of the solvent in vacuo, the crude product was purified by HPLC (μ-Porasil, 15% ethyl acetate in hexane). There was obtained 65.5 mg 22% of recovered aldol and 74 mg (25%) of crystalline ketone **26**, mp 70.0–70.5 °C: R_f 0.63 (hexane–ethyl acetate, 2:1); IR ($CHCl_3$) 3400, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) (360 MHz) δ 6.71 (s, 1 H), 5.10 (br s, 1 H), 3.37 (s, 3 H), 3.27 (AB q, 2 H, J = 8.7 Hz, $\Delta\nu_{AB}$ = 38.4 Hz), 2.60 (m, 1 H), 2.58 (AB q, 2 H, J = 10.8 Hz, $\Delta\nu_{AB}$ = 78.3 Hz), 1.5–2.5 (m, 9 H), 1.68 (d, 3 H, J = 1.4 Hz), 6.99 (d, 3 H, J = 6.5 Hz), 0.82 (d, 3 H, J = 6.5 Hz). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.85; H, 9.14.

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Hydrolysis of *N*-(Pivaloyloxy)-*p*-acetotoluidide: N–O Bond Cleavage Reactions of a Model Proximate Carcinogen

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The hydrolysis reactions of *N*-(pivaloyloxy)-*p*-acetotoluidide (**1a**), a model for the carcinogenic metabolites of polycyclic aromatic amides, were investigated by a combination of UV spectroscopy, product analyses, and HPLC methods at 70 °C over the pH range 2.0–8.0. Under these conditions **1a** undergoes exclusive N–O bond cleavage to yield products characteristic of processes involving nitrenium ion pairs. In many ways the reactions of **1a** in aqueous solution parallel those of the analogous sulfuric acid ester, **1b**. However, two unique products, 3-(pivaloyloxy)-4-methylacetanilide (**2b**) and 4-acetotoluidide (**9**), which have no analogues in the reactions of **1b** under these conditions, were isolated. The first-order rate constant for the decomposition of **1a**, which is independent of pH and buffer composition, is (380 ± 60)-fold less than the corresponding rate constant for **1b** under the same conditions. The characteristics of the hydrolysis reaction of **1a** are considerably different from those of the *N*-acetoxy-*N*-arylacetamides which undergo a considerable amount of acyl transfer under similar conditions. These results indicate that pivalic acid esters may be more appropriate models for the proximate carcinogens derived from *N*-hydroxy-*N*-arylacetamides than are the acetic acid esters if, indeed, nitrenium ions are the ultimate carcinogens.

Sulfuric acid esters appear to be important carcinogenic metabolites of polycyclic *N*-aryl-*N*-hydroxyamides.[1,2] The chemistry of a series of *N*-(sulfonatooxy)acetanilides, which are monocyclic analogues of the polycyclic sulfuric acid esters, has been the subject of a number of investigations in this laboratory.[3] In aqueous solution these compounds decompose via heterolytic N–O bond cleavage to yield tight nitrenium ion–sulfate ion pairs which undergo internal return to yield rearrangement products, and solvent-separated ion pairs which are attacked by external nucleophiles or reducing agents.[3] The closely related methanesulfonic acid esters of the *N*-hydroxyacetanilides, investigated by Gassman and Granrud, behave in a similar fashion.[4]

Carboxylic acid esters of the *N*-hydroxyacetanilides are also of interest since they present the opportunity to investigate the effect of the leaving group on the chemistry of ester derivatives of *N*-hydroxy amides. In addition, carboxylic acid esters apparently are also important carcinogenic metabolites of certain *N*-aryl-*N*-hydroxy amides.[1] *N*-acetoxy-*N*-arylacetamides have been used as model proximate carcinogens in a large number of in vivo and in vitro studies,[1,5] and a number of studies involving the solution chemistry of *N*-acetoxy-*N*-arylacetamides have appeared.[6,7] However, these acetic acid esters undergo facile acyl transfer reactions[6e,7b] which complicate the investigation of the chemistry of the N–O bond in such compounds.

