Conclusions

(a) Pteridine, the parent ring of a well-known class of natural products, appears to be the strongest base within the diazinodiazine series. Taking into account that isomers are being compared, it is likely that this feature is maintained in condensed phase. The preferred protonation site of pteridine is N1.

(b) Pyrazino[2,3-*c*]pyridazine (**4**) is predicted to be protonated at N1. The energy differences among the cation protonated at N1 and the rest are so significant that, even in solution, protonation at N1 may be largely predominant. In the light of these results and former results from our work,[8] explanations offered by Glidewell et al.[3] concerning the reactivity of **1** should be partly revised.

(c) The basicity of any α-nitrogen is quite enhanced when it has a peri nitrogen.

(d) The basicity of N2 or N3 of 2,3,*m*,*n*-tetraazanaphthalenes is larger than that of N1 or N2 of 1,2,*m*,*n*-tetraazanaphthalenes.

(e) The basicity of an α-nitrogen is much lower when another α-nitrogen (para) is present in the same ring.

(f) The basicity of a β-nitrogen is lower when another β-nitrogen lies in the opposite position of the other ring (diago).

Registry No. **2**, 6133-45-5; **2**·H^+, 115340-47-1; **3**, 6133-46-6; **3**·H^+, 115340-48-2; **4**, 254-96-6; **4**·H^+, 115340-49-3; **5**, 253-74-7; **5**·H^+, 115340-50-6; **6**, 254-62-6; **6**·H^+, 115340-51-7; **7**, 6133-50-2; **7**·H^+, 115340-52-8; **8**, 254-82-0; **8**·H^+, 115340-53-9; **9**, 91-18-9; **9**·H^+, 115340-54-0; **10**, 253-88-3; **10**·H^+, 115340-55-1; **11**, 254-64-8; **11**·H^+, 115340-56-2; **12**, 255-53-8; **12**·H^+, 115340-57-3; **13**, 254-95-5; **13**·H^+, 115340-58-4; **14**, 253-61-2; **14**·H^+, 115340-59-5; **15**, 82810-12-6; **15**·H^+, 115340-60-8; H^+, 12408-02-5.

Acid-Catalyzed Hydrolysis of *N*-Hydroxyacetanilides: Amide Hydrolysis vs N–O Bond Heterolysis

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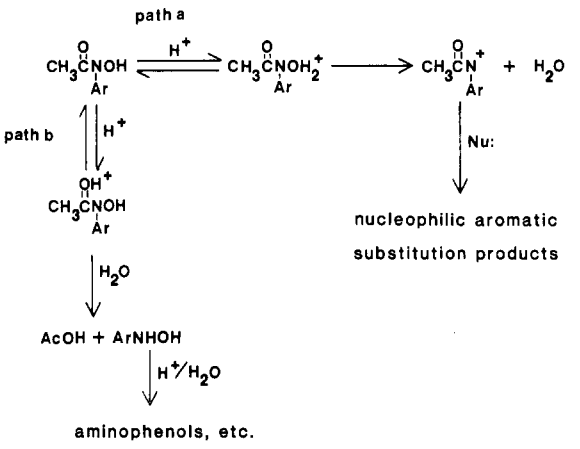
Although it has been widely assumed that *N*-hydroxy-*N*-aryl amides decompose in acidic solution by acid-catalyzed N–O bond heterolysis, we have found that the *N*-hydroxyacetanilides **1a–e** largely decompose by the alternative amide hydrolysis pathway. The immediate products of hydrolysis, the hydroxylamines **2a–e**, can be detected by direct or indirect methods, but these materials also decompose via the Bamberger rearrangement under the reaction conditions. Only the *p*-EtO- and *p*-MeO-substituted *N*-hydroxyacetanilides (**1a** and **1b**) exhibit any sign of N–O bond heterolysis, and only as a minor component (ca. 7%) of the overall hydrolysis. No change in mechanism could be found for **1d** in H_2SO_4 solutions as concentrated as 9 M. The lack of reactivity of **1a–e** to N–O bond heterolysis is largely due to unfavorable protonation of the OH group. Protonation of the carbonyl oxygen is favored over the hydroxyl oxygen by ca. 7 orders of magnitude.

It is widely assumed, with little supporting evidence, that *N*-hydroxy-*N*-arylacetamides decompose in acidic aqueous solution via N–O bond heterolysis to yield *N*-acetyl-*N*-arylnitrenium ions (Scheme I, path a).[1] Sulfuric, methanesulfonic, and carboxylic acid esters of such compounds have recently been shown to undergo uncatalyzed N–O bond heterolysis under various conditions to yield nitrenium ion species,[2-4] but the chemistry of *N*-hydroxy-*N*-arylamides in H_2O has not been investigated in detail. Acid hydrolysis of the amide functionality followed by Bamberger rearrangement[5] of the resulting *N*-aryl-

Scheme I



hydroxylamines (Scheme I, path b) would also appear to be a viable reaction possibility in the absence of experimental data.

