liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–7.38 (m, 5 H), 6,44 (d, J = 15.9 Hz, 1 H), 6.26 (dt, J = 15.9, 6.6 Hz, 1 H), 2.34–2.45 (m, 2 H), 2.30 (t, J = 6.6 Hz, 2 H), 1.11 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 137.6 (s), 130.7 (d), 129.0 (d), 128.3 (d), 126.8 (d), 125.9 (d), 89.7 (s), 77.6 (s), 32.8 (t), 31.3 (q), 27.3 (s), 19.0 (t).

(*E*)-1,3-Nonadien-5-yne (25): colorless liquid; bp 49 °C (8 torr); IR (neat) 1630, 2230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.5–6.1 (m, 2 H), 5.6 (dt, J = 15.0, 2.5 Hz, 1 H), 5.2 (d, J = 15.5 Hz, 1 H), 4.9 (d, J = 9.3 Hz, 1 H), 2.3 (td, J = 7.1, 2.5 Hz, 2 H), 1.5 (m, 2 H), 1.0 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.8 (d), 136.2 (d), 118.4 (t), 112.6 (d), 93.3 (s), 79.6 (s), 22.1 (t), 21.5 (t), 13.4 (q); MS, m/e 120. Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89,61; H, 10.39.

(*E*)-1,3-Decadien-5-yne (26): colorless liquid; bp 81 °C (18 torr); IR (neat) 1625, 2220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.5–6.1 (m, 2 H), 5.6 (dt, J = 15, 2.5 Hz, 1 H), 5.3 (d, J = 15.3 Hz, 1 H), 5.1 (d, J = 8.0 Hz, 1 H), 2.3 (td, J = 7.1, 2.5 Hz, 2 H), 1.5 (m, 4 H), 0.9 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.8 (d), 136.3 (d), 118.3 (t), 112.7 (d), 93.4 (s), 79.5 (s), 30.8 (t), 22.0 (t), 19.3 (t), 13.5 (q); MS, m/e 134. Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.06; H, 10.94.

(*E*)-1,3-Dodecadien-5-yne (27): colorless liquid; bp 65 °C (2.0 torr); IR (neat) 1630, 2230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.5–6.1 (m, 2 H), 5.6 (dt, J = 15.0, 2.5 Hz, 1 H), 5.2 (d, J = 15.2 Hz, 1 H), 5.1 (d, J = 9.3 Hz, 1 H), 2.3 (td, J = 7.1, 2.5 Hz, 2 H), 1.4 (m, 8 H), 0.9 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.8 (d), 136.2 (d), 118.4 (t), 112.6 (d), 93.6 (s), 79.4 (s), 31.3 (t), 28.7 (t), 28.6 (t), 22.5 (t), 19.6 (t), 14.0 (q); MS, m/e 162. Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.67; H, 11.33.

Methyl (*E*,*Z*)-5,9-Dimethyl-2,6-decadienoate (30). Methyl (*E*)-5,9-dimethyl-2-decen-6-ynoate (**19**) (0.53 g), 75 mg of 5% Pd–$BaSO_4$, ca. 20 mg of quinoline, and 3 mL of methanol were placed in a 50-cm^3 flask which had been flushed with hydrogen and the mixture was stirred at 25 °C for 72 h. Vacuum distillation of the reaction mixture gave **30** (0.50 g, yield 95%): colorless liquid; bp 80 °C (2 torr); ^{1}H NMR ($CDCl_3$) δ 6.90 (dt, J = 15.6, 7.0 Hz, 1 H), 5.73 (d, J = 15.6 Hz, 1 H), 5.29 (dt, J = 10.0, 6.5 Hz, 1 H), 5.10 (dd, J = 10.0, 7.9 Hz, 1 H), 3.70 (s, 3 H), 2.57 (m, 1 H), 2.13 (dd, J = 7.0, 6.5 Hz, 2 H), 1.89 (dd, J = 6.4, 6.0 Hz, 2 H), 1.50 (m, 1 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 6 H); MS, m/e 210. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 73.97; H, 10.51.

Methyl *erythro*-5,8,8-trimethyl-2-nonen-6-ynoate-*4*-*d* (33): Colorless liquid; bp 98 °C (6 torr); IR (neat) 1650, 1720, 2150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (dd, J = 15.6, 7.5 Hz, 1 H), 5.87 (dd, J = 15.6, 1.2 Hz, 1 H), 3.73 (s, 3 H), 2.54 (dq, J = 6.9, 6.9 Hz, 1 H), 2.28 (m, 1 H), 1.18 (s, 9 H), 1.14 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.9 (s), 146.8 (d), 122.5 (d), 90.4 (s), 81.5 (s), 51.4 (q), 39.5 (td, J_{C-D} = 20 Hz), 31.4 (q), 27.3 (s), 25.3 (d), 21.2 (q); MS, m/e 209. Anal. Calcd for $C_{13}H_{19}DO_2$: C, 74.60; H, 10.11. Found: C, 74.08; H, 9.85.

Registry No. **1**, 827-19-0; **2**, 693-02-7; **3**, 917-92-0; **4**, 629-05-0; **5**, 536-74-3; **6**, 7154-75-8; **7**, 79159-62-9; **8**, 79159-61-8; **9**, 70600-70-3; **10**, 79159-60-7; **11**, 79159-59-4; **12a**, 94426-44-5; **12b**, 94426-45-6; **13**, 94426-46-7; **14**, 82315-94-4; **15**, 94426-47-8; **16**, 94426-48-9; **17**, 94426-49-0; **18**, 94426-50-3; **19**, 94426-51-4; **20a**, 94426-52-5; **20b**, 94426-53-6; **21a**, 94426-54-7; **21b**, 94426-55-8; **22a**, 94426-56-9; **22b**, 94426-57-0; **23a**, 94426-58-1; **23b**, 94426-59-2; **24a**, 94426-60-5; **24b**, 94426-61-6; **25**, 66426-76-4; **26**, 66426-78-6; **27**, 66426-80-0; **30**, 94426-62-7; **32**, 6833-44-9; **33**, 94458-39-6; **34** (R = *n*-Pr), 94426-63-8; **35** (R = *n*-Pr), 94426-64-9; **36** (R = *n*-Pr), 94426-65-0; **37** (R = *n*-Pr), 94426-66-1; A, 79169-54-3; B, 79169-53-2; C, 42516-72-3; $RuH_2(PPh_3)_4$, 19529-00-1; $RuH_2[P(p\text{-}PhOMe)_3]_4$, 94458-40-9; $RuH_2[P(p\text{-}PhMe)_3]_4$, 94458-41-0; $RuH_4(PPh_3)_3$, 31275-06-6; $RuH_2[PPh_2Me]_4$, 23940-61-6; $RuH_2[PPhMe_2]_4$, 54831-65-1; CH_2=CHCH=CH_2, 106-99-0; CH_2=$C(CH_3)$CH=CH_2, 78-79-5; (*E*,*E*)-$CH_3(CH$=$CH)_2CO_2Me$, 689-89-4; (*E*)-CH_2=CHCH=$CHCO_2Me$, 2409-87-2; (*E*)-CH_2=CHCH=CHPh, 16939-57-4; (*E*)-PhC≡CCH=CHPh, 13343-79-8; (*Z*)-PhC≡CCH=CHPh, 13343-78-7; CH_2=$C(CH_3)C(CH_3)$=CH_2, 513-81-5; $(CH_3)_2$C=CHCH=$C(CH_3)_2$, 764-13-6; CH_2=CHCH=CHOAc, 1515-76-0; CH_2=C=CH_2, 463-49-0; *n*-PrC≡CD, 7299-47-0; $RuCl_3$, 10049-08-8; $NaBH_4$, 16940-66-2; P(*n*-Bu)$_3$, 998-40-3; PEt_3, 554-70-1; 1,3-cyclohexadiene, 592-57-4; 1,3-cyclooctadiene, 1700-10-3; furan, 110-00-9.