Accordingly, we have synthesized and investigated the aqueous solution chemistry of *N*-(pivaloyloxy)-*p*-acetotoluidide (**1a**). The bulky pivalic acid ester was chosen so that the acyl transfer side reaction would be suppressed.

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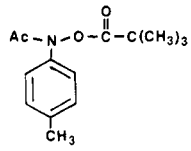
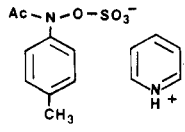
This particular model compound was also chosen because the corresponding sulfuric acid ester, **1b**, is reasonably representative of the class of compounds to which it belongs[3a,b] and because **1b** undergoes some unusual reactions with nucleophiles that are also characteristic of ester derivatives of the well-known carcinogen N-hydroxy-N-acetyl-2-aminofluorene.[8] Indeed, **1a** undergoes exclusive



1a



1b

N–O bond cleavage in aqueous solution; however, its rate of decomposition is 380-fold slower than that of **1b**, under identical conditions. The characteristics of the hydrolysis reactions of **1a** are compared and contrasted herein to those of **1b** which we recently reported in this journal.[3b] Although there are many similarities between the reactions of **1a** and **1b**, there are also some differences which are of interest. The results of this study clearly indicate that the pivalate esters are superior to their acetate ester analogues as sources of arylnitrenium ions, which are thought to be the ultimate carcinogens derived from aromatic amides.[1]

Experimental Section

All solvents used were reagent grade and were purified, if necessary, according to commonly known procedures. Reported melting points are uncorrected. Me_4Si was used as an internal standard for NMR spectra. The synthesis of **1a** from N-hydroxy-p-acetotoluidide and pivaloyl chloride has been previously described.[9]

Kinetic Measurements. All kinetics were performed in 5 vol % CH_3CN–H_2O. Procedures for purification of solvents, preparation of solutions, and monitoring the progress of the reactions by UV absorption spectroscopy have been described.[3a]

Kinetic experiments were carried out at 70.0 ± 0.1 °C over the pH range 2.0–7.5 in HCl solutions and in acetate or phosphate buffers. Total buffer concentration was 0.05 M, and ionic strength was maintained at 0.50 M in all solutions with KCl. The concentration of **1a** used was ca. 5×10^{-5} M. Absorbance vs. time data were collected, as long as isosbestic points held, by monitoring the changes in UV absorbance at the wavelength of maximum absorbance change at each pH (between 216 and 220 nm in all cases). Pseudo-first-order rate constants were calculated by a nonlinear least-squares fit of the absorbance vs. time data to the standard first-order rate equation.[3a,10]

Kinetics of the decomposition of **1a** and formation of individual hydrolysis products were carried out at 70.0 ± 0.5 °C by HPLC methods previously described.[3a] The progress of the hydrolysis reactions run at pH 2.4, 4.7, and 6.7 was followed on a μ-Bondapak C-18 column with 6/4 MeOH/H_2O serving as eluent. The hydrolysis reaction run at pH 7.8 was followed on an Ultrasphere-Octyl column (Beckman) with 6/4 MeOH/H_2O serving as eluent. Absorbance was monitored at 250 nm in all cases. Peak area vs. time data were fit to the standard first-order rate equation as described above.

Product Analyses. Product studies were carried out in solutions identical with those used in the kinetic measurements except that the concentration of **1a** employed was higher (ca. 1.25 mM). Analyses of reaction mixtures were performed by isolation of products or by HPLC methods as previously described.[3a] Two sets of column conditions were needed to achieve adequate separation of all products. These were as follows: μ-Bondapak C-18 column, 1/1 MeOH/H_2O eluent, 1 mL/min; Ultrasphere-Octyl column, 1/1 MeOH/H_2O eluent, 1 mL/min. All products, save **2a**, **2b**, and **10**, are known compounds which were previously isolated, purified, and identified in the study of the hydrolysis of **1b**.[3b,c] Isolation and characterization of **2a**, **2b**, and **10** are outlined below.

