orously stirred overnight at room temperature and then diluted in methanol (2 mL). After filtration over Celite 545, the filtrate was evaporated under vacuum, diluted in ether, and then dried over magnesium sulfate. Flash chromatography (elution with methylene chloride–ethyl acetate, 65:35) gave the methyl ester LTB_4 **12** (41 mg; 70%): $[\alpha]^{20}_D$ +4.6° (*c* 0.39, CCl_4); IR (NaCl film) 3400 (OH), 3000 (=CH), 1730 (C=O), 1595 (C=C—C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (1 H, dd, *J* = 14.5 Hz, *J* = 11 Hz, H_8), 6.3 (1 H, ddd, *J* = 15 Hz, *J* = 10.5 Hz, *J* = 1 Hz, H_{10}), 6.21 (1 H, dd, *J* = 14.5 Hz, *J* = 10.5 Hz, H_9), 6.07 (1 H, t, *J* = 11 Hz, H_7), 5.77 (1 H, dd, *J* = 15 Hz, *J* = 6.3 Hz, H_{11}), 5.55 (1 H, m, *J* = 10.5 Hz, *J* = 7 Hz, H_{15}), 5.54 (1 H, dd, *J* = 11 Hz, *J* = 9.5 Hz, H_6), 5.34 (1 H, m, *J* = 10.5 Hz, *J* = 7 Hz, H_{14}), 4.57 (1 H, m, *J* = 9.5 Hz, H_5), 4.2 (1 H, q, *J* = 6.3 Hz, H_{12}), 3.65 (3 H, s, OCH_3), 2.33 (4 H, m, H_4) and H_{13}), 2.02 (2 H, q, *J* = 6 Hz, H_{16}), 1.72–1.60 (5 H, m, aliphatics H and OH), 1.36–1.21 (7 H, m, aliphatics H and OH), 0.87 (3 H, t, *J* = 6.5 Hz, CH_3-20).

(5*S*,6*Z*,8*E*,10*E*,12*R*,14*Z*)-5,12-Dihydroxyeicosa-6,8,10,14-tetraenoic Acid (1). To a solution of methyl ester **12** (400 μg, 1.1 mmol) in methanol (320 μL) and water (80 μL) was added potassium carbonate (1.6 mg, 11 μmol). After the mixture was stirred for 18 h at room temperature under argon atmosphere, the methanol was evaporated by a stream of argon and the residue was purified on a C_{18}-Sep-Pak cartridge. Elutions with water (5 × 1 mL) removed the carbonate salts (pH = 8.9 to neutrality). Then, two elutions (2 × 2 mL) with methanol afforded leukotriene B_4 (360 μg, 95%). The methanol was removed under a stream of argon. The retention time of LTB_4 by HPLC analysis was identical with that of the natural product (column Spherisorb ODS C_{18}), eluent: 15–100% of CH_3CN/H_2O = 0.05% H_3PO_4, 35 min).

Registry No. 1, 71160-24-2; 2, 111137-93-0; 3, 156-60-5; 4, 90108-28-4; 5, 97579-36-7; 6, 76745-20-5; (*Z*)-7a, 111037-26-4; (*E*)-7a, 111037-35-5; (*Z*)-7b, 111037-27-5; (*E*)-7b, 111037-36-6; 8, 136693-10-2; 9, 136693-11-3; (*Z*)-10a, 111037-31-1; (*E*)-10a, 111037-37-7; (*Z*)-10b, 111037-32-2; (*E*)-10b, 106031-61-2; 11, 136693-12-4; 12, 83058-42-8; (bromomethylene)triphenylphosphorane, 39598-55-5.

Supplementary Material Available: ^1H NMR spectra for compounds 2, 4, 7bZ, 7bE, 8, 9, 10a, 10b, 10bE, 11, and 12 (11 pages). Ordering information is given on any current masthead page.

1,3-Dialkyl-3-acyltriazenes: Products and Rates of Decomposition in Acidic and Neutral Aqueous Solutions

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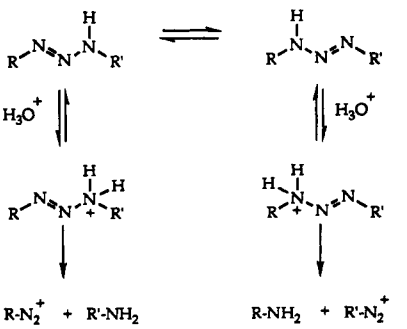
The products and mechanism of hydrolytic decomposition of a series of 1,3-dialkyl-3-acyltriazenes were studied in both acidic and neutral buffers. In the acidic region, the products are alkyl alcohols derived from the N(1) alkyl group and amides derived from the intact N(3) portion of the molecule. The solvent deuterium isotope effect (k_{H_2O}/k_{D_2O}) is less than 1.0. The mechanism is specific acid catalyzed, involving rapid reversible protonation of the 3-acyl group followed by scission of the N(2)–N(3) bond to generate an amide and an alkyl diazonium ion. The (2-hydroxyethyl)diazonium ion gives ethylene glycol and acetaldehyde, while the (2-chloroethyl)diazonium ion yields 2-chloroethanol. In the neutral region, the products are similar to those found in acidic buffers, alkyl alcohols, and amides. At this pH the (2-chloroethyl)diazonium ion produces ethylene glycol and acetaldehyde in addition to 2-chloroethanol. The solvent deuterium isotope effect (k_{H_2O}/k_{D_2O}) is greater than 1.0. The mechanism involves unimolecular heterolysis of the N(2)–N(3) bond to form an amide anion and an alkyldiazonium ion. The methyldiazonium ion leads to incorporation of deuterium in the methyl group of the products, indicating the existence of an equilibrium between the metastable methyldiazonium ion and diazomethane.

Introduction

The preparation[1] and proteolytic decomposition of 1,3-dialkyltriazenes[2] and 1,3,3-trialkyltriazenes[3] have been investigated in substantial detail. These simple alkyltriazenes decompose rapidly in aqueous solutions by an acid-catalyzed process which results in the formation of alkylamines and alkyl alcohols, the latter via an alkyldiazonium ion intermediate.[2] The situation is more complicated for unsymmetrical 1,3-dialkyltriazenes,[4] which exist in two rapidly equilibrating tautomeric forms and give rise competitively to two different pairs of alkyldiazonium ions and alkylamines (Scheme I). The rate of decomposition and product distribution for unsymmetrical 1,3-dialkyltriazenes is controlled by the stability of the two possible alkyldiazonium ions and the population and basicity of the two tautomeric forms. The intermediate formed in the rate-determining step of the hydrolytic

Scheme I



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[⊥] NCI—Frederick Cancer Research and Development Center.

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(2) Smith, R. H.; Denlinger, C. L.; Kupper, R.; Mehl, A. F.; Michejda, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 3726–3730.
(3) Smith, R. H.; Denlinger, C. L.; Kupper, R.; Koepke, S. R.; Michejda, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 1056–1059.

