

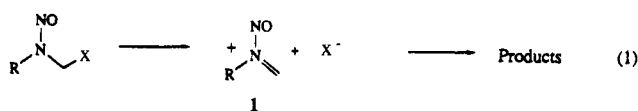
Generation and Direct Measurement of the Reactivity of an *N*-Nitrosiminium Cation with Nucleophiles in Aqueous Media

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N-Nitrosiminium ions (**1**) are proposed intermediates in the solvolytic decomposition of certain carcinogenic α -substituted nitrosamines.^{1,2} Despite this, almost nothing of a quantitative



nature is known of the reactivities and selectivities of *N*-nitrosiminium ions. These properties to some extent determine the fate of the alkylating equivalent carried by the *N*-alkyl-*N*-nitroso moiety that is responsible for the biological activities of α -substituted nitrosamines, so a quantitative understanding is of considerable importance. The "azide clock" method has proved useful in providing accurate estimates of the lifetimes of reactive carbocations in nucleophilic media,^{3,4} and we have employed this technique to determine the reactivity of some simple *N*-nitrosiminium cations.⁵ However, this technique is only valid over a fairly small range of reactivity where the reaction of azide ion is diffusion controlled,⁶ and our initial studies have shown that the reactivity of *N*-nitrosiminium ions varies greatly with changes in structure. Therefore we have sought alternative, direct, means of studying the chemistry of these reactive intermediates. The present communication reports a method for generation and observation of an *N*-nitrosiminium cation that has enabled the first direct measurement of rate constants for its reactions with nucleophiles.

McClelland and Steenken^{6,7} have demonstrated the utility of 4-cyanophenol ethers in the generation of carbocations by KrF laser flash photolysis, and we have employed this approach in the present report. Excitation at 248 nm of aqueous solutions containing 7×10^{-5} M of the precursor **2**⁸ (eq 2) elicited a transient species with a broad UV absorbance between $\lambda = 300$ and 340 nm whose decay, monitored at 325 nm, gave good first-order kinetics. Evidence that this transient is not a radical species is found in the fact that the rate constant for decay of the transient is not measurably affected by the presence of oxygen: the rate constants for its decay in argon-saturated and oxygen-saturated aqueous solutions containing 0.001 M NaOH,

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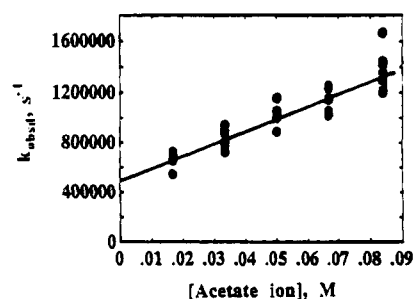
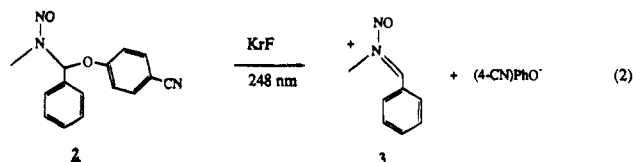
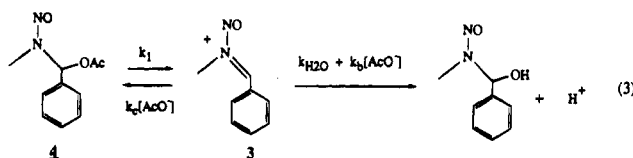


Figure 1. Plot of k_{obsd} for the decay of the transient obtained from KrF laser flash photolysis of **2**, against acetate ion concentration in aqueous solution, buffer ratio $[A^-]/[HA] = 9$, 1% by volume acetonitrile, ionic strength 1 M (NaClO₄) at 25 °C.



10% acetonitrile by volume, ionic strength 0.1 M (NaClO₄) are $1.10 (\pm 0.05) \times 10^6$ and $1.06 (\pm 0.07) \times 10^6$ s⁻¹, respectively.⁹

Evidence that the transient is due to the cation **3** (eq 2) is found in the observation that its chemical reactivity is, within experimental error, identical with that of the *N*-nitrosiminium cation intermediate generated in the thermal solvolysis of the acetate ester **4** (eq 3). The decay of the transient generated by



