Solvolysis of *N*-Sulfonoxyacetanilides in Aqueous and Alcohol Solutions: Generation of Electrophilic Species

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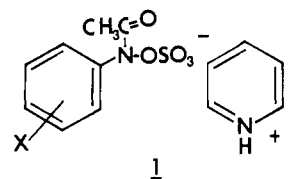
Abstract: A series of ring-substituted *N*-sulfonoxyacetanilides (**1a–f**) were synthesized, and their solvolysis reactions in aqueous and alcohol solvents were studied. These compounds serve as models for the carcinogenic metabolites of polynuclear aromatic amides. Kinetic and product studies yielded evidence for solvolysis via N–O bond cleavage in aqueous solution with generation of tight ion pairs and solvent-separated ion pairs. The tight ion pairs, which cannot be trapped by nucleophiles or reducing agents, give rise to *o*-sulfonoxyacetanilides, while the solvent-separated ion pairs can be trapped by these reagents to yield ring-substituted compounds and reduction products. The para-substituted *N*-sulfonoxyacetanilides yield substantial amounts of highly electrophilic *p*-benzoquinone imine derivatives such as **10** during solvolysis in aqueous media. In ethanol these esters solvolyze exclusively via S–O bond cleavage with apparent production of SO_3. This study demonstrates that electrophilic species other than nitrenium ions can be generated during the solvolysis of *N*-sulfonoxy-*N*-arylamides. These species may play a role in the in vivo activity of these metabolites.

The sulfate esters of *N*-hydroxy-*N*-arylacetamides have been implicated as important carcinogens derived from the hepatic metabolism of polynuclear aromatic amides including *N*-acetyl-2-aminofluorene.[1,2] Although it is widely assumed that these compounds decompose in vivo and in vitro to yield aromatic nitrenium ions which serve as the ultimate carcinogenic electrophiles,[1,3] there is, in fact, little direct evidence for this.[3] Because of the difficulty encountered in synthesizing and purifying these sulfate esters,[2a,c,4] most of the previously reported chemical studies have been performed on their considerably more stable acetate ester analogues.[3] Apart from the esthetic desirability of working with the sulfate esters there is also the real possibility that the two classes of compounds may exhibit significantly different chemistry. In fact, it is already known that the acetate esters undergo rapid acyl transfer reactions under some conditions.[5] Since this possibility was not appreciated until fairly recently, it brings into question many of the conclusions derived from studies on the acetate esters, especially since careful product analyses, with few exceptions,[3c,e] have not been performed in these studies.

Previous attempts to synthesize the sulfate esters have resulted, for the most part, in impure preparations not suitable for use in a careful mechanistic study of the chemistry of these compounds.[4,6] However, we have now succeeded in synthesizing and purifying a series of *N*-sulfonoxyacetanilides **1a–f** as their pyridinium salts, and we have commenced an investigation into the solvolysis reactions of these species in aqueous and alcoholic solvents.



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

In aqueous solution these compounds undergo intramolecular rearrangement reactions and also generate species by N–O bond cleavage which are subject to reduction by a variety of reagents. Most of the results in aqueous solution can be explained by a scheme similar to the Winstein ion-pair mechanism for S_N1 solvolysis of alkyl halides and tosylates,[7] although at this time alternative possibilities cannot be excluded. In alcoholic solvents S–O bond cleavage with apparent generation of SO_3 predominates. The implication of these results with respect to the problem of chemical carcinogenesis is discussed.

Experimental Section

Synthesis and Characterization of 1a–f. The esters were prepared from the corresponding hydroxylamines which can be obtained by reduction of commercially available nitro aromatics according to published procedures.[8] The hydroxylamines can be acetylated with acetyl chloride in anhydrous ether to yield the corresponding *N*-hydroxyacetanilides.[9] Physical and spectral data for these compounds are comparable to those previously reported.[9] Two of these compounds, *N*-hydroxy-*p*-bromoacetanilide and *N*-hydroxy-3,4-dichloroacetanilide, have not been described previously. Data on these compounds are presented below. The final products could be obtained simply by reaction of the *N*-hydroxyacetanilides with pyridine–sulfur trioxide complex (obtained from Aldrich). The pyridinium salts of the sulfate esters were reasonably stable if stored under vacuum over P_2O_5 at −10 °C. The esters were routinely recrystallized (see below) before use. The sulfate esters do not melt

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reversibly, but decompose at temperatures which depend on the rate of heating. Anhydrous ethyl ether was used as obtained; all other solvents were purified according to commonly known procedures. Me_4Si and DSS were used as internal standards for all NMR spectra. Details of the synthetic procedures and data on the compounds follow.

***N*-Hydroxy-*p*-bromoacetanilide**: mp 130–132 °C; IR (KBr) 3140, 2980, 2860, 1620, 1485, 1380 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.13 (3 H, s), 7.2–7.7 (4 H, m, para-substituted aromatic), 8.7 (1 H, s, broad).

***N*-Hydroxy-3,4-dichloroacetanilide**: mp 133–135 °C; IR (KBr) 3140, 2940, 1630, 1480, 1375, cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.16 (3 H, s), 7.25–7.65 (3 H, m), 8.6 (1 H, s, broad).

***N*-Sulfonoxyacetanilide (1b).** *N*-Hydroxyacetanilide (500 mg, 3.3 mmol) was added to a stirred suspension of 1.06 g (6.7 mmol) of pyridine–sulfur trioxide complex in 5 mL of dry CH_2Cl_2 containing 0.8 mL of dry pyridine. The resulting mixture was stirred at room temperature under a positive pressure of N_2. The progress of the reaction was monitored by TLC on silica gel using ether as eluent. After 5 days 10 mL of CH_2Cl_2 were added to the mixture which was then filtered through a sintered glass filter using a dry vacuum. The filter cake was washed with 10 to 15 mL of CH_2Cl_2 and discarded. The filtrate was rotary evaporated under a dry vacuum leaving a gummy oil. This material was kept under a vacuum of at least 10^{-2} mm for several hours before being triturated with 10 mL of anhydrous ether. The material was stirred with the ether under N_2 for 20 to 30 min before the ether was removed by pipet. This procedure was repeated several times until the gummy solid had been transformed into a fine white powder. The powder was taken up in about 15 mL of CH_2Cl_2 and filtered to remove a small amount of insoluble material. The resulting solution was rotary evaporated under a dry vacuum, and the solid which remained was recrystallized from dry CH_3CN to yield white to tan microcrystals of the product. Yields of the purified product ranged from approximately 400 to 700 mg (40–68% of theoretical): IR (KBr) 3250, 3080, 2980, 2880, 1680, 1618, 1490, 1290, 1235, 1050 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.29 (3 H, s), 7.1–7.6 (5 H, m), 7.7–8.9 (5 H, m, pyridinium resonance), 15.0 (1 H, s, broad). Anal. Calcd for $C_{13}H_{14}N_2O_5S$: C, 50.32; H, 4.55; N, 9.03. Found: C, 50.12; H, 4.64; N, 9.06.

The ring-substituted *N*-sulfonoxyacetanilides were synthesized by essentially identical procedures. Physical and spectral data for these compounds follow.

***N*-Sulfonoxy-*p*-acetotoluidide (1a)**: IR (KBr) 3240, 3080, 2980, 2900, 1675, 1605, 1490, 1285, 1240, 1047 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.22 (3 H, s), 2.26 (3 H, s), 7.0–7.5 (4 H, m, para-substituted aromatic), 7.7–8.9 (5 H, m, pyridinium resonance), 15.0 (1 H, s, broad).

***N*-Sulfonoxy-*p*-chloroacetanilide (1c)**: IR (KBr) 3250, 3085, 2970, 2860, 1640, 1492, 1289, 1265, 1048 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 2.32 (3 H, s), 7.27–7.48 (4 H, m, para-substituted aromatic), 7.93–8.72 (5 H, m, pyridinium resonance), 15.65 (1 H, s, broad). Anal. Calcd for $C_{13}H_{13}N_2O_5ClS$: C, 45.29; H, 3.80; N, 8.13; Cl, 10.28; S, 9.30. Found: C, 45.30; H, 3.91; N, 8.05; Cl, 10.47; S, 9.26.

