Novel Triazenes and Triazolines from the Base-Catalyzed Hydrolysis of 1,3-Dialkyl-3-acyltriazenes

Richard H. Smith, Jr.,*[,†,‡] Brian D. Wladkowski,[†] Julie A. Herling,[†] Timothy D. Pfaltzgraff,[†] Jesse E. Taylor,[†] Erin J. Thompson,[†] Brunon Pruski,[‡,∥] John R. Klose,[§] and Christopher J. Michejda[‡]

Department of Chemistry, Western Maryland College, Westminster, Maryland 21157, Molecular Aspects of Drug Design Section, ABL-Basic Research Program, NCI-Frederick Cancer Research and Development Center, Frederick, Maryland 21702, and Chemical Synthesis and Analysis Laboratory, Program Resources Incorporated/Dyn Corporation, NCI-Frederick Cancer Research and Development Center, Frederick, Maryland 21702

Received June 10, 1992

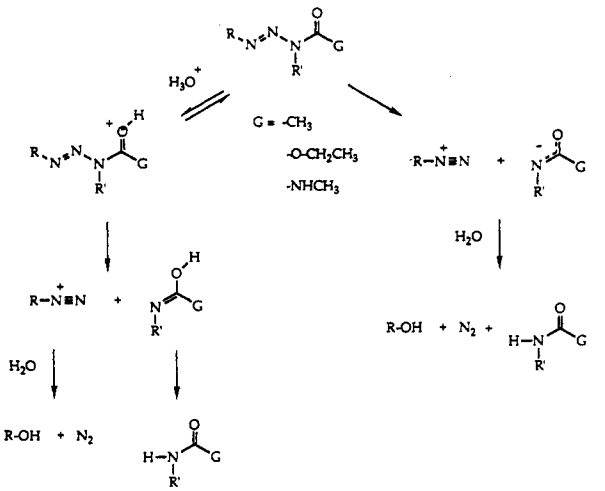
The products and mechanism of hydrolytic decomposition of a series of 1,3-dialkyl-3-acyltriazenes were studied in alkaline buffers. In general the mechanism of decomposition involves deacylation leading to the formation of the parent 1,3-dialkyltriazene. The solvent deuterium isotope effect (k_{H_3O}/k_{D_3O}) is less than 1.0, indicating specific base catalysis. A plausible mechanistic explanation is rapid reversible attack by hydroxide ion, followed by rate-limiting heterolysis of the N(1)–acyl bond. The resultant, 1,3-dialkyltriazene is somewhat unstable under the reaction conditions and undergoes subsequent hydrolysis, a reaction previously shown to be specific acid-catalyzed. When the N(1) alkyl group is 2-chloroethyl, unusual products are obtained. For the 3-acetyl and 3-carbethoxy derivatives, the initial deacylation product, 1-(2-chloroethyl)-3-methyltriazene, efficiently cyclizes to form 1-methyltriazoline. The 3-(methylcarbamoyl) derivative does not deacylate, but instead undergoes dehydrohalogenation to 1-vinyl-3-methyl-3-(methylcarbamoyl)triazene.

Introduction

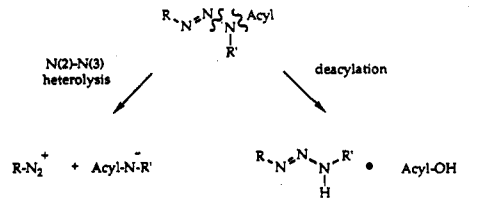
Several years ago we described the synthesis of a new class of alkyltriazenes, 1,3-dialkyl-3-acyltriazenes.[1] These compounds are more stable than the parent 1,3-dialkyltriazenes, which undergo rapid specific acid-catalyzed decomposition in aqueous buffers to produce alkylamines and an alkyldiazonium ion intermediate.[2] In our initial report,[1] we noted that the hydrolytic decomposition of 1,3-dialkyl-3-acyltriazenes exhibits a complex dependence upon the pH of the aqueous reaction medium. The pH versus log k_{obs} plots for the hydrolysis reaction are in general triphasic. Acid and base-catalyzed pathways are evident at the respective extremes of the pH scale, and at near neutral pH there exists a domain in which the rate of hydrolysis is independent of the hydronium ion concentration. Sometime later, Iley et al.[3] reported that 3-acyl-3-alkyl-1-aryltriazenes undergo a general base-catalyzed decomposition in the presence of organic bases in ethanol.