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Scheme II

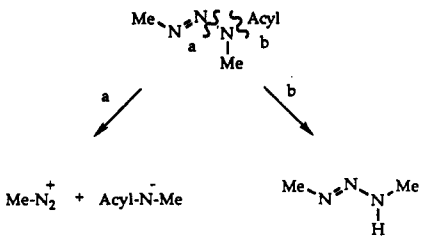
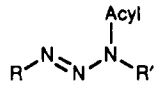


Table I. Structures and Abbreviations of Compounds Investigated



abbrev	R	R′	acyl
DMA	Me	Me	acetyl[a]
DMC	Me	Me	carbethoxy
DMM	Me	Me	methylcarbamoyl[c]
MHM	Me	2-hydroxyethyl	methylcarbamoyl
HMA	2-hydroxyethyl	Me	acetyl
HMC	2-hydroxyethyl	Me	carbethoxy
HMM	2-hydroxyethyl	Me	methylcarbamoyl
CMA	2-chloroethyl	Me	acetyl
CMC	2-chloroethyl	Me	carbethoxy
CMM	2-chloroethyl	Me	methylcarbamoyl
HBzM	2-hydroxyethyl	benzyl	methylcarbamoyl
CBzM	2-chloroethyl	benzyl	methylcarbamoyl

[a] $CH_3C(O)$–. [b] $CH_3CH_2OC(O)$–. [c] $CH_3NHC(O)$–.

decomposition of alkyltriazenes is an alkyldiazonium ion, not the corresponding alkyl carbocation.

Several years ago we reported the preparation of a new class of alkyltriazenes, 1,3-dimethyl-3-acyltriazenes.[5] These derivatives are more stable to proteolytic decomposition than the parent 1,3-dimethyltriazene. Although the product of hydrolysis, the methyldiazonium ion, is the same, the mechanism of decomposition of 1,3-dimethyl-3-acyltriazenes is more complex. Three separate, pH-dependent pathways are evident: acid and base catalysis at the respective extremes of the pH scale and a pH-independent process in the near neutral region.[5] Mechanistically, two distinct modes of decomposition can be envisioned as shown in Scheme II. The first is characterized by heterolytic cleavage of the N(2)–N(3) bond to generate the methyldiazonium ion from the N(1) residue and an amide species from N(3). The second pathway proceeds by initial deacylation, cleavage of the N(3)–acyl bond, to form 1,3-dimethyltriazene which subsequently undergoes rapid hydrolysis in the manner described above.

In this paper, we present a more detailed investigation of the products and kinetics of the acid-catalyzed and uncatalyzed decomposition of 1,3-dialkyl-3-acyltriazenes. The compounds studied are listed in Table I. The primary objective of the study was to distinguish between the two general mechanistic pathways, heterolysis and deacylation, in each pH domain.

Experimental Section

Safety Note. Triazenes are potent biological alkylating agents and should be considered to be toxic and potentially carcinogenic. Efficient hoods and protective clothing should be used at all times. Alkyl azides, the starting materials for most of the syntheses described, are treacherously explosive substances and should be treated with extreme caution. Wherever possible, these substances should only be handled in solution.

Materials. All chemicals were reagent grade (Aldrich Chemical Co.), used as purchased without further purification. The preparation of the triazenes used in this study have been previously published.[5,6] 1-(2-Hydroxyethyl)-3-benzyl-3-(methylcarbamoyl)triazene (HBzM) and 1-(2-chloroethyl)-3-benzyl-3-(methylcarbamoyl)triazene (CBzM) were prepared in a similar fashion. Their spectral properties are presented below. The preparation of 1-methyl-3-(2-hydroxyethyl)-3-(methylcarbamoyl)triazene (MHM) is also described below. Buffers for kinetic measurements were prepared as previously reported[2] with water distilled from $KMnO_4$. A Fisher Accumet Model 825MP digital pH meter and a Fisher (13-620-270) high ionic strength combination electrode (calomel reference) were used in pH measurements. UV spectra were recorded on either a Hewlett-Packard Model 8450A double-beam diode-array processor or a Shimadzu Model UV-2100 spectrophotometer. NMR spectra were obtained on a Varian XL-200 spectrometer. Exact mass measurements were determined on either a VG-Micromass, ZAB-2F (for FAB spectra), or a VG 70-250 (for EI spectra) mass spectrometer. Mass measurements were confirmed by peak matching. The purity of all title compounds was judged to be >95% by ^1H NMR spectral determinations (spectra available as supplementary material).

1-(2-Hydroxyethyl)-3-benzyl-3-(methylcarbamoyl)triazene (HBzM): UV (CH_3CN) λ_{max} 243 nm (log ϵ 3.98); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.28 (1 H, t, J = 5.9 Hz), 2.98 (3 H, d, J = 6.9 Hz), 3.81 (4 H, m), 5.13 (2 H, s), 6.38 (1 H, broad), 7.24 (5 H, m); proton decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 27.02, 43.91, 61.02, 63.61, 127.0, 127.89, 128.26, 136.79, 155.52; exact mass calcd m/z for MH^+, $C_{11}H_{17}N_4O_2$ 237.1351, found 237.1348 (by FAB).

1-(2-Chloroethyl)-3-benzyl-3-(methylcarbamoyl)triazene (CBzM): UV (CH_3CN) λ_{max} 247 nm (log ϵ 3.96); ^1H NMR ($CDCl_3$, Me_4Si) δ 2.97 (3 H, d, J = 4.8 Hz), 3.77 (2 H, t, J = 5.7 Hz), 3.98 (2 H, t, J = 5.7 Hz), 5.14 (2 H, s), 6.34 (1 H, broad), 7.25 (5 H, m); proton decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 27.02, 41.93, 43.71, 62.49, 126.92, 128.15, 128.24, 136.52, 155.30; exact mass calcd m/z for MH^+, $C_{11}H_{16}ClN_4O$ 255.1013, found 255.1040 (by FAB).

Preparation of 1-Methyl-3-(2-hydroxyethyl)-3-(methylcarbamoyl)triazene (MHM). A 1.0 M solution (100 mL) of tetra-*n*-butylammonium fluoride in tetrahydrofuran was added dropwise to a stirred solution of 1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyl-3-(methylcarbamoyl)triazene[6] (27.0 g, 0.095 mol) in 256 mL of tetrahydrofuran at −10 °C. The reaction solution was allowed to warm gradually to 10 °C over 1 h. The volume of the solution was then reduced 50% in a rotary evaporator at 25 °C and the resultant solution chromatographed on a column of 250 g of silica gel 60 (EM, neutral, 70–230 mesh) packed in ether. The column was eluted with 5 L of ether. The final 3 L of eluant was concentrated in a rotary evaporator, and the residue (6.7 g) was recrystallized from methylene chloride–ether to give 4.24 g of 1-(2-hydroxyethyl)-3-methyl-3-(methylcarbamoyl)triazene (HMM)[6] (0.0265 mol, 27.8%): mp 72–74 °C. The spectral properties of this compound have been previously reported.[6]

The mother liquor from the recrystallization was evaporated, and the residue (2.2 g) was rechromatographed on a column of 25 g of silica gel 60 packed in 25% (v/v) ether in petroleum ether (30–60 °C). The column was eluted with a graduated series of solvents: 25% (v/v) ether in petroleum ether to 60% (v/v) methylene chloride in ether. Two substances were separated by this method. Ether–petroleum ether eluted an additional 0.4 g of HMM. Methylene chloride–ether mixtures gave 0.2 g (1.25×10^{-3} mol, 1.3%) of a different substance, colorless needles of mp 73–75 °C. The R_f (0.49) of this new material was slightly less than the R_f (0.53) of HMM on a silica gel 60 (EM) TLC plate eluted with 25% (v/v) methylene chloride in ether and visualized with I_2. Spectral analysis showed this compound to be 1-methyl-3-(2-hydroxyethyl)-3-(methylcarbamoyl)triazene (MHM): UV (CH_3CN) λ_{max} 245 nm (log ϵ 3.94); ^1H NMR ($CDCl_3$, Me_4Si) δ 2.89 (3 H, d, J = 3.9 Hz), 3.26 (1 H, t, J = 5.4 Hz), 3.55 (3 H, s), 3.61 (2 H, q, J = 5.3), 4.11 (2 H, d, J = 5.3), 6.36 (1 H, broad);

(4) Smith, R. H., Jr.; Wladkowski, B. D.; Mehl, A. F.; Cleveland, M. J.; Rudrow, E. A.; Chmurny, G. N.; Michejda, C. J. *J. Org. Chem.* **1989**, *54*, 1036–1042.

