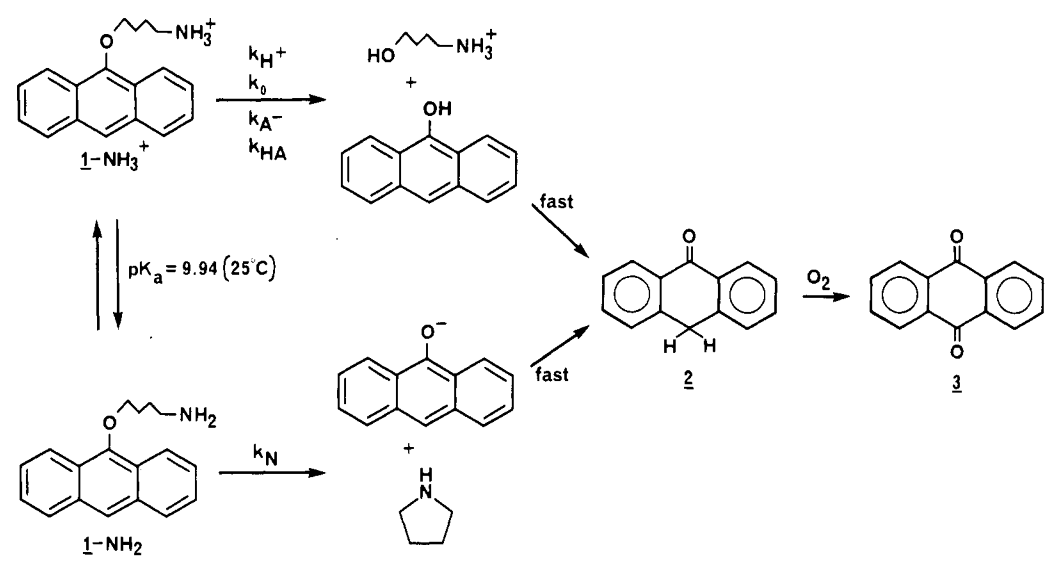

(1)

amounts of anthrone and anthraquinone (3) were formed depending on the reaction pH and amount of O_2 present. For example, both 2 and 3 were found in degraded reaction samples of low to neutral pH, whereas only 3 was detected in spent solutions of high pH. Anthrol was not found under any experimental conditions; this is because of the rapid tautomerism of anthrol to anthrone. Pyrrolidine was detected in near quantitative yields when the hydrolysis reaction was carried out at high pH (see Experimental Section), whereas, in degraded solutions of low or neutral pH, 4-amino-1-butanol was detected as the amine-containing hydrolysis fragment.

In eq 1 and what follows, the rate constant subscripts denote the catalytic species; for example, k_{H^+}, k_0, and k_N are the rate constants for specific hydronium ion catalysis, spontaneous or water-catalyzed hydrolysis, and an intramolecular reaction with the terminal amine at high pH, respectively. Similarly, the rate constants, k_{A^-} and k_{HA} (vide infra), denote catalysis by buffer base (carboxylate) and buffer acid (carboxylic acid), respectively. The hydrolysis rates of 1 were determined at several temperatures (25, 40, 60, and 80 °C) and pHs (pH 1 to 12) at 0.15 M ionic strength. It was necessary to use constant ionic strength because the reaction rate increased linearly with ionic strength (μ); for example, the acid-catalyzed hydrolysis of 1 at 25 °C obeyed the relationship, $k_{H^+} = [(0.79 \pm 0.05) + \mu(1.23 \pm 0.09)] \times 10^{-6}\ M^{-1}\ s^{-1}$. At pHs less than 2, rate constants were determined from dilute hydrochloric acid (H^+/H_2O) or deuterated (>98% isotopic purity) hydrochloric acid (D^+/D_2O) solutions. In the pH 2–12 range, the observed rate constants (shown in Figure 1) were obtained from 0.01 M buffer solutions or, when carboxylic acid buffers were used, from the rate constant found by extrapolation of the serially diluted buffer to zero buffer concentration. Rate constants determined by either of these methods were similar, indicating only a slight contribution to the overall rate by buffer catalysis in kinetic runs carried out in 0.01 M buffer.

