Hydrolysis Reactions of *N*-Sulfonatooxy-*N*-acetyl-1-aminonaphthalene and *N*-Sulfonatooxy-*N*-acetyl-2-aminonaphthalene: Limited Correlation of Nitrenium Ion Azide/Solvent Selectivities with Mutagenicities of the Corresponding Amines

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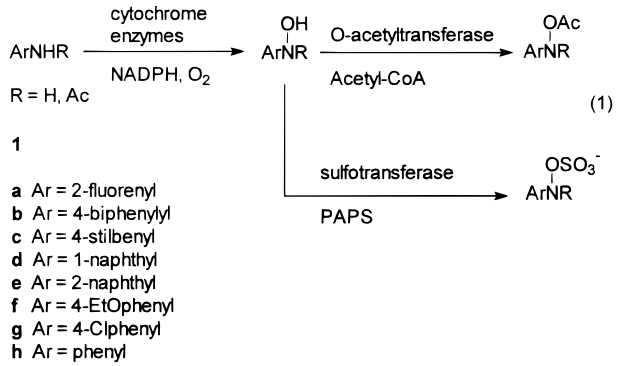
The hydrolysis reactions of the title compounds *N*-sulfonatooxy-*N*-acetyl-1-aminonaphthalene, **2d,** and *N*-sulfonatooxy-*N*-acetyl-2-aminonaphthalene, **2e**, in 5% CH_3CN-H_2O (20 °C, pH 5.7−7.5, $\mu = 0.5$) appear to involve nitrenium ion intermediates that exhibit very small azide/solvent trapping efficiencies. The azide/solvent selectivities, *S*, were estimated from fitting azide- and solvent-derived product yields as a function of $[N_3^-]$. The derived values of *S* for the *N*-acetyl-*N*-(1-naphthyl)-nitrenium ion (**3d**) of 0.7 ± 0.1 M^{-1} and the *N*-acetyl-*N*-(2-naphthyl)nitrenium ion (**3e**) of 1.5 ± 0.2 M^{-1} show that these ions have short lifetimes (ca. 10^{-10} s) in aqueous solution. In turn, these results suggest that the hydrolysis reactions of **2d** and **2e** should proceed, in part, through ion-pair and/or preassociation pathways. The decrease in the yield of the rearrangement products *N*-acetyl-1-amino-2-sulfonatooxynaphthalene, **6**, and *N*-acetyl-2-amino-1-sulfonatooxynaphthalene, **11**, with increasing $[N_3^-]$ indicates that this is the case. Plots of log(mutagenicity) toward *Salmonella typhimurium* TA 98 and TA 100 for a series of polycyclic and monocyclic aromatic amines vs log(*S*) for $ArNAc^+$ show that there is no general correlation of mutagenicity with nitrenium ion selectivity, but there does appear to be a limited correlation of these two quantities for five polycyclic amines for which there are reliable mutagenicity and nitrenium ion selectivity data. These results suggest that nitrenium ion selectivity is one of several factors that determines the mutagenicity of aromatic amines.

It has been known for some time that the mutagenicity and carcinogenicity of aromatic amines and amides are attributable to their ester metabolites (eq 1).[1] It has also



been shown that these esters generate nitrenium ions in an aqueous environment.[2] Esters derived from strongly carcinogenic and mutagenic amines such as 2-aminofluorene (**1a**) and 4-aminobiphenyl (**1b**), or the corresponding amides, produce long-lived, highly selective nitrenium ions that react efficiently with N_3^- and deoxyguanosine in the presence of the aqueous solvent.[2,3,4] The adducts formed with deoxyguanosine have been implicated in the mutagenicity and carcinogenicity of the amines and amides.[1]

The rate constant ratio k_{az}/k_s (eq 2) is a measure of the kinetic lability of the nitrenium ion because k_{az} is diffusion-limited at ca. 5×10^9 M^{-1} s^{-1} ($T = 20$ °C, $\mu = 0.5$) for nitrenium ions with $k_s > 10^4$ s^{-1}.[3,5] This includes the highly selective nitrenium ions derived from **1a** and **1b**.[2,3] Since nitrenium ions have been implicated in the adduct-forming reactions with deoxyguanosine,[4] it is not unreasonable to suggest that there may be a correlation of k_{az}/k_s for the nitrenium ions with the carcinogenicity or mutagenicity of the corresponding amines. Quantitative carcinogenicity data are difficult to obtain, but

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(1) Miller, J. A. *Cancer Res.* **1970**, *30*, 559−576. Kriek, E. *Biochim. Biophys. Acta* **1974**, *335*, 177−203. Miller, E. C. *Cancer Res.* **1978**, *38*, 1479−1496. Miller, E. C.; Miller, J. A. *Cancer* **1981**, *47*, 2327−2345. Miller, J. A.; Miller, E. C. *Environ. Health Perspect.* **1983**, *49*, 3−12. Garner, R. C.; Martin, C. N.; Clayson, D. B. In *Chemical Carcinogens*, 2nd ed.; Searle, C. E., Ed.; ACS Monograph 182; American Chemical Society: Washington, DC, 1984; Vol. 1, pp 175−276. Beland, F. A.; Kadlubar, F. F. *Environ. Health Perspect.* **1985**, *62*, 19−30. Kadlubar, F. F.; Beland, F. A. *Polycyclic Hydrocarbons and Carcinogenesis*; ACS Symposium Series 283; American Chemical Society: Washington, DC, 1985; pp 341−370.

(2) Novak, M.; Kahley, M. J.; Eiger, E.; Helmick, J. S.; Peters, H. E. *J. Am. Chem. Soc.* **1993**, *115*, 9453−9460. Novak, M.; Kahley, M. J.; Lin, J.; Kennedy, S. A.; Swanegan, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 11626−11627.

(3) Davidse, P. A.; Kahley, M. J.; McClelland, R. A.; Novak, M. *J. Am. Chem. Soc.* **1994**, *116*, 4513−4514. McClelland, R. A.; Davidse, P. A.; Hadzialic, G. *J. Am. Chem. Soc.* **1995**, *117*, 4173−4174.

(4) Novak, M.; Kennedy, S. A. *J. Am. Chem. Soc.* **1995**, *117*, 574−475.

(5) Sukhai, P.; McClelland, R. A. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1529−1530. Ren, D.; McClelland, R. A. *Can. J. Chem.* **1998**, *76*, 78−84.

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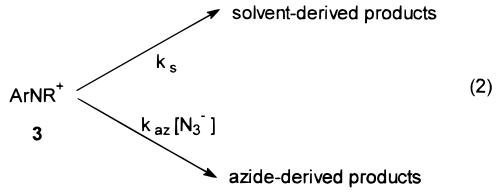


(2)

quantitative mutagenicity data from Ames tests of the amines are readily available.[6−9] These data have previously been correlated with the calculated stabilities of nitrenium ions determined from semiempirical calculations,[6] and, in a multivariate analysis, with octanol−water partition coefficients, and LUMO and HOMO energies of the amines.[7] The proposed correlation of nitrenium ion kinetic lability, measured by k_{az}/k_s, with the mutagenicity of the corresponding amines has not been tested because of a lack of azide/solvent selectivity data for nitrenium ions generated from the more weakly mutagenic polycyclic amines such as 1- and 2-aminonaphthalene (**1d** and **1e**, respectively).