More recently we presented the details of the mechanism of these acid-catalyzed and uncatalyzed hydrolysis reactions (Scheme I).[4] 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. The result of this process is an alkyldiazonium ion derived from the N(1) alkyl group and an amide derived from the N(3) portion of the molecule. In neutral aqueous solutions, decomposition is by an uncatalyzed process involving the unimolecular heterolysis of the N(2)–N(3) bond. The initial products are an alkyldiazonium ion from N(1) and an amide anion from 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, both the acid-catalyzed and uncatalyzed decomposition of 1,3-dialkyl-3-acyltriazenes follow the same general mechanistic pattern, heterolysis

Scheme I



Scheme II



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.

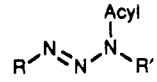
The hydrolysis of 1,3-dialkyl-3-acyltriazenes in alkaline buffers proved more complex. There exist two different pathways by which the decomposition might formally

[†] Western Maryland College.
[‡] NCI-Frederick Cancer Research and Development Center.
[§] Chemical Synthesis and Analysis Laboratory, PRI-FCRDC.
[∥] On leave from Adam Mickiewicz University, Poznan, Poland.

(1) Smith, R. H., Jr.; Mehl, A. F.; Hicks, A. E.; Denlinger, C. L.; Kratz, L.; Andrews, A. W.; Michejda, C. J. *J. Org.* **1986**, *51*, 3751–3757.
(2) Smith, R. H., Jr.; Denlinger, C. L.; Kupper, R.; Mehl, A. F.; Michejda, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 3726–3730.
(3) Iley, J.; Ruecroft, G.; Carvalho, E.; Rosa, E. *J. Chem. Res., Synop.* **1989**, 162–163.
(4) Smith, R. H., Jr.; Wladkowski, B. D.; Herling, J. A.; Pfaltzgraff, T. D.; Pruski, B.; Close, J.; Michejda, C. J. *J. Org. Chem.* **1992**, *57*, 654–661.

0022-3263/92/1957-6448$03.00/0

Table I. Structures and Abbreviations of Compounds Investigated



abbrev	R	R'	acyl
DMA	Me	Me	acetyl[a]
DMC	Me	Me	carbethoxy[b]
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
VMM	vinyl	Me	methylcarbamoyl

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

proceed (Scheme II). The first is characterized by heterolytic cleavage of the N(2)–N(3) bond leading to an alkyldinitrogen species (e.g. diazonium ion or diazotate) from the N(1) residue and an amide species from N(3), a process somewhat analogous to that followed in acidic and neutral solutions. The second pathway proceeds by initial deacylation, cleavage of the N(3)–acyl bond, to form a 1,3-dialkyltriazene which subsequently undergoes rapid hydrolysis in a manner which we have previously delineated.[2,5] In the present work we present evidence which demonstrates that in alkaline hydrolysis the dominant pathway involves deacylation and results in several novel products. In addition, we have observed a new decomposition pathway in the case of one 1-(2-chloroethyl)-3-methyl-3-acyltriazene, CMM. The compounds studied are listed in Table I.

Experimental Section

Safety Note. Triazenes are potent biological alkylating agents and should be considered to be potentially toxic and carcinogenic. At all times, efficient hoods and protective clothing should be used in working with these substances. Alkyl azides are treacherously explosive and should be treated with extreme caution. Wherever possible, these compounds should only be handled in solution.

Materials. All chemicals were reagent grade (Aldrich Chemical Co.) and were used as purchased without further purification. The synthesis of the triazenes in this study has been reported elsewhere,[1,6] as has the method employed for buffer preparation.[2] 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 a VG 70-250 mass spectrometer using a peak matching technique. All samples submitted for exact mass determination were shown to be >97% pure by ^1H NMR analysis. Gas chromatographic analyses were performed on a Perkin-Elmer Sigma 3B gas chromatograph interfaced to an Apple IIe microcomputer. Data acquisition and peak integration employed Interactive Microware's Lab Data Manager I software package. Methanol analyses were performed at 130 °C with a 6-ft, 2-mm i.d. glass column packed with 80/100 mesh Super Q, using ethanol as an internal standard.