***N*-Sulfonoxy-*p*-bromoacetanilide (1d)**: IR (KBr) 3240, 3080, 2980, 2910, 1683, 1615, 1490, 1290, 1255, 1050 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 2.29 (3 H, s), 7.38 (4 H, s), 7.7–8.9 (5 H, m, pyridinium resonance), 15.0 (1 H, s, broad). Anal. Calcd for $C_{13}H_{13}N_2O_5BrS$: C, 40.12; H, 3.37; N, 7.20; Br, 20.53; S, 8.24. Found: C, 39.97; H, 3.50; N, 7.17; Br, 20.39; S, 8.40.

***N*-Sulfonoxy-*m*-bromoacetanilide (1e)**: IR (KBr) 3245, 3080, 2970, 2880, 1690, 1620, 1490, 1295, 1250, 1040 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 2.36 (3 H, s), 7.18–7.62 (4 H, m), 7.93–8.72 (5 H, m, pyridinium resonance), 15.5 (1 H, s, broad). Anal. Calcd for $C_{13}H_{13}N_2O_5BrS$: C, 40.12; H, 3.37; N, 7.20. Found: C, 40.08; H, 3.42; N, 7.22.

***N*-Sulfonoxy-3,4-dichloroacetanilide (1f)**: IR (KBr) 3245, 3080, 2970, 2860, 1710, 1620, 1465, 1290, 1235, 1040 cm^{-1}; ^1H NMR (60 MHz, D_2O) δ 2.32 (3 H, s), 7.4–7.7 (3 H, m), 7.9–8.9 (5 H, m). Anal. Calcd for $C_{13}H_{12}N_2O_5Cl_2S$: C, 41.17; H, 3.20; N, 7.39. Found: C, 41.33; H, 3.22; N, 7.44.

Kinetic Measurements. All kinetics were performed in 5 vol % CH_3CN–H_2O solutions. All water used in the kinetic studies was distilled, deionized, and then distilled again in an all-glass apparatus. Water was stored in an all-glass container until used for the kinetics. Reagent grade CH_3CN was purified as previously described.[10] The purified CH_3CN was stored in an all-glass container at −10 °C. Kinetic solutions were prepared in volumetric flasks by adding 5 vol % CH_3CN to the appropriate aqueous solution and bringing the resulting solution to volume with water. All solutions containing buffers and HCl were maintained at 0.5 M ionic strength (KCl). The pH of buffer solutions was measured at 40.0 ± 0.1 °C. No corrections were applied to the pH meter reading.

Kinetic data were gathered by monitoring the changes in UV absorbance of solutions containing the sulfate esters. A Cary Model 210 UV–visible spectrometer equipped with thermostated cell holders was used to record absorbance changes. Kinetic measurements were done at 10° intervals between 30.0 ± 0.1 and 80 ± 0.1 °C. Kinetic runs were performed at at least three different temperatures in this range for each of the esters.

The concentration of ester used in this study was ca. 5.0×10^{-5} M which was obtained by injecting 15 μL of a ca. 0.01 M solution of the appropriate ester in CH_3CN into 3.0 mL of the kinetic solution in the thermostated cell holder. Repetitive wavelength scans showed that isosbestic points held for at least 2 half-lives, usually longer. Changes in UV absorbance were monitored at 218 nm for **1a**, 249 nm for **1b**, 249.5 nm for **1c** and **1d**, and 250 nm for **1e** and **1f**. Kinetics performed on **1a–d** in KI solution were monitored at 352 nm which corresponds to the absorption maximum of I_2 in this solvent system. Absorbance by KI made it impossible to monitor the rates of this reaction at the wavelengths used in the other kinetic studies.

Pseudo-first-order rate constants were calculated using a nonlinear least-squares program. A_∞, A_0, and k, the pseudo-first-order rate constant, are treated as variable parameters which are adjusted to optimize the fit of the absorbance vs. time data to the first-order rate equation. In all cases good agreement was obtained between observed and calculated A_0 and A_∞ values. Rate constants calculated by this method are comparable to those determined by more traditional methods. In the case of the KI reactions, calculated A_∞ values were used to determine the concentration of I_2 present at the end of the reaction. In all cases at least 2 half-lives of data (usually 3 to 4 half-lives) were used in the calculations.

Product Analyses. Product studies were performed in 5% CH_3CN–H_2O or in D_2O. A higher ester concentration (ca. 1.25 mM) was employed in these studies than in the kinetic studies. Three different methods were employed.

Method a. The ester, in 500 μL of CH_3CN, was injected into the solution (100 mL) which had been incubating at the appropriate temperature in a water bath for at least 0.5 h. The solution was incubated for 5 to 6 half-lives (as calculated from the rate data), cooled to room temperature, and extracted five times with 50-mL portions of CH_2Cl_2 followed by three extractions with 50 mL of ethyl acetate. This was sufficient to remove all organic products save acetamide and the *o*- or *p*-sulfonoxyacetanilides **4**, **12**, and **13** (see Results). The organic extracts were combined and evaporated to dryness; the residue which remained was subjected to preparative layer chromatography on silica gel (CH_2Cl_2/ethyl acetate eluent). HPLC analysis (μ-Bondapak C-18 reverse-phase column, methanol/water solvent, Beckman Model 155 variable wavelength UV detector) was used to monitor the purity of the solvolysis products isolated in this manner. All the products obtained from the organic extracts are known compounds, and in all cases except **3**, **5**, and **6**, identification was based on direct comparison with commercially available samples of the authentic compound. These three compounds were identified from their IR and NMR spectra, and by comparison of their melting points with literature values.[11]

The water-soluble *o*- and *p*-sulfonoxyacetanilides **4**, **12**, and **13**, which were not extractable into organic solvents, could be isolated from the reaction mixtures after extraction by freeze-drying. The pyridinium salts of these compounds were taken up into CH_3CN to separate them from other materials which remained after freeze-drying. Since the sulfonoxy compounds were difficult to purify, they were characterized and quantified by conversion into the corresponding *o*- or *p*-hydroxyacetanilides **3**, **11**, and **2**. This was accomplished by heating the CH_3CN solutions of the pyridinium salts of **4**, **12**, and **13** to boiling for approximately 20 min. A D_2O solution of 2-sulfonoxy-4-chloroacetanilide (**4**) was prepared for NMR analysis in the following manner. Approximately 10 mg of **1c** were dissolved in 10 mL of D_2O (99.8% deuterated, Aldrich), and the resulting solution was incubated at 40 °C for 8 half-lives. After cooling, the solution was extracted with 10-mL aliquots of ethyl acetate until HPLC analysis showed only the peaks due to **4** and the pyridinium ion. The solution was brought to basic pD by addition of one drop of 30% KOD in D_2O (Aldrich) and extracted again with ethyl acetate to remove pyridine. Finally, the solution was extracted with CH_2Cl_2 to remove traces of ethyl acetate and kept under a dry vacuum at room temperature until the volume of D_2O had been reduced by approximately 50%. DSS was added as an internal standard and the ^1H NMR spectrum was obtained: (250 MHz) δ 2.20 (3 H, s), 7.33 (1 H, dd, J = 2.4, 8.7 Hz), 7.50 (1 H, d, J = 2.4 Hz), 7.65 (1 H, d, J = 8.7 Hz). An identical NMR

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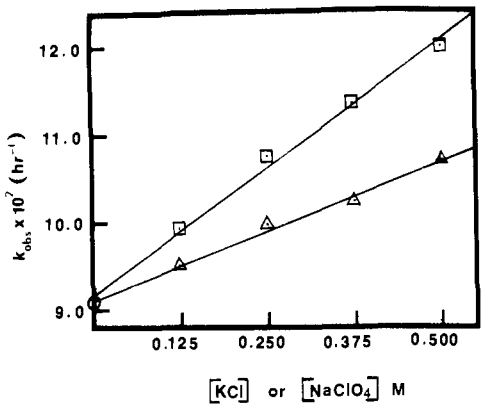


Figure 1. Rate constants for the solvolysis of **1c** in 5% CH_3CN–H_2O vs. concentration of KCl (triangles) or $NaClO_4$ (squares). Lines were calculated from a nonweighted least-squares fit of the data.

spectrum was obtained from **4** synthesized by reaction of **3** with pyridine–sulfur trioxide complex in pyridine/CH_2Cl_2.

