Azide and Solvent Trapping of Electrophilic Intermediates Generated during the Hydrolysis of *N*-(Sulfonatooxy)-*N*-acetyl-4-aminostilbene

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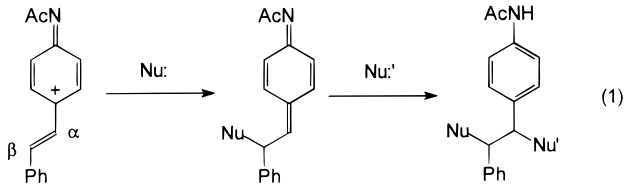
Hydrolysis of the carcinogenic title compound **1a** in 5 vol % CH_3CN-H_2O, $\mu = 0.5$, 20 °C at pH 7.2 in 0.02 M phosphate buffer, yields the rearranged material 3-(sulfonatooxy)-*N*-acetyl-4-aminostilbene (**4**) (23 ± 1%), *threo*-1,2-dihydroxy-1-phenyl-2-(4-acetamidophenyl)ethane (**5**) (57 ± 2%), and *erythro*-1,2-dihydroxy-1-phenyl-2-(4-acetamidophenyl)ethane (**6**) (20 ± 2%) in the absence of added nucleophiles. Addition of N_3^- has no effect on the rate constant for decomposition of **1a** (ca. 1.9×10^{-2} s^{-1}), but generates a number of adducts that result from trapping of three different electrophilic intermediates. The ortho-N_3 adduct 3-azido-*N*-acetyl-4-aminostilbene (**7**) is produced from trapping of the nitrenium ion **2**. A fit of the product yield data as a function of $[N_3^-]$ provides the ratio k_{az}/k_s of 280 ± 10 M^{-1} for competitive trapping of **2** by N_3^- and H_2O. The nucleophilic aromatic substitution product **7** is a minor reaction product. The predominant site of attack by N_3^- on **2** (ca. 85%) is at the β-vinyl carbon to produce the quinone imide methide **3b**. Attack of H_2O at the same site produces the analogous intermediate **3a**. Both of these electrophilic species are competitively trapped by N_3^- and H_2O with trapping ratios k_{az}'/k_s' for **3b** of 107 ± 8 M^{-1} and k_{az}''/k_s'' for **3a** of 39 ± 2 M^{-1}. The reactivity patterns of **2** are unlike those of other *N*-arylnitrenium ions that undergo predominant nucleophilic aromatic substitution with nucleophiles such as N_3^-. The quinone imide methides that are produced by nucleophilic attack on the β-carbon of **2** react selectively enough with nonsolvent nucleophiles that they may be physiologically relevant.

The carcinogenic esters of *N*-hydroxy-*N*-(4-stilbenyl)-acetamide, **1**, generate rather unique products from their reactions with aqueous or alcohol solvents, or guanosine, as shown in Scheme 1.[1] Esters of other *N*-arylhydroxamic acids yield hydrolysis products resulting from nucleophilic attack on the proximal aromatic ring and react with guanosine to form the ubiquitous C-8 adduct.[2,3] These results have led to the reasonable suggestion that nucleophilic attack occurs at the β-carbon of the initially formed nitrenium ion, **2**, followed by a second nucleophilic attack on the resulting quinone imide methide, **3** (eq 1).[1]



2 **3** **a** Nu = OH **b** Nu = N_3 (1)

Although **2** and **3** appear to be involved in the chemistry of **1**, no detailed quantitative study of the reactivities and selectivities of these electrophilic species have been reported. The viability of these electrophiles as a source of cellular damage cannot be assessed without quantitative data concerning their reactivity and selectivity. As a result of a kinetic and N_3^- trapping study of the hydrolysis of **1a**, we can report that **1a** undergoes exclusive N−O bond heterolysis in aqueous solution under physiological pH conditions and that **2** is a reasonably selective ion ($k_{az}/k_s = 280$ M^{-1}) that undergoes initial nucleophilic attack by N_3^- primarily, but not exclusively, at the β-carbon. The two quinone imide methides, **3a** and **3b**, are responsible for most of the products generated in our study, and their reactivities can also be probed by N_3^-/solvent partitioning. The reactivity patterns of **2** are unique among *N*-arylnitrenium ions, so unique that the term "nitrenium ion" may have little value in describing **2**.

Results and Discussion

The hydrolysis rate constant, k_o, for **1a** measured at 20 °C in 5% CH_3CN-H_2O ($\mu = 0.5$, $NaClO_4$) is independent of pH in phosphate buffers (0.02 M) from pH 5.5 to 7.5 with an average value of $(1.89 \pm 0.01) \times 10^{-2}$ s^{-1} (see the Supporting Information for a table of all rate constants obtained in this work). This result is similar to that observed for other esters of *N*-arylhydroxamic acids.[2,4] A Hamett plot of log k_o vs σ^+ for a series of *N*-sulfonatooxy-*N*-arylacetamides, including **1a**, is shown

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(1) (a) Scribner, J. D. *J. Org. Chem.* **1976**, *41*, 3820−3824. (b) Franz, R.; Neumann, H.-G. *Chem. Biol. Interact.* **1988**, *67*, 105−116. (c) Scribner, J. D.; Smith, D. L.; McCloskey, J. A. *J. Org. Chem.* **1978**, *43*, 2085−2087.

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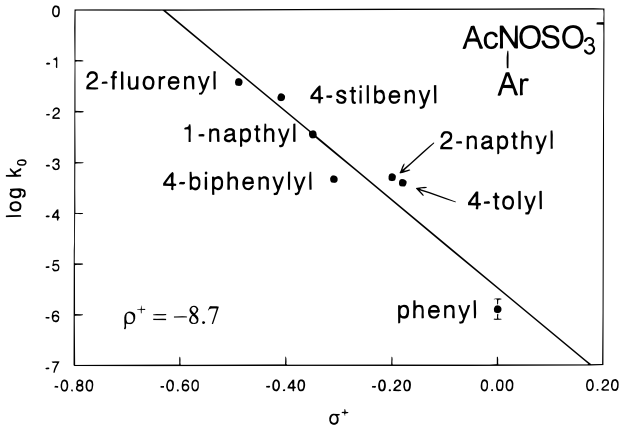
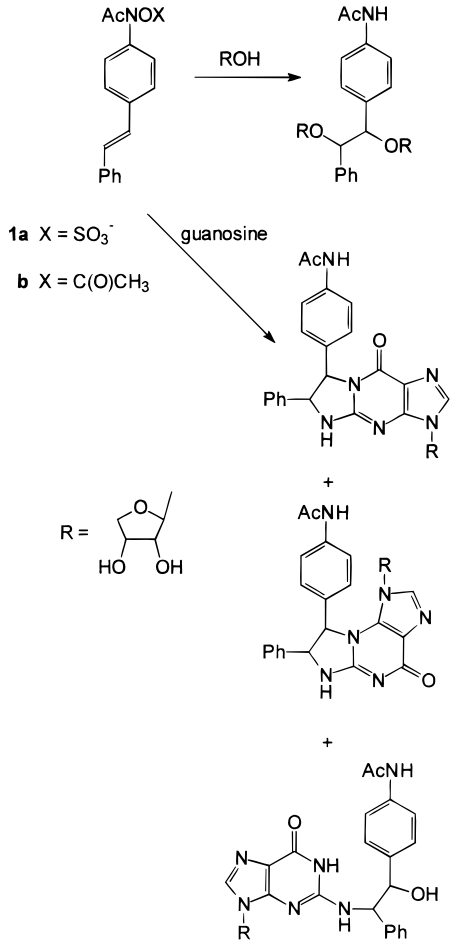