In the absence of buffer catalysis, plots of log k_{obs} vs. pH for 1 (Figure 1) showed three distinct regions of curvature having a slope of −1 in the acid region, a narrow plateau near pH 6, and an increase in rate near the pK_a to a second plateau region at high pH, in accord with eq 2. The

$$k_{obs} = (k_{H^+}[H^+] + k_0)[H^+]/(K_a + [H^+]) + k_N K_a/(K_a + [H^+]) \tag{2}$$

quotients, $[H^+]/(K_a + [H^+])$ and $K_a/(K_a + [H^+])$, represent the fractions of protonated and deprotonated substrate, respectively, and K_a is the dissociation constant for 1 at the reaction temperature. Figure 1 also shows that the rate behavior defined by eq 2 is observed over a range of temperatures. Nonlinear least-squares analysis[15] of log k_{obs} vs. pH using eq 2 gives the rate constants and K_a values shown in Table I. The temperature-dependent rate constants for 1 show linear Arrhenius behavior, and Table II gives the activation parameters for k_{H^+}, k_0, and k_N.

Table I. Temperature-Dependent Dissociation Constants and Rate Constants for the Hydrolysis of 1 in Aqueous Solution

	temperature, °C		
rate constant	40	60	80
k_{H^+} (M^{-1} s^{-1})[a,b]	6.0×10^{-5}	5.2×10^{-4}	2.3×10^{-3}
k_0 (s^{-1})[a]	4.8×10^{-9}	1.3×10^{-8}	4.5×10^{-8}
k_N (s^{-1})[a]	6.6×10^{-8}	5.6×10^{-7}	5.3×10^{-6}
$k_{CH_3COO^-}$ (M^{-1} s^{-1})	c	c	3.5×10^{-7}
k_{CH_3COOH} (M^{-1} s^{-1})	c	c	9.7×10^{-7}
k_{ClCH_2COOH} (M^{-1} s^{-1})	c	c	2.2×10^{-5}[d]
$k_{Cl_2CHCOOH}$ (M^{-1} s^{-1})	c	c	1.3×10^{-4}
K_a[a,e]	3.0×10^{-10}	1.0×10^{-9}	1.4×10^{-9}

[a] Derived from nonlinear least-squares analysis of eq 2. The reaction solutions have been corrected for activity by using the following temperature-dependent activity coefficients of f_{H^+}: 40 °C, 0.773; 60 °C, 0.762; 80 °C, 0.752; see ref 14. [b] The bimolecular rate constant for reaction of 1 in D^+/D_2O at 25 °C was determined to be $(4.99 \pm 0.21) \times 10^{-6}\ M^{-1}\ s^{-1}$. [c] Not determined. [d] Chloroacetic acid buffers are rather unstable at 80 °C and so these kinetics were determined from ~10% reaction or less, i.e., before the buffer pH changed significantly. [e] K_A for 1-NH_3^+ at 25 °C was determined to be 1.15×10^{-10}.

Table II. Activation Parameters for the Hydrolysis of Anthryl Ether 1

rate constant	E_a (kcal mol^{-1})	ln A	$\Delta H^‡$ (kcal mol^{-1})	$\Delta S^‡$ (cal K^{-1} mol^{-1})
k_{H^+}	20.1	22.6	19.4	−15.7
k_0	12.3	0.52	11.6	−59.8
k_N	24.2	22.2	23.4	−16.8

Acid-Catalyzed Hydrolysis of 9-Anthryl Ether 1. Experimental observation of specific and general acid catalysis and a solvent isotope effect greater than unity are indicative that the acid-catalyzed hydrolysis of 1 proceeds by rate-determining carbon protonation and subsequent

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[15] Bevington, P. R. *Data Reduction and Error Analysis for the Physical Sciences*; McGraw-Hill: New York, 1969.

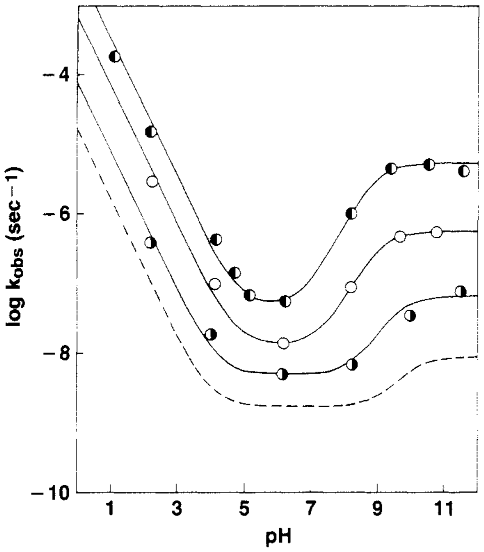
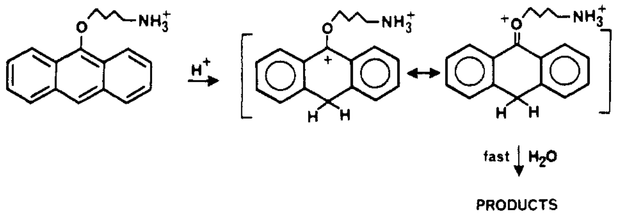