Method b. The ester, in 50 μL of CH_3CN, was injected into the solution (10 mL) which had been incubating at the appropriate temperature in a water bath for at least 0.5 h. Aliquots (2 μL) were removed periodically and subjected to HPLC analysis (μ-Bondapak C-18 reverse-phase column, 50:50 methanol/water solvent, UV absorbance monitored at 249 or 225 nm). In this manner the concentration of the products could be monitored as a function of time after calibration with known concentrations of authentic samples. After 5 to 6 half-lives the reaction mixtures were extracted as in method a. The residue remaining after evaporation of the organic solvents was taken up into 5 mL of CH_3CN, and the infinity concentrations of these products were determined from the average of three HPLC runs. The sulfonoxy products **4**, **12**, and **13** were converted into the hydroxyacetanilides **3**, **2**, and **11** as in method a. These materials were then taken up into 5 mL of CH_3CN and their concentrations determined by triplicate runs on the HPLC.

Method c. The solid ester was added to 1 or 2 mL of D_2O. After the ester had gone into solution, an aliquot was removed and placed in an NMR tube. The tube was brought to temperature in the probe of a Bruker WM-250 NMR spectrometer, and FT ^1H NMR spectra were obtained during the course of the reaction using the kinetics program written for the Aspect 2000 computer. The chemical shift region from ca. δ 1.9 to 2.4, which contained methyl resonances of the acetyl group of the starting material and all acetylated products, was most amenable to analysis. Peaks were assigned on the basis of chemical shift comparisons with authentic samples in D_2O at the same temperature. Yields were obtained by integration.

Some of the product studies employed $FeCl_2$ solutions which are oxidized rapidly by air. These solutions were prepared under dry N_2 in an inert atmosphere box from freshly recrystallized $FeCl_2$ and degassed buffer solutions. The appropriate amount of ester and the $FeCl_2$ solution were combined, sealed in a container equipped with a neoprene septum cap, and removed from the glove box. The solution was then incubated at the appropriate temperature, and aliquots were removed at intervals with a syringe and subjected to HPLC analysis.

Studies with *N*-Acetyl-*p*-benzoquinone Imine (10). This compound was prepared according to published procedures[12] and was hydrolyzed in aqueous solutions similar to those used for the product studies on **1b** and **1c**. Product analyses were performed as described above in method b.

Studies in Alcoholic Solvents. The reactions of **1b** and **1c** in ethanol and methanol were studied in much the same manner as in the aqueous solutions. In ethanol product studies were particularly straightforward since only the corresponding *N*-hydroxyacetanilides, **15** and **16**, and ethyl sulfate were detectable as products. Identities of **15** and **16** were confirmed by comparison with authentic material synthesized as described above.

Results

Good pseudo-first-order kinetics were observed in 5 vol % CH_3CN–H_2O at temperatures ranging from 30 to 80 °C for at least 2 half-lives when the reactions of the esters **1a–f** were monitored by UV absorption spectroscopy. Half-lives at 50 °C ranged from approximately 70 s for **1a** to about 2 days for **1f**.

The pseudo-first-order rate constants are pH independent from pH 3.0 to 7.0 and show little sensitivity to buffer concentration in either acetate or phosphate buffers. Table I is a compilation of rate constants observed for the reactions of **1c** under various conditions.[13] The rate constants typically increase by 15 to 35% as the ionic strength is increased from 0.0 to 0.5 M with either KCl or $NaClO_4$. Figure 1 shows that these salt effects are linear

Table I. Pseudo-First-Order Rate Constants for the Solvolysis of **1c** in Aqueous Solution

conditions[a]	temp (°C)	rate constants (h^{-1})[b]
0.5 M KCl	60	$7.80 \pm 0.06 \times 10^{-1}$
0.5 M KCl	50	$2.99 \pm 0.02 \times 10^{-1}$
no added salts	60	$6.00 \pm 0.06 \times 10^{-1}$
no added salts	50	$2.39 \pm 0.01 \times 10^{-1}$
0.5 M KCl	40	$10.70 \pm 0.08 \times 10^{-2}$
0.375 M KCl		$10.21 \pm 0.05 \times 10^{-2}$
0.250 M KCl		$9.98 \pm 0.08 \times 10^{-2}$
0.125 M KCl		$9.52 \pm 0.07 \times 10^{-2}$
0.5 M $NaClO_4$		$11.99 \pm 0.09 \times 10^{-2}$
0.375 M $NaClO_4$		$11.36 \pm 0.07 \times 10^{-2}$
0.250 M $NaClO_4$		$10.75 \pm 0.07 \times 10^{-2}$
0.125 M $NaClO_4$		$9.92 \pm 0.07 \times 10^{-2}$
0.5 M KI[c]		$10.64 \pm 0.04 \times 10^{-2}$
no added salts		$9.08 \pm 0.08 \times 10^{-2}$
9:1 K_2HPO_4/KH_2PO_4 pH 7.63, 0.05 M B_T		$1.58 \pm 0.04 \times 10^{-1}$
1:1 K_2HPO_4/KH_2PO_4 pH 6.66, 0.05 M B_T		$1.50 \pm 0.04 \times 10^{-1}$
1:9 K_2HPO_4/KH_2PO_4 pH 5.67, 0.05 M B_T		$1.68 \pm 0.05 \times 10^{-1}$
9:1 KOAc/HOAc pH 5.63, 0.05 M B_T		$1.13 \pm 0.01 \times 10^{-1}$
1:1 KOAc/HOAc pH 4.68, 0.05 M B_T		$1.25 \pm 0.02 \times 10^{-1}$
1:9 KOAc/HOAc pH 3.68, 0.05 M B_T		$1.01 \pm 0.01 \times 10^{-1}$
0.001 M HCl, pH 3.12		$9.89 \pm 0.05 \times 10^{-2}$
0.0005 M HCl, pH 2.41		$1.08 \pm 0.02 \times 10^{-1}$
0.01 M HCl, pH 2.11		$1.17 \pm 0.03 \times 10^{-1}$

[a] All solutions contained 5 vol % CH_3CN. Ionic strength was maintained at 0.5 M (KCl) in all buffer solutions and HCl solutions. [b] Rate constants were determined as described in the Experimental Section and are reported with their standard deviations. [c] This is the rate constant for the appearance of I_2 as described in the Experimental Section. The decomposition of the ester cannot be monitored directly in KI because of strong absorbance in the UV by the salt.

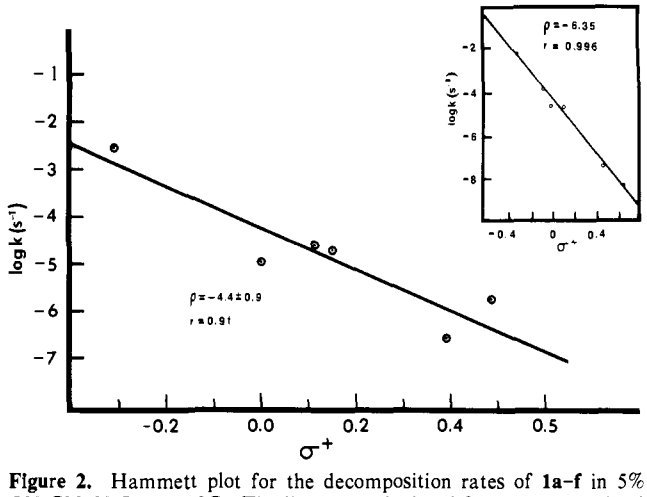


Figure 2. Hammett plot for the decomposition rates of **1a–f** in 5% CH_3CN–H_2O at 40 °C. The line was calculated from a nonweighted least-squares fit of the data. Insert: Hammett plot for ring-substituted *N-tert*-butyl-*N*-chloroanilines in EtOH at 25 °C. Data from ref 13.

(12) (a) Blair, I. A.; Boobis, A. R.; Davies, D. S.; Cresp, T. M. *Tetrahedron Lett.* **1980**, *21*, 4947–4950. (b) Dahlin, D. C.; Nelson, S. D. *J. Med. Chem.* **1982**, *25*, 885–886.

(13) Rate constants for the solvolysis of the other esters under various conditions are available. See Supplementary Material.