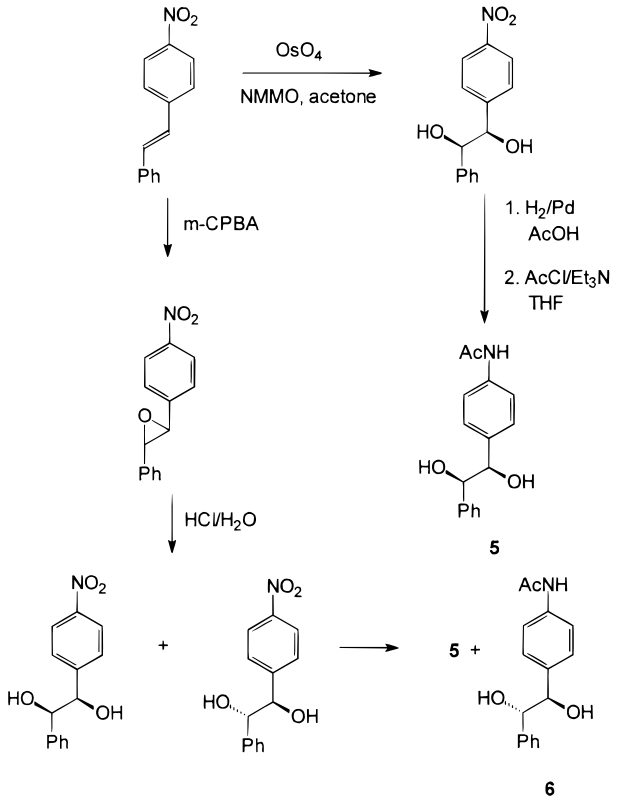
Figure 1. Correlation of hydrolysis rate constants (k_o) for sulfuric acid esters of *N*-arylhydroxamic acids vs σ^+. All data were obtained at, or extrapolated to, 20 °C in 5 vol % CH_3CN-H_2O at $\mu = 0.5$. Individual rate constants are reported in this work or in refs 2, 4, and 5.

Scheme 1

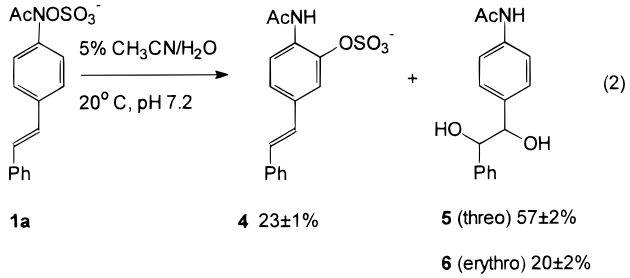


in Figure 1. The large negative ρ^+ of −8.7 is consistent with heterolytic N−O bond cleavage with incipient nitrenium ion formation for all members of this series, which includes four well-known carcinogens.[2,5] The ρ^+ value is in the range previously observed for other reactions in which an ArN−X bond is thought to undergo rate-limiting heterolytic cleavage.[6]

Scheme 2



At 20 °C and pH 7.2 in the absence of added nucleophiles, only three hydrolysis products are observed: the rearranged material **4** (23 ± 1%) and the threo and erythro diols **5** (57 ± 2%) and **6** (20 ± 2%) (eq 2). The



observation of the diols is consistent with previously reported product mixtures from **1b** obtained in 40% aqueous acetone and 40% CH_3OH/H_2O, as is the low stereoselectivity of the diol-forming reactions.[1a]

The identities of the two diols were confirmed by their synthesis as shown in Scheme 2. Hydroxylation of *trans*-4-nitrostilbene with OsO_4 proceeds stereoselectively to yield the threo nitrodiol that is then elaborated into **5**. Acid-catalyzed hydrolysis of *trans*-4-nitrostilbene oxide yields an approximately 50/50 mixture of both diastereomeric nitrodiols. This mixture was then converted into a mixture of **5** and **6**. The rearranged product **4** was also

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identified by independent synthesis (see the Experimental Section).

Addition of N_3^- to reaction solutions leads to no observable change in k_o. For example, at pH 7.2 in 0.02 M N_3^- solutions, k_o remains at $(1.89 \pm 0.04) \times 10^{-2}$ s^{-1}. Under these same conditions, the yields of **5** and **6** are reduced by about 85% (vide infra), but the yield of **4** is unaffected (Figure 2A). Similar results have been observed in hydrolysis reactions of other esters of *N*-arylhydroxylamines and *N*-arylhydroxamic acids.[2,4] This indicates that the rearranged product and the diols are produced from different reaction paths. We, and others, have suggested that the rearranged products are produced from internal return of a short-lived tight ion pair, while solvent adducts are derived from a free nitrenium ion if the ion is sufficiently long-lived.[2,4] The nitrenium ion can be trapped by any nucleophile present in solution, and N_3^- has been shown to be a particularly good trap for these cations.[2,4,7]

A variety of azide-containing products are produced in this reaction (Scheme 3). HPLC of reaction mixtures provided a quick way to distinguish products in which the stilbene conjugation was intact (significant absorbance at $\lambda > 300$ mn) from those, such as **5** and **6**, in which the conjugation was lost (no significant absorbance at $\lambda > 300$ nm). For that reason, all HPLC analyses were performed at both 250 and 317 nm. One azide adduct, **7**, is observed at 317 nm. The yield of this product increases rapidly with increasing $[N_3^-]$ at low $[N_3^-]$, but reaches a limiting yield of ca. 13% at $[N_3^-] \geq 0.10$ M (Figure 2A). The rate constant ratio for trapping of the nitrenium ion by N_3^- and the aqueous solvent, k_{az}/k_s, can be obtained by fitting the data in Figure 2A to eq 3 where $[\mathbf{7}]_{max}$ is the limiting yield of **7** at high $[N_3^-]$, k_{az} is the second-order rate constant for trapping of the cation by N_3^-, and k_s is the pseudo-first-order rate constant for trapping of the cation by solvent. The derived value of

$$[\mathbf{7}] = \left(\frac{k_{az}/k_s[N_3^-]}{1 + k_{az}/k_s[N_3^-]}\right)([\mathbf{7}]_{max}) \qquad (3)$$

k_{az}/k_s of 280 ± 10 M^{-1} shows that the cation **2** is a reasonably selective species and is most certainly long-lived enough to be in diffusional equilibrium with the solvent and external nucleophiles. If k_{az} is diffusionally limited at ca. 5.0×10^9 M^{-1} s^{-1}, as is the case for several other nitrenium ions under these conditions,[7] k_s is ca. 1.8×10^7 s^{-1}.

The dependence of the yields of the other N_3^- adducts on $[N_3^-]$ is considerably more complicated than that of **7**. All of these adducts absorb significantly only at $\lambda <$ 300 nm, so in all of them the stilbene conjugation is lost. The product yields of these adducts were analyzed in terms of the mechanism of Scheme 3.