Ester derivatives of *N*-arylhydroxylamines are difficult to prepare and are very reactive, but esters of the corresponding *N*-acetyl-*N*-arylhydroxyamines are easier to prepare, store, and study.[2] Since the *N*-acetyl group has only a minimal effect on nitrenium ion reactivity (ca. 2−8-fold decrease in k_{az}/k_s),[2,3] data on the selectivity of *N*-acetylnitrenium ions can usefully substitute for those of the corresponding unsubstituted ions. In this paper we report azide/solvent selectivity data for the nitrenium ions **3d** and **3e** derived from hydrolysis of the corresponding esters **2d** and **2e** (Scheme 1). A limited correlation of mutagenicity data with azide/solvent selectivity data for polycyclic amines can be demonstrated. This correlation breaks down for monocyclic amines. The implications of this correlation and the possible reasons for its breakdown are discussed herein. In an accompanying paper we present a computational study that attempts to shed light on the reasons for the variations in azide/solvent selectivity and hydration regioselectivity with nitrenium ion structure.[10]

Results

In 0.01 M phosphate buffers from pH 5.7 to pH 7.5, prepared in 5 vol % CH_3CN-H_2O with a constant ionic strength of 0.5 ($NaClO_4$), the decomposition of both **2d** and **2e** occurred in a first-order fashion with pH-independent rate constants, k_o, of $(3.5 \pm 0.2) \times 10^{-3}$ s^{-1} and $(5.1 \pm 0.1) \times 10^{-4}$ s^{-1}, respectively, at 20 °C. Rate constant data obtained for both compounds are provided in Table 1. These hydrolysis rate constants fit on a previously published correlation line of log k_o vs σ^+ for sulfuric acid esters of a variety of *N*-acetyl-*N*-arylhydroxylamines.[11] The slope of that line, ρ^+, is -8.7 ± 1.0.[11]

Scheme 1

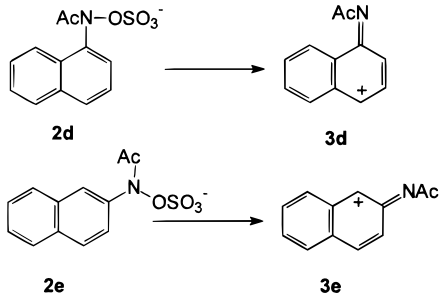


Table 1. Rate Constants for Hydrolysis of 2d and 2e[a]

ester	pH	[N_3^-], M	k_{obs},[b] (s^{-1})
2d	5.7	0	$(3.23 \pm 0.10) \times 10^{-3}$
2d	6.2	0	$(3.54 \pm 0.10) \times 10^{-3}$
2d	7.2	0	$(3.39 \pm 0.11) \times 10^{-3}$
2d	7.5	0	$(3.60 \pm 0.12) \times 10^{-3}$
2d	7.2	0.190	$(3.30 \pm 0.10) \times 10^{-3}$
2d	7.2	0.475	$(3.51 \pm 0.09) \times 10^{-3}$
2e	5.7	0	$(5.14 \pm 0.02) \times 10^{-4}$
2e	6.2	0	$(5.11 \pm 0.08) \times 10^{-4}$
2e	6.7	0	$(5.13 \pm 0.05) \times 10^{-4}$
2e	7.2	0	$(5.14 \pm 0.05) \times 10^{-4}$
2e	7.5	0	$(5.20 \pm 0.08) \times 10^{-4}$
2e	7.2	0.190	$(5.15 \pm 0.06) \times 10^{-4}$
2e	7.2	0.475	$(5.20 \pm 0.05) \times 10^{-4}$

[a] Conditions: 5 vol % CH_3CN/H_2O, 0.01 M NaH_2PO_4/Na_2HPO_4 buffer; $\mu = 0.5$ ($NaClO_4$ or NaN_3), 20 °C. [b] Averages of at least two duplicate runs. Data taken at 310 and 320 nm for **2d**, and at 290 nm for **2e**.

Product studies performed at pH 7.2 are summarized in Scheme 2. The products of the decomposition of **2d** and **2e** were identified by comparison to authentic compounds synthesized by standard methods. The products of the decomposition of **2d** quantitatively account for this ester. The possible ortho-substituted product **4** could not be detected by HPLC. Control experiments with authentic **4** showed that the limit of detection for this compound under the reaction conditions was ca. 2%.

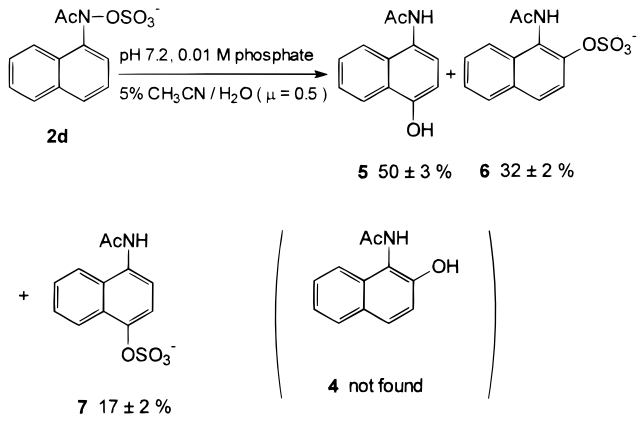
The observed products of **2e** leave ca. 20% of this ester unaccounted for. Under high concentration conditions a tarry precipitate was noted in addition to the two products shown in Scheme 2, but no characterizable products were isolated from this residue. The two possible products **8** and **10** were synthesized for comparison purposes, but they could not be detected in the reaction mixtures. Detection limits were ca. 1% for **8** and ca. 2% for **10**.

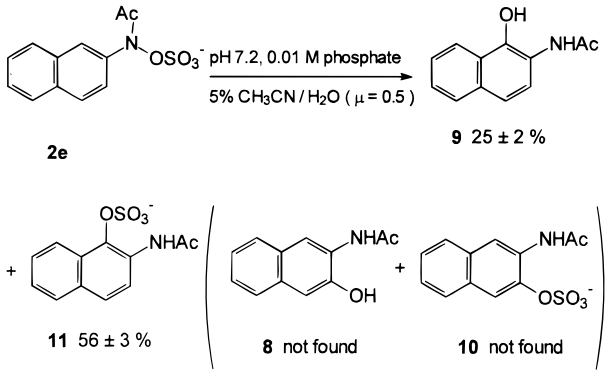
The high yields of the rearrangement products **6** and **7** derived from **2d**, and **11** derived from **2e**, suggest that neither of these compounds generate nitrenium ions that will be efficiently trapped by N_3^-.[12] Scheme 3 shows that low yields of azide adducts can be observed at relatively high concentrations of N_3^-. One of the isolated azide adducts, **16**, could not be directly derived from a nitrenium ion, but the other products are consistent with direct trapping of **3d** or **3e**.

Table 1 shows that, within experimental error, the hydrolysis rate constants for **2d** and **2e** are not affected

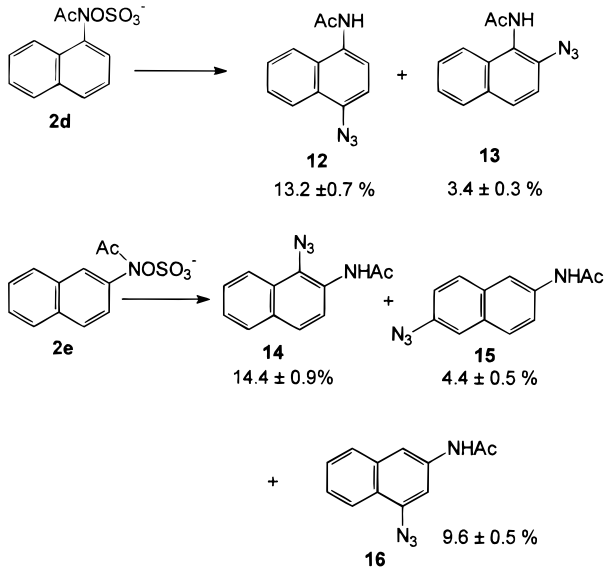
(6) Ford, G. P.; Herman, P. S. *Chem.-Biol. Interact.* **1992**, *81*, 1−18.
(7) Debnath, A. K.; Debnath, G.; Shusterman, A. J.; Hansch, C. *Environ. Mol. Mutagen.* **1992**, *19*, 37−52.
(8) (a) Scribner, J. P.; Fisk, S. R.; Scribner, N. K. *Chem.-Biol. Interact.* **1979**, *26*, 11−25. (b) VanderBijl, P.; Gelderblom, W. C. A.; Thiel, P. G. *J. Dental Assoc. S. Africa* **1984**, *39*, 535−537. (c) Mortelmans, K.; Haworth, S.; Lawlor, T.; Speck, W.; Tainer, B.; Zeiger, E. *Environ. Mutagen.* **1986**, *8 [Suppl 7]*, 1−117. (d) Zeiger, E.; Anderson, B.; Haworth, S.; Lawlor, T.; Mortelmans, K. *Environ. Mutagen.* **1988**, *11* [Suppl. 12], 1−158.
(9) Parodi, S.; Taningher, M.; Russo, P.; Pala, M.; Tamaro, M.; Monti-Bragadin, C. *Carcinogenesis* **1981**, *2*, 1317−1326. Rashid, K. A.; Arjmand, M.; Sandermann, H.; Mumma, R. O. *J. Environ. Sci. Health* **1987**, *B22*, 721−729.
(10) Novak, M.; Lin, J. *J. Org. Chem.*, in press.
(11) Novak, M.; Kayser, K. J.; Brooks, M. E. *J. Org. Chem.* **1998**, *63*, 5489−5496.
(12) Novak, M.; Kahley, M. J.; Lin, J.; Kennedy, S. A.; James, T. G. *J. Org. Chem.* **1995**, 60, 8294−8304.