Hydrolysis of *N*-(Sulfonatooxy)-*p*-acetotoluidide: Solution Chemistry of Models for Carcinogenic Metabolites of Aromatic Amides

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The hydrolysis reactions of the title compound, a model for the carcinogenic metabolites of polycyclic aromatic amides, were investigated over the pH range 1.0–8.0 by UV spectroscopic methods, product analyses, HPLC, and ^{1}H NMR. This compound is unique among the *N*-(sulfonatooxy)acetanilides that have been studied to date in that over most of the pH range examined it exhibits non-first-order reaction kinetics. Product analyses indicate that, like the other *N*-(sulfonatooxy)acetanilides, the hydrolysis of this compound involves N–O bond cleavage, and the kinetics of the N–O bond cleavage process are consistent with a mechanism that includes generation of nitrenium ion–sulfate ion pairs. Four transient species, **9**–**12**, were generated in sufficient quantity to be detected during the hydrolysis reaction. On the basis of isolated decomposition products and kinetic and spectral data obtained during the course of the hydrolysis reaction, the intermediate **9** was identified as 4-hydroxy-4-methylcyclohexa-2,5-dien-1-one *N*-acetylimine, while **10** and **11** were identified as the isomeric *cis*- and *trans*-*N*-acetyl-2-amino-5,6-dihydroxy-5-methylcyclohexa-1,3-dienes. These species are analogous to materials isolated by Gassman and Granrud from the methanolysis reactions of the methanesulfonate ester of *N*-hydroxy-*p*-acetotoluidide. The fourth intermediate, **12**, has been tentatively identified as 4-(sulfonatooxy)-4-methylcyclohexa-2,5-dien-1-one. The pH dependence of the hydrolysis reactions of **9** and **10** have also been thoroughly investigated. Both are subject to acid catalysis of hydrolysis and give rise to a number of products.

There is considerable evidence that several carcinogenic aromatic amides such as *N*-acetyl-2-aminofluorene (AAF) are metabolically activated by *N*-hydroxylation followed by esterification.[1,2] The sulfuric acid esters appear to be

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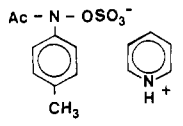
the most important metabolites,[2] although other species may also play a role in vivo.[3] As a result of these findings a number of investigations into the chemistry of esters of N-hydroxy-*N*-arylamides have been reported.[4-8]

Results of early solvolysis studies performed, for the most part, with *N*-acetoxy-*N*-arylacetamides, were interpreted in terms of reversible formation of nitrenium ion intermediates although little direct evidence for the existence of these species was offered.[4] However, recent ^{18}O-labeling studies have shown that these acetate ester model compounds do not form nitrenium ions reversibly.[5] In benzene, *N*-(pivaloyloxy)acetanilides react via homolytic rather than heterolytic N–O bond cleavage.[6]

A linear free energy plot of the rates of rearrangement of methanesulfonate esters of several *N*-hydroxyacetanilides in $CDCl_3$ is consistent with a mechanism involving nitrenium ion intermediates.[7a] The hydrolysis reactions of *N*-(sulfonatooxy)acetanilides involve N–O bond cleavage and proceed via the formation of tight and solvent-separated ion pairs to yield a complex mixture of solvolysis products including electrophilic quinone and quinoid species.[8] However, these same compounds undergo S–O bond cleavage in ethanol to generate *N*-hydroxyacetanilides and ethyl sulfate.[8] It is now apparent that the chemistry of this class of compounds is exceedingly complex.

The most reactive member of the series of *N*-(sulfonatooxy)acetanilides that have been investigated, *N*-(sulfonatooxy)-*p*-acetotoluidide, **1**, behaves in a unique fashion



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during solvolysis in aqueous solution. Under most pH conditions the overall hydrolysis reaction exhibits non-first-order characteristics. Kinetic data derived from UV absorption spectroscopy and HPLC methods indicate that several intermediates build up to detectable levels during the hydrolysis of **1** in neutral to weakly acidic media. Analysis of the kinetic behavior of these intermediates, the products derived from their decomposition, and ^1H NMR data of the hydrolysis reaction in D_2O have been used to assign reasonable structures to these species, which are reported herein. One of these intermediates, **10**, has been isolated from the aqueous reaction mixtures, albeit in an impure form. The results and conclusions of this study are in many ways similar to those of a recent report on the methanolysis of the methanesulfonate ester of *N*-hydroxy-*p*-acetotoluidide[7b] but also differ in several important aspects. It is now possible as a result of this and other studies[4-8] to present a fairly detailed picture of the complex solution chemistry of this important class of compounds.

Experimental Section

The synthesis, characterization, and handling of **1** has been described previously.[8] All solvents were purified according to commonly known procedures. Me_4Si or DSS was used as the internal standard for NMR spectra.

Kinetic Measurements. All kinetics were performed in 5 vol % CH_3CN–H_2O solutions. Procedures for purification of solvents, preparation of solutions, and monitoring the progress of reactions by UV absorption spectroscopy have been described.[8]

Kinetic measurements were performed at 40.0 ± 0.1 and 20.0 ± 0.1 °C over the pH range 1.0–8.0 in HCl solutions and in acetate or phosphate buffers. All solutions were maintained at 0.5 M ionic strength (KCl). The concentration of ester used was ca. 5×10^{-5} M.

Repetitive wavelength scans showed that, except at pH <3.1, the reaction kinetics do not conform to those of a typical pseudo-first-order process. Two, and sometimes three, consecutive reactions were observed. Absorbance changes were monitored either at wavelengths corresponding to isosbestic points of one of these reactions or at wavelengths at which significant absorbance changes occurred for all steps of the overall reaction. Isosbestic points, and wavelengths chosen to monitor the reactions, are reported in the Results section.

Absorbance vs. time data were fit by a nonlinear least-squares procedure[9] to either the standard first-order rate equation or to eq 1, the rate equation for two consecutive first-order processes. In the former case A_0, A_∞, and k, the pseudo-first-order rate constant, were treated as variable parameters. In the latter case five adjustable parameters, A_1, A_2, A_∞, and k_1 and k_2 were used. In all cases there was good agreement between observed and calculated values of A_0 and A_∞.

Kinetics of the formation of individual solvolysis products were monitored at 20 ± 1 °C by the HPLC method previously described.[8] Absorbance of products was monitored at either 225 nm or 250 nm. The concentration of **1** employed was ca. 1.25 mM. Peak area vs. time data were fit either to the first-order rate equation or to eq 1 as described above.

Product Analyses. Product studies were performed in solutions identical with those used for the kinetics measurements except that the concentration of **1** employed was higher (ca. 1.25 mM). Analyses of reaction mixtures were performed by isolation of products or by HPLC methods as previously described.[8] All stable reaction products, except **2**, are known compounds which were isolated and purified by the methods described previously[8] and were identified by comparison of physical and spectral properties with those in the literature.[10] Compound **2**, 2-(sulfonatooxy)-4-methylacetanilide, was isolated as previously described for 2-(sulfonatooxy)-4-chloroacetanilide.[8] The ^1H NMR spectrum of this material was identical with that for **2** obtained by treatment of **3**, 2-hydroxy-4-methylacetanilide, with pyridine·SO_3 in pyridine/CH_2Cl_2 (D_2O, 250 MHz): δ 1.99 (3 H, s), 2.14 (3 H, s), 6.92 (1 H, dd, J = 1.2, 8.2 Hz), 7.04 (1 H, d, J = 1.2 Hz), 7.27 (1 H, d, J = 8.2 Hz). This material is cleanly converted into **3** upon boiling a solution of its pyridinium salt in CH_3CN for several minutes.

NMR Experiments. The progress of the hydrolysis reaction of **1** in D_2O was monitored by ^1H NMR (250 MHz) at ca. 5 °C. Acetate buffers used to control pD were made from dried KOAc (to bring total buffer concentration to 0.05 M), standardized 1.68 M DCl (prepared from 37% DCl in D_2O, Aldrich), and D_2O (99.8%, Sigma). Phosphate buffers were made from KH_2PO_4, standardized 1.0 M KOH, and D_2O. The phosphate buffers were then freeze-dried and brought back to volume with fresh D_2O.

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(10) Physical and spectral data for **3**–**8** are available. See: supplementary material section.