2-(Pivaloyloxy)-4-methylacetanilide (2a). This compound was isolated from hydrolysis reaction mixtures by extraction into CH_2Cl_2 and was purified by repetitive preparative layer chromatography (silica gel GF 250; 4/1 CH_2Cl_2/EtOAc eluent): mp 129.5–130.5 °C; IR (KBr) 3230, 3045, 2980, 1750, 1662, 1510, 1103 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.85 (1 H, d, J = 8.1 Hz), 7.04 (1 H, d, J = 8.1 Hz), 6.93 (1 H, s, br), 6.90 (1 H, s), 2.33 (3 H, s), 2.08 (3 H, s), 1.38 (9 H, s). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.72; H, 7.84; N, 5.54. A compound with identical chromatographic, physical, and spectral properties was prepared from the reaction of 2-hydroxy-4-methylacetanilide (**3**)[3b] with pivaloyl chloride in dry CH_2Cl_2 in the presence of N-ethylmorpholine.

3-(Pivaloyloxy)-4-methylacetanilide (2b). This material was isolated and purified in the same manner as **2a**: mp 112–112.5 °C; IR (KBr) 3295, 3120, 2960, 2920, 2870, 1748, 1665, 1610, 1550, 1509, 1115 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.29 (1 H, s), 7.18 (1 H, s, br), 7.15 (2 H, s), 2.11 (3 H, s), 2.10 (3 H, s), 1.37 (9 H, s). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.68; H, 7.78; N, 5.66. A compound with identical chromatographic, physical, and spectral properties was prepared from the reaction of 3-hydroxy-4-methylacetanilide (**6**)[3b] with pivaloyl chloride in dry CH_2Cl_2 in the presence of N-ethylmorpholine.

2-Hydroxy-4-methylpivalanilide (10). When authentic **2a**, synthesized as indicated above, was incubated in pH 6.7 or 7.8 phosphate buffer two products were formed as **2a** decomposed. These materials were extracted into CH_2Cl_2 and were purified by preparative layer chromatography as indicated above. One of these compounds was identical with 2-hydroxy-4-methylacetanilide (**3**).[3b] The other compound, **10**, had the following physical and spectral properties: mp 135–136 °C; IR (KBr) 3430, 3100, 2970, 2870, 1640, 1611, 1601, 1540, 1282 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 8.88 (1 H, s), 7.55 (1 H, s, br), 6.84 (1 H, d, J = 8.0 Hz), 6.79 (1 H, d, J = 1.0 Hz), 6.68 (1 H, dd, J = 1.0, 8.0 Hz), 2.28 (3 H, s), 1.33 (9 H, s). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.21; H, 8.31; N, 6.63. A compound identical with **10** was synthesized by reaction of 2-hydroxy-4-methylaniline (Aldrich) with pivaloyl chloride in dry ether in the presence of N-ethylmorpholine.

Results

Repetitive wavelength scans confirmed that the hydrolysis reactions of **1a** at 70 °C followed a first-order pattern for at least three half-lives at pH <6.0. At higher pH the reaction noticeably deviated from first-order behavior at an earlier point. This was later determined to be due to the base-catalyzed decomposition of one of the initial hydrolysis products (see below). Since this subsequent reaction was relatively slow in the pH range studied, no attempt was made to fit absorbance vs. time data to an equation for consecutive first-order processes.[3b] Instead, absorbance vs. time data were collected at each pH for as long as the initially observed isosbestic points held (always at least 1.8 half-lives), and these data were fit[10] to the first-order rate equation to obtain k_{obsd}. In all cases satisfactory fits were obtained; however, the values of k_{obsd} at higher pH were determined with less precision than those at lower pH since in these cases the reaction was followed for less time.

The data presented in Table I show that, within experimental error, k_{obsd} is insensitive to changes in pH and buffer composition over the pH range studied. The average value of k_{obsd} for **1a** of $(1.17 \pm 0.10) \times 10^{-4}$ s^{-1} is (380 ± 60)-fold less than the first-order rate constant for the decomposition of **1b** at 70 °C [$(4.4 \pm 0.6) \times 10^{-2}$ s^{-1}] extrapolated from data taken in the temperature range from 20 to 50 °C.[3a,b]

The pH dependence of the isosbestic points is an indication that the nature of the hydrolysis products changes