Scheme 2





Scheme 3[a]



[a] All yields determined at 0.475 M N_3^-.

by N_3^- up to ca. 0.5 M. Although the trapping efficiencies are low (vide infra), the hydrolysis rate constants should have increased by a measurable amount if trapping by N_3^- occurred during the rate-limiting step. For example, at 0.5 M N_3^- the hydrolysis rate constant, k_o, for **2d** should have increased by ca. 18%, and that for **2e** by ca. 38%, if the trapping had occurred during the rate-limiting step. These are relatively small rate accelerations that could be masked by specific salt effects, so it is not possible on the basis of the rate data to completely rule out trapping via a concerted process that avoids the nitrenium ion.

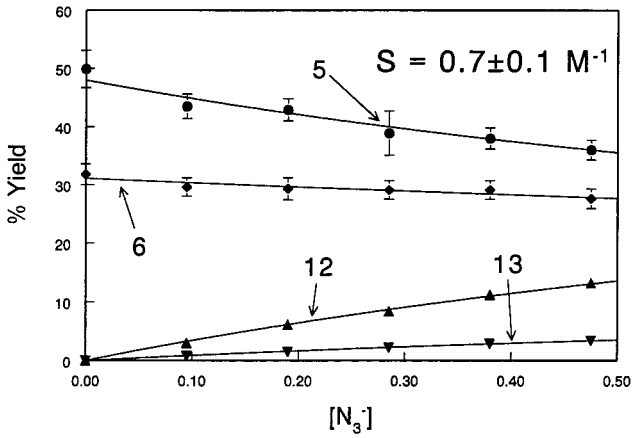


Figure 1. Product yields for **2d** at pH 7.2 as a function of $[N_3^-]$. Yields of **5** and **6** were fit to eq 3, and yields of **12** and **13** were fit to eq 4. The best fit value of S was obtained from fits of the yields of **5**, **12**, and **13**.

Trapping data for **2d** as a function of $[N_3^-]$ are shown in Figure 1. The azide/solvent selectivity, S, was estimated from a fit of the solvent-derived products, Solv (**5**), and azide-derived products, Az (**12**, **13**), respectively, to eqs 3 and 4.[12,13] S is equal to k_{az}/k_s of eq 2 if all trapping

$$[\text{Solv}] = [\text{Solv}]_o/(1 + S[N_3^-]) \quad (3)$$

$$[\text{Az}] = S[N_3^-][\text{Az}]_\infty/(1 + S[N_3^-]) \quad (4)$$

occurs at the free ion stage, but the decrease in the yield of the rearrangement product **6** with increasing $[N_3^-]$ indicates that some trapping occurs at an earlier step in the mechanism, possibly at the ion-pair stage or by a preassociation mechanism.[12] The other rearrangement product, **7**, could not be followed in N_3^--containing solutions because the HPLC peak for N_3^- and **7** coincide under our HPLC conditions. The best fit value of S of 0.7 ± 0.1 M^{-1} confirms that azide trapping in this system is very unselective.

Trapping data for **2e** as a function of $[N_3^-]$ are shown in Figure 2. Data for the solvent-derived product, **9**, and the azide-derived products, **14** and **15**, were fit to eqs 3 and 4 to provide the value of S of 1.5 ± 0.2 M^{-1}. In addition to the three azide-derived products **14**−**16**, there were two other apparent azide adducts that were produced in too low a yield to characterize. These two materials behaved similarly to **14** and **15**. The yield of the rearrangement product, **11**, is also affected by N_3^-, but to a lesser extent than **9**. This is similar to what was observed for **2d**.

The azide adduct **16** is not produced by the same trapping process that produces **14** or **15**. The N_3^--dependent yield of **16** can be fit by eq 5, where S is fixed

$$\mathbf{16}\% = S'[N_3^-]\mathbf{16}_o/(1 + S'[N_3^-])(1 + S[N_3^-]) \quad (5)$$

at 1.5 M^{-1} and S' and $\mathbf{16}_o$ are least-squares parameters. The best fit values for S' and $\mathbf{16}_o$ are 8.9 ± 0.7 M^{-1} and

(13) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689−4691, 4691−4692; **1984**, *106*, 1383−1396.

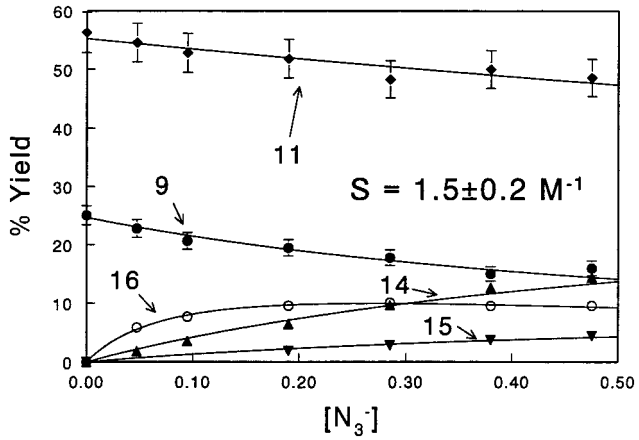


Figure 2. Product yields for **2e** at pH 7.2 as a function of $[N_3^-]$. Yields of **9** and **11** were fit to eq 3, and yields of **14** and **15** were fit to eq 4. The yield of **16** was fit to eq 5. The best fit value of *S* was obtained from fits of the yields of **9**, **14**, and **15**.

Table 2. Mutagenicity and Azide/Solvent Selectivity for Aromatic Amines

		log (*m*)[a]	
amine	log(*S*)[b]	TA 98	TA 100
1a	4.77[c]	1.75 ± 0.18[f]	1.44 ± 0.29[f]
1b	2.97[c]	0.72 ± 0.27[f]	1.23 ± 0.27[f]
1c	2.45[d]	0.46 ± 0.30[g]	1.10 ± 0.60[g]
1d	−0.15	−0.65 ± 0.22[f]	−0.34 ± 0.35[f]
1e	0.18	0.14 ± 0.33[f]	0.83 ± 0.19[f]
1f	2.73[c]	−2.3 ± 0.2[h]	−0.6 ± 0.2[h]
1g	0.46[e]	−2.5 ± 0.1[h]	−1.5 ± 0.2[h]
1h	−0.15[c]	<−3.3[i]	<−2.7[i]

[a] log(*m*) is expressed as the logarithm of revertants/nmol of amine with standard deviations for multiple determinations from different laboratories. [b] Azide/solvent selectivity for $ArNAc^+$. [c] Source: ref 2 or 3. Data are averaged where independent measurements were taken. [d] Source: ref 11. [e] Source: ref 12. [f] Source: ref 6. [g] Source: ref 8a. [h] Source: ref 7 and 8b,c,d. [i] Upper limits for **1h** based on the smallest observable effect at a 500 μg dose, see ref 9.