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Table II. Rates[a] of Decomposition of 1,3-Dialkyl-3-acyltriazenes[b] as a Function of pH in 0.1 M Lysine Buffers[c] at 70 °C

pH	DMA	DMC	DMM	MHM	HMA	HMC	HMM	CMA	CMC	CMM
2.1	1.08E-02[d]				7.02E-03			9.85E-04	1.30E-02	
2.3	7.18E-03				4.71E-03	2.63E-02		6.31E-04	8.60E-03	
2.5	5.05E-03	2.56E-02		8.95E-02	2.82E-03	1.66E-02		4.57E-04	5.79E-03	
3.0	1.91E-03	1.08E-02	1.02E-01	3.16E-02	1.31E-03	7.01E-03	4.95E-02	1.62E-04	1.82E-03	1.60E-02
3.5	1.13E-03	5.78E-03	3.63E-02	1.09E-02	7.11E-04	3.90E-03	1.81E-02	8.26E-05	7.62E-04	6.19E-03
4.0		3.86E-03		4.68E-03			5.87E-03			
4.5			3.79E-03				1.87E-03			6.39E-04
5.5	7.45E-04	3.01E-03	1.13E-03	1.47E-03	4.48E-04	2.29E-03	5.63E-04	4.38E-05	2.57E-04	1.39E-04
6.5										
7.5	7.16E-04	2.96E-03	3.34E-04	1.34E-03	4.53E-04	2.22E-03	2.16E-04	4.46E-05	2.46E-04	2.46E-05
8.5										1.89E-05
9.5	8.07E-04	2.93E-03	2.86E-04	1.37E-03	4.96E-04	2.25E-03	1.93E-04	1.90E-04	3.00E-04	2.73E-05
10.5								5.40E-05	5.13E-04	
11.5	1.34E-03	3.61E-03	2.86E-03	1.30E-03	1.16E-03	3.38E-03	1.98E-04	2.90E-03	2.33E-03	1.02E-04
12.5	1.32E-02	1.55E-02	3.01E-04	1.54E-03	2.16E-02	1.86E-02	2.50E-04	4.65E-02	1.87E-02	9.60E-04

[a] The rate constants (k_{obsd} s^{-1}) are an average of at least two independent runs varying no more than ±3%. [b] Triazene initial concentration 3.0×10^{-5} M. [c] Ionic strength of 0.25 M held constant with added $NaClO_4$. [d] Read as 1.08×10^{-2}.

proton decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 27.47, 43.45, 49.44, 61.32, 157.01; exact mass calcd m/z for $C_5H_{12}N_4O_2$ 160.0960, found 160.0962 (by EI).

Product Studies. The products of the decomposition of the various triazenes were determined by carrying out the reactions in 0.05 M buffers of sodium phosphate or sodium phosphate plus 0.05 M maleic acid in D_2O adjusted to the appropriate pH with a D_2O solution of NaOD. Buffer was added to a weighed amount of triazene, sealed in vials containing a magnetic stirring bar, and incubated with stirring at 70 °C in an oil bath for at least four half-lives, as determined by separate kinetic measurements. The triazene concentration in each reaction was 0.050 M. At the end of the reaction, an aliquot of the reaction solution was removed and analyzed by ^1H NMR. The pH of each final reaction mixture was measured and in each case had varied no more than ±0.8 pH units for the pH 7.5 runs and ±0.1 for the pH 2.5 runs. Assignment of the NMR peaks arising from the various products was made by comparison with authentic samples and confirmed by coincidence of peaks upon addition of authentic materials. In representative reactions, the amide products were isolated by methylene chloride extraction, purified by distillation or recrystallization and compared spectroscopically with authentic materials. Yields were determined by comparative integration of the product peaks and confirmed by use of the vinyl signal from the maleic acid as an internal standard. In the case of the 1-methyltriazenes, corrections were made for small amounts of alkylation of maleic acid, the vinyl signals of the methyl ester being distinct from those of the free acid. (Representative spectra available as supplementary material.)

Kinetic Studies. Rates of triazene decomposition in aqueous solution were followed spectrophotometrically on either a Hewlett-Packard Model 8450A double-beam diode-array processor or a Shimadzu Model UV-2100 spectrophotometer. In the case of the Shimadzu spectrophotometer, the analogue output of absorbance versus time was recorded on an Apple IIe computer equipped with an Interactive Microwave Ada-Lab data acquisition board. The reaction solutions were contained in thermostated 1-cm cells, and the temperature was held constant to within ±0.1 °C. The disappearance of each triazene was followed by monitoring the change in absorbance at its respective λ_{max} (see references on preparation in Materials section). In a typical kinetic run, the reaction cuvette was charged with 1.341 mL of a 0.1 M lysine buffer (ionic strength = 0.25 M maintained with added $NaClO_4$), and the reaction was initiated by the addition of 9 μL of a 4.5×10^{-3} M solution of the triazene in acetonitrile; the final triazene concentration was 3.0×10^{-5} M. The reference cuvette contained 1.341 mL of buffer and 9 μL of acetonitrile. Volume measurements were made using calibrated continuously adjustable digital micropipettes (Gilson Pipetman). A minimum of 100 absorbance vs time readings were obtained over 3.5 half-lives. The first-order rate constants were calculated from these data by means of a computer program based on the Guggenheim approximation least-squares method.[7]

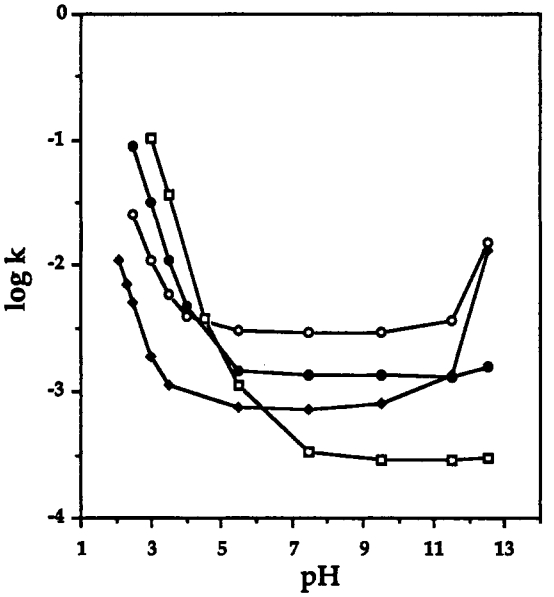

Figure 1. 1,3-Dimethyl-3-acyltriazene pH profiles in 0.1 M lysine buffer, 70 °C: DMC (○), MHM (●), DMA (♦), DMM (□).

Results

pH Dependence of the Rate of Decomposition. The rate of decomposition of each triazene was determined over a pH range beginning near 2.0 and extending to either pH 13.0 or the highest pH at which the rate was not too rapid to be measured. The observed rate constants, which were cleanly first-order, are listed in Table II. The graphic display of these data in Figures 1–3 clearly shows the triphasic nature of the dependence of rate upon pH. Each compound shows a region in which the rate is inversely proportional to pH and a region in which the rate is directly proportional to pH (with the possible exception of MHM). These regions are separated by a pH independent region in the near neutral pH range.

