Acid- and Base-Dependent Hydrolysis of *N*-(Sulfonatooxy)-3-bromoacetanilide: Involvement of *N*-(3-Bromophenyl)hydroxylamine-*O*-sulfonate

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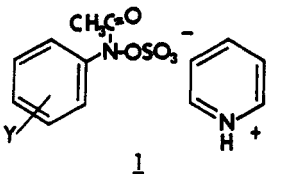
N-(Sulfonatooxy)-3-bromoacetanilide (**1e**) undergoes hydrolysis at 80 °C in the range pH 1.0–8.0 by acid- and base-dependent processes and by an uncatalyzed path. The uncatalyzed reaction exhibits the same characteristics as the uncatalyzed N–O bond-cleavage reactions of the more reactive *N*-(sulfonatooxy)acetanilides. The pH-dependent pathways involve the hydrolysis of **1e** to form *N*-(3-bromophenyl)hydroxylamine-*O*-sulfonate (**2**). This material cannot be directly detected under the conditions of this study, but its existence can be inferred from product study and trapping data. Although **2** undergoes decomposition entirely by heterolytic N–O bond cleavage to yield nitrenium ion intermediate **14**, a less reactive analogue of **2**, *N*-(3-bromophenyl)-*O*-pivaloylhydroxylamine (**4**), apparently undergoes competitive homolytic and heterolytic N–O bond cleavage to yield both the arylamino radical **17** and the nitrenium ion **14**. Both **2** and **4** serve as models for certain suspected carcinogenic metabolites of polycyclic aromatic amines and amides.

A number of polycyclic aromatic amides, including *N*-acetyl-2-aminofluorene and *N*-acetyl-2-aminophenanthrene, have been shown to be converted into potent carcinogens in laboratory animals.[2] It is known that these materials are metabolized, in part, via N-hydroxylation, and there is now considerable evidence that sulfuric acid esters of the resulting *N*-hydroxyamides are among the more important ultimate carcinogenic metabolites of this class of compounds.[2] We have been investigating the chemistry of a series of ring-substituted *N*-(sulfonatooxy)acetanilides (**1**), which serve as models for the polycyclic esters.[3] Our investigations have shown that these model carcinogens decompose in aqueous solution via N–O bond cleavage to yield *N*-acylnitrenium ion–sulfate ion pairs that subsequently undergo internal return or are attacked by nucleophiles and reducing agents.[3] The more reactive members of the series (**1a–d**) undergo hydrolysis in the range pH 1.0–8.0 without acid or base catalysis of the N–O bond-cleavage event.[3a,b] However, preliminary data suggested that the hydrolysis rates of the less reactive members of the series may exhibit moderate pH dependence.[3a] As a result, we commenced a detailed investigation of the hydrolysis of *N*-(sulfonatooxy)-3-bromoacetanilide (**1e**). The results of that study are reported herein.

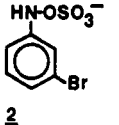


1

	Y
1a	p-CH_3
b	H
c	p-Cl
d	p-Br
e	m-Br
f	3,4-diCl

In the range pH 1.0–8.0, the hydrolysis of **1e** at 80 °C does exhibit both hydronium and hydroxide ion dependent processes, as well as a significant pH-independent reaction. The pH-independent reaction has characteristics that are essentially identical with those previously exhibited by the hydrolyses of **1a–d**.[3] Both the acid- and base-dependent reactions, which become significant at pH <3.5 and >6.5, respectively, apparently involve hydrolysis of the amide bond of **1e** to generate *N*-(3-bromophenyl)hydroxylamine-*O*-sulfonate (**2**). This reactive intermediate is not directly detectable under the conditions of this study, but its existence can be inferred from an examination of reaction products and KI-trapping experiments.

All available evidence indicates that **2** decomposes by heterolysis of the N–O bond to generate a nitrenium ion intermediate. The same intermediate apparently is generated during the Bamberger rearrangement[4] of *N*-(3-bromophenyl)hydroxylamine (**3**), a reaction that yields product mixtures very similar to those obtained from **2**. Although we were not able to synthesize **2**, we have made a less reactive analogue, *N*-(3-bromophenyl)-*O*-pivaloylhydroxylamine (**4**). Preliminary studies have shown that **4** also decomposes in aqueous solution in part via a heterolytic process although there is a competing decomposition pathway that apparently involves radical[5] or radical-cation[6] intermediates.



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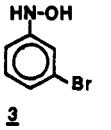

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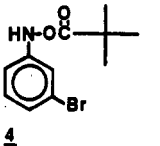

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Since there is evidence that some of the metabolic activation pathways for carcinogenic polycyclic aromatic amides and amines involve the formation of deacylated materials similar to **2** and **4**,[7] the chemistry of these

(1) (a) Miami University. (b) Clark University.

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transient species is of considerable interest.

Experimental Section

The synthesis, characterization, and handling of **1e** have been described previously.[3a] All solvents used in synthetic procedures or product studies were reagent grade and were purified, if necessary, by commonly known methods. Me_4Si or DSS were used as the internal standard for NMR spectra.

Kinetic Measurements. Kinetics were performed in 5 vol % CH_3CH–H_2O or CD_3CN–D_2O solutions. General procedures and methods for following the progress of reactions by UV absorption spectroscopy and HPLC methods have been previously described.[3a,b] Kinetic measurements were performed at 80.0 ± 0.1 °C at pH 1.0–8.0 in HCl solutions and in acetate and phosphate buffers, all maintained at 0.5 M ionic strength with KCl. Corresponding measurements were made in deuteriated solutions that employed equivalent buffer systems and the same ionic strength. All pH or pD measurements were taken at 80.0 ± 1.0 °C with an Orion Model 801 digital pH meter equipped with a Radiometer Model GK 2402C combination electrode. Measurements on standardized solutions of HCl showed no difference between pH (as determined by titration) and the pH meter reading. Similar measurements on standardized DCl solutions provided a relationship between pD and pH meter reading:

$$\text{pD} = \text{pH meter reading} + 0.31 \quad (1)$$

Measurements of pH or pD in standardized solutions of KOH or KOD provided pK_w values (on the molarity scale) for the protiated and deuteriated solvents of 12.73 and 13.54, respectively. These values are comparable to pK_w for pure H_2O and D_2O at 80 °C of 12.62 and 13.43 that can be calculated from extrapolation of data obtained at 0–50 °C.[8] The observed values were used in all calculations.

It was necessary to exclude O_2 from the solutions used in the UV studies. This was done as previously described.[9] Kinetic runs were initiated by injection of 15 μL of a 0.01 M solution of **1e** in CH_3CN or CD_3CN into 3 mL of the appropriate buffer, which had incubated at 80 °C for at least 0.5 h in a thunberg cuvette, to obtain initial concentrations of **1e** of 5.0×10^{-5} M. Absorbance vs. time data were fit either to the standard first-order rate equation or to a rate equation for consecutive first-order processes (eq 2) by methods previously described.[3a,b,9] The quality of the fits was satisfactory in all cases.

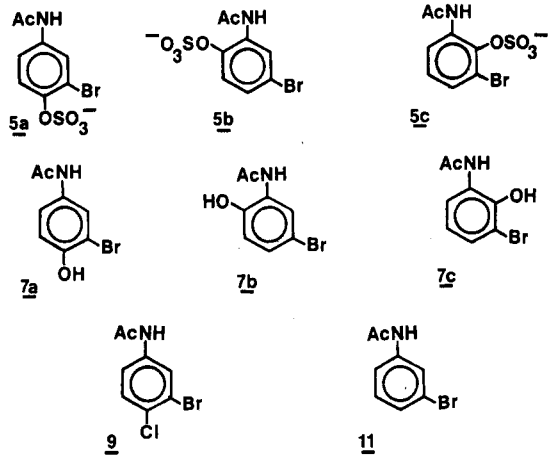
$$A_t = A_1e^{-k_1t} + A_2e^{-k_2t} + A_\infty \quad (2)$$

The kinetics of the decomposition of **1e** and the formation of several of its hydrolysis products were also monitored at 80.0 ± 0.1 °C by HPLC methods that have been described.[3a] Since O_2 was not removed from these solutions, only the formation of products stable to O_2 (below) could be monitored. Reactions were initiated by injection of 250 μL of a 0.1 M solution of **1e** in CH_3CN into 50 mL of the appropriate buffer, which had incubated at 80 °C for 0.5 h, to obtain an initial concentration of **1e** of 5.0×10^{-4} M. At intervals, 5-μL aliquots were removed for HPLC analysis (μ-Bondapak C-18 reversed-phase column, 50/50 MeOH–H_2O, 1 mL/min, UV absorbance monitored at 250 nm). Peak area vs. time data were plotted and fit to the appropriate rate equation.

