PERKIN 2

Spectroscopic characterization by laser flash photolysis of electrophilic intermediates derived from 4-aminostilbenes. Stilbene “nitrenium” ions and quinone methide imines†

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This paper reports the observation in water–acetonitrile solutions of two electrophiles derived from 4-amino- and 4-acetylaminostilbene carcinogens—the ‘nitrenium’ ion $ArCH{=}CHC_6H_4{-}N^+R$ and the quinone methide imine $ArCHOH{-}CH{=}C_6H_4{=}NR$. One example where R = acetyl (Ar = phenyl) is included, with the photochemical precursor *N*-(sulfonatooxy)-*N*-acetyl-4-aminostilbene (**1**). There are six examples where R = H, with substituents in Ar of 4-H, 4-Br, 3-Me, 4-Me, 4-NMeAc, 4-MeO; an azidostilbene **12** is the precursor for this series. The ‘nitrenium’ ions are characterized by a strong absorption in the region from 500–600 nm. Lifetimes range from 40 ns (R = acetyl, Ar = C_6H_5) to 160 ns (R = H, Ar = C_6H_5) to 16 μs (R = H, Ar = 4-$MeOC_6H_4$). These cations react with water at the β-carbon, *i.e.* through the resonance contributor $ArCH^+{-}CH{=}C_6H_4{=}NH$, and the substituent effect in the R = H series shows a close parallel to reactions of other benzylic-cations. However, both the spectra of the cations and the unusually long lifetimes show that there must be substantial delocalization of the positive charge throughout the structure. The quinone methide imines, the immediate products of water addition, are observed at 300–400 nm following the decay of the cation. The imine with R = H (all Ar) exists as both the neutral compound and the conjugate acid, with a pK_a of 8.3 being obtained from both the spectral change and the rate–pH profile. The latter shows a plateau region in acid (lifetime of 4 ms) due to reaction of the cationic form with water. A plateau region in base is also assigned to the reaction of the cation, this time with hydroxide ion. The acylimine (R = Ac) shows an H^+-dependent reaction below pH 8 where a sharp break to an OH^--dependent reaction occurs. The latter is assigned to the neutral form reacting directly with hydroxide ion. The acid region represents equilibrium protonation followed by rapid reaction with water. The absence of a break in the rate–pH profile suggests that the cation has a pK_a value less than 2. Application of previously measured azide-trapping data provides an estimate of $pK_a = 1.6$ with the lifetime of the cation of 7 ns. This study reinforces conclusions made previously in a study of the ground state solvolysis of the *N*-acetyl derivative **1**. The aminostilbene system is an unusual arylamine carcinogen in both the nature of the reaction of the ‘nitrenium’ ion, and in the formation of a subsequent electrophile, the quinone methide imine. The present study reports the first kinetic information regarding the latter class in water. At pH 7, both the NH and *N*-acetyl derivatives are quite long-lived. Both react at this pH through their conjugate acid form, which in one resonance form, can be regarded as benzylic-type cation.

In a recent paper[1] one of our groups reported a kinetic and product investigation of the aqueous solvolysis of *N*-(sulfonatooxy)-*N*-acetyl-4-aminostilbene (**1**, Scheme 1). In pH 7.2 phosphate buffer, products are the rearranged sulfate **2** (23%) and a 3 : 1 ratio of the *threo–erythro* diols **3t** : **3e** (77%). The addition of the clock nucleophile azide had no effect on the rate constant for the solvolysis, nor on the yield of **2**. There were however a number of azide adducts **4**–**7** formed at the expense of **3**. Based on these observations and on the quantitative dependence of the product ratios on the concentration of azide ion, the mechanism of Scheme 1 emerged. The rate limiting step is ionization to an ion pair **8**, whose collapse is responsible for the sulfate **2**. Separation leads to a sequence with three electrophilic intermediates that partition between reaction with solvent and with azide. The free ion **9** reacts at the β-carbon of the C=C bond to form **10** from water and **11** from azide. In a minor pathway, azide also reacts to form the ring-substituted product **7**. The intermediates **10** and **11** are quinone methide (quinomethane) acylimines. In a further competition they react with water and azide at the methide carbon to form **3** through **6**, each as a mixture of *threo–erythro* diastereomers. The quantitative analysis provided the three partitioning ratios $k_{az}:k_w$—280 ± 10 mol dm^{-3} for **9**, 39 ± 2 mol dm^{-3} for **10**, and 107 ± 8 mol dm^{-3} for **11**.

Arylamines and amides have seen extensive investigation because of their use in the chemical industry and their presence in, for example, tobacco smoke, automobile exhaust, and cooked meats and fish.[2,3] Many of the compounds are potent mutagens and carcinogens. This is known to be the result of metabolic activation to esters such as **1** that react with DNA to form covalent adducts *via* an intermediate cation formed in an S_N1 ionization.[4] This cation is usually termed a “nitrenium” or “arylnitrenium” ion, although both theory[5,6] and experiment[7,8] show that it is better represented by imino-carbocation resonance structures such as **9** shown in Scheme 1.

On the surface, 4-aminostilbene and its *N*-acetyl derivative would appear to be typical arylamine carcinogens. The products, including those derived from the DNA bases, are however unique.[1,9–11] Esters derived from other carcinogens invariably react with water and azide in the proximal aromatic ring,[12–15] and they react with guanine derivatives to form the

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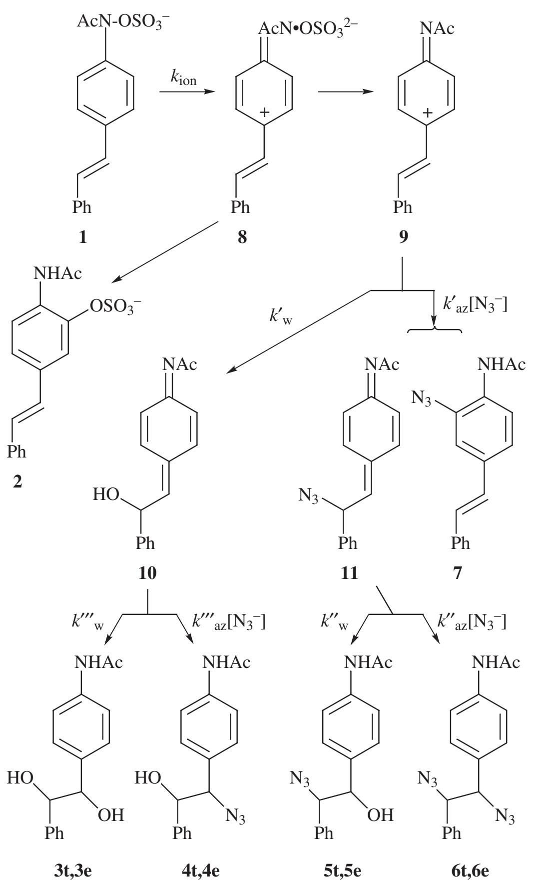
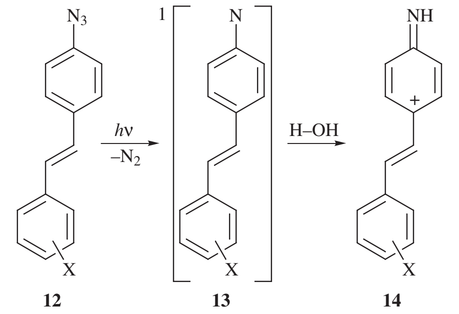
† Quinomethane is the IUPAC recommended name for quinone methides.