20 ± 1%, respectively. The form of the trapping equation is consistent with azide trapping of an intermediate solvent-derived product of **3e**. The extrapolated yield of this intermediate product of 20 ± 1% is equivalent, within experimental error, to the amount of material unaccounted for in the hydrolysis of **2e** in the absence of N_3^-. The trapping equations predict that the yield of **16** should continue to drop at higher $[N_3^-]$ while the yields of **14** and **15** continue to increase. Although the quantitative predictions of the trapping equations will be affected by the lack of constant ionic strength at N_3^- > 0.5 M, as well as by other factors,[12] the yields observed by HPLC of **14** (30.8 ± 1.5%), **15** (9.1 ± 0.5%), and **16** (6.0 ± 0.5%) in a pH 7.2 phosphate buffer at 2.0 M N_3^- are in qualitative agreement with the predicted trends.

Table 2 presents data on log(*S*) and log(mutagenicity) for five polycyclic and three monocyclic amines for which both measurements are available. The mutagenicity data are expressed in terms of log[(histidine revertants)/(nmol of amine)] for two *Salmonella typhimurium* strains (TA 98 and TA 100) commonly used in Ames tests.[14] All data were taken under conditions in which the "S-9" fraction of rat liver homogenates, induced by Arachlor 1254 or other PCB preparations, was added directly to the Petri plates.[6−9,14] Without activation by mammalian liver homogenates, aromatic amines exhibit little or no mutagenicity to *Salmonella*.[6−9] Mutagenicity data taken by different laboratories can vary considerably, so wherever possible, averages of multiple determinations should be used in correlation analyses. Mutagenicity data for **1a**, **1b**, **1d**, and **1e** were previously collected from the literature by Ford and Herman.[6] They averaged data taken from a minimum of five sources for each compound. We have used their results in Table 2. Data for **1c** under appropriate conditions are available from only one source.[8a] This paper also reported mutagenicity data for TA 98 and TA 100 for the other four polycyclic amines of Table 2. For TA 98 the log(*m*) data reported in that paper for those four amines have an average absolute deviation of 0.10 and a maximum deviation of 0.18 from the averaged values reported in Table 2. For that reason we are reasonably confident of the value reported for log(*m*) of **1c** against TA 98. The estimated standard deviation in this value was taken from the standard deviations of the other four polycyclic amines. For TA 100 the log(*m*) data reported in that paper have an average absolute deviation of 0.40 and a maximum deviation of 1.04 from the averaged data reported in Table 2. Accordingly, we are less confident in this value. The order of mutagenicity reported for the four amines in this paper is in agreement with the averaged data reported in Table 2 for both TA 98 and TA 100, so we are reasonably confident in the order of mutagenicity reported for the five polycyclic amines in Table 2.

Mutagenicity data for the two monocyclic amines **1f** and **1g** are also averages taken from multiple measurements.[7,8b−d] The upper limits for log(*m*) reported for aniline, **1h**, are estimated on the basis of the assumption that a 10% increase in revertants above background could have been consistently detected at a dose of 500 μg.[9] The upper limit for TA 100 is greater than for TA 98 because of the higher spontaneous mutation rate of TA 100.[9]

Log(*S*) values are those of the N-acetylated nitrenium ions because those data are currently more generally available over a wide range of nitrenium ion reactivity and because log(*S*) for $ArNAc^+$, including unselective ions similar to **3d** and **3e**, are consistently about 0.30−0.90 unit below those of the corresponding $ArNH^+$.[2,3,10,12] For log(*S*) ≥ 2.0 the values reported in Table 2 are, in fact, $\log(k_{az}/k_s)$ for the free ions determined either by competition methods or by direct measurements on ions generated by laser flash photolysis.[2,3,11,12] Independent measurements on the same ions (derived from **1a** and **1b**) by the Novak and McClelland laboratories indicate that the errors in log(*S*) for these ions are small (<0.1).[2,3] Values reported for log(*S*) < 2.0 were from fits to eq 3 or 4 made without attempting to separate the selectivities of the free ion, the ion pair, or any preassociation processes that may occur.[2,12]

Figures 3 and 4 show that there is no general correlation of log(*m*) with log(*S*) for all the amines, but the polycyclic amines do show reasonable correlations of log(*m*) with log(*S*). For the TA 98 strain of *Salmonella* the slope of the correlation line is 0.40 ± 0.08 with a correlation coefficient, *r*, of 0.947. For TA 100 the slope of the correlation line is comparable (0.28 ± 0.11) but *r* is smaller at 0.820. No correlation lines are drawn for the monocyclic amines because of the paucity of data and

(14) Maron, D. M.; Ames, B. N. *Mutat. Res.* **1983**, *113*, 173-215.

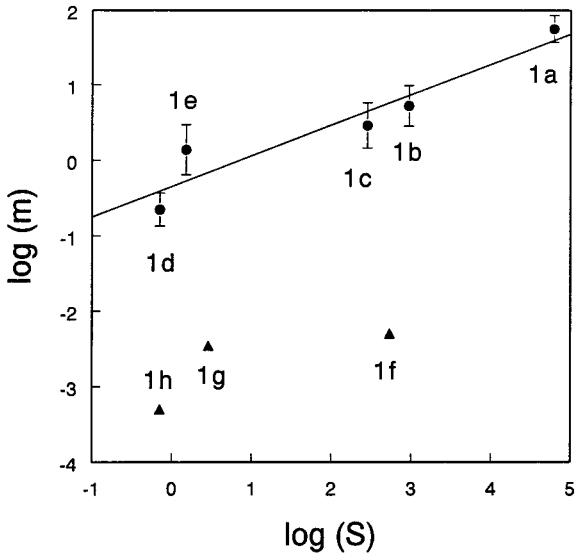


Figure 3. log(mutagenicity) for $ArNH_2$ expressed as log(revertants/nmol) vs log(*S*) for $ArNAc^+$ for *S. Typhimurium* TA 98: polycyclic amines (●), monocyclic amines (▲). The line is the least-squares correlation line for the polycyclic amines.

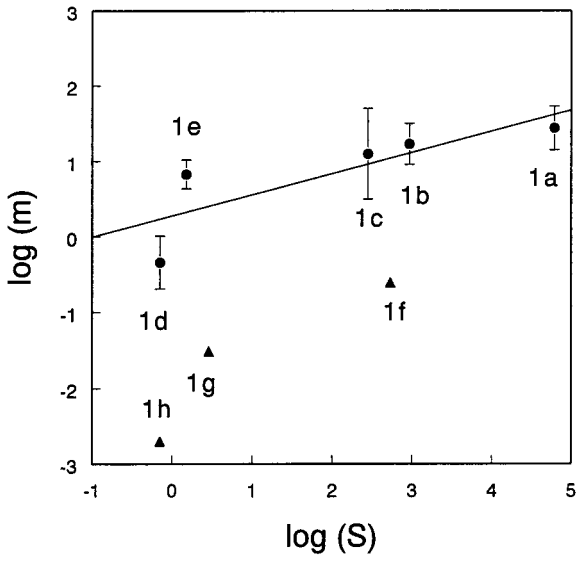
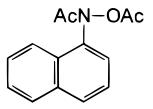


Figure 4. log(mutagenicity) for $ArNH_2$ expressed as log(revertants/nmol) vs log(*S*) for $ArNAc^+$ for *S. Typhimurium* TA 100: polycyclic amines (●), monocyclic amines (▲). The line is the least-squares correlation line for the polycyclic amines.