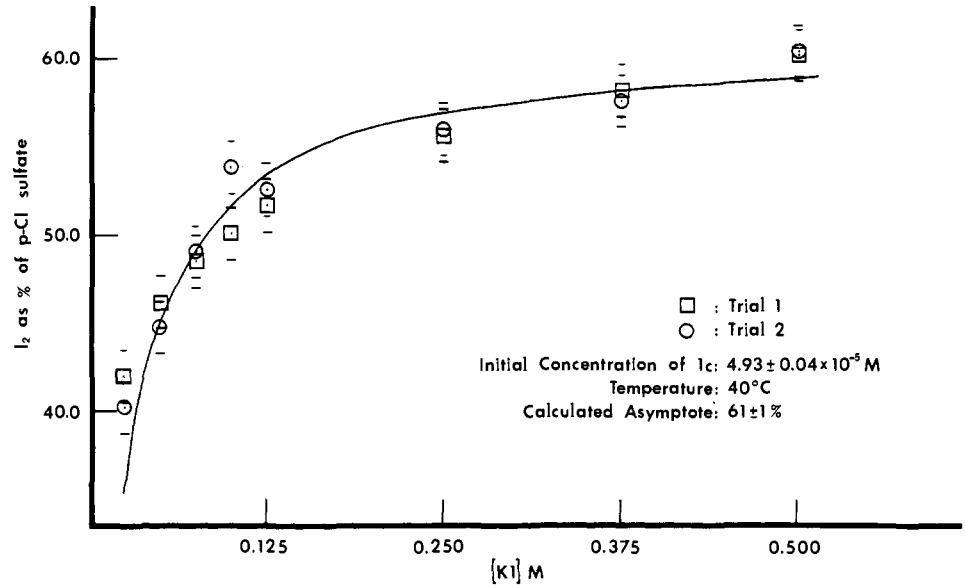


Figure 3. I_2 formed during the KI reaction as a % of the initial *p*-Cl sulfate ester (**1c**) present vs. concentration of KI. The line was calculated from a weighted least-squares fit of the data to eq 1.

Table II. Activation Parameters for the Solvolysis of the Sulfate Esters in 5% CH_3CN–H_2O

	no salts added		in the presence of 0.5 M KCl	
ester	$\Delta H^{\ddagger}$ [a] (kcal/mol)	$\Delta S^{\ddagger}$ [a] (eu)	$\Delta H^{\ddagger}$ [a] (kcal/mol)	$\Delta S^{\ddagger}$ [a] (eu)
1a	16.7 ± 0.1	−17.1 ± 0.8	17.0 ± 0.1	−15.7 ± 0.2
1b	20.6 ± 0.6	−15.2 ± 2.1	21.3 ± 0.3	−12.8 ± 0.8
1c	19.0 ± 0.1	−18.9 ± 0.1	20.0 ± 0.1	−15.6 ± 0.2
1d	19.0 ± 0.1	−19.3 ± 0.4	20.2 ± 0.1	−15.5 ± 0.4
1e	22.1 ± 0.2	−18.3 ± 0.4	22.9 ± 0.2	−15.7 ± 0.6
1f	19.6 ± 0.3	−22.5 ± 0.8	19.8 ± 0.1	−21.9 ± 0.4

[a] Activation parameters were calculated from a weighted linear least-squares fit of ln (k/T) vs. $1/T$ and are reported with their standard deviations.

for both KCl and $NaClO_4$ in the concentration ranges studied.

Correlation of the solvolysis rate constants in 5 vol % CH_3CN–H_2O at 40 °C vs. Brown's σ^+ parameter is relatively poor (r = 0.91) with a ρ of −4.4 ± 0.9 (Figure 2). The slope is insensitive to temperature. A ρ of −4.5 ± 0.9 can be calculated by extrapolation of the rate constants to 25 °C. Similar results were obtained from rate constants determined in 0.5 M KCl. Figure 2 also contains a Hammett plot of the solvolysis rate constants of ring-substituted *N-tert*-butyl-*N*-chloroanilines in ethanol at 25 °C vs. the σ^+ parameter.[14] These rate constants show a better correlation (r = 0.996) and a steeper slope (ρ = −6.35).[14] These compounds appear to undergo solvolysis in alcoholic solvents via a nitrenium ion intermediate.[14,15] Activation parameters determined for the solvolysis reactions in 5% CH_3CN–H_2O and in 5% CH_3CN–H_2O, 0.5 M KCl, are reported in Table II.

The esters decompose in KI solution with the production of I_2. The rates of I_2 production are comparable to the rates of ester decomposition in KCl solution. The I_2 yield can be calculated from the infinity absorbance at 352 nm. Plots of I_2 yield as a percent of initial ester concentration vs. KI concentration can be fit by a standard saturation curve (eq 1). The yield of I_2 at

$$I_2\% = \frac{[KI](I_2\%_{sat})}{K + [KI]} \quad (1)$$

saturation, $I_2\%_{sat}$, is less than 100% in all the cases examined. The saturation yield of I_2 is 86 ± 6% for **1a**, 38 ± 9% for **1b**, 61 ± 1% for **1c**, and 59 ± 2% for **1d**. Figure 3 is a plot of I_2 yield vs. KI concentration for **1c**.

The results of a detailed study of the products formed during the solvolysis of **1c** at 40 °C under various conditions are summarized in Table III. With one notable exception, the identities and yields of the various products are highly dependent on the reaction conditions. For example, the yields of 4-hydroxyacetanilide (**2**), 2-hydroxy-4-chloroacetanilide (**3**), and 1,4-benzoquinone (**8**) decrease by 35 to 50% when 0.5 M KCl is added. When KCl is present both 2,4-dichloroacetanilide (**5**) and 3-chloro-4-hydroxyacetanilide (**6**) are formed. The yield of **6** decreases from 7.3 ± 1.2% at pH 3.1 to less than 0.5% at pH 6.7. The yields of **2** and **8** also show pH dependence. At the low buffer concentrations used in this study, no products could be detected which were due to attack of phosphate or acetate on the aromatic ring.

The yield of 2-sulfonoxy-4-chloroacetanilide (**4**), is notably independent of conditions. Within experimental error, the yield of this product is invariant to changes in salt concentration or pH. The average yield of **4** under the six sets of conditions reported in Table III is 38% with a standard deviation of only ±2%. Control experiments show that **4** does not hydrolyze to **3** at significant rates under the reaction conditions. Such a reaction could account for no more than 10% of the reported yield of **3** under any conditions examined.

The products isolated from the solvolysis of **1c** in 0.5 M KI are also notable. In addition to **4**, only two other products, **2** and 4-chloroacetanilide (**7**), were detected. Both of these are apparently produced by a reduction reaction involving I^-. There is an excellent correlation between the sum of the yield of the two reduction products (62 ± 4%) and the yield of I_2 at saturation noted above (61 ± 1%). Examination of Figure 3 shows that at 0.5 M in KI the saturation yield of I_2 has essentially been attained.[16]

The solvolysis of **1c** also yields **7** in the presence of other soft bases and reducing agents. Other conditions under which **7** has been detected include: 0.5 M KBr (26 ± 2% of **7** detected); 0.5 M KSCN (25 ± 1); 0.5 M $K_2S_2O_3$ (2.2 ± 0.1%); and 0.25 M $FeCl_2$ in 1:1 HOAc/KOAc buffer, 0.05 M B_T (4.4 ± 0.2%). A substantial yield of **2** (30 ± 1%) was also observed in the presence of $FeCl_2$. Similar oxidation–reduction reactions have been reported for a number of carcinogenic *N*-acyloxypurines[17] and *N*-acet-

(14) Gassman, P. G.; Campbell, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 2567–2569; **1972**, *94*, 3891–3896.

(15) Gassman, P. G.; Campbell, G. A.; Frederick, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 7377–7378; **1972**, *94*, 3884–3891.

(16) A similar correlation has been found between the isolated yield of reduction products and the I_2 yield determined from the kinetics for **1d**: Novak, M.; Pelecanou, M., unpublished results.