Table I. Pseudo-First-Order Rate Constants for the Hydrolysis of 1 at 40 °C

buffer[a]	concn, M	pH[b]	10^3k_0, s^{-1}	k', s^{-1}	k'', s^{-1}
K_2HPO_4/KH_2PO_4	0.05	7.97	3.55 ± 0.14		$6.65 \pm 0.10 \times 10^{-4}$
K_2HPO_4/KH_2PO_4	0.01	7.97	3.45 ± 0.06		$6.93 \pm 0.13 \times 10^{-4}$
K_2HPO_4/KH_2PO_4	0.05	7.63	2.92 ± 0.02		$9.41 \pm 0.09 \times 10^{-4}$
K_2HPO_4/KH_2PO_4	0.01	7.63	3.02 ± 0.01		$9.74 \pm 0.05 \times 10^{-4}$
K_2HPO_4/KH_2PO_4	0.01	7.19	2.98 ± 0.05		$1.68 \pm 0.03 \times 10^{-3}$
K_2HPO_4/KH_2PO_4	0.01	6.69	2.82 ± 0.02		$3.57 \pm 0.01 \times 10^{-3}$
K_2HPO_4/KH_2PO_4	0.01	6.20	3.08 ± 0.04		$1.13 \pm 0.02 \times 10^{-2}$
K_2HPO_4/KH_2PO_4	0.01	5.72	3.24 ± 0.08	$1.70 \pm 0.08 \times 10^{-4}$	$>2.0 \times 10^{-2}$ [c]
KOAc/HOAc	0.01	5.68	2.96 ± 0.07	$1.78 \pm 0.05 \times 10^{-4}$	fast[c]
KOAc/HOAc	0.01	5.17	3.13 ± 0.05	$2.97 \pm 0.04 \times 10^{-4}$	fast[c]
KOAc/HOAc	0.05	4.66	3.32 ± 0.06	$5.31 \pm 0.06 \times 10^{-4}$	fast[c]
KOAc/HOAc	0.01	4.66	3.43 ± 0.06	$5.21 \pm 0.06 \times 10^{-4}$	fast[c]
KOAc/HOAc	0.01	4.20	3.13 ± 0.05	$8.91 \pm 0.15 \times 10^{-4}$	
KOAc/HOAc	0.01	3.74	3.04 ± 0.08	$2.29 \pm 0.10 \times 10^{-3}$	
KOAc/HOAc	0.01	3.58	3.19 ± 0.10[d]	$3.19 \pm 0.10 \times 10^{-3}$ [d]	
HCl	0.001	3.08	3.04 ± 0.02	[e]	
HCl	0.005	2.34	2.86 ± 0.02		
HCl	0.010	2.04	2.94 ± 0.05		
HCl	0.10	1.02	3.34 ± 0.03		

[a] Ionic strength = 0.50 M (KCl). [b] ± 0.02 at 40 °C. [c] Deviations from expected kinetic behavior at early reaction times clearly indicate that the process associated with k'' is still occurring, but the rate constant cannot be accurately determined. [d] The rate constants k_0 and k' are essentially indistinguishable at this pH. This is an average of the two values obtained from the least-squares calculation of 3.24×10^{-3} and 3.14×10^{-3} s^{-1}. [e] Slight deviation from first-order behavior can be observed, but k' cannot be accurately determined.

Buffers used in these studies were made at pD 5.87 (acetate), and 5.92 and 7.84 (phosphate). Measured pD values were not corrected. Reactions were initiated by addition of sufficient quantity of 1 to buffers held at 5 ± 1 °C to bring the initial concentration of 1 to ca. 1 mg/mL. The solutions were then quickly transferred to the probe of the NMR which was thermostated at ca. 5 °C. FT ^1H NMR spectra were obtained during the course of the hydrolysis reaction by use of the kinetics program written for the Aspect 2000 computer.

Isolation and Characterization of *cis*-*N*-Acetyl-2-amino-5,6-dihydroxy-5-methylcyclohexa-1,3-diene (10). The hydrolysis reaction of ca. 6.0 mM 1 in 10 mL of 0.05 M KOAc/HOAc buffer, pH 4.6, at 5 °C was monitored by HPLC as described above until the concentration of **10** reached a maximum at ca. 5 h. The reaction was then quenched by addition of sufficient 1 M KOH to bring the pH above 10. The aqueous mixture was extracted 3 times with 20-mL volumes of CH_2Cl_2 and twice with 20 mL of ethyl acetate. At this point only **2** and **10** could be detected by HPLC analysis of the aqueous solution which was then lyophilized. Care was taken during all these procedures to keep the temperature of the reaction mixture below 5 °C. The residue remaining after lyophilization was triturated with ca. 10 mL of $CHCl_3$. This brought **10** into solution along with traces of **2** and decomposition products of **10**. Attempts to purify **10** invariably led to its decomposition. Spectral data were obtained from the crude material: IR (neat) 3400 (b), 2960, 2920, 1665 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.31 (3 H, s), 2.06 (3 H, s), 3.99 (1 H, m, unresolved), 5.3 (2 H, m, broad), 5.75 (1 H, dd, J = 2.0, 10.0 Hz), 5.88 (1 H, d, J = 10.0 Hz), 6.33 (1 H, m, unresolved), 6.58 (1 H, s, broad). Attempts to prepare the *O,O*-dimethyl derivative of **10** by reaction with dimethyl sulfate or trimethyloxonium tetrafluoroborate led to decomposition of the material. The stereochemistry of **10** has been tentatively assigned on the basis of a kinetic argument (see Discussion section).

Results

Repetitive wavelength scans of the hydrolysis of 1 at 40 °C in the pH region 1.0–8.0 showed that only at pH <3.1 did the time course of the reaction follow a first-order pattern. Rate constants, k_0, for the hydrolysis of 1 in HCl solutions from pH 1.02 to 3.08, calculated from absorbance data at 218 nm, are reported in Table I. Within experimental error, these constants are independent of pH.

At all other pH values repetitive wavelength scans showed more complicated behavior. In buffer solutions from pH 3.5 to 5.7 two consecutive reactions were observed. Over most of the pH range one of the processes was significantly slower than the other, and it exhibited an isosbestic point at 218 ± 1 nm.[11] Absorbance data collected at 235 nm were fit[9] very well by eq 1, where A_∞ is

$$A_t = A_\infty + A_1e^{-k_1t} + A_2e^{-k_2t} \quad (1)$$

the absorbance at infinite time, k_1 and k_2 are pseudo-first-order rate constants, and A_1 and A_2 are arbitrary amplitude factors. Equation 1 is valid for consecutive first-order processes involving three species.[12]

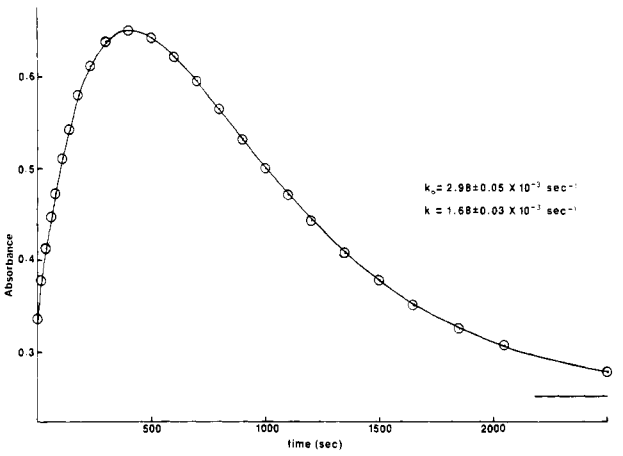


Figure 1. Absorbance at 244 nm vs. time for the hydrolysis of 1 at pH 7.19 and 40 °C. The points are experimental; the curve was generated from a least-squares fit to eq 1.

Above pH 6.0 the reaction characteristics changed considerably. Although, as shown in Figure 1, absorbance data collected at either 244 or 250 nm were still fit well by eq 1, the isosbestic point at 218 nm could no longer be observed. However, another, pH dependent, isosbestic point which changed from 220.8 nm at pH 7.97 to 225.8 nm at pH 7.19 was observed.[13] Examination of the rate constants in Table I shows that the kinetic data can only be accounted for by three separate reactions. In fact, in the pH region from 4.6 to 5.7, careful examination of absor-

(11) The isosbestic point appears to vary slightly with pH.
(12) Moore, J. W.; Pearson, R. G. "Kinetics and Mechanism", 3rd ed.; Wiley; New York, 1981; pp 290–296.
(13) The isosbestic cannot be observed at lower pH because k'' becomes too large.

Table II. Rate Parameters Derived for the Hydrolysis of 1 at 40 °C[a]

k_0	$3.1 \pm 0.2 \times 10^{-3}$ s^{-1}
k_c'	$2.0 \pm 0.3 \times 10^{-4}$ s^{-1}
k_{H^+}'	11.3 ± 0.2 M^{-1} s^{-1}
k_c''	$4.6 \pm 1.7 \times 10^{-4}$ s^{-1}
k_{H^+}''	$1.71 \pm 0.06 \times 10^{4}$ M^{-1} s^{-1}

[a] Ionic strength = 0.50 M (KCl).

bance vs. time behavior shows that all three processes can be observed, although the rate constant for the third process is too large compared to the other two to be accurately measured.

The rate constant for one of the processes (k_0), which was observed in all the buffer solutions, is clearly independent of pH and buffer concentration, and is, within experimental error, equivalent in magnitude to k_0 determined in HCl solutions. Absorbance data collected at the isosbestic points for the other processes observed in the buffer solutions can be fit to the first-order rate equation to give a rate constant identical, within experimental error, with the pH invariant rate constant calculated from eq 1. For example, at pH 4.66 a rate constant of $(3.27 \pm 0.04) \times 10^{-3}$ s^{-1} can be calculated from data taken at 218 nm, while the pH-invariant rate constant calculated from data taken at 235 nm is $(3.43 \pm 0.06) \times 10^{-3}$ s^{-1}. It is apparent that k_0 in HCl and the pH invariant constants in the buffer solutions are rate constants for the same process.