We have examined the hydrolysis of the *N*-hydroxyacetanilides **1a–e** in HCl solutions in the pH range 0.3–3.0 at 50 °C and found that these compounds undergo reaction primarily via path b to yield the corresponding hydroxylamines **2a–e**, which also decompose under these conditions, but which can be detected either directly by HPLC or UV spectroscopy or indirectly by product study comparisons. Path a is a minor contributor (<10%) to the hydrolysis of only **1a** and **1b**. Examination of the hy-

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(2) (a) Novak, M.; Pelecanou, M.; Roy, A. K.; Andronico, A. F.; Plourde, F. M.; Olefirowicz, T. M.; Curtin, T. J. *J. Am. Chem. Soc.* **1984**, *106*, 5623–5631. (b) Novak, M.; Pelecanou, M.; Pollack, L. *J. Am. Chem. Soc.* **1986**, *108*, 112–120. (c) Novak, M.; Pelecanou, M.; Zemis, J. N. *J. Med. Chem.* **1986**, *29*, 1424–1429. (d) Novak, M.; Roy, A. K. *J. Org. Chem.* **1985**, *50*, 571–580.

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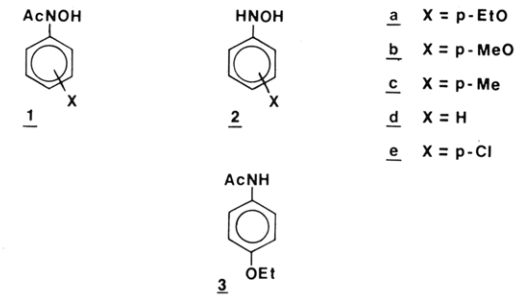
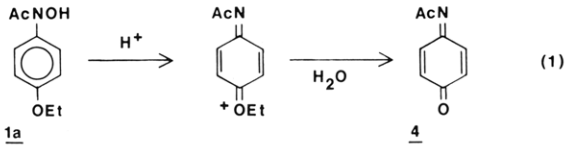


drolysis of the unsubstituted compound **1d** in aqueous sulfuric acid provided no evidence for a change in mechanism up to 9 M H_2SO_4 (ca. 60 wt % H_2SO_4).

N-Hydroxyphenacetin (**1a**) is a metabolite of the analgesic phenacetin (**3**), which appears to be responsible, at least in part, for the toxic and carcinogenic effects of **3**.[6] *N*-hydroxy derivatives of polycyclic aromatic amides such as 2-acetylaminofluorene also appear to be proximate carcinogens.[7] It has been suggested that **1a** decomposes into the liver toxin *N*-acetyl-*p*-benzoquinone imine (**4**)[8] by way of a nitrenium ion intermediate (eq 1) and that this



(1)

may be biologically relevant.[1a,6c] Our results indicate that eq 1 is a very slow and inefficient route to **4** and not likely to be important in vivo.

Experimental Section

The synthesis and purification of **1a–e** and **2a–e** have been described.[2a–c] The *N*-hydroxyamides **1a–e** show no sign of decomposition when stored at −25 °C after recrystallization, but the hydroxylamines **2a–e** do decompose slowly after purification even at −25 °C. These materials were used as quickly as possible after recrystallization from benzene/hexane mixtures. All solvents used in synthesis of these compounds and isolation of reaction products were reagent grade and were purified, if necessary, by standard methods.

Kinetic Measurements. All kinetics in HCl solutions were performed in 5 vol % CH_3CN/H_2O at 50.0 ± 0.1 °C under a N_2 atmosphere. Ionic strength was maintained at 0.5 M with KCl for all HCl solutions. H_2SO_4 solutions, which contained no CH_3CN, were made from reagent grade acid and were titrated against standardized NaOH solutions. Procedures for purification of solvents, preparation of solutions, maintenance of a N_2 atmosphere in thunberg cuvettes, and general methods for following reaction kinetics by UV spectroscopy and HPLC methods have been described.[2a,b]

Initial concentrations of **1a–e** and **2a–e** of ca. 5.0×10^{-5} M were obtained by injection of 15 μL of ca. 0.01 M CH_3CN (or 0.01 M aqueous solutions for kinetics in H_2SO_4) solutions of the appropriate material into 3.0 mL of the kinetic solution. Repetitive wavelength scans were used to determine appropriate wavelengths for kinetic analysis. These were 245 nm for **1a** and **1b**, 242 nm for **1c** and **2c**, 242 nm and 222 nm for **1d** and **2d**, and 250 nm and 225 nm for **1e** and **2e**. Absorbance vs time data were fit to the first-order rate equation or to the equation for consecutive first-order processes (eq 2) as described elsewhere.[2a,b] The pH

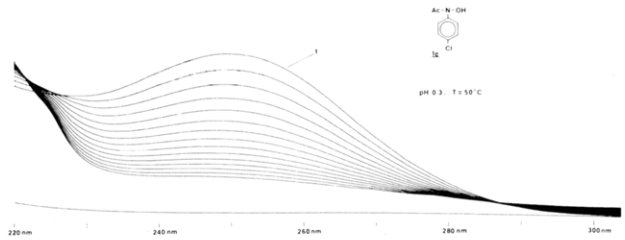


Figure 1. Repetitive UV absorbance scans collected during the hydrolysis of **1e** in pH 0.3 HCl at 50 °C. Initial concentration of **1e** is 5.0×10^{-5} M. Cycle time is 10 min. The first scan is labeled for clarity.