Figure 1. Log (rate)–pH profiles for the hydrolysis of anthryl ether 1 at 40 °C (◑), 60 °C (○), and 80 °C (◐). The drawn lines are from the best-fit values of k_{H^+}, k_0, k_N, and K_a obtained by nonlinear least-squares analysis using eq 2. The dashed line is the calculated log (rate)–pH profile at 25 °C using rate constants calculated from the Arrhenius activation parameters of Table II and is included to show the ever-increasing contribution of k_0 at lower temperatures.

fast attack of water (A-S_E2 mechanism, eq 3), as do vinyl ethers.[6-8]



(3)

Hydrolysis of 1 in H^+/H_2O and D^+/D_2O shows a k_{H^+}/k_{D^+} deuterium isotope effect of 1.85 ± 0.09 at 25 °C, implying rate-determining proton transfer from solvent to substrate.[16] Solvent isotope effects for acid-catalyzed vinyl ether hydrolysis are also greater than unity, ranging from 1.7 for dimethylfuran[17] to 4.2 for ethyl cyclooctenyl ether.[8] Most arylalkyl ethers, on the other hand, are expected to show isotope effects less than unity as predicted for a mechanism involving rapid preequilibrium protonation on oxygen.[18]

Anthryl ether 1 also shows general acid catalysis by acetic, chloroacetic, and dichloroacetic acid (Table I and Figure 2). Carboxylic acid catalytic coefficients for reaction of 1 were determined by measuring the hydrolysis rates at constant ionic strength in a series of buffers of constant buffer ratio but at changing total buffer concentration. Both the acetic and chloroacetic acid buffers showed constant hydronium ion concentration upon dilution of the buffer solutions and so the effect of the buffer was obtained by least-squares regression analysis of k_{obs} vs. carboxylic acid concentration. Dichloroacetic acid, however, gave a series of buffer solutions whose hydronium ion concentrations decreased with decreasing buffer concentration. Such buffer failure[14] was compensated for by adjusting the observed rate constants within a given series of buffer solutions to a common hydronium ion concentration; the value of k_{H^+} at 80 °C used for this correction was determined from HCl solution. Distinction between acetic acid and acetate catalysis was made by determining the hydrolysis rates at several pH's. In acetic acid buffers, the observed rates obeyed eq 4 so that, rearranging and

$$k_{obs} = k_{H^+}[H^+] + k_0 + k_{HA}[HA] + k_{A^-}[A^-] \qquad (4)$$

$$k' = \frac{k_{obs} - k_{H^+}[H^+] - k_0}{B_T} = k_{HA}[HA]/B_T + k_{A^-}[(B_T - [HA])/B_T] \qquad (5)$$

dividing both sides by the total buffer concentration B_T gives eq 5. Thus, plotting the pseudo-first-order rate constants k_{obs} vs. B_T at a constant pH affords $k_{H^+}[H^+] + k_0$ as the intercept and k' as the slope (Figure 2). A secondary plot of these slopes vs. the fraction of free acid, $[HA]/B_T$, gives k_{A^-} and k_{HA} as the 0 and 1 intercepts, respectively (see Figure 3 and Table I). Catalysis by the conjugate buffer base is unimportant for carboxylic acid buffers of low pH because $k_{HA}[HA] \gg k_{A^-}[A^-]$ by at least a factor of 20.[19]

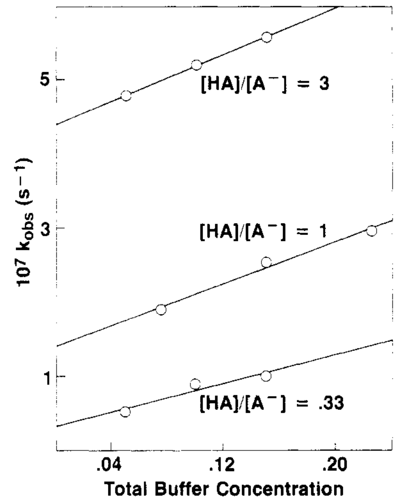


Figure 2. Dependence of k_{obs} for reaction of 1 at 80 °C on the total acetate buffer concentration. The buffer ratios ($[HA]/[A^-]$) are shown in the figure.