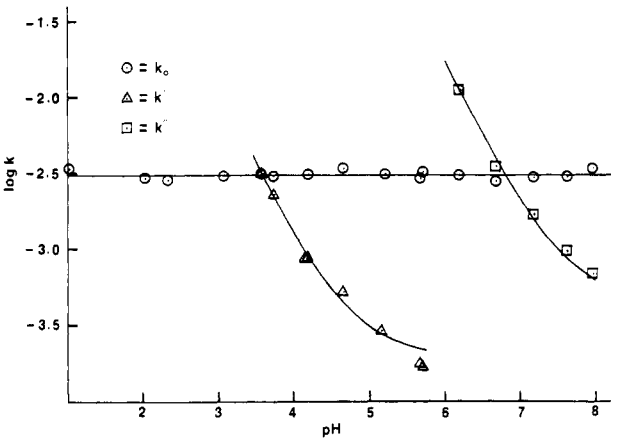


Figure 2. Plots of log k vs. pH for k_0, k', and k'' at 40 °C. The lines for k' and k'' were generated by a least-squares fit to eq 2.

The other two rate constants, k' and k'', are clearly dependent on pH but insensitive to buffer concentration. The pH dependence of both rate constants can be adequately expressed by eq 2. Values of k_c', k_c'', k_{H^+}', and

$$k = k_c + k_{H^+}[H^+] \quad (2)$$

k_{H^+}'' are presented in Table II along with the average value

Table III. Yields of Products Obtained from the Hydrolysis of 1 at 40 °C under Various pH Conditions[a]

product	0.005 M HCl pH 2.3[b,c]	1/1 KOAc/HOAc pH 4.6[b,d]	1/1 K_2HPO_4/KH_2PO_4 pH 6.7[b,d]	9/1 K_2HPO_4/KH_2PO_4 pH 7.8[b,d]
2-(sulfonatooxy)-4-methylacetanilide (2)	14 ± 1	15 ± 2	15 ± 2	14 ± 2
2-hydroxy-4-methylacetanilide (3)	*e*	*e*	*e*	*e*
4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (4)	26 ± 4	49 ± 7	65 ± 7	37 ± 3
4-hydroxymethylacetanilide (5)	3 ± 1	4 ± 1	7 ± 1	7 ± 1
3-hydroxy-4-methylacetanilide (6)	26 ± 3	9 ± 1	*e*	
3-methyl-4-hydroxyacetanilide (7)	12 ± 2	6 ± 1	12 ± 2	43 ± 5
2-chloro-4-methylacetanilide (8)	5 ± 1	7 ± 1	8 ± 1	6 ± 1

[a] Initial concentration of 1 was ca. 1.25 mM. Yields are reported with respect to 1 initially present. The solvent was 5% CH_3CN–H_2O. [b] Yields determined by HPLC. Isolation of products was used as a check of accuracy. [c] Ionic strength = 0.5 M (KCl). [d] Ionic strength = 0.5 M (KCl), total buffer concentration was 0.05 M. [e] Less than 0.5%.

Table IV. Comparison of Rate Constants for the Hydrolysis of 1 from HPLC and UV Absorption Data at 20 °C

conditions[a]	method[b]	product observed	10^2k_0, min^{-1}	$10^3k'$, min^{-1}	$10^2k''$, min^{-1}
0.10 M HCl, pH 1.02	UV		2.63 ± 0.01		
0.005 M HCl, pH 2.34	UV		2.15 ± 0.02		
0.005 M HCl, pH 2.3	HPLC	1 → 2[c]	2.2 ± 0.1		
	HPLC	4[d]	2.4 ± 0.2		
	HPLC	6	2.3 ± 0.2		
	HPLC	7	2.4 ± 0.2		
	HPLC	8	3.0 ± 0.2		
KOAc/HOAc, 0.01 M, pH 4.66	UV		2.46 ± 0.02	3.43 ± 0.04	
KOAc/HOAc, 0.05 M, pH 4.6	HPLC	1 → 2[c]	2.8 ± 0.2		
	HPLC	4[d]	3.0 ± 1.6	4.7 ± 0.7	
	HPLC	6	4.1 ± 2.5	4.4 ± 0.5	
	HPLC	7[e]	2.2 ± 11.0	5.0 ± 0.2	
	HPLC	8	2.7 ± 0.2		
	HPLC	10[f]	3.0 ± 0.4	4.6 ± 0.9	
K_2HPO_4/KH_2PO_4, 0.01 M, pH 7.63	UV		2.34 ± 0.04		1.72 ± 0.03
K_2HPO_4/KH_2PO_4, 0.05 M, pH 7.8	HPLC	1 → 2[c]	2.4 ± 0.1		
	HPLC	4[d,g]			1.4 ± 0.1
	HPLC	7	2.5 ± 2.5		1.1 ± 0.3
	HPLC	8	3.1 ± 0.4		

[a] Ionic strength was maintained at 0.5 M (KCl). [b] Kinetic determinations performed by UV absorption spectroscopy were done in a manner identical with the methods described at 40 °C. In the HPLC method aliquots (2 μL) were removed at intervals and subjected to analysis by HPLC. Products were detected by uv monitoring at 225 or 250 nm. [c] These two species coelute under the HPLC conditions employed, so that the observed peak area is due to both. [d] The product 5 appears as a shoulder on the peak for 4 under the HPLC conditions employed, so that an analysis for 5 cannot be done. Differences in product yields and extinction coefficients are such that the presence of 5 does not seriously affect the analysis of 4. [e] The data for this species fit the first-order rate eq almost as well to give a rate constant of $(5.8 \pm 0.7) \times 10^{-3}$ min^{-1}. The low yield of 7 under these conditions led to considerable scatter in the data. [f] This is the intermediate observed in acetate buffers. [g] It was not possible to obtain good peak area data for 4 at early reaction times due to interference by another peak due to an intermediate. The value of k'' was calculated from data taken after 4 half-lives for the k_0 process.

for k_0. Figure 2 shows that the quality of the fit of k' and k'' to eq 2 is good.

The results of product studies performed under various pH conditions are reported in Table III. The yields of several products, particularly **4**, **6**, and **7**, are sensitive to pH. In contrast, the yield of 2-(sulfonatooxy)-4-methylacetanilide (**2**) is, within experimental error, constant under all pH conditions studied. The yield of the corresponding product obtained from the hydrolysis of *N*-(sulfonatooxy)-*p*-chloroacetanilide was also observed to be insensitive to changes in pH.[8] Under all conditions in which KCl was present moderate yields of 2-chloro-4-methylacetanilide (**8**) were obtained, but products due to nucleophilic attack by buffer salts could not be detected at the low buffer concentrations used (0.05 M).

HPLC was used to monitor the progress of the hydrolysis reaction to determine if intermediates could be detected chromatographically and to determine which products were obtained from these species. These studies were performed at 20 °C since the half-life of **1** is too short to allow monitoring of the reaction by HPLC at 40 °C. Peak area vs. time data obtained for each product from the HPLC experiments were fit[9] to either the first-order rate equation or to eq 1. The rate constants obtained in this fashion are compared to k_0, k', and k'' obtained by UV absorption spectroscopy at 20 °C in Table IV.

In HCl solution at pH 2.3, plots of peak area vs. time for all products took on a typical first-order appearance. Rate constants, k_0, for the appearance of all products ranged from 2.2×10^{-2} to 3.0×10^{-2} min^{-1} and were in good agreement with k_0 of $(2.15 \pm 0.02) \times 10^{-2}$ min^{-1} obtained by UV spectroscopy. No evidence for the existence of an intermediate could be obtained under these conditions.

In acetic acid buffer at pH 4.6, considerably different results were obtained. The peak area vs. time curves for **4**, **6**, and probably **7**,[14] took on a distinctly biphasic appearance, while the data for **1** → **2**[15] and **8** remained first order in nature. In addition, an intermediate, referred to herein as **10**, was observed to build up and decay during the course of the hydrolysis reaction. Peak area vs. time curves for **1** → **2**, **4**, **6**, **8**, and **10** are presented in Figure 3. Under the conditions of the HPLC experiments (μ-Bondapak C-18 reverse-phase column; 50/50 methanol-/H_2O eluent, 1 mL/min) **10** had a retention time of 3.8 min which was similar to the retention time exhibited by **4** of 4.2 min. All other products except **5** had significantly longer retention times. The values of k_0 calculated from a fit of peak area vs. time data to the first-order rate equation or to eq 1 ranged from 2.2×10^{-2} to 4.1×10^{-2} min^{-1}. These are in reasonable agreement with k_0 obtained by UV spectroscopy of $(2.46 \pm 0.02) \times 10^{-2}$ min^{-1}. The values of k' obtained by fit of peak area vs. time data for **4**, **6**, **7**, and **10** ranged from 4.6×10^{-3} to 5.0×10^{-3} min^{-1}. These are all somewhat larger than the value of $(3.43 \pm 0.04) \times 10^{-3}$ min^{-1} obtained by UV methods. Since addition of ca. 1.25 mM **1**, as its pyridinium salt, invariably causes a decrease in the pH of buffer solutions, and k' is known to increase with decreasing pH, this result is not surprising. Under the circumstances, the agreement between the two methods is excellent.