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Table I. First-Order Rate Constants for the Hydrolysis of 1a at 70 °C

buffer[a]	pH[b]	$10^4 k_{obsd}$, s^{-1}
K_2HPO_4/KH_2PO_4	7.23	1.00 ± 0.08
K_2HPO_4/KH_2PO_4	6.64	1.32 ± 0.08
K_2HPO_4/KH_2PO_4	6.02	1.11 ± 0.01
KOAc/HOAc	5.66	1.16 ± 0.01
KOAc/HOAc	5.30	1.06 ± 0.02
KOAc/HOAc	4.69	1.19 ± 0.02
KOAc/HOAc	4.12	1.21 ± 0.02
KOAc/HOAc	3.77	1.11 ± 0.02
HCl	3.12	1.15 ± 0.01
HCl	2.42	1.24 ± 0.01
HCl	2.11	1.32 ± 0.04

[a] Ionic strength = 0.50 M (KCl). Total buffer concentration = 0.05 M. [b] ±0.02 at 70 °C.

with pH. Table II, which lists the yields of products isolated after five to six hydrolysis half-lives for **1a**, shows that this is the case. The products **4–8** were also observed among the hydrolysis products of **1b**.[3b]

The rearrangement product 2-(pivaloyloxy)-4-methylacetanilide (**2a**) decomposes into 2-hydroxy-4-methylacetanilide (**3**)[11] and 2-hydroxy-4-methylpivalanilide (**10**) in the more basic buffers (see below). The combined yields of **2a** and its decomposition products **3** and **10** are approximately constant under all conditions, so that it appears that the yield of **2a** is insensitive to pH. This was also the case for the analogous product isolated from the hydrolysis of **1b**, 2-(sulfonatooxy)-4-methylacetanilide.[3b] The other rearrangement product, 3-(pivaloyloxy)-4-methylacetanilide (**2b**), has no analogue in the reactions of **1b**. This material is stable under all the pH conditions examined so that its decreased yield in the phosphate buffers is real. The reduction product 4-acetotoluidide (**9**) is formed in moderate yields in the more basic buffers. Although acetanilide reduction products are commonly observed when the *N*-(sulfonatooxy)acetanilides undergo hydrolysis in the presence of reducing agents,[3a,c] they have not been observed when these compounds undergo hydrolysis in ordinary phosphate buffers.

The progress of the hydrolysis reaction was followed by HPLC methods which allowed the concentrations of **1a** and individual hydrolysis products to be monitored separately.[3a,b] Rate data obtained at four different pH values from these studies are presented in Table III. The decomposition of **1a** always followed a first-order pattern with rate constants which ranged from 1.0×10^{-4} to 1.4×10^{-4} s^{-1}. These values are in good agreement with the rate constant obtained by spectrophotometric methods [$(1.17 \pm 0.10) \times 10^{-4}$ s^{-1}] and indicate that the decomposition of **1a** is not catalyzed by either acids or bases in the pH range of this study. At pH 2.4 and 4.7 all hydrolysis products were formed in a first-order manner with rate constants that were equivalent, within experimental error, to the rate constant for the decomposition of **1a**. At pH 6.7 this general pattern was followed with the exception of the concentration vs. time data for **2a**. Under these conditions **2a** decomposed slowly. As it did, two new products, **3** and **10**, appeared. At pH 7.8 this trend was more pronounced: **2a** decomposed more rapidly and greater yields of **3** and **10** were observed. However, the isomeric material, **2b**, continued to be produced in a first-order manner. The formation of the reduction product, **9**, was characterized by a lag phase. At this pH, the peak area vs. time data for the HPLC peak corresponding to **4**, **5**, and **7**[12] did not fit a first-order pattern either. The peak area for these components at the completion of the reaction was considerably lower (by ~30%) than that predicted from data taken in the first half-life of the hydrolysis reaction.