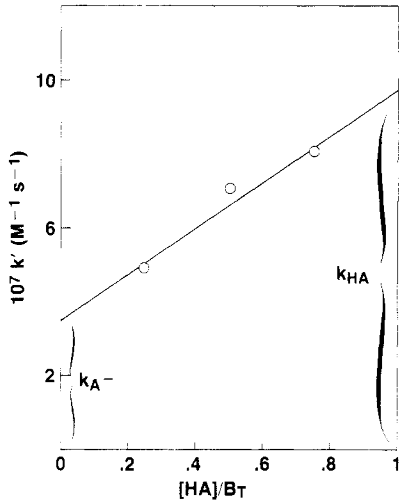


Figure 3. Dependence of the apparent rate constant k' for buffer catalysis of 1 at 80 °C on the composition of acetate buffer. The 0 and 1 intercepts are k_{A^-} and k_{HA}, respectively.

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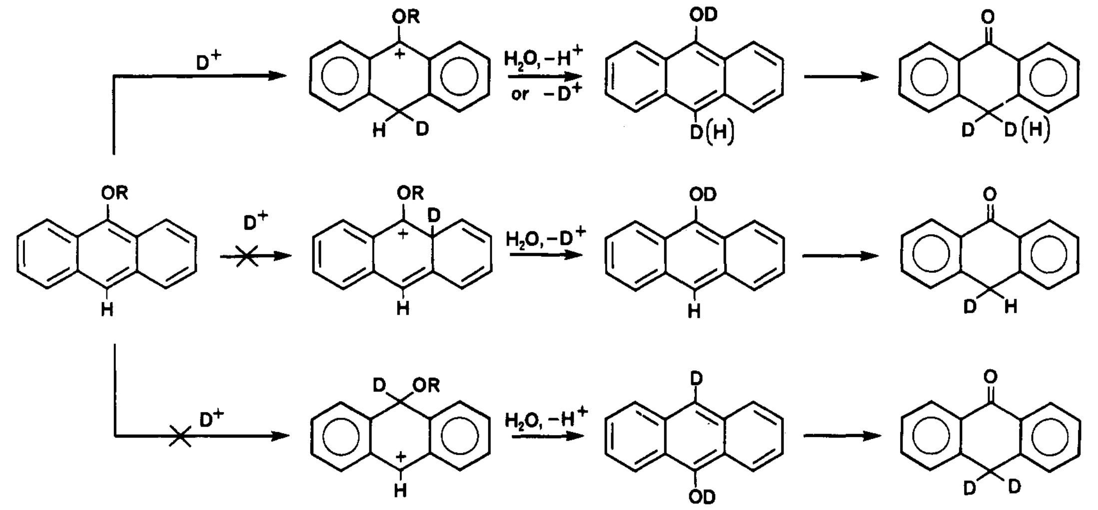
(18) Laughton, P. M.; Robertson, R. E. In *Solute-Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel-Decker: New York, 1969.

(19) This estimate is based on the difference in the rate constants, k_{CH_3COOH} and k_{ClCH_2COOH}, and assuming that $k_{ClCH_2COO^-}$ is less than or equal to $k_{CH_3COO^-}$.



(6)

(7)

(8)

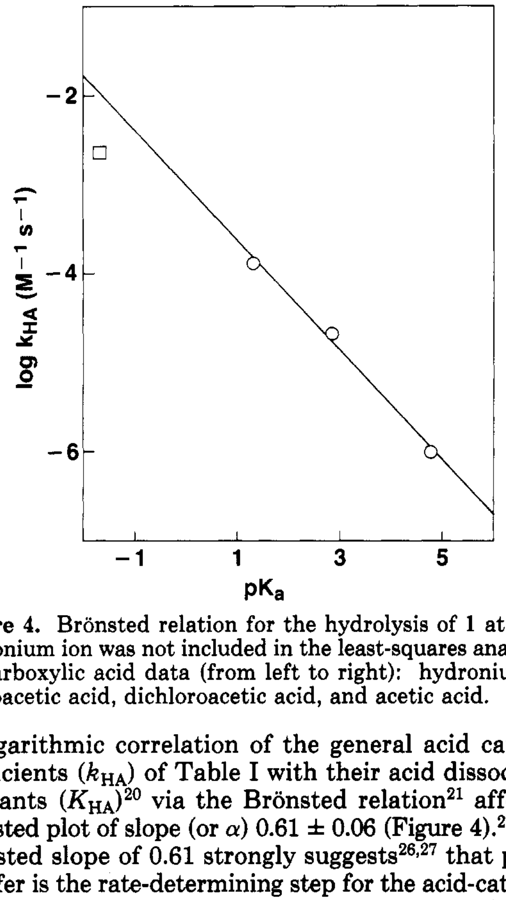


Figure 4. Brönsted relation for the hydrolysis of 1 at 80 °C. Hydronium ion was not included in the least-squares analysis of the carboxylic acid data (from left to right): hydronium ion, chloroacetic acid, dichloroacetic acid, and acetic acid.