Solvent Deuterium Isotope Effect. Solvent deuterium isotope effects were determined by carrying out parallel reactions in aqueous and deuterium oxide buffers at the same pH (pD), ionic strength, and temperature. The pH of the deuterium oxide buffer was corrected according to the relationship $pD = pH_{nominal} + 0.4$.[8] As in the pH dependence studies, the buffer contained 0.1 M lysine with the ionic strength = 0.25 M, maintained with added Na-

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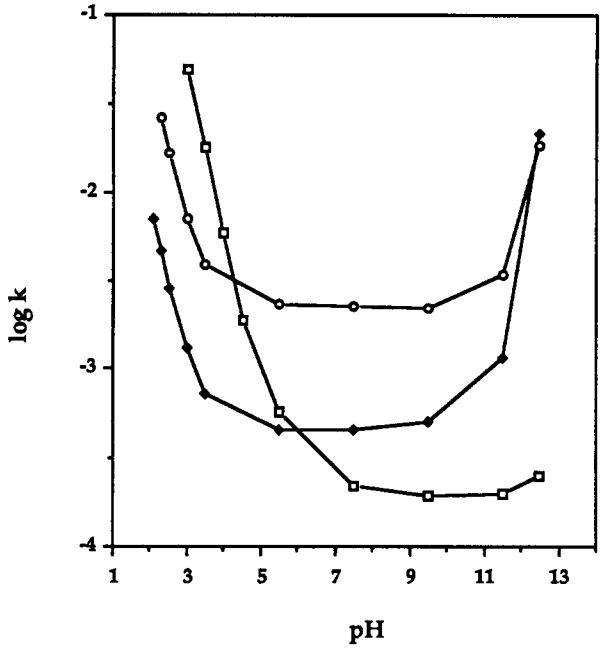


Figure 2. 1-(2-Hydroxyethyl)-3-methyl-3-acyltriazene pH profiles in 0.1 M lysine buffer, 70 °C: HMC (○), HMA (♦), HMM (□).

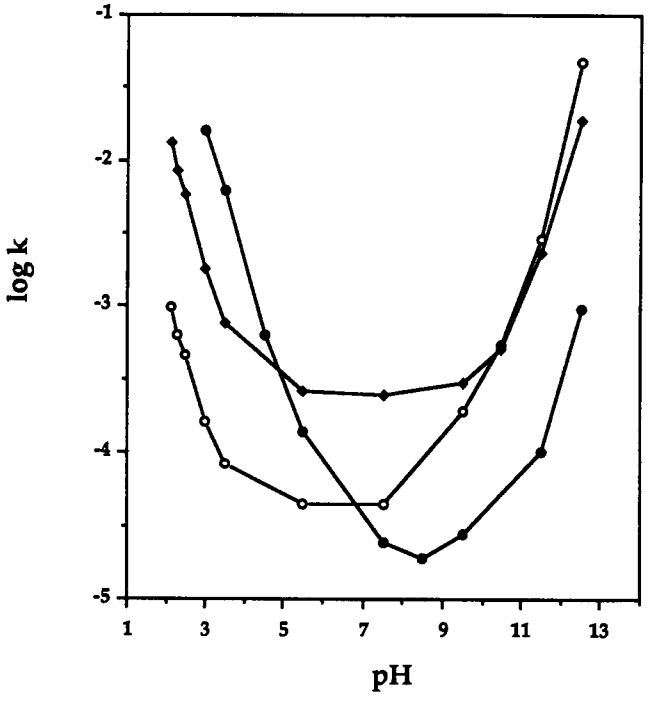


Figure 3. 1-(2-Chloroethyl)-3-methyl-3-acyltriazene pH profiles in 0.1 M lysine buffer, 70 °C: CMC (♦), CMA (○), CMM (●).

ClO_4. The solvent isotope effect was measured at pH 3.0 and 7.5. The data are presented in Table III. It is clear that the observed rate constant for all of the compounds is faster in D_2O than in H_2O buffer at pH 3.0, but slower at pH 7.5.

Product Studies. The products of the decomposition of each of the triazenes were determined by ^1H NMR analysis at pH 2.5 and 8.0 in 0.05 M phosphate buffer and in 0.05 M phosphate buffer containing 0.05 M maleic acid. In the latter buffer, the vinyl proton signal of maleic acid was used as an internal standard to determine quantitative yields. Buffers containing phosphate alone were used to double check yields in those compounds where small amounts of alkylation (primarily methylation) of maleic acid occurred. These data are presented in Table IV. For

Table III. Solvent Isotope Effects on the Rates[a] of Decomposition of 1,3-Dialkyl-3-acyltriazenes in Aqueous Buffers[b]

	pH 3.0			pH 7.5		
	k_{H_2O}	k_{D_2O}	k_{H_2O}/k_{D_2O}	k_{H_2O}	k_{D_2O}	k_{H_2O}/k_{D_2O}
DMA	1.91E-03[c]	3.61E-03	0.53	7.16E-04	6.09E-04	1.18
DMC	1.08E-02	1.45E-02	0.74	2.96E-03	2.59E-03	1.14
DMM	1.02E-01	1.59E-01	0.64	3.34E-04	3.08E-04	1.09
MHM	3.16E-02	4.28E-02	0.74	1.33E-03	1.16E-03	1.15
HMA	1.31E-03	2.33E-03	0.56	4.53E-04	4.15E-04	1.09
HMC	7.01E-03	9.16E-03	0.76	2.22E-03	1.91E-03	1.16
HMM	4.95E-02	7.76E-02	0.64	2.16E-04	1.91E-04	1.13
CMA	1.62E-04	3.05E-04	0.53	4.37E-05	3.93E-05	1.11
CMC	1.82E-03	2.89E-03	0.63	2.46E-04	2.04E-04	1.21
CMM	1.60E-02	2.74E-02	0.58	2.46E-05	2.45E-05	1.00
HBzM				5.15E-04	4.41E-04	1.17

[a] The rate constants (k_{obsd} s^{-1}) are the average of at least two separate determinations. [b] 0.1 M lysine buffers, ionic strength 0.25 M maintained with $NaClO_4$, 70 °C. [c] Read as 1.91×10^{-3}.

Table IV. Products and Yields from the Hydrolysis of 1,3-Dialkyl-3-acyltriazenes in Aqueous Buffers[a] at 70 °C.

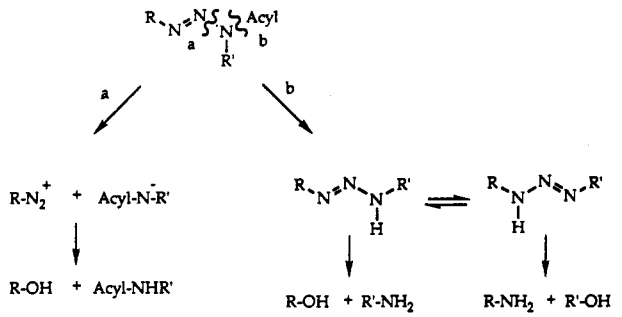
	N3 product[b] at pH 2.5 and 8.0	N1 products[c]	pH 2.5	pH 8.0
DMA	*N*-methylacetamide	methanol	100[d]	98.7[e]
DMC	ethyl *N*-methylcarbamate	methanol	97.2[d]	78.4[f]
DMM	*N,N'*-dimethylurea	methanol	98.1[d]	94.9[g]
MHM	*N*-(2-hydroxyethyl)-*N'*-methylurea	methanol	100[d]	85.5[h]
HMA	*N*-methylacetamide	ethylene glycol	57.5	44.6
		acetaldehyde[i]	40	30.5
HMC	ethyl *N*-methylcarbamate	ethylene glycol	60.3	40.6
		acetaldehyde[i]	35.3	36.5
HMM	*N,N'*-dimethylurea	ethylene glycol	64.6	39.7
		acetaldehyde[i]	29.2	33.7
CMA	*N*-methylacetamide	2-chloroethanol	98.5	63.3
		ethylene glycol		16.9
		acetaldehyde[i]		14.8
CMC	ethyl *N*-methylcarbamate	2-chloroethanol	103	59.6
		ethylene glycol		18.6
		acetaldehyde[i]		13.0
CMM	*N,N'*-dimethylurea	2-chloroethanol	95.6	62.5
		ethylene glycol		21.9
		acetaldehyde[i]		11.7