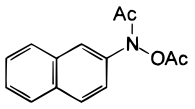
the fact that log(*m*) for **1h** is the upper limit for both TA 98 and TA 100.

Discussion

The hydrolysis reactions of **2d** and **2e** follow a pattern previously established for other esters of *N*-arylhydroxamic acids.[2,11,12] Both exhibit uncatalyzed hydrolysis reactions in a broad pH range around neutrality,[2,12] and the rate constants for hydrolysis are correlated by σ^+ with a large, negative ρ^+ that indicates that a significant amount of positive charge has accumulated on the aryl moiety in the rate-limiting transition state.[11] The solvent-derived and rearrangement products observed for both **2d** and **2e** are consistent with a reaction that involves heterolytic N−O bond cleavage.[12] The products of hydrolysis of **2d** are consistent with those previously reported for the hydrolysis of the acetic acid ester **17d** at 40 °C in 60/40 acetone−water.[15] The ortho/para product ratio for the two rearrangement products **6**/**7** is 1.9 for **2d**. The reported ratio of the corresponding products derived from **17d** is 1.5.[15] The combined yield of those two products of 68% is somewhat larger than the combined yield of **6** and **7** of 50 ± 3%. This is not unexpected, because it has previously been shown that acetic acid esters of *N*-arylhydroxamic acids generate higher yields of rearrangement products than the corresponding sulfuric acid esters.[16] The only significant difference reported in the hydrolysis products of **2d** and **17d** is a 5% yield of **4** reported from hydrolysis of **17d**.[15] We could not detect **4** among the hydrolysis products of **2d**. This difference could be due to the different reaction conditions or to partial hydrolysis of the ortho-rearrangement product of **17d**.



17d



17e

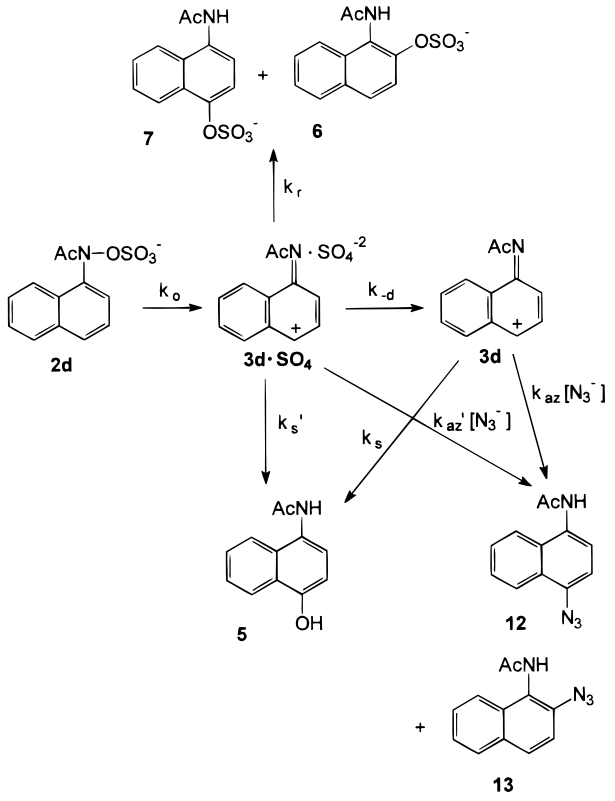
Unlike **2d** and **17d**, **2e** and **17e** behave very differently. The products of hydrolysis of **2e** are consistent with N−O bond heterolysis, but **17e** generates only the corresponding hydroxamic acid at 40 °C in 60/40 acetone−water.[15] We have previously shown that changing the leaving group from a sulfate to carboxylate can change the hydrolysis mechanism from N−O bond heterolysis to acyl transfer, so this difference between **2e** and **17e** is not unprecedented.[2,16a] In the less polar 60/40 acetone−water solvent mixture the N−O bond heterolysis will be suppressed compared to the acyl transfer reaction.[16] That rate suppression, in combination with the poorer leaving group in **17d** and **17e** is apparently sufficient to change the mechanism of solvolysis from N−O bond heterolysis to acyl transfer for **17e**. If the 6.9-fold rate enhancement observed for N−O bond heterolysis of **2d** over **2e** in our solvent system also holds for **17d** and **17e** in acetone−water, it would be possible for **17d** to exhibit the N−O bond heterolysis mechanism under those conditions.

N_3^- changes the reaction products of **2d** and **2e** without changing the rate constant for hydrolysis. In both cases the trapping is inefficient. The small rate increases expected if N_3^- trapping were occurring via a concerted (S_N2) mechanism could have been masked by salt effects. It is not possible to rule out concerted trapping of **2d** or **2e** by N_3^- through the rate data alone. If N_3^- were trapping **2d** or **2e** via a concerted process that avoided the nitrenium ions **3d** and **3e**, the solvent-derived and rearrangement products should respond to $[N_3^-]$ in the same way. Although Figures 1 and 2 show that the rearrangement products **6** derived from **2d**, and **11** derived from **2e**, are sensitive to the addition of N_3^-, these two products respond to $[N_3^-]$ in a manner that is quantitatively different from that of the solvent-derived products **5** from **2d** and **9** from **2e**. For **2d** the yield of the rearrangement product **6** can be fit to eq 3 to yield an apparent selectivity ratio of 0.25 ± 0.06 M^{-1}. The

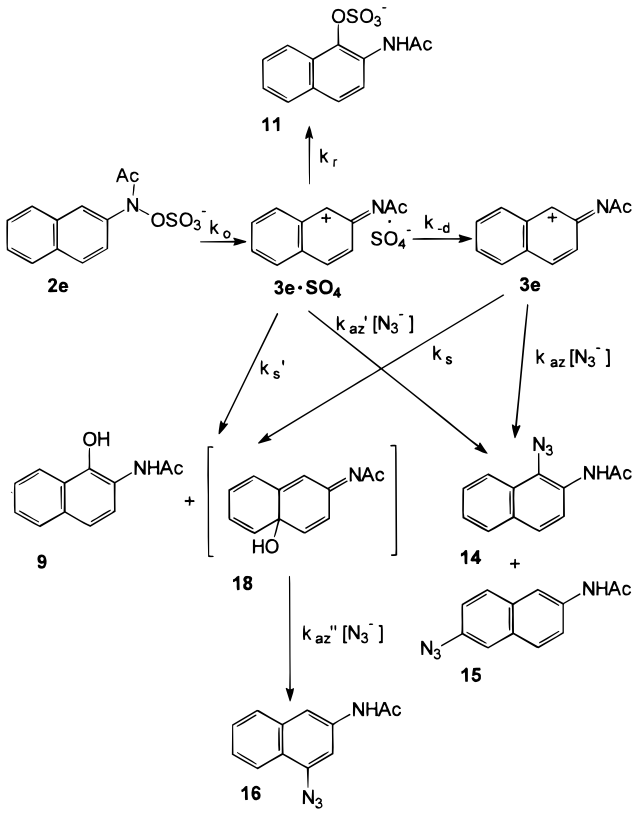
(15) Underwood, G. R.; Davidson, C. M. *J. Chem. Soc., Chem. Commun.* **1985**, 555−556.

(16) (a) Novak, M.; Roy, A. K. *J. Org. Chem.* **1985**, *50*, 571−580. (b) Novak, M.; Roy, A. K. *J. Org. Chem.* **1985**, *50*, 4884−4888.

Scheme 4



Scheme 5



selectivity ratio that characterizes the behavior of **5** (and the azide-derived products **12** and **13**) is 0.7 ± 0.1 M^{-1}. Similarly, a fit of the yields for **11** to eq 3 provides an apparent selectivity ratio of 0.33 ± 0.07 M^{-1} while the solvent- and azide-derived products of **2e** are best fit by a selectivity ratio of 1.5 ± 0.2 M^{-1}. The azide trapping of the rearrangement products and the solvent-derived products must occur, at least in part, at two different points in the hydrolysis mechanism.