If each product can be produced via two paths as in eq 3, then it is possible to calculate the relative importance

$$\text{2-8} \xleftarrow{k_0} \mathbf{1} \xrightarrow{k_0} \mathbf{10} \xrightarrow{k'} \text{2-8} \qquad (3)$$

of the two paths for each product from the least-squares parameters of the fit to eq 1. The concentration of a particular product produced by the first-order path as a function of time is given by eq 4 where $C_\infty°$ is the concentration of product produced exclusively by the first-order path at infinite time. The concentration of product produced by the path containing the intermediate **10** as a function of time is given by eq 5,[12] where C_∞' is defined

$$C_t° = C_\infty° - C_\infty° e^{-k_0 t} \qquad (4)$$

$$C_t' = C_\infty' + \frac{k_0 C_\infty' e^{-k't}}{k' - k_0} - \frac{k' C_\infty' e^{-k_0 t}}{k' - k_0} \qquad (5)$$

in a manner analogous to $C_\infty°$. The sum of these equations gives the overall concentration of the product as a function of time, where C_t is the sum of $C_t°$ and C_t', and C_∞ is the sum of $C_\infty°$ and C_∞'. Comparison of eq 1 and 6 shows that the relative importance of the two paths of eq 2 can be determined from the least-squares parameters A_∞, A_1, A_2, k_1, and k_2. For **6** this analysis shows that $C_\infty°$ is, within experimental error, equal to 0.0, so that all of this product

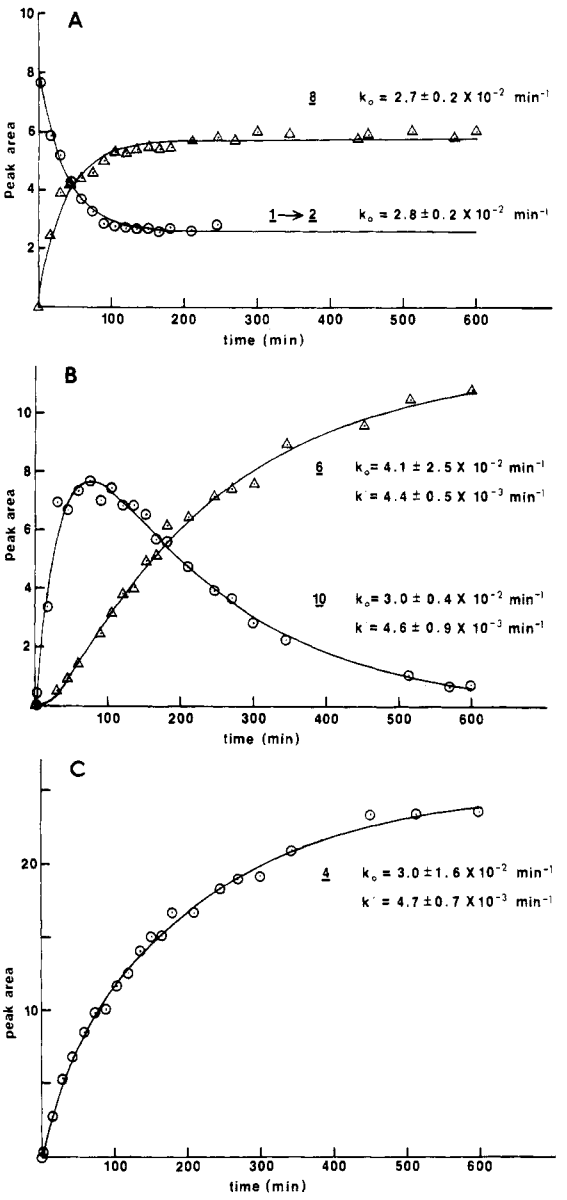


Figure 3. Plots of HPLC peak areas vs. time for the products derived from the hydrolysis of **1** in acetate buffer at pH 4.6 and 20 °C. The points are experimental; the curves and associated rate constants were generated by least-squares fits to either the first-order rate equation or eq 1. (A) Data for **1** → **2** and **8** fit to the first-order rate equation. (B) Data for **6** and the intermediate, **10**, fit to eq 1. (C) Data for **4** fit to eq 1.

(14) See footnote e, Table IV.
(15) See footnote c, Table IV.

$$C_t = C_\infty + (C_\infty - C_\infty^\circ)\frac{k_0 e^{-k't}}{k' - k_0} - \left(C_\infty^\circ + \frac{(C_\infty - C_\infty^\circ)k'}{k' - k_0}\right)e^{-k_0 t} \quad (6)$$

is produced via the intermediacy of **10**. In contrast, the same analysis for **4** shows that 30 ± 10% of the dienone is produced via the first-order path. It is not possible to make definitive conclusions for **5** and **7**, although in the latter case it does appear that a significant fraction (ca. 30%) of the product is produced by the first-order path. Since the kinetic data for **2** and **8** are fit well by the first-order rate equation, it appears that these products are formed exclusively via the first-order path.

In phosphate buffer at pH 7.8, the results of the HPLC study were different from those obtained either at pH 2.3 or 4.6. The plots of peak area vs. time for **1** → **2**[15] and **8**, however, did remain first order in nature. The rate constants, k_0, of (2.4 ± 0.1) × 10^{-2} min^{-1} and (3.1 ± 0.4) × 10^{-2} min^{-1} calculated from this data were in excellent agreement with k_0 of (2.34 ± 0.04) × 10^{-2} min^{-1} determined spectrophotometrically. Only traces of **10** were detectable at this pH. Under these conditions **10** did not decompose to a significant extent during the course of the reaction. Another transient species, **9**, was also observed. This species, which had an HPLC retention time about 0.15 min longer than that of **4**, reached a maximum concentration about 45 to 60 min into the hydrolysis reaction and subsequently decayed away rapidly. It was not possible to do a complete kinetic analysis for **9** because of interference by other peaks, specifically those of **4** and **5**. For the same reason it was not possible to do a complete kinetic analysis of the peak area data for **4**. However, a fit of the data for **4**, taken after 4 half-lives of the k_0 process, to the first-order rate equation gave a rate constant of (1.4 ± 0.1) × 10^{-2} min^{-1} which is in good agreement with k'' determined spectrophotometrically at pH 7.63 of (1.72 ± 0.03) × 10^{-2} min^{-1}. It was possible to determine both k_0 and k'' from the data for **7**. These values are in good agreement with those obtained spectrophotometrically (see Table IV). The least-squares parameters for **7** indicated that within experimental error all of this product was formed via a path involving an intermediate as in eq 7. Qualitatively, the same conclusion could be made for **4**.

$$1 \xrightarrow{k_0} 9 \xrightarrow{k''} 7 \quad (7)$$

Small but somewhat larger amounts of **10** could be detected by HPLC at pH 6.7 in phosphate buffer. Under these conditions the decomposition of **10** was very slow. Detailed kinetic analyses were not performed at this pH, but it was obvious that **4** and **7** were produced at a rate much too large to be accounted for by the decomposition of **10**. The intermediates **9** and **10**, as well as the dienone **4**, had much stronger absorbance at 225 nm than at 250 nm. This was not the case for the other products.