$$A_t = A_1 \exp(-k_1 t) + A_2 \exp(-k_2 t) + A_\infty \quad (2)$$

of HCl solutions was determined after reaction at 50.0 ± 0.1 °C with an Orion Model 701A digital pH meter equipped with a Radiometer GK 2402C combination electrode. Measurement of pH of standardized solutions established a constant correction between meter reading and pH in the pH range 0.3–3.0:

$$\text{pH} = \text{meter reading} - 0.05 \quad (3)$$

Product Analysis. Product studies were performed in solutions identical with those used in the kinetic studies except for higher initial concentrations of **1** or **2** (ca. 1.0×10^{-4} M). Procedures for isolating products and quantifying yields by HPLC methods have been published.[2a,b] The HPLC conditions used in this study were: μ-Bondapak C-18 column, 50/50 MeOH/H_2O eluent, 1 mL/min, UV detector at 225 or 250 nm.

Products were identified by comparison to commercially available materials (**7c–e**, **8**, **9**, **10**) or to materials available from previously published studies (**6**, **11**).[2b,d] A sample of **7a** (3-chloro-4-phenetidine) was prepared by decomposition of **2a** in concentrated HCl at room temperature under N_2. The hydrochloride salt of **7a** was purified by recrystallization from concentrated HCl. The neutral form was extracted from 5% $NaHCO_3$ with CH_2Cl_2. After rotary evaporation a yellowish oil, which solidified upon refrigeration, was obtained: mp 21–23 °C (lit.[9] mp 24 °C); NMR (HCl salt, 90 MHz, $(CD_3)_2SO$) δ 1.30 (3 H, t, J = 6.97 Hz), 4.03 (2 H, q, J = 6.97 Hz), 6.0 (3 H, s, broad), 6.95 (1 H, dd, J = 2.57, 8.80 Hz), 7.13 (1 H, d, J = 2.57 Hz), 7.44 (1 H, d, J = 8.80 Hz).

Most products were stable to the reaction conditions in the absence of O_2, but both *p*-benzoquinone (**10**) and 3-chloro-4-hydroxyacetanilide (**11**) decomposed at moderate rates. Yields of **10** and **11** were determined by fitting concentration (A_t) vs time data to eq 4, where k_1 and k_2 are rate constants for the formation

$$A_t = A_o(k_1/(k_2 - k_1))(\exp(-k_1 t) - \exp(-k_2 t)) \quad (4)$$

and decomposition of **10** and **11** and A_o is the yield of **10** or **11** in appropriate units.

Product studies performed with *N*-acetyl-*p*-benzoquinone imine (**4**) and *N*-(pivaloyloxy)phenacetin (**12**) were carried out as described elsewhere.[2b,c]

pK_a Measurement for Protonated 1c. Measurements of the ionization constant of protonated **1c** were made at 25 °C to decrease interference from the hydrolysis reaction. Solutions were prepared by injection of 15 μL of a freshly prepared 0.01 M aqueous solution of **1c** into 3.0 mL of a standardized H_2SO_4 solution incubated at 25 °C for 15 min. Wavelength scans showed that an isosbestic held at 234 nm throughout the concentration range 0.1–9.0 M H_2SO_4 and the wavelength of largest absorbance change (ca. 0.2 AU) was 255 nm. Absorbance at 255 nm was

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(8) Blair, T. A.; Boobis, A. R.; Davies, D. S. *Tetrahedron Lett.* **1980**, *21*, 4947–4950. Dahlin, D. C.; Nelson, S. D. *J. Med. Chem.* **1982**, *25*, 885–886. Miner, D. J.; Kissinger, P. T. *Biochem. Pharmacol.* **1979**, *28*, 3285–3290. Dahlin, D. C.; Miwa, G. T.; Lu, A. Y. H.; Nelson, S. D. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 1327–1331. Corcoran, G. B.; Mitchell, J. R.; Vaishnav, Y. N.; Horning, E. C. *Mol. Pharmacol.* **1980**, *18*, 536–542.

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Table I. Pseudo-First-Order Rate Constants for Hydrolysis of 1e and Bamberger Rearrangement of 2e in HCl Solutions[a]

hydrolysis rate constants for 1e[c]			Bamberger rearrangement rate constants for 2e:[d] k_3, $\times 10^4$ s^{-1}
pH[b]	k_1, s^{-1}	k_2, $\times 10^4$ s^{-1}	
0.31	$(2.12 \pm 0.01) \times 10^{-4}$	6.90 ± 0.50	7.83 ± 0.03
0.31	$(1.99 \pm 0.03) \times 10^{-4}$ [d]	7.61 ± 0.20[d]	
1.01	$(4.33 \pm 0.01) \times 10^{-5}$	5.47 ± 0.48	5.48 ± 0.06
1.32	$(2.15 \pm 0.01) \times 10^{-5}$	3.06 ± 0.39	3.70 ± 0.03

[a] Conditions: 5 vol % CH_3CN/H_2O, μ = 0.5 M (KCl), T = 50.0 ± 0.1 °C. Each rate constant was determined from a single experiment. Error limits are estimated from the standard deviations of the fit and appropriate propagation formula. [b] ±0.02 at 50 °C. [c] Measured at 250 nm. [d] Measured at 225 nm.

plotted vs H_a[10] for 14 solutions in the range 0.1–9.0 M H_2SO_4, and the data were fit to eq 5 (K_a, ϵ_{HA}, ϵ_A were treated as variable

$$A = \epsilon_{HA}(h_a/(K_a + h_a)) + \epsilon_A(K_a/(K_a + h_a)) \quad (5)$$

parameters). The standard deviation of the fit was excellent (±0.003 au) and both ϵ_{HA} and ϵ_A were in good agreement with values determined graphically.

