Reexamination of the Mechanisms of Decomposition of Simple α-Acetoxynitrosamines in the Physiological pH Range[1]

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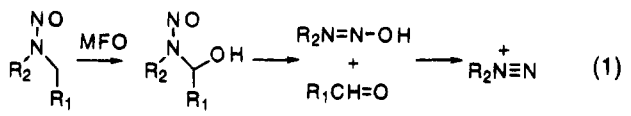
Rate constants, k_o, for the buffer independent decay of eight α-(acyloxy)nitrosamines were determined in aqueous media, 25 °C, ionic strength 1 M ($NaClO_4$), 1% (v/v) in acetonitrile in the pH range 2–13. The pH–rate profile of log k_o against pH, from pH 2 to 13, indicates a rate law that includes two terms: k_1, a pH independent term, and k_{OH}, a hydroxide ion dependent term. Values of the entropy of activation for the pH independent reactions of 1-(*N*-nitrosoethylamino)-ethyl acetate (**3**), (*N*-nitrosomethylamino)methyl acetate (**1**), and (*N*-nitrosobutylamino)methyl acetate (**9**) are determined to be $\Delta S^{\ddagger} = 0.7$ (±1.5), 3 (±3), and −5 (±3) cal deg^{-1} mol^{-1}, respectively. (*N*-Nitrosobutylamino)methyl benzoate (**11**) and (*N*-nitrosobutylamino)methyl pivaloate (**12**) decompose with pH independent rate constants that are larger than that of the corresponding acetate **9** by factors of 2.3 and 3.4, respectively. The value of ρ^* for alkyl substituents attached to nitrogen, not containing the acetoxy group, is $\rho^* = -5.99$ for four methyl acetates. It is concluded that the pH independent decomposition involves the formation of *N*-nitrosiminium ion intermediates. The greater reactivity of the benzoate and pivaloate, compared to the acetate, in the case of (*N*-nitrosobutylamino)methyl esters, combined with the product analysis previously reported for the reaction of the ethyl acetates indicates no measurable anchimeric assistance in the decay of the *Z* forms of the α-(acyloxy)nitrosamines studied in the present report. The value of ρ^* for the pH independent decay of the ethyl acetates is $\rho^* = -1.50$. The smaller value, in comparison to that for the methyl acetates, is ascribed either to a change in transition structure or to a difference, between methyl and ethyl acetates, in the nature of the rate-limiting step of the reactions. The rate constants, k_{OH}, for the hydroxide ion-catalyzed decay of (*N*-nitrosobutylamino)methyl benzoate (**11**) and (*N*-nitrosobutylamino)methyl pivaloate (**12**) are smaller than that for the corresponding acetate **9** by factors of 7 and 16, respectively. This observation is consistent with the deduction of others that the mechanism of this reaction involves a rate-limiting reaction at the carbonyl group.

Introduction

The carcinogenicity and mutagenicity of many dialkylnitrosamines is thought to be due in part to the fact that they may be enzymatically α-hydroxylated in vivo by mixed function oxygenases (MFO) and subsequently decompose to diazonium ion precursors, as in eq 1, that



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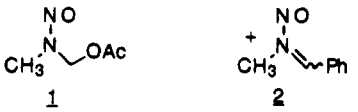
ultimately alkylate DNA.[2] α-Acetoxynitrosamines have played an important role in attempts to understand the molecular basis of dialkylnitrosamine activity because they are sources of α-hydroxylated nitrosamines and models of possible transportable metabolites of dialkylnitrosamines.[2,3] The solution chemistry of α-acetoxynitrosamines and related α-substituted nitrosamines is thus of considerable importance and is currently an active area of investigation.

Almost 25 years ago, the first synthesis and study of the stability in aqueous solution of the simplest α-acetoxynitrosamine, **1**, was reported.[4] (*N*-Nitrosomethylamino)methyl acetate, **1**, was reported to decompose in



phosphate-buffered aqueous media with a maximal half-life (20 days) at pH 5.2. The stability and similarity with ethyl acetate of the pH of maximum stability led to the proposal that **1** decomposes by the "normal"–carbonyl attack–mechanism of hydrolysis.

Subsequently, a study[5] of a large number of α-acetoxynitrosamines led to the conclusions that two factors determined reactivity: (1) the ability to stabilize a nitrosiminium ion intermediate through alkyl group substitution at R_1 (eq 2) and (2) the proportion of the *Z* form, which increases with substitutions at R_2 (eq 2), that was proposed to react with anchimeric asssistance involving nucleophilic assistance on the part of the nitroso oxygen. The mechanism of the latter reaction was not explicitly indicated. The apparent isolation and characterization of the *N*-nitrosiminium ion **2** was claimed to support the notion that all α-acetoxynitrosamines decompose via *N*-nitrosiminium ions. This generalization cannot logically be applied to the less reactive α-acetoxy nitrosamines such as **1** that presumably form less stable

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(1) We define "simple" to mean the title compounds, **8**, or the structure in Table 1, in which R_1 and R_2 = alkyl or R_1 = H.

