

Dynamics of Ionization Reactions of β -Substituted Radicals. Substituent and Solvent Effects

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Abstract: The dynamics of reactions of carbon-centered 1-arylalkyl radicals with bromine or chlorine attached to the carbon adjacent (β) to the radical center have been examined using nanosecond laser flash photolysis. The primary reaction of the radicals containing the electron-donating 4-methoxy group on the phenyl ring is highly dependent on the solvent composition. In weakly ionizing solvents such as acetonitrile, the radicals decay in a second-order manner indicating that coupling of two radical centers is the primary mode of radical decay. However, when the ionizing ability of the solvent is increased by addition of water, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), or 2,2,2-trifluoroethanol (TFE), heterolysis of the β -substituent becomes the dominant mode of decay. The occurrence of the heterolysis reaction is demonstrated unambiguously by direct observation of the radical cation produced as the primary, heterolysis product. The rate constants for and yield of the heterolysis reaction are found to be dependent on both the solvent ionizing ability and radical structure. In neat water or neat HFIP the reactions become extremely fast and occur with rate constants in the 10^7 s⁻¹ to $\geq 10^8$ s⁻¹ range. For the β -bromophenethyl and β -bromo-4-methylphenethyl radicals, no heterolysis is observed even under strongly ionizing conditions, indicating that the rate constant for ionization is strongly influenced by the substituent on the phenyl ring. For radicals with an additional β -phenyl substituent, rapid heterolysis takes place leading to the formation of the stilbene radical cation. The formation of a radical/radical cation equilibrium was observed under the appropriate conditions only for the 4-methoxyphenethyl radical derivatives.

Introduction

Carbon-centered radicals with leaving groups such as OH, OR, NH₂, or halogens attached to the carbon adjacent (β) to the radical center play an important role in a wide variety of biological and chemical processes. For example, radicals with a hydroxy, ammonium, or phosphate group at the β -position are thought to be primary intermediates in some enzyme catalyzed reactions, such as the reduction of diols and ethanolamines by diol dehydrase and ethanolamine deaminase, respectively, and the ribonucleotide reductase catalyzed conversion of ribonucleotides to deoxyribonucleotides.^{1–4} In addition, 4'-deoxyribonucleotide radicals produced by hydrogen atom abstraction from the α -carbon of a sugar moiety of DNA have been postulated to be important intermediates in radical induced cleavage of DNA strands.^{5–8} Furthermore, radicals possessing a β -acetate or phosphate group have been implicated as important intermediates in oxidative lipid damage.⁹

Homolytic cleavage of the carbon-leaving group bond to generate an alkene^{10,11} and rearrangement by a 1,2 shift of the

leaving group to generate a more stable radical^{12–14} are two well-known reactions of β -substituted radicals. In addition, these radicals undergo solvolysis reactions involving either acid-catalyzed or uncatalyzed heterolysis of the carbon-leaving group bond to generate a radical cation that is then trapped by solvent (or another nucleophile).¹⁵ These heterolysis reactions are thought to be important for radicals generated enzymatically and in the bond cleavage step of radical-induced DNA strand cleavage. As a result, significant effort has been directed toward studying the reactions of these simple radicals. ESR¹⁵ and product studies^{4,7} have been especially useful to establish the existence of the solvolysis reaction by detecting the presence of substitution products. Results from pulse radiolysis studies have provided some information about the dynamics of the reactions of these radicals, especially with respect to second-order rate constants for the acid-catalyzed dehydration of a variety of 2-hydroxy-1-alkoxy alkyl radicals¹⁵ as well as rate constants for the acid-catalyzed reactions of 1-alkoxy radicals with phosphate groups at the 2-position.¹⁶

Much less is known about the dynamics of the uncatalyzed heterolysis of the carbon-leaving group bond in β -substituted radicals. A limited number of rate constants for the heterolysis of alkyl radicals with leaving groups such as halides, sulfate, and acetate in the β -position have been measured in wholly

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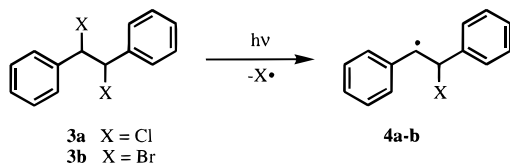
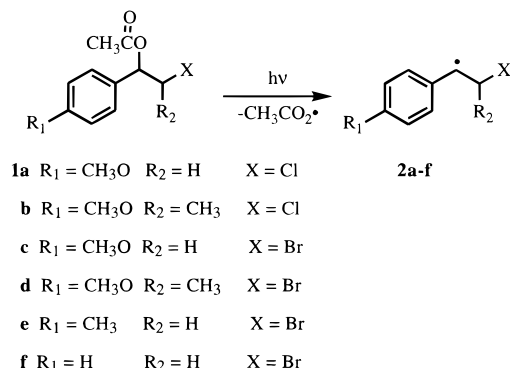
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Scheme 1



aqueous solution.^{6,17} However, in those studies, simple heterolysis is not necessarily the only reaction available to the radical,⁵ and the measured rate constants may include significant contributions from other competing processes such as solvolysis by an $\text{S}_{\text{N}}2$ ¹⁸ mechanism or rapid homolysis of the β -group.¹¹ One way to identify heterolysis as an important mode of reaction for these radicals is to provide direct evidence that the decay of the radicals leads to the formation of a radical cation as the primary product.^{19–21} In recent years, substituted styrene and stilbene radical cations have been shown to be readily detectable in solution using fast reaction techniques such as laser flash photolysis.^{22–26} The relatively long lifetime of these radical cations opens up the possibility that the ionization of β -substituted radicals can be studied directly by monitoring the formation of the substituted styrene radical cations under appropriate conditions.