Logarithmic correlation of the general acid catalytic coefficients (k_{HA}) of Table I with their acid dissociation constants (K_{HA})[20] via the Brönsted relation[21] affords a Brönsted plot of slope (or α) 0.61 ± 0.06 (Figure 4).[22] The Brönsted slope of 0.61 strongly suggests[26,27] that proton transfer is the rate-determining step for the acid-catalyzed hydrolysis of 1. The negative deviation of the hydronium ion from the Brönsted plot of carboxylic acids is probably due to either the energy-raising interaction of the positively charged catalyst H^+ with the positively charged substrate 1-NH_3^+, or to the use of 55 M as the concentration of pure water, a value that may be too low if only the concentration of non-hydrogen-bonded water should be considered.[28,29]

Other experimental observations that are consistent with a mechanism involving rate-determining proton transfer to 1 are (i) a positive kinetic electrolyte effect with sodium chloride (vide supra), (ii) formation of the expected products, 4-amino-1-butanol, anthrone, and anthraquinone, and (iii) the similarity of activation parameters observed for reaction of 1 (Table II) and those reported for vinyl ethers;[30] for example, hydrolysis of ethyl vinyl ether[1] gave $\Delta H^{\ddagger}$ = 14 kcal mol^{-1} and $\Delta S^{\ddagger}$ = -11 cal K^{-1} mol^{-1}.

The mechanistic details of the acid hydrolysis reaction have been further resolved by the use of isotope tracers. Reaction of 1 in either D^+/D_2O or $H^+/H_2{}^{18}O$ resulted in significant uptake of the isotope tracer in the product anthrone. For example, when the reaction was carried out in D^+/D_2O, mass spectral analysis of the anthrone product showed that 74% was dideuterated and that the remaining anthrone consisted primarily of the monodeuterated product. Hydrolysis of 1 to give ~74% dideuterated anthrone is only possible for protonation at the 10-position followed by an intramolecular competitive isotope effect of ~2.8, as shown by eq 6. If protonation were to occur at a bridging carbon resulting in the formation of a less favorable oxonium intermediate (eq 7), the anthrone product would contain only a single deuterium atom. If, on the other hand, protonation were to occur at the 9-position to give the resonance-stabilized carbonium intermediate of eq 8, the resulting anthrone would be 100% dideuterated. Neither of these alternate pathways by themselves can explain the observed deuterium isotope incorporation, and since anthrone is unable to undergo isotope exchange under the reaction conditions used (see Experimental Section), the formation of 74% doubly

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(20) *CRC Handbook of Biochemistry. Selected Data for Molecular Biology*; Sober, H. A.; CRC Press: Cleveland, 1968.

(21) Brönsted, J. N.; Pedersen, K. *Z. Phys. Chem.* **1924**, *108*, 185.

(22) The K_{HA} values for carboxylic acids used herein were determined at 25 °C (not at 80 °C); this, however, is not expected to have an appreciable effect on α since the pK_a's for carboxylic acids are rather insensitive to temperature.[23] Correction to account for pK_a values at 80 °C by use of the Valentiner equation[24] and the appropriate coefficients for substituted carboxylic acids[25] shows that the pK_a change is only 0.1–0.3 pK_a unit and so does not much affect the Brönsted exponent.

(23) Ellis, A. J. *J. Chem. Soc.* **1963**, 2299.

(24) Valentiner, S. *Z. Phys. Chem.* **1907**, *42*, 253.

(25) Everett, D. H.; Wynne-Jones, W. F. K. *Trans. Faraday Soc.* **1939**, *35*, 1350.

(26) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475.

(27) Kresge, A. J. In *Proton Transfer Reactions*; Caldin, E. F., Gold, V., Eds.; Wiley and Sons: New York, 1975.

(28) See, for example: Williams, J. M., Jr.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* **1968**, *6*, 67.

(29) Bell, R. P. *Trans. Faraday Soc.* **1943**, *39*, 253.

(30) The entropy of activation can sometimes be used to distinguish between the A-1 and A-2 hydrolysis mechanisms,[31] but the large negative $\Delta S^{\ddagger}$ values for the A-2 and A-S_E2 mechanisms do not allow a mechanistic distinction between these latter two pathways to be made based solely on $\Delta S^{\ddagger}$ alone.[32] This has been emphasized by Schaleger and Long,[33] and the value of $\Delta S^{\ddagger}$ reported herein is given only to show that $\Delta S^{\ddagger}$ for reaction of 1 is consistent with (although not proof for) a mechanism involving rate-determining proton transfer to carbon.