The diastereomeric diazides **8** and **9** reach limiting yields with increasing $[N_3^-]$ more slowly than **7** does (Figure 2B). The stereochemical assignments for **8** and **9** are based on ^{13}C chemical shift analogies to the known threo and erythro diols **5** and **6**. In particular, the ^{13}C chemical shifts of the α- and β-carbons of the erythro diol **6** are found 0.8 ppm upfield from those of the threo diol **5.** A similar 0.9 ppm shift in the analogous ^{13}C resonances of **8** and **9** was used to assign these structures. The threo diazide **8** predominates ([**8**]/[**9**] = 1.8) as does the threo diol **5** ([**5**]/[**6**] = 2.9). If **8** and **9** are derived from N_3^- trapping of the quinone imide methide, **3b**, their

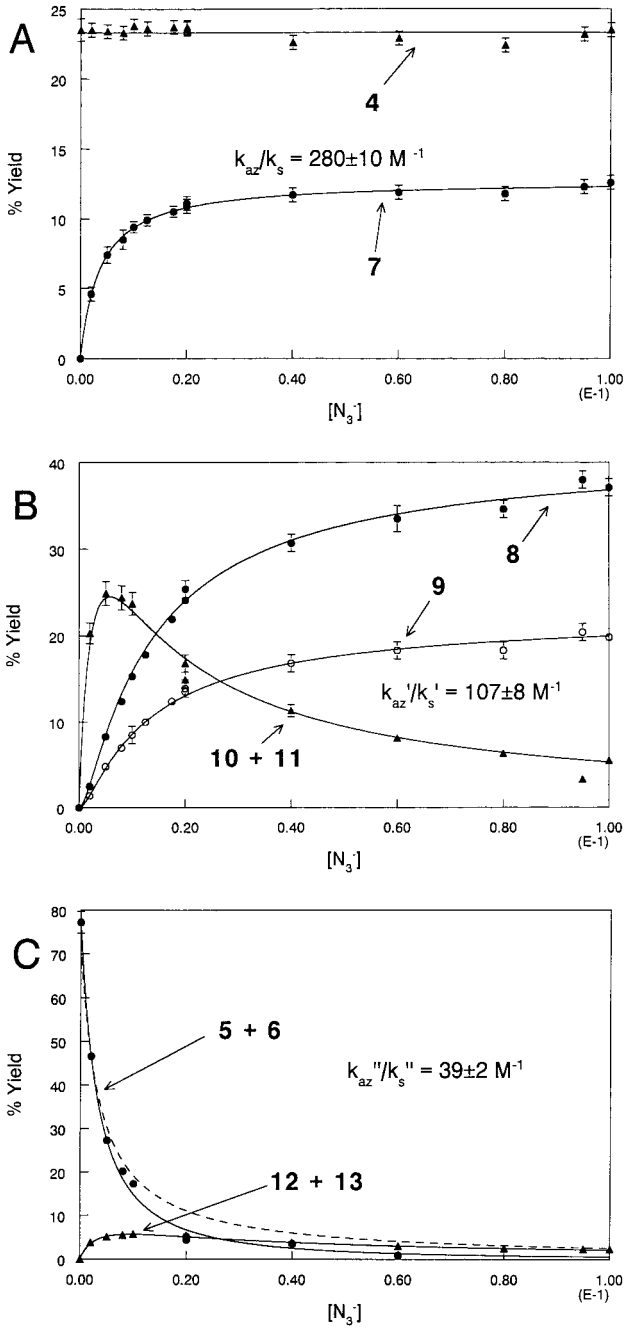
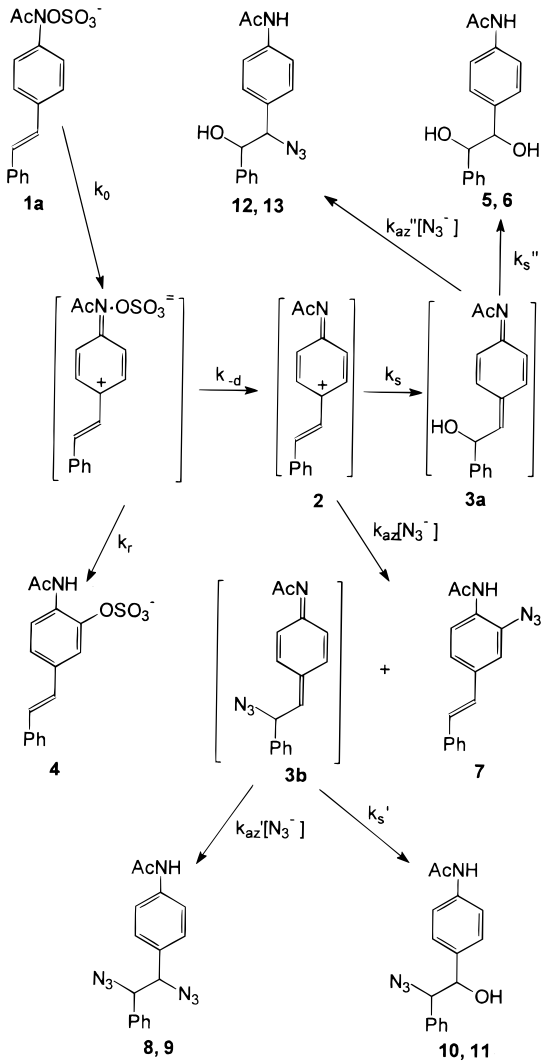


Figure 2. Yields of reaction products derived from **1a** as a function of N_3^-. (A) Yields of **4** and **7**. The theoretical line for **4** is the average of all the data points. The theoretical line for **7** was obtained by a least-squares fit to eq 3. The best fit value of k_{az}/k_s is shown. (B) Yields for **8**, **9**, and the sum of **10** and **11**. Data for **8** and **9** were fit to eq 4 with a fixed value of k_{az}/k_s of 280 M^{-1}. The theoretical lines for **8** and **9** are the result of a refit of the data with the average value of k_{az}'/k_s' of 107 M^{-1} obtained from the original least-squares fits. The data for **10** and **11** were fit to eq 5 with the fixed values for k_{az}/k_s and k_{az}'/k_s' as shown. (C) Yields for the sum of **5** and **6** and the sum of **12** and **13**. The data for **5** and **6** were fit to eq 6 (solid line) and to an equation containing only the k_{az}/k_s term of eq 6 (dashed line). The data for **12** and **13** were fit to eq 7 with the assumption that $[\mathbf{12} + \mathbf{13}]_{max}$ is equivalent to $[\mathbf{5} + \mathbf{6}]_{max}$. All fits were performed with a fixed value of k_{az}/k_s of 280 M^{-1}.

(7) Davidse, P. A.; Kahley, M. J.; McClelland, R. A.; Novak, M. *J. Am. Chem. Soc.* **1994**, *116*, 451−452. McClelland, R. A.; Davidse, P. A.; Hadzialic, G. *J. Am. Chem. Soc.* **1995**, *117*, 4173−4174.