(2) Lawley, P. D. In *Chemical Carcinogens*; Searle, C. D., Ed.; ACS Monograph Series 182; American Chemical Society: Washington, DC, 1984. Lijinsky, W. *Chemistry and Biology of N-nitroso Compounds*; Cambridge University Press: Cambridge, 1992.

(3) Gold, B.; Linder, W. B. *J. Am. Chem. Soc.* **1979**, *101*, 6772.

(4) Roller, P. P.; Shimp, D. R.; Keefer, L. K. *Tetrahedron. Lett.* **1975**, *25*, 2065.

(5) Wiessler, M. In *N-Nitrosamines*; Anselme, J.-P., Ed.; American Chemical Society: Washington, DC, 1979; p 57.

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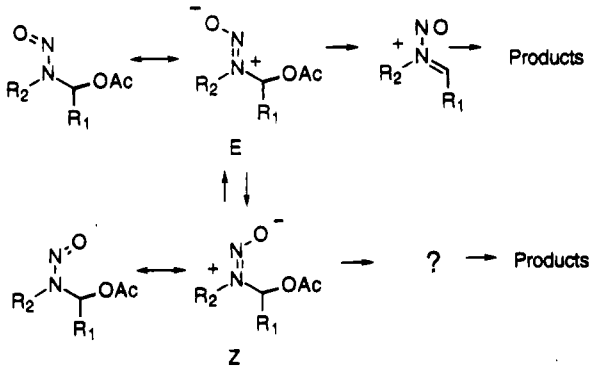
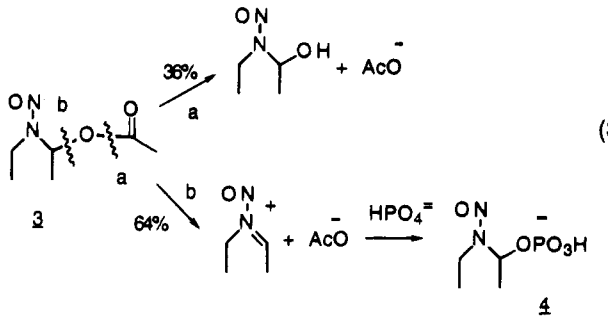


(2)

cations, and the conclusions in any case contrast with that of the previous[4] study. Further, the contradiction between this generality and the supposed special reaction mechanism of the *Z* forms was not resolved.

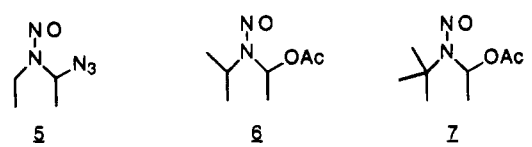
Recently it was proposed[6] that 1-(*N*-nitrosoethylamino)ethyl acetate (**3**; eq 3) decomposes in aqueous media by competitive *O*-acyl (36%) and *O*-alkyl (64%) bond cleavages as in eq 3. This conclusion was based on



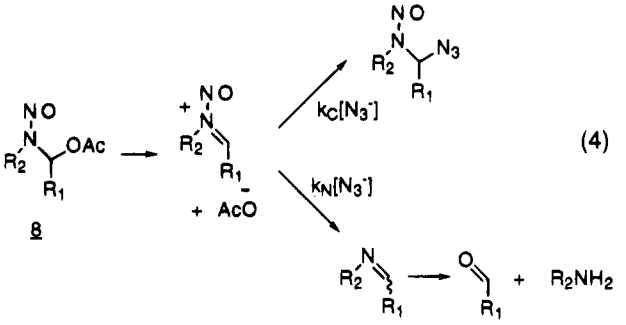
(3)

the apparent limiting yields of the phosphatooxy adduct **4** formed and the absence of effect upon the rate constant of the reaction of increasing concentrations of phosphate buffer. The claim that there are concurrent *O*-alkyl and *O*-acyl cleavage pathways contradicts the conclusion above[5] that the reactions occur exclusively via *N*-nitrosiminium ions. Further, the rate constant required for the proposed competitive *O*-acyl bond cleavage is extraordinarily large given the known rate constants for such processes for similar systems. The half-time for decomposition of 1-(*N*-nitrosoethylamino)ethyl acetate (**3**; eq 3) that is proposed to occur by *O*-acyl bond cleavage is on the order of a few minutes at pH = 7, whereas that for decay of ethyl acetate, which should have a comparable reactivity, is on the order of 2.8 years![7]

This perplexing pastiche of mechanistic possibilities has led us to study the decomposition of α-acetoxynitrosamines in aqueous solutions in some further detail. We recently reported[8] that the decomposition of **3** in the presence of azide ion yields up to 98 ± 2% of the azide adduct **5** and 3% of ethylammonium ion (reaction in D_2O) with no effect of azide ion concentration on the rate



constant for the decay of **3**. Similar results, with substantially greater percentages of reaction at the nitroso nitrogen, were obtained for the decomposition of **6** and **7** in aqueous solutions containing azide ion. These results require that these compounds decompose quantitatively via an *N*-nitrosiminium cation that reacts with azide ion, as in eq 4, either at the imino carbon to give



(4)

azide adducts (via k_C) or at the nitroso nitrogen to yield the imine that subsequently hydrolyzes to the alkylamine (or alkylammonium ion) (via k_N). These results indicate that ≤1% of the observed reaction can be due to a concurrent *O*-acyl bond cleavage pathway as in eq 3, path a.