Table III. Yields of Products Isolated from the Solvolysis of **1c** in 5% CH_3CN-H_2O at 40 °C[a]

product	no added salts[b]	0.5 M KCl[b]	0.5 M KI[c]	0.001 M HCl[b,d] pH 3.1	1:1 HOAc/KOAc[b,e] pH 4.7	1:1 K_2HPO_4/KH_2PO_4[b,e] pH 6.7
4-hydroxyacetanilide (**2**)	6.3 ± 0.8	3.7 ± 0.5	15 ± 3	4.1 ± 0.3	10 ± 1	14 ± 1
2-hydroxy-4-chloroacetanilide, (**3**)	9.7 ± 0.6	4.9 ± 0.4		4.3 ± 0.5	4.1 ± 0.3	1.6 ± 0.2
2-sulfonoxy-4-chloroacetanilide (**4**)	41 ± 2	41 ± 2	37 ± 2	36 ± 3	37 ± 2	38 ± 3
2,4-dichloroacetanilide (**5**)		20 ± 3		17 ± 1	22 ± 1	21 ± 1
3-chloro-4-hydroxyacetanilide (**6**)		8.0 ± 1.5		7.3 ± 1.2	5.0 ± 0.9	trace[f]
4-chloroacetanilide (**7**)			47 ± 3			
1,4-benzoquinone (**8**)	27 ± 5[g] (18)[h]	18 ± 4[g] (11)[h]		(14)[h]	(8)[h]	4 ± 1[g] (3)[h]

[a] Initial concentration of **1c** was approximately 1.25 mM. Yields are reported with respect to **1c** initially present. [b] Yields determined from HPLC peak areas as described in method b in the Experimental Section. [c] Yields determined by isolation of the products as described in method a in the Experimental Section. Yields were confirmed by method c. [d] Ionic strength = 0.5 M (KCl). [e] Ionic strength = 0.5 M (KCl); total buffer concentration was 0.05 M. [f] Less than 0.5%. [g] This product decomposes during the reaction and cannot be isolated quantitatively. The reported yields were determined from the yield of acetamide, the by-product of formation of **8**. Acetamide yields were determined by method c. [h] These are lower limits determined by extrapolation of the concentration vs. time data for **8** taken in the early part of the reaction before significant decomposition of **8** has occurred. The spectrophotometric rate constants were assumed to apply to the formation of **8** in these extrapolations.

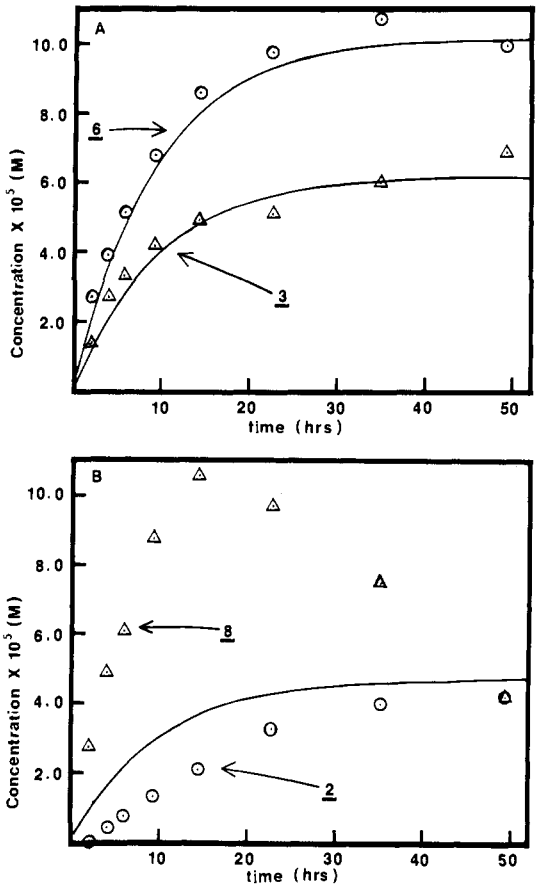


Figure 4. (A) Concentration vs. time curves for the production of **3** (triangles) and **6** (circles) during the solvolysis of **1c** in 0.5 M KCl at 40 °C. Initial concentration of **1c** was 1.28 mM. Theoretical lines were calculated from the spectrophotometric rate constant ($1.07 \pm 0.01 \times 10^{-1}$ h^{-1}) and the concentrations of **3** and **6** determined at the end of the reaction. Rate constants calculated directly from the concentration vs. time data for **3** and **6** were $1.07 \pm 0.20 \times 10^{-1}$ h^{-1} and $1.15 \pm 0.09 \times 10^{-1}$ h^{-1}. (B) Concentration vs. time curves for the production of **2** (circles) and **8** (triangles) during the solvolysis of **1c** in 0.5 M KCl at 40 °C. Initial concentration of **1c** was the same as in A. Theoretical line for **2** was calculated from the spectrophotometric rate constant and the concentration of **2** determined at the end of the reaction.

oxy-*N*-acetyl-2-aminofluorene.[18]

HPLC analysis was used to follow the concentration of each product during the course of the solvolysis reactions for five of the six cases shown in Table III. This method could not be used in 0.5 M KI solutions because of the strong UV absorbance of this salt. ^1H NMR was used to follow the course of the reaction in this case. These analyses showed that, with the exception of **2** and **8**, the concentration of the products increased during the reaction in a first-order manner. Figure 4A provides an example of this behavior for the time course of the appearance of **3** and **6** in 0.5 M KCl. Rate constants calculated from the concentration vs. time data were in good agreement (±15%) with those obtained spectrophotometrically under the same conditions.

Table IV. Solvolysis Products of **1b** in 5% CH_3CN-H_2O Containing 0.5 M KCl at 40 °C[a]

product	% yield[b]
2-hydroxyacetanilide (**11**)	1.8 ± 0.2
4-hydroxyacetanilide (**2**)	39 ± 2
2-sulfonoxyacetanilide (**12**)	40 ± 2
4-sulfonoxyacetanilide (**13**)	6.7 ± 0.5
2-chloroacetanilide (**14**)	trace[c]
4-chloroacetanilide (**7**)	2.5 ± 0.1

[a] Concentration of **1b** was approximately 1.25 mM. Yields are reported with respect to **1b** initially present. [b] Determined from HPLC peak areas as described in method b in the Experimental Section. [c] Less than 0.5%.

The typical behavior of the concentration vs. time curves for **2** and **8** in the absence of added reducing agents is shown in Figure 4B. The appearance of **2** is characterized by a definite lag phase. Initially the concentration of **8** increases with time, but within 1 to 2 half-lives definite deviation from first-order behavior is observed and eventually the concentration of **8** begins to decrease with time. For this reason estimates of the yield of **8** based on examination of the reaction mixture after 5 to 6 half-lives are too low. The estimates given in Table III were based either on the yield of acetamide, which is a by-product of the formation of **8**, or on an extrapolation of the initial rate of appearance of **8** before significant decomposition has occurred. This extrapolation assumes that the rate constant for the appearance of **8** is identical with the spectrophotometric rate constant.

HPLC analysis at 225 nm indicates that hydroquinone is one of the products that **8** decomposes into during the solvolysis of **1c**. This material was isolated from some of the reaction mixtures as further confirmation of its identity. The hydroquinone that is produced during the reaction can account for approximately 20 to 30% of the decomposition products of **8**.

At 40 °C in the presence of 1.0 mM pyridinium sulfate, benzoquinone (**8**) decomposes at rates comparable to those observed in the product studies. The half-lives measured for benzoquinone under these conditions were 1.5 h in 1:1 K_2HPO_4/KH_2PO_4 buffer, 3.0 h in 1:1 KOAc/HOAc buffer, and 50 h in 0.001 M HCl. However, no hydroquinone was detected under these conditions.

If a reducing agent such as KI or Fe^{2+} is present in sufficient concentration during the solvolysis, the production curve for **2** takes on a typical first-order appearance, and neither **8** nor hydroquinone can be detected.

(17) (a) Parham, J. C.; Templeton, M. A.; Teller, M. N. *J. Org. Chem.* **1978**, *43*, 2325–2330. (b) Parham, J. C.; Templeton, M. A. *Cancer Res.* **1980**, *40*, 1475–1481. (c) Parham, J. C.; Templeton, M. A. *J. Org. Chem.* **1982**, *47*, 652–657.

(18) Ströher, G.; Salemnick, G. *Cancer Res.* **1975**, *35*, 122–131.

The results of less detailed product studies on the solvolysis of the unsubstituted ester, **1b**, in 0.5 M KCl are presented in Table IV. The ortho/para product ratios for the hydroxyacetanilides and sulfonoxyacetanilides are of interest. The pertinent ratio for the hydroxyacetanilides, **11**:**2**, is 0.046 ± 0.006. The corresponding ratio for the sulfonoxyacetanilides, **12**:**13**, is 6.0 ± 0.5. The former evidently is representative of an intermolecular reaction, while the latter ratio is typical of an intramolecular process.[19] The solvolysis of **1b** is far less sensitive to the presence of Cl^- than is the solvolysis reaction of **1c**. In 0.5 M KCl only about 2.5% of the products isolated from the reaction of **1b** are chlorinated materials. Under identical conditions 28% of the products isolated from the solvolysis of **1c** arise as a result of attack of Cl^- on the aromatic ring.