Results and Discussion

All studies were performed under a N_2 atmosphere since **2a–e** and several of the hydrolysis products are subject to air oxidation under the reaction conditions. The sensitivity of *N*-arylhydroxylamines to air oxidation under similar conditions has been noted previously.[5b,c] Repetitive wavelength scans of the hydrolysis of **1a–e** at pH 0.3 and 50 °C were not consistent with a simple first-order process. The repetitive wavelength scan for **1e** shown in Figure 1 is typical. Absorbance vs time data taken at either 250 or 225 nm for **1e** were fit well by eq 2, the rate equation for two consecutive first-order processes. Rate constants obtained from those fits in the pH range 0.3–1.3 are shown in Table I. One of the rate constants (k_1) is strongly pH dependent, and a plot of log k_1 vs pH has a slope of −1.0. The other rate constant (k_2) barely changes with pH. Under the same conditions **2e** decomposes in a first-order manner. The rate constant for this reaction (k_3) is also reported in Table I. Although there is significant uncertainty in the measured values of k_2 due to the relative magnitude of the amplitude factors A_1 and A_2, the two rate constants k_2 and k_3 are equivalent within experimental error. It was shown previously that the rate constants for the Bamberger rearrangement of ring-substituted *N*-phenylhydroxylamines reach a plateau in acid solution at pH < pK_a of the conjugate acid of the hydroxylamine.[5b,c] The pK_a of the conjugate acid of **2e** can be estimated to be 1.4 ± 0.1 from a correlation of pK_a vs σ for a number of *N*-phenylhydroxylamines.[5b,c]

Similar results were obtained for **1d** and **2d**. Absorbance vs time data taken at pH 0.33 and 222 nm for **1d** fit eq 2 to give two rate constants, $(1.40 \pm 0.14) \times 10^{-5}$ s^{-1} and $(3.47 \pm 0.32) \times 10^{-4}$ s^{-1}. Under the same conditions **2d** decomposed in a first-order manner with a rate constant, also determined from data taken at 222 nm, of $(3.81 \pm 0.02) \times 10^{-4}$ s^{-1}. The kinetics of the Bamberger rearrangement of **2d** have been investigated in detail,[5b,c] so we did not examine this reaction further. Instead absorbance data for the hydrolysis of **1d** were taken at 242 nm, a wavelength at which the rearrangement of **2d** shows no significant absorbance changes, and fit to the first-order rate equation

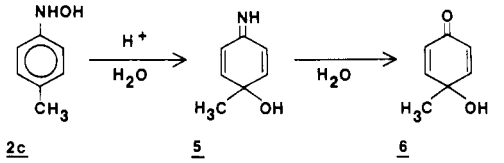
(10) Yates, K.; Stevens, J. B.; Katritzky, A. R. *Can. J. Chem.* **1964**, *42*, 1957–1970.

Table III. Second-Order Hydrolysis Rate Constants for 1a–e[a]

N-hydroxyamide	k_H, $\times 10^4$ M^{-1} s^{-1}	*N*-hydroxyamide	k_H, $\times 10^4$ M^{-1} s^{-1}
1a	3.34 ± 0.07	**1d**	3.50 ± 0.06
1b	3.18 ± 0.20	**1e**	4.42 ± 0.08
1c	3.01 ± 0.12		

[a] Determined from the data in Tables I and II from the equation: log k_H = log k_1 + pH. The values are reported with their standard deviations.

to obtain k_1. These pseudo-first-order rate constants were found to be linearly dependent on $[H^+]$. It has been shown that the Bamberger rearrangement of **2c** yields the imine **5**, which subsequently undergoes hydrolysis into 4-hydroxy-4-methylcyclohexa-2,5-dien-1-one, **6**, (eq 6).[5a,c]



2c 5 6 (6)

Accordingly, as previously reported,[5c] we observed biphasic kinetics for the rearrangement of **2c** at pH 1.30. Two rate constants, $(1.9 \pm 0.1) \times 10^{-2}$ and $(1.22 \pm 0.01) \times 10^{-4}$ s^{-1}, were obtained from absorbance vs time data taken at 242 nm. The larger constant has previously been shown to be associated with the first process of eq 6, while the smaller rate constant is associated with the hydrolysis of **5** into **6**.[5c] Under identical conditions the hydrolysis kinetics of **1e** were also biphasic with rate constants of $(1.58 \pm 0.01) \times 10^{-5}$ and $(1.32 \pm 0.03) \times 10^{-4}$ s^{-1}. The former rate constant (identified as k_1) depends linearly on $[H^+]$ while the latter is essentially pH independent in the pH range 0.3–2.0. The smaller of the two rate constants observed for the rearrangement of **2c** is numerically equivalent to this latter rate constant and shows the same lack of pH dependence. No rate constant corresponding to the **2c** → **5** process was detected, but this is not surprising since **2c** could not build up to significant levels in the sequence shown in eq 7. In

$$\mathbf{1c} \rightarrow \mathbf{2c} \rightarrow \mathbf{5} \rightarrow \mathbf{6} \quad (7)$$

the pH range of our study the rate constant for the decomposition of **2c** into **5** is always at least (6.5×10^2)-fold larger than the rate constant for the hydrolysis of **1c**.