[a] 0.05 M phosphate buffer containing 0.05 M maleic acid as internal standard. [b] N3 products were formed in virtually quantitative yields. [c] Percentages based on yield of the N3 product. [d] As CH_3OD. [e] As CH_3OD, 45.2; CH_2DOD, 36.8; MeD_2PO_4, 15.3; Me_2DPO_4, 1.4. [f] As CH_3OD, 40.1; CH_2DOD, 30.9; MeD_2PO_4, 7.4; Me_2DPO_4, trace. [g] As CH_3OD, 46.7; CH_2DOD, 37.5; MeD_2PO_4, 15.1; Me_2DPO_4, 1.6. [h] As CH_3OD, 44.8; CH_2DOD, 32.2; MeD_2PO_4, 8.5; Me_2DPO_4, trace. [i] Detected as an approximately 1:0.8 ratio of acetaldehyde and its hydrate.

each of the 10 compounds, the products formed at both pH 2.5 and 8.0 were essentially those resulting from scission of the N(2)–N(3) bond. At most only small amounts (<5%) of products resulting from deacylation, scission of the N(3)–carbonyl bond, were observed.

Thus, the dominant products are those in which the N(3) portion of the molecule remains intact, resulting in the formation of *N*-methylacetamide from 3-acetyltriazenes (DMA, HMA, CMA), ethyl *N*-methylcarbamate from 3-carbethoxytriazenes (DMC, HMC, and CMC), *N,N'*-dimethylurea from 3-(methylcarbamoyl)triazenes (DMM, HMM, and CMM), and *N*-(2-hydroxyethyl)-*N'*-methylurea from MHM. Authentic samples of *N*-methylacetamide, ethyl *N*-methylcarbamate, and *N,N'*-dimethylurea were subjected to the same reaction conditions for the same periods of time to ascertain their stability. In each case these amides were determined to be stable under the reaction conditions. The N(1) portion of the molecule loses molecular nitrogen and results in the formation of a variety of products derived from the N(1) alkyl group. For the 1-methyltriazenes (DMA, DMC,

Scheme III



DMM, and MHM) the major product is methanol with lesser amounts of methyl and dimethyl phosphate in a 10:1 ratio. The methanol to methyl phosphate ratio is about 4.3:1 in all cases. The (2-hydroxyethyl)triazenes (HMA, HMC, and HMM) produce ethylene glycol, acetaldehyde, and 1,1-dihydroxyethane in a roughly 2.5:1:1 ratio. The (2-chloroethyl)triazenes give either 2-chloroethanol (pH = 2.5) or 2-chloroethanol, ethylene glycol, acetaldehyde, and 1,1-dihydroxyethane (pH = 8.0) in a ratio of ~ 7.5:2.5:1:1, respectively. At most only trace amounts of alkylated phosphate were observed from the (hydroxyethyl)- and (chloroethyl)triazenes.

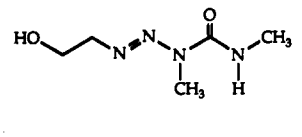
Discussion

Previous work on 1,3-dimethyl-3-acyltriazenes[5] revealed that the mechanism of hydrolysis in aqueous buffers was very different from that of the parent 1,3-dialkyltriazenes. The pH–rate profiles of the acyltriazenes, with the possible exception of DMM, are triphasic, consisting of acid- and base-catalyzed regions separated by an uncatalyzed domain. Two fundamentally different hydrolysis pathways are possible: heterolysis of the N(2)–N(3) bond which leads to formation of the methyldiazonium ion and an amide anion and deacylation which results in formation of the parent 1,3-dimethyltriazene. In neutral buffers, the former pathway was indicated by the isolation of substantial amounts of ethyl *N*-methylcarbamate from the decomposition of 1,3-dimethyl-3-carbethoxytriazene, DMC. Had deacylation occurred, the products would have been ammonia, carbon dioxide, and 1,3-dimethyltriazene, the latter decomposing further to methanol and methylamine under the reaction conditions. Since methanol is also a product of the N(2)–N(3) heterolysis pathway, it was not possible to determine accurately, from the alcohol products alone, whether any portion of the starting material, DMC, decomposed via deacylation. Clearly, a more detailed investigation of the product distribution and a more informative starting material were needed to more precisely define the course of the reaction.

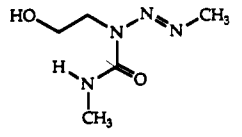
A 1,3-dialkyl-3-acyltriazene in which the two alkyl groups are different provides a convenient method to distinguish between the two mechanistic pathways. As shown in Scheme III, N(2)–N(3) heterolysis leads to alcohol products derived only from the N(1) alkyl group. Deacylation, on the other hand, involves the generation of an unsymmetrical 1,3-dialkyltriazene which decomposes further to give alcohol products derived competitively from both the N(1) and N(3) alkyl groups.

Triazenes bearing a variety of different alkyl substituents on N(1) and N(3) and different N(3) acyl groups were studied to provide, by their effects on the rate of hydrolysis, more detailed information on the nature of the species generated during the hydrolysis reaction. Thus, the series of 1,3-dialkyl-3-acyltriazenes described in this and the previous report[6] were prepared and the products and kinetics of their decomposition were studied in both the acidic and neutral pH regions. The products of decomposition and kinetics in the basic regions are more complex and will be treated in a later publication.

The preparation of one triazene, 3-(2-hydroxyethyl)-1-methyl-3-(methylcarbamoyl)triazene, MHM, deserves special comment. The synthesis of 1-(2-hydroxyethyl)-3-methyl-3-(methylcarbamoyl)triazene, HMM, was described previously.[6] This preparation involves the acylation of 1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyltriazene with methylisocyanate and subsequent removal of the *tert*-butyldimethylsiloxy protecting group with tetra-*n*-butylammonium fluoride. Chromatography of the mother liquor from the recrystallization of HMM revealed the presence of an additional product. The mass spectrum showed it to be an isomer of HMM. The ^{1}H NMR spectrum of this isomer indicated the presence of a more deshielded NCH_3 and a less deshielded NCH_2 group than those found in HMM. These chemical shifts are consistent with a structure bearing a methyl group on the saturated nitrogen, N(3), and a 2-hydroxyethyl group on the unsaturated nitrogen, N(1). This minor product is the result of the acylation of 1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyltriazene on the less favored, more sterically hindered nitrogen atom. ^{1}H-NMR analysis of the initial acylation product mixture revealed that this isomer, the TBDMS derivative of MHM, comprises about 14% of the total acylated product.



HMM



MHM

Acid-Catalyzed Decomposition. In the acid-catalyzed pH domain, the products formed (Table IV) are exclusively those resulting from heterolysis of the N(2)–N(3) bond. The N(3) fragment was detected intact as the corresponding amide formed by addition of a hydrogen atom to N(3). In the 3-acetyltriazene decompositions, trace amounts (<5%) of acetic acid were detected indicating the possibility of a very small amount of either deacylation or hydrolysis of the product *N*-methylacetamide. The latter possibility seems unlikely in light of control experiments which showed *N*-methylacetamide to be stable under the reaction conditions.

Products derived from the remainder of the molecule are consistent with the formation of an alkyldiazonium ion from the N(1) alkyl group. A virtually quantitative yield of methanol results from the reaction of water with the methyldiazonium ion. No significant amount of alkylation of either phosphate or maleic acid was observed at pH 2.5.