N-Acetyl-*p*-benzoquinone imine (**10**) was subjected to the same solvolysis conditions as **1c**. This material hydrolyzed very rapidly with half-lives ranging from 7.0 min in the phosphate buffer to less than 30 s in 0.001 M HCl. The solvolysis products obtained from **10** were **2**, **6**, and **8**. The yields of these products varied with pH in the same manner as the yields of the same products did in the solvolysis reactions of **1c**. The relative yields obtained for these three species from the two sets of solvolysis reactions were also comparable. In the presence of $FeCl_2$, **10** yields only the reduction product **2**.

In ethanol neither **1b** nor **1c** reacts via cleavage of the N–O bond. The only products isolated from the solvolysis of **1c** in ethanol at 40 °C were *N*-hydroxy-4-chloroacetanilide (**15**) (83 ± 3%) and ethyl sulfate (isolated in quantitative yield as the pyridinium salt). In ethanol-d_6, ^1H NMR experiments show that **1b** decomposes exclusively to *N*-hydroxyacetanilide (**16**). These products must arise from S–O bond cleavage. In methanol-d_4 **1c** yields a mixture of products; however, **15** is the predominant product (~85%). The other products appear to result from N–O bond cleavage. The *N*-hydroxyacetanilides have not been detected in the product mixtures of solvolysis experiments run in H_2O. These products are difficult to detect at low levels because they do not give sharp well-defined HPLC peaks and they also streak very badly on TLC plates. It would be possible for as much as a 5% yield of these products to escape detection in the solvolysis experiments performed in H_2O.

When the solvolysis of **1c** was performed in ethanol containing 0.1 M KI, no I_2 could be detected, and no reduction products similar to those obtained in aqueous solution were isolated. The only detectable products were **15** and ethyl sulfate which were also produced in the absence of KI.

The rate constant for solvolysis of **1c** in ethanol is concentration dependent. The half-live of the solvolysis reaction at 40 °C decreases from 13.0 h at 5.0×10^{-5} M in **1c** to 3.7 h at 1.25 mM in **1c**. The products, however, do not change. This same phenomenon is observed for the solvolysis of **1b** in ethanol. As previously noted, rate constants for solvolysis of these esters in aqueous solution are not concentration dependent.

Discussion

Solvolysis of 1a–f in Aqueous Solution. Although the correlation is poor, the slope of the plot, shown in Figure 2, of log k_{obsd} vs. σ^+ (ρ = −4.4 ± 0.9 at 40 °C, and −4.5 ± 0.9 at 25 °C) for the solvolysis of the *N*-sulfonoxyacetanilides in 5% CH_3CN–H_2O indicates that the solvolysis proceeds via heterolytic cleavage of the N–O bond with the development of a large positive charge on nitrogen in the rate-determining step. The sensitivity to changes in the aromatic substituent is somewhat less than that observed by Gassman for the solvolysis of ring-substituted *N*-*tert*-butyl-*N*-chloroanilines in ethanol (ρ = −6.35).[14] This reaction almost certainly involves the intermediacy of a delocalized nitrenium ion.[14,15] Two opposing effects must be considered when comparing the two slopes: (a) the aqueous environment would better stabilize the transition state leading to the nitrenium ion and decrease the sensitivity of the reaction to substituent effects, and (b) the electron-donating properties of the N-substituents, the acetyl and *tert*-butyl groups, are such that the stability of the transition state leading to the acetanilidium ion should be more sensitive to substituent effects. Direct comparison of the solvolysis rates of **1a–f** in ethanol with those of the *N*-*tert*-butyl-*N*-chloroanilines is not useful because the *N*-sulfonoxyacetanilides undergo S–O bond cleavage in alcoholic solvents (see below). The available data indicate that the solvent plays a dominant role in determining the magnitude of the Hammett slope for these reactions. Indeed, the ρ observed for the thermal rearrangement of a series of methanesulfonate esters of *N*-hydroxyacetanilides in chloroform is −9.24.[20]

The activation parameters measured for the solvolysis reactions of the *N*-sulfonoxyacetanilides are reported in Table II. These parameters were also reported for the solvolysis reactions of *N*-*tert*-butyl-*N*-chloroanilines.[14] Direct comparisons of the activation parameters can be made between the two sets of compounds in the three cases where the ring substitution patterns are identical (**1a**,**b**,**c**, and the corresponding aniline derivatives). In the absence of added salts $\Delta H^{\ddagger}$ is more favorable for the *N*-sulfonoxyacetanilides by an average value of 3.0 ± 1.5 kcal/mol. This is apparently a result of the dominant role of the solvent in determining the potential energy of the transition state. However, $\Delta S^{\ddagger}$ is less favorable for the solvolysis of the three *N*-sulfonoxyacetanilides by an average value of 13.9 ± 4.6 eu. This apparently reflects a tighter transition state structure and/or a higher degree of solvent ordering in the vicinity of the developing acetanilidium ion. Either effect would be consistent with the expected lower intrinsic stability of the acetanilidium ions compared with the *N*-*tert*-butylanilinium ions. Table II shows that the addition of a salt has only a moderate effect on the activation parameters for the solvolysis of **1a–f**. The Hammett slope and activation parameters could also be interpreted in terms of a mechanism involving solvent-assisted ionization of the substrate. There are not sufficient data available to make a distinction between these possibilities.

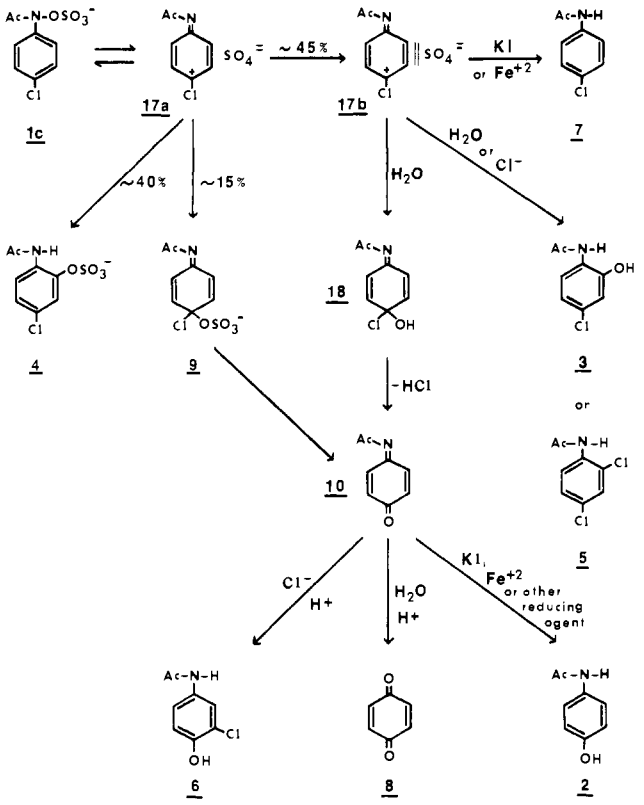
No evidence could be found for nucleophilic participation in an S_N2 or S_N2' mechanism by Cl^- or any other nucleophilic species employed in the study. The moderate salt effects observed in these solvolysis reactions are reminiscent of those observed in the S_N1 solvolysis of alkyl halides.[7a] No correlation was found between the magnitude of the salt effects and the product distributions. For example, although the solvolysis rate of **1b** is increased by 28% by the addition of 0.5 M KCl, only about 2.5% of the solvolysis products derived from **1b** in 0.5 M KCl contain chlorine. Figure 1 shows that salt effects in $NaClO_4$ solutions are comparable to those observed in KCl solutions.

The product studies performed on the solvolysis reactions of **1c** are reported in Table III. These results indicate that the solvolysis reaction proceeds via two distinct paths. The intermediate involved in one of the paths can be trapped by nucleophiles or reducing agents, while the other path, leading to 2-sulfonoxy-4-chloroacetanilide (**4**), is insensitive to the presence of trapping agents. In fact, the yield of **4** remained constant, within experimental error, under all the conditions that were studied. The product study performed in 0.5 M KI and the accompanying kinetic study are particularly illustrative. In 0.5 M KI the reduction products 4-chloroacetanilide (**7**) and 4-hydroxyacetanilide (**2**) account for 62 ± 4% of the reaction yield. The only product which is not formed by I^- mediated reduction is **4**, which was isolated in 37 ± 2% yield. The kinetic study showed that the I_2 yield in the reaction approaches an asymptote of 61 ± 1% at high KI concentration. At concentrations of 0.5 M in KI the I_2 yield is very close to the saturation limit. It is evident that KI can trap only a portion of the reaction; the path leading to **4** is insensitive to the presence of KI. The reduction by KI of a number of carcinogenic *N*-acyloxypurines[17] and *N*-acetoxy-*N*-acetyl-2-aminofluorene[18] has been reported previously. This oxidation–reduction reaction with KI appears to be a general reaction of

(19) 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.