Product Analyses. Product studies were performed in solutions of the same volume and initial concentration of **1e** as described above for the HPLC kinetic studies. It was necessary to outgas the aqueous solution for several hours with O_2-free N_2 presaturated with 5 vol % CH_3CN–H_2O supplied through a syringe needle inserted into a septum cap covering the flask containing the solution of interest. After incubation for 0.5 h at 80 °C, a CH_3CN solution of **1e** was injected by syringe. Hydrolysis reactions were allowed to proceed for 5 half-lives as calculated from the kinetic data before they were quenched by immersion in an ice–salt water bath followed by extraction with CH_2Cl_2 (2 × 25 mL) and EtOAc (2 × 25 mL). In solutions of pH >3.0 HPLC analysis showed that this extraction removed all organic products except the sulfate esters **5a–c** and **6a–c**. These materials could be isolated as their pyridinium salts by lyophilization of the aqueous solution followed by trituration of the residue with CH_3CN saturated with pyridinium sulfate. Satisfactory methods to separate **5a–c** and **6a–c** could not be found, so they were converted into the corresponding acetamidophenols **7a–c** and aminophenols **8a–c** by heating the CH_3CN solution of their pyridinium salts to boiling as previously described[3a] or by heating in N_2-saturated 1.0 N HCl at 80 °C for 0.5 h. The yields of **5a–c** and **6a–c** could then be determined by HPLC analysis of the resulting mixtures of **7a–c** and **8a–c**.[3a]

The organic-extractable products, except **13**, were separated and purified by methods described elsewhere.[3a] These materials were identified from spectral data and literature comparisons (**7b**, **7c**), by independent syntheses (**7a**, **8a**, **9**, **10**, **11**), by derivatization (**8b**, **8c**), or by comparison with commercially available material (**12**).[10] After identification, product yields were determined by HPLC analysis of the crude organic extracts.[3a] Control experiments showed that the yields of all products except **8a–c** were not affected by the presence of O_2.

Control experiments were performed to test the stability of the acylated products **5a–c**, **7a–c**, **9**, **11**, and **13** to the hydrolysis conditions. Solutions of these materials in CH_3CN were injected into aqueous solutions at pH 1.0 and 7.8 that were subsequently incubated at 80 °C for 5 hydrolysis half-lives of **1e** (40 min at pH 1.0, 8.0 h at pH 7.8). The concentrations of these materials were monitored by HPLC during the course of the incubation, and they were isolated by the methods described above at the end of the incubation. Recovery yields were determined by HPLC methods. The stability of **5a–c** was also monitored at intermediate pH by the same methods.



Detection of *N*-Hydroxy-3-bromoacetanilide (13). This material decomposes very rapidly in aqueous solution at 80 °C and is difficult to isolate from reaction mixtures when produced in low yield so it was necessary to detect it in situ by an HPLC method developed by Corbett.[11] The strong chelator desferyl mesylate (Ciba-Geigy) was added (0.01% w/v) to the 50/50 MeOH–H_2O eluent normally used for HPLC. Under these conditions a sharp peak due to authentic **13**[3a] was detected with a retention time of 10.5 min on the μ-Bondapak C-18 column. This eluent system was used in attempts to detect **13** at pH 1.0 and 7.8 by injection of reaction mixtures during the course of the

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(9) Novak, M.; Pelecanou, M.; Pollack, L. *J. Am. Chem. Soc.* **1986**, *108*, 112–120.

(10) Details of the characterization and synthesis of authentic samples for compounds **7–12** and **16** are available as supplementary material.

(11) Corbett, M. D.; Chipko, B. R. *Anal. Biochem.* **1979**, *98*, 169–177.

hydrolysis of **1e**. The yield of **13** was determined from the observed peak areas for **13**, the known rate constants for hydrolysis of **1e** and **13**, and eq 3, where A_0 is the yield of **13** in appropriate

$$A_0 = B_t/[k_1(k_2 - k_1)^{-1}(e^{-k_1t} - e^{-k_2t})] \quad (3)$$

units, B_t is the measured concentration of **13** at time t, k_1 is the hydrolysis rate constant for **1e**, and k_2 is the hydrolysis rate constant for **13**. The magnitude of k_2 was determined to be (4.0 ± 0.4) × 10^{-4} s^{-1} at both pH values from HPLC data on the hydrolysis of **13**. Hydrolysis rate constants for **1e** can be determined from data in the Results. Decomposition products of **13** were not characterized, but they do not correspond to any of the major hydrolysis products of **1e**. HPLC peaks corresponding to these materials were found in reaction mixtures of **1e** in which **13** had been detected.

NMR Experiments. The progress of the hydrolysis of **1e** was monitored in 0.001 N DCl (μ 0.50 M, KCl) by ^1H NMR (250 MHz) at ca. 80 °C. The DCl solution was prepared from standardized ca. 1.6 M DCl, D_2O (99.8%, Aldrich), and dried KCl. The hydrolysis reaction was initiated by addition of sufficient **1e** to the DCl solution to bring the concentration to ca. 1 mg/mL. The solution was transferred to the probe of the NMR thermostated at ca. 80 °C. FT ^1H NMR spectra were obtained during the course of the reaction by use of a kinetics program written for the Aspect 2000 computer.

Bamberger Rearrangement of *N*-(3-Bromophenyl)-hydroxylamine (3). The rearrangement of **3**[12] was performed in 0.1 N HCl under conditions identical with those used for the hydrolysis of **1e**. The reaction was allowed to proceed for 5 half-lives as calculated from published kinetic data,[4b] before products were isolated and characterized as described above.

***N*-(3-Bromophenyl)-*O*-pivaloylhydroxylamine (4).** A solution of 500 mg of **3**[12] (2.66 mmol) and 0.31 mL of *N*-ethylmorpholine (1 equiv) in 10 mL of dry Et_2O was stirred under N_2 at ca. 0 °C while a solution of 0.33 mL of pivaloyl chloride (1 equiv) in 10 mL of Et_2O was added from a pressure-equalizing funnel over a period of 45 min. The solution was stirred at 0 °C for another 45 min, filtered to remove a white precipitate, washed (2 × 10 mL) with ice-cold saturated aqueous $NaHCO_3$ and then with ice-cold distilled H_2O (10 mL), dried briefly over $MgSO_4$, and evaporated under reduced pressure. The residue was quickly taken up into 1–2 mL of CH_2Cl_2 and subjected to column chromatography (silica gel, CH_2Cl_2 eluent). Fractions containing the desired product were pooled and evaporated under reduced pressure to yield 200–300 mg (28–41%) of an unstable yellow to red oil that solidified upon storage at −70 °C: IR (neat) 3230, 2975, 1740, 1595, 1480, 1275, 1100 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 1.30 (9 H, s), 6.9–7.2 (4 H, m), 8.78 (1 H, s, br); MS, m/e 271 (M^+), 273 ($M + 2^+$). The compound was 95–98% pure by HPLC and ^1H NMR analysis, but attempts at further purification led to decomposition. Spectral data are comparable to those of *N*-(4-nitrophenyl)-*O*-pivaloylhydroxylamine, which is considerably more stable.[5] Solutions of **4** in most solvents were unstable at room temperature, but CH_3CN solutions of **4** could be kept frozen at −70 °C for periods of several days without appreciable decomposition. Kinetics and product studies of the decomposition of **4** at pH 1.0 and 4.7 and 40 °C were performed in the same manner as indicated above for **1e**. Initial concentrations of **4** in both sets of studies were ca. 7.0 × 10^{-5} M. One of the decomposition products of **4**, 2-bromo-1,4-benzoquinone (**16**), was too volatile to isolate in the usual fashion.[3a] It was characterized by HPLC comparison to authentic **16**[10] and by reduction to 2-bromo-1,4-dihydroxybenzene, with excess $K_4Fe(CN)_6$. The reduction product was then isolated and characterized by comparison to authentic 2-bromo-1,4-dihydroxybenzene.[10]