The hydrolysis reaction was followed by ^1H NMR (250 MHz) in D_2O at 5 °C to obtain structural information concerning the intermediates. In these studies pD was controlled by KOAc/AcOD buffers, or K_2DPO_4/KD_2PO_4 buffers. At pD 7.84 in phosphate buffer **1** disappeared in a first-order manner with a half-life of approximately 1.5 h. The hydrolysis product formed in greatest yield (ca. 50% to 60% of the total) was **4**. However, far less than half of the final yield of **4** was produced at the half-life of **1**. This can be seen in Figure 4 which presents a portion of the NMR spectrum from ca. δ 1.6 to 1.2 observed during the course of the reaction at this pD. At early reaction times the predominant reaction product is a species which

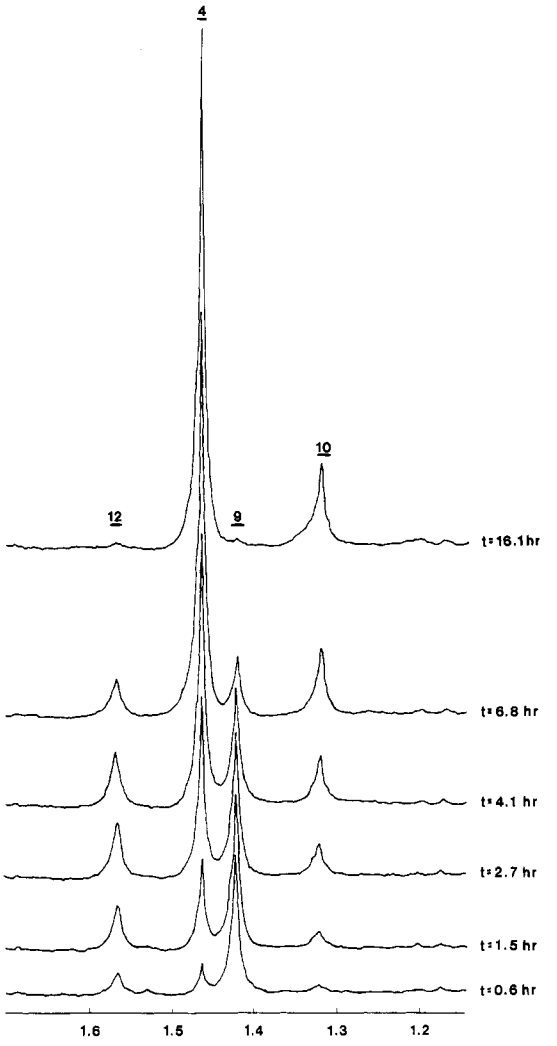


Figure 4. Portion of the ^1H NMR spectrum taken during the hydrolysis of **1** in D_2O at pD 7.84 and 5 °C as a function of time.

has a peak at δ 1.43. This material reaches a maximum concentration about 2 h into the reaction and subsequently decays away. The time course of appearance of **4** indicates that it is produced as a result of hydrolysis of this intermediate. The ^1H NMR spectrum of this species, which is apparently identical with the intermediate **9** observed in the HPLC experiments at pH 7.8, can be observed at early reaction times (D_2O, 250 MHz): δ 1.43 (3 H, s), 2.30 (3 H, s), 6.23 (2 H, d, J = 10.1 Hz), 6.74 (2 H, d, J = 10.1 Hz). Another transient reaction product, **12**, which has a peak at δ 1.57 is observed during the reaction. This material, which reaches a maximum concentration about 4.0 h into the reaction, decays away at a slower rate than does **9**. Analysis of the peak area data indicates that the overall yield of **12** is about 10% that of **9**. Due to interference by other resonance peaks it was not possible to obtain a complete NMR spectrum of **12**. However, a resonance that is associated with the peak at δ 1.57 was observed at δ 5.96. This resonance is apparently the upfield portion of an AB quartet (J = 10.3 Hz). Finally, another peak at δ 1.33 appears during the hydrolysis reaction. This peak is due to the intermediate **10** (see below). At this temperature and pD, **10**, which accounts for ca. 5% of the hydrolysis products, did not decompose to a significant extent during the time the reaction was observed. This material appears to be derived from decomposition of **9**.

At pD 5.92 in phosphate buffer, the half-life of **1** remains constant at about 1.5 h. **9** can be observed only at very

early reaction times (<0.5 h) and then only at very low concentration. **12** can be observed, and its rate of disappearance is the same as at pD 7.84. A significant amount of **4** is produced at early reaction times in an apparently first-order process. The species which has a resonance at δ 1.33 is also produced in a first-order manner with a rate comparable to the rate of disappearance of **1**. This compound shows signs of significant decomposition only after long reaction times (>7 h). However, if the solution is warmed, or if the pD of the solution is lowered by addition of DCl, it decomposes rapidly into a mixture of **4**, **6**, and **7**. The ^{1}H NMR spectrum of this species, which appears to be identical with **10** observed previously in the HPLC experiments, can be observed without interferences from other resonance peaks (D_2O, 250 MHz): δ 1.33 (3 H, s), 2.03 (3 H, s), 4.12 (1 H, d, J = 4.8 Hz), 5.85–5.95 (2 H, m), 6.03 (1 H, d, br, J = 4.8 Hz). During the decomposition of **10** very small amounts of another transient material, **11**, are produced. This species, which accounts for less than 5% of the decomposition products of **10**, persists after **10** has disappeared. Its ^{1}H NMR spectrum indicates that it is an isomer of **10** (D_2O, 250 MHz): δ 1.30 (3 H, s), 2.06 (3 H, s), 4.29 (1 H, d, J = 4.5 Hz), 5.85–6.00 (2 H, m). The peak for the proton which is coupled to the proton appearing at δ 4.29 is obscured, perhaps under the signal for the upfield portion of the AB quartet of **4** which appears at δ 6.20. Identical results were obtained in acetate buffer at pD 5.87 except that the region from ca. δ 2.1 to 1.8 of the spectrum was obscured.

Attempts to isolate **9** and **12** failed due to their considerable kinetic lability in aqueous solution and the fact that they could not be extracted from the reaction mixture with organic solvents. The intermediate **10** was isolated from the reaction mixture as described in the Experimental Section. However, even in organic solvents **10** decomposes at an appreciable rate and attempts to purify this material or to convert it into a stable derivative were not successful. Spectral data obtained from the crude isolated material, and reported in the Experimental Section, were consistent with those obtained from aqueous reaction mixtures, and with the structural assignment made for **10** (see Discussion section). No attempt was made to isolate **11** which is produced in very low yield.

Discussion

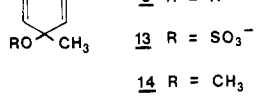
N-(Sulfonatooxy)acetanilides other than **1** undergo hydrolysis in neutral to weakly acidic media in a pseudo-first-order manner with rate constants that are independent of pH and buffer concentration.[8] A plot of log k_{obsd} vs. σ^+, which included k_0 for **1**, had a slope of −4.4 ± 0.9 at 40 °C. An intermediate which led to all reaction products, except the *o*-sulfonatooxy product analogous to **2**, could be trapped with reducing agents to yield the corresponding acetanilide. The experimental results were interpreted in terms of a mechanism involving both intimate and solvent-separated nitrenium ion pairs. The former was assumed to yield the *o*-sulfonatooxy product via internal return, while the latter led to the other solvolysis products and was also trapped by reducing agents to yield the acetanilide product.[8] A linear free energy relationship (ρ = −9.24) for the rearrangement of methanesulfonate esters of a series of ring-substituted *N*-hydroxyacetanilides in $CDCl_3$ provided evidence for a mechanism involving ion pairs.[7a] ^{18}O scrambling observed during the rearrangement of *N*-benzoyl-*O*-sulfonylphenylhydroxylamines to *O*-sulfonyl-*o*-benzamidophenols in a variety of solvents has also been used to support a mechanism involving partial oxygen equilibration in short-lived tight ion pair intermediates.[16]

Not all recent results in similar systems have been interpreted in terms of ion pair reactions. Spin-trapping studies have shown that *N*-(pivaloyloxy)acetanilides decompose in benzene solution via radical rather than ionic pathways.[6] In alcoholic solvents the *N*-(sulfonatooxy)-acetanilides undergo S–O rather than N–O bond cleavage.[8] Substituent effects observed in the acid-catalyzed rearrangement of *N*-phenylhydroxylamines have been used to suggest the intermediacy of imine structures with positive charge localized at the 2- and 4-positions of the ring.[17] It is not clear, however, how these species differ from resonance structures for a highly delocalized nitrenium ion. It has also been proposed that the reaction of bisulfite ion with *N*-phenylhydroxylamine is an S_N2' process that involves no ionic intermediates.[18]

An S_N2' process cannot be entirely ruled out as the source of some reaction products such as **2** and **8**. However, it is clear that in aqueous solution the majority of solvolysis products are produced via an ionic pathway. Since the rate constant k_0 observed during the hydrolysis of **1** is constant from pH 1.0 to 8.0, is insensitive to buffer concentration, and also fits on the Hammett line, it is apparent that the hydrolysis process for **1** must also predominately involve heterolytic N–O bond cleavage to yield ion pairs.

However, in addition to the pH-independent reaction, two pH dependent processes with rate constants k' and k'' were observed during the hydrolysis of **1**, as shown in Figure 2. HPLC results showed that these rate constants measure the rate of decomposition of two intermediates, **9** and **10**, that are generated during the reaction. Both of these compounds were detected in the ^{1}H NMR experiments performed in D_2O. The NMR experiments also provided evidence for two other minor transient species, **11** and **12**, which were not detected in either the UV kinetics or HPLC experiments.