In the present work, we describe results concerning the reactions of 2-halo-1-arylalkyl radicals **2a–f** and the 2-halo-1,2-diphenylethyl radicals **4a,b**, generated by laser photolysis of the precursors **1a–f** and **3a,b** in Scheme 1. Our results show that heterolysis of the β -group to give styrene or stilbene radical cations does take place in solution and that this reaction dominates other processes in ionizing solvents such as water, 2,2,2-trifluoroethanol (TFE), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). The heterolysis reactions are often very fast proceeding with rate constants exceeding 10^8 s^{-1} but are otherwise influenced in the same way as other $\text{S}_{\text{N}}1$ type reactions with respect to the nature of the leaving group, the ionizing

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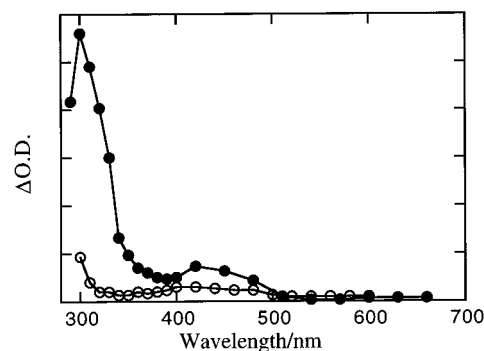


Figure 1. Transient absorption spectra obtained immediately after 266-nm laser irradiation of 1-acetoxy-2-chloro-1-(4-methoxyphenyl)ethane **1a** in (●) nitrogen-saturated acetonitrile and (○) oxygen-saturated acetonitrile.

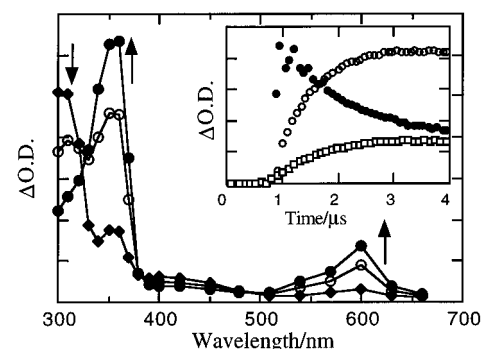
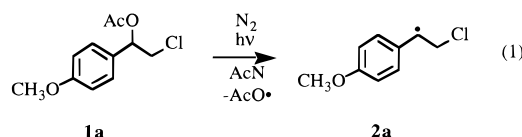


Figure 2. Transient absorption spectra obtained after 266-nm laser irradiation of 1-acetoxy-2-chloro-1-(4-methoxyphenyl)ethane **1a** in nitrogen-saturated 83% TFE/17% AcN. Spectra were recorded (◆) 0.3 μs , (○) 1.2 μs , and (●) 4 μs after the laser pulse. The inset shows the time-resolved decay at (●) 305 nm and growth at (○) 360 nm and (□) 600 nm.

ability of the solvent, and the stability of the initially formed cationic intermediate.

Results

Heterolysis in Acetonitrile Mixtures. As shown in Figure 1, 266-nm laser photolysis of 1-acetoxy-2-chloro-1-(4-methoxyphenyl)ethane **1a** in nitrogen-saturated acetonitrile (AcN) gives a transient species with an absorption maximum near 300 nm. The transient decays in a second-order manner and is long-lived under nitrogen-saturated conditions but is completely quenched by the addition of oxygen, Figure 1. This behavior and the location of the absorption maximum near 300 nm²⁷ are consistent with identification of the transient as the β -chloro-4-methoxyphenethyl radical **2a** produced by photolysis, eq 1.



In a nitrogen-saturated TFE/AcN mixture containing 83% (by volume) TFE, laser photolysis of the same precursor also gives the β -chloro radical **2a** immediately after the laser pulse, Figure 2. However, in this solvent, the radical decays much more rapidly than in acetonitrile with a first-order rate constant of $2.3 \times 10^6 \text{ s}^{-1}$. In addition, as the radical decays, a second transient species with absorption maxima at 360 and 600 nm is

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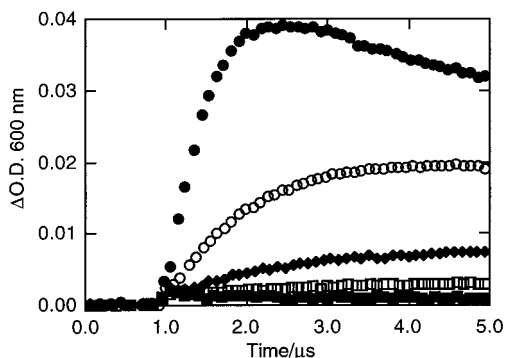
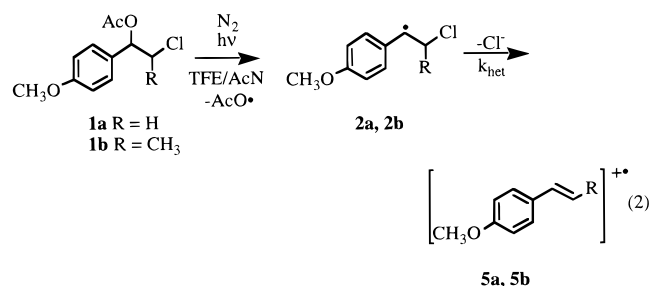


Figure 3. Time resolved growth at 600 nm observed upon 266-nm laser irradiation of 1-acetoxy-2-chloro-1-(4-methoxyphenyl)ethane **1a** in nitrogen-saturated TFE/AcN mixtures containing (■) 33%, (□) 50%, (◆) 67%, (○) 83%, and (●) 100% TFE.

concurrently formed, Figure 2. The absorption spectrum of this transient species is identical to that obtained previously for the radical cation of 4-methoxystyrene,²³ and we can therefore identify the transient produced in 83% TFE as the 4-methoxystyrene radical cation **5a**, eq 2.

As shown in the inset of Figure 2, the rate constant for the decay of the β -chloro radical at 305 nm closely matches the rate constant for the growth of the radical cation at 360 and 600 nm, indicating that the radical cation is produced from a reaction of the photogenerated radical. Moreover, formation of the radical cation is completely quenched in oxygen-saturated 83% TFE. Since the reactivity of the radical cation is known to be insensitive to oxygen concentration,²³ the disappearance of the radical cation can be attributed to trapping of the radical by oxygen. These results therefore provide strong evidence that the radical cation is produced upon reaction of the radical, namely by heterolysis of the carbon–chlorine bond adjacent to the radical center, eq 2.