The decomposition of authentic **2a**[13] at 70 °C in pH 6.7 and 7.8 buffers was studied by HPLC methods. At both pH values **2a** decomposed exclusively to **3** and **10**. Pseudo-first-order rate constants for the decomposition of **2a** were calculated from peak area vs. time data. These were $(9.1 \pm 0.5) \times 10^{-5}$ s^{-1} at pH 7.8 and $(9.7 \pm 0.8) \times 10^{-6}$ s^{-1} at pH 6.7. Preliminary results indicate that the rate of this reaction is insensitive to buffer concentration. Under the same conditions the isomeric material, **2b**, was considerably more stable. After 8 h of incubation of authentic **2b**[13] at 70 °C in pH 7.8 buffer, only traces of 3-hydroxy-4-methylacetanilide (**6**) could be detected. After this same amount of time in the same buffer, the decomposition of **2a** was essentially complete.

Discussion

N-Acetoxy-*N*-arylacetamides have been used for some time as model proximate carcinogens in both in vitro and in vivo studies.[1,5] They have been used in place of the analogous *N*-(sulfonatooxy)-*N*-arylacetamides largely because of their relative ease of synthesis and greater stability. These compounds were widely thought to undergo predominant, if not exclusive, N–O bond cleavage to yield nitrenium ions which are presumed to be the ultimate carcinogens.[1] In an early study, the observation of nonlinear plots of rate constants vs. salt concentration for the hydrolysis of several *N*-acetoxy-*N*-arylacetamides was interpreted in terms of reversible formation of nitrenium ion–acetate ion pairs.[6a] However, recently it has been shown that, under the same conditions as in the earlier study, the same *N*-acetoxy-*N*-arylacetamides specifically labeled with ^{18}O in the ester carbonyl do not undergo ^{18}O scrambling which would be required if ion pairs were formed reversibly.[7a] Furthermore, the solvolysis of *N*-acetoxy-*N*-acetyl-4-aminobiphenyl under these conditions was shown in another labeling study to proceed entirely by C–O bond cleavage to yield *N*-hydroxy-*N*-acetyl-4-aminobiphenyl and acetic acid.[7b] The acetic acid ester corresponding to **1a** also undergoes exclusive C–O bond cleavage in 60/40 acetone/H_2O.[7c] Other workers have shown that several other *N*-acetoxy-*N*-arylacetamides undergo acyl transfer reactions under various conditions.[6e,14] It is now clear that under many conditions the predominant, if not exclusive, reaction of *N*-acetoxy-*N*-arylacetamides is acyl transfer. If nitrenium ions are the ultimate carcinogens derived from aromatic amides then the *N*-acetoxy-*N*-arylacetamides are poor models for the proximate carcinogens.

However, the products isolated from the hydrolysis reactions of the pivalic acid ester (**1a**) in 5% CH_3CN–H_2O (Table II), demonstrate that this compound undergoes exclusive N–O bond cleavage. The products **4–8** were previously isolated from the hydrolysis reactions of the corresponding sulfuric acid ester, **1b**, and are indicative of a process which involves a nitrenium ion intermediate.[3b] The products **2a** and **2b** are similar to those previously attributed to internal return, with rearrangement, of a tight nitrenium ion–sulfate ion pair.[3a,b] The methanesulfonic

(11) Traces of **3** were isolated during the hydrolysis of **1b** also (ref 3b). Small amounts of this compound are probably formed by direct attack of H_2O.

(12) See footnote *c*, Table III.

(13) Synthesized as described in the Experimental Section.

(14) Barry, E. J.; Gutmann, H. R. *J. Biol. Chem.* **1973**, *248*, 2730–2737.

Table II. Yields of Products Obtained from the Hydrolysis of 1a at 70 °C under Various pH Conditions[a]

product	0.005 M HCl, pH 2.4[b,c]	1/1 KOAc/HOAC, pH 4.7[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-(pivaloyloxy)-4-methylacetanilide (**2a**)[e]	45 ± 5	45 ± 7	35 ± 5	11 ± 2
3-(pivaloyloxy)-4-methylacetanilide (**2b**)	10 ± 1	10 ± 2	5 ± 1	2 ± 1
2-hydroxy-4-methylacetanilide (**3**)[f]	g	g	6 ± 2	16 ± 3
4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (**4**)	15 ± 2	28 ± 2	23 ± 3	12 ± 2
4-hydroxymethylacetanilide (**5**)	3 ± 1	3 ± 1	3 ± 1	3 ± 1
3-hydroxy-4-methylacetanilide (**6**)	13 ± 1	2 ± 1	g	
3-methyl-4-hydroxyacetanilide (**7**)	11 ± 1	4 ± 1	13 ± 1	23 ± 3
2-chloro-4-methylacetanilide (**8**)	5 ± 1	6 ± 1	5 ± 1	3 ± 1
4-acetotoluidide (**9**)			3 ± 1	12 ± 2
2-hydroxy-4-methylpivalanilide (**10**)[f]	g	2 ± 1	4 ± 1	10 ± 1