Scheme 1

ubiquitous 8-arylamino adduct.[4,16,17] With the exception of the minor product **7**, nucleophiles generally attach to the stilbene derivatives at the C=C. Another interesting feature of the stilbenes is the proposed generation of a second electrophile, the quinone methide imine. Such an intermediate may explain an unusual product observed with cytidine and 1-methylcytosine,[10] and may account for interstrand DNA cross links found in rats treated with *N*-acetyl-4-aminostilbene.[11,18]

From the measured $k_{az}:k_w$ ratio, the azide-clock assumption[8,19] that k_{az} is 5×10^9 mol^{-1} dm^3 s^{-1} leads to a lifetime ($1/k_w$) of 56 ns for the cation **9**. The quinone methide derivatives **10** and **11** exhibit lower selectivities. However, the application of the azide-clock method to these is questionable. Over the past few years, methods have been developed for the direct observation of arylnitrenium ions using the technique of laser flash photolysis (LFP).[7,8,20] There is no uncertainty with this approach since absolute rate constants are directly measured. We felt it of importance to apply LFP in the stilbene system. This would provide a spectral comparison of **9** with other arylnitrenium ions, and, because of the uncertainty introduced by the different reactivity pattern, to see whether the azide-clock assumption does apply. We also felt that it might be possible to observe the quinone methide imine. Indeed this was the case. We have also studied six NH derivatives **14**, generated photochemically from azide precursors **12** (Scheme 2). This has



X = H (**a**), 4-Br (**b**), 3-Me (**c**), 4-Me (**d**), 4-NMeCOCH$_3$ (**e**), 4-MeO (**f**)

Scheme 2

allowed us to probe the effect of substituents in the distant aromatic ring, as well as to evaluate the difference between *N*-acetyl and NH on the reactivity of both the "nitrenium" ion and the quinone methide imine.

Results

N-Acetyl system

As shown in Fig. 1, laser photolysis of **1** results in absorbance in the region 500–600 nm. This decays very rapidly with single exponential kinetics (Inset A), with a lifetime (1/*k*(obs)) of 37 ns in a 40% acetonitrile solution. The same *k*(obs) is found from 450–600 nm, indicating the presence of one intermediate. The decay is accelerated by azide ion (Inset C), with *k*(obs) linear in the concentration of the nucleophile.

The absorbance above 450 nm decays to essentially zero in the fast process, but at its completion, there is absorbance

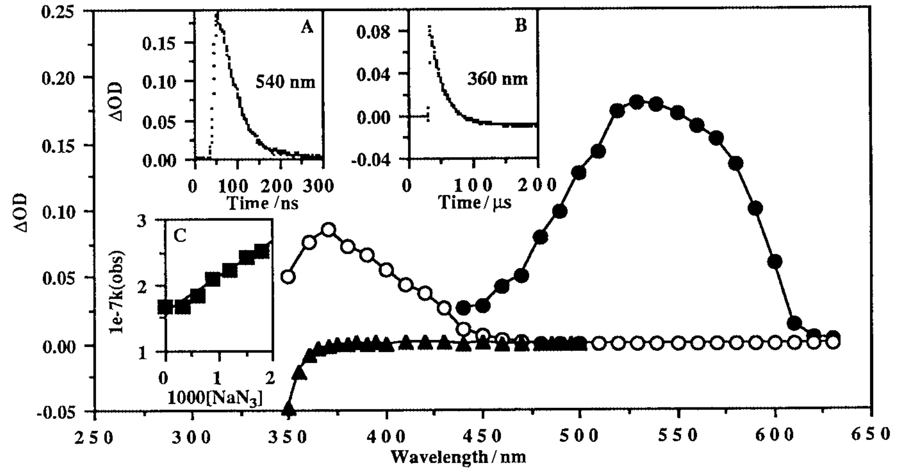


Fig. 1 The main Figure shows spectra obtained by laser flash photolysis following 248 nm (KrF*) irradiation of *N*-(sulfonatooxy)-*N*-acetyl-4-aminostilbene **1** (~50 µmol dm^{-3}) in 40% acetonitrile containing 0.001 mol dm^{-3} CH$_3$COOH–0.001 mol dm^{-3} CH$_3$COONa (pH 5). The points (●) were obtained over a 10 ns window immediately following the completion of the laser pulse, (O) at the completion of the fast process (290–300 ns), and (▲) at the completion of the slow process (190–200 µs). Inset A shows the fast decay at 540 nm, and Inset B the slow decay at 360 nm. Inset C shows the dependence of the observed rate constant for the fast decay at 540 nm (10^{-7} s^{-1}, 20 ± 1 °C) on the concentration of sodium azide (plotted as mmol dm^{-3}). This solution contained 5% acetonitrile, with 0.002 mol dm^{-3} NaH$_2$PO$_4$–0.002 mol dm^{-3} Na$_2$HPO$_4$ and 0.5 mol dm^{-3} NaClO$_4$.

present at 350–450 nm. Based on the results with the NH compounds (see below), we suspect that this has at least in part grown during the decay at the higher wavelengths. Unfortunately, severe noise prevented monitoring below 420 nm for about 100 μs following the laser pulse, so that the rise could not be observed. What is clear is that this absorbance is not stable (Inset B). It decays to zero above 370 nm, and to negative ΔODs below this. The latter are the result of the use of the OD before the laser pulse as the reference. The precursor **1** has a λ_{max} at 320 nm, with the absorption band extending to 360 nm. Thus, while the 360 nm intermediate is more strongly absorbing at 350–360 nm than the precursor, the product of the decay is not.

As shown in Fig. 2, the decay of the 360 nm intermediate is strongly pH dependent. The reaction is catalyzed by H^+ below pH 8, where a sharp break to OH^- catalysis occurs. The fit is not improved by the inclusion of a pH independent reaction. There is no sign of curvature in the acid region, up to the limit of ~10^7 s^{-1} imposed by the noise problem referred to in the last paragraph. The rapid decay at 500–600 nm is pH independent over this same region.