The fact that formation of the heterolysis product is rapid in 83% TFE but is not observed in neat acetonitrile suggests that the rate constant for radical cation formation is strongly influenced by the nature of the solvent. The effect of solvent is clearly illustrated by the data in Figure 3 which shows the time-dependent change in optical density at 600 nm due to radical cation formation upon β -heterolysis of the radical **1a** in various TFE/AcN mixtures. In the mixed TFE/AcN solvent containing 33% TFE, a small amount of radical cation growth is observed with a first-order rate constant of approximately $5.1 \times 10^5 \text{ s}^{-1}$. As the amount of TFE is increased to 50%, a more substantial growth is observed with a larger rate constant of $6.4 \times 10^5 \text{ s}^{-1}$. As the TFE content is then increased to 66% and 83%, the rate constant continues to increase to $1.1 \times 10^6 \text{ s}^{-1}$ and $2.3 \times 10^6 \text{ s}^{-1}$, and reaches a value of $k = 1.1 \times 10^7 \text{ s}^{-1}$ in neat TFE. The growth curves in Figure 3 also show that the increase in the rate constant for radical cation formation as a function of TFE content in acetonitrile is accompanied by a significant increase in the maximum optical density at 600 nm

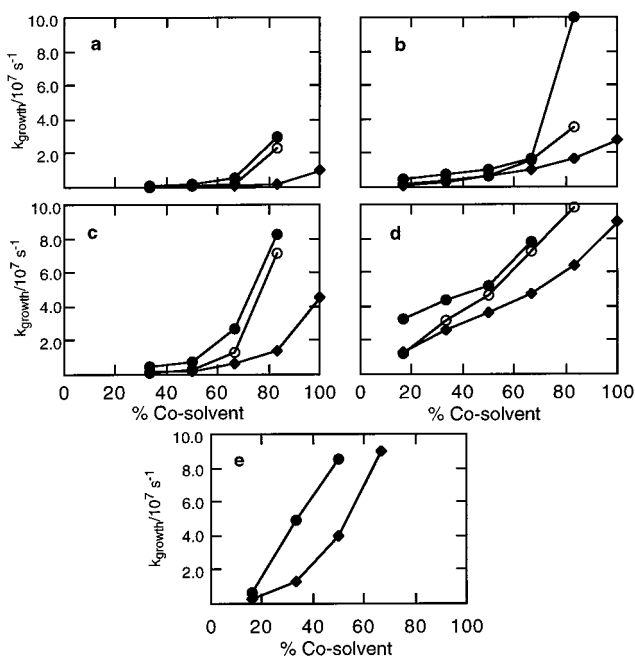


Figure 4. Growth of radical cation at 600 nm upon 266-nm irradiation of (a) 1-acetoxy-2-chloro-1-(4-methoxyphenyl)ethane **1a**; (b) 1-acetoxy-2-chloro-1-(4-methoxyphenyl)propane **1b**; (c) 1-acetoxy-2-bromo-1-(4-methoxyphenyl)ethane **1c**; (d) 1-acetoxy-2-bromo-1-(4-methoxyphenyl)propane **1d**; and (e) the radical cation at 475 nm upon 266-nm irradiation of 1,2-dichloro-1,2-diphenylethane **3a** as a function of (●) water, (○) HFIP, or (◆) TFE content in nitrogen-saturated acetonitrile.

after complete formation of the radical cation. Thus, in 100% TFE, the optical density at 600 nm after the radical cation is fully formed is approximately 15 times greater than in 33% TFE.

Ionization of the chloro group from the β -chloro-4-methoxyphenethyl radical **1a** was also examined in HFIP/AcN mixtures and in water/AcN mixtures. In HFIP/AcN mixtures containing from 33% HFIP to 83% HFIP, time-resolved growth of the radical cation was observed, with the rate constant increasing from $3.5 \times 10^5 \text{ s}^{-1}$ in 33% HFIP to $2.3 \times 10^7 \text{ s}^{-1}$ in 83% HFIP. In 100% HFIP, the rate constant for radical cation formation exceeded the $1 \times 10^8 \text{ s}^{-1}$ time-resolution of our laser system. Similar results were obtained for reaction in water/AcN mixtures. In this solvent system, the rate constant for radical cation growth increased from $1.3 \times 10^6 \text{ s}^{-1}$ in 33% water to $3.0 \times 10^7 \text{ s}^{-1}$ in 83% water. In 100% aqueous solution, the rate constant for the growth was again beyond the resolution of the laser system. These data are summarized in Figure 4a.

Results similar to those described above were observed upon 266-nm laser flash photolysis of 1-acetoxy-2-chloro-1-(4-methoxyphenyl)propane **1b**. In nitrogen-saturated acetonitrile, only the β -chloro-4-methoxyphenylpropyl radical **2b**, eq 2, with an absorption maximum at 310 nm and a slow, second-order decay was observed. Upon the addition of ionizing solvents like water, HFIP or TFE to the acetonitrile, the radical decay became more rapid and was accompanied by the formation of the radical cation of anethole **5b** with absorption maxima at 380 and 600 nm, indicating that radical **2b** also undergoes β -heterolysis of chloride ion under ionizing conditions, eq 2. As for the reaction of radical **2a** described above, the rate constant for the formation of the anethole radical cation from radical **2b** was measured in water/AcN, HFIP/AcN, and TFE/AcN mixtures. In each case, the observed rate constant increased with increasing water, HFIP or TFE content, and eventually became too fast to measure. These results are summarized in Figure 4b.

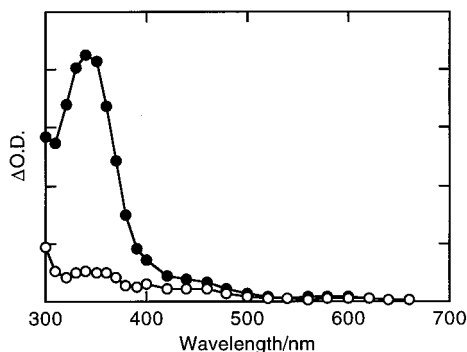


Figure 5. Absorption spectra immediately after 266-nm laser irradiation of 1-acetoxy-2-bromo-1-(4-methoxyphenyl)ethane **1c** in (●) nitrogen-saturated acetonitrile and (○) oxygen-saturated acetonitrile.

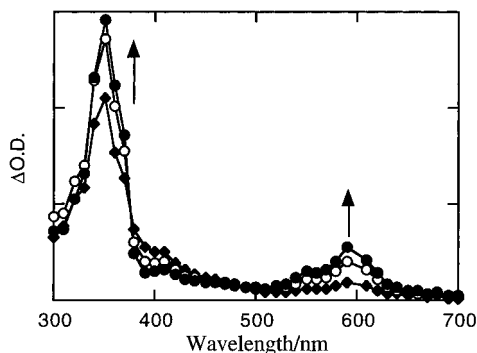
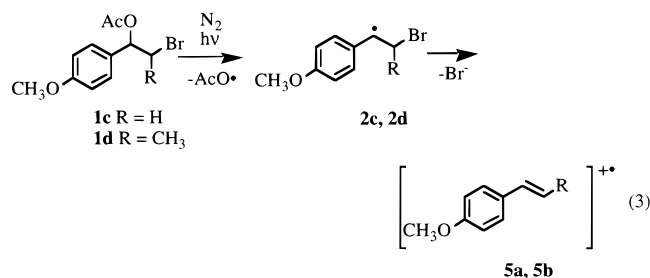


Figure 6. Absorption spectra after 266-nm laser irradiation of 1-acetoxy-2-bromo-1-(4-methoxyphenyl)ethane **1c** in nitrogen-saturated 50% water/50% AcN. Spectra were recorded (◆) 0.16 μ s, (○) 0.63 μ s and (●) 1.25 μ s after the laser pulse.