[a] Initial concentration of **1a** was ca. 1.25 mM. Yields are reported with respect to **1a** initially present. [b] Yields determined by HPLC. Isolation of products was used to check yields in some cases. [c] Ionic strength = 0.50 M (KCl). [d] Ionic strength = 0.50 M (KCl). Total buffer concentration = 0.05 M. [e] This product decomposes into **3** and **10** in the more basic buffers. [f] Product of the decomposition of **2a**. [g] Less than 0.5%.

Table III. First-Order Rate Constants Obtained from HPLC Experiments at 70 °C

conditions[a]	material observed[b]	$10^4 k_{obsd}$, s^{-1}
0.005 M HCl, pH 2.4	**1a**	1.39 ± 0.23
	2a	1.10 ± 0.30
	4, **5**, **7**[c]	1.01 ± 0.10
	6	0.99 ± 0.17
KOAc/HOAc, 0.05 M, pH 4.7	**1a**	1.02 ± 0.10
	2a	1.21 ± 0.24
	2b	0.97 ± 0.22
	4, **5**, **7**[c]	1.02 ± 0.06
K_2HPO_4/KH_2PO_4, 0.05 M, pH 6.7	**1a**	1.30 ± 0.05
	4, **5**, **7**[c]	1.17 ± 0.15
K_2HPO_4/KH_2PO_4, 0.05 M, pH 7.8	**1a**	1.42 ± 0.06
	2b	1.03 ± 0.26

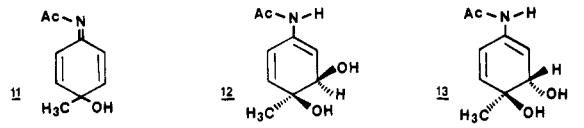
[a] Ionic strength = 0.5 M (KCl). Initial concentration of **1a** was ca. 1.25 mM. [b] Aliquots (2 μL) were removed from the reaction mixture and subjected to HPLC analysis by one of the methods described in the Experimental Sections. [c] Under the conditions employed these materials were not resolved into separate peaks.

acid esters of the *N*-hydroxyacetanilides also yield similar products which appear to arise from nitrenium ion intermediates.[4] No *N*-hydroxy-*p*-acetotoluidide, which would be indicative of an acyl transfer reaction,[3a,7b] was detected.

The kinetics of the decomposition of **1a** also resemble that previously observed for the *N*-(sulfonatooxy)acetanilides.[3a,b] In both cases the first-order rate constant for the decomposition of the ester in aqueous solution is independent of pH and buffer composition (see Table I). The hydrolysis rates of esters of *N*-hydroxy compounds which do undergo acyl transfer are very sensitive to pH and buffer concentration.[7b,15] It appears that the bulky pivalic acid esters, in which the acyl transfer reaction is suppressed, would be better models for proximate carcinogens than the acetic acid esters if nitrenium ions are, indeed, the ultimate carcinogens.[16]

The average value of k_{obsd} for **1a** [$(1.17 \pm 0.10) \times 10^{-4}$ s^{-1}] is (380 ± 60)-fold less than the corresponding rate constant for **1b** extrapolated to 70 °C from data taken at lower temperatures.[3a,b] The value of $\Delta \log k_{obsd}$ of 2.58 ± 0.07 is comparable to ΔpK_a for pivalic acid and HSO_4^- of ca. 3.1.[17] The rate of decomposition of Ar(Ac)N–OX in aqueous solution is, therefore, very sensitive to the pK_a of XOH. The N–O bond appears to be completely, or nearly completely, broken in the rate-determining transition state of the reaction.