(20) Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498–1499.

Scheme I



aromatic nitrenium ions. Indeed, **7** is the expected product of the reduction of the acetanilidium ion derived from **1c**.

There is little doubt that **4** is produced by an intramolecular reaction. The KI reaction can be used to monitor the yield of **4** indirectly at low concentrations of **1c** since I^- effectively traps all other products to produce I_2. These data and the isolated yields obtained at higher concentration make it apparent that the yield of **4** remains constant at approximately 40% over a concentration range of **1c** from 0.05 to 1.25 mM. In the solvolysis of **1b** both 2-sulfonoxyacetanilide (**12**) and 4-sulfonoxyacetanilide (**13**) are produced with an ortho/para product ratio of 6.0 ± 0.5 in 0.5 M KCl and 5.1 ± 0.9 in the absence of added salts. Such high ortho/para product ratios are generally considered as evidence for intramolecular processes.[19]

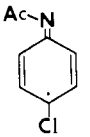
A mechanism which is consistent with all the data for the solvolysis of **1c** is presented in Scheme I. It is an adaptation of Winstein's ion-pair mechanism for the S_N1 solvolysis of alkyl halides.[7a] The experimental data require a minimum of two distinct ion pairs. The tight ion pair, **17a**, can lead to the rearrangement product **4** by internal return.[7b-d] This species apparently cannot be trapped by external nucleophiles or reducing agents. The solvent-separated ion pair, **17b**, can account for the products **3**, **5**, and **7**. Since none of the added reagents affect the yield of **4**, it is apparent that return to **17a** from **17b** does not occur.[7b,c] The other products, **2**, 1,4-benzoquinone (**8**), and 3-chloro-4-hydroxyacetanilide (**6**), cannot be produced directly from either **17a** or **17b**. However, two reasonable pathways exist which can explain these products. Attack of H_2O at the para position of **17b** would yield **18** which can eliminate HCl to yield *N*-acetyl-*p*-benzoquinone imine (**10**). This compound is a suspected toxic metabolite of phenacetin and 4-hydroxyacetanilide (**2**).[12,21] It is readily reduced to **2**,[12a] and it reacts with sulfur nucleophiles to yield adducts analogous to **6**.[12a] It also hydrolyzes rapidly to **8** in an apparently acid-catalyzed reaction.[21c] Under the reaction conditions employed in this study **10** yields **2**, **6**, and **8** in proportions which are consistent with those observed in the solvolysis reactions of **1c**. Since the yields of **6** and **8** increase with decreasing pH at the apparent expense of **2**, it is likely that both of these species are produced through the intermediacy of the N-protonated conjugate acid of **10**.

Another pathway can lead to **10** from the tight ion pair **17a**. Internal return from **17a** with rearrangement can yield **9** which would be expected to rapidly decompose to **10**. The overall yield of **10** can approach 30–35%. In the absence of added salts, decomposition products of **10** account for 33 ± 5% of **1c**, and in the presence of 0.25 M $FeCl_2$ the reduction product of **10**, **2**, is isolated in 30 ± 1% yield.

The relative proportions assigned to the paths for the breakdown of **17a** as shown in Scheme I were determined assuming that KI completely scavenges **17b** to yield **7**. This appears reasonable, since no **3** could be detected in the presence of KI. If this is so, then the 15% of the reduction product **2** which is isolated in the KI reaction must be produced by the sequence **17a** → **9** → **10** → **2**.

In Scheme I there are two intermediate species which are subject to reduction, **17b** and **10**. These yield two different reduction products, **7** and **2**, respectively. Under all the reaction conditions examined small to moderate yields of **2** can be isolated. The sigmoidal nature of the production curve for **2** (Figure 4B) indicates that it is produced through the action of a reducing agent that is generated in situ during the solvolysis reaction. Hydroquinone can also be isolated. This species accounts for a fraction of the 1,4-benzoquinone (**8**) which decomposes during the reaction. The same reducing agent may be responsible for the formation of hydroquinone. At present this reducing agent has not been identified. When Fe^{2+} or KI are present in sufficient quantities during the reaction the production curve for **2** takes on a typical first-order appearance, and neither **6** nor **8** or its reduction product, hydroquinone, can be detected. Studies with authentic **10** have shown that it is quantitatively converted to **2** in the presence of $FeCl_2$.

The ion pair **17b** is also subject to reduction by I^- and Fe^{2+}, as well as by Br^-, SCN^-, and $S_2O_3^{2-}$. A mechanism has been proposed for the I^- mediated reduction of other aromatic nitrenium ions.[17c] It involves nucleophilic attack of I^- on the ion to form an *N*-iodo adduct. A second nucleophilic attack by I^- is presumed to occur at iodine generating I_2 and the reduction product. This mechanism is most unlikely for the Fe^{2+} mediated reaction. A more likely mechanism involves one-electron transfer to generate Fe^{3+} and the amidyl radical, **19**, followed by a second one-electron



19

reduction to generate **7**. It has recently been found that radical species similar to **19** can be generated directly from the pivaloxy analogues of **1a** and **1b**, and from *N*-pivaloxy-*p*-nitroacetanilide during the thermal decomposition of these species in benzene solution.[10] It is entirely possible that alternative two-electron and one-electron reduction processes can occur.

The decomposition of **8** is quite rapid during the product studies run at 1.25 mM in **1c**. Half-lives for **8** decrease with increasing pH and range from about 50 h (0.001 M HCl) to about 1.0 h (phosphate buffer). These half-lives are such that if **8** were to decompose this rapidly during the kinetic studies, serious deviation from first-order behavior would be observed. However, control experiments show that the decomposition rate of **8** is highly dependent on the pyridinium ion concentration. The kinetic studies were performed with 5.0×10^{-5} M **1c** so that pyridinium ion concentrations are almost two orders of magnitude lower than they are in the product studies. Under these conditions **8** is stable enough that the kinetics determinations can be made without serious complications.

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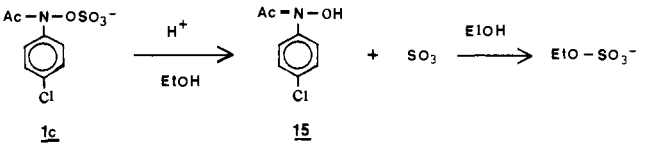
Scheme II



1c 15

There are reasonable alternative mechanisms to the one presented in Scheme I. Although several rearrangements similar to those reported here have been explained in terms of ion-pair return,[15,20,22] there is evidence that others may involve concerted cyclic processes,[23] or π complexes.[24] Although it is very likely that **2**, **3**, and **5–8** are produced through the intermediacy of a nitrenium ion or ion pair, the rearrangement to produce **4** need not proceed through an ionic intermediate. The available trapping data could be used to support a mechanism involving completely separate pathways for the production of **4** and the other materials. This possibility is under investigation.

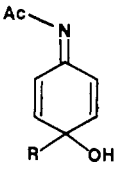
Preliminary investigations into the solvolysis products of the other members of this series of compounds show that the mechanism of Scheme I is quite general.[25] The *o*-sulfonoxyacetanilide rearrangement products have been detected in all the cases examined, and other products similar to those obtained in the studies on **1b** and **1c** have been detected. Attack of H_2O on the para position of the ring is a predominant reaction in all cases. In the case of **1a**, **1c**, and **1d** this leads to high yields of quinoid compounds and their various decomposition products. This same type of attack on **1b** and **1e**, in which the para position is not blocked, leads to high yields of *p*-hydroxyacetanilides. One major difference between the esters which have substituents at the para position and those which do not is their susceptibility to attack by Cl^-. The esters **1a**, **1c**, and **1d** all yield significant amounts of products which result from attack of Cl^- on the ring, while **1b** and **1d** show very little tendency to react with Cl^-.

Solvolysis of 1b and 1c in Alcohol Solvents. In ethanol none of the solvolysis products found in the aqueous solutions can be detected. Both **1b** and **1c** decompose exclusively into the corresponding *N*-hydroxyacetanilides, **16** and **15**, and ethyl sulfate. Neither I_2 nor **7** could be detected during the solvolysis of **1c** in 0.1 M KI in ethanol. These compounds undergo solvolysis in ethanol with exclusive S–O bond cleavage. Apparently the free energies of the ion-pair intermediates increase sufficiently in the less effectively solvating ethanol to make the alternative S–O bond cleavage pathway predominant. Kinetic studies show that the reaction rate constant increases with the concentration of **1c**, although the reaction remains first order. Pyridinium ion may serve as a catalyst for the reaction.