Laser irradiation of the bromo derivatives, 1-acetoxy-2-bromo-(4-methoxyphenyl)ethane **1c** or 1-acetoxy-2-bromo-(4-methoxyphenyl)propane **1d**, in nitrogen-saturated acetonitrile led to the formation of the β -bromo radicals **2c** or **2d**, eq 3, with an absorption maximum at 350 nm, Figure 5. While the position of the maximum is unusual for benzylic radicals, it matches closely that obtained for the β -bromo-4-methoxyphenylpropyl radical previously generated.²³ In dry, nitrogen-



saturated acetonitrile, there was no evidence that radicals **2c** or **2d** undergo heterolysis to give the 4-methoxystyrene radical cation **5a** or the anethole radical cation **5b**. However, in TFE, HFIP, or water mixed with acetonitrile, loss of bromide clearly takes place and leads to the formation of the radical cations, eq 3, with absorption maxima near 350 and 600 nm. The growth of the 4-methoxystyrene radical cation by heterolysis of the β -bromo radical **2c** in 50% aqueous acetonitrile is shown in Figure 6. In this case, it is difficult to match the decay of the radical with the growth of the radical cation, since the major absorption band of the radical is almost at the same position as the 350 nm band of the radical cation. Observed rate constants for radical cation formation from radicals **2c** and **2d** were

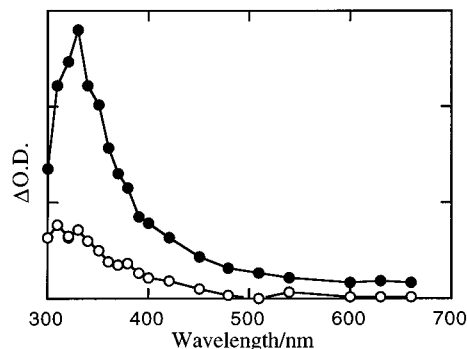


Figure 7. Absorption spectra immediately after 266-nm laser irradiation of 1-acetoxy-2-bromo-1-(4-methylphenyl)ethane **1e** in (●) nitrogen-saturated acetonitrile and (○) oxygen-saturated acetonitrile.

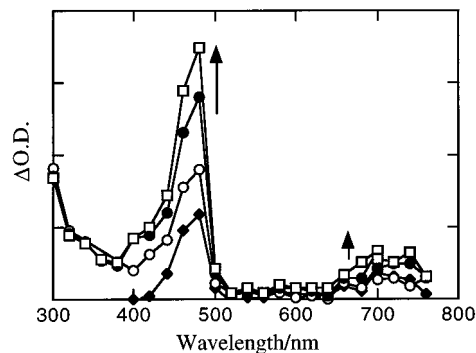


Figure 8. Absorption spectra after 266-nm laser irradiation of 1,2-dichloro-1,2-diphenylethane **3a** in 33% TFE/67% AcN. Spectra were recorded (◆) 20 ns, (○) 50 ns, (●) 180 ns, and (□) 400 ns after the laser pulse.

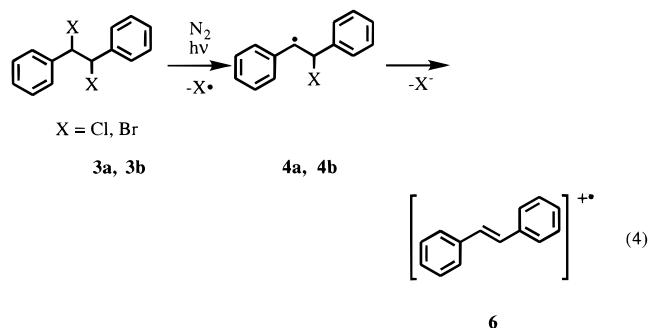
measured in the same solvents as described above for the β -chloro radicals **2a** and **2b**. The results are summarized in Figure 4c,d.

β -Bromo radicals **2e** and **2f** with absorption at 330 nm, Figure 7, are produced in nitrogen-saturated acetonitrile by laser irradiation of **1e** and **1f**. However, unlike the 4-methoxy derivatives discussed above, no evidence for the formation of the radical cation of styrene or 4-methylstyrene that would be produced by heterolysis of the β -bromo group was observed as the radicals decayed in TFE or HFIP, nor did the lifetime of the radicals change with solvent ionizing ability. It has previously been shown that the radical cations of 4-methylstyrene and styrene are sufficiently long-lived in these solvents to be observed.²³ The fact that the radical cations were not detected, together with the observation that the lifetimes of the radicals remained essentially unchanged upon going from acetonitrile to HFIP, indicates that the heterolysis of these radicals is too slow to compete with other reactions of the radical.

A different result is obtained for the β -substituted 1,2-diphenylethyl radicals **4a** and **4b**, which differ from the unreactive radical **2f** by the presence of a phenyl group instead of a hydrogen at the carbon undergoing ionization. The time-dependent absorption spectrum generated upon 266 nm irradiation of 1,2-dichloro-1,2-diphenylethane **3a** in 33% TFE/AcN is shown in Figure 8. After the laser pulse, a strong absorbance band at 475 nm and a weaker band at 700 nm that grow in a first-order manner with equal rate constants of $1.3 \times 10^7 \text{ s}^{-1}$ are clearly observed. These absorption bands can be confidently assigned to the *trans*-stilbene radical cation **6** on the basis of its known absorption spectrum.²⁸ The growth of the stilbene

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radical cation is completely quenched upon the addition of oxygen, indicating that the radical cation is produced by heterolysis of the β -chloro radical generated by laser irradiation of the 1,2-dichloro-1,2-diphenylethane **3a**, eq 4.