In the cases of **1d** and **1e** the Bamberger rearrangement of the corresponding hydroxylamines **2d** and **2e** is slow enough that they should be directly detectable in hydrolysis reaction mixtures of **1d** and **1e** at pH ≤1.5. In fact, at pH 1.0 HPLC analysis at early reaction times of hydrolysis mixtures of **1d** or **1e** indicated the presence of materials with retention times equivalent to **2d** (11.4 min) or **2e** (19.4 min). These species decayed away in a manner consistent with that of the authentic compounds. It is clear from the kinetic data and these results that path b of Scheme I is significant for the hydrolysis of **1c–e**.

Both **2a** and **2b** decompose very rapidly under our reaction conditions with half-lives of less than 10 s. The kinetics of the relatively slow hydrolysis of **1a** and **1b** are still biphasic in nature, however. This is due to the slow decomposition of the hydrolysis products **10** and **11** (see below). It was possible to obtain k_1, the pseudo-first-order rate constants for the hydrolysis of **1a** and **1b**, from fits of absorbance vs time data to eq 2.

The values of k_1 determined for **1a–d** in HCl solutions in the pH range 0.3–3.0 are reported in Table II in the microfilm edition (see supplementary material). In all cases plots of log k_1 vs pH were linear with slopes ranging

Table IV. Yields of Hydrolysis Products of 1a and 1c–e and Bamberger Rearrangement Products of 2a and 2c–e[a]

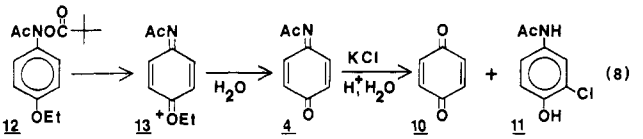
product	% yield[b] from 1	% yield[b] from 2
From 1a and 2a[c]		
1,4-benzoquinone (10)	92 ± 9	97 ± 9
3-chloro-4-hydroxyacetanilide (11)	6 ± 1	
3-chloro-4-phenetidine (7a)	trace[e]	trace[e]
From 1c and 2c[d]		
4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (6)	72 ± 5	68 ± 8
2-chloro-4-methylaniline (7c)	20 ± 1	21 ± 1
From 1d and 2d[d]		
4-aminophenol (9)	47 ± 8	48 ± 8
4-chloroaniline (8)	16 ± 1	16 ± 2
2-chloroaniline (7d)	8 ± 1	8 ± 1
From 1e and 2e[d]		
2,4-dichloroaniline (7e)	70 ± 6	74 ± 8

[a] Conditions the same as in kinetic study except for initial concentrations of 1 or 2 (ca. 1.0×10^{-4} M). [b] Determined from HPLC peak integration by triplicate injections after ca. 8 half-lives as calculated from the kinetic data, unless otherwise indicated. [c] pH = 0.3. Both 10 and 11 are unstable under these conditions so their yields were determined from eq 4 as described in the Experimental Section. [d] pH = 1.0. [e] Less than 1%.

from −0.98 to −1.01. The values of k_H, the second-order rate constants for acid-catalyzed hydrolysis of **1a–e**, are reported in Table III. These rate constants exhibit very little sensitivity to the ring substituent. The rates of decomposition of ring substituted *N*-(sulfonatooxy)- or *N*-(pivaloyloxy)acetanilides in aqueous solution are very sensitive to substituents ($\rho^+ \approx -4.0$ to −6.0) as expected for reactions involving rate limiting N–O bond heterolysis.[2a,b] The substitutent effect for protonation of the OH group in 1 (Scheme I) is not known, but it would be expected that $\rho \approx -1.0$ on the basis of analogy to similar protonation equilibria.[11] It is clear that the lack of sensitivity of k_H to substituent effects is not consistent with a significant N–O bond heterolysis component (Scheme I, path a).

Results of detailed product analyses for the hydrolysis of 1 and Bamberger rearrangement of **2** are presented in Table IV. It is obvious that **1c–e** and **2c–e** yield the same products in essentially equivalent yields. The products observed for **2c–e** are those expected for Bamberger rearrangement in the presence of significant Cl^- concentration.[5] The dienone **6** has been observed previously in both the Bamberger rearrangement of **2c**[5a,c] and the hydrolysis of *N*-(sulfonatooxy)-*p*-acetotoluidide.[2d] Decomposition of **2c–e** by path a of Scheme I would have yielded ring chlorinated and hydroxylated acetanilides.[2] Although these species are hydrolyzed under the reaction conditions, they decompose slowly enough to be easily detected. For example, 2- and 4-chloroacetanilide are hydrolyzed to the corresponding anilines with half-lives in excess of 24 h at pH 1.0 and 50 °C. The half-life of **1d** at pH 1.0 is 5.6 h. Neither chloroacetanilide or any other acetanilide could be detected by HPLC at any time during the hydrolysis of **1d**. It appears that **2c–e** undergo hydrolysis in dilute acid only by path b of Scheme I. An upper limit of ca. 1% can be placed on the amount of material hydrolyzed by path a on the basis of our inability to detect products for this path.