Many, though not all, of the reaction products are derived from the breakdown of **9** and **10**. HPLC experiments showed that **2** and **8** are produced in a first-order manner with a rate constant identical, within experimental error, with k_0 under all pH conditions examined. These materials are made by pathways that do not involve **9** or **10**.



9 R = H

13 R = SO_3^-

14 R = CH_3

In contrast, at pH 7.8 HPLC experiments indicated that both **4** and **7** are produced in a biphasic manner as a result of decomposition of **9**. The rate constants associated with the formation of **4** and **7** are comparable to k_0 and k'' measured spectrophotometrically under the same conditions. At pD 7.84 an intermediate, which decomposes largely into **4**, can be detected by NMR. This species, which accounts for a large portion of the hydrolysis products of **1** (ca. 70%) is apparently identical with **9** observed in the HPLC experiments. On the basis of its ^{1}H NMR spectrum, its HPLC and UV absorption characteristics, and its decomposition products, **9** has been identified as 4-hydroxy-4-methylcyclohexa-2,5-dien-1-one *N*-acetylimine.

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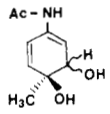
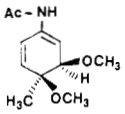


10, 11



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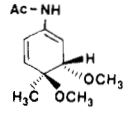

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Another intermediate which was observed at this pD, **12**, has tentatively been identified as 4-(sulfonatooxy)-4-methylcyclohexa-2,5-diene-1-one. The partial NMR spectrum obtained for this species is consistent with this assignment, as are the hydrolysis characteristics of the intermediate. In addition, the NMR experiments show that, at early reaction times when the yield of **4** is low, the yield of acetamide is too large to be accounted for by **4** alone. In fact, the sum of the yields of **4** and **12** are, to a good approximation, equal to the yield of acetamide under these conditions. The most likely source of **12** would be 4-(sulfonatooxy)-4-methylcyclohexa-2,5-dien-1-one *N*-acetylimine (**13**) which was not detected in any of the experiments. Neither **12** nor **13** would have been detected in the HPLC experiments since both of these species would have retention times similar, if not identical, with **1** and **2** under the chromatographic conditions employed. Since **12** represents only a small fraction of the reaction products it could easily have escaped detection in the kinetics experiments. The logical hydrolysis product of **12** is **4**, but since **4** is a major product of the reaction produced by other pathways, and **12** is a very minor product, this cannot be demonstrated unequivocally. However, no other products arising as a result of decomposition of **12** were detected in the NMR experiments.

Gassman and Granrud, in their study of the methanolysis of the methanesulfonate ester of *N*-hydroxy-*p*-acetotoluidide, isolated **14** which has a structure directly analogous to **9**.[7b] These authors reported no intermediates analogous to **13** which would most likely be derived from internal return of a tight ion pair. However, previous results with the *N*-(sulfonatooxy)acetanilides have shown that migration of the sulfonatooxy group to the ortho or para position of the aromatic ring is a facile process in aqueous solution.[8]

Because of their considerable kinetic lability and high water solubility neither **9** nor **12** have been successfully isolated from the aqueous reaction medium. However, the ^{1}H NMR spectrum of **9** obtained during the hydrolysis of **1** in D_2O, the decomposition products of **9**, and the strong analogy to **14**, which was isolated and characterized by Gassman and Granrud,[7b] leave little doubt about the identity of **9**. At this time the structural assignment made for **12** remains tentative.

Both the HPLC and NMR experiments indicate that minor amounts of the transient species **10** are produced during hydrolysis of **9** under neutral pH conditions. The yield of **10** is so low under these conditions that the decomposition of this material cannot be detected in the UV kinetics experiments above pH 6.0. This intermediate becomes a predominant product under more acidic conditions, but **4**, **5**,[19] and **7** are the major products of decomposition of **9** under neutral conditions. In the pH region 6.0–8.0 the decomposition of **9** involves both a pH-independent path and a specific acid-catalyzed path. Variations in product yields with pH under these conditions indicate that **7** is produced via the pH-independent path. At pH 7.8, **7** accounts for 49 ± 7% of the products derived from **9** while the pH-independent path accounts for 63 ± 28% of the overall rate of decomposition of **9**. At pH 6.7, **7** accounts for 14 ± 3% of the products, and the pH-independent path accounts for 12 ± 5% of the rate of decomposition of **9**. The critical intermediate involved in the specific acid-catalyzed path would most likely be the N-protonated conjugate acid of **9**.

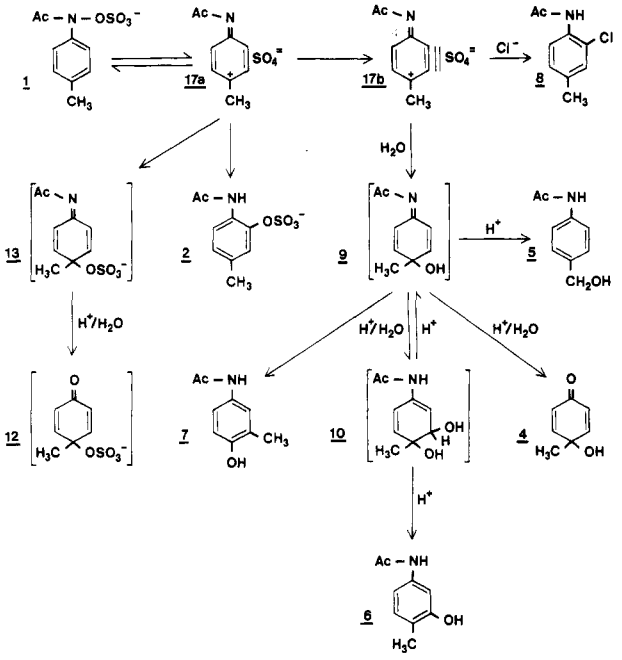
Under mildly acidic conditions in acetate buffers **10** becomes the major hydrolysis product of **9**. Decomposition products of **10** account for ca. 50% of the overall yield of hydrolysis products at pH 4.6. Significant amounts of **10** can be detected by HPLC under these conditions and the rate constants governing the formation and decomposition of **10** are comparble to k_0 and k' measured spectrophotometrically under the same conditions. At this pH **4**, **6**, and **7** are produced in a biphasic manner also with rate constants comparable to k_0 and k'. The intermediate can be observed in the NMR experiments which confirm that it decomposes into **4**, **6**, and **7**. Additionally, **10** has been isolated in an impure form from which spectral data have been obtained. On the basis of the available experimental data, and by analogy to similar compounds isolated by Gassman and Granrud, **10** has been identified as one of the isomeric *N*-acetyl-2-amino-5,6-dihydroxy-5-methylcyclohexa-1,3-dienes. Gassman and Granrud isolated both the *cis*- and *trans*-5,6-dimethoxy derivatives **15** and **16** in nearly equivalent yields.[7b] Indeed, during the decomposition of **10** at 5 °C under mildly acidic conditions, a very small amount of **11** can be detected by NMR. This species appears to be an isomer of **10**. Gassman and Granrud noted that **15** decomposed more rapidly under acidic conditions than did **16**, most likely because it can undergo a facile anti elimination which **16** cannot.[7b] Since **11** is more stable under acidic conditions than **10**, it is likely that **10** is the cis isomer. It is of interest to note that in this study **10** is the predominant product of acid-catalyzed conjugate addition of H_2O to **9**. Detectable amounts of its isomer appear in low yield only during the subsequent decomposition of **10**.

Since **4**–**7** are produced as the result of decomposition of the two intermediates **9** and **10**, the kinetics of their formation are complicated and change significantly with pH. At pH 7.8, both **4** and **7** are produced as a result of hydrolysis of **9**, but **6** cannot be detected. At pH 4.6, approximately 70% of **4** and **7**[20] are produced in a biphasic manner with rate constants that correspond to k_0 and k', the rate constant for the decomposition of **10**. The remaining 30% of these products are formed in a first-order fashion with rate constant k_0. This portion of these products is probably produced directly from the rapid hydrolysis of **9** at this pH. Kinetic studies indicate that **9** is formed at this pH, but that it decomposes very rapidly so that any products derived from it would, to a good approximation, appear to be produced in a first-order manner with a rate constant k_0. Indeed, **10**, which at higher pH can be demonstrated to be derived from the decomposition of **9**, is also generated at pH 4.6 via an apparent first-order process with a rate constant comparable to k_0. The 70% of the hydrolysis products **4** and **7** which result from the decomposition of **10** likely arise through the reversion of **10** to **9** by acid-catalyzed dehydration, and the subsequent rapid hydrolysis of **9**. However, the available data do not require this interpretation. The kinetic data for **6** demonstrate that all of this product is derived from decomposition of **10** at pH 4.6. As indicated above, at pH 7.8, **6** cannot be detected at all, while

(19) This product is probably produced as a result of dehydration of **9** followed by acid-catalyzed hydration of the resulting 4-methylene-2,5-cyclohexadien-1-one *N*-acetylimine. This likely intermediate has not been detected, however.