In neat acetonitrile, the stilbene radical cation was not observed, and we expected to observe a transient due to the presence of the β -chloro-1,2-diphenylethyl radical **4a**. Absorption in the 300–330 nm region that could be due to the radical was detected. However, while this absorption was quenched by oxygen as expected for a radical species, the absorption was weak with no defined maximum, and confident assignment of this absorption to the radical **4a** could not be made.

As shown in Figure 4e, the observed rate constant for stilbene radical cation formation from the β -chloro radical **4a** showed a similar solvent effect to that measured for the reactions of radicals **2a–d**, with the rate constant increasing from $6.1 \times 10^6 \text{ s}^{-1}$ in 17% aqueous acetonitrile to greater than $1 \times 10^8 \text{ s}^{-1}$ in 66% aqueous acetonitrile. An increase in the rate constant for stilbene radical cation formation was also observed as TFE content in acetonitrile was increased, Figure 4e.

The *trans*-stilbene radical cation was also produced upon photolysis of 1,2-dibromo-1,2-diphenylethane **3b**. In this case, formation of the radical cation was an exceptionally fast process in ionizing solvents, taking place with rate constants near 10^8 s^{-1} even in water/acetonitrile mixtures containing as little as 10% water. As a result of the large rate constants associated with this reaction, detailed solvent effects were not investigated.

Ionization in Water/Methanol Mixtures. Solvent ionizing abilities as measured by *Y* values are not readily available for acetonitrile mixtures but are known for water/methanol mixtures.²⁹ The rate constants for the formation of the heterolysis product of the radicals **2a–d** and **4a** were therefore measured in water/methanol mixtures from 0% to 70% water. In each case, the rate constants for growth of the radical cations increased as a function of water content. The results are given in Figure 9 as the rate constants plotted against *Y* values.

Determination of Radical/Radical Cation Equilibrium Constants. It has previously been demonstrated that substituted styrene radical cations often undergo efficient and rapid addition of nucleophiles to the β -position to produce the same type of β -substituted radicals generated in the present work.^{23,30–34} On the other hand, the results described above provide clear evidence that these radicals rapidly undergo the reverse reaction under certain conditions and lose the nucleophile to regenerate

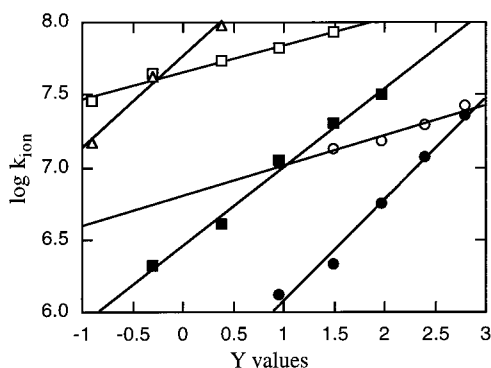
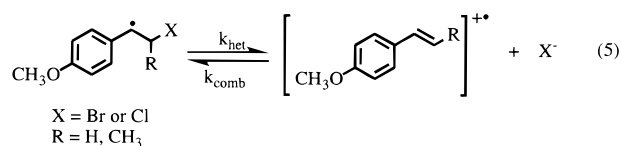


Figure 9. Relationship between the observed rate constants for the formation of radical cations at 600 nm upon 266-nm irradiation of (●) 1-acetoxy-2-chloro-1-(4-methoxyphenyl)ethane **1a**; (■) 1-acetoxy-2-bromo-1-(4-methoxyphenyl)ethane **1c**; (○) 1-acetoxy-2-chloro-1-(4-methoxyphenyl)propane **1b**; (□) 1-acetoxy-2-bromo-1-(4-methoxyphenyl)propane **1d**; and at 475 nm upon 266-nm irradiation of (△) 1,2-dichloro-1,2-diphenylethane **3a** and solvent ionizing ability (*Y*-values) of methanol/water mixtures.

the radical cation. This situation whereby both the formation of the β -substituted radical by nucleophilic addition to a radical cation and decomposition of the radical by β -heterolysis are rapid processes leads to the possibility that an equilibrium state containing the β -radical and the radical cation, eq 5, can be generated in the presence of an appropriate amount of a suitable nucleophile, either chloride or bromide.



Assuming that heterolysis is the dominant reaction of the radical, measuring the rate constant for radical cation formation as a function of the concentration of either chloride or bromide, depending on the identity of the β -substituent, is one method for evaluating rate constants for the formation of the equilibrium state. Under these conditions, the observed rate constant for the decay of the radical represents the rate constant for the approach to equilibrium, and the rate equation for the decay of the β -substituted radical and the formation of the radical cation will have the following form, eq 6.

$$k_{\text{obs}} = k_{\text{het}} + k_{\text{comb}}[\text{X}^-] \quad (6)$$

According to this rate equation, the observed rate constant for the formation of the radical cation should increase as a function of the concentration of the common-ion, with the intercept representing the rate constant for heterolysis, k_{het} , and the slope representing the rate constant for the addition of the nucleophile to the radical cation, k_{comb} .

As shown in Figure 10, the rate constant for the formation of the 4-methoxystyrene radical cation upon reaction of β -chloro-4-methoxyphenethyl radical in 50% aqueous acetonitrile did indeed increase as the concentration of chloride was increased from 0.0015 to 0.007 M. A good linear relationship is observed, and from the slope a second-order rate constant of $3.6 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for the addition of chloride to the radical cation of 4-methoxystyrene can be established. In addition, the optical density at 600 nm after the radical cation was fully formed decreased significantly as the concentration of chloride increased. This is consistent with the formation of a radical/radical cation equilibrium, with the radical cation component

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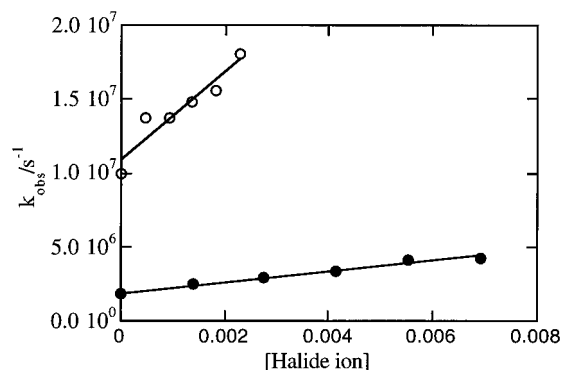


Figure 10. Relationship between the rate constants for the formation of the radical cations upon 266-nm laser irradiation of (●) 1-acetoxy-2-chloro-1-(4-methoxyphenyl)ethane **1a** and chloride concentration and (○) 1-acetoxy-2-bromo-1-(4-methoxyphenyl)ethane **1c** and bromide ion concentration in nitrogen-saturated 50% water/50% acetonitrile.