Scheme 3



yields will be given by eq 4, where the rate constants are defined in Scheme 3. We fit the data for [**8**] and [**9**] to

$$[\mathbf{8}] = \left(\frac{k_{az}/k_s[N_3^-]}{1 + k_{az}/k_s[N_3^-]}\right)\left(\frac{k_{az}'/k_s'[N_3^-]}{1 + k_{az}'/k_s'[N_3^-]}\right)([\mathbf{8}]_{max}) \quad (4)$$

eq 4 by using both a fixed value of k_{az}/k_s of 280 M^{-1} and by allowing k_{az}/k_s to vary as a least-squares parameter. The results of both fitting procedures were nearly equivalent. We report the results with the fixed value of k_{az}/k_s because we want to show that a common set of rate constant ratios can fit all the data adequately. The fits for **8** and **9** provided k_{az}'/k_s' of 113 ± 5 M^{-1} for **8** and 101 ± 5 M^{-1} for **9**. The mean value of 107 ± 8 M^{-1} was used to construct the theoretical lines for **8** and **9** in Figure 2B. The calculated limiting yields for **8** and **9** are 42 ± 4% and 23 ± 2%, so, within experimental error, **4** and **7**−**9** account for all reaction products at high [N_3^-].

The intermediate **3b** must also be trapped by H_2O, and the azo alcohols **10** and **11** are the products of such trapping. The two diastereomers were not separated from each other, but the stereochemical assignments were made on the mixture as described above for **8** and **9**. The threo diastereomer predominates in this case also ([**10**]/[**11**] = 3.1). Under our analytical HPLC conditions, the two diastereomers coelute as a single peak. The combined yield of the two compounds should be given by eq 5, where $[\mathbf{10} + \mathbf{11}]_{max}$ is the theoretical maximum yield

$$[\mathbf{10} + \mathbf{11}] = \left(\frac{k_{az}/k_s[N_3^-]}{1 + k_{az}/k_s[N_3^-]}\right)\left(\frac{1}{1 + k_{az}'/k_s'[N_3^-]}\right)([\mathbf{10} + \mathbf{11}]_{max}) \quad (5)$$

of these two products if the k_{az}' process did not occur. The theoretical line for [**10** + **11**] in Figure 2B was calculated from the previously determined values for k_{az}/k_s and k_{az}'/k_s' of 280 M^{-1} and 107 M^{-1}, respectively. Only $[\mathbf{10} + \mathbf{11}]_{max}$ was varied to obtain the fit. As required by the mechanism of Scheme 3, the calculated limiting maximum yield for **10** + **11** ($[\mathbf{10} + \mathbf{11}]_{max}$) of 68 ± 3% is in very good agreement with the combined calculated limiting yields for **8** and **9** of 65 ± 5%.

The diols **5** and **6** should be the products of solvent trapping of the intermediate **3a**. This intermediate should also be trapped by N_3^-. We have evidence that this occurs. Under the HPLC conditions used in our product study, **5** and **6** coelute. The combined yield of these diols decreases rapidly with increasing [N_3^-] (Figure 2C). The yield of these two diols falls off more rapidly with increasing [N_3^-] than predicted for a simple trapping involving only the cation **2** but is fit well by eq 6, in which it is assumed than **3a** can be partitioned between H_2O and N_3^-. The fit provides a value of k_{az}''/k_s'' of 36 ± 7 M^{-1}.

$$[\mathbf{5} + \mathbf{6}] = \left(\frac{1}{1 + k_{az}/k_s[N_3^-]}\right)\left(\frac{1}{1 + k_{az}''/k_s''[N_3^-]}\right)([\mathbf{5} + \mathbf{6}]_{max}) \quad (6)$$

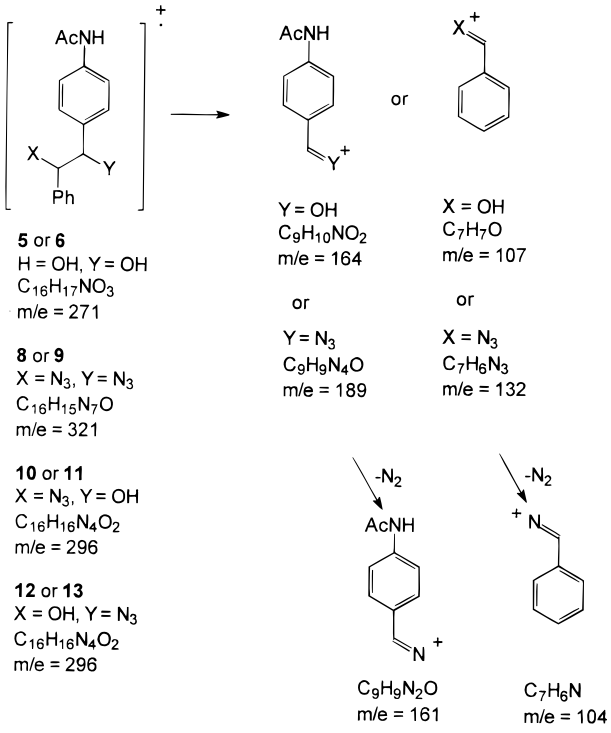
These fitting results suggest that **3a** is trapped by both N_3^- and H_2O, but this could be an artifact produced by a systematic error in the HPLC data. More convincingly, there is an HPLC peak observed at 250 nm that changes with [N_3^-] in the manner expected for the azo alcohols **12** and **13**. The data for that peak are also included in Figure 2C. The HPLC data were fit to eq 7 with k_{az}/k_s fixed at 280 M^{-1}.

$$[\mathbf{12} + \mathbf{13}] = \left(\frac{1}{1 + k_{az}/k_s[N_3^-]}\right)\left(\frac{k_{az}''/k_s''[N_3^-]}{1 + k_{az}''/k_s''[N_3^-]}\right)([\mathbf{12} + \mathbf{13}]_{max}) \quad (7)$$

The resulting value of k_{az}''/k_s'' of 39 ± 2 M^{-1} is in excellent agreement with that determined from the fit of the data for **5** and **6**. The fit requires an HPLC molar response factor of 2.1 × 10^{10} μV s M^{-1} at 250 nm for the HPLC peak that is presumed to be **12** and **13**. This is within the range of the measured molar response factors of 1.3−2.2 × 10^{10} μV s M^{-1} at 250 nm for the isolated products **5**, **6**, and **8**−**11**. The combined yield of **12** and **13** predicted by these fits is only ca. 6% under the most favorable conditions ([N_3^-] = 0.01 M). We were able to isolate a sufficient quantity of one of the two diastereomers for characterization, but we cannot make NMR stereochemical assignments without samples of both compounds. On the basis of the predominance of the threo isomers in the other cases, it is likely we have isolated the threo diastereomer **12**.