In the present report we summarize additional evidence that is inconsistent with a mechanism involving rate limiting reaction at the carbonyl group for the pH independent decomposition reaction of α-acetoxynitrosamines. Further, there is evidence against the notion that the *Z* forms decompose with anchimeric assistance. It is concluded that even the simplest α-acetoxynitrosamine, **1**, decomposes with the intermediacy of an *N*-nitrosiminium cation.

Experimental Section

Warning! Many α-acetoxynitrosamines are proven to be powerful direct-acting carcinogens. Procedures must be carried out with due precautions. Manipulations were carried out by personel wearing frequently changed double pairs of disposable gloves. Contaminated, and potentially contaminated, materials were treated with 50% aqueous sulfuric acid containing the commercially available oxidant "No Chromix" (Aldrich Chemical).

Organic chemicals were standard ACS, reagent grade or better. In some cases, for materials suitable for kinetics, further purification by recrystallization or distillation was carried out as appropriate. Inorganic chemicals were purchased as ACS grade or better and used without further purification. Water for analytical procedures and kinetics was distilled in glass. (*N*-Nitrosomethylamino)methyl acetate (**1**) was purchased from the NCI Chemical Carcinogen Repository.

Synthesis. Methyl Acetates. These were generally synthesized by the reaction of the imine[9] (cyclic triamine form) with $NOBF_4$ in the presence of acetic acid and triethylamine and subsequently purified by chromatography on silica gel. A typical procedure is given for (*N*-nitroso-*N*-butylamino)methyl acetate (**9**).

(*N*-Nitrosobutylamino)methyl Acetate (9). Tributyltrimethylenetriamine, 1.02 g, was added to a solution of 30 mL of dry CH_2Cl_2, 1.21 g of dry Et_3N, and 0.72 g of glacial acetic acid in a 50 mL round bottom flask. $NOBF_4$, 1.40 g,

(6) Mochizuki, M.; Anjo, T.; Sekiguchi, N.; Ikarashi, A.; Suzuki, A.; Wakabayashi, Y.; Okada, M. *Chem. Pharm. Bull.* **1986**, *34*, 3956.

(7) At pH = 7, the hydroxide ion reaction is dominant for the decomposition of ethyl acetate, and the second-order rate constant for this reaction is 6.8 M^{-1} min^{-1} at 25 °C, ionic strength 1 M. Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 837.

(8) (a) Rajamäki, M.; Vigroux, A.; Chahoua, L.; Fishbein, J. C. *J. Org. Chem.* **1995**, *60*, 2324. (b) Vigroux, A.; Kresge, A. J.; Fishbein, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 4433.

(9) Graymore, J. *J. Chem. Soc.* **1932**, 1353.

was slowly added to the reaction mixture, which bubbled and turned yellow. When the bubbling ceased, the mixture was transferred to a separatory funnel and washed three times with water. The organic layer was dried over Na_2SO_4 and filtered into a 25 mL round bottom flask. The solvent was evaporated under a gentle stream of argon. The crude material was an orange-yellow oil. The product was purified by preparative silica gel TLC using 1:5 ether/hexane as the eluting solvent. The retention factor of the product was 0.4. Further purification was done using preparative TLC and an eluting solvent of 49:1 benzene/ethyl acetate. The retention factor of the product was 0.2: ^{1}H-NMR ($CDCl_3$) δ *E* isomer (88%) 0.90 (t, 3H), 1.28 (m, 2H), 1.45 (m, 2H), 2.13 (s, 3H), 3.55 (t, 2H), 6.10 (s, 2H), *Z* isomer 1.00 (t, 3H), 1.45 (m, 2H), 1.78 (m, 2H), 2.05 (s, 3H), 4.25 (t, 2H), 5.33 (s, 2H). Anal. Calcd: C, 48.27; H, 8.10; N, 16.08. Found: C, 48.50; H, 8.05; N, 15.99.

(*N*-Nitrosoisopropylamino)methyl acetate (10): ^{1}H-NMR ($CDCl_3$) δ *E* isomer (67%) 1.15 (d, 6H), 2.10 (s, 3H), 4.85 (m, 1H), 6.15 (s, 2H), *Z* isomer (33%) 1.45 (d, 3H), 2.05 (s, 3H), 4.85 (m, 1H), 5.33 (s, 2H). Anal. Calcd: C, 44.99; H, 7.55; N, 17.49. Found: C, 45.15; H, 7.71; N, 17.72.