Results and Discussion

Repetitive wavelength scans of the hydrolysis of **1e** at 80 °C showed that a simple first-order reaction occurred at all pH >3.5 if care was taken to remove O_2 from the hydrolysis solutions. In the range pH 3.5–6.5 the presence or absence of O_2 had little effect on the repetitive wavelength scans, but at pH >6.5 the presence of O_2 remarkably complicated the kinetic behavior. This was shown (below) to be due to the oxidation of aminophenols that become major hydrolysis products at pH >6.5. Absorbance vs. time data collected at the pH-dependent wavelength of maximum absorbance change (233–295 nm) were fit to the standard first-order rate equation to obtain k_{obsd}, the pseudo-first-order hydrolysis rate constant. Experiments with serial dilutions of acetate and phosphate buffers (0.050–0.0125 M) showed that k_{obsd} was insensitive to buffer concentration at a given pH in the range 3.5–8.0. At pH <3.5 (HCl solutions) repetitive wavelength scans showed more complicated behavior. The initial rapid hydrolysis of **1e** (confirmed by HPLC data) was followed by a process that was ca. 20–30-fold slower. This second process involves the decomposition of one or more of the initial hydrolysis products of **1e** (below). The rate constant for the hydrolysis of **1e**, k_{obsd}, was determined either from a fit of absorbance vs. time data taken at the wavelength of maximum absorbance change to eq 2, the rate equation for two consecutive first-order processes, or by a fit of absorbance vs. time data, taken at an isosbestic point for the second reaction, to the first-order rate equation. Both

Table I. Hydrolysis Rate Constants for *N*-(Sulfonatooxy)-3-bromoacetanilide (1e) Determined by UV Spectroscopic Methods

buffer[a]	pH[b]	k_{obsd},[c] s^{-1}
HCl	1.00	(1.32 ± 0.03) × 10^{-3}
HCl	1.31	(7.08 ± 0.10) × 10^{-4}
HCl	1.63	(3.98 ± 0.03) × 10^{-4}
HCl	2.02	(1.45 ± 0.02) × 10^{-4}
HCl	2.05	(1.27 ± 0.02) × 10^{-4}
HCl	2.35	(9.01 ± 0.19) × 10^{-5}
HCl	2.63	(6.90 ± 0.15) × 10^{-5}
HCl	3.02	(3.75 ± 0.02) × 10^{-5}
HOAc/KOAc	3.64	(2.50 ± 0.06) × 10^{-5}
HOAc/KOAc	4.21	(2.09 ± 0.07) × 10^{-5}
HOAc/KOAc	4.74	(2.03 ± 0.02) × 10^{-5}
HOAc/KOAc	5.22	(1.97 ± 0.05) × 10^{-5}
HOAc/KOAc	5.75	(2.06 ± 0.03) × 10^{-5}
KH_2PO_4/K_2HPO_4	5.76	(2.31 ± 0.10) × 10^{-5}
KH_2PO_4/K_2HPO_4	6.24	(2.68 ± 0.06) × 10^{-5}
KH_2PO_4/K_2HPO_4	6.80	(2.98 ± 0.04) × 10^{-5}
KH_2PO_4/K_2HPO_4	7.25	(5.09 ± 0.04) × 10^{-5}
KH_2PO_4/K_2HPO_4	7.77	(1.10 ± 0.08) × 10^{-4}
KH_2PO_4/K_2HPO_4	7.89	(1.24 ± 0.07) × 10^{-4}

[a] Conditions: 5 vol % CH_3CN–H_2O, μ 0.50 M (KCl); T = 80.0 ± 0.1 °C. [b] ±0.02 at 80 °C. [c] The values in HCl solutions are averages of two rate constants calculated from data taken at two different wavelengths as described in the text. The values in acetate and phosphate buffers are averages of four rate constants taken from buffers in the concentration range 0.0125–0.050 M at each pH.

Table II. Hydrolysis Rate Constants for 1e in CD_3CN–D_2O Determined by UV Spectroscopic Methods

buffer[a]	pD[b]	k_{obsd},[c] s^{-1}
DCl	1.00	(1.81 ± 0.01) × 10^{-3}
DCl	2.07	(1.78 ± 0.02) × 10^{-4}
DCl	2.99	(3.76 ± 0.10) × 10^{-5}
DOAc/KOAc	4.00	(1.99 ± 0.05) × 10^{-5}
DOAc/KOAc	4.76	(1.70 ± 0.02) × 10^{-5}
DOAc/KOAc	5.68	(1.59 ± 0.02) × 10^{-5}
DOAc/KOAc	6.21	(1.70 ± 0.02) × 10^{-5}
KD_2PO_4/K_2DPO_4	6.28	(1.63 ± 0.02) × 10^{-5}
KD_2PO_4/K_2DPO_4	7.24	(2.24 ± 0.02) × 10^{-5}
KD_2PO_4/K_2DPO_4	8.26	(6.30 ± 0.13) × 10^{-5}
KD_2PO_4/K_2DPO_4	8.38	(8.46 ± 0.30) × 10^{-5}

[a] Conditions: 5 vol % CD_3CN–D_2O, μ 0.50 M (KCl); T = 80.0 ± 0.1 °C. [b] ±0.02 at 80 °C. [c] Each rate constant is the result of a single determination; buffer concentrations were 0.05 M.

(12) Haworth, R. D.; Lapworth, A. *J. Chem. Soc.* **1921**, *119*, 768–777; *Ibid.* **1925**, *127*, 2970.

Table III. Derived Rate Parameters for the Hydrolysis of 1e[a]

solvent	$10^2k_H(k_D)$, M^{-1} s^{-1}	10^5k_0, s^{-1}	$k_{OH}(k_{OD})$, M^{-1} s^{-1}
5 vol % CH_3CN–H_2O	1.50 ± 0.08	2.03 ± 0.05	8.59 ± 0.88
5 vol % CD_3CN–D_2O	1.91 ± 0.14	1.63 ± 0.02	10.06 ± 0.89
k_{H_2O}/k_{D_2O}	0.79 ± 0.07	1.25 ± 0.03	0.85 ± 0.12

[a] Parameters obtained from a weighted least-squares fit to eq 4.