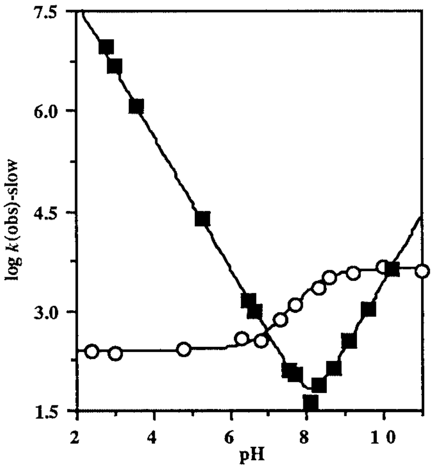


Fig. 2 Log *k*(obs) (s^{-1}, 20 ± 1 °C) *versus* pH for the slow kinetic phase (decay of quinone methide acylimine or imine) following irradiation of *N*-(sulfonatooxy)-*N*-acetyl-4-aminostilbene **1** (■) and 4-azido-4′-methylstilbene **12d** (○) in 40% acetonitrile and 20% acetonitrile respectively. 'pH' was calculated from the value obtained with a pH meter, with a small correction based on the pH of a solution of 0.002 mol dm^{-3} HCl. Lines drawn through the experimental data are based upon eqn. (3) (**1**) and eqn. (2) (**12d**) using the parameters given in the text.

N–H System

Shown in Fig. 3 are transient spectra obtained with 4-azidostilbene **12a**. Comparison with Fig. 1 shows that the initial spectrum is very similar to that found with **1**, although the decay with the azide is a factor of four less rapid. Interestingly the outcome of that decay at the lower wavelengths is dependent on the pH of the solution.‡ At pH < 7, the absorbance increases from 260 to 400 nm, while at pH 10–11, there is a decrease above 340 nm, with a more substantial increase at 260–300 nm. In all cases the changes follow exponential kinetics with the same *k*(obs) as obtained for the decay at 500–600 nm. This implies that the absorbance at the lower wavelengths is due to products of the reaction of the 500–600 nm intermediate.

The plot shown in the Inset to Fig. 3 suggests that these products are an acid–base pair. The data in this Figure were obtained by measuring the pH dependence of the optical density at 370 nm at the completion of the fast decay. Conditions, *i.e.* the laser power and the substrate concentration, were the same throughout. The data were fitted to the equation for a titration curve (eqn. (1)), giving $pK_a = 8.4 \pm 0.1$.

$$\mathrm{OD(obs)} = \frac{\mathrm{OD(acid)}[\mathrm{H}^+] + \mathrm{OD(base)}K_a}{[\mathrm{H}^+] + K_a} \qquad (1)$$

Similar behavior is seen with the substituted azidostilbenes **12b**–**f**. The decay in the region 500–600 nm is in every case a single exponential, although the rate constant does depend on the substituent in the distant ring. The reactions are accelerated by azide ion, although here there is less of a substituent effect. These rate constants, along with those for **1**, are summarized in Table 1.

As with **1**, the absorbance at lower wavelengths decays on longer times. Rate constants (measured at pH 7) were found to be independent of substituent within experimental error. The

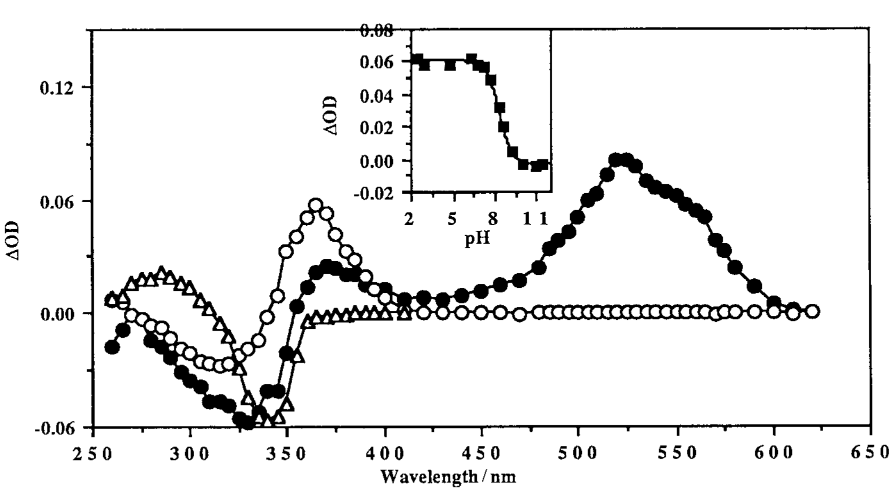


Fig. 3 The main Figure shows spectra obtained by laser flash photolysis following 248 nm (KrF*) irradiation of 4-azidostilbene **12a** (10 μmol dm^{-3}) in 20% acetonitrile. The points (●) were obtained in a 30 ns window immediately following the completion of the laser pulse in a solution of pH 6.4 (0.004 mol dm^{-3} NaH_2PO_4–0.001 mol dm^{-3}), with the points (○) being obtained at 1.8–2.0 μs at the completion of the fast process in this solution (1.8–2 μs). The points (△) were also obtained at 1.8–2.0 μs, but at the completion of the fast process in a solution of pH 10.3 (0.001 mol dm^{-3} $NaHCO_3$–0.002 mol dm^{-3} Na_2CO_3). The initial spectrum in the latter solution is not shown, since it was the same as that in the pH 6.4 experiment. The Inset shows the pH dependence of the optical density reading at 370 nm obtained at 1.8–2.0 μs. The curve through the points in the inset is based on eqn. (1).

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‡ Several factors contribute to the ability to monitor the lower wavelengths with **12a**. Compared to **1** the reaction is slower. More importantly, with **12a** there is no perturbation at the fast times. Finally the photochemistry is more efficient with the azide. This has the practical consequence that lower concentrations can be employed, making it possible to work in a region where there is strong precursor absorbance.

Table 1 Rate constants (20 ± 1 °C) for the reactions of stilbene cations (measured at 525–550 nm)

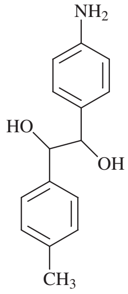
Precursor	k_s[a]/s^{-1}	k_{az}[b]/mol^{-1} dm^3 s^{-1}
1	$(2.6 \pm 0.2) \times 10^7$ [c]	
1	$(1.6 \pm 0.2) \times 10^7$ [d]	$(5.3 \pm 0.6) \times 10^9$ [d]
12a	$(6.3 \pm 0.3) \times 10^6$ [e]	$(7.9 \pm 0.9) \times 10^9$ [e]
12b	$(6.5 \pm 0.3) \times 10^6$ [e]	$(7.8 \pm 0.2) \times 10^9$ [e]
12c	$(4.6 \pm 0.2) \times 10^6$ [e]	$(7.8 \pm 0.2) \times 10^9$ [e]
12d	$(1.5 \pm 0.1) \times 10^6$ [e]	$(7.4 \pm 0.6) \times 10^9$ [e]
12e	$(5.6 \pm 0.3) \times 10^5$ [e]	$(6.5 \pm 0.8) \times 10^9$ [e]
12f	$(6.1 \pm 0.1) \times 10^4$ [e]	$(4.2 \pm 0.1) \times 10^9$ [e]

[a] First-order rate constant for decay in solvent alone. [b] Second-order rate constant for quenching by azide ion. [c] 40% acetonitrile, ionic strength = 0. [d] 5% acetonitrile, ionic strength = 0.5 mol dm^{-3} with $NaClO_4$. [e] 20% acetonitrile, ionic strength = 0.004 mol dm^{-3}, 0.001 mol dm^{-3} KH_2PO_4, 0.001 mol dm^{-3} K_2HPO_4.