Mass spectrometry played a critical role in assigning structures to the diol, diazide, and azo alcohol products

Scheme 4

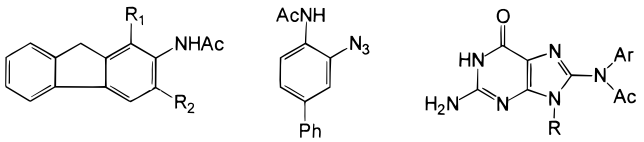


5, **6**, **8**−**11**, and **12** or **13**. The dominant fragmentation pattern in the EI-MS of all of these compounds involves cleavage of the $C_\alpha-C_\beta$ bond with the positive charge located on either of the two fragments (Scheme 4). The initially formed daughter ions at *m/e* 107, 132, 164, or 189 are readily observed while the parent ions are weak or unobservable. The azide-containing daughter ions at *m/e* 132 or 189 are subject to loss of N_2 to generate prominent ions at 104 or 161. The acylated ions at *m/e* 164 and 161 are also subject to loss of ketene to generate ions at *m/e* 122 and 119, respectively (not shown in Scheme 4). The fragmentation patterns provide unequivocal evidence of structure, particularly in the case of the regioisomers **10**, **11** and **12**, **13**.

Under all the reaction conditions employed, repetitive wavelength scans from 340 to 250 nm were consistent with a simple first-order decay of **1a**. Therefore, all the intermediates that are trapped by N_3^- in this study are steady-state intermediates that do not reach detectable concentrations under typical hydrolysis conditions. None of them can be detected directly by our methods, but the trapping data leave little doubt about their existence.

Table 1 summarizes the results of our product analysis at pH 7.2. It shows that predicted and observed product yields are in very good agreement. It is clear that all the data can be fit by a common set of rate constant ratios for trapping of the three intermediates. The trapping of nitrenium ions by nucleophiles has previously been shown to be pH independent except at very low pH, where the nitrenium ion may be protonated to produce a dication.[2,4,7] The quinone imide methides **3a** and **3b** are likely to show pH-dependent trapping based on literature precedent,[8] but we have not examined the trapping behavior at other pH values. It is clear that under physiological pH conditions intermediates such as **3a** and **3b** will be generated and that they will be reasonably selective in their reactions with nucleophiles.

These results confirm the previous suggestions that quinone imide methide intermediates such as **3a** and **3b** play an important role in the chemistry of the stilbenyl esters such as **1a** and **1b**. Our results show that, within experimental error, H_2O attacks **2** only at the β-carbon of the cation to produce **3a**. The significantly stronger and less selective nucleophile N_3^- will attack the ortho-carbon of the proximal ring in **2**, but even this nucleophile shows a greater preference to attack the β-carbon: 5/1 β-attack/ortho-attack from the ratio ([**8**] + [**9**])/[**7**] at high [N_3^-]. The adduct **7**, a minor product of the reaction of **2** with N_3^-, is analogous to the exclusive products of N_3^- reaction with other nitrenium ions such as the *N*-acetyl-*N*-(2-fluorenyl)nitrenium ion (**14a**,**b**) and the *N*-acetyl-N-(4-biphenylyl)nitrenium ion (**15**).[2] The previously



14a $R_1 = N_3$, $R_2 = H$ **15** **16**

b $R_1 = H$, $R_2 = N_3$

identified products of the reaction of **1b** with guanosine also show a high preference for β-attack with a nucleophile that ordinarily generates a C-8 adduct such as **16**.[1b,3] The selectivity of **2** expressed as k_{az}/k_s is smaller than that of the analogous fluorenyl (6.2×10^4 M^{-1}) or biphenylyl (1×10^3 M^{-1}) ions, but significantly larger than that of ions such as the *N*-acetyl-*N*-(4-tolyl)nitrenium ion (0.6 M^{-1}).[2,7] It is not yet known whether **2** will show significant selectivity toward reaction with deoxyguanosine, a hallmark of other nitrenium ions derived from strongly carcinogenic polycyclic aromatic amines or amides.[3]

The term "nitrenium ion" has been retained to describe the cationic intermediates derived from N−O bond heterolysis of esters of *N*-arylhydroxamic acids and *N*-arylhydroxylamines even though it has long been recognized that these ions undergo nucleophilic attack by small hard nucleophiles on the ortho and para carbons of the aromatic ring much more readily than on nitrogen.[2,4,7] Calculations of the properties of these ions at both the semiempirical and ab initio level agree that the majority of the charge density resides in the aromatic ring.[2,9] Nonetheless, "nitrenium ion" is a useful term because it describes a group of cations with similar chemical properties and it recognizes the fact that these ions do retain reactivity at nitrogen with a variety of soft nucleophiles such as glutathione, aromatic amines, and guanosine.[3,10]

The term may be stretched to the limit of its usefulness to describe **2**, however. This ion shows little "nitrenium

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Table 1. Values of Rate Constant Ratios and Limiting Product Yields Determined from the Fits and Observed Product Yields[a]

	rate constant ratios (M^{-1})				
products	k_{az}/k_s	k_{az}'/k_s'	k_{az}''/k_s''	predicted limiting yields[g] (%)	obsd yields (%)
7	280 ± 10[b]			13 ± 1	12.4 ± 0.5 (0.5 M N_3^-)
8		113 ± 5[c,d]		42 ± 4	40 ± 1 (0.5 M N_3^-)
9		101 ± 5[c,d]		23 ± 2	22 ± 1 (0.5 M N_3^-)
10 + **11**				25 ± 2 (0.006 M N_3^-)	25 ± 2 (0.005 M N_3^-)
5 + **6**			36 ± 7[e,f]	78 ± 2	77 ± 3 (0.0 M N_3^-)
12 + **13**			39 ± 2[e,f]	5.7 ± 0.7 (0.010 M N_3^-)	

[a] All products were determined at 20 °C in 0.02 M pH 7.2 phosphate buffers at $\mu = 0.5$. Initial concentration of **1a** was 5.3×10^{-5} M. [b] Determined from a least-squares fit of the product yield data for **7** to eq 3. [c] Determined from a least-squares fit of the product yield data for **8** or **9** to eq 4. [d] The average value of 107 ± 8 M^{-1} was used in all subsequent calculations. [e] Determined from a least-squares fit of the product yield data for **5** and **6** to eq 6 or **12** and **13** to eq 7. [f] The weighted average value of 39 ± 2 M^{-1} was used in all subsequent calculations. [g] Calculated from the appropriate equation (3, 4, 5, 6 or 7) at [N_3^-] where the highest yield of that product is predicted. The average values for the rate constant ratios, as used in the fits shown in Figure 2, were used in these calculations.

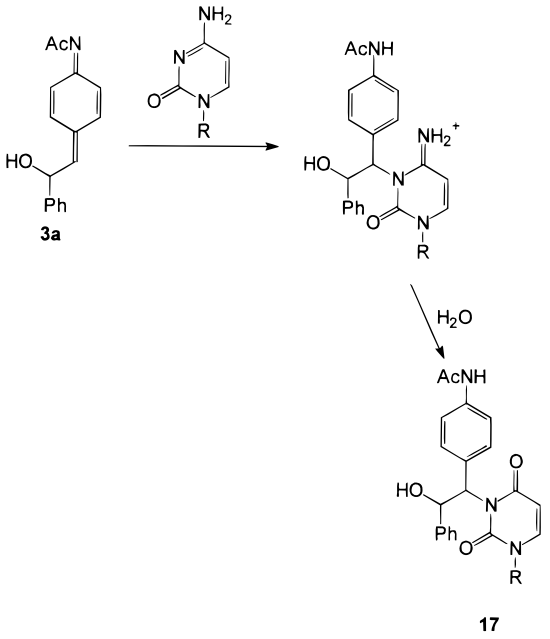
ion" character. It will generate about 15% of the expected product of nucleophilic aromatic substitution, **7**, when it reacts with the strong and unselective N_3^-, but it does not generate a similar product from reaction with H_2O. It certainly does not react with guanosine in the manner expected for a nitrenium ion. Scribner has suggested that "the '*N*-acetyl-*N*-(4-stilbenyl)nitrenium ion' is no such thing...".[1a] We find ourselves in substantial agreement with that statement.