Differential azide trapping of solvent-derived products and rearrangement products in other cases in which overall trapping is inefficient have been explained by a mechanism in which azide traps both an ion pair and the free ion.[12] Such a mechanism is shown for **2d** in Scheme 4. N_3^- must trap the ion pair **3d·SO₄** less efficiently than the free ion **3d** even if $k_{az}' \approx k_{az}$ and $k_s' \approx k_s$ because the rearrangement (k_r) and diffusional separation (k_{-d}) of the ion pair are significant competitive processes that draw off much of the ion pair.[12]

If it is assumed, as was done previously,[12] that $k_{az} = 5 \times 10^9$ M^{-1} s^{-1}, $k_{-d} = 1.0 \times 10^{10}$ s^{-1}, and $k_s' = k_s$, a fit to the data essentially equivalent to that shown in Figure 1 can be obtained if $k_r = 1.7 \times 10^{10}$ s^{-1}, $k_{az}' = 8.0 \times 10^9$ M^{-1} s^{-1}, and $k_s = 5.7 \times 10^9$ s^{-1}. The value of k_{az}' is larger than the approximate diffusion-controlled limit of 5×10^9 M^{-1} s^{-1} under these conditions.[3,12] This suggests that some N_3^- trapping may occur by a preassociation process.[12] No attempt was made to fit the data to a mechanism including a preassociation process, but we have previously shown that including such a process lowers the best-fit value of k_{az}'.[12]

A similar mechanism shown in Scheme 5 accounts for the N_3^--dependent behavior of the various reaction products of **2e**. The unique feature of this scheme is the pathway that leads to one of the azide-derived products, **16**. Both the structure of **16** and the dependence of its yield on [N_3^-] indicate that it cannot be generated via the same path as the other two observed azide-derived products, **14** and **15**. The intermediate **18** that would result from attack of H_2O on the bridgehead carbon 4a could lead to **16** via an addition−elimination path. The product **16** is unusual, but not unprecedented, and similar azide- and solvent-derived products have been explained by addition−elimination pathways on an initial unstable adduct such as **18**.[12,17] We were not able to find a stable product derived from **18** in the absence of N_3^-, so we do not know its fate under these conditions.

The product yield data of Figure 2 can be quantitatively fit to the mechanism of Scheme 5 with the usual assumptions[12] concerning k_{az}, k_{-d}, and the equivalence of k_s and k_s', if $k_r = 1.7 \times 10^{10}$ s^{-1}, $k_{az}' = 1.0 \times 10^{10}$ M^{-1} s^{-1}, $k_s = 3.6 \times 10^9$ s^{-1}, and $k_{az}''/k_s'' = 8.9$ M^{-1}. The quality of the fit is equivalent to that shown in Figure 2 for fits to eqs 3, 4, and 5.

The product data show that the reaction of N_3^- with both **3d** and **3e** is less regioselective than the reaction of those same ions with H_2O. For example, **3d** leads to both the 4- and 2-substituted azide adducts **12** and **13**, but only the 4-substituted naphthol **5** is generated by reaction with water. This has been observed previously in the reaction of other unselective nitrenium ions with N_3^- and H_2O.[12] This is initially surprising since $S \approx 1.0$ M^{-1} for these ions, but the inherent reactivity of these ions with H_2O is actually about 50-fold less than with N_3^- because S is a ratio of the rate of the second-order process leading to azide adducts and the rate of the pseudo-first-order process leading to solvent adducts ([H_2O] ≈ 53 M). The regioselectivity of the reaction of such ions with H_2O can

(17) Novak, M.; Lin, J. *J. Am. Chem. Soc.* **1996**, *118*, 1302−1308.

be greater than that for the reaction with N_3^- because the activation barrier for reaction with H_2O can be up to ca. 2 kcal/mol greater at 20 °C than the activation barrier for the reaction with N_3^-.

The mutagenicity or carcinogenecity of any compound is a function of a large number of variables. Included among these are the rates and efficiencies of metabolism of the compound into the ultimate mutagenic or carcinogenic species, the chemical stability of that metabolite, its transport properties across membranes, the efficiency of the metabolite's reactions with DNA, the genetic effect of the specific DNA adduct formed, and the susceptibility of that adduct to the organism's DNA repair machinery.[6,7,18] Given this complexity, it is remarkable that mutagenicity can be correlated to any single chemical or physical property of a series of compounds, or even to multiple properties.

The octanol−water partition coefficient, *P*, is often one of the variables used in quantitative structure−activity relationships including those that correlate mutagenic or carcinogenic properties.[19] Hydrophobicity, as measured by *P*, should play a role in the transport properties of mutagens, their reactions with DNA, and the specific genetic effects and susceptibility to repair of the mutagen−DNA adducts, so the success of these correlations is not entirely surprising. Recently a QSAR of the mutagenicity of 88 amines to *S. typhimurium* TA 98 showed a strong dependence on log(*P*) with weaker dependence on the LUMO and HOMO energies of the amines.[7] A similar correlation of the mutagenicity of 67 amines to TA 100 was also reported.[7] The correlation to HOMO energies suggests that the rate of amine oxidation is an important factor in determining the mutagenicity of amines, but the correlation to LUMO energies is more difficult to understand.[7]

Ford and Herman have also examined the correlation of log(*m*) for TA 98 and TA 100 with ΔH of eq 6 calculated

$$\mathrm{ArNHOH} + \mathrm{PhNH^+} \rightarrow \mathrm{ArNH^+} + \mathrm{PhNHOH} \quad (6)$$

from the semiempirical AM1 method.[6] In this isodesmic reaction ΔH becomes more negative as $ArNH^+$ becomes more stable relative to its hydroxylamine precursor. The authors showed that there was a general tendency for log(*m*) to increase as ΔH became more negative, but many points deviated severely from the correlation lines calculated from the four amines for which the mutagenicity data were judged to be of highest quality and for which the amino group was not adjacent to a point of ring fusion.[6] Their procedure was more successful at correlating mutagenicity data for a series of heterocyclic amines than for the carbocyclic amines.[20] To the extent that ΔH of eq 6 can be related to the rate of ionization of the hydroxylamines or esters, Ford and Herman's results suggest that mutagenicity correlates positively with the rates of nitrenium ion formation from their precursors.[6]

We have examined the possible correlation of log(*m*) with log(*S*), the experimental azide/solvent selectivity of the nitrenium ions. We decided to use log(*S*) rather than $\log(k_{az}/k_s)$ because the former measurement does not depend on any particular mechanistic assumptions about free ions, ion pairs, or preassociation trapping.[12] For the more selective ions with log(*S*) > 2.0 the two ratios are equivalent.[12] They differ from each other only when trapping at some point other than the free ion becomes important.[12] The difference between the two ratios is small until the ion's lifetime ($1/k_s$) approaches ca. 10^{-10} s.[12] This appears to occur in the case of **3d**, **3e**, and **3h** among the eight ions listed in Table 2.[10,12] Since the reaction of the ion with N_3^- is diffusion-limited as long as $k_s > 10^4\ s^{-1}$, log(*S*) is directly related to the lifetime of the ion in an aqueous environment.[2,3]

Figures 3 and 4 show that amines that generate monocyclic nitrenium ions are considerably less mutagenic than their analogues that generate polycyclic ions of similar log(*S*). Considering the strong correlation of log(*m*) with log(*P*) discussed above, this is not surprising. The molecular reasons for this difference are less obvious. It could be due to different transport properties for the more hydrophilic monocyclic amines and their metabolites, to different rates of metabolism, to faster repair rates for the DNA adducts of the less bulky amines, or to smaller genetic effects of the less bulky adducts.