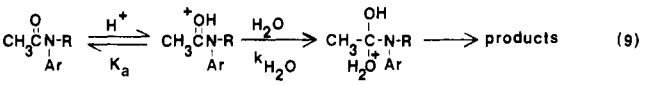
The product data for **1a** and **2a** do show some differences, which are attributable to path a. The Bamberger rearrangement of **2a** yields *p*-benzoquinone (**10**) and traces of 3-chloro-4-phenetidine (**7a**). The hydrolysis of **1a** yields one additional product, 3-chloro-4-hydroxyacetanilide (**11**). At pH 0.3 both **10** and **11** decompose slowly at rates about 10-fold slower than **1a**. To accurately determine yields of these products it was necessary to fit concentration vs time data to eq 4 as described in the Experimental Section. This increased the calculated yields by ca. 30% over the highest yields of both **10** and **11** observed during the course of the hydrolysis (ca. 6.5 h after initiation of the reaction). We have previously shown that *N*-(pivaloyloxy)phenacetin (**12**) decomposes in >90% yield by way of a nitrenium ion species (**13**) into *N*-acetyl-*p*-benzoquinone imine (**4**), which is subsequently hydrolyzed in solutions containing KCl into **10** and **11** (eq 8).[2c] At pH 0.3 and 50 °C, the yields of **10**



(8)

and **11** obtained from either **4** or **12** are 11 ± 1% and 84 ± 2%, respectively. The decomposition of **1a** by path a of Scheme I should also yield **4**, which would then yield **10** and **11** in the same proportions observed for authentic **4**. In this way we calculated that path a accounts for 7 ± 1% of the decomposition of **1a** at pH 0.3. The rest of the hydrolysis of **1a** occurs via path b. At pH 1.0 and 2.0 we found essentially equivalent results. The decomposition of **1b** under these conditions also yields **10** and **11** in the same proportions as observed for **1a**. Previously the isolation of **10** from acid hydrolysis mixtures of **1a** was taken as evidence for the formation of **4** via eq 1, and it was assumed, based on this observation, that path a was the major hydrolysis reaction for **1a**.[1a] In fact, **10** is produced by both hydrolysis paths of Scheme I and cannot be used to distinguish between them.

After correction of k_H for **1a** and **1b** for the proportion of hydrolysis by path a, a correlation of log k_H for **1a–e** vs σ gave $\rho = 0.33 \pm 0.05$ ($r = 0.964$). A correlation of hydrolysis rate constants for a series of ring substituted acetanilides (**14**) in 1.0 M H_2SO_4 at 100 °C gives $\rho = 0.54 \pm 0.07$ ($r = 0.941$).[12] This low sensitivity to substitutent effects can be shown to be due to compensating effects in the protonation step of eq 9 (pK_a vs σ gives $\rho = -1.4$)[13] and



(9)

1 R=OH

14 R=H

the attack of H_2O on the protonated amide, k_{H_2O} of eq 9 ($\rho = 1.9$).[12] The similarity in sensitivity to substituent effects indicates that in dilute acid the hydrolyses of **1** and **14** occur by the same mechanism.

We examined the hydrolysis behavior of **1d** in H_2SO_4 from 0.1 to 9.0 M acid to determine if a change in a_{H_2O} might lead to a change in mechanism and to compare the hydrolysis of **1d** with that of acetanilide in H_2SO_4.[12,14] The pK_a of protonated **1d** was determined by spectrophotometric titrations in H_2SO_4 solutions at 25 °C. Absorbance data collected at 255 nm fit a theoretical titration curve (eq 5) only if the H_A acidity scale[10] was used. It has previously been shown that titrations of acetanilide and its

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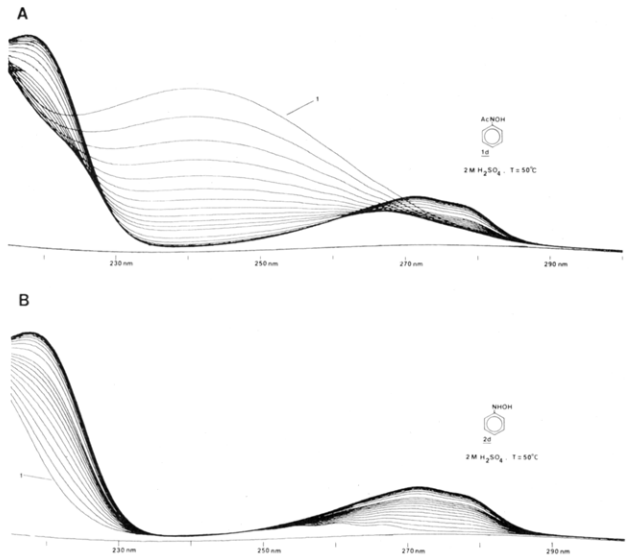


Figure 2. Repetitive UV absorbance scans collected during the hydrolysis of **1d** and Bamberger rearrangement of **2d** in 2 M H_2SO_4 at 50 °C. Initial concentrations were 5.0×10^{-5} M in both cases. Cycle times were intially 5 min and then 15 min for both compounds. The first scans are labeled. (A) Repetitive wavelength scans for **1d**. (B) Repetitive wavelength scans for **2d**.