The unique chemistry of **2** is responsible for the quinone imide methides, such as **3a** and **3b**, that show significant electrophilic reactivity. At pH 7.2, their N_3^-/solvent selectivities (k_{az}'/k_s' for **3b** and k_{az}''/k_s'' for **3a**) are ca. 2−7-fold smaller than **2**, but they still exhibit a fair degree of discrimination between nucleophiles under physiological pH conditions. In all the cases that we were able to isolate, both diastereomers that result from attack of H_2O or N_3^- on **3a** or **3b**, the threo compound predominates over the erythro diastereomer by a factor of ca. 2−3. The most stable conformation of **3a** or **3b** is expected to be the conformer in which the C−H bond of the β-carbon is coplanar with the π-bond involving the α-carbon.[11] The predominance of the threo products may be due to preferential attack of the second nucleophile on the sterically more accessible face of the most stable conformer.

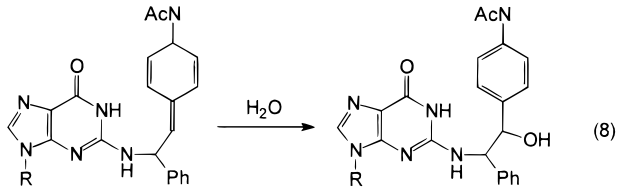
The quinone imide methides may be important physiologically. The intermediate **3a** will most certainly be produced in vivo from decomposition of carcinogenic esters such as **1a** and **1b**. It will then react with cellular nucleophiles. This intermediate provides the most logical explanation for the observed product of the reaction of **1b** with cytidine and 1-methylcytosine (Scheme 5).[1c] The product, **17**, has previously been explained by nucleophilic attack of *N*-3 of the pyrimidine on the β-carbon of **2**, followed by H_2O attack on the α-carbon, an intramolecular deamination involving the α-OH, a rearrangement of the *N*-3 of the pyrimidine from the β- to the α-carbon, and attack of H_2O on the resulting benzylic cation.[1c] The mechanism of Scheme 5 is decidedly more simple and direct.

It has previously been suggested that quinone imide methides may be responsible for the interstrand cross-links in DNA that are induced in vivo by treatment of

Scheme 5



rats with *trans*-*N*-acetyl-4-aminostilbene.[1b,12] Since the intermediate, **18**, that appears to be responsible for the observed guanosine adducts can apparently react with H_2O (eq 8), it could most certainly serve as a cross-linking agent for reaction with a nucleophilic site on the complementary strand of duplex DNA.



(8)

Although it has become clear that N−O bond heterolysis of carcinogenic ester derivatives of *N*-arylhydroxylamines and *N*-arylhydroxamic acids to produce "nitrenium ions" is the dominant, if not exclusive, mode of decomposition of these metabolites in an aqueous environment, it has become equally clear that each individual cation exhibits quite unique chemistry related to its

(11) Dorigo, A. E.; Pratt, D. W.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6591−6600. Karabatsos, G. J.; Fenoglio, D. J. In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; Wiley: New York, 1970; Vol. 5.

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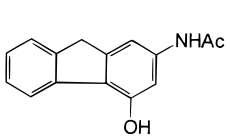
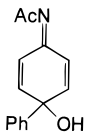
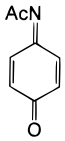
structure. The wide variety of chemistry possible in these species can be seen in the major H_2O trapping products derived from **2** (**5** and **6**), *N*-acetyl-*N*-(2-fluorenyl)nitrenium ion (**19**), *N*-acetyl-*N*-(4-biphenylyl)nitrenium ion (**20**), and *N*-acetyl-*N*-(4-ethoxyphenyl)nitrenium ion (**21**).[2,4,13] Similar variety is seen in the N_3^- adducts of



19



20



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these ions.[2,4] In many cases initial nucleophilic attack on the cation yield other electrophilic species that may also be relevant to the biological effects of the parent esters.[2,4] The chemistry of "nitrenium ions" is considerably more rich and variable than was previously appreciated.

Experimental Section

Preparation of solutions for kinetic and product studies, purification of solvents, and general procedures used in these studies are described elsewhere.[2] All studies were performed in 5 vol % CH_3CN-H_2O at an ionic strength of 0.5 maintained with $NaClO_4$ and/or NaN_3. Phosphate buffers (0.02 M in total phosphate) were used to maintain pH. ^{13}C NMR spectra for all new products are available in the Supporting Information. Hydrogen substitution assigned to ^{13}C peaks was determined by appropriate DEPT experiments.

Kinetics and Product Studies. Kinetics were performed at 20 °C at an initial concentration of **1a** of ca. 5×10^{-5} M obtained by injection of 15 μL of a 0.01 M stock solution of **1a** in DMF into 3 mL of the buffer. Wavelength scans were performed from 340 to 250 nm, and kinetic data were collected at 317 nm.

HPLC of these reaction solutions at pH 7.2 were performed after 10 half-lives of the reaction by injection of 20 μL of the reaction solution onto an analytical C-8 column. The column was eluted with 65/35 MeOH/H_2O buffered with 0.025 M 1/1 NaOAc/HOAc at a flow rate of 1 mL/min. UV absorbance was monitored at 250 and 317 nm. All products were monitored as a function [N_3^-]. Extinction coefficients for quantitative analysis of HPLC data were determined from synthesized (**4**−**6**) or isolated (**7**−**11**) samples. For coeluting materials (**5**, **6**, and **10**, **11**), weighted average extinction coefficients were calculated from appropriate mixtures of those products.

Products were isolated from reactions run at higher initial concentrations of **1a** (ca. 1.0 mM) in 150 mL of pH 7.2 buffer containing 0.0, 0.005, and 0.5 M NaN_3. After 10 half-lives of the reaction, the aqueous solution was extracted with CH_2Cl_2 (4 × 50 mL) to remove **7**−**11** and **12** or **13**. After evaporation of the solvent, these products were purified by column chromatography on silica gel using 9/1 CH_2Cl_2/EtOAc as eluent or by preparative HPLC on a C_8 column with 65/35 MeOH/H_2O as eluent. Other products (**4**−**6**) were isolated by multiple EtOAc extractions (50 mL). These were purified on 230−400 mesh C_{18}-reversed phase silica gel using 40/60 MeOH/H_2O as the eluent. All products were characterized as described below.