There can be considerable differences in the efficiency of the N-oxidation and subsequent esterification for individual amines. Amines that have significant alternative metabolic paths may exhibit reduced mutagenicity that could account for the scattered nature of the plots in Figures 3 and 4. For example, phenetidine, **1f**, undergoes a cytochrome P-450 catalyzed O-deethylation reaction to produce the inactive compound *p*-aminophenol, in addition to the N-oxidation pathway.[21] The O-deethylation reaction can be a major metabolic path for **1f**.[21] This alternative metabolism will have the effect of reducing the mutagenicity of **1f** in Ames tests. However, alternative metabolic paths that reduce the efficiency of N-oxidation are not exclusively found for monocyclic amines. Most polycyclic amines that have been examined carefully have major C-oxidation pathways that produce inactive metabolites.[22] These alternative metabolic paths appear to cause scatter in quantitative structure−activity relationships, but do not appear to be the major reason for the reduced mutagenicity of monocyclic aromatic amines.

Among the five polycyclic amines there is a good correlation of log(*m*) with log(*S*) for both TA 98 and TA 100. This does not appear to be due to a correlation of log(*P*) with log(*S*). The regression line for this correlation (not shown) has a slope of 0.21 ± 0.13 with $r = 0.688$. Since the number of data points is small, it is not clear how general this log(*m*)−log(*S*) relationship is for polycyclic amines. There are other polycyclic amines with reliable mutagenicity data against TA 98 and TA 100.[6] Measurements of log(*S*) for these systems will be made in the future.

The correlation is reasonable because ions with long lifetimes in aqueous solution (large log(*S*)) should be able to react more selectively with nucleophilic sites on DNA.

(18) Vance, W. A.; Wang, Y. Y.; Okamoto, H. S. *Environ. Mutagen.* **1987**, *9*, 123−141. Vance, W. A.; Okamoto, H. S.; Wang, Y. Y. In *Carcinogenic and Mutagenic Responses to Aromatic Amines and Amides*; King, C. M., Romano, L. J., Schuetzle, D., Eds.; Elsevier: Amsterdam, 1988; pp 291−302.

(19) Benigni, R.; Andreoli, C.; Guiliani, A. *Mutat. Res.* **1989**, *221*, 197−216.

(20) Ford, G. P.; Griffin, G. R. *Chem.-Biol. Interact.* **1992**, *81*, 19−23.

(21) Nohmi, T.; Mizokami, K.; Kawano, S.; Fukuhara, M.; Ishidate, M. *Jpn. J. Cancer Res.* **1987**, *78*, 153−161.

(22) Thorgeirsson, S. S.; Glowinski, I. B.; McManus, M. E. *Rev. Biochem. Toxicol.* **1983**, *5*, 349−386. Hammons, G. J.; Guengerich, F. P.; Weis, C. C.; Beland, F. A.; Kadlubar, F. F. *Cancer Res.* **1985**, *45*, 3578−3585.

This is definitely true for reaction with monomeric deoxyguanosine.[4,23] If other factors do not interfere, the more selective ions should generate a higher yield of DNA−carcinogen adducts and lead to a greater level of mutagenicity.

Clearly no single chemical or physical property will perfectly correlate with a biological effect such as mutagenicity or carcinogenicity. Limited or imperfect correlations to one or to multiple variables can be valuable in understanding the molecular factors that are important to the biological effect. The selectivity or kinetic stability of putative reactive intermediates should be one of the factors considered in developing these correlations.

Experimental Section

General procedures for following reaction kinetics by UV methods and characterization of product mixtures by HPLC have been published.[2] All reactions were performed at 20 °C in 5 vol % CH_3CN-H_2O solutions containing a 0.01 M NaH_2PO_4/Na_2HPO_4 buffer in the pH range 5.7−7.5. Ionic strength was maintained at 0.5 with $NaClO_4$ and/or NaN_3.

Kinetics and Product Studies. Reaction mixtures for UV kinetic studies were prepared by injecting 15 μL of a ca. 0.01 M solution of **2d** or **2e** in DMF into 3 mL of the buffer that had been incubating at 20 °C for at least 20 min. This produces a solution with an initial concentration of ca. 5×10^{-5} M. Wavelengths used for the kinetic studies were 310 and 320 nm for **2d**, and 290 nm for **2e**.

Solutions for HPLC analysis of reaction mixtures were prepared as above except for a higher initial concentration of the esters of ca. 1×10^{-4} M obtained by doubling the concentration of the stock solutions to ca. 0.02 M. After 5 half-lives, as calculated from the kinetic data, reaction mixtures were analyzed by HPLC on a C-8 column with $MeOH/H_2O$ solvent mixtures ranging from 50/50 to 70/30 $MeOH/H_2O$. All HPLC solvents were buffered with 0.025 M 1/1 HOAc/NaOAc, and 20 μL injections were made from the reaction mixtures. All analyses were performed in triplicate. HPLC analyses of the reaction mixtures derived from **2d** were performed at 280 nm. Analyses of mixtures derived from **2e** were performed at 270 nm.

The products **5**, **6**, **7**, **9**, and **11** were identified by HPLC comparison to authentic samples synthesized as described below. Authentic samples of the three products not found in the reaction mixtures (**4**, **8**, **10**) were also available to help confirm the absence of these materials. Each of the products was also identified by ^{1}H NMR of reaction mixtures prepared as follows. A 25 μL aliquot of a 0.021 M solution of **2d** or **2e** in DMF-d_7 was injected into 0.5 mL of a 0.01 M 1/1 NaD_2PO_4/Na_2DPO_4 buffer in D_2O in an NMR tube. After mixing, the solution was transferred to the probe of a 300 MHz NMR, and ^{1}H spectra were obtained as a function of time. The identities of the final reaction products were confirmed by comparison to ^{1}H NMR spectra of the authentic compounds obtained under the same conditions.

The azide adducts **12**, **13**, **14**, **15**, and **16** were isolated and identified as described below.

Synthesis. *N*-Sulfonatooxy-*N*-acetyl-1-aminonaphthalene (2d). This compound was synthesized as its K^+ salt by minor variations on a procedure previously published for the synthesis of *N*-sulfonatooxy-*N*-acetyl-2-aminofluorene.[24] The reaction time was increased to 2.5 h, and the volumes of DMF and MeOH used to dissolve the crude K^+ salt were reduced by ca. 25%. In a typical preparation 0.10 g (0.5 mmol) of *N*-acetyl-*N*-(1-naphthyl)hydroxylamine[25,26] yielded 0.11 g (0.34 mmol, 69%) of **2d**. ^{1}H NMR (300 MHz, DMSO-d_6 (45 °C)) δ 7.95−7.75 (3H, m), 7.55−7.45 (4H, m), 2.39 (3H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6 (45 °C)) δ 172.7 (C), 137.7 (C), 133.5 (C), 129.7 (C), 128.1 (CH), 127.6 (CH), 126.6 (CH), 125.9 (CH), 125.6 (CH), 125.0 (CH), 123.9 (CH), 21.2 (CH_3).

***N*-Sulfonatooxy-*N*-acetyl-2-aminonaphthalene (2e).** This compound was synthesized as described above for **2d** from the isomeric hydroxamic acid.[27] Yields were similar to those obtained for **2d**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (1H, d, J = 1.9 Hz), 7.88−7.80 (3H, m), 7.60 (1H, dd, J = 8.8, 2.1 Hz), 7.49−7.44 (2H, m), 2.34 (1H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 172.0 (C), 138.6 (C), 132.6 (C), 130,8 (C), 127.7 (CH), 127.3 (CH), 127.2 (CH), 126.2 (CH), 125.5 (CH), 122.2 (CH), 120.1 (CH), 22.2 (CH_3).

The acetamidonaphthols **4**, **5**, **8**, and **9** are known compounds that were synthesized by acetylation of the corresponding aminonaphthols.[28−31] The corresponding sulfuric acid esters **6**, **7**, **10**, and **11** were synthesized from the appropriate acetamidonaphthols by an adaptation of the methods used to synthesize **2d** and **2e**. Synthesis and characterization of these compounds are provided in the Supporting Information.