Table V. Pseudo-First-Order Hydrolysis Rate Constants for 1d in H_2SO_4[a]

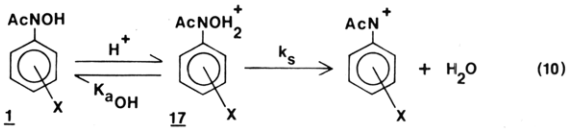
concn of H_2SO_4, M	H_A[b]	k_1,[c] s^{-1}
0.1	0.85	$(2.90 \pm 0.01) \times 10^{-5}$
1.0	−0.31	$(3.53 \pm 0.01) \times 10^{-4}$
2.0	−0.88	$(6.99 \pm 0.06) \times 10^{-4}$
3.0	−1.25	$(1.01 \pm 0.02) \times 10^{-3}$
4.0	−1.58	$(1.14 \pm 0.02) \times 10^{-3}$
5.0	−1.88	$(1.06 \pm 0.02) \times 10^{-3}$
6.0	−2.18	$(8.55 \pm 0.15) \times 10^{-4}$
7.0	−2.45	$(6.13 \pm 0.17) \times 10^{-4}$
8.0	−2.73	$(3.46 \pm 0.06) \times 10^{-4}$
9.0	−3.03	$(1.40 \pm 0.01) \times 10^{-4}$

[a] $T = 50.0 \pm 0.1$ °C. Initial concentration of **1d** was 5.0×10^{-5} M. [b] See ref 10. [c] Determined at 242 nm from a single experiment.

ring-substituted derivatives in H_2SO_4 are best correlated by the H_A scale.[13] The pK_a of the conjugate acid of **1d** determined by this method is -1.68 ± 0.02. The OH group has a rather weak effect on acidity since at the same temperature the pK_a of protonated acetanilide is -1.54 ± 0.04.[13] Repetitive wavelength scans of the hydrolysis of **1d** and **2d** in H_2SO_4 (Figure 2) showed the same behavior that was observed in dilute HCl. The presence of **2d** was ascertained from fits of absorbance vs time data at 222 nm for both **1d** and **2d** in 2 M H_2SO_4. The UV absorbance scan at the completion of the reaction was consistent with that of 4-aminophenol (**9**) in all H_2SO_4 solutions from 0.1 to 9.0 M. This material has previously been identified as the only product of the Bamberger rearrangement of **2d** in concentrated H_2SO_4.[5a,c] Absorbance vs time data taken at 242 nm fit the first-order rate equation well. Pseudo-first-order hydrolysis rate constants, k_1, are reported in Table V. These show a maximum in the hydrolysis rate at about 4.0 M H_2SO_4. This is a familiar aspect of acid-catalyzed amide hydrolysis, including hydrolysis of acetanilides,[12] which has been explained by a decrease in the rate of the second step of eq 9 with decreasing a_{H_2O}.[14] A plot of the Yates r function[11] ($\log k_1 - \log (h_A/(K_a + h_A))$) vs $\log a_{H_2O}$[15] was linear for all data at $[H_2SO_4] \geq 2.0$ M ($r = 0.998$). The slope of 2.0 ± 0.1 is somewhat smaller than that typically observed for amide hydrolysis (2.6–3.5),[11,12,14] but the linearity of the plot up to 9.0 M H_2SO_4 indicates that no significant unimolecular process (such as path a of Scheme I) is taking place.[11,14] We did not examine the hydrolysis of **1d** beyond 9.0 M H_2SO_4 because it is known that acetanilide undergoes ring sulfonation in concentrated H_2SO_4 (>14.0 M),[16] and a unimolecular hydrolysis process also begins to compete with the bimolecular process for a number of substituted acetanilides in highly concentrated H_2SO_4 (>12.0 M).[12,17] It appears that **1d** undergoes acid-catalyzed hydrolysis in dilute and moderately concentrated acid solutions by a mechanism identical with that of ordinary amides. There is no evidence for the process of path a in Scheme I in acid solutions up to 9.0 M H_2SO_4. Similar mechanistic conclusions have previously been reached for the acid-catalyzed hydrolysis of benzohydroxamic acids and related species.[18]

The pseudo-first-order hydrolysis rate constant for **1d** in 1 M H_2SO_4 at 50 °C is 13.3-fold larger than that estimated from interpolation of rate data for acetanilide in 1 M H_2SO_4 at various temperatures.[12,16] After compensation for pK_a differences this implies that k_{H_2O} (eq 9) for **1d** is ca. 18-fold larger than that for acetanilide. We found a similar acceleration of amide hydrolysis by the sulfonoxy group in the acid-catalyzed hydrolysis of *N*-(sulfonatooxy)-3-bromoacetanilide (**15**).[19]