The (2-hydroxyethyl)diazonium ion leads, by direct reaction with water, to ethylene glycol, and by a 1,2-hydride shift, to acetaldehyde, detected as an approximately 1:1 mixture of the aldehyde and its hydrate. The ratio of ethylene glycol to acetaldehyde varied somewhat, but on average was about 1:0.6. The (2-chloroethyl)diazonium ion gave an essentially quantitative yield of 2-chloroethanol.

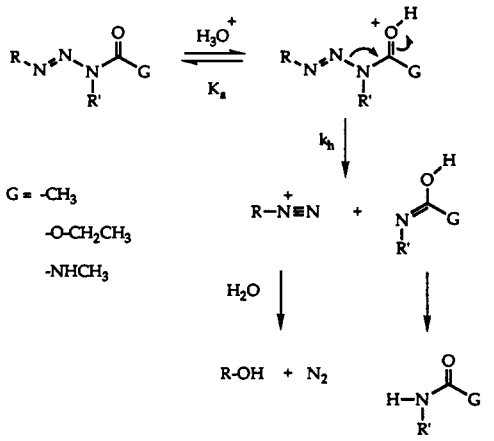
Kinetic studies reveal that the hydrolysis of each of the triazenes studied is acid catalyzed; the slope of each of the log k versus pH plots is approximately equal to −1 in the linear portion of the curve. The solvent deuterium isotope effects, k_{H_2O}/k_{D_2O}, are all significantly less than 1 (average = 0.64) (see Table III), indicating that this a specific acid-catalyzed process. The catalytic rate constants, k_{cat}, calculated from the slope of the linear portion of the k_{obs} versus $[H_3O^+]$ plots, are listed in Table V.

Table V. Calculated Rates Constants for the Hydrolysis of 1,3-Dialkyl-3-acyltriazenes in Aqueous Buffers[a] over a Range of pH Values at 70 °C

	k_{cat}[b]	k_{uncat}[c]
DMA	1.28 (7)	7.159E-04[d]
DMC	7.14 (7)	2.956E-03
DMM	101.83 (6)	2.858E-04
MHM	27.94 (5)	1.332E-03
HMA	0.83 (7)	4.527E-04
HMC	4.72 (7)	2.237E-03
HMM	49.40 (6)	1.933E-04
CMA	0.12 (7)	4.359E-05
CMC	1.63 (7)	2.462E-04
CMM	16.09 (6)	1.893E-05

[a] 0.1 M lysine buffer, 0.25 M ionic strength (maintained with $NaClO_4$). [b] Calculated from the slope of the k_{obsd} versus $[H_3O^+]$ plot for each compound using the lower pH rates listed in Table II. The total number of points in each plot are indicated in parentheses. [c] Calculated from the average of the k_{obsd} values (Table II) in the zero slope region of the log (k_{obsd}) versus pH curves (Figures 1–3). [d] Read as 7.159×10^{-4}.

Scheme IV



Molecular orbital calculations[9] suggested that the most likely site for protonation is the carbonyl oxygen atom. The proton affinity for N(3) protonation was less favorable. Protonation at either N(3) or the carbonyl oxygen results in significant lengthening of the N(2)–N(3) bond, but not the N(3)–carbonyl carbon bond. Thus, these calculations predicted N(2)–N(3) heterolysis to be preferred over deacylation, in agreement with the present experimental results.

Qualitatively informative linear relationships between log k and various σ constants were obtained, despite the fact that true Hammett linear free energy analyses could not be performed (only three different substituents on N(1) and N(3) were studied). Plots of the log k_{cat} versus σ^I[10] (Figure 4) for the various N(1) alkyl groups in each series of 3-acyltriazenes give straight lines with negative slopes. Similar plots of log k_{cat} versus σ^-[11] (Figure 5) for the various N(3) acyl groups in each series of 1-alkyltriazenes give straight lines with negative slopes. The overall rate constant for the proposed reaction mechanism shown in Scheme IV is $k_{obs} = K_a k_h$, where K_a is the equilibrium constant for the protonation of the triazene and k_h is the rate constant for the subsequent N(2)–N(3) heterolysis step. K_a should be diminished by electron-withdrawing substituents on either N(1) or N(3) due to decreased basicity of the triazene. On the other hand, electron-withdrawing substituents should enhance k_h if located on N(3), but diminish k_h if located on N(1). The negative slopes of the N(1) alkyl group plots (Figure 4) are con-

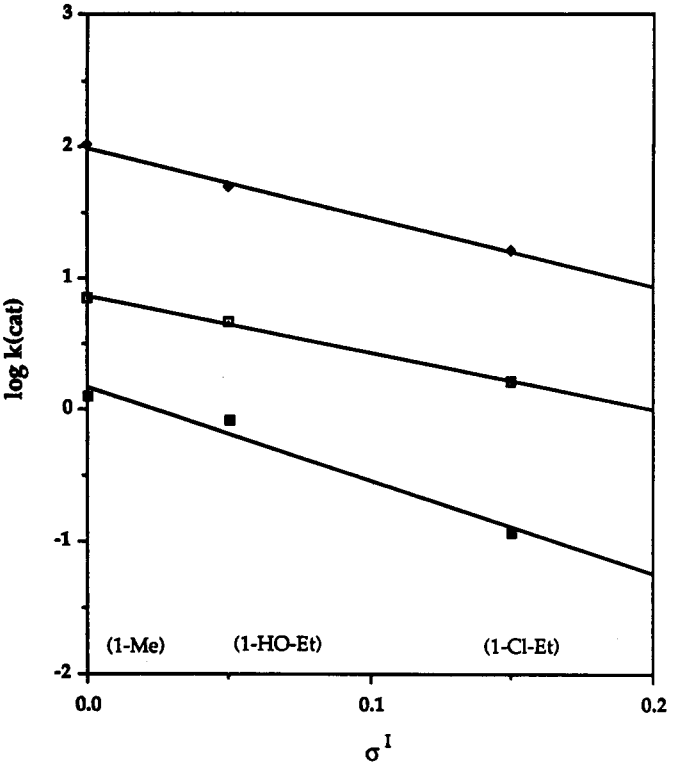


Figure 4. Plot of log k_{cat} versus σ^I for the N(1) alkyl group in each series of 3-acyltriazenes. For each line the 1-alkyl group points are, left to right, methyl, 2-hydroxyethyl, and 2-chloroethyl. 3-Acyl group: 3-methylcarbamoyl (♦), 3-carbethoxy (□), 3-acetyl (■). The slopes of the lines are −5.3, −4.3, and −7.1, respectively.

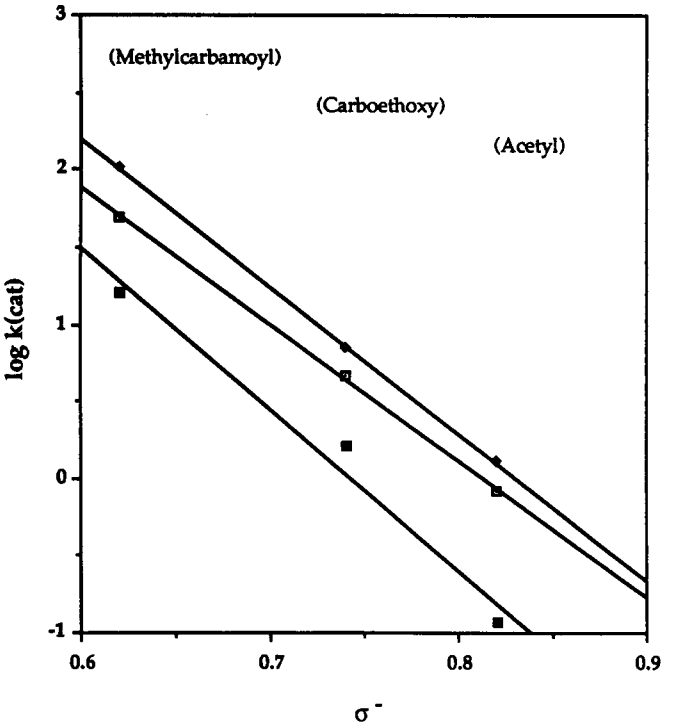


Figure 5. Plot of log k_{cat} versus σ^- for the N(3) acyl group in each series of 1-alkyltriazenes. For each line the 3-acyl group points are, left to right, methylcarbamoyl, carbethoxy, and acetyl. 1-Alkyl group: methyl (♦), 2-hydroxyethyl (□), 2-chloroethyl (■). The slopes of the lines are −9.5, −8.8, and −10.5, respectively.