1-Methyltriazoline (MT). Solution A. Dry trimethyloxosulfonium iodide (64.4 g, 0.29 mol) was added to a flask containing sodium hydride (8.4 g of 80% dispersion in mineral oil, 0.29 mol, previously washed three times with 100 mL of pentane and dried briefly in vacuum). The solids were not mixed. Dry tetrahydrofuran (THF, 200 mL) was added cautiously with gentle stirring. When all of the THF had been added and gas evolution had subsided, the suspension was stirred under nitrogen at room temperature for 2 h.

Solution B. To a suspension of sodium azide (15.22 g, 0.234 mol) in 100 mL of dimethyl sulfoxide (DMSO) and 250 mL of pentane was added dropwise methyl iodide (33.22 g, 0.234 mol) over a period of 1 h. The suspension was stirred for 4 h at room temperature, and the pentane layer was separated. The yield was taken to be ~50% based on past experience, and thus a 2:1 ratio of ylide to azide was assumed.

The methyl azide solution (B) was added dropwise over 2 h to the THF solution of dimethyloxosulfonium methylide (A) at room temperature under nitrogen. The resulting milky solution was stirred overnight. The solvents were removed on a rotary evaporator at 18 mm, 25 °C, and the residue was dissolved in 400 mL of pentane, filtered, and concentrated on a rotary evaporator at 18 mm, 25 °C to 3.61 g of a pale yellow oil which showed two spots (R_f 0.4 and 0.55) on TLC (silica gel, pretreated and eluted with 5% (v/v) isopropylamine in pentane). The lower R_f material was isolated by chromatography on a column of silica gel 60A (40 g) packed in and eluted with a 5% (v/v) solution of isopropylamine in pentane. Concentration of this fraction followed by distillation gave 0.740 g (7.62 mmol, 3.3%) of a colorless liquid: bp 55 °C (8 mm); UV (CH_3CN) λ_{max} 239 nm (log ϵ 3.53), 264 nm (log ϵ 3.45); ^1H NMR ($CDCl_3$, Me_4Si) δ 2.95 (2 H, t, J = 10.7 Hz), 3.25 (3 H, s), 4.16 (2 H, t, J = 10.7 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 38.00, 48.05, 65.57; exact mass calcd m/z for $C_3H_7N_3$ (M^+) 85.06399, found 85.06344 (by EI).

Isolation of 1-Methyltriazoline from CMA Hydrolysis. A solution of 1-(2-chloroethyl)-3-methyl-3-acetyltriazene (1.06 g, 6.48 mmol) in 75 mL of pH 13, 0.1 M lysine buffer was heated at 40 °C for 35 min under nitrogen. The reaction solution was cooled and extracted three times with 30 mL of methylene chloride. The combined methylene chloride extracts were dried over anhydrous sodium sulfate and concentrated at reduced pressure (18 mm) at 8 °C to give 0.50 g of a yellow oil. The residue was distilled (30 °C, 2 mm) to give 0.380 g (4.46 mmol, 68.9%) of a colorless liquid. The spectral properties were identical to those of MT prepared above.

1-(2-Hydroxyethyl)-3-methyltriazene (HMT). A solution of 1-(2-hydroxyethyl)-3-methyl-3-acetyltriazene (0.22 g, 1.52 mmol) in 4 mL of 1.0 N aqueous sodium hydroxide was heated for 1 h at 70 °C under nitrogen. The reaction mixture was cooled and extracted with four 5-mL portions of methylene chloride containing 5% (v/v) of isopropylamine. The methylene chloride extracts were combined and dried over anhydrous sodium sulfate, and the methylene chloride was removed under a stream of dry nitrogen gas. The resultant yellow oil was distilled by means of a short-path distillation apparatus using a dry ice cooled receiver to give 0.020 g (0.19 mmol, 13%) of a colorless liquid: bp 40 °C (0.01 mm); UV (CH_3CN) λ_{max} 232 nm (log ϵ 3.87); ^1H NMR (pH 13 NaOD–D_2O, Me_4Si) δ 2.70 (3 H, s), 3.49 (2 H, t, J = 6.4 Hz), 4.09 (2 H, t, J = 6.4 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 61.86, 76.79, 77.20. Due to the instability of this triazene, a molecular ion for exact mass determination could not be obtained by either EI or CI methods. However, the rate of hydrolysis of HMT, 7.38×10^{-5} s^{-1} (at 25 °C in pH 9.5, 0.1 M lysine buffer, μ = 0.25 M maintained with $NaClO_4$), is consistent with the assigned structure, as are the products of that hydrolysis (see Results).