4-methyl system was chosen for detailed study, with rate constants being measured at either 370 nm (pH < 8.5) or 290 nm (pH > 8.5). The rate–pH profile for this system is also provided in Fig. 2. This shows quite different behaviour from the one in the *N*-acetyl system, with pH independent regions in acid and base, separated by a slight increase in rate from pH 7 to pH 8.5.

Products

The azide **12d** was chosen for examination in this respect. The ^{1}H NMR spectrum of a scaled-up photolysis suggested the presence of the *threo* and *erythro* diols **15t** and **15e**, the analogs of **3t**, **3e**. Authentic samples of **15** were then prepared using strategies similar to ones employed for **3**. This provided **15t** in pure form, while **15e** was obtained as a mixture with **15t**. With the assumption that the sensitivity of **15e** is the same as that of **15t**, the amounts produced by 300 nm irradiation of **12d** were determined by quantitative HPLC. A 5 : 1 ratio of **15t** : **15e** was observed in all injections, with total yields of 67 ± 5% in 40% acetonitrile and 42 ± 5% in 60% acetonitrile. These yields are based on the amount of azide that had reacted, and they are independent of irradiation time up to about 90% conversion.



15t,15e

Discussion

Identification of initial transient as stilbene cation

In a previous study, we found that the *N*-acetylnitrenium ions derived from 4-aminobiphenyl and 2-aminofluorene could be observed with LFP upon irradiation of the same compounds employed in studies of the ground state solvolysis, including a sulfate ester.[21] Although the actual photophysical details are unknown, a net photoheterolysis is obviously implicated. While the NH analogs would presumably be obtained in the same way, this is not practical due to the very rapid ground state solvolysis of the appropriate precursors. Aryl azides have however provided a very useful alternative. The photochemistry here involves the formation of a singlet arylnitrene as the initial intermediate. The trick is to protonate this nitrene before competing reactions[22] occur. While added strong acids can accomplish this,[23–25] in many cases protonation by solvent water molecules is all that is needed to obtain high yields of the nitrenium ion.[26–33] An attractive feature of the azide approach is that there is no problem distinguishing nitrenium ion formation from other pathways, since the products are very different.

In the present study we employed the sulfonatooxy compound **1** as the precursor in the *N*-acetyl system and a series of azidostilbenes **12a**–**f** for NH cations. There is compelling evidence that both approaches have worked, *i.e.* that the transients at 500–600 nm after the laser pulse are the cations **9** and **14a**–**f** respectively.

(i) The precursors **1** and **12a** result in intermediates with very similar spectra. This is a feature of these types of cations seen previously in comparing *N*-acetyl and N–H in the biphenyl-4-yl and fluoren-2-yl systems.[26,27] The two intermediates are clearly not the same, since they decay at different rates. The rate difference, a factor of four in the present case, is also typical of these types of cations.[13,15,26,27]

(ii) The quenching by azide ion is clearly indicative of a cationic intermediate. Moreover, with the transient from **1**, the azide–water ratio of $(3.3 \pm 0.6) \times 10^2$ mol^{-1} dm^3 determined by LFP is within experimental error, the same as the value of $(2.8 \pm 0.1) \times 10^2$ obtained in the study of the ground state solvolysis. This is excellent evidence that the photochemical intermediate is the same as the ground state intermediate. It can also be noted that the trend in k_{az} observed in the NH series has the expected form.[20] For the more reactive cations k_{az} is effectively constant at 8×10^9 mol^{-1} dm^3 s^{-1}, indicative of azide ion reacting at the diffusion limit. As stabilizing substituents are added, especially 4′-methoxy, the rate constant decreases somewhat.

(iii) The diol products expected[1] from the intermediate cation **14d** are found after irradiation of the azide **12d**. The yield is reasonable, although clearly not quantitative. The trend, the product from the cation increasing in more aqueous solutions, is however similar to that observed with 4-azidobiphenylyl.[27] Based on data with that compound, we predict that the yield of the diols (and thus nitrenium ion) in 20% acetonitrile is 80–85%. This is the solvent mixture employed for the LFP experiments, but solubility considerations prevented its use in the product analyses where significantly higher concentrations of the precursor were required.

(iv) The stilbene cations react with water at the β-carbon with respect to the nitrogen.[1] This is the benzylic α-carbon with respect to the substituents of the series **14a**–**f**. These clearly affect the rate constants k_s in the manner expected for benzylic cations.

Structure and reactivity of stilbene cations

A quantitative consideration of point (iv) is provided in Fig. 4. This correlates data for two series of cations against the stilbene cations bearing the same substituents. A phenethyl cation **18** obviously resembles the stilbene analog, at least in terms of the resonance contributor of the latter (**16**) where the positive charge is on the carbon where the solvent is actually reacting. The biphenyl-4-ylnitrenium ions **17** react with water at the position *para* to the NH group. Thus these are also benzylic-type cations in terms of the second ring, and indeed substituents in that ring have a pronounced effect.[28] Although the data are limited, there are clearly excellent linear correlations. Thus, despite the quite diverse nature of the three types of cations, they are ‘benzylic’ ions[§] in their reactions with solvent.

[§] It can be noted that none of the series shows good correlations with σ^+, with the points for the *para* π donors deviating in the direction that requires a greater stabilizing effect than that expressed in σ^+.[20]

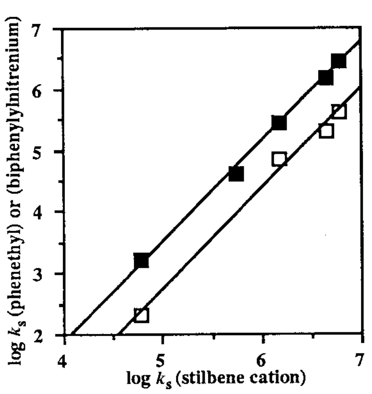
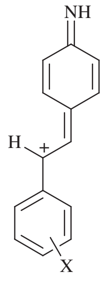


Fig. 4 Linear free energy correlations of solvent reactivities of carbocations. Data on the 'x' axis are the stilbene cations (**14**↔**16**) of this study, where k_s is the rate constant in 20% acetonitrile. The points (■) refer to biphenyl-1-ylnitrenium ions **17**, where k_s also refers to 20% acetonitrile.[28] The points (□) refer to phenethyl cations **18**, where k_s is the decay rate constant in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).[34] Both lines have slopes of 1.6.