(*N*-Nitrosobutylamino)methyl benzoate (11): ^{1}H-NMR ($CDCl_3$) δ *E* isomer (89%) 0.90 (t, 3H), 1.28 (m, 3H), 1.45 (m, 2H), 3.60 (t, 2H), 6.40 (s, 2H), 7.4–8.1 (4d, 5H), *Z* isomer 1.00 (t, 3H), 1.45 (m, 2H), 1.78 (m, 2H), 4.30 (t, 2H), 5.60 (s, 2H), 7.4–8.1 (4d, 6H).

(*N*-Nitrosobutylamino)methyl pivaloate (12): ^{1}H-NMR ($CDCl_3$) δ *E* isomer (91%) 0.90 (t, 3H), 1.25 (s, 9H), 1.28 (m, 2H), 1.45 (m, 2H), 3.55 (t, 2H), 6.15 (s, 2H), *Z* isomer 1.00 (t, 3H), 1.20 (s, 9H), 1.45 (m, 2H), 1.78 (m, 2H), 4.25 (t, 2H), 5.35 (s, 2H). Anal. Calcd: C, 55.53; H, 9.32; N, 12.95. Found: C, 55.45; H, 9.22; N, 12.84.

Ethyl Acetates. These were synthesized by similar procedures, and the physical properties were previously reported.[8a] We erroneously assigned[8a] the spectral data of the *E* form to the *Z* form and vice versa in the case of **6**. The *E*/*Z* ratio for **7** is 1/4. These data are in agreement with the original assignments made by Wiessler.[5]

Kinetics. Kinetic runs were carried out in 3 mL of aqueous solution in a quartz cuvette stoppered with a rubber septum that was secured by a rubber band. The runs were initiated when solutions containing substrates dissolved in acetonitrile were injected into the cuvettes to give final substrate concentrations between 0.0001 and 0.0002 M. The final concentration of acetonitrile was 0.7% by volume. The kinetics of decay were monitored at 245 or 250 nm for all compounds, except (*N*-nitrosobutylamino)methyl pivaloate (**12**), the decay of which was monitored at 244 nm, using Hewlett Packard 8452A, Milton Roy 3000, or Milton Roy 1001$^+$ spectrophotometers, all of which were thermostated by circulating water baths.

The first-order rate constants were obtained by analyzing the exponential decay of absorbance of the starting material for 3 half-lives or, for reactions with half-lives longer than 1 h, by using the method of initial rates. In the initial rate method, the slope of the plot of absorbance versus time was obtained for the first 5–10% of the reaction. This value of the slope, when divided by both the concentration of substrate and the extinction coefficient, yielded the first-order rate constant, k_{obsd}.

The pH values were obtained after the kinetic runs using a pH meter with attached combination electrode. Two-point calibrations were done prior to recording pH values. Calibrations were carried out using commercially available standards or standards prescribed by *The Merck Index*, 8th ed.[10]

Results

First-order rate constants, k_{obsd}, for the decay of eight α-(acyloxy)nitrosamines were determined in aqueous (1% acetonitrile) buffer systems at 25 °C, ionic strength 1 M ($NaClO_4$). Both exponential decay and initial rate methods were used to determine values of k_{obsd}, and the two methods gave agreement within 6% in the two cases in which they were compared—50% anion and 90% anion acetate buffers with (*N*-nitrosobutylamino)methyl acetate (**9**).

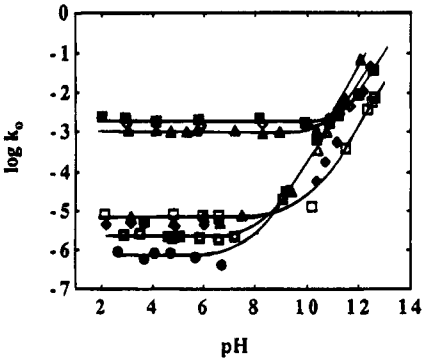


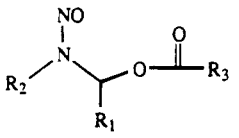
Figure 1. Plots of log k_o, the buffer independent rate constant for decay of α-(acyloxy)nitrosamines, as a function of pH for reactions at 25 °C, ionic strength 1 M ($NaClO_4$), 1% acetonitrile by volume. Symbols for different compounds that are defined by number according to the general structural formula and key given in Table 1: (●) **1**, (boldfaced □) **9**, (△) **10**, (◆) **11**, (□) **12**, (▲) **3**, (◇) **6**, and (■) **7**.