Table IV. Hydrolysis Rate Constants for 1e Determined by HPLC Methods[a]

pH[b]	matl obsd	k_{obsd}, s^{-1}
2.10	1e	(1.19 ± 0.09) × 10^{-4}
3.58	7a	(2.06 ± 0.16) × 10^{-5}
4.73	7a	(2.16 ± 0.22) × 10^{-5}
5.74	7a	(2.23 ± 0.14) × 10^{-5}
7.25	7a	(5.18 ± 0.14) × 10^{-5}
7.89	7a	(1.27 ± 0.08) × 10^{-4}

[a] Conditions are the same as in the UV spectroscopic studies except for higher initial concentrations of 1e (5.0×10^{-4} M). [b] ±0.02 at 80 °C.

methods gave comparable results. The values of k_{obsd} obtained at various pH are listed in Table I. The rate constants obtained in an analogous fashion in deuteriated solution are shown in Table II. The logarithms of k_{obsd} are plotted vs. pH in Figure 1. Data previously reported for the hydrolysis of *N*-(sulfonatooxy)-4-methylacetanilide[3b] are also shown in Figure 1 for comparison purposes. It is obvious that k_{obsd} for 1e contains terms dependent on $[H^+]$ and $[OH^-]$ as well as a pH-independent term. A nonlinear least-squares fit of k_{obsd} to eq 4 gave

$$k_{obsd} = k_H[H^+] + k_0 + k_{OH}[OH^-] \quad (4)$$

a satisfactory result. Table III contains the derived rate parameters obtained from a fit of both the H_2O and D_2O data to eq 4. The value of k_0 in H_2O [(2.03 ± 0.05) × 10^{-5} s^{-1}] is in good agreement with the rate constant of 1.9 × 10^{-5} s^{-1} reported earlier for the uncatalyzed hydrolysis.[3a] The previously reported value was based on fewer data points. Solvent isotope effects, k_{H_2O}/k_{D_2O}, listed in Table III, are inverse for k_H and k_{OH} and normal for k_0.

The hydrolysis kinetics were also followed by HPLC methods in part to verify the results obtained by UV spectroscopy. At pH 2.10 the disappearance of 1e was followed; at all other pH values the appearance of 4-acetamido-2-bromophenol (7a) was monitored. Peak area vs. time data fit the first-order rate equation well in all cases. The values of k_{obsd} obtained in this manner are shown in Table IV and plotted in Figure 1. Examination of the rate constants obtained by the two methods shows

Table V. Yields of Hydrolysis Products of 1e in 5% CH_3CN–H_2O at 80 °C[a]

product	0.1 N HCl, μ 0.5 M (KCl), pH 1.0	0.1 N HI, μ 0.5 M (KI), pH 1.0	1:1 HOAc–KOAc,[b] μ 0.5 M (KCl), pH 4.7	9:1 KH_2PO_4–K_2HPO_4,[b] μ 0.5 M (KCl), pH 5.8
4-(sulfonatooxy)-3-bromoacetanilide (5a)	c	c	2.6 ± 0.1	3.0 ± 0.1
2-(sulfonatooxy)-5-bromoacetanilide (5b)	c	c	36.2 ± 3.2	36.0 ± 2.2
2-(sulfonatooxy)-3-bromoacetanilide (5c)	c	c	16.5 ± 2.5	16.6 ± 1.5
4-(sulfonatooxy)-3-bromoaniline (6a)		e		
2-(sulfonatooxy)-5-bromoaniline (6b)	7.4 ± 0.4	e		
2-(sulfonatooxy)-3-bromoaniline (6c)	0.14 ± 0.02	e		
4-acetamido-2-bromophenol (7a)	0.47 ± 0.04	0.21 ± 0.01	29.9 ± 1.5	28.5 ± 0.7
2-acetamido-4-bromophenol (7b)	0.30 ± 0.10	0.18 ± 0.01	1.3 ± 0.1	0.98 ± 0.12
2-acetamido-6-bromophenol (7c)	0.18 ± 0.06	0.12 ± 0.05	0.93 ± 0.08	0.27 ± 0.09
4-amino-2-bromophenol (8a)	52.6 ± 2.0	28.8 ± 0.8		1.9 ± 0.3
2-amino-4-bromophenol (8b)	9.3 ± 0.6	8.0 ± 0.5		
2-amino-6-bromophenol (8c)	4.0 ± 0.2	3.8 ± 0.3		
3-bromo-4-chloroacetanilide (9)[f]			2.1 ± 0.3	2.1 ± 0.3
3-bromo-4-chloroaniline (10)[f]	3.7 ± 0.2			
3-bromoacetanilide (11)		0.22 ± 0.01		
3-bromoaniline (12)		26.1 ± 1.0		
N-hydroxy-3-bromoacetanilide (13)	3.6 ± 0.7	e	c	c

product	9:1 KH_2PO_4–K_2HPO_4,[b] μ 0.5 M (KI), pH 5.8	1:9 KH_2PO_4–K_2HPO_4,[b] μ 0.5 M (KCl), pH 7.8	1:9 KH_2PO_4–K_2HPO_4,[b] μ 0.5 M (KI), pH 7.8
4-(sulfonatooxy)-3-bromoacetanilide (5a)	2.8 ± 0.3	0.55 ± 0.05	e
2-(sulfonatooxy)-5-bromoacetanilide (5b)	37.4 ± 2.5	5.8 ± 0.5	e
2-(sulfonatooxy)-3-bromoacetanilide (5c)	14.8 ± 1.2	2.5 ± 0.5	e
4-(sulfonatooxy)-3-bromoaniline (6a)		tr[d]	e
2-(sulfonatooxy)-5-bromoaniline (6b)		17.0 ± 1.9	e
2-(sulfonatooxy)-3-bromoaniline (6c)		5.5 ± 0.9	e
4-acetamido-2-bromophenol (7a)	15.1 ± 0.9	4.8 ± 0.1	3.0 ± 0.1
2-acetamido-4-bromophenol (7b)	0.77 ± 0.13	tr[d]	tr[d]
2-acetamido-6-bromophenol (7c)	0.27 ± 0.03		
4-amino-2-bromophenol (8a)	1.1 ± 0.2	41.2 ± 3.0	19.6 ± 0.8
2-amino-4-bromophenol (8b)		2.1 ± 0.1	1.4 ± 0.1
2-amino-6-bromophenol (8c)		0.44 ± 0.03	0.30 ± 0.09
3-bromo-4-chloroacetanilide (9)[f]		0.24 ± 0.07	
3-bromo-4-chloroaniline (10)[f]		2.5 ± 0.1	
3-bromoacetanilide (11)	10.7 ± 0.5		1.4 ± 0.3
3-bromoaniline (12)	1.0 ± 0.1		10.6 ± 0.9
N-hydroxy-3-bromoacetanilide (13)	c		e

[a] Initial concentration of 1e was ca. 5.0×10^{-4} M. Yields, reported with respect to 1e initially present, were determined by HPLC methods. These reactions were run in the absence of O_2. [b] Total buffer concentration 0.05 M. [c] Not determined due to product instability. [d] Less than 0.1%. [e] Not determined. [f] This material was always accompanied by much smaller amounts of two products that appear to be its isomers. These products were not characterized due to very low yields.

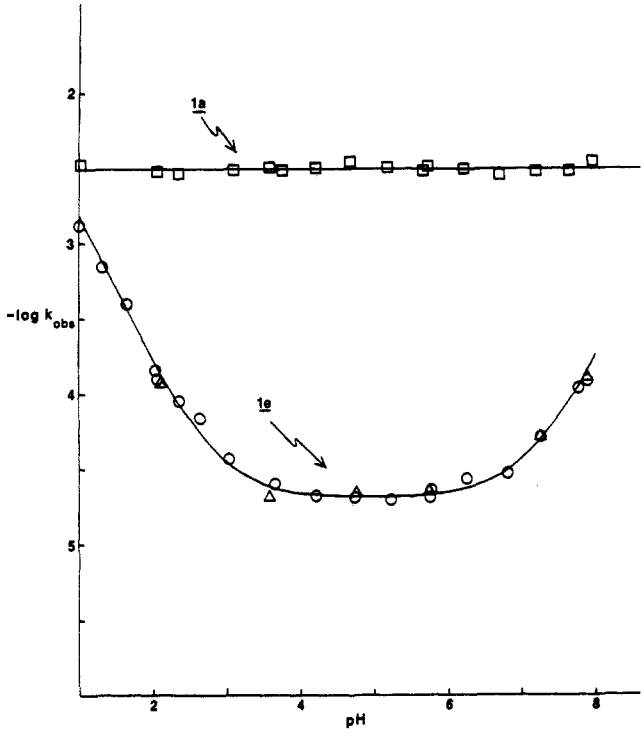


Figure 1. log k_{obsd} vs. pH for **1a** (at 40 °C) and **1e** (at 80 °C). Data for **1a** are from ref 3b. Data for **1e** were obtained by UV spectrophotometry (circles) and HPLC methods (triangles). Theoretical curve for **1e** was obtained by a least-squares fit of the rate data to eq 4.

that there is good agreement between the two sets of values.