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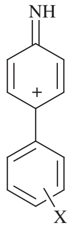

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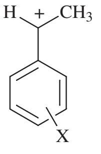


18

An interesting feature is that the effect is not as great in the stilbene series, as seen in the slopes of the two correlation lines being (fortuitously) 1.6. While this might be related to the position of the transition state, another possibility is that there is substantial delocalization of the positive charge in the stilbene cations away from the 'benzyl' ring, *i.e.* that resonance contributors such as **14** are still important. The comparison with the phenethyl cations suggests that this must be the case. Thus while the substituent effect in the stilbene series correlates with that of the phenethyl one, the latter are much more reactive. In fact the weakly nucleophilic solvent HFIP is required for study of this series (at least with a ns LFP apparatus).

The difference is also apparent in the absorption spectra. The 4-methoxyphenethyl cation, for example, has its λ_{max} at 340 nm, some 200 nm lower than the stilbene analog. This suggests again that the latter is a much more delocalized system. This is also seen in the comparison with the biphenyl-4-ylnitrenium ion, whose λ_{max} is only 460 nm. The conclusion is that although the stilbene cations react with water as 'benzylic' cations, the positive charge is delocalized extensively throughout the ion.

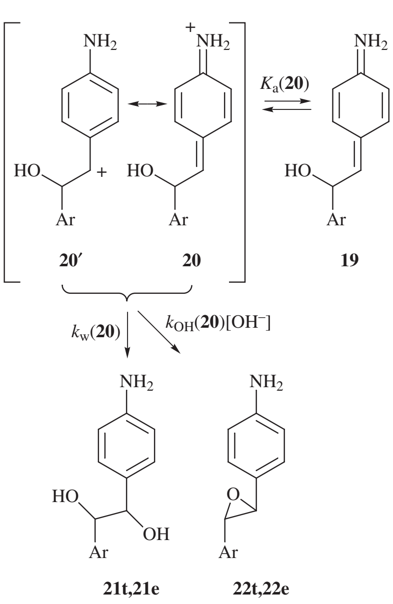
Quinone methide imine

The immediate product of water addition is a second intermediate, a quinone methide imine or acylimine. We propose that these are the intermediates observed at lower wavelengths at the conclusion of the decays at 500–600 nm. Now the behaviour is very dependent on the nitrogen substituent. This is expected since the imine group plays an important role in the subsequent reaction.

A mechanism for the NH compounds consistent with the observations is provided in Scheme 3. The spectroscopic titration (Inset to Fig. 3) suggests that, depending on pH, the imine exists in its neutral (**19**) and protonated (**20**) forms. The pH independent region in acid in the rate–pH profile (Fig. 2) clearly represents the cation reacting with water. We suggest that the plateau in base also represents a reaction of this cation, now with hydroxide ion. There is a kinetically equivalent process for the latter, namely water reacting with imine. This, however, is highly unlikely, since the kinetics require that this reaction actually be faster than the water–cation combination. Eqn. (2)

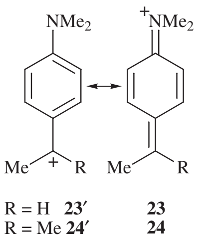
$$k(\text{obs})\text{-slow} = \frac{k_w(\mathbf{20})[\mathrm{H}^+] + k_{\mathrm{OH}}(\mathbf{20})K_w}{[\mathrm{H}^+] + K_a(\mathbf{20})} \qquad (2)$$

applies to this kinetic system, and a fit of the data provides the parameters $k_w(\mathbf{20}) = (2.5 \pm 0.1) \times 10^2\ \mathrm{s}^{-1}$, $k_{\mathrm{OH}}(\mathbf{20}) = (1.0 \pm 0.2) \times 10^{10}\ \mathrm{mol}^{-1}\ \mathrm{dm}^3\ \mathrm{s}^{-1}$ (pK_w = 14.6 in 20% acetonitrile, see Experimental), and p$K_a(\mathbf{20})$ = 8.2 ± 0.1. A point of consistency is seen in the good agreement of the kinetic pK_a with the value from the spectroscopic titration.

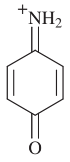


Scheme 3

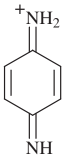
It can be noted that the protonated imine is an α-substituted *p*-aminobenzyl cation when written as **20′**. In this respect, the cation behaves in manner very similar to *p*-dimethylamino derivatives **23′** and **24′** (which obviously can also be written as bis-methylated quinone methide imines **23** and **24**). Thus, **23** and **24** have λ_{max} values at 360 nm[34] and 380 nm[35] respectively. While the spectrum of **20** is complicated because of the overlap with the precursor, it must have its λ_{max} in a similar region. In addition, the phenethyl derivative **23** decays in 50:50 water–2,2,2-trifluoroethanol with $k_s = 4.0 \times 10^1\ \mathrm{s}^{-1}$, and, in a comparison of greater relevance to the solvent of the present work, the cumyl derivative **24** decays in 2:1 water–acetonitrile with $k_w = 1.5 \times 10^2\ \mathrm{s}^{-1}$. The rate constant $k_w(\mathbf{20})$ is clearly of the same order of magnitude. The cations **23** and **24** are kinetically (and presumably thermodynamically) highly stabilized by the *p*-dimethylamino group, an effect that has has been known for some time.[36] The 4-amino group obviously has a similar cation-stabilizing effect.



One surprise that emerges is the pK_a(**20**) value of 8.3, which indicates a relatively strongly basic imine group in the conjugate base **19**. Comparisons here include protonated benzoquinone monoimine **25**, pK_a = 3.7,[37] the quinone diimine derivative **26**, pK_a = 5.75,[37] and the hemiacetal **27**, pK_a = 4.2,[31] all of which



25



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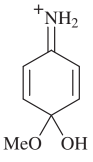


27

indicate substantially less basic imines. This relative basicity of **19** may be a manifestation of an effect recently predicted by gas phase calculations of quinone imine and diimine derivatives.[38,39] In one aspect of this work, substantial enhancements of imine basicity were found for *p*-quinone methide imine systems where the methide group provides stabilization of the positive charge, *i.e.* where resonance forms such as **20′** make a significant contribution. A possible source of this enhanced basicity is the increased aromatization that occurs upon protonation.