During the hydrolysis reactions of **1b** it was possible to detect a number of unstable intermediates identified as **11** and the cis and trans isomers **12** and **13**, which subsequently decomposed into the hydrolysis products **4**–**7**.[3b]



In the present case it was not possible to detect these intermediates, but **4**–**7** were observed. Since the yields of these materials depended on pH in the same manner as was previously observed for **1b**,[3b] it is likely that **11**–**13** are also intermediates in the hydrolysis of **1a**. Rate constants for the decomposition of the intermediates at 40 °C[3b] were all larger than k_{obsd} measured for **1a** at 70 °C. Since these rate constants must be even larger at 70 °C than at 40 °C, there is little likelihood that the intermediates involved could be detected in the present case.

All the *N*-(sulfonatooxy)acetanilides undergo a rearrangement process which leads to 2- or 4-(sulfonatooxy)-acetanilides.[3a,b] Since the yield of these products could not be significantly altered by the addition of nucleophiles or reducing agents, which did alter the yields of other products, it was proposed that these species were formed by internal return of a tight ion pair. The combined yields of the analogous product **2a** and its decomposition products, **3** and **10**, are also essentially invariant to pH changes (Table II). It is likely that **2a** also arises from the internal return of a tight ion pair. The decomposition of **2a** into **3** and **10** appears to be a specific-base-catalyzed process, and it must involve intramolecular participation by the amide functionality, since the isomer of **2a**, **2b**, is stable under these conditions. At least one of the products, **10**, must be formed by nucleophilic participation of the amide nitrogen, a reaction for which there is considerable intermolecular precedent.[18]

The isomeric material, **2b**, in which the pivaloyloxy group is at the 3-position, is also formed during the hydrolysis of **1a**. No analogous 3-(sulfonatooxy)acetanilides have been detected in the reactions of the sulfuric acid esters.[3] Since direct attack of the pivalate ion on the 3-position of the aromatic ring of the nitrenium ion is an unlikely process, a sequence that begins with the tight ion pair, **14a**, and involves a 1,2-migration, as shown in eq 1,

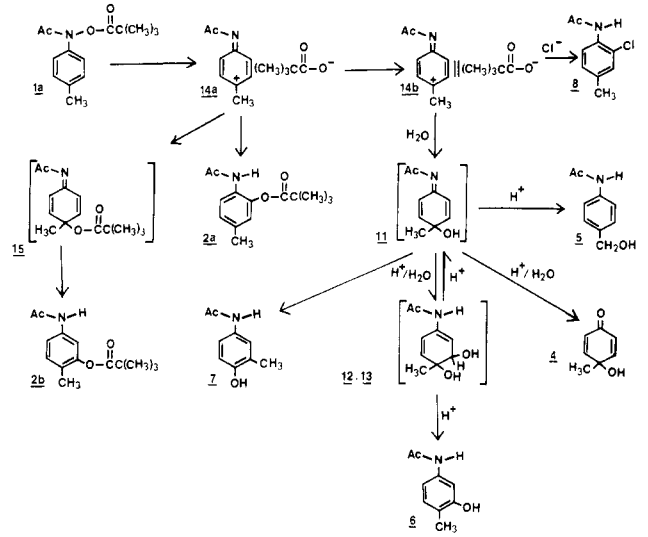
(15) McCarthy, D. G.; Hegarty, A. F.; Hathaway, B. J. *J. Chem. Soc., Perkin Trans. 2* **1977**, 224–231. McCarthy, D. G.; Hegarty, A. F. *Ibid.* **1977**, 231–238.

(16) We are currently studying the reactions of the sulfuric and pivalic acid esters of *N*-hydroxy-*N*-acetyl-2-aminofluorene.

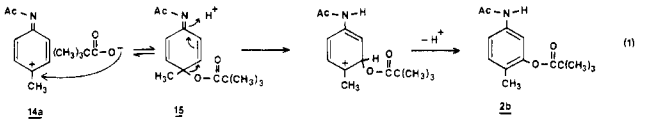
(17) "CRC Handbook of Chemistry and Physics", 61st ed.; CRC Press: Boca Raton, FL, 1980; pp D-164–D-167.