Rate constants, k_o, for the buffer independent decay of the α-(acyloxy)nitrosamines were obtained from the extrapolation to zero buffer concentration of plots of k_{obsd} against buffer concentration. Reasonably accurate values (±10%) could be obtained because the effects of the buffers chosen were minimal. The largest effects of added buffer are summarized briefly. A 5-fold increase in k_{obsd} above the extapolated value at zero buffer concentration was observed for the decay of (*N*-nitrosomethylamino)methyl acetate (**1**) at 0.5 M diphosphate buffer (50% dianion). A 2-fold increase was observed under the same conditions in the decay of (*N*-nitrosobutylamino)methyl acetate (**9**). Morpholine buffer concentrations up to 0.3 M (50%+) increased the value of k_{obsd} above that extrapolated to zero buffer by less than a factor of 3 in the cases of (*N*-nitrosomethylamino)-methyl acetate (**1**) and (*N*-nitrosoisopropylamino)methyl acetate (**10**). Other buffers, the concentrations of which had smaller effects on k_{obsd}, that were employed in the cases of some or all the compounds were formate, acetate, chloroacetate, phosphate, triethylamine, methoxylamine, 2-(4-morpholino)ethanesulfonic acid (MES), morpholino-propanesulfonic acid (MOPS), and 3-(cyclohexylamino)-1-propanesulfonic acid (CAPS). In the case of the ethyl acetates, hydrazine (50%, 1+), morpholine (40%+), and ethylenediamine (50%, 1+) buffers increased the rate constants for decay above the buffer independent rate constant by less than a factor of 2 at 0.3 M. The values of k_o as a function of pH are plotted in Figure 1.

Activation parameters for the pH independent decomposition of three α-acetoxynitrosamines were determined and are summarized in Table 2. In the cases of (*N*-nitrosomethylamino)methyl acetate (**1**) and (*N*-nitrosobutylamino)methyl acetate (**9**), the values of k_o for a given temperature were determined using 50% anion [(*N*-nitrosomethylamino)methyl acetate (**1**)] or 90% and 20% anion [(*N*-nitrosobutylamino)methyl acetate (**9**)] acetate buffers and extrapolating to zero buffer concentration from plots containing at least three buffer concentrations. In the case of 1-(*N*-nitrosoethylamino)ethyl acetate (**3**), the values of k_o for a given temperature were taken as the values of k_{obsd} in cacodylate buffers (50% anion, 0.3

(10) *The Merck Index*, 8th ed.; Stecher, P. G., Ed.; Merck & Co.: Rahway, NJ, 1968.

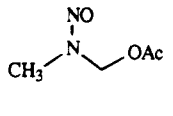
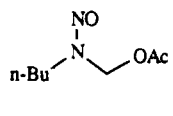
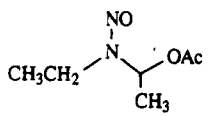
Table 1. Rate Constants for the Decay of α-(Acyloxy)nitrosamines in Water (25 °C, ionic strength 1 M ($NaClO_4$), 1% acetonitrile by volume)



R_1	R_2	R_3	compd no.	$10^3 k_1$[a] (s^{-1})	k_{OH}[b] ($M^{-1}\ s^{-1}$)
H	CH_3	CH_3	1	0.00059	2.53[c]
H	$CH_2(CH_2)_2CH_3$	CH_3	9	0.0020	2.39
H	$CH_2(CH_2)_2CH_3$	Ph	11	0.0045	0.34
H	$CH_2(CH_2)_2CH_3$	$C(CH_3)_3$	12	0.0069	0.15
H	$CH(CH_3)_2$	CH_3	10	0.0059	1.5
CH_3	CH_2CH_3	CH_3	3	1.03	3.2
CH_3	$CH(CH_3)_2$	CH_3	6	1.43	0.99
CH_3	$C(CH_3)_3$	CH_3	7	2.02	0.91

[a] ±<10%. [b] ±<15%, unless otherwise stated. [c] ±<20%.

Table 2. Activation Parameters for the pH Independent Decay (k_1 process) of α-Acetoxynitrosamines in Aqueous Solutions (ionic strength 1 M ($NaClO_4$), 1% acetonitrile by volume

$\Delta H^{\ddagger}$	27 ± 1	24 ± 1	21.7 ± 0.5
$\Delta S^{\ddagger}$	3 ± 3	-5 ± 3	0.7 ± 1.5

M), and a check at 25 °C indicated that the value of k_{obsd} at 0.3 M buffer was different from k_o by <5%.