The results of product studies performed under various conditions are reported in Table V. The yields reported in Table V were obtained by HPLC analysis of reaction mixtures after 5 hydrolysis half-lives of **1e**. The aminophenols **8a–c** can only be detected at pH ≥3.0 if the hydrolysis reaction is run under O_2-free conditions. Even at pH 1.0 the yields of **8a–c** are reduced by 10–20% in the presence of O_2. Experiments with authentic **8a** at pH 7.8 showed that it rapidly decomposed at 80 °C in the presence of O_2 to yield highly colored materials that were not characterized. The increase in absorbance measured at λ >300 nm as **8a** decomposed was also observed when **1e** decomposed at pH 7.8 in the presence of O_2. Since the yields of the other hydrolysis products are insensitive to the presence of O_2, it is apparent that O_2 does not react directly with **1e** or any of its hydrolysis intermediates but simply oxidizes **8a–c** after they are formed. The data in Table V show that various acetanilide derivatives (**5a–c**, **7a–c**, **9**, **11**) predominate in the pH region in which k_0 primarily governs the reaction rate, while deacylated materials (**6a–c**, **8a–c**, **10**, **12**) are produced in the pH regions in which k_H and k_{OH} govern.

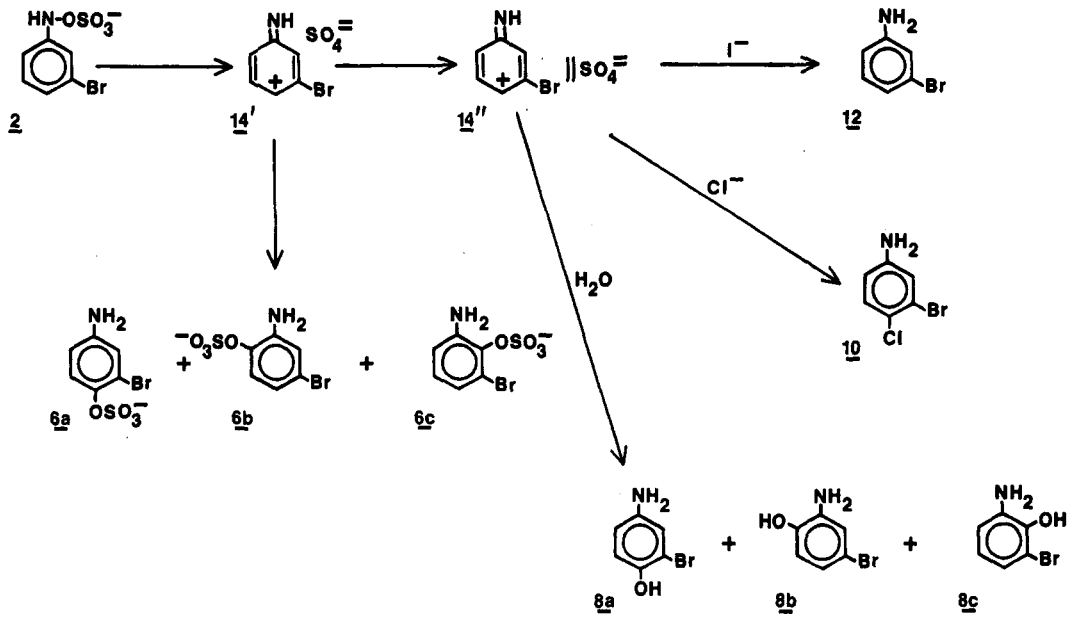
The sulfate esters **5a–c** undergo hydrolysis under the experimental conditions to form the acetamidophenols **7a–c**. It was possible to follow the kinetics of hydrolysis of **5b** and **5c** by HPLC monitoring of the appearance of **7b** and **7c** when mixtures of **5a–c**, isolated from product studies, were subjected to the hydrolysis media. The concentration of **5a** in these mixtures was too low to obtain reliable kinetic results, but it appeared to undergo hydrolysis at rates similar to **5b**. Both **5b** and **5c** were subject to acid-catalyzed and uncatalyzed hydrolysis. Rate constants (approximately 20% errors) for the acid-catalyzed hydrolysis of **5b** and **5c** were 0.6×10^{-2} and 1.1×10^{-2} M^{-1} s^{-1}, respectively, while the rate constants for the uncatalyzed process were 1.0×10^{-8} and 8.0×10^{-8} s^{-1}, respectively. The deacylated sulfate esters **6b** and **6c** undergo hydrolysis to the aminophenols **8b** and **8c**, respectively, with rate constants comparable to **5b** and **5c**. Comparison of these rate constants with those in Table III shows that at pH >3.5 the hydrolysis of **5a–c** and **6a–c** does not interfere significantly with the hydrolysis of **1e**, but at lower pH these processes do become competitive with the hydrolysis of **1e**. Although separate kinetic events were not detected in the UV study and HPLC and UV kinetics results are in good agreement, the hydrolysis of **5a–c** and **6a–c** must interfere to some extent with the measurement of the hydrolysis rates of **1e** under acidic conditions.

The various acetanilide derivatives **7a–c**, **9**, and **11** are stable at pH 7.8. These materials can be recovered in 95–98% yield after 5 hydrolysis half-lives of **1e**. Under acidic conditions they do undergo slow hydrolysis. At pH 1.0 the recoveries of these materials after 5 hydrolysis half-lives of **1e** are reduced to 85–90%. This is consistent with the slow absorbance changes observed under acidic conditions after the hydrolysis of **1e** is essentially complete. In any case, the hydrolyses of **7a–c**, **9**, and **11** are too slow at any pH to account for significant amounts of the deacylated products **8a–c**, **10**, and **12**.

Previously we have shown that **1a–d** undergo hydrolysis by N–O bond cleavage without catalysis to generate intimate and solvent-separated ion pairs.[3] A number of related N–X compounds, where X is a good leaving group, have been shown to decompose in various solvents by similar mechanisms.[9,13–15] The characteristics of the pH-independent hydrolysis of **1e**, which predominates at pH 4.7 and 5.8, are similar to those of **1a–d**, and a mechanism essentially identical with that previously presented[3a,c] can explain this reaction. The rearrangement products **5a–c** are evidently produced by internal return of an intimate ion pair. The average ortho/para product ratio for **5a–c** observed at pH 4.7 and 5.8 of 18.9 ± 1.9 is somewhat larger than that previously observed for *N*-(sulfonatooxy)acetanilide (**1b**; 6.0 ± 0.5)[3a] and is characteristic of an intramolecular process.[16] The lack of any substantial effect on the yields of **5a–c** by the reducing agent I^- at pH 5.8 is also characteristic of the series and indicates that there is little or no return of the solvent-separated ion pair to the intimate ion pair.[3a,c] The effect of I^- on the yields of the other products, and the formation of **11**, shows that the solvent-separated ion pair can be trapped competitively by nucleophiles and reducing agents.[3,17] The ortho/para product ratio for the acetamidophenols **7a–c** cannot be determined with great accuracy since significant amounts of **7b** and **7c** are actually formed by the slow hydrolysis of **5b** and **5c** over the pH range in which k_0 governs the rate. Calculations based on the observed rate constants indicate that ca. 80% of **7c** formed at pH 5.8 is due to hydrolysis of **5c**, while 10% of **7b** produced at this pH is due to hydrolysis of **5b**. At pH 4.7 these proportions are approximately 90% and 30%, respectively. In any case,

(13) Gassman, P. G.; Campbell, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 2567–2569; **1972**, *94*, 3891–3896. Gassman, P. G.; Campbell, G. A.; Frederick, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 7377–7378; **1972**, *94*, 3884–3891.
(14) Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498–1499; **1984**, *106*, 2448–2449.
(15) Underwood, G. R.; Kirsch, R. B. *J. Chem. Soc., Chem. Commun.* **1985**, 136–138.
(16) Hughes, E. D.; Jones, G. T. *J. Chem. Soc.* **1950**, 2678–2684. Neale, R. S.; Scheppers, R. G.; Walsh, M. R. *J. Org. Chem.* **1964**, *29*, 3390–3393.
(17) Parham, J. C.; Templeton, M. A.; Teller, M. N. *J. Org. Chem.* **1978**, *43*, 2325–2330. Parham, J. C.; Templeton, M. A. *Cancer Res.* **1980**, *40*, 1475–1481. Parham, J. C.; Templeton, M. A. *J. Org. Chem.* **1982**, *47*, 652–657. Stroher, G.; Salemnick, G. *Cancer Res.* **1975**, *35*, 122–131.