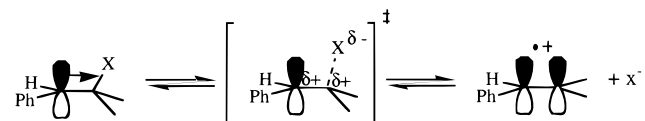
decreasing as the concentration of the chloride ion increases. Similar results were obtained by monitoring the rate constant for the growth of the 4-methoxystyrene radical cation by ionization of the β -bromo-4-methoxyphenethyl radical as a function of bromide concentration. A reasonably linear plot is again observed, Figure 10, with the slope corresponding to the addition of bromide to the radical cation of $k_{\text{comb}} = 3.1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.

When similar experiments were carried out with the β -chloro and the β -bromo-4-methoxyphenylpropyl radicals in 50% aqueous acetonitrile, the observed rate constants for formation of the anethole radical cation by heterolysis of the β -halide were not affected by halide concentrations up to 0.05 M. This suggests that the rate constants for heterolysis of the radicals under these conditions, $k_{\text{het}} = 1.1 \times 10^7 \text{ s}^{-1}$ for the β -chloro derivative and $k_{\text{het}} = 5.2 \times 10^7 \text{ s}^{-1}$ for the β -bromo derivative (Figure 4c,d), are considerably more rapid than the rate constant for the addition of the corresponding halide to the radical cations, even at halide ion concentrations up to 0.05 M.

Discussion

Observation of the aryl alkene radical cations in the present work provides unambiguous evidence that the β -substituted arylethyl radicals **2a–d** and **4a,b** undergo heterolytic cleavage of the carbon-leaving group bond in ionizing solvents. Thus, the observed rate constants for the formation of the radical cations measured in the present work must include a term for the rate constant for the heterolysis reaction of the radical. However, the observation of the formation of the radical cations does not necessarily rule out the possibility that the observed rate constants also contain components for other reactions available to the radical, such as rapid homolysis or $\text{S}_{\text{N}}2$ substitution. Since homolysis is unlikely to be strongly influenced by solvent polarity, the dramatic increase in the magnitude of the rate constant for the reaction of the radical as solvent ionizing ability increases can be attributed to an increased rate constant for the heterolysis process. Thus, in solvents where the rate constant for radical cation formation is significantly greater than the reaction of the radical in neat acetonitrile, it seems reasonable to conclude that homolysis does not contribute significantly to the measured rate constants. In addition, a close correspondence is seen between the increase in the relative yield of the radical cation as measured by the absorbance at 600 nm and the magnitude of the rate constant for the radical reaction as the ionizing ability of the solvent is increased. This clearly suggests that competing processes such as homolysis or $\text{S}_{\text{N}}2$ substitution which would decrease the yield

Scheme 2



of radical cation are not taking place. Thus, the rate constants measured in the ionizing solvents reflects predominantly (if not exclusively) the heterolysis reaction of the radical.

A significant observation from these results is that ionization of bromide and chloride from the β -substituted radicals is an extremely fast reaction, with the first-order rate constants exceeding $1 \times 10^8 \text{ s}^{-1}$ in highly ionizing solvents such as neat water or HFIP. The radical moiety therefore has an enormous rate accelerating effect on the rate constants for the heterolysis of the primary or secondary halides. For example, the prototypical secondary halide, isopropyl bromide, undergoes solvolysis in water (at 50 °C) with a rate constant³⁵ of about $1 \times 10^{-5} \text{ s}^{-1}$ that is at least 10^{13} times smaller than the rate constant for ionization of bromide from the secondary β -bromo radical **2d** studied in the present work. The magnitude of the accelerating effect can also be illustrated by comparing the rate constant for $\text{S}_{\text{N}}1$ ionization of 4-methoxyphenethyl chloride of approximately 1000 s^{-1} in 20% aqueous acetonitrile³⁶ to the rate constant of $4.6 \times 10^6 \text{ s}^{-1}$ for ionization of chloride from the β -chloro-4-methoxyphenylpropyl radical **2b** in 17% aqueous acetonitrile. In this case, insertion of the CH^{\bullet} group between the anisyl group and the carbon bearing the chloride leaving group causes a 5000-fold increase in the rate constant for heterolysis.

A simple explanation for the observed rate accelerating effect of the radical center is that the positive charge formed upon ionization is not localized at the carbon undergoing ionization but is instead delocalized into the adjacent, half-filled p-orbital of the radical center, Scheme 2.

Thus, in a similar manner to the mechanisms by which a lone pair of electrons of oxygen in α -alkoxymethylhalides or π -electrons of unsaturated carbons in α -vinylmethyl halides increase rate constants for solvolysis by stabilizing the incipient carbocation, the half-filled orbital can interact directly with the σ -bond undergoing cleavage to stabilize the positive charge formed in the heterolysis reaction. In fact, the acceleration provided by the radical center is similar to that provided by resonance donating groups such as oxygen or vinyl groups, as exemplified by the 10^{13} -fold increase in the rate constant for solvolysis of methoxymethyl chloride compared to solvolysis of *n*-propyl chloride.³⁷

Further evidence for the direct participation of the radical center in the heterolysis reaction comes from the effect of substituents on the aromatic ring. In our experiments, we could find no evidence for heterolysis of the β -bromo-4-methylphenethyl radical **2e** or the β -bromophenethyl radical **2f**, indicating that heterolysis of these radicals not bearing the highly electron-donating 4-methoxy group takes place with a rate constant $< 10^5 \text{ s}^{-1}$ even in highly ionizing solvents such as HFIP.³⁸ This upper limit is considerably smaller than rate constants of $> 10^8 \text{ s}^{-1}$ measured for the heterolysis of the corresponding 4-methoxy substituted radical **2c** in neat HFIP and water. The heterolysis process is therefore very sensitive to the substituents on the aryl ring, with the electron-donating 4-methoxy group accelerating

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heterolysis of the β -substituent. Since substituents have only a small effect on benzyl radical stability, the large substituent effect must be due to stabilization of the positive charge formed as the heterolysis reaction proceeds to the transition state. Given that the radical center sits between the phenyl ring and the site of ionization, the large substituent effect indicates that the electron-donating stabilizing effect of the phenyl substituent is transmitted effectively through the radical center and is consistent with electron-donation from the radical center to the carbon-leaving group bond undergoing heterolysis.