1-Vinyl-3-methyl-3-(methylcarbamoyl)triazene (VMM). A solution of 1-(2-chloroethyl)-3-methyl-3-(methylcarbamoyl)-triazene (0.331 g, 1.85 mmol) in 30 mL of pH 11.5, 0.1 M lysine buffer was heated at 70 °C under nitrogen for 118 h. Periodically throughout the reaction, the pH was readjusted to 11.5 by the addition of a 1.0 N solution of sodium hydroxide. The reaction mixture was cooled and extracted four times with 50 mL of methylene chloride. The combined methylene chloride extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure (18 mm) at room temperature. The residue, which contained one major component by TLC (R_f 0.51 on a silica gel plate eluted with diethyl ether), was chromatographed on a 1 × 4 in column of silica gel 60A packed in pentane and eluted

(5) 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.

(6) Smith, R. H., Jr.; Mehl, A. F.; Shantz, D. L., Jr.; Chmurny, G. N.; Michejda, C. J. *J. Org. Chem.* **1988**, *53*, 1467–1471.

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

	product	% yield		product	% yield
DMA	acetate	100	CMA	acetate	100
	1,3-dimethyltriazene	105.2		1-methyltriazoline	97.1
DMC	ethanol	100	CMC	ethanol	100
	1,3-dimethyltriazene	100		1-methyltriazoline	75.1
				methylamine	19.8
DMM	*N,N'*-dimethylurea	41.4			
	1,3-dimethyltriazene	36.4	CMM	1-vinyl-3-methyl-3-(methylcarbamoyl)triazene	70.6
	methylamine	57.2		methylamine	29.3
	methanol	31.4[b]		1-vinyl-3-methyltriazene	21.9
	methyl phosphate	4.7			
			MHM	*N*-(2-hydroxyethyl)-*N'*-methylurea	20
HMA	acetate	100		1-(2-hydroxyethyl)-3-methyltriazene	21
	1-(2-hydroxyethyl)-3-methyltriazene	102.6		methylamine	80
	methylamine	3.1		ethanolamine	17
HMC	ethanol	100	VMM	1-vinyl-3-methyltriazene	83.3
	1-(2-hydroxyethyl)-3-methyltriazene	100		methylamine	100
HMM	*N,N'*-dimethylurea	56.5			
	1-(2-hydroxyethyl)-3-methyltriazene	5.9			
	methylamine	32.3			
	ethylene glycol	28.1[c]			

[a] pH 13.0, 0.05 M phosphate buffer containing 0.05 M maleic acid as internal standard. [b] Yield by gas chromatography. [c] Yield by ^{1}H NMR, therefore artificially low due to deuterium exchange.

with 25% (v/v) diethyl ether in pentane. Combination and evaporation of the appropriate fractions gave 0.065 g of a solid which was recrystallized from pentane to yield 0.041 g (0.29 mmol, 16%) of colorless needles: UV (CH_3CN) λ_{max} 222 nm (log ϵ 2.64), 276 nm (log ϵ 4.25); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.95 (3 H, d, J = 4.8 Hz), 3.35 (3 H, s), 5.40 (1 H, d, J = 7.6 Hz), 5.77 (1 H, d, J = 15.3 Hz), 6.35 (1 H, broad), 7.14 (1 H, d of d, J = 7.6 and 15.3 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 27.04, 28.29, 116.51, 146.97, 155.18; exact mass calcd m/z for $C_5H_{11}N_4O$ (MH^+) 143.0932, found 143.0920 (by FAB).

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 pH 13.0 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 4 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 ^{1}H NMR. A long delay time (12 s) was determined empirically and used to assure relaxation of all protons for accuracy of integrations. The pH of each final reaction mixture was measured and in each case had varied by no more than ±0.4 pH units. 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. 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 some of the compounds, significantly less than stoichiometric amounts of the alcohol products were seen in the ^{1}H NMR. Gas chromatography was used verify the presence of these alcohols.

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 analog output of absorbance versus time was recorded on an Apple IIe computer equipped with an Interactive Microware 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 buffers of pH > 10.5, because lysine absorbance interferes below 235 nm, measurements were made at 237 nm or at the λ_{max} of the triazene, whichever was greater. For those triazenes followed at wavelengths other than their λ_{max}, the triazene concentration was increased 33% to assure an initial absorbance of at least 0.3. 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 (12 μL when not at the λ_{max}) 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 (the addition of 9 μL of acetonitrile proved unnecessary). 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 method.[7] In those cases where a quasi-stable product is formed and subsequently decomposed to a significant extent during of the kinetic run, the data were treated by a consecutive first-order kinetics program which employs an iterative curve fitting routine.[8] This latter method was necessary wherever the initial and secondary reaction rates were within 1 order of magnitude of each other. The rate of hydrolysis of each of these secondary products was confirmed independently by separate measurements in the same buffer.