Synthesis. N−(Sulfonatooxy)-*N*-acetyl-4-aminostilbene (1a). *N*-Hydroxy-*N*-acetyl-4-aminostilbene was synthesized as described in the literature.[14,15] This compound was then esterified using DCC and H_2SO_4 as previously described for N-(sulfonatooxy)-*N*-acetyl-2-aminofluorene:[16] ^1H NMR (300 MHz, DMSO-d_6) δ 7.59 (2H, m), 7.53 (2H, d, J = 8.8 Hz), 7.46 (2H, d, J = 8.8 Hz), 7.39−7.33 (2H, m), 7.27−7.15 (3H, m), 2.29 (3H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 172.0 (C), 140.6 (C), 137.3 (C), 133.8 (C), 128.9 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 126.6 (CH), 126.1 (CH), 122.4 (CH), 22.5 (CH_3).

3-(Sulfonatooxy)-*N*-acetyl-4-aminostilbene (4). 3-Hydroxy-*N*-acetyl-4-aminostilbene[15] was esterified on a 25 mg scale by a procedure similar to that described above for **1a**. Reaction time was 2.5 h. The crude product derived from evaporation of the NH_3-saturated MeOH containing KOAc was dissolved in 3 mL of H_2O, filtered to remove insoluble materials, and lyophilized to obtain **4:** ^1H NMR (300 MHz, DMSO-d_6) δ 9.25 (1H, s), 8.01 (1H, d, J = 8.5 Hz), 7.75 (1H, m), 7.58 (2H, d, J = 7.4 Hz), 7.42 (1H, d, J = 1.7 Hz), 7.32 (2H, m), 7.23 (1H, m), 7.19 (1H, d, J = 16.2 Hz), 7.10 (1H, d, J = 16.2 Hz), 2.34 (3H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 168.0 (C), 144.6 (C), 137.3 (C), 132.9 (C), 131.2 (C), 128.9 (CH), 127.9 (CH), 127.7 (CH), 126.6 (CH), 122.8 (CH), 121.5 (CH), 121.1 (CH), 24.4 (CH_3).

***threo*-1,2-Dihydroxy-1-phenyl-2-(4-nitrophenyl)-ethane.** This material was made from *trans*-4-nitrostilbene[14a] by adaptation of a procedure for the synthesis of (*R*,*R*)-1,2-diphenyl-1,2-ethanediol.[17] In our procedure, we did not use the chiral auxiliary so a racemic mixture of the threo diols was obtained. The crude diol obtained from the procedure was used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ 8.05 (2H, d, J = 8.8 Hz), 7.36 (2H, d, J = 8.7 Hz), 7.18−7.10 (5H, m), 5.74 (1H, d, J = 4.7 Hz), 5.57 (1H, d, J = 4.6 Hz), 4.81 (1H, t, J = 5.0 Hz), 4.69 (1H, t, J = 4.9 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 150.8 (C), 146.4 (C), 141.9 (C), 128.5 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 122.5 (CH), 77.0 (CH), 76.6 (CH).

***threo*-1,2-Dihydroxy-1-phenyl-2-(4-aminophenyl)-ethane.** In a 500 mL hydrogenation flask, 50 mg of threo nitrodiol was dissolved in 50 mL of AcOH, and 12 mg of 10% Pd−C catalyst was added. The reaction mixture was hydrogenated at 50 psi for 3 h. The catalyst was filtered from the solution, and the AcOH was removed at reduced pressure. The crude product was dried under vacuum: ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 147.5 (C), 142.8 (C), 129.5 (C), 128.0 (CH), 127.4 (CH), 127.4 (CH), 126.7 (CH), 113.2 (CH), 78.2 (CH), 78.0 (CH).

***erythro*/*threo*-1,2-Dihydroxy-1-phenyl-2-(4-nitrophenyl)-ethane.** In a 50 mL round-bottom flask, 128 mg (0.53 mmol) of *trans*-4-nitrostilbene oxide[18] and 20 mL of H_2O were combined. Concentrated HCl (1 mL) was added, and the mixture was heated at 45 °C under N_2 until all components dissolved (ca. 15 h). The reaction mixture was quenched with 1.6 g of NaOAc·$3H_2O$, and the solvent was removed under reduced pressure. The residue was extracted (5 × 3 mL) with Et_2O, and the combined Et_2O extracts were dried over Na_2SO_4. After rotary evaporation, the crude product was dried under vacuum for 24 h to yield a ca. 50/50 mixture of the two diastereomeric diols. NMR data for the erythro diol were obtained by subtracting the known peaks for the threo diol from the NMR spectra of the mixture: ^1H NMR (300 MHz, DMSO-d_6) δ 8.13 (2H, d, J = 8.4 Hz), 7.51 (2H, d, J = 8.5 Hz), 7.28−7.16 (5H, m), 5.60 (2H, s(br)), 4.75 (1H, d, J = 6.1 Hz), 4.63 (1H, d, J = 6.1 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 151.5 (C), 146.6 (C), 143.0 (C), 128.8 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 122.6 (CH), 76.9 (C), 76.6 (C).

***erythro*/*threo*-1,2-Dihydroxy-1-phenyl-2-(4-aminophenyl)ethane.** The nitrodiol mixture was reduced as described above for the threo compound. The erythro NMR spectrum was obtained by subtraction: ^{13}C NMR (75.5 MHz,

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(18) Reif, D. J.; House, H. O. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 860−862.

DMSO-d_6) δ 148.0 (C), 143.8 (C), 129.6 (C), 128.1 (CH), 127.6 (CH), 127.3 (CH), 126.6 (CH), 113.4 (CH), 77.3 (CH), 77.1 (CH).

***threo*- and *erythro*-1,2-Dihydroxy-1-phenyl-2-(4-acetamidophenyl)ethane (5 and 6).** The appropriate amino diol (88 mg, 0.39 mmol) was dissolved in 20 mL of dry THF followed by the addition of 54 μL of Et_3N. This mixture was stirred as 30 μL of acetyl chloride in 1 mL of THF was added slowly. After being stirred at room temperature for 20 min, the mixture was heated on a steam bath for another 20 min. After cooling, 25 mL of brine was added, and the layers were separated. The aqueous layer was extracted (5 × 25 mL) with more THF. The combined THF extracts were evaporated, and the crude product was dried under vacuum. The product was purified by TLC on silica gel with 9/1 EtOAc/CH_2Cl_2 eluent.

5: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.86 (1H, s), 7.35 (2H, d, J = 8.5 Hz), 7.13 (3H, m), 7.05 (2H, m), 6.96 (2H, d, J = 8.5 Hz), 5.36 (2H, s(br)), 4.53 (1H, d, J = 6.5 Hz), 4.50 (1H, d, J = 6.5 Hz), 1.99 (3H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 168.4 (C), 142.7 (C), 138.2 (C), 137.2 (C), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.0 (CH), 118.2 (CH), 78.1 (CH), 77.8 (CH), 24.3 (CH_3); high-resolution MS $C_{16}H_{17}NO_3$ requires *m/e* 271.1209, found 271.1186 (0.2); $C_9H_{10}NO_2$ requires *m/e* 164.0712, found 164.0744 (100); C_7H_8NO requires *m/e* 122.0606, found 122.0626 (84); C_7H_7O requires *m/e* 107.0497, found 107.0488 (12).