Cation stabilizing groups such as methyl or phenyl attached directly to the carbon undergoing ionization also play an important role in determining the overall reaction rate constant. The β -methyl substituted radicals **2b** and **2d** undergo heterolysis with rate constants that are consistently larger than the heterolysis rate constants for the corresponding β -unsubstituted radicals **2a** and **2c**. The rate acceleration caused by the β -methyl group can be attributed, at least in part, to the electron-donating ability of the methyl groups that stabilize the positive charge formed at the carbon undergoing ionization. It should also be noted that the oxidation potential of anethole is about 100 mV lower than that for 4-methoxystyrene,³⁹ indicating that the presence of the methyl group at the β -position has a substantial stabilizing effect on the radical cation formed by ionization of the leaving group. Thus, faster ionization in the presence of the β -methyl group may also be a reflection of the increased stability of the radical cation.

The presence of a phenyl group at the β -position has an even more dramatic effect on the rate constants for ionization than a methyl group. No ionization of the β -bromophenethyl radical **2f** was observed, even in a highly ionizing solvent like HFIP. On the other hand, the β -chloro- (**4a**) and the β -bromo (**4b**) substituted 1,2-diphenylethyl radicals, which have a phenyl group at the β -position, undergo rapid ionization. In fact, heterolysis of bromide from radical **4b** was the fastest reaction measured in the present work, and ionization of chloride from **4a** takes place with rate constants of $8.5 \times 10^7 \text{ s}^{-1}$ in 50% aqueous acetonitrile and $3.9 \times 10^7 \text{ s}^{-1}$ in 50% TFE/50% AcN that are considerably larger than the rate constants for ionization of chloride from the 4-methoxyphenethyl and the 4-methoxyphenyl propyl radicals. Since the oxidation potential for stilbene^{40,41} is approximately 100–200 mV higher than the oxidation potentials of 4-methoxystyrene and anethole, the relatively faster rate constants for heterolysis to give the stilbene radical cation cannot be explained solely on the basis of radical cation stability. Instead, the large rate enhancement must result from stabilization of the positive charge by the phenyl group as the heterolysis reaction proceeds to the transition state.

The greater leaving ability of bromide ion relative to chloride ion in simple S_N1 reactions is well-known in physical organic chemistry. This well-established order is clearly followed for the reactions of the β -halo radicals studied in the present work,

(38) Note that failure to observe the radical cations from the β -bromo-4-methylphenethyl radical does not necessarily indicate that ionization is not taking place. Ionization may be occurring, but, given the higher oxidation potential of 4-methylstyrene, rapid electron-transfer of the radical cation/bromide ion pair may take place to give the neutral 4-methylstyrene and a bromine atom. If this reaction does occur, the initial ionization step would still be solvent dependent, and the observed decay of the radical would increase in ionizing solvents. Since the decay of the β -bromo-4-methylphenethyl radical and the phenyl unsubstituted derivative remained unchanged upon going from acetonitrile to water, ionization followed by electron-transfer is not likely to be a dominant process under our conditions.

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which shows that in any given solvent mixture, ionization of the β -bromo radicals takes place with rate constants that are 5–50 times greater than ionization of the corresponding β -chloro radicals.

Effect of Solvent on Rate Constant for Ionization. Rate constants for nucleophilic substitution of alkyl halides are strongly influenced by solvent, with Y parameters for solvent ionizing ability being derived from the effect of solvent on the rate constants for rate-limiting ionization of substrates such as adamantyl derivatives. In general, the rate constants for the heterolysis of the β -substituted radicals studied in the present work behave as expected with respect to increasing ionizing ability of the solvent,⁴² with heterolysis being fastest in acetonitrile solutions containing water followed by solutions containing HFIP and then TFE.⁴³ Interestingly, however, the magnitude to which the rate constants are influenced by ionizing ability of the solvent is strongly dependent on the structure of the radical. For example, the rate constant for the loss of bromide from the β -bromo-4-methoxyphenylpropyl radical **2d** increases 2.5-fold upon going from 50% TFE/50% AcN to 100% TFE, whereas the rate constant for the same reaction of the β -bromo-4-methoxyphenethyl radical **2c** increases by almost 20-fold under identical conditions.

A more accurate assessment of the effect of solvent ionizing ability on the rate constants for the ionization reaction of the β -substituted radicals can be obtained from Winstein plots of the data obtained in methanol/water mixtures. These plots of the rate constant vs Y values²⁹ for each methanol/water mixture are shown in Figure 9. All the plots are reasonably linear but have slopes that change substantially depending on the nature of the leaving group and the presence or absence of alkyl or phenyl groups at the β -position. Thus, $m = 0.72$ calculated from the slope of the plot of the rate constant for heterolysis of the β -chloro-4-methoxyphenethyl radical **2a** as a function of Y is considerably larger than $m = 0.54$ from the slope of the same plot for the corresponding β -bromo-substituted radical **2c**. Similarly, the m value of 0.21 for the heterolysis of the β -chloro-4-methoxyphenylpropyl radical **2b** is slightly larger than the m value of 0.18 measured for the β -bromo derivative **2d**. In addition, ionization of chloride or bromide from the 4-methoxyphenethyl radicals **2a** and **2c** to give the 4-methoxystyrene radical cation is significantly more sensitive to solvent ionizing ability than formation of the more stable anethole radical cation produced by ionization of chloride or bromide from the 4-methoxyphenylpropyl radicals **2b** and **2d**.

This variation in m value can be explained by noting that the observed rate constants for heterolysis of the carbon–bromine bond are substantially larger than those for the ionization of chloride. The higher reactivity for the β -bromo derivatives indicates an earlier transition state that should be less sensitive to environmental effects such as solvent polarity. The decrease in the m value upon addition of a β -methyl group is also consistent with the higher reactivity and earlier transition state induced by the cation stabilizing influence of the β -methyl group.

On the other hand, despite the fact that heterolysis of the 1,2-diphenylethyl radical **4a** is more rapid than heterolysis of the other radicals studied in the present work, it shows considerable sensitivity to solvent ionizing ability, with $m = 0.62$. In this case, the positive charge at the carbon undergoing

(42) An increased rate constant for β -heterolysis of model compounds of 4'-DNA radicals upon going from methanol to 1:1 acetonitrile:water has recently been demonstrated.⁴

(43) $Y(\text{H}_2\text{O}) = 4.1$; $Y(\text{HFIP}) = 3.8$; $Y(\text{TFE}) = 1.8$. Y values taken from: March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; p 361.