(9) Ozment, J. L.; Schmiedekamp, A. M.; Schultz-Merkel, L. A.; Smith, R. H., Jr.; Michejda, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 397–405.
(10) Charton, M. *J. Org. Chem.* **1964**, *29*, 1222–1227.
(11) Exner, O. In *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; pp 439–540, esp. p 485.

sistent with this analysis; electron withdrawal from N(1) diminishes k_{obs}. Electron-withdrawing acyl groups on N(3) likewise decrease k_{obs}, suggesting that the dominant effect of the acyl group is exerted upon K_a, a reflection of the order of basicity: ketone < ester < amide.[12]

Consistent with the mechanism shown in Scheme IV, replacement of the N(3) methyl with an electron-withdrawing benzyl group retards the rate of the acid-catalyzed decomposition. In a pH 3.0, 0.1 M lysine buffer at 70 °C, the rate of decomposition for 1-(2-hydroxyethyl)-3-benzyl-3-(methylcarbamoyl)triazene, HBzM, is 9.24×10^{-3} s^{-1} as compared to 4.95×10^{-2} s^{-1} for HMM (Table II) and 2.43×10^{-3} s^{-1} for 1-(2-chloroethyl)-3-benzyl-3-(methylcarbamoyl)triazene, CBzM, as compared to 1.72×10^{-2} s^{-1} for CMM.[13] Substitution of a 2-hydroxyethyl group for the N(3) methyl similarly causes a decrease, as seen by comparing k_{cat} for MHM and DMM, 28 and 102, respectively.

These data taken together give a clear picture of the mechanism (Scheme IV). 1,3-Dialkyl-3-acyltriazenes decompose in acidic solutions by a specific acid-catalyzed process which involves rapid reversible protonation, possibly of the carbonyl oxygen atom, followed by rate-determining heterolysis of the N(2)–N(3) bond with the formation of an alkyldiazonium ion derived from the N(1) alkyl group and an amide derived from the N(3) portion of the molecule.

Uncatalyzed Decomposition. In the neutral pH region, the products of hydrolysis are predominantly those produced by N(2)–N(3) bond scission. As in the acid-catalyzed reaction, the N(3) portion of the triazene survives intact. These data appear in Table IV. Only the 3-acetyl triazenes appear to show any significant amount of deacylation, as evidenced by the presence of about a 5% yield of acetic acid.

The formation of an alkyldiazonium ion is again indicated by the formation of alcohols from the N(1) alkyl group. The yields of products derived from the methyldiazonium ion vary somewhat, but are generally >90%. The constitution of the methanol derived from reaction with water is particularly interesting. In addition to CH_3OD, the product observed at pH 2.5, the ^1H NMR spectrum shows the presence of a substantial amount of CH_2DOD. The CH_3OD/CH_2DOD ratio is ~1:0.77, very close to the value (1:0.75) obtained previously from mass spectrometric measurement.[14] The present finding reiterates the fact that the methyldiazonium ion (pK_a = 10.0 ± 0.3)[15] is in equilibrium with diazomethane in aqueous solution.[14] Deuterium incorporation is not observed at pH 2.5 because the high hydronium ion concentration shifts the equilibrium away from diazomethane. Methyl dihydrogen phosphate and dimethyl hydrogen phosphate, observed in a 10:1 ratio, account for the remainder of the methyldiazonium ion trapped by reaction with the buffer. In these products the CH_3:CH_2D ratio was ~1:0.75.

The (2-hydroxyethyl)diazonium ion again leads, by direct reaction with water, to ethylene glycol and acetaldehyde, the latter detected as an approximately 1:1 mixture of the aldehyde and its hydrate. The ratio of ethylene glycol to acetaldehyde was approximately 1:0.80. In D_2O the α-hydrogens of the aldehyde and its hydrate are completely exchanged by deuterium atoms, but the aldehydic and *gem*-diol methine protons are unmistakable. This exchange reaction was not observed to be significant at pH 2.5.

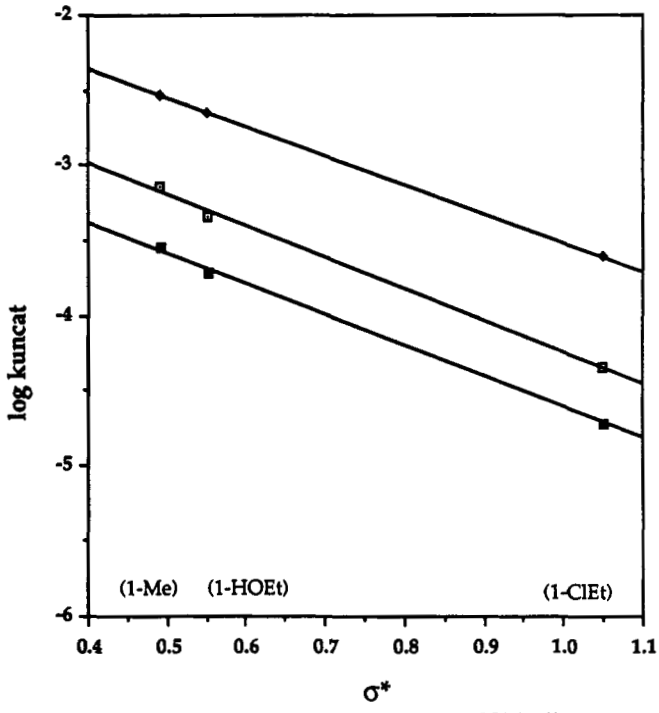


Figure 6. Plot of log k_{uncat} versus σ^* for the N(1) alkyl group in each series of 3-acyltriazenes. For each line the 1-alkyl group points are, left to right, methyl, 2-hydroxyethyl, and 2-chloroethyl. 3-Acyl group: 3-carbethoxy (♦), 3-acetyl (□), 3-methylcarbamoyl (■). The slopes of the lines are −1.9, −2.1, and −2.1, respectively.

The (2-chloroethyl)diazonium ion gave products which were somewhat different from those observed at pH 2.5. Although the major product was still 2-chloroethanol, significant amounts of ethylene glycol and acetaldehyde were also formed. These latter products may be the result of the formation of the 2-(chloroethyl)diazotate anion at neutral pH. This ion has previously been postulated to undergo cyclization to an oxadiazoline by the intramolecular displacement of chloride.[16] Subsequent reaction of the oxadiazoline with water would account for the formation of ethylene glycol and acetaldehyde. The product distribution previously reported[16] is somewhat different (ethylene glycol/acetaldehyde between 1:1 and 1:2) from that observed in this work. 2-Chloroethanol is stable under the reaction conditions.