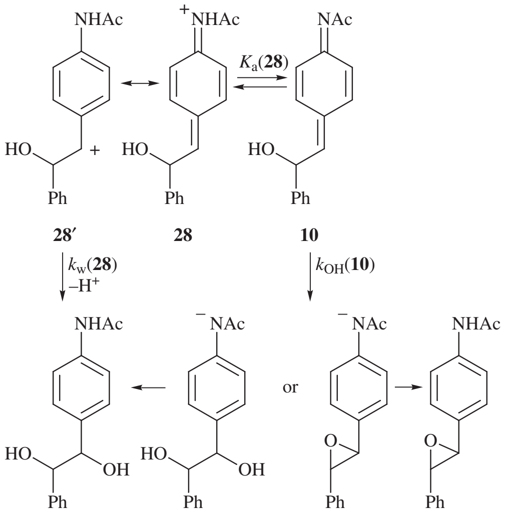
We speculate that the hydroxide-cation reaction does not represent hydroxide addition to the benzylic carbon, but rather hydroxide-catalyzed formation of the epoxides **22**. Studies of epoxide hydrolysis *via* relatively stabilized cationic intermediates[40,41] are revealing in this context. What has been observed is that the H$^+$-catalyzed reaction has the ring-opening as the rate-limiting step. This means that a β-hydroxy-substituted carbocation (such as **20**) adds water to the carbocation center faster than the β-hydroxy group reacts reforming the epoxide. In contrast, the epoxide ring-opening is reversible when the hydrolysis occurs at higher pH by a pH-independent mechanism. In this reaction, the intermediate β-hydroxy-cation partitions between hydroxide addition to the carbocation center, and the reverse of the ring-opening step, a hydroxide-catalyzed ring closure. The reversibility indicates that the latter is the faster process.

Quinone methide acylimine

The decay of the acetyl derivative **10** follows eqn. (3), showing

$$k(\text{obs})\text{-slow} = k_{\mathrm{H}}(\mathbf{10})[\mathrm{H}^+] + k_{\mathrm{OH}}(\mathbf{10})\left(\frac{K_{\mathrm{w}}}{[\mathrm{H}^+]}\right) \qquad (3)$$

regions of H$^+$ and OH$^-$ catalysis. Values of $k_{\mathrm{H}}(\mathbf{10}) = 4.5 \times 10^9$ mol^{-1} dm^3 s^{-1} and $k_{\mathrm{OH}}(\mathbf{10}) = 2.6 \times 10^8$ mol^{-1} dm^3 s^{-1} (pK_w of 15 in 40% acetonitrile) provide the best fit of the data. Our proposed mechanism is shown as Scheme 4, with the H$^+$-dependence being explained by water reacting with the conjugate acid **28**↔**28′** (a substituted 4-acetylaminobenzyl cation), and the OH$^-$ dependence by hydroxide reacting directly with the neutral imine. The latter becomes possible in the acylimine derivative since the developing negative charge on nitrogen is stabilized by the adjacent carbonyl. As with the imino derivative, we also speculate that the hydroxide reaction actually results in ring closure to the epoxide.



Scheme 4

With the proviso that the protonation step is a pre-equilibrium, $k_{\mathrm{H}}(\mathbf{10})$ of eqn. (3) is equal to $k_{\mathrm{w}}(\mathbf{28})$: $\mathrm{K}_a(\mathbf{28})$. Since there is no sign of a downward break in the rate–pH profile even at pH ~3, pK_a(**28**) must be less than 2, and k_w(**28**) must be greater than 5×10^7 s^{-1}. This magnitude for the rate constant is not unexpected, since the amido group is considerably less stabilizing than amino.[42] As noted in the Introduction, an azide–water selectivity of 39 mol dm^{-3} was previously obtained for **10**. This ratio was measured at pH 7.2 where the present results show that the water reaction is acid-catalyzed. If this is also true for azide, the ratio refers to the competition between azide ion and water for the cation **28**. The azide-clock assumption will surely apply in such a case, so that k_w(**28**) can be estimated as ~1×10^8 s^{-1} and pK_a(**28**) ~ 1.6. What we suggest in other words is that the relatively small azide–water selectivity observed for the quinone methide acylimine is a reflection of the reactions occurring *via* a reactive cation, the conjugate acid.

It can also be noted that if this analysis is correct, **10** is considerably more basic than other acylimines. Examples here are protonated *N*-acetyl-*p*-benzoquinone monoimine[43] and some protonated cyclohexa-2,4-dienone *N*-acetylimines,[44] which have been estimated to have pK_a values of -5 ± 2 and -4 ± 0.2 respectively. This enhancement of the basicity of **10** could be a manifestation of the same effect responsible for the increased basicity in the quinone methide imine.

Summary

This study reports the spectroscopic characterization of the cations formed by ionization of esters derived from 4-amino and 4-acetylaminostilbenes. The cations react at the β-carbon of the carbon–carbon double bond, and indeed substituents in the ring conjugated to this carbon show an effect on reactivity typical of benzylic-type cations. However, the absorption spectra of the stilbene cations are very different from simple benzyl cations. Moreover the stilbene derivatives are much longer-lived. These differences can be explained by extensive delocalization of the positive charge throughout the cation.

Direct spectroscopic evidence has also been obtained for a second intermediate previously proposed to form in these systems, a quinone methide imine or acylimine. In both the *N*-acetyl and NH series this intermediate is quite long-lived near neutral pH, with lifetimes of the order of 1 ms. The reaction of both derivatives at neutral pH actually occurs *via* the conjugate acids, which can be viewed as 5-amino and 4-acetylaminobenzyl cations. In the NH series, the cation is actually the predominant form in the acid–base equilibrium at neutral pH. The strong stabilization effect of the 4-amino group accounts for the relatively long lifetime. The 4-acetylaminobenzyl cation is much shorter lived, but the lifetime of the quinone methide acylimine at neutral pH approaches that of the NH compound because there is only a very small amount of the cation present in the acid–base equilibrium. This study also provides evidence that quinone methide imines (and acylimines) have enhanced basicity relative to other imines (and acylimines).

Experimental

N-(Sulfonatooxy)-*N*-acetyl-4-aminostilbene (**1**) was available from a previous study.[1] The azidostilbenes were prepared as follows: A mixture of 4-nitrophenylacetic acid, an appropriately substituted benzaldehyde and piperidine were heated at 150–160 °C for 4 h as described.[45] The reaction mixture was cooled to room temperature and the solidified material was recrystallized from absolute ethanol to obtain the substituted 4-nitrostilbene. The nitro group was reduced by adding hydrazine hydrate (1.5 mL) to a suspension of the nitrostilbene (1 g) and 10% Pd/C (500 mg) in 1 : 1 dichloromethane–ethanol (50 mL). The reaction mixture was stirred at room temperature for 1–2 h, with TLC monitoring. The mixture was filtered directly into hexane (200 mL). The solid 4-aminostilbene derivative was collected and recrystallized from ethanol. The azides were prepared by the following variation of a standard procedure.[46] A solution or suspension of the arylamine (0.01 mol) in 95% ethanol (10 ml) was treated with concentrated sulfuric acid (0.5 ml) with cooling in an ice–water bath. After stirring for 10 min, amyl nitrite (0.6 ml) was added in small portions and the reaction temperature was raised to 40 °C. The reaction mixture was stirred for 20 min at 35–40 °C. The aryldiazonium salt was precipitated by diluting the reaction mixture with ether (200 ml), with repeated washing with ether. The solid was then treated at 0 °C with a saturated solution of sodium azide and sodium acetate. After stirring for 30 m at 0 °C and 1 h at room temperature, ether was added, and the ether layer washed with water, 25% sulfuric acid, water, 10% sodium hydroxide solution, a saturated sodium chloride solution and finally with water. The ethereal extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The 4-azidostilbenes were purified by column chromatography (silica). The compounds appeared from their NMR spectra to be only the *trans* isomer.