Table 1. Rate Constants and Equilibrium Constants for the β -Halo-4-methoxyphenethyl Radical–4-Methoxystyrene Radical Cation Equilibrium in 50% Aqueous Acetonitrile (25 °C)

halide	$k_{\text{comb}}/\text{M}^{-1} \text{ s}^{-1}$	$k_{\text{het}}/\text{s}^{-1}$	K_{eq}/M
Br ⁻	3.1×10^9	7.0×10^6	0.0023
Cl ⁻	3.6×10^8	1.8×10^6	0.0050

ionization may not be delocalized into the adjacent benzyl radical moiety to the same degree as delocalization into the strongly resonance donating 4-methoxybenzyl radical moiety of radicals **2a–d**. Less delocalization of charge in the transition state would leave the ionization reaction more dependent on solvent stabilization of the charge and would therefore increase the sensitivity of the rate constant to solvent ionizing ability.

Note that the m values derived from the slopes of the plots in Figure 9 are all significantly less than 1. Small m values sometimes indicate significant nucleophilic assistance and substantial S_N2 character in the substitution reaction. This is unlikely in our experiments, since the initial cationic product from the ionization reaction is observed directly. The small m values therefore reflect the remarkably high velocity of the ionization processes which suggests a very early transition state and a corresponding decrease in the sensitivity to solvent ionizing power. Similar small m values for slower ionization reactions that have early transition states due to strain have been noted.⁴⁴

Radical/Radical Cation Equilibrium. Nucleophiles are well-known to add to the β -position of aryl alkene radical cations to generate β -heteroatom substituted radicals that then go on to give final products.^{30,31} The results from the present work show that in some cases, such as in polar, ionizing solvents, addition of the nucleophile will be reversible, especially under circumstances where the nucleophile is also a good leaving group. These results imply that the efficiency of product formation by nucleophilic addition to radical cations will not only be related to the rate constant for nucleophilic addition but also to the magnitude of the reverse heterolysis reaction. In addition, unusually slow rate constants for addition of nucleophiles to radical cations may be, in part, because of a rapid reversible ionization.⁴⁵ For example, the lifetime of the anethole radical cation has been found to be completely insensitive to bromide and chloride ion at concentrations up to 1.0 M.²³ While the rate constant for addition of these nucleophiles to the anethole radical cation should be considerably less than diffusion controlled in aqueous solution, the fact that ionization of chloride and bromide takes place with rate constants $> 1 \times 10^8 \text{ s}^{-1}$ indicates that the anethole radical cation would not be quenched by these nucleophiles, even if the second-order rate constants for nucleophilic addition are as fast as $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.

Equilibrium constants for the radical/radical cation equilibrium reaction determined by combination of the rate constants for addition, k_{comb} , of halides to the radical cation and heterolysis, k_{het} , of the halides are shown in Table 1. These equilibrium constants indicate that at chloride concentrations up to 0.005 M and bromide concentrations up to 0.0023 M, the dominate species present at equilibrium will be the radical cation, with the nucleophile adduct being the less favored species.

Conclusion

The primary mode of decay of the radicals **2a–d** and **4a,b** under ionizing conditions is heterolytic cleavage of the β -chloro or β -bromo substituent to generate the corresponding radical cations. The ionization reactions are remarkably fast, taking place with rate constants in the 10^7 s^{-1} to $\geq 10^8 \text{ s}^{-1}$ range in neat HFIP or neat water. These large rate constants highlight the ability of the radical centers to interact with the positive charge formed as the heterolysis process proceeds from the initial state to the transition state. The kinetics for the ionization of the β -substituted radicals are otherwise controlled by factors such as solvent ionizing ability, nature of leaving group and electronic effects in the same way as typical S_N1 ionization. However, the sensitivity of the heterolysis reactions to solvent ionizing ability is distinctly dependent on the nature of the leaving group and the structure of the radical cation product. Investigations into the reactivity of these kinds of radicals with different substituents at the β -position as well as efforts to detect S_N2 substitution reactions are currently in progress.

Experimental Section

Materials. The radical precursors, 1-acetoxy-2-chloro-1-(4-methoxyphenyl)ethane **1a**, 1-acetoxy-2-chloro-1-(4-methoxyphenyl)propane **1b**, 1-acetoxy-2-bromo-1-(4-methoxyphenyl)ethane **1c**, 1-acetoxy-2-bromo-1-(4-methoxyphenyl)propane **1d**, 1-acetoxy-2-chloro-1-(4-methylphenyl)ethane **1e**, and 1-acetoxy-2-chloro-1-(phenyl)ethane **1f**, were prepared by bromination or chlorination of the appropriate styrene in glacial acetic acid. 1,2-Dichloro- and 1,2-dibromo-1,2-diphenylethane, **3a** and **3b**, respectively, were prepared by either chlorination or bromination of *trans*-stilbene. All materials were characterized by ¹H- and ¹³C-NMR (Bruker 250 MHz) using CDCl₃ as the solvent. Acetonitrile (AcN) was spectroscopic grade (Omnisolve, BDH). 2,2,2-Trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) were purchased from Aldrich and used as received. Methanol and water were doubly distilled prior to use.

Laser Flash Photolysis. The nanosecond laser flash photolysis system at Dalhousie University is of standard design.^{46,47} The samples, typically 2.5 mL, were contained in $7 \times 7 \text{ mm}^2$ laser cells made out of Suprasil quartz tubing and bubbled with a slow stream of dry nitrogen for 20 min prior to laser irradiation. The excitation source was the fourth harmonic from a Continuum Nd:YAG NY-61 laser (266 nm; $\leq 8 \text{ ns/pulse}$; $\leq 15 \text{ mJ/pulse}$). Transient signals from a monochromator/photomultiplier system were initially captured by a Tektronix 620A digital oscilloscope and transferred to a Power Macintosh computer. The experiments are computer controlled using the Power Macintosh and software written using the Labview programming language. The absorbance of the substrates at 266 nm was ≈ 0.3 in the $7 \times 7 \text{ mm}^2$ laser cells. The kinetic experiments were carried out in individual static samples; in these experiments, each sample was exposed to a maximum of three laser pulses. The spectra were obtained under solvent flow conditions to ensure that there was no build-up of photolysis products during the laser experiments.

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Supporting Information Available: Tables of observed rate constants (3 pages). See any current masthead page for ordering and Internet access instructions.

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