laser flash photolysis of **2** is accelerated by increasing concentrations of acetate buffers as illustrated in Figure 1, and experiments at different buffer ratios indicate that the acetate anion is the active species. The slope-to-intercept ratio for the plot in Figure 1 gives the ratio of rate constants for reaction of the cation with acetate ion and solvent, $k_{\text{AcO}}/k_{\text{H}_2\text{O}} = 21.2 \pm 0.2$ M⁻¹. The corresponding reactivity ratio for the thermal solvolysis of the acetate ester **4** can be obtained from the effect of added acetate ion on its rate constant for decomposition. The first-order rate constant for solvolysis of the acetate ester **4** is decreased by increasing concentrations of acetic acid buffer as indicated in Figure 2. This "common ion effect" is consistent with a free *N*-nitrosiminium ion intermediate. The data are most consistent with the scheme of eq 3 in which the acetate ion acts both as a nucleophile to regenerate the starting material, by k_c , and as a general base catalyst of hydration, by k_b .¹⁰ The rate equation for the mechanism of eq 3 is given by eq 4. Nonlinear least squares fitting of the data to eq 4 yields values for the parameters $k_c/k_{\text{H}_2\text{O}} = 20.0 (\pm 0.3)$ M⁻¹, $k_b/k_{\text{H}_2\text{O}} = 1.10$

(9) In this work the errors cited for absolute values are standard deviations while the errors cited for ratios of rate constants are the estimated propagated errors, $\sigma/n = \sqrt{(\sigma_a/n_a)^2 + (\sigma_b/n_b)^2}$.

(10) We favor general base catalyzed hydration by acetate ion as opposed to the alternative denitrosation by acetate ion attack on the nitroso group of **3**.⁵ This is based on the fact that azide ion shows a selectivity (k_c/k_N) for reaction at the carbon (k_c) of **3** compared to the nitroso nitrogen (k_N) of **3** of $k_c/k_N \sim 19$, and we presume that k_c/k_N is substantially larger than this in the case of acetate ion due to the weaker nucleophilicity of acetate ion compared to azide ion. Such a substantially larger value of k_c/k_N cannot account quantitatively for the residual acetate-independent reaction ($\sim 5\%$ of k_{obsd} at $[AcO^-] = 0$) at high acetate ion concentration. It is important to note that the certainty of this deduction does not materially affect the conclusion that **3** is a common intermediate to the photolysis of **2** and the solvolysis of **4**.

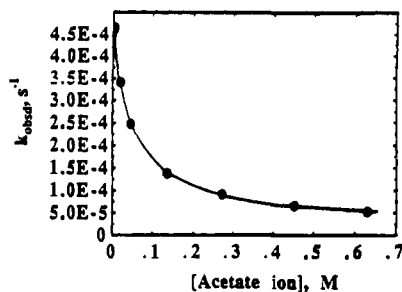


Figure 2. Plot of k_{obsd} , for decay of the ester **4**, against acetate ion concentration, under the same conditions as in Figure 1.

$$k_{\text{obsd}} = \frac{k_1 \left[\frac{k_b [\text{AcO}^-]}{k_{\text{H}_2\text{O}}} + 1 \right]}{\frac{(k_c + k_b) [\text{AcO}^-]}{k_{\text{H}_2\text{O}}} + 1} \quad (4)$$

(± 0.06) M^{-1} , and $k_1 = 4.62 (\pm 0.03) \times 10^{-4} \text{ s}^{-1}$. These values generate the solid line fit in Figure 2. The sum of the ratios of rate constants that are first order in acetate ion divided by that for the reaction of water, $(k_c + k_b)/k_{\text{H}_2\text{O}}$, gives the acetate-to-water reactivity ratio $k_{\text{Ac}}/k_{\text{H}_2\text{O}} = 21.1 \pm 0.3 \text{ M}^{-1}$. This value is, within experimental error, the same as that for reaction of the acetate ion with the transient in Figure 1, $k_{\text{Ac}}/k_{\text{H}_2\text{O}} = 21.2 \pm 0.2 \text{ M}^{-1}$ (above).

Rate constants for the reactions of a number of nucleophilic/basic substances with the *N*-nitrosiminium ion **3** that were directly measured by laser flash photolysis of **2** are reported in Table 1. That the predominant reaction is indeed nucleophilic is indicated by (1) the fact that, at 0.1 M azide ion, decomposition of the acetate ester **4** gives a 95% yield of the azide adduct¹¹ resulting from C–N₃ bond formation; (2) the analysis of the common ion effect illustrated in Figure 2 which shows that the nucleophilic, as opposed to the general base catalyzed, reaction of acetate is the predominant path for reaction of acetate ion, $k_c/k_b \sim 19$, eq 3; (3) observations reported in the literature that decomposition of a variety of α -acetoxy-*N*-nitrosamines in the presence of phosphate buffers give high yields of the α -phosphonoxy-*N*-nitrosamines;¹² (4) the azide ion/hydrazine/cyanide ion reactivity order that is consistent with cation capture¹³ but is different from what is expected for general base catalysis of hydration. It cannot be ruled out that, in the case of the reactions of cyanide ion and hydrazine, some of the nucleophilic reaction occurs at the nitroso nitrogen of the *N*-nitrosiminium cation as is preceded by the results for related systems.⁵

The reaction of azide ion with the cation is nearly, but not quite, diffusion limited. McClelland and Steenken⁶ have shown recently that rate constants for the diffusion-limited reaction of

(11) Yields determined by HPLC by interpolation from a three-point standard curve generated from the authentic material. ¹H-NMR (CDCl₃): δ 2.82 (3H, s); 7.42 (5H, m); 7.44 (1H, s). Anal. Calcd on the basis of 9% (determined by ¹H-NMR) contamination by benzaldehyde: C, 52.86; H, 4.80; N, 33.35. Obsd: C, 52.57; H, 4.85; N, 32.55.