Results

Product Studies. The products of the decomposition of each of the triazenes were determined by ^{1}H NMR analysis at pH 13.0 in 0.05 M buffers of sodium phosphate, or sodium phosphate plus 0.05 M maleic acid, in D_2O. These data are presented in Table II.

The 3-acetyl (DMA, HMA, and CMA) and 3-carboethoxy (DMC, HMC, and CMC) triazenes exclusively decompose by deacylation, cleavage of the N(3)–carbonyl carbon bond, to produce a 1,3-dialkyltriazene and either acetic acid or ethanol (and presumably CO_2), respectively. Where the N(1)-alkyl group is methyl (DMA and DMC), the dialkyltriazene formed is 1,3-dimethyltriazene (DMT). For the 1-(2-hydroxyethyl)triazenes, HMA and HMC, the dialkyltriazene product is 1-(2-hydroxyethyl)-3-methyltriazene (HMT). Interestingly, the 1-(2-chloroethyl)triazenes, CMA and CMC, did not yield the expected 1-(2-chloroethyl)-3-methyltriazene (CMT). Instead, 1-methyltriazoline (MT) was the major product formed. The structure of 1-methyltriazoline was confirmed by isolation of the material from the hydrolysis of CMA and comparison of its spectral properties with an authentic sample prepared by a modification of the method developed by Gaudiano[9] The production of a 23.6% yield of methyl-

(7) Guggenheim, E. A. *Philos. Mag.* **1926**, *2*, 538–543.
(8) The kinetics program was based on the algorithm presented in Wiberg, K. B. *Physical Organic Chemistry*; Wiley: New York, 1966; pp 567–574.

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

pH	DMA	DMC	DMM	HMA	HMC	HMM	MHM	CMA	CMC	CMM	VMM
2.1	1.08E-02			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		2.82E-03	1.66E-02		8.95E-02	4.57E-04	5.79E-03		3.72E-03
3.0	1.91E-03	1.08E-02	1.02E-01	1.31E-03	7.01E-03	4.95E-02	3.16E-02	1.62E-04	1.82E-03	1.60E-02	
3.5	1.13E-03	5.78E-03	3.63E-02	7.11E-04	3.90E-03	1.81E-02	1.09E-02	8.26E-05	7.62E-04	6.19E-03	
4.0		3.86E-03				5.87E-03	4.68E-03				
4.5			3.79E-03			1.87E-03				6.39E-04	
5.5	7.45E-04	3.01E-03	1.13E-03	4.48E-04	2.29E-03	5.63E-04	1.47E-03	4.38E-05	2.57E-04	1.39E-04	
6.5											
7.5	7.16E-04	2.96E-03	3.34E-04	4.53E-04	2.22E-03	2.16E-04	1.34E-03	4.46E-05	2.46E-04	2.45E-05	
8.5										1.89E-05	
9.5	8.18E-04[d]	2.93E-03	2.86E-04	4.63E-04[d]	2.25E-03	1.93E-04	1.37E-03	1.90E-04	3.00E-04	2.73E-05	
10.5								5.55E-04[d]	5.13E-04		
11.5	1.34E-03	3.61E-03	2.86E-04	1.16E-03	3.38E-03	1.98E-04	1.30E-03	2.90E-03	2.33E-03	1.02E-04	
12.0	3.33E-03	6.36E-03		3.92E-03	7.21E-03			8.90E-03	6.48E-03	3.00E-04	
12.5	1.32E-02	1.55E-02	3.01E-04	2.16E-02	1.86E-02	2.50E-04	1.54E-03	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%. E-0x means 10^{-x}. [b] Triazene initial concentration 3.0×10^{-5} M. [c] Ionic strength of 0.25 M held constant with added $NaClO_4$. [d] Rate constant calculated by consecutive first-order curve-fitting method.

amine in the CMC decomposition results from the hydrolysis of either CMT or MT. A more detailed study of the hydrolysis of 1-alkyltriazolines will be published in the near future.