(18) March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; pp 389–390.

Scheme I

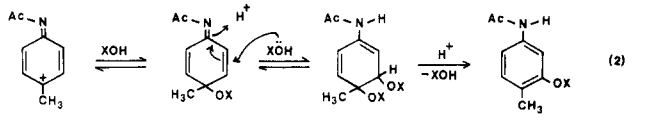


appears to be the most reasonable explanation for the formation of **2b**. The decreased yield of **2b** at higher pH



(1)

can be explained if the 1,2-migration is an acid-catalyzed process. Meta-substitution products have been reported previously to result from the reactions of certain nucleophiles with *N*-acetoxy-*N*-acetyl-2-aminofluorene.[8] Results obtained by Gassman and Granrud[4b] and ourselves[3b] indicated that such products were obtained by an addition–elimination sequence, as in eq 2. However, the ob-



(2)

servation of **2b** in the present study suggests that an alternative process, favored by others,[8b] which involves a 1,2-migration, as in eq 1, is also possible. In any case, the mechanism of eq 2 cannot explain the formation of significant amounts of **2b** because the concentration of free pivalic acid present during the hydrolysis reaction is always considerably less than 1 mM, so that it cannot compete effectively with other nucleophiles present in solution.

Acetanilides are formed when *N*-(sulfonatooxy)acetanilides undergo hydrolysis in the presence of reducing agents.[3] However, the hydrolysis of the *N*-(sulfonatooxy)acetanilides in ordinary phosphate buffer does not yield these products. The 4-acetotoluidide (**9**) isolated during the hydrolysis of **1a** in phosphate buffers is, therefore, an unusual product. The HPLC data taken at pH 7.8 indicate that the formation of **9** is coupled to a decreased yield of at least one of the products **4**, **5**, and **7**.[12] At the present time we do not have sufficient data to speculate intelligently about the mechanism of formation of **9** under these conditions.

Scheme I presents a mechanistic interpretation consistent with the observations made during the hydrolysis reactions of **1a**. With the exception of the path leading to **2b**, Scheme I is essentially identical with that presented earlier to explain the hydrolysis reactions of **1b**.[3b] No pathway leading to **9** is included since we currently do not have an adequate explanation for its origin. The decomposition of **2a** into **3** and **10** has been left out for the sake of clarity. We have no evidence that requires internal return of the tight ion pair, **14a**, to **1a**, although internal return with rearrangement to form **2a** and **2b** does occur. In fact, the formation of the tight ion pair may be the rate-determining step of the reaction.

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Registry No. **1a**, 88867-64-5; **1b**, 91631-50-4; **2a**, 98922-96-4; **2b**, 98922-97-5; **3**, 13429-10-2; **4**, 23438-23-5; **6**, 5307-07-3; **7**, 16375-90-9; **10**, 98922-98-6.

Highly Efficient NaOCl Olefin Epoxidations Catalyzed by Imidazole or Pyridine "Tailed" Manganese Porphyrins under Two-Phase Conditions. Influence of pH and of the Anchored Axial Ligand

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Mn(III) tetraarylporphyrins **2** and **3**, bearing a pyridine or an *N*-alkyl-substituted imidazole function anchored by an aliphatic chain, are extremely efficient catalysts for olefin epoxidations carried out with NaOCl under aqueous–organic two-phase conditions. Reaction rates are strongly increased by lowering the pH of the aqueous phase, and at pH 9.5 catalyst turnovers are in the range of 0.8–3.3 per s at 0 °C. At the lower pH values rates are only slightly affected by the presence of a phase-transfer catalyst, whereas the latter becomes important at the pH of commercial bleach (12.5–13.0). A similar behavior has been found for epoxidations catalyzed by Mn(III) tetraphenylporphyrin **1**, carried out in the presence of a molar excess of 3-pycoline or *N*-hexylimidazole. The latter is a particularly efficient axial ligand.

Synthetic metalloporphyrins are efficient models of the cytochrome P-450 family of monooxygenase enzymes and have been largely used as catalysts in oxidations of organic substrates.[1] The discovery that manganese(III) tetra-

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