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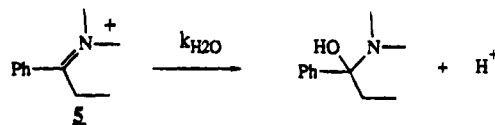
Table 1. Rate Constants for the Decay of the *N*-Nitrosiminium Ion **3** in Aqueous Solutions, 25 °C

nucleophile	k ($\text{M}^{-1} \text{ s}^{-1}$) ^a	
	$\mu = 0.5 \text{ M}$, 1% CH ₃ CN ^b	$\mu = 0.1 \text{ M}$, 10% CH ₃ CN ^b
HOCH ₂ CH ₂ S ⁻	$2.8 (\pm 0.2) \times 10^9$ ^c	
N ₃ ⁻	$1.98 (\pm 0.02) \times 10^9$ ^d	$3.76 (\pm 0.04) \times 10^9$ ^e
H ₂ NNH ₂	$1.86 (\pm 0.07) \times 10^8$ ^c	$1.74 (\pm 0.01) \times 10^8$ ^c
NC ⁻	$2.2 (\pm 0.2) \times 10^7$ ^c	$5.68 (0.05) \times 10^7$ ^c
HPO ₄ ²⁻	1.7×10^7 ^f	
H ₂ PO ₄ ⁻	2.0×10^6 ^f	
H ₂ O	$7.58 (\pm 0.06) \times 10^5$ ^g	$1.0 (\pm 0.1) \times 10^6$ ^h

^a Except as noted, the rate constants were obtained as the values of the slopes of plots of k_{obsd} against nucleophile concentration. Standard deviations are cited. Units apply except as noted for the reaction of H₂O. ^b Ionic strength held constant with NaClO₄. ^c Reactions in 10⁻³ M NaOH. ^d Reactions carried out in 0.02 M cacodylic acid buffers, 50% anion. ^e Reactions carried out in 0.05 M biphosphate buffers, 50% dianion. ^f From the appropriate intercept of the plot of the observed second-order rate constant versus percent phosphate dianion that contained two points for reactions in 20% and 80% phosphate dianion. ^g Units of s⁻¹. The mean of the intercept value of the plots cited in footnote *a* for experiments with phosphate buffers, hydrazine, and cyanide ion. ^h Units of s⁻¹. The mean of the intercept value of the plots cited in footnote *a* for experiments with hydrazine and cyanide ion and an experiment in which k_{obsd} was measured as a function of biphosphate buffer concentration (50% dianion). The slope of the plot of k_{obsd} against buffer in this experiment gave the observed second-order rate constant of $3.5 (\pm 0.2) \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.

azide ion with carbocations are in the range of $(5-7) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. There is no apparent reason in the present case why the rate constant for the diffusion-limited reaction of azide ion with the *N*-nitrosiminium cation **3** should be smaller. Evidence that the azide reaction is at least partly activation limited is found in the larger rate constant for reaction of the bigger β -mercaptoethanol anion (Table 1), the diffusion-limited reaction rate constant for which should be smaller than that of the smaller azide ion.

The *N*-methyl-*N*-nitroso moiety proves to be a good cation-stabilizing substituent. The rate constant for solvent capture of the benzyl cation in aqueous alcoholic media has been estimated¹⁴ to be about 10^{11} s^{-1} so the cation **3** is less reactive by roughly a factor of 10^5 . This stabilization is, however, considerably smaller than the stabilization provided by a simple dimethylamino group, as can be seen in the difference between the rate constant $k_{\text{H}_2\text{O}}$ for **3** and that reported for the nucleophilic attack by water on the iminium ion **5**, $k_{\text{H}_2\text{O}} = 2 \times 10^{-3} \text{ s}^{-1}$.¹⁵



A significant fraction of the 10^8 difference in reactivity between **3** and **5** must be due to the electron-withdrawing effect of the nitroso group.

Work is in progress to determine by direct methods the effects of structure upon the reactivity and selectivity of these reactive intermediates in nitrosamine carcinogenesis.

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