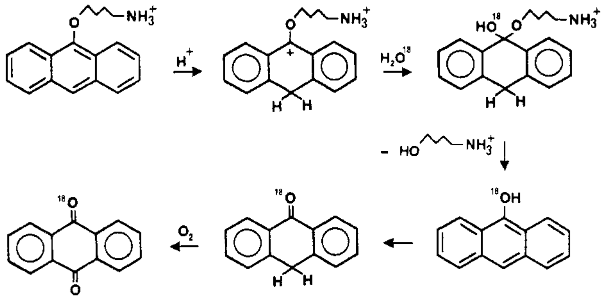
(31) Taft, R. W.; Purlee, E. L.; Riesz, P.; DeFazio, C. A. *J. Am. Chem. Soc.* **1955**, *77*, 1584.

(32) Willi, A. V. In *Comprehensive Chemical Kinetics*"; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: New York, 1977.; Vol. 8.

(33) Schaleger, L. L.; Long, F. A. *Adv. Phys. Org. Chem.* **1963**, *1*, 1.

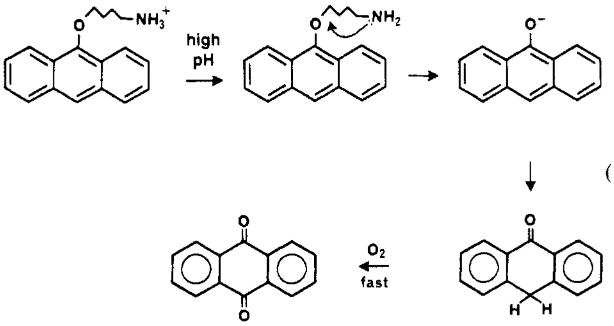
deuterated anthrone can be explained only by exclusive proton transfer at the 10-position, with an intramolecular isotope effect of ~2.8 for proton loss upon collapse of the oxonium intermediate. Protonation at other ring positions (not shown) has been found to be significantly slower than the ortho and para sites[34,35] and so does not complicate the isotope incorporation analysis.

The site of water attack on the oxonium ion intermediate can also be deduced from the deuterium incorporation experiments mentioned earlier and from ^{18}O-incorporation experiments. It is shown that water does not attack the alkyl side chain of the oxonium intermediate since, if it did, α-carbon attack would release 100% H,D-anthrone when the reaction is carried out in D^+/D_2O, contrary to the 74% doubly deuterated anthrone observed experimentally. Further, when the acid-catalyzed hydrolysis reaction of 1 was carried out in ^{18}O-isotopically labeled water (87% isotopic purity), the ^{18}O content of the product (anthrone) was identical (87 ± 1%) to the ^{18}O content of the $H^+/H_2{}^{18}O$, indicating that $H_2{}^{18}O$ attack must occur at the 9-position of the oxonium intermediate, as shown in eq 9.



(9)

Base-Catalyzed Hydrolysis of 9-Anthryl Ethers. Hydrolysis of 1 in basic solution is pH-independent and can be explained by an intramolecular displacement reaction whereby the free amine group attacks the alkyl carbon adjacent to the oxygen, as shown in eq 10. This mechanism accounts for the large increase in reaction rate from pH 7 to pH 10 and the plateau region at high pH in the log (rate)–pH profile (Figure 1). Above pH 10, hydrolysis of 1 is first order in free amine and zero order in both protonated amine and hydroxide ion. The plateau region at high pH has other kinetically equivalent reactions such as the spontaneous (or water-catalyzed) hydrolysis of 1-NH_2; however, they are not consistent with formation of the cyclic amine, pyrrolidine. This product results from intramolecular amine attack on the α-carbon and is favored by the five-membered ring transition state. Anthraquinone is detected as the other major product for this reaction because the anthrol formed from the ether hydrolysis reaction is rapidly converted to anthraquinone in the presence of hydroxide ion and molecular oxygen.[36]



(10)