(20) Due to scatter in the data obtained for **7**, the error limit includes 100% for this product.

Scheme I



only traces of **10** can be observed. It is apparent that **6** is derived exclusively from **10** via acid-catalyzed dehydration.

Under more acidic conditions (pH <3.0) none of the intermediates can be detected. This is to be expected since kinetic data show that the decomposition of **9** and **10** are acid catalyzed, and under these conditions both k' and k'' are considerably larger than k_0.

The mechanism of Scheme I is consistent with the data presented in this and the previous paper[8] on the solvolysis reactions of *N*-(sulfonatooxy)acetanilides. The tight ion pair **17a** can undergo internal return to reform **1**, or the rearrangement products **2** or **13**. The tight ion pair can also form the solvent-separated ion pair **17b** which gives rise to the other products. The proportion of products derived from the tight ion pair is significantly less for **1** than for *N*-(sulfonatooxy)-*p*-chloracetanilide or the unsubstituted ester.[8] This is consistent with the expected stability of the nitrenium ions involved.

It is now possible to make a number of generalizations concerning the reactivity patterns of ester derivatives of *N*-hydroxy-*N*-arylacetamides. The modes of reaction are very sensitive to the leaving group ability of the ester moiety and to solvent polarity. In aqueous solution the *N*-(sulfonatooxy)acetanilides undergo predominant or exclusive *N*–O bond cleavage with generation of ion pair intermediates.[8] However, in alcoholic solvents the same species undergo predominant S–O bond cleavage.[8] In contrast, methanesulfonate esters of *N*-hydroxyacetanilides undergo N–O bond cleavage and ion pair reactions even in $CDCl_3$.[7a] This is no doubt due to both the better leaving group ability of the methanesulfonate ion and the unavilability of a facile mechanism for S–O bond cleavage in these species. There is mounting evidence that acetate esters, which have been used for some time as models for the carcinogenic metabolites of *N*-arylacetamides such as AAF,[4] react in aqueous solution in large part by acyl transfer, rather than nitrenium ion, pathways.[5,21,22] It is apparent that simple *N*-acyl arylnitrenium ions or ion pairs have only moderate stability in polar solvents and that changes in either solvent polarity or leaving group can lead to completely different reaction paths.

It has been shown that in nonpolar environments such as benzene certain esters of this type can undergo radical reactions apparently involving homolytic N–O bond cleavage.[6,23] It remains to be seen if these radical reactions have any relevance to the biological activity of these species, but they do demonstrate the varied chemistry that can be expected from these compounds.

A number of questions concerning the hydrolysis reactions of these esters remain unanswered., One of these involves the possibility of catalysis of N–O bond cleavage. The more reactive *N*-(sulfonatooxy)acetanilides show no catalysis of this process by hydronium ion down to a pH of 1.0. Moderate rate accelerations have been observed below pH 3.0 for the less reactive members of this series,[8] but the nature of this process has not been carefully investigated. No other examples of catalysis of N–O bond cleavage in ester derivatives of *N*-hydroxy-*N*-arylacetamides have been reported. In the absence of experimental data, metal ion catalysis would also apear to be a possibility, especially for the sulfate esters. Esters of this type have been reported to undergo redox reactions with a number of common reducing agents such as KI and Fe^{2+}.[8,24] Although some mechanistic proposals have been put forth,[8,24] the nature of these reactions remains unclear. Some of the adducts isolated from the reaction of purine bases with model esters in both in vivo and in vitro experiments are apparently derived from nucleophilic attack on the nitrogen of the model compound.[1-4] This type of reaction has not been reproduced in model systems with non-purine bases, and the mechanism of the process which yields such products is still subject to question. Aspects of all of these problems are under investigation in this laboratory.

Finally, meta substitution products have been reported previously to result from the reactions of certain nucleophiles with *N*-acetoxy-*N*-acetyl-2-aminofluorene.[25] Similar products have been isolated from the reaction of *N*-acetyl-*p*-benzoquinone imine with nucleophiles.[8,26] It has been postulated that these products arise from an initial dienone imine intermediate similar to **9**.[25] However, there has been some controversy concerning subsequent reaction steps. Scribner proposed that an addition elimination sequence similar to **9** → **10** → **6** occurred,[25a] while others have favored a 1,2-migration.[25b] The study of Gassman and Granrud[7b] and this work both support the former proposal.

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Supplementary Material Available: Physical and spectral data for solvolysis products 3–8 (3 pages). Ordering information is given on any current masthead page.

Thermolysis and Photolysis of the Azoalkane 4,5-Diaza-7,8,8-trimethyltricyclo[4.2.1.$0^{3,7}$]non-4-ene: 1,3-Diradical and Diazoalkane Formation

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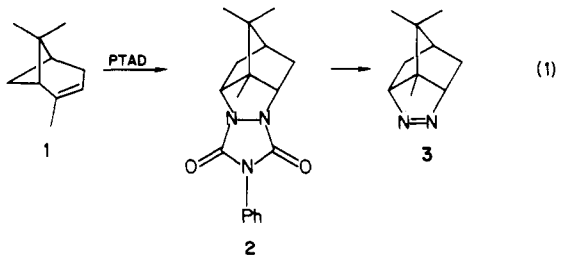
On benzophenone-sensitized photolysis at 350 nm the azoalkane **3** denitrogenates exclusively into 2,3,3-trimethyltricyclo[2.2.1.$0^{2,6}$]heptane (**5**), while direct photolysis at 350 nm affords the tricycloheptane **5** as major product and 2,3,3-trimethyl-4-vinylcyclopentene (**6**) as minor product. With increasing temperature the vinylcyclopentene **6** increases in the direct photolysis. On preparative laser photolysis at 333 nm the diazo-2-(2,3,3-trimethylcyclopenten-4-yl)ethane (**8**) accumulates, which on subsequent photolysis is shown to produce the vinylcyclopentene **6** via the corresponding carbene intermediate. The diazoalkane **8** does not cyclize back to the azoalkane **3**. The thermolysis leads essentially quantitatively to the tricycloheptane **5**, with only traces of the vinylcyclopentene **6**. These results are rationalized mechanistically in terms of a diazenyl diradical as common intermediate for all three denitrogenation modes. It is proposed that the divergent chemical behavior of the diazenyl diradicals produced in the three forms of activation (triplet-sensitized and direct photolysis and thermolysis) is best understood in terms of distinct spin multiplicities and electronic configurations of the diradical intermediates. In this tritopic process it is shown by means of a Salem diagram that the $D_{\sigma,\sigma}$ diazenyl diradical serves as precursor to the tricycloheptane **5** via the 1,3-diradical **4**, while the $D_{\sigma,\pi}$ diradical is responsible as intermediate for the vinylcyclopentene **6** via the diazoalkane **8**.

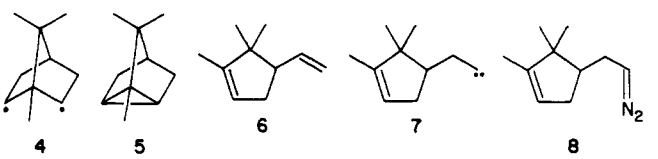
Introduction

Recently it was shown[1] that α-pinene (**1**) gives on cycloaddition with 4-phenyl-1*H*-1,2,4-triazole-3,5-dione (PTAD) the rearranged urazole **2** in fair yields (eq 1).

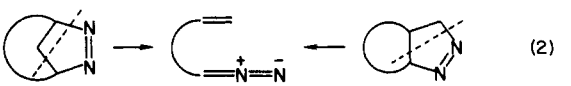


Since such urazoles can be readily converted into their corresponding azoalkanes on hydrolysis–oxidation,[2] it was of mechanistic interest to prepare the azoalkane **3** from urazole **2** and explore its thermolytic and photolytic behavior. Via nitrogen extrusion such azoalkanes serve as convenient precursors to 1,3-diradicals.[3]

In the particular case of azoalkane **3** the 1,3-diradical **4** was expected, which should cyclize into the tricycloheptane **5** or possibly rearrange via 1,2-shift to revert to α-pinene (**1**), although such diradical rearrangements are not common.[4] However, the unexpected formation of the



vinylcyclopentene **6** as minor product[5] implicated the carbene **7** as the immediate precursor, presumably formed from the intermediary diazoalkane **8** via nitrogen loss. Indeed, numerous examples of retrocleavages of azoalkanes into diazoalkanes (eq 2) have been documented during the



past years.[6] Consequently, a thorough investigation of the

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