6 (by subtraction): ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.90 (1H, s), 7.41 (2H, d, J = 8.5 Hz), 7.18 (3H, m), 7.10−7.02 (4H, m), 5.47 (2H, s(br)), 4.53 (1H, d, J = 5.0 Hz), 4.49 (1H, d, J = 5.0 Hz), 2.00 (3H, s); ^{13}C (75.5 MHz, DMSO-d_6) δ 168.4 (C), 143.6 (C), 131.4 (C), 131.0 (C), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.0 (CH), 118.5 (CH), 77.3 (CH), 77.0 (CH), 25.1 (CH_3); high-resolution MS: $C_{16}H_{17}NO_3$ requires *m/e* 271.1209, found 271.1233 (0.2); $C_9H_{10}NO_2$ requires *m/e* 164.0712, found 164.0732 (100); C_7H_8NO requires *m/e* 122.0606, found 122.0656 (64); C_7H_7O requires *m/e* 107.0497, found 107.0500 (3.7).

Azide Adducts. These were isolated as described above and purified by chromatographic methods (also described above) to yield the compounds **7**−**9**, the mixture of **10** and **11**, and **12** or **13**.

3-Azido-*N*-acetyl-4-aminostilbene (7): IR (KBr) 2120, 1660, 1600, 1530, 1300 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, d, J = 8.4 Hz), 7.45 (3H, m) 7.35−7.15 (5H, m), 6.98 (2H, s), 2.15 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.9 (C), 144.8 (C), 136.9 (C), 133.7 (C), 131.6 (C), 128.9 (CH), 128.7 (CH), 127.8 (CH), 127.1 (CH), 126.5 (CH), 124.0 (CH), 120.7 (CH), 115.0 (CH), 24.8 (CH_3); high-resolution MS $C_{16}H_{14}N_4O$ requires *m/e* 278.1176, found 278.1155 (9.5%).

***threo*-1,2-Diazido-1-phenyl-2-(4-acetamidophenyl)ethane (8):** IR (KBr) 2105, 1665, 1600, 1535, 1255, 825 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.25 (3H, m), 7.17 (3H, m), 7.05−6.90 (4H, m), 4.54 (2H, s), 2.07 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.3 (C), 138.2 (C), 135.6 (C), 131.4 (C), 128.7 (CH), 128.6 (CH), 128.3 (CH), 127.6 (CH), 119.4 (CH), 70.6 (CH), 70.1 (CH), 24.6 (CH_3); high-resolution MS $C_{16}H_{16}N_7O$ (M + 1) requires *m/e* 322.1416, found 322.1442 (0.1); $C_9H_9N_4O$ requires *m/e* 189.0777, found 189.0808 (3.4); $C_9H_9N_2O$ requires *m/e* 161.0715, found 161.0679 (93); $C_7H_6N_3$ requires *m/e* 132.0562 found 132.0540 (1.5); $C_7H_7N_2$ requires *m/e* 119.0609, found 119.0635 (81); C_7H_6N requires *m/e* 104.0501, found 104.0494 (39).

***erythro*-1,2-Diazido-1-phenyl-2-(4-acetamidophenyl)ethane (9):** IR (KBr) 2100, 1665, 1600, 1535, 1255, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (3H, m), 7.30 (3H, m), 7.20−7.10 (4H, m), 4.59 (2H, s), 2.13 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.3 (C), 138.4 (C), 135.7 (C), 131.2 (C), 129.0 (CH), 128.7 (CH), 128.7 (CH), 127.9 (CH), 119.6 (CH), 69.6 (CH), 69.2 (CH), 24.7 (CH_3); high-resolution MS $C_{16}H_{16}N_7O$ (M + 1) requires *m/e* 322.1416, found 322.1418 (0.1); $C_9H_9N_4O$ requires *m/e* 189.0777, found 189.0770 (2.4); $C_9H_9N_2O$ requires *m/e* 161.0715, found 161.0711 (76); $C_7H_6N_3$ requires *m/e* 132.0562, found 132.0591 (1.3); $C_7H_7N_2$ requires *m/e* 119.0609, found 119.0605 (69); C_7H_6N requires *m/e* 104.0501, found 104.0483 (37).

***threo*-1-Azido-2-hydroxy-1-phenyl-2-(4-acetamidophenyl)ethane (10)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.30 (1H, m) 7.32 (2H, d, J = 8.4 Hz), 7.24−7.18 (3H, m), 7.08−7.04 (2H, m), 7.01 (2H, d, J = 8.5 Hz), 4.70 (1H, d, J = 8.1 Hz), 4.57 (1H, d, J = 8.0 Hz), 2.11 (3H, s); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 167.8 (C), 137.6 (C), 135.8 (C), 134.8 (C), 128.1 (CH), 128.0 (CH), 127.5 (CH), 127.2 (CH), 118.7 (CH), 77.1 (CH), 72.4 (CH), 24.0 (CH_3); high-resolution MS (mixture of **10** and **11**) $C_{16}H_{17}N_4O_2$ (M + 1) requires *m/e* 297.1351, found 297.1327 (0.2); $C_9H_{10}NO_2$ requires *m/e* 164.0712, found 164.0694 (80); C_7H_8NO requires *m/e* 122.0606, found 122.0581 (71); C_7H_6N requires *m/e* 104.0501, found 104.0495 (29).

***erythro*-1-Azido-2-hydroxy-1-phenyl-2-(4-acetamidophenyl)ethane (11)** (by subtraction, some peaks are obscured by those of the major isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (2H, d, J = 8.6 Hz) 7.19 (2H, d, J = 8.3 Hz) 4.78 (1H, d, J = 6.6 Hz) 4.65 (1H, d, J = 6.6 Hz), 2.14 (3H, s); ^{13}C NMR (75.5 MHz, CD_2Cl_2) 137.8 (C), 135.3 (C), 128.3 (CH), 128.2 (CH), 127.7 (CH), 127.3 (CH), 118.8 (CH), 76.1 (CH), 70.8 (CH).

2-Azido-1-hydroxy-1-phenyl-2-(4-acetamidophenyl)-ethane (12 or 13): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (2H, d, J = 8.5 Hz), 7.20−7.18 (3H, m), 7.09−7.06 (3H, m), 7.03 (2H, d, J = 8.5 Hz), 4.71 (1H, d, J = 8.1 Hz), 4.59 (1H, d, J = 8.1 Hz), 2.14 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.1 (C), 139.1 (C), 138.0 (C), 131.7 (C), 128.6 (CH), 128.2 (CH), 128.2 (CH), 126.9 (CH), 119.4 (CH), 77.9 (CH), 72.4 (CH), 24.7 (CH_3); high-resolution MS $C_{16}H_{17}N_4O_2$ (M + 1) requires *m/e* 297.1351, found 297.1360 (0.7); $C_{16}H_{16}N_4O_2$ requires *m/e* 296.1273, found 296.1295 (0.1); $C_9H_9N_4O$ requires *m/e* 189.0777, found 189.0810 (2.1); $C_9H_9N_2O$ requires *m/e* 161.0715, found 161.0724 (44); $C_7H_7N_2$ requires *m/e* 119.0609, found 119.0612 (93); C_7H_7O requires *m/e* 107.0497, found 107.0481 (77).

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Supporting Information Available: Table of hydrolysis rate constants for **1a** in the presence and absence of N_3^-, and ^{13}C NMR spectra for **1a**, **4**−**11**, and **12** or **13** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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