Discussion

The pH rate profile in Figure 1 indicates that, in the pH range studied, the rate law for the buffer independent decomposition of all the α-(acyloxy)nitrosamines studied contains two terms, as in eq 5: a pH independent term,

$$k_{obsd} = k_1 + k_{OH}[OH^-] \quad (5)$$

k_1, and a hydroxide ion dependent term, k_{OH}. The values of the rate constants for each of the compounds, determined by a nonlinear least squares fit to eq 5, are summarized in Table 1. Some of the fits to the data using these values are indicated by the solid lines in Figure 1 (other fits omitted for clarity).

pH Independent Mechanism (k_1). (A) Formation of *N*-Nitrosiminium Ions. The azide ion-trapping experiments carried out with substituted ethyl acetates (**3**, **6**, and **7**) at a pH at which the pH independent reaction is dominant show that the products quantitatively account for the starting materials and require that ~100% of the reaction occurs through an *N*-nitrosiminium ion intermediate (eq 4).[8a] The value for the entropy of activation for the decomposition of 1-(*N*-nitrosoethylamino)ethyl acetate (**3**; eq 3), $\Delta S^{\ddagger} = 0.7 \pm 1.5$ cal deg^{-1} mol^{-1} (Table 2), is also consistent with rate-limiting dissociation to an ion pair or solvent-separated ions.[11] The typical values for $\Delta S^{\ddagger}$ for the pH independent "water" reactions involving rate-limiting reactions at the carbonyl group of esters, anhydrides, and acyl halides are substantially different outside experimental error, ranging from 40 to 50 cal deg^{-1} mol^{-1}.[12] The original proposal that there are concurrent *O*-alkyl and *O*-acyl group cleavage reactions in the case of **3**, as in eq 3, was based on the observation of less than quantitative limiting yields, with increasing phosphate buffer concentration, of the phosphate adduct **4**. Alternative explanations for this observation that are fully consistent with essentially exclusive reaction by *O*-alkyl cleavage are concurrent denitrosation by phosphate ions of the *N*-nitrosiminium cation and/or concurrent hydration of the *N*-nitrosiminium ion that is catalyzed by phosphate ions.[8]

Three experimental results are also inconsistent with rate-limiting reaction at the carbonyl group in the case of the less reactive methyl acetates (**8**, R_1 = H) as well. First, the values of the entropies of activation (Table 2) for the decomposition of (*N*-nitrosobutylamino)methyl acetate (**9**) and (*N*-nitrosomethylamino)methyl acetate (**1**) of $\Delta S^{\ddagger} = -5 \pm 3$ and 3 ± 3 cal deg^{-1} mol^{-1}, respectively, are, like those of the ethyl acetates, near zero. These values are also different from, and outside the range of, the large negative values observed for the carbonyl attack mechanism for a variety of carboxylic acid derivatives that are hydrolytically both more and less reactive.[12]

Second, the effect on reactivity of phenyl and *tert*-butyl substituents in the acyl portion of the methyl esters is opposite what is expected for a mechanism involving rate-limiting reactions at the carbonyl group of the ester. (*N*-Nitrosobutylamino)methyl benzoate (**11**) and (*N*-nitrosobutylamino)methyl pivaloate (**12**) decompose with pH independent rate constants that are larger than that of the corresponding acetate **9** by factors of 2.3 and 3.4, respectively. By contrast, benzoyl and pivaloyl esters that decompose by carbonyl attack mechanisms are typically 1−2 orders of magnitude less reactive than their acetate analogues due to unfavorable steric interactions in the transition states and tetrahedral intermediates involved in these reactions and to the ground state stabilization of the carbonyl group by the benzene ring of benzoate esters.[13]

Third, the large sensitivity of the reaction rate constant to substituents on the nitrogen is unexpected for rate-limiting reaction involving the carbonyl group. The slope of the plot of Figure 2, $\rho^* = -5.99$ ($r^2 = 0.977$), indicates that substituents on the nitrogen experience a large increase in positive charge in going from the ground state to the transition state. By comparison the value of ρ^* is −3 to −4.5 for substituents attached to the "remaining group" in the acid-catalyzed hydrolysis of acetals that occurs with the rate-limiting formation of an oxo carbocation.[14] The effect of substituents on the nitrogen upon the rate constants for the rate-limiting reactions of nucleophiles at the carbonyl group is predicted to be substantially smaller due to the remoteness of the substitution. The sensitivity to alkyl group substitution in the alcohol moiety of the rate constants for water-catalyzed hydrolysis of simple esters is unknown. However, the sensitivity of the rate constants for acid-

(11) Hovinen, J.; Finneman, J. I.; Satapathy, S. N.; Ho, J.; Fishbein, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 10322.

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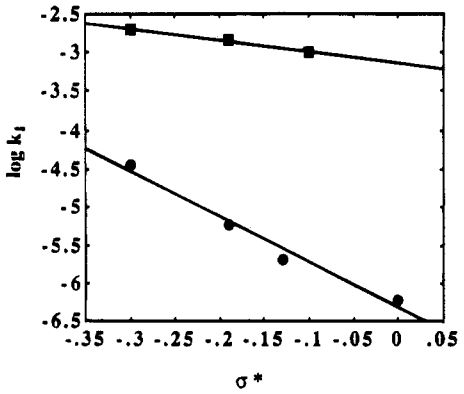
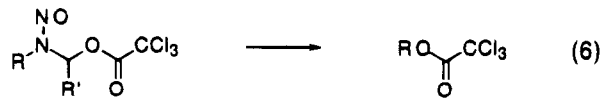