The lack of reactivity of **1** via eq 10 is due to the very unfavorable protonation of the OH group. The overall rate constant for the process of eq 10 is $k_s/K_{a_{OH}}$. An estimate



of k_s for **1b** of 2.6×10^4 s^{-1} can be obtained from the rate constant for N–O bond heterolysis of *N*-(pivaloyloxy)-4-methoxyacetanilide (**16**) at 50 °C (1.12×10^{-1} s^{-1})[2b] and β_{lg} for this process (−0.8).[20] This value and the overall second-order rate constant for the reaction of eq 10 for **1b** obtained from the kinetic and product study data (2.2×10^{-5} M^{-1} s^{-1}) provide an estimate of p$K_{a_{OH}}$ for the hydroxyl protonated conjugate acid (**17b**) of **1b** of -9 ± 2. This estimate appears to be reasonable since substitution of the acetamido group for H in NH_4^+ lowers the pK_a by 6.0 units.[21] The p$K_{a_{OH}}$ of **17a** would be similar to that of **17b** and the other members of the series would be even stronger acids. Since N–O bond heterolysis is highly sensitive to ring substitution, k_s will be significantly smaller for all *N*-hydroxyacetanilides with ring substituents less electron donating than *p*-MeO, and the reaction of path a in

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Scheme I will not compete with hydrolysis of the amide bond (path b). Suggestions that acid catalyzed N–O bond heterolysis of *N*-hydroxy-*N*-arylamides may be important in vivo processes[1a,6c] must be viewed with suspicion in view of these results.

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Supplementary Material Available: Table II, pseudo-first-order rate constants for the hydrolysis of **1a–d** in dilute HCl (1 page). Ordering information is given on any current masthead page.

A Desirable Route to Heterodimers of 1,4-Dihalobenzenes and Anthracene and Their Photoproperties and Thermal Properties

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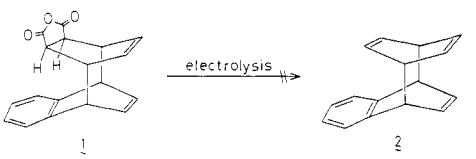
Received January 6, 1988

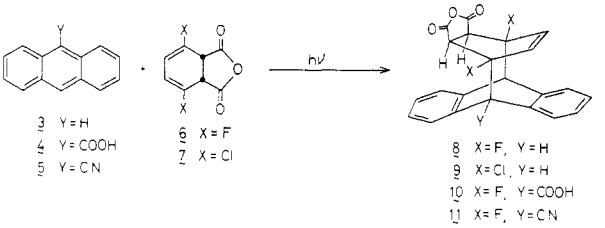
Electronic oxidative bisdecarboxylation of photoadducts of 2,5-dihalo-1,2-dihydrophthalic anhydride and anthracene gave the corresponding energy-rich heterodimers **12** and **13**. The quantum yields of the formation of the excited anthracene from **12** and **13** by the irradiation of 280-nm light were 0.65 and 0.25, respectively. We assumed that the heterodimers of **12** and **13** form biradicaloid intermediates during thermal retro [4πs + 4πs] cycloaddition and consumed their stored energy without any visible light. However, we observed emission light from 340 to 460 nm through a glass filter and the formation of anthracene using Nd-YAG laser IR light (1.06 μm) by the multiphoton absorption, when fine powders of **12** and **13** were used.

Heterodimers of arenes are a group of important energy-rich molecules. Although benzene[1c] and condensed aromatic hydrocarbons, such as anthracene[1a] and naphthalene,[1b] undergo photodimerization, the synthesis of these energy-rich heterodimers has not been accomplished by photocycloaddition of benzenes and other arenes. A few heterodimers have been synthesized by an application of photocycloaddition of substituted 1,3-cyclohexadienes to arenes followed by conversion of substituents to an olefinic bond using carefully controlled methods.[2] A desirable and economical route to heterodimers is direct oxidative bisdecarboxylation of photocycloadducts of 1,2-dihydrophthalic anhydrides and arenes. However, when the diacid derived from **1** was subjected to electronic oxidative bisdecarboxylation directly under a variety of conditions, the expected heterodimer **2** was not detected among the products (Scheme I).[3] Now we have overcome this difficulty by the introduction of halogen atoms on the bridgehead of [4πs + 4πs] photoadducts (**8** and **9**). Thus we report here the synthesis and photoconversion to excited anthracene through the adiabatic process of heterodimers **12** and **13**. The kinetic behavior of thermal retro [4πs + 4πs] cycloaddition of these heterodimers was also studied. This study presents an analysis of the chemiluminescent and dark reaction pathways for these thermal

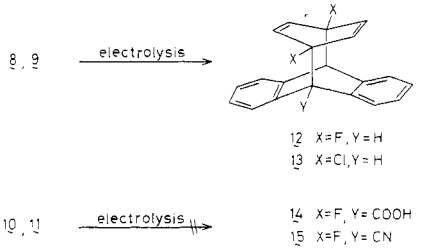
Scheme I



Scheme II



Scheme III



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