The 3-(methylcarbamoyl)triazenes, DMM and HMM, decompose by more complex routes at pH 13.0. The observed products indicate a competition between deacylation and N(2)–N(3) heterolysis. As with the analogous acetyl and carbethoxy triazenes, the deacylation of DMM and HMM leads to the formation of the respective 1,3-dialkyltriazenes, DMT and HMT. However, the added production of *N,N'*-dimethylurea by both DMM and HMM demonstrates significant competition from the N(2)–N(3) heterolysis pathway.

1-(2-Chloroethyl)-3-methyl-3-(methylcarbamoyl)triazene (CMM) follows a totally different route, dehydrohalogenation. The major product is 1-vinyl-3-methyl-3-(methylcarbamoyl)triazene (VMM) with minor amounts of methylamine and 1-vinyl-3-methyltriazene (VMT). These latter two products are the result of the subsequent deacylation of VMM, as shown by an independent hydrolysis of this compound. In the study of the decomposition of VMM, the yield of methylamine exceeded that of 1-vinyl-3-methyltriazene (VMT). This presumably is the result of a subsequent hydrolysis of VMT.

It should be noted that the deacylation products derived from the acyl portion of the triazenes are shown in Scheme I and elsewhere simply as acyl-OH. This structure is literally correct only for the 3-acetyl derivatives, where it represents acetic acid. In the case of the 3-carbethoxy and 3-(methylcarbamoyl) derivatives, the specific acyl-OH is unstable and would decompose to CO_2 and either ethanol or methylamine, respectively.

The product distributions from several of the above-mentioned triazenes, DMM, HMM, CMC, and VMM, require additional comment. Deacylation of each of these compounds leads initially to a 1,3-dialkyltriazene, which is known to decompose under the reaction conditions to an alkylamine and an alcohol.[2] ^1H NMR analysis of the products showed the presence of the amines in the amounts expected. Signals for the corresponding alcohols and alkyl phosphates (in ~6:1 molar ratio) were present, but in lower than stoichiometric amounts. Gas chromatographic analysis was used to verify the formation of methanol from DMM and VMM, and ethylene glycol from HMM and CMC. The ^1H NMR signals for the CH protons of these alcohols and those of the corresponding alkyl phosphates integrated low due to deuterium exchange. We have previously reported the observation of deuterium incorporation in reactions involving alkyldiazonium ion intermediates.[10]

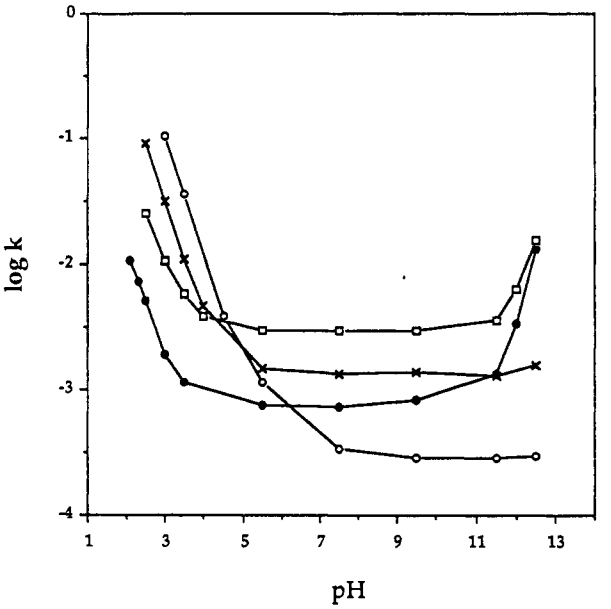


Figure 1. 1,3-Dimethyl-3-acyltriazene pH profiles in 0.1 M lysine buffer, 70 °C: DMA (●), DMC (□), DMM (○), MHM (×).

In relation to previous work on the decomposition of unsymmetrical 1,3-dialkyltriazenes,[5] the products of the hydrolysis of 1-(2-hydroxyethyl)-3-methyltriazene were determined at pH 7.5 in a D_2O, 0.05 M phosphate buffer by ^1H NMR analysis: 2-aminoethanol, 54%; methanol, 32%; methylamine, 46%; ethylene glycol, 32%. The alcohol yields again appear low due to deuterium incorporation. The amine ratio is, however, a good indication that diazonium ions were produced in approximately equal amounts from the N(1) and N(3) alkyl groups, with formation of the methyldiazonium ion being slightly preferred over the 2-(hydroxyethyl)diazonium ion (54:46).

pH Dependence of the Rate of Decomposition. The rate of decomposition of each triazene was determined over a pH range extending to either pH 12.5 or the highest pH

(9) Gaudiano, G.; Umani-Ronchi, A.; Bravo, P.; Acampora, M. *Tetrahedron Lett.* **1967**, 107–111.