Syntheses

4-Azidostilbene (12a). δ_H (400 MHz, $CDCl_3$) 7.50 (two overlapping doublets, $J \sim 7$–8 Hz, 4H), 7.37 (t, $J = 6.9$ Hz, 2H), 7.29 (t, $J = 7.0$ Hz, 1H), 7.07 (s, 2H (vinylic H)), 7.02 (d, $J = 8.5$ Hz, 2H). *m*/*z* 221 (3, M^+), 207 (15, $M^+ - N$), 193 (100, $M^+ - N_2$), 178 (90).

4′-Bromo-4-azidostilbene (12b). δ_H (400 MHz, $CDCl_3$) 7.48 (d, $J = 8.6$ Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.6$ Hz, 2H), 7.055 (d, $J = 14$ Hz, 1H), 7.02 (d, $J = 8.6$ Hz, 2H), 6.98 (d, $J = 14$ Hz). *m*/*z* 301, 299 (16; M^+), 273, 271 (87, $M^+ - N_2$), 191, 193 (45), 190, 192 (55), 165 (100). High resolution MS calc. for $C_{14}H_{10}N_3Br$ 299.0058, found 299.0048.

3′-Methyl-4-azidostilbene (12c). δ_H (400 MHz, $CDCl_3$) 7.50 (d, $J = 8.5$ Hz, 2H), 7.33 (s, 1H), 7.32 (d, $J \sim 7$ Hz, 1H), 7.28 (t, $J = 7.0$ Hz, 1H), 7.09 (d, $J = 7.1$ Hz, 1H), 7.05 (d (highly distorted), $J = 13$–14 Hz, 1H), 7.045 (d (highly distorted), $J = 13$–14 Hz, 1H), 7.02 (d, $J = 8.5$ Hz, 2H), 2.38 (s, 3H). *m*/*z* 235 (22; M^+), 207 (100; $M^+ - N_2$), 192 (54). High resolution MS calc. for $C_{15}H_{12}N_3$ 235.1109, found 235.1108.

4′-Methyl-4-azidostilbene (12d). δ_H (400 MHz, $CDCl_3$) 7.48 (d, $J = 8.6$ Hz, 2H), 7.40 (d, $J = 7.9$ Hz, 2H), 7.17 (d, $J = 7.7$ Hz, 2H), 7.03 (s, 2H (vinylic H)), 7.01 (d, $J \sim 8$–9 Hz, 2H), 2.36 (s, 3H). *m*/*z* 235 (21; M^+), 207 (100; $M^+ - N_2$), 192 (55). High resolution MS calc. for $C_{15}H_{12}N_3$ 235.1109, found 235.1110.

4′-Methoxy-4-azidostilbene (12f). δ_H (400 MHz, $CDCl_3$) 7.47 (d, $J = 8.6$ Hz, 2H), 7.44 (d, $J = 8.7$ Hz, 2H), 7.02 (d, $J = 16$ Hz, 1H), 7.01 (d, $J = 8.2$ Hz, 2H), 6.93 (d, $J \sim 16$ Hz, 1H), 6.89 (d, $J = 8.8$ Hz, 2H), 3.83 (s, 3H). *m*/*z* 251 (20; M^+), 223 (100; $M^+ - N_2$), 192 (88). High resolution MS calc. for $C_{15}H_{13}N_3O$ 251.1058, found 251.1065.

4′-Acetamido-4-azidostilbene. δ_H (400 MHz, $CDCl_3$) 7.50 (d, $J = 8.5$ Hz, 2H), 7.49 (d, $J = 8.4$ Hz), 7.25 (d, $J = 8.4$ Hz, 2H), 7.2 (s (broad), 1H) 7.03 (d, $J = 8.6$ Hz, 2H), 7.01 (s, 2H (vinylic H)), 2.18 (s, 3H). *m*/*z* 278 (33, M^+), 250 (100, $M^+ - N_2$), 208 (62), 207 (64). High resolution MS calc. for $C_{16}H_{14}N_4O$ 278.1168, found 278.1173.

4′-(*N*-Methylacetamido)-4-azidostilbene (12e). **12e** was prepared by dissolving 4′-acetamido-4-azidostilbene (1 mmol) and methyl iodide (1.2 mmol) in anhydrous dimethyl sulfoxide (20 dm^3) and adding sodium hydride (1.2 mmol) under argon. After stirring one hour at room temperature, the reaction mixture was diluted with ether (5 dm^3), and the organic layer was washed with water and dried over magnesium sulfate. After removal of the ether solvent the product was purified by column chromatography. δ_H (400 MHz, $CDCl_3$) 7.53 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 8.6$ Hz), 7.17 (d, $J = 8.0$ Hz, 2H), 7.065 (d (highly distorted), $J = 14$–15 Hz, 1H), 7.055 (d (highly distorted), $J = 14$–15 Hz), 7.03 (d, $J = 8.6$ Hz, 2H), 3.28 (s, 3H), 1.99 (s, 3H). *m*/*z* 292 (32, M^+), 278 (9, $M^+ - N$), 264 (100, $M^+ - N_2$), 250 (10, $M^+ - N_3$), 222 (55), 221 (65). High resolution MS calc. for $C_{17}H_{16}N_4O$ 292.1324, found 292.1331.

***threo*-1,2-Dihydroxy-1-(4-aminophenyl)-2-(4-methylphenyl)-ethane.** This compound was prepared by treating 4′-methyl-4-nitrostilbene with cold basic potassium permanganate for 15 h as described in the literature.[47] The material obtained after standard workup was contaminated with the starting stilbene, but this was separated by column chromatography. The diol had mp 168–169 °C. δ_H (200 MHz, $CDCl_3$) 8.07 (d, $J = 8.6$ Hz, 2H), 7.26 (d, $J = 8.6$ Hz, 2H), 7.08 (d, $J = 8.7$ Hz, 2H), 7.00 (d, $J = 8.3$ Hz, 2H), 4.84 (d, $J = 7.7$ Hz, 1H), 4.60 (d, $J = 7.6$ Hz, 1H), 2.33 (s, 3H). *m*/*z* 256 (~1, $M^+ - 17$), 153 (60), 136 (38), 135 (29), 121 (100).