Scheme I



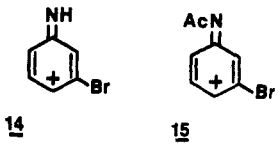
the ortho/para ratio can be no greater than ca. 0.035. The ratio observed for the analogous products of **1b** was 0.046 ± 0.006.[3a] In this case there was no problem with competitive hydrolysis of the rearrangement products since the hydrolysis rate of **1b** is ca. 50-fold greater than that of **1e** under identical conditions. Both of these values are consistent with intermolecular processes.[16] The small amounts of 4-amino-2-bromophenol (**8a**) and 3-bromoaniline (**12**) detected in experiments done at pH 5.8 are likely products of the hydroxide-dependent hydrolysis, which accounts for ca. 4% of the overall hydrolysis rate at this pH, since hydrolysis of the corresponding acetanilides **7a** and **11** is too slow at this pH to account for these materials.

The solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}, for k_0 is 1.25 ± 0.03. Solvent isotope effects for the hydrolysis of alkyl halides are remarkably insensitive to mechanism (S_N1 or S_N2) and generally fall in the range 1.2–1.3.[18] Alkyl sulfonates usually exhibit somewhat smaller solvent isotope effects, ca. 1.1.[18] No similar collection of data is available for the hydrolysis of the N–X bond, and it is clear that the value observed here cannot be used as a diagnostic indicator for a particular mechanism. Nevertheless, the value is in the range that one might expect from an examination of isotope effects for the hydrolysis of the C–X bond.

At pH 1.0 the hydronium ion dependent process (k_H) accounts for >98% of the hydrolysis rate of **1e**, and at this pH the deacylated materials **6a–c**, **8a–c**, and **10** account for the major portion of the hydrolysis products. Since 85–90% of the acetanilide derivatives **7a–c** and **9** are recovered unreacted after 5 hydrolysis half-lives of **1e** at pH 1.0, and the yields of these materials are very low at this pH (Table V), their hydrolysis obviously cannot account for significant amounts **8a–c** or **10**. The sulfate esters **5a–c** do undergo hydrolysis under these conditions, but they are converted into **7a–c**, not **8a–c**. Moderate yields of *N*-hydroxy-3-bromoacetanilide (**13**) indicate that S–O bond cleavage is a minor path that competes with the major acid-catalyzed reaction. When the hydrolysis is performed at pH 1.0 in the presence of 0.5 M I^-, **12** becomes a major product apparently formed predominately at the expense of **8a**. Control experiments showed that I^- does not react with any of the known hydrolysis products of **1e** to generate **12**. Most of the observed yields of the aminophenols **8b** and **8c** at this pH can be accounted for by the hydrolysis of the corresponding sulfate esters **6b** and **6c**.

The formation of **8a–c**, **10**, and **12** is consistent with the competitive nucleophilic attack and reduction of deacylated nitrenium ion **14**. Nucleophilic substitution products analogous to **8a–c** and **10** are generated during the photochemical or thermal decomposition of phenyl azide in acetic acid–ethanol mixtures.[19] The unsubstituted phenylnitrenium ion was proposed as an intermediate in this reaction, and similar intermediates have been invoked to explain nucleophilic substitution reactions of arylhydroxylamines and nitro- or nitrosoarenes.[20] The *N*-*tert*-butyl-*N*-arylnitrenium ions generated during the alcoholysis of *N*-*tert*-butyl-*N*-chloroanilines also gave similar substitution products,[13] and the I^--mediated reduction of nitrenium ions is a well-known reaction.[3,17]

It is unlikely that **14** is formed from the *N*-acylnitrenium ion **15**. This ion is too short lived, and its reactions with nucleophiles and reducing agents are too efficient for acid-catalyzed hydrolysis of **15** to be a viable route to **14**.



In any case, such a process would occur after rate-determining formation of **15** and, therefore, could not account for the observed acid catalysis of hydrolysis of **1e**. We believe that the most reasonable source of **14** is *N*-(3-bromophenyl)hydroxylamine-*O*-sulfonate (**2**), which is formed by acid-catalyzed hydrolysis of the amide bond of **1e**.

At pH 7.8 the uncatalyzed reaction only accounts for 17% of the overall hydrolysis rate, and the combined yield

(18) Laughton, P. M.; Robertson, R. E. *Can. J. Chem.* **1956**, *34*, 1714–1718; **1959**, *37*, 1491–1497. Robertson, R. E.; Laughton, P. M. *Can. J. Chem.* **1957**, *35*, 1319–1324. Treindl, L.; Robertson, R. E.; Sugamori, S. E. *Can. J. Chem.* **1969**, *47*, 3397–3404.

(19) Takeuchi, H.; Koyama, K. *J. Chem. Soc., Chem. Commun.* **1981**, 202–204. Takeuchi, H.; Koyama, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1269–1273.

(20) Abramovitch, R. A.; Jeyaraman, R. In *Azides and Nitrenes*; Scriven, E. F. V., Eds.; Academic: New York, 1984; pp 297–357.

of the acylated products **5a–c**, **7a–c**, and **9** is 13.9 ± 0.7%. The remaining products are formed by the hydroxide-dependent processes (k_{OH}), and they are remarkably similar to the deacylated products formed at pH 1.0. Since all the acylated products are quite stable at this pH, and I^- has the same effect on reaction products that it has at pH 1.0, it appears that **2** is also formed by alkaline hydrolysis of the amide bond of **1e**.

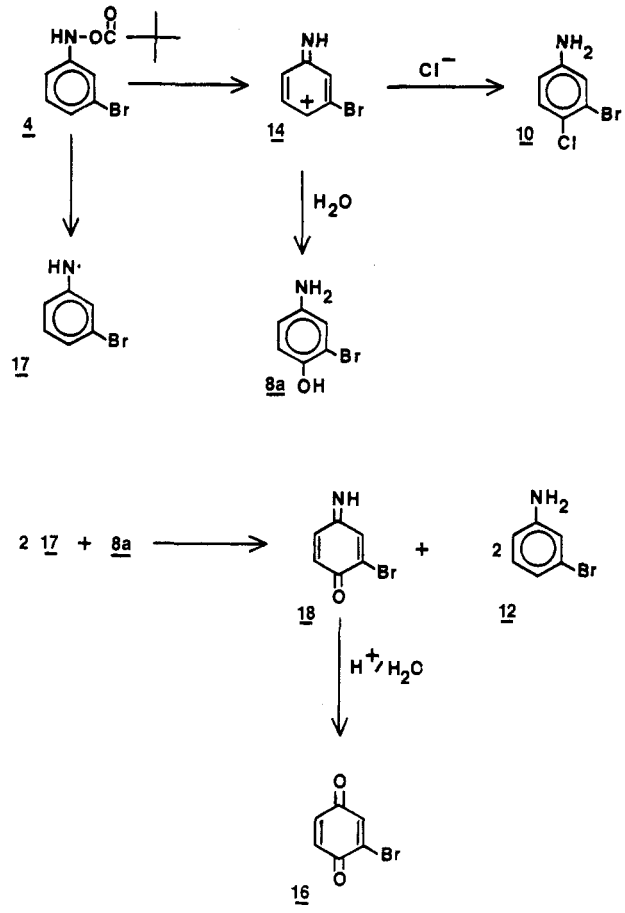
Scheme I presents a mechanism for the decomposition of **2** in aqueous solution, which accounts for our observations. The intimate ion pair **14′** formed by heterolysis of the N–O bond of **2** can undergo internal return to form the sulfate esters **6a–c** or can collapse to the solvent-separated ion pair **14″** that can be attacked by nucleophiles or reducing agents. The high proportion of ortho substitution observed among the sulfate esters **6a–c** is consistent with this mechanism.[3,16] The much lower ortho/para ratio of 0.062 observed for the aminophenols **8a–c** at pH 7.8 is consistent with intermolecular attack of H_2O.[3,16] The apparently higher ortho/para ratio for **8a–c** at pH 1.0 is caused by hydrolysis of **6a–c** to the corresponding aminophenols.