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

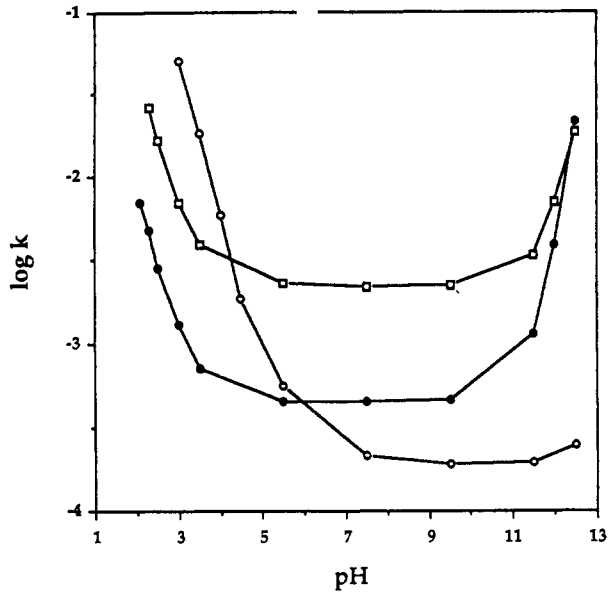


Figure 2. 1-(2-Hydroxyethyl)-3-methyl-3-acyltriazene pH profiles in 0.1 M lysine buffer, 70 °C: HMA (●), HMC (□), HMM (○).

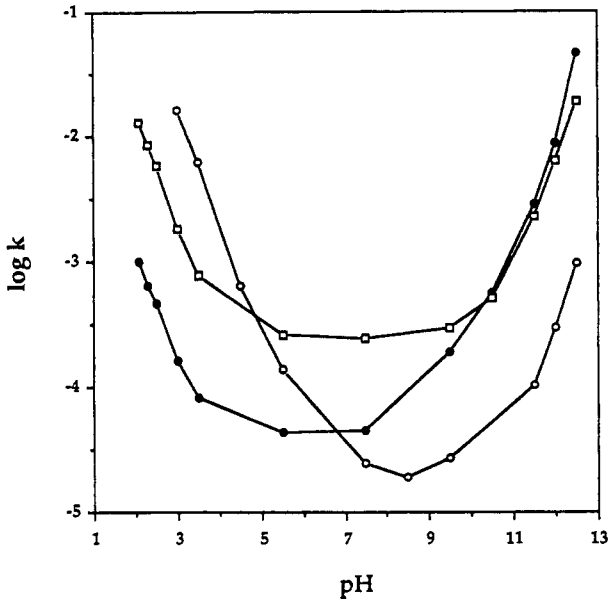


Figure 3. 1-(2-Chloroethyl)-3-methyl-3-acyltriazene pH profiles in 0.1 M lysine buffer, 70 °C: CMA (●), CMC (□), CMM (○).

at which the rate of decomposition was not too rapid to be measured. The rate constants are listed in Table III and graphically displayed in Figures 1–3. To give a complete picture of the triphasic pattern of triazene decomposition, data are also included for the decomposition of these compounds in the acidic and neutral pH regions. These data were discussed in an earlier publication, as was the Guggenheim method which was generally used in the calculation of the rate constants.[2]

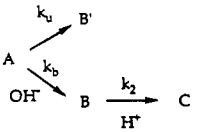
The kinetic analysis of the rate took into account the presence of two competing reactions, uncatalyzed and base-catalyzed hydrolysis. Both of these reactions follow simple first-order kinetics. The observed rate constant, k_{obs}, calculated from the disappearance of triazene with time using the Guggenheim method, is the sum of the two rate constants, $k_{obs} = k_u + k_b$. The specific rate constant for the uncatalyzed reaction is k_u. The rate constant for the base-catalyzed process is $k_b = k_{OH^-}[OH^-]$, where k_{OH^-} is the specific hydroxide ion catalyzed rate constant. The value k_{OH^-} was determined from the slope of the $[OH^-]$ vs