***threo*-1,2-Dihydroxy-1-(4-aminophenyl)-2-(4-methylphenyl)-ethane (15t).** **15t** was obtained by reduction of the above nitro compound as described above. The desired product was obtained by column chromatography (silica). mp 130–131 °C. δ_H (400 MHz, $CDCl_3$) 7.03 (s, 4H), 6.93 (d, $J = 8.5$ Hz, 2H), 6.55 (d, $J = 8.4$ Hz, 2H), 4.65 (d, $J = 7.5$ Hz, 1H), 4.58 (d, $J = 7.5$ Hz, 1H), 2.29 (s, 3H). *m*/*z* 243 (4, M^+), 226 (5), 225 (5), 209 (2), 196 (19), 122 (100). High resolution MS calc. for $C_{15}H_{17}NO_2$ 243.1259, found 243.1270.

***erythro*/*threo*-1,2-Dihydroxy-1-(4-nitrophenyl)-2-(4-methylphenyl)ethanes.** These compounds were obtained from *trans*-4′-methyl-4-nitrostilbene by epoxidation with *m*-chloroperbenzoic acid,[48] followed by hydrolysis under acidic conditions using the method previously described from *trans*-4-nitrostilbene oxide.[1] The NMR spectrum of the *erythro* isomer was obtained by subtracting that of the pure *threo* isomer obtained as described above. δ_H (200 MHz, $CDCl_3$) 8.14 (d, $J = 8.6$ Hz, 2H), 7.39 (d, $J = 8.6$ Hz, 2H), 7.10 (d, $J = 8.7$ Hz, 2H), 7.00 (d, $J = 8.3$ Hz, 2H), 4.99 (d, $J = 6$ Hz, 1H), 4.79 (d, $J = 6$ Hz, 1H), 2.35 (s, 3H).

***erythro*/*threo*-1,2-Dihydroxy-1-(4-aminophenyl)-2-(4-methylphenyl)ethanes (15e/15t).** **15e** and **15t** were obtained by reduction of the nitro compound as described above. The *erythro* : *threo* ratio was 1 : 4. The NMR spectrum of the *erythro* isomer was δ_H (400 MHz, $CDCl_3$) 7.18 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.6$ Hz, 2H), 6.63 (d, $J = 8.6$ Hz, 2H), 4.69 (d, $J = 5.9$ Hz, 1H), 4.63 (d, $J = 5.9$ Hz, 1H), 2.33 (s, 3H).

Analyses

Laser flash photolysis experiments involved *ca.* 20 ns pulses at 248 nm (60–120 mJ per pulse) from a Lumonics excimer laser (KrF emission). A pulsed Xenon lamp providing monitoring light. The sample was placed in a 4 × 1 × 1 cm cuvette, irradiated with the laser on the 4 × 1 face, and monitored perpendicular so that the path length was 4 cm. The cuvette was replaced with a fresh solution after each irradiation. After passing through a monochromator, the signal from the photomultiplier tube was digitized and sent to a computer for analysis.

Experiments with *N*-(sulfonatooxy)-*N*-acetyl-4-aminostilbene **1** were performed by adding a stock solution of the substrate in DMF (~0.01 mol dm^3) to the appropriate aqueous acetonitrile solution. The half-life of this substrate in 95:5 water–acetonitrile is 35 s. Thus, experiments in this solvent were performed by injecting the stock DMF solution directly into the cuvette. This allowed the irradiation to be performed within 15 s of preparation of the solution. The half-life in 60:40 water–acetonitrile is 1 h, so that solutions of the same concentration could be prepared by injecting the stock DMF solution into the aqueous acetonitrile solution in a volumetric flask. Experiments with the azides **12a**–**12f** were performed by adding stock solutions (~0.005 mol dm^3) of the substrates in acetonitrile to 80:20 water–acetonitrile.

Spectra were constructed point-by-point by irradiating solutions of the same concentration at varying wavelengths over a short period of time to ensure constant laser power. The data were transferred to a spreadsheet file that allowed ΔOD values to be plotted against wavelength at varying times after the laser irradiation. The titration curve shown as the Inset to Fig. 3 was constructed by preparing a series of solutions of varying pH with the same concentration of the substrate **12a**. These were irradiated over a short period of time on the same day, at a monitoring wavelength of 370 nm. The ΔOD was obtained as the average of the values in the window 1.8–2.0 µs after the laser pulse.

Kinetic experiments were performed by fitting the ΔOD–time data to the exponential equation. In general excellent fits were obtained, with rate constants for replicate experiments agreeing to ±2%. The quenching experiments with azide ion were carried out by measuring the observed rate constant in 5–6 solutions of sodium azide over a concentration range 0–0.002 mol dm^3. Plots of k(obs) *versus* [NaN$_3$] were linear, with values of k_{az} being obtained as the linear regression slope.

Conventional flash photolysis experiments were performed using an apparatus previously described,[49] with the sample being irradiated with a broad band flash lamp of *ca.* 100 µs duration.

Rate constants for the quinone methide *N*-acylimine **10** were obtained from the decay at 370 nm following irradiation of **1**. The values in Fig. 2 from pH 6–10 were obtained with the lamp flash photolysis apparatus, with LFP being employed below pH 6. All the rate constants for the quinone methide imine **20d**$\rightleftharpoons$**19d** were obtained with lamp flash photolysis of the azide **12d**, with monitoring wavelengths of 290 nm and 360 nm above and below pH 8.5 respectively. These experiments were performed in dilute buffer solutions (maximum buffer concentration 0.002 mol dm^3). Experiments in both a 1:1 acetate: acetic acid buffer and a 1:1 K$_2$HPO$_4$–KH$_2$PO$_4$ buffer showed that rate constants increased by less than 10% from 0.002–0.01 mol dm^3 total buffer concentration.

The ‘pH’ in the water–acetonitrile mixtures was obtained by correcting the value obtained with the pH meter using the difference between 2.70 and the measured value for a solution of 0.002 mol dm^3 HCl in the same solvent. The pK_{w} values were obtained from the corrected ‘pH’ in 0.002 mol dm^3 NaOH.

Product analyses were performed with a Waters HPLC system using a C^{18} column with 2 cm^3 min^{-1} flow rate of 50:50 water–acetonitrile with the UV-visible detector set at 260 nm. Solutions of the azide **12d** (5×10^{-4} mol dm^{-3}) in 60:40 and 40:60 water–acetonitrile were irradiated for varying periods of time, and the areas of the azide precursor, and the *erythro*–*threo* diols obtained. The response factors for the azide and the *threo* diol were determined by injecting solutions of known concentration of the authentic samples. The response factor of the *erythro* diol was assumed to be the same as the *threo* diol. The yields of the diols were calculated based on the amount of azide that had actually reacted.

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