Inspection of the pH–rate profiles (Figures 1 and 2) of the 1-methyl- and 1-(2-hydroxyethyl)triazenes reveal broad regions where the reaction rate is independent of pH, pH 5.5–11 for the 3-acetyl and 3-carbethoxy derivatives and pH 7.5–12.5 for the 3-(methylcarbamoyl)triazenes. The 1-(2-chloroethyl)triazenes (Figure 3) show much more narrow pH-independent domains due to the onset of a base-catalyzed pathway; pH 5.5–7.5 for the 3-acetyltriazene, 5.5–8.5 for the 3-carbethoxytriazene, and a narrow region ca. pH 8.5 for the 3-(methylcarbamoyl)triazene, CMM. The solvent deuterium isotope effects, k_{H_2O}/k_{D_2O}, measured at pH 7.5 are all greater than 1.0 (average = 1.13) (see Table III), in keeping with a reaction which involves

(12) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; pp 220–221 and references therein.

(13) These rates for CBzM and CMM were obtained in 0.1 M lysine buffers of ionic strength 0.25 M, maintained by the addition of sodium sulfate instead of sodium perchlorate. Sulfate causes a slight (~10%) increase in the rate of the decomposition, but does not otherwise alter the reaction. The previously reported[2] difficulty in measuring pH in perchlorate buffers is significantly reduced in sulfate buffers.

(14) Smith, R. H.; Koepke, S. R.; Tondeur, Y.; Denlinger, C. L.; Michejda, C. J. *J. Chem. Soc., Chem. Commun.* **1985**, 936–937.

(15) McGarrity, J. F.; Smyth, T. *J. Am. Chem. Soc.* **1980**, *102*, 7303–7308.

(16) Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* **1981**, *46*, 2479–2489.

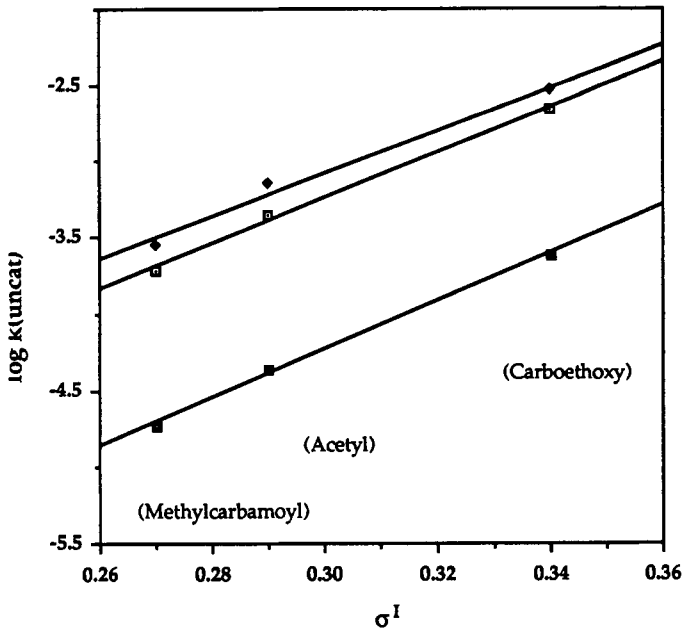
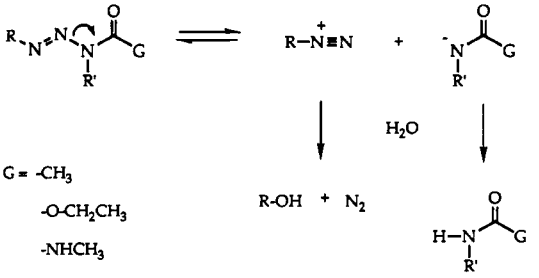


Figure 7. Plot of log k_{uncat} versus σ^I for the N(3) acyl group in each series of 1-alkyltriazenes. For each line the 3-acyl group points are, left to right, methylcarbamoyl, carbethoxy, and acetyl. 1-Alkyl group: methyl (♦), 2-hydroxyethyl (□), 2-chloroethyl (■). The slopes of the lines are −14.1, −14.9, and −15.7, respectively.

the ionization of a neutral molecule in the rate determining step.[17]

The average rate constant, k_{uncat} (Table V), for each compound was calculated from the zero slope portion of the pH–rate profile. Plots of k_{uncat} versus σ^* [18] (Figure 6) for the various N(1) alkyl groups of each series of 3-acyltriazenes, as in the acid-catalyzed domain, give straight lines with negative slopes. It is clear that inductively electron-withdrawing groups on N(1) retard the rate of hydrolysis. Similar plots of log k_{uncat} versus σ^I [10] (Figure 7) for the N(3) acyl groups for each series of 1-alkyltriazenes give straight lines with definitely positive slopes. Thus, unlike in the acid-catalyzed reaction, electron withdrawal from N(3) enhances the rate of hydrolysis, suggesting the development of a negative charge on N(3) during formation of the transition state. This notion is further supported by the fact that substitution of an inductively withdrawing benzyl or 2-hydroxyethyl group for the N(3) methyl enhances the rate of the uncatalyzed decomposition. The rate of decomposition at pH 7.5 is 5.15 × 10^{-4} s^{-1} for 1-(2-hydroxyethyl)-3-benzyl-3-(methylcarbamoyl)triazene, HBzM, as compared to 1.93 × 10^{-4} s^{-1} for HMM[19] and 4.14 × 10^{-5} s^{-1} for 1-(2-chloroethyl)-3-benzyl-3-(methylcarbamoyl)triazene, CBzM, compared to 2.53 × 10^{-5} s^{-1} for CMM.[12] Similarly, the rate of decomposition of MHM is 1.33 × 10^{-3} s^{-1} as compared to 3.34 × 10^{-4} s^{-1} for DMM (see Table II). It is interesting that the 3-(methylcarbamoyl)triazenes are the most reactive of the acyl derivatives in the acid-catalyzed reaction but the least reactive in the uncatalyzed case.

Scheme V



The weight of the evidence strongly supports the conclusion that 1,3-dialkyl-3-acyltriazenes decompose in neutral aqueous solutions by an uncatalyzed process involving the unimolecular heterolysis of the N(2)–N(3) bond as shown in Scheme V. The initial products are an alkyldiazonium ion from N(1) and an amide anion from the N(3). Protonation of the amide anion by solvent water produces an amide derivative. The alkyldiazonium ion decomposes further by reaction with water to produce various alcohols.

Thus it is now clear that the acid-catalyzed and uncatalyzed decomposition of 1,3-dialkyl-3-acyltriazenes follows the same general mechanistic pattern, heterolysis of the N(2)–N(3) bond. The N(3) portion of the molecule remains intact and an alkyldiazonium ion is generated solely from the N(1) alkyl group.

The hydrolysis of 1,3-dialkyl-3-acyltriazenes in alkaline buffers is more complex and will be treated in a forthcoming report.

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Registry No. DMA, 87031-64-9; DMC, 88211-12-5; DMM, 103711-40-6; MHM, 137668-37-2; MHM (TBDMS deriv), 137668-40-7; HMA, 113274-27-4; HMC, 113274-26-3; HMM, 113274-28-5; HMM (TBDMS deriv), 113274-25-2; CMA, 113274-30-9; CMC, 113274-29-6; CMM, 113274-31-0; HBzM, 137668-38-3; CBzM, 137668-39-4; D_2, 7782-39-0.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for HBzM, CBzM, and MHM and representative ^1H NMR spectra of product mixtures: pH 2.0, CMM; pH 8.0 DMA (D incorporation), and HMM (Figures SF1–SF10) (10 pages). Ordering information is given on any current masthead page.

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(19) This value is slightly different from that in Table II because the perchlorate containing buffer was prepared at a different time.[2]