Figure 2. Plot of log k_1, the pH independent rate constant for decay of α-acetoxynitrosamines at 25 °C, ionic strength 1 M, 1% by volume acetonitrile, against σ^*: (●) methyl acetates, point for the *tert*-butyl group from ref 6, and (■) ethyl acetates.

catalyzed hydrolysis, in which the transition state contains a full positive charge compared to the uncharged ground state, sets an upper limit for sensitivity expected for the uncatalyzed reaction. Indeed, ρ^* for the acid-catalyzed hydrolysis of acetate esters that occurs by rate-limiting carbonyl attack is smaller and *of opposite sign*, $\rho^* = 1.7$ ($r = 0.97$).[15] The sensitivity to substitution at the position 2 atoms removed from the alcohol oxygen, analogous to the position of substitution in the present case, is expected to be smaller with a value of ρ^* that is more nearly equal to zero.

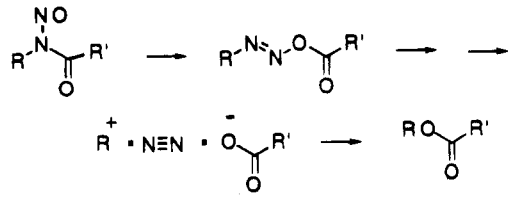
In summary, the simplest α-acetoxyalkylnitrosamine, **1**, and those with more electron-donating alkane substituents, in R_1 and R_2 of **8** (eq 4), decompose in a pH independent reaction that involves the formation of *N*-nitrosiminium ion intermediates. In the physiological pH range, this mechanism of decomposition is competitive with the hydroxide ion-catalyzed mechanism or is the dominant reaction mechanism, depending upon the substituents R_1 and R_2. The contribution of the *N*-nitrosiminium ion-forming reaction is expected to diminish with the introduction of electron-withdrawing substituents in R_1 or R_2. This is predicted because of the expected decrease in the magnitude of the rate constants for reactions involving the formation of *N*-nitrosiminium ions and because of a corresponding increase in the rate constants for both the hydroxide ion-catalyzed and pH independent "water-catalyzed" hydrolysis mechanisms involving rate-limiting reactions at the carbonyl group of the ester function.

(B) No Anchimeric Assistance. Anchimeric assistance involving nitrosooxygen attack at the carbonyl carbon is likely responsible for the formation in nonpolar solvents of esters from α-(acyloxy)nitrosamines that contain strong electron-withdrawing groups in the acyl functionality (eq 6).[5,18] This presumption is based on the



(6)

precedent of the nitrosamide and related rearrangements[19] that yield esters by recombination of nitrogen-separated ion pairs, as in eq 7 (or by displacement on a



(7)

diazonium ion by the carboxylate counterion), formed in the decomposition of diazo ester intermediates.

Such a mechanism does not appear to be operative in the aqueous decomposition chemistry of the simple[1] α-(acyloxy)nitrosamines studied here for the following reasons.

(1) The absence of a decrease in reactivity of the (*N*-nitrosobutylamino)methyl esters as the leaving group is changed from acetate (**9**) to benzoate (**11**) or pivaloate (**12**) militates against anchimeric assistance by nitroso oxygen attack at the carbonyl carbon of the ester. The *E* and *Z* forms of the (*N*-nitrosobutylamino)methyl esters are likely in rapid exchange relative to the decomposition reaction.[20] If the *Z* form is significantly more reactive than the *E* form, then much of the decomposition reaction must occur through the *Z* form because the two forms differ by only ~1 kcal/mol in energy ($E/Z = 7$). As discussed in the previous section, a decrease in reactivity would be predicted in changing the leaving group from acetate to benzoate or pivaloate, opposite of what is observed.

(2) The products reported previously[8a] for the decomposition of ethyl acetates **6** and **7** in the presence of 0.2 M azide ion in aqueous solutions are not expected for anchimeric assistance involving nitroso oxygen attack at the carbonyl group. Essentially quantitative yields of the corresponding azide adducts and ammonium ions are obtained from **6** and **7** at 0.2 M azide ion, as in eq 4. The percentages of **6** and **7** that are in the *Z* form are significant: 20% for **6** and 80% for **7**. If the proposed anchimeric assistance mechanism were operative, a minimum[21] of 20%, from **6**, and 80%, from **7**, of the products should be those derived from the diazoester that would be an intermediate in such a reaction. In the presence of azide ion, these products would include (from **6**) 2-propanol, propene, propyl acetate, and 2-propyl azide and (from **7**) *tert*-butyl alcohol, isobutene, *tert*-butyl acetate, and *tert*-butyl azide, none of which were observed.