The effect of alkyl chain length on the k_N rate constants for anthryl ether hydrolysis further supports the mechanism of eq 10. It was found that 1 reacted ~35-fold faster than the 3-methylene derivative ($k_N = 1.5 \times 10^{-7}\ s^{-1}$) and ~15 times faster than the 5-methylene analogue ($k_N = 3.6 \times 10^{-7}\ s^{-1}$) when the pseudo-first-order rate constants for these were determined at 80 °C in 0.1 M KOH, i.e., in the plateau region at high pH. The relative rates of k_N at 80 °C for the 3-, 4-, and 5-methyleneanthryl ethers (1:35:3, respectively) show the same relative ordering of reactivity for intramolecular cyclization as observed previously for bromoalkylamines,[37,38] chloroalkylamines,[39] aminoalkyl sulfates,[40] bromoalkyldimethylamines,[41] and other chainlike compounds possessing an amino group and a good leaving group.[42-44]

Conclusion

9-Anthryl ethers are a special subclass of aryl alkyl ethers in that acid-catalyzed hydrolysis occurs by rate-determining proton transfer to carbon rather than by preequilibrium protonation of oxygen, as is observed for other aryl ethers. Anthryl ether hydrolysis has been observed at all pHs, and catalysis has been detected with general acids and bases and possibly water.[45] This study delineates some of the aqueous reaction conditions under which 9-anthroxy-protected alcohols/anthryl ethers are reactive and shows that, under acid conditions, the 9-anthroxy group behaves more like a vinyl ether than an aryl ether.

Experimental Section

Materials. Anthryl ether 1 and its 3- and 5-methylene analogues were prepared by the Institute of Organic Chemistry (Syntex Research) as follows: For the synthesis of 1 an approximate 4-fold excess of 4-chlorobutanol was refluxed for 5 h with anthrone in toluene containing a trace of sulfuric acid catalyst. The resulting 1-chloro-4-(9-anthroxy)butane was treated with phthalimide potassium salt to replace chlorine, giving the phthalimide derivative. After solvent removal and isolation, this derivative was refluxed in EtOH with a slight molar excess of hydrazine for approximately 4 h; the free amine was then converted to the acetate salt with acetic acid. 1: mp 155.5–157.5 °C. Elemental analysis. Calcd: C, 73.86, H, 7.14, N, 4.31. Found: C, 73.73, H, 7.15, N, 4.26. ^1H NMR (ppm): 8.34 (s) [10-H]; 8.24 (m), 7.53 (m) [ring]; 4.16 (t) [$-OCH_2-$]; 2.83 (t) [$-CH_2NH_2$]; 2.05 (t of t), 1.85 (t of t) [$-CH_2-$]; 1.80 (s) [acetate]. Typically, 1 was handled as the acetate or hydrochloride salt because of the greater stability of the salts over the free base form. Anthrone (2), anthraquinone (3), chloroacetic acid, dichloroacetic acid, sodium heptanesulfonate, phenyl isothiocyanate, 4-amino-1-butanol, pyrrolidine, KH_2PO_4, H_3PO_4, D_2O, DCl, and NaCl were of the highest grade commercially available (Aldrich or Mallinckrodt) and were used without further purification. Oxygen-18-labeled water (90% isotopic purity) was obtained from Merck, Sharpe and Dohme; sufficient HCl was added to make the final ^{18}O abundance 87%. The mobile phase was prepared from HPLC-grade methanol, tetrahydrofuran (Burdick and Jackson), and distilled, deionized water. Standard solutions of HCl and NaOH (Baker Analytical) and commercially available buffer solutions (Anachemia or Radiometer) were used for the preparation and

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pH determination of the acetate buffer solutions.

Apparatus. The separation and kinetic analysis of **1**, **2**, and **3** was carried out on an HPLC system consisting of a Micromeritics Model 725 autoinjector, Model 110A Altex pump, SP Model 770 spectrophotometric detector, and an SP 4000 computing integrator. The following RP-HPLC conditions provided a linear response throughout the range of 0.015–1.5 μg injected: column, Whatman Partisil 5 ODS 3 (25 × 0.4 cm, 5 μm); mobile phase, methanol–0.01 M phosphate buffer (pH 4)–tetrahydrofuran (47.5:40:12.5, v/v); flow rate, 1 mL/min; detection, 253 nm; typical retention times, **1**, 10.5 min; **2**, 14 min; **3**, 15.7 min; 3-methylene analogue of **1**, 8.6 min; 5-methylene analogue of **1**, 12.6 min. pHs were determined on a Radiometer PHM 64 pH meter and Model GK2401C combination electrode. Electron impact mass spectra were obtained on a Varian MAT 1125 or 311A direct inlet mass spectrometer.