The familiar unimolecular solvolysis mechanism of monosulfate esters[26] shown in Scheme II is consistent with the data, although a mechanism involving direct nucleophilic attack of ethanol on the sulfate ester cannot be ruled out.

Solvolysis in methanol represents an intermediate situation between the extremes of exclusive N–O or S–O bond cleavage. Products derived from both types of reactions can be identified when **1c** undergoes solvolysis in this solvent. The S–O bond cleavage is still predominant, however, since **16** accounts for 85% of the reaction product yield.

Implications of This Study with Respect to Chemical Carcinogensis. From the point of view of chemical carcinogensis, the most important result of this study is the demonstration that electrophilic species other than nitrenium ions can be generated during the solvolysis of *N*-sulfonoxy-*N*-arylacetamides. In particular, quinone imine derivatives similar to **10** or **20** could serve as important



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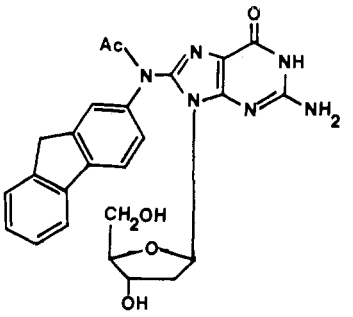
electrophiles in vivo. The antitumor activity of a number of quinone and quinoid drugs is well known.[27] However, these species have never been considered as potential electrophilic intermediates in chemical carcinogenesis caused by *N*-sulfonoxy or *N*-acetoxy derivatives of aromatic amines or amides, in large part because it has not been realized previously that they can form during the solvolysis of these compounds. In fact, such quinoid species could provide a rational explanation for one of the most puzzling reactions of the well-known carcinogen *N*-acetoxy-*N*-acetyl-2-aminofluorene. This compound is known to react in vivo and in vitro with deoxyquanosine to yield *N*-(deoxyguanosin-8-yl)-*N*-acetyl-2-aminofluorene (**21**).[1,2] When nitrenium ions are veri-



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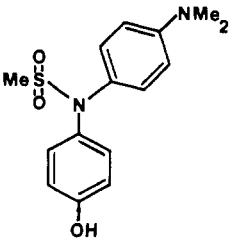
fiably generated, they tend to react with deoxyguanosine at O-6[28,29] or N-1.[29] Initially, this unusual product was attributed to the reaction with deoxyguanosine of a low-lying triplet state of the nitrenium ion derived from *N*-acetoxy-*N*-acetyl-2-aminofluorene.[3b] Recent molecular orbital calculations suggest that the triplet state lies at too high an energy for such a species to be a viable intermediate.[3d] It is known, however, that quinone imine derivatives such as *N*-(methanesulfonyl)-*p*-benzoquinone imine react with aromatic carbon nucleophiles such as *N*,*N*-dimethylaniline to yield adducts similar to **22**.[30] The possibility that such an intermediate



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(25) Preliminary results show that **1d** yields 2-sulfonoxy-4-bromoacetanilide in approximately 40% yield in 0.5 M KCl. Other products include 2-chloro-4-bromoacetanilide (24%) and decomposition products of **10**: **2** (2%), **6** (5%), and **8** (10%). In 0.5 M KI only the *o*-sulfonoxy product (35%), **2** (7%), and *p*-bromoacetanilide (50%) can be isolated. The solvolysis of **1a** in 0.5 M KCl yields *o*-sulfonoxy-*p*-acetotoluidide (10%) and *o*-chloro-*p*-acetotoluidide (7%). All other isolated products (accounting for 56% of **1a**) appear to be isolated from **20** (R = CH_3). The solvolysis of **1e** in 0.5 M KCl yields large amounts of 3-bromo-4-hydroxyacetanilide, but only traces (<0.5%) of ring-chlorinated products: Novak, M.; Pelecanou, M.; Roy, A. K., unpublished results.

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is responsible for the unusual reaction with deoxyguanosine is under investigation in this laboratory.

It is also possible that electrophilic species such as SO_3 could play a role in the in vivo chemistry of the carcinogenic sulfate esters. In fact, as a result of this investigation it is obvious that the chemistry of the sulfuric acid esters of *N*-hydroxy-*N*-arylamides is considerably more complicated than previously appreciated. It is our intention to continue to investigate the chemistry of these species with special emphasis on the points mentioned above.

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Registry No. **1a**, 91631-50-4; **1b**, 91631-52-6; **1c**, 91631-54-8; **1d**, 91631-56-0; **1e**, 91631-58-2; **1f**, 91631-60-6; *N*-hydroxy-*p*-bromoacetanilide, 67274-48-0; *N*-hydroxy-3,4-dichloroacetanilide, 86412-49-9.

Supplementary Material Available: Table of pseudo-first-order rate constants for the solvolysis of *N*-sulfonoxyacetanilides in aqueous solution (2 pages). Ordering information is given on any current masthead page.

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Deuterium Fractionation Factor for Unhydrated Hydronium Ion. Deuterium Isotope Effects on Proton-Transfer Equilibria in Acetonitrile

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Abstract: Spectrophotometric measurements of pK_a values for three *N*,*N*-dimethylanilinium ion indicators have been made in CH_3CN–H_2O and CH_3CN–D_2O solvent mixtures throughout the range of water content from a mole fraction of 1.00 down to a mole fraction of 3×10^{-4}. The three indicator bases were *N*,*N*-dimethyl-*p*-nitroaniline, *N*,*N*-dimethyl-3,5-dinitro-4-toluidine, and 4-chloro-*N*,*N*-dimethyl-2,6-dinitroaniline. The observed H_2O/D_2O isotope effects on the pK_a values allow estimation of the value of ℓ_1, the deuterium fractionation factor relative to L_2O for unhydrated L_3O^+ (where L = H or D) in CH_3CN; that value is near 0.79. (Compare $\ell = 0.69$ for L_3O^+ in L_2O.) This observation implies that if, as has commonly been assumed, the low value of ℓ in liquid L_2O results from strong hydrogen bonding of L_3O^+ to three L_2O molecules, then hydrogen bonding of L_3O^+ to CH_3CN molecules in liquid CH_3CN is almost as effective in weakening the force field experienced by the three fractionated L's in L_3O^+ as is hydrogen bonding to L_2O molecules in liquid L_2O. The observation that ℓ_1 is significantly less than 1.0 also supports our contention that the absence of an H_2O/D_2O *kinetic* isotope effect on methyl transfer to L_2O in CH_3CN implies that no significant L_2O–CH_3 bond is present in the transition state and thus that the activation process for those methyl transfers is predominantly a fluctuation in solvent polarization.

It has been known for almost a half a century[1] that in aqueous solutions the D/H ratio in "hydrogen ion" differs from the D/H ratio in the water in which that hydrogen ion is dissolved. It also has been known for about two decades[2-6] that this D/H fractionation occurs at three sites in the hydrogen ion (thus confirming its formulation as hydronium ion, L_3O^+, where L denotes either H or D) and that the value of the fractionation factor relative to L_2O, ℓ, is 0.69 ± 0.02 near 25 °C. However, the molecular origin of this fractionation remains uncertain. Most attempts to account for this value of ℓ have emphasized the importance of hydrogen bonding of the L_3O^+ moiety to three L_2O molecules, giving $(L_2O\text{--}L)_3O^+$, or of the effect of such hydrogen bonding on the libration frequencies of the L_3O^+ unit.[7-10] Yet others have qualitatively attributed this fractionation to the effect of the positive charge on the internal vibrations of L_3O^+.[11]

Knowledge of the true origin of the value of ℓ in aqueous solution would further our understanding of the structure of aqueous solutions, obviously an important topic, and also would allow a more certain interpretation of kinetic deuterium isotope effects on alkyl transfers to water (eq 1) in aprotic solvents. There

$$L_2O + RX \rightarrow ROL_2^+ + X^- \qquad (1)$$

exists strong evidence[12-15] that solvent repolarization is rate determining in these reactions, a controversial conclusion. That evidence is based in part on our observation[12,13] that values of k_{H_2O}/k_{D_2O} for methyl transfers from CH_3OClO_3, $CH_3OSO_2CF_3$, and $CH_3S^+C_4H_4$ to L_2O which is a dilute solute in acetonitrile

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