(C) Differences between Methyl and Ethyl Acetates. There is a large difference between the methyl and ethyl acetates (eq 4; **8**, R_1 = H and CH_3, respectively) in the sensitivity of the rate constants (k_1) for the pH independent decomposition to substituents on the amino nitrogen atom. Figure 2 illustrates that ρ^* for the ethyl

(15) Based on three points including the methyl, ethyl, and isopropyl groups.[16] The same order of reactivity is observed in the acid-catalyzed hydrolysis in aqueous 62% acetone solutions.[17]

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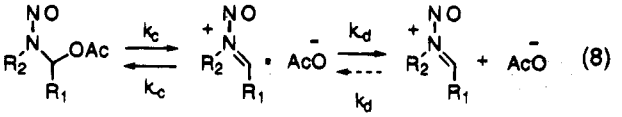
(21) If the isomers are in rapid exchange[20b] relative to the rate of decomposition, then the yields of products from the "anchimeric assistance" pathway would be greater. If the isomers are not in rapid exchange, the observation that these compounds decompose with clean first-order kinetics indicates no measureable anchimeric assistance.

acetates ($\rho^* = -1.5$, $r^2 = 0.990$) is nearly 4-fold smaller than ρ^* for the methyl acetates.

One possible explanation for the decreased sensitivity compared to the methyl acetates is that, in the case of the ethyl acetates, there is a shift to an earlier transition state for formation of the nitrosiminium ion. Such a shift would be consistent with a Hammond effect that is expected on the basis of the stabilizing interaction of a methyl group, compared to hydrogen, with the carbocationic resonance form of the *N*-nitrosiminium ion.

It is alternatively plausible that the rate-limiting step for decay of the methyl acetates is different from that of the ethyl acetates; the differences in the transition states for the two steps could account for the differences in sensitivity to substituents. For the purposes of illustration, the k_1 process could be divided into two microscopic steps, as in eq 8, in which the intimate ion pair **13** is the



(8)

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immediate product of carbon–oxygen bond fission of the ester. If the step k_c were rate limiting for the solvolysis of the ethyl acetates while the k_{-d} step were rate limiting for the methyl acetates, then the substituent effects on the solvolysis reactions of ethyl and methyl acetates would be expected to be different and consistent with what is observed; the value of ρ^* for solvolysis of the ethyl acetates would be less negative, due to *partial* bond cleavage in the rate-limiting step, k_c, than in the case of the methyl acetates for which the rate-limiting step, k_{-d}, is preceded by *complete* bond fission.

Such a difference in the rate-limiting step is plausible on the basis of the small amount of quantitative data that we have so far. For the ethyl acetates studied, the k_c step in eq 8 is likely mostly or entirely rate limiting as shown by the following analysis. Upper limit values for the rate constants[22] for capture by acetate ion of the nitrosiminium ions from **3**, **6**, and **7** are near or below the value of $(5-9) \times 10^8\ M^{-1}\ s^{-1}$ determined for encounter limited capture (k_d rate limiting, eq 8) that is based on the reaction of 1-phenethyl cations with carboxylate anions.[23] This means that the capture of the nitrosiminium ions is partly or wholly activation limited—k_{-c} is partly or wholly rate limiting. In the reverse direction, by microscopic reversibilty, solvolysis of the ethyl acetates occurs with k_c partly or wholly rate limiting. In the case of the methyl acetates, the cationic intermediates are likely more reactive than the analogously substituted ethyl acetates due to the absence in the former of the additional cation-stabilizing methyl group. The larger rate constants, k_{-c}, in the case of the cations from the methyl acetates, in the predicted absence of a difference in k_d, suggest that in the solvolysis of the methyl acetates the k_{-d} step could be predominantly rate limiting.

Hydroxide Ion Reaction (k_{OH}). Roller and coworkers[4] first suggested the carbonyl attack mechanism for this reaction, and our data on the effect of substituents in the acyl group are consistent with this conclusion. In the case of the (*N*-nitrosobutylamino)methyl esters, the decreased reactivity of the benzoate (**11**) and pivaloate (**12**) esters compared to acetate ester **9**, by factors of 7 and 16, respectively, is as expected for a mechanism involving a nucleophilic reaction at the carbonyl group.[13]

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Supporting Information Available: Experimental conditions and values of k_{obsd} and k_o for the decomposition of α-(acyloxy)nitrosamines (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(22) The upper limit values of rate constants for capture of the cations from **3**, **6**, and **7** by acetate ion are 2×10^9, 4.8×10^8, and $6.3 \times 10^7\ M^{-1}\ s^{-1}$ and are calculated from the values of k_{H_2O} determined earlier[8a] and the acetate ion-to-water selectivity, k_{Ac}/k_{H_2O}, for the nitrosiminium ion **2** of $k_{Ac}/k_{H_2O} = 21\ M^{-1}$.[8b] This selectivity value is likely larger than those for the nitrosiminium ions from the ethyl acetates **3**, **6**, and **7** on the basis of their greater reactivity[8] and the reactivity–selectivity principle.

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