In the uncatalyzed hydrolysis of **1e** the rearrangement products **5a–c** account for ca. 65% of the observed product yield, while **6a–c** account for only about 30–35% of the product yield derived from **2**. This result is consistent with expectations. We have shown previously that under a given set of conditions the yield of rearrangement products decreases as nitrenium ion stability increases.[3] Since **14** is expected to be more stable than **15**, the lifetime of **14′**, the intimate ion pair, will be short relative to the lifetime of **15′**; **14′** will rapidly decay to **14″**, the solvent-separated ion pair; and the proportion of rearrangement products formed will be lower.

The Bamberger rearrangement of *N*-(3-bromophenyl)-hydroxylamine (**3**) should generate the same nitrenium ion, **14**, produced during the decomposition of **2** and should, therefore, produce the same products.[4,20] Although **3** has been reported to yield predominately **8a** when subjected to the rearrangement conditions, detailed product study data were not given.[4b] In 0.1 N HCl under conditions identical with those used for the hydrolysis of **1e**, **3** underwent rearrangement to form **8a** (64.8 ± 3.4%), **8b** (2.3 ± 0.4%), **8c** (0.21 ± 0.05%), **10** (6.7 ± 0.1%), and **12** (1.6 ± 0.1%). The relative yields of the aminophenols **8b** and **8c** produced from **2** at pH 1.0 are larger because significant amounts of these materials are formed by hydrolysis of **6b** and **6c** at this pH. Of course, the sulfate esters cannot be formed from **3**. The relative yields of **8a–c** derived from **2** at pH 7.8, at which **6a–c** are more stable, are very similar to the results obtained for **3** at pH 1.0. The relative yield of **10** derived from both sources is comparable, but **3** also yields a small amount of **12** not generated from **2** in the absence of KI. This may be due to a competing radical process that occurs with **3** but not **2** (below). In the presence of 0.5 M I^- at pH 1.0 a ca. 40% yield of **12** is detected. This result is consistent with observations reported in Table V for the hydrolysis of **1e** under the same conditions.

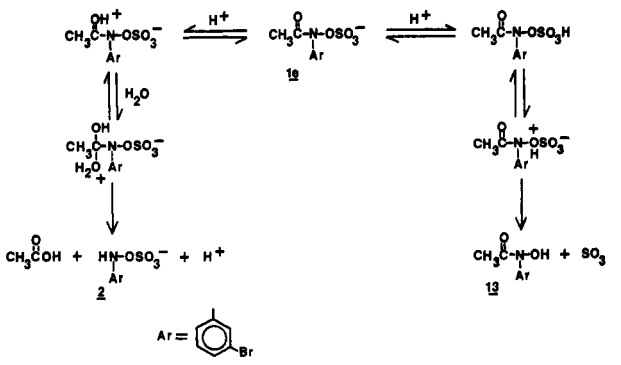
We were not able to detect **2** by spectroscopic methods during the hydrolysis of **1e**, and attempts to synthesize it have failed. However, we have made the more stable analogue *N*-(3-bromophenyl)-*O*-pivaloylhydroxylamine (**4**), and we have performed preliminary hydrolysis studies on this compound. HPLC data indicate that **4** decomposed at 40 °C in pH 1.0 solution with a rate constant of (1.2 ± 0.2) × 10^{-4} s^{-1}, while at 80 °C at the same pH it decomposed with a rate constant of ca. 4.0 × 10^{-3} s^{-1}, which is about 3-fold larger than the rate constant for the decomposition of **1e** under the same conditions. Product studies were performed at 40 °C at an initial concentration of **4** of 7.0 × 10^{-5} M. Under these conditions **10** is detected in a yield of 3.3 ± 0.6%, which is comparable to the yield of the same material in the hydrolysis of **1e** at pH 1.0 (Table V). However, only traces (ca. 0.2%) of **8a** were detected. Two products not formed during the hydrolysis of **1e** under these conditions, **12** (33.0 ± 1.5% yield) and 2-bromo-1,4-benzoquinone (**16**; 15.1 ± 1.5% yield), were detected. An intractable tarry residue was also formed, and this material made up a larger proportion of the products at higher concentrations of **4**. When the hydrolysis of **4** was performed in the presence of added **8a**, the aminophenol was consumed and larger yields of **12** and **16** were produced. When **4** (7.0 × 10^{-5} M) was subjected to hydrolysis at pH 1.0 in the presence of 1.5 equiv of **8a**, the yields of **12** and **16** (based on **4** originally present) increased to 58.7 ± 2.5% and 35.4 ± 5.2%, respectively. The yield of **10** was apparently unaffected at 2.9 ± 0.2%. Similar results were obtained at pH 4.7. A number of as of yet unidentified products were also observed. These may be rearrangement products analogous to **6a–c**.

Scheme II

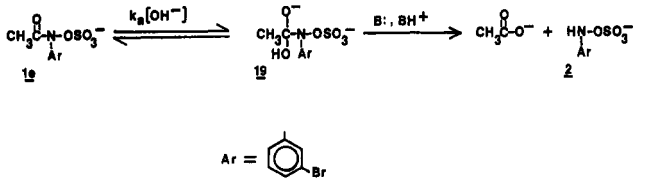


The mechanism of Scheme II can explain these results. The observed products can be accounted for by assuming the existence of competitive heterolytic and homolytic processes that yield **14** and the *N*-arylamino radical **17**. We have previously shown that the *N*-(pivaloyloxy)acetanilides undergo homolysis in benzene to yield acetanilido radicals.[5] However, Hoffman has recently provided evidence that in aliphatic N–OX systems homolysis of a protonated or metalated species may occur to produce not a neutral radical, but a radical cation.[6] Our present data cannot exclude this possibility, but the fact that the reaction

Scheme III



Scheme IV



behaves in much the same way at pH 4.7 as at pH 1.0 argues in favor of the neutral radical. The cation **14** should yield significant amounts of **8a** and **10**. The yield of **10** is comparable to that obtained from **2**, but **8a** is apparently consumed during the hydrolysis of **4** with the corresponding formation of **12** and **16** in a molar ratio of 2/1. Arylamino radicals such as **17** are weak H· acceptors, but they can be reduced by strong donors such as *p*-phenylenediamine and aminophenols.[21] Aminophenols can be oxidized under acidic conditions in two successive one-electron steps.[22] Therefore, **17** and **8a** may react in a 2/1 ratio to yield the quinone imine **18** and **12**. In 0.1 M HCl rapid hydrolysis of **18** will yield **16**.[23] The decrease in the yields of **10**, **12**, and **16** at higher concentrations of **4**, and the corresponding increase in the proportion of tarry products, also argues for a free-radical component to the decomposition of **4**.