Kinetics. In order to obtain pseudo-first-order kinetics, the buffer concentration ($\sim$0.01–0.15 M, $\mu = 0.15$) was always maintained in excess over the anthryl ether concentration ($\sim 1.0 \times 10^{-5}$ M). In a typical experiment, 5-mL aliquots of reaction solution containing a small amount (3.25 μg/mL) of the acetate salt of **1** were transferred to pretreated amber ampules, flame-sealed, and stored at 25, 40, 60, and 80 °C. At known time intervals, ampules were removed from the constant-temperature bath and refrigerated. Upon removal of the last sample, the stored samples were then all analyzed on the same day. Usually, 8–12 samples per kinetic run were collected, and the peak area integrations were converted to concentrations or percent remaining values by use of linear response calibration curves determined for solutions of known concentration of **1**, **2**, and **3**.

pK_a Determinations. The pK_a value for **1** was determined at 25 °C by the solubility–ionization method of Albert and Serjeant[46] using 0.001 M phosphate buffer with an ionic strength of 0.15 M (NaCl). pK_as at higher temperatures (40, 60, and 80 °C) were obtained from a four parameter (k_{H^+}, k_0, k_N, and K_a) fit[15] of the pH–rate profiles.

Product Identification. Large scale separation and collection of **2** and **3** was carried out by using the aforementioned HPLC method except that methanol–water–tetrahydrofuran (44:44:12, v/v) was used for the HPLC mobile phase. The positive identification of **2** and **3** was confirmed by comparison of the UV and electron impact mass spectra and HPLC retention times with authentic samples. Analysis of the amine reaction products derived from the side chain was carried out by quantitative preparation of the phenylthiourea derivative (by reaction of phenyl isothiocyanate and the amine[47]) and then HPLC detection using the same conditions as for **1**.

Isotopic Analysis. The deuterium or ^{18}O incorporation of the product, anthrone, was determined as follows: Approximately 1 mg of **1** was dissolved in either 500 μL of 0.15 M D^+/D_2O or $H^+/H_2{}^{18}O$, the samples were degassed under argon, and then they were stored at 40 °C for 4 days. Under these reaction conditions, anthrone precipitated slowly as needle-like crystals from the reaction solution. These crystals were filtered, washed with water, and analyzed by mass spectroscopy. Control experiments were carried out with both solubilized and suspended anthrone in D^+/D_2O or $H^+/H_2{}^{18}O$ to ensure that anthrone was not susceptible to isotopic exchange under the reaction conditions or that trace amounts of D_2O or $H_2{}^{18}O$ did not give erroneous mass spectral results. The deuterium or ^{18}O content of the anthrone was determined by comparison of the relative intensities of the $M - 1^+$, M^+, and $M + 1^+$ peaks (*m/e* 194 for anthrone). The experimental error on these single isotope determinations was estimated to be less than 2%.

Note Added in Proof: Incubation of **1** in tritiated $H^+/{}^3H_2O$ showed no radiolabeled remaining **1** when **1** was analyzed by radio-HPLC after approximately 1 half-life. This is further evidence for rate-determining proton transfer in this reaction.

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Anionic Phosphorus as a Nucleophile. An Anion Chain Arbuzov Mechanism

L. Gene Spears, Jr., Andrew Liao, David Minsek, and Edward S. Lewis*

The Department of Chemistry, Rice University, Houston, Texas 77251

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The reaction of the anion of dineopentyl phosphonate with alkyl iodides is kinetically second order and yields the P-alkylated dineopentyl alkylphosphonate. This supports, as previously suggested, a simple S_N2 mechanism for the reaction. Rate constants in sulfolane are reported. Trimethyl phosphate and phosphonate esters also alkylate this nucleophile. When dimethyl phosphonate dissolved in tetrahydrofuran or in benzene is treated with solid sodium hydride at room temperature, the initially formed anion is virtually quantitatively alkylated by remaining neutral ester before it can react with sodium hydride, yielding monomethyl phosphonate anion and dimethyl methylphosphonate. This major side reaction is less important with diethyl phosphonate and is not detected with the neopentyl ester. It does not occur with butyllithium as the base or with sodium hydride at −78 °C in either THF or benzene as the solvent. This fast reaction appears to be a surface reaction. The anion of diphenylphosphinite is similarly alkylated by methyl diphenylphosphinite, yielding methyldiphenylphosphine oxide and regenerating the anion, thus constituting a new anionic chain mechanism for the Arbuzov reaction.

The reaction of the anion of diethyl phosphonate with alkyl halides with the formation of a new carbon–phosphorus bond is of considerable synthetic value[1] and is known as the Michaelis–Becker reaction.[2] The anion was made by the ionization of the PH bond by a very strong base, such as an alkyllithium. Only a little work on the mechanism of this reaction has been done. A rough kinetic study[3] agreed with the suggestion[4] that it is a simple S_N2

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