Isolation and Characterization of Azide Adducts. Azide adducts for both **2d** and **2e** were isolated from reaction mixtures containing 0.5 or 2 M NaN_3 dissolved in a pH 7.2 Na_2HPO_4/NaH_2PO_4 buffer (0.01 M) in 5 vol % CH_3CN/H_2O. Initial concentrations of **2d** or **2e** of ca. 1 mM were obtained by injecting a ca. 0.15 M solution of the ester in DMF into the aqueous buffer in a ratio of 1 mL of the DMF solution/150 mL of buffer. Reactions were run at 20 °C for 10 half-lives as calculated from the kinetic data. For **2d**, HPLC, performed as described above for the product studies, confirmed the presence of two new peaks not observed in hydrolysis mixtures containing no NaN_3. The major product, **12**, precipitated from the reaction mixture and was isolated by vacuum filtration after the mixture was cooled to ca. 4 °C. The precipitated material was recrystallized from CH_2Cl_2.

***N*-Acetyl-1-amino-4-azidonaphthalene (12).** Mp 169−173 °C dec; IR (KBr) 3265, 2130, 1655, 1540 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.94 (1H, s), 8.08−8.01 (2H, m) 7.70 (1H, d, J = 8.1 Hz), 7.64−7.55 (2H, m), 7.42 (1H, d, J = 8.1 Hz), 2.17 (3H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 169.1 (C), 132.5 (C), 130.9 (C), 128.5 (C), 126.8 (CH), 126.5 (CH), 125.9 (C), 123.1 (CH), 122.2 (CH), 122.0 (CH), 114.5 (CH), 23.4 (CH_3); high-resolution MS, $C_{12}H_{10}N_4O$ requires *m/e* 226.0854, found 226.0841 (1%).

The minor product, **13**, was isolated from the reaction mixture, contaminated with **12** and minor amounts of hydrolysis products, by extraction with CH_2Cl_2. The CH_2Cl_2 extract containing **13** was evaporated to dryness, and the residue was subjected to preparative TLC on silica gel with 4/1 CH_2Cl_2/EtOAc. The band containing **13** was ca. 85% pure by NMR, but showed only a single HPLC peak. Because very little sample was obtained, the product was characterized without further purification. The impurity appears to be an isomer of **12** and **13**.

***N*-Acetyl-1-amino-2-azidonaphthalene (13).** IR (KBr) 3235, 2120, 1660, 1525 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (1H, d, J = 8.8 Hz), 7.79−7.75 (2H, m), 7.53−7.40 (2H, m), 7.30 (1H, d, J = 8.8 Hz), 7.04 (1H, s (br)) 2.32 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.7 (C), 133.0 (C), 131.3 (C), 131.0 (C), 129.3 (CH), 128.3 (CH), 127.5 (CH), 125.7 (CH), 123.1 (CH), 122.0 (C), 117.0 (CH), 23.4 (CH_3); high-resolution MS, $C_{12}H_{10}N_4O$ requires *m/e* 226.0854, found 226.0882 (1%); $C_{12}H_{10}N_2O$ requires *m/e* 198.0793, found 198.0815 (7%).

For **2e**, HPLC showed five new product peaks absent in hydrolysis mixtures not containing NaN_3. These products were extracted from the mixture with CH_2Cl_2. After evaporation of

(23) Kennedy, S. A.; Novak, M.; Kolb, B. A. *J. Am. Chem. Soc.* **1997**, *119*, 7654−7664.
(24) Smith, B. A.; Springfield, J. R.; Gutman, H. R. *Carcinogenesis* **1986**, *7*, 405−411.
(25) Patrick, T. B.; Schield, J. A.; Kirchner, D. G. *J. Org. Chem.* **1974**, *39*, 1758−1761.
(26) Mudaliar, A.; Agrawal, Y. K. *J. Chem. Eng. Data* **1979**, *24*, 246−247.
(27) Westra, J. G. *Carcinogenesis* **1981**, *2*, 355−357.
(28) Michel, O.; Grandmougin, E. *Chem. Ber.* **1892**, *25*, 3429−3434.
(29) Kehrmann, F.; Kissine, D. *Chem. Ber.* **1914**, *47*, 3096−3100.
(30) Goldstein, H.; Gardiol, P. *Helv. Chim. Acta* **1937**, *20*, 516−520.
(31) Grandmougin, E. *Chem. Ber.* **1906**, *39*, 2494−2497.

the extraction solvent, the products were separated on a C-18 reversed-phase silica gel column using 1/1 MeOH/H_2O as eluent. Only three products were isolated in quantities that allowed for characterization.

***N*-Acetyl-2-amino-1-azidonaphthalene (14).** Mp 107−110 °C dec; IR (KBr) 3250, 2120, 1660, 1531 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (1H, d, J = 9.0 Hz), 8.04 (1H, d, J = 8.4 Hz), 7.82 (1H, d, J = 8.5 Hz), 7.74 (1H, s (br)) 7.69 (1H, d, J = 9.0 Hz), 7.58−7.43 (2H, m), 2.29 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.7 (C), 131.5 (C), 128.8 (C), 128.7 (CH), 127.8 (C), 127.1 (CH), 126.9 (CH), 125.6 (CH), 123.1 (C), 121.2 (CH), 121.2 (CH), 24.6 (CH_3); high-resolution MS, $C_{12}H_{10}N_4O$ requires *m/e* 226.0854, found 226.0856 (1%); $C_{12}H_{10}N_2O$ requires *m/e* 198.0793, found 198.0794 (19%); $C_{10}H_7N_2$ requires *m/e* 155.0610, found 155.0614 (100%).

***N*-Acetyl-2-amino-6-azidonaphthalene (15).** IR (KBr) 3295, 2110, 1660, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (1H, d, J = 2.0 Hz), 7.76 (1H, d, J = 8.8 Hz), 7.68 (1H, d, J = 8.9 Hz), 7.40 (1H, dd, J = 8.9, 2.0 Hz), 7.35 (1H, d, J = 2.1 Hz), 7.34 (1H, s (br)), 7.12 (1H, dd, J = 8.7, 2.2 Hz), 2.22 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.4 (C), 136.7 (C), 134.9 (C), 131.4 (C), 131.1 (C), 129.6 (CH), 127.8 (CH), 120.9 (CH), 119.4 (CH), 116.7 (CH), 115.5 (CH), 24.7 (CH_3); high-resolution MS, $C_{12}H_{10}N_4O$ requires *m/e* 226.0854, found 226.0864 (8%); $C_{12}H_{10}N_2O$ requires *m/e* 198.0793, found 198.0813 (55%); $C_{10}H_7N_2$ requires *m/e* 155.0610, found 155.0621 (87%).

***N*-Acetyl-2-amino-4-azidonaphthalene (16).** Mp 168−171 °C dec; IR (KBr) 3320, 2110, 1665, 1540 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.27 (1H, s), 8.05 (1H, d, J = 1.8 Hz), 7.89 (1H, d, J = 7.7 Hz), 7.82 (1H, d, J = 8.1 Hz), 7.62 (1H, d, J = 1.8 Hz), 7.51 (1H, m), 7.41 (1H, m), 2.10 (3H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 168.5 (C), 137.5 (C), 135.4 (C), 134.5 (C), 127.5 (CH), 127.4 (CH), 125.2 (CH), 123.8 (C), 122.4 (CH), 113.3 (CH), 108.0 (CH), 24.7 (CH_3); high-resolution MS, $C_{12}H_{10}N_4O$ requires *m/e* 226.0854, found 226.0857 (16%); $C_{12}H_{10}N_2O$ requires *m/e* 198.0793, found 198.0796 (58%); $C_{10}H_7N_2$ requires *m/e* 155.0610, found 155.0601 (35%).

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Supporting Information Available: ^{13}C NMR spectra for **2d**, **2e**, **6**, **7**, and **10**−**16** and synthesis and characterization of **4**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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