Since neither **12** nor **16** is detected in the product mixtures derived from **1e** in 0.1 N HCl, it is apparent that the radical pathway does not occur for **2**. Hoffman has recently shown in aliphatic systems that the proportion of hydrogen abstraction product increases as the leaving group becomes poorer.[6] Systems with good leaving groups react entirely by ionic pathways.[6] In our case sulfate is a much better leaving group than pivalate, so our results are in accord with Hoffman's observations. The small amount of **12** formed during the Bamberger rearrangement of **3** in 0.1 N HCl may indicate that a minor radical pathway also contributes to the reactivity of **3** under these conditions.

A triplet nitrenium ion[24] might also abstract H· from **8a** to yield **12**, but if that were the case, both **2** and **4** should give similar products since the singlet to triplet conversion must occur after ionization. Further studies on **4** and related compounds are in progress and will be reported at a later date.

Typically, the hydrolysis rate constants for *N*-(sulfonatooxy)acetanilides are 300–500-fold larger than those for the corresponding *N*-(pivaloyloxy)acetanilides under the same conditions.[25] In both cases heterolytic N–O bond cleavage is the predominant or exclusive pathway for decomposition. If a similar rate difference holds for the heterolytic pathways of **2** and **4**, and heterolysis represents ca. 20% of the overall rate of decomposition of **4**, then we can estimate that the hydrolysis rate constant of **2** at 80 °C is approximately (2.4–4.0) × 10^{-1} s^{-1}. Since the hydrolysis rate constant for **1e** in 0.1 N HCl is only 1.3 × 10^{-3} s^{-1}, it would clearly not be possible to detect **2** by direct methods under the conditions of our experiments.

A mechanism for the acid-catalyzed hydrolysis of **1e** is shown in Scheme III. Two paths are shown. The minor path (ca. 3.6% of the total) is equivalent to the acid-catalyzed unimolecular decomposition of monosulfate esters.[26] This path accounts for the formation of **13** under acidic conditions. The major path is essentially identical with the currently accepted mechanism for the acid-catalyzed hydrolysis of the great majority of amides.[27] This route leads to **2**. Available data for the hydrolysis of ring-substituted acetanilides in dilute to moderately concentrated acid (<65% H_2SO_4) are consistent with this mechanism.[28]

Both of these mechanisms would show a first-order dependence of hydrolysis rate on $[H^+]$ in dilute acid ($[H^+] \leq 1.0$ M).[26,27] Figure 1 shows that this is, in fact, the case. The solvent deuterium isotope effect for k_H must largely measure the isotope effect on the major pathway. In dilute acid, in which the amide is not fully protonated, the mechanism for amide hydrolysis predicts that an inverse solvent isotope effect should be observed,[27a,b] and this is the case.[29] For example, the solvent isotope effect for the hydrolysis of acetamide at 25 °C in dilute acid is 0.67.[29a] The value observed for **1e** of 0.79 ± 0.07 is in the expected range for amide hydrolysis in dilute acid.[27a,b] The mechanism of Scheme III requires that acetic acid be formed in a first-order manner at the same rate that **1e** disappears. The ^1H NMR experiments in 0.001 N DCl [μ 0.50 M (KCl)] at ca. 80 °C confirmed that the acyl methyl resonance of **1e** (δ 2.31) disappears in a first-order manner as the acyl methyl resonance of acetic acid (δ 2.09, confirmed by comparison to an authentic sample) grows in, also in a first-order fashion. The rate constant for this process [(3.9 ± 0.3) × 10^{-5} s^{-1}] is comparable to k_{obsd} measured spectrophotometrically at pD 3.0 [(3.76 ± 0.10) × 10^{-5} s^{-1}]. Integration of ^1H NMR signals shows that acetic acid accounts for 55 ± 10% of **1e** originally present. At pD 3.0, k_D accounts for 54% of the overall hydrolysis rate of **1e**.

The normally accepted mechanism of alkaline hydrolysis of anilides, shown in Scheme IV for **1e**, involves uncatalyzed addition of OH^- to form the tetrahedral intermediate **19** followed by water-catalyzed, OH^--catalyzed, or general-acid–base-catalyzed breakdown of **19** to products.[27b,30-32]

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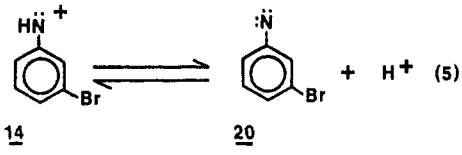
Since no general catalysis, or nonlinear terms in [OH^-], were observed, k_a must be the rate-determining step of alkaline hydrolysis of **1e**. This is unusual at low [OH^-],[30] but not unprecedented.[31] If the magnitude of k_a can be depressed, usually by steric effects, then k_a can be rate determining even at low [OH^-].[31] In the case of **1e** electrostatic repulsion of OH^- and the negatively charged **1e** can provide the basis for lowering the magnitude of k_a. The observed solvent isotope effect, k_{H_2O}/k_{D_2O}, for **1e** of 0.85 ± 0.12 is in general agreement with previous measurements for k_a that are usually in the range 0.6–0.8.[31a,32]

The more reactive esters **1a–d** do not exhibit either acid- or base-catalyzed hydrolysis but undergo uncatalyzed N–O bond cleavage throughout the pH range examined in this study.[3a,b] Preliminary studies have shown that *N*-(sulfonatooxy)-3,4-dichloroacetanilide (**1f**) behaves in much the same way as **1e**. Apparently the catalyzed processes can only be observed when the uncatalyzed heterolysis is suppressed by the presence of strongly electron-withdrawing groups on the ring. The effect of ring substituents on the hydrolysis of anilides is much less pronounced than that observed for heterolysis of the N–O bond of *N*-(sulfonatooxy)acetanilides.[3a,28,30-32]

The nitrene **20** is the conjugate base of the nitrenium ion **14** (eq 5). Arylnitrenes do not exhibit the normal

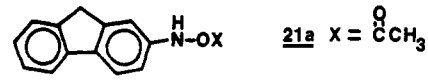


(5)

14 **20**

reactivity patterns of the more reactive alkylnitrenes. When they are generated in protic solvents, they usually undergo nucleophilic aromatic substitution, presumably through the intermediacy of the nitrenium ion or a similar species.[19,20,33] Arylnitrenes formed in the presence of strong nucleophiles such as alkylamines or alkoxides often undergo nucleophilic attack accompanied by ring expansion to produce 3*H*-azepine derivatives.[34] No products of this type were detected in the product studies at either pH 1.0 or 7.8. Hydrolysis of **1e** in a solution of 5 M Et_2NH in H_2O led to a complex mixture of products, but no azepine derivatives were detected.[35] We are currently attempting to trap nitrenes that may be generated during the decomposition of **4** and related compounds in basic media.

The chemistry of **2** and **4** is of considerable interest with respect to the mechanisms of chemical carcinogenesis of aromatic amides and amines. There is evidence that binding of *N*-hydroxy-*N*-acetyl-2-aminofluorene to DNA is activated by N–O acyltransferase, which apparently produces *N*-acetoxy-2-aminofluorene (**21a**).[7a-c,g] There is also evidence that the sulfate derivative **21b** may be a carcinogenic metabolite of *N*-acetyl-2-aminofluorene in infant male mice.[7e] Similar derivatives of a number of polycyclic aromatic amines have been implicated as possible carcinogenic metabolites.[7d,f,h,i] Our results indicate that the primary, if not exclusive, mode of reactivity of the sulfate derivatives will be heterolytic N–O bond cleavage to generate nitrenium ion intermediates. There is likely to be a significant radical component to the reactions of the carboxylic acid esters. These radical pathways may play a role in the carcinogenic behavior of such esters.



21a X = $\overset{O}{\overset{\|}{C}}CH_3$

21b X = SO_3^-

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Supplementary Material Available: Synthesis and characterization of the hydrolysis products (5 pages). Ordering information is given on any current masthead page.

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(35) An authentic sample of 6-bromo-2-(diethylamino)-3*H*-azepine was prepared, for comparison purposes, by deoxygenation of 3-bromonitrosobenzene with triethyl phosphite in Et_2NH–MeOH according to a procedure in ref 33a. No other isomeric azepines were detected in the reaction.