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

	k_{OH^-}[b]	k_u[c]
DMA	3.93×10^{-1} (6)	7.16×10^{-4}
DMC	3.98×10^{-1} (6)	2.96×10^{-3}
DMM	4.96×10^{-4} (3)	2.86×10^{-4}
HMA	6.76×10^{-1} (5)	4.53×10^{-4}
HMC	5.22×10^{-1} (5)	2.24×10^{-3}
HMM	1.53×10^{-3} (4)	1.93×10^{-4}
MHM	6.43×10^{-3} (4)	1.33×10^{-3}
CMA	1.45 (7)	4.36×10^{-5}
CMC	5.84×10^{-1} (7)	2.46×10^{-4}
CMM	2.98×10^{-2} (8)	1.89×10^{-5}

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

Scheme III



k_{obs} plot. Although the intercept of this plot is k_u, a more reliable value for k_u was obtained from zero slope portion of the log k_{obs} vs pH plot rate, where $k_u \gg k_b$ and, hence, $k_{obs} \cong k_u$. The values thus obtained for k_u and k_{OH^-} are listed in Table IV.

Scheme III illustrates a potential complicating feature of the base-catalyzed deacylation. The initial reaction product, the corresponding 1,3-dialkyltriazene, absorbs in the UV and can itself undergo further decomposition by an acid-catalyzed pathway. Thus the potential for consecutive first-order kinetics exists. The formation of a UV-absorbing product does not in itself prevent the accurate determination of k_b or k_{OH^-} by the Guggenheim method.[11] However, if $k_2 \cong k_b$, the Guggenheim method will produce a low value for k_{obs}. In this situation, a better value for the true k_{obs} can be obtained by a consecutive first-order iterative curve-fitting method.[8] Because k_2 and k_b represent acid- and base-catalyzed reactions, respectively, the $k_2 \cong k_b$ condition can be satisfied at only one pH point for each compound. In fact, a consecutive first-order treatment proved necessary for only three k_{obs} calculations and these are so indicated in Table III.

Solvent Deuterium Isotope Effect. Solvent deuterium isotope effects were measured by carrying out parallel reactions in protium and deuterium oxide buffers at the same pOH (pOD), ionic strength, and temperature. The measured pH of the deuterium oxide buffer was corrected according to the relationship $pD = pH_{nominal} - 0.4$.[12] The solvent isotope effect was measured at pH 12.0 in 0.1 M lysine buffers with $NaClO_4$ added to maintain ionic strength. The data are presented in Table V. It should be noted that the k_{H_2O} values are different from those presented in Table III. In preparing the buffers used in this experiment, it was deemed more important to assure an accurate 0.4 pH unit difference in the H_2O and D_2O buffers, and hence no attempt was made to further adjust these buffers to obtain rates which corresponded with those of the initial pH–rate study.

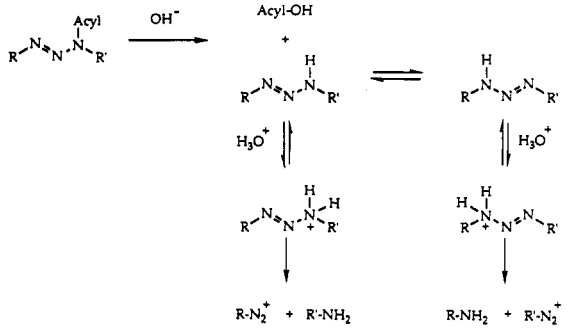
(11) King, E. L. *J. Am. Chem. Soc.* **1952**, *74*, 563.
(12) Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *102*, 188–190.

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

	k_{H_2O}	k_{D_2O}	k_{H_2O}/k_{D_2O}
DMA	4.62	9.81	0.47
DMC	8.34	12.0	0.70
DMM	0.290	0.244	1.20
HMA	6.07	15.1	0.40
HMC	9.58	13.8	0.69
HMM	0.208	0.190	1.10
CMA	13.3	34.6	0.38
CMC	8.97	14.0	0.64
CMM	0.445	1.07	0.42

[a] The rate constants (k_{obsd}, $s^{-1} \times 10^3$) are an average of at least two independent runs varying no more than ±3%. [b] Triazene initial concentration 3.0×10^{-5} M. [c] 0.1 M lysine buffer, pH 12.00, 0.25 M ionic strength (maintained with $NaClO_4$). Nominal pH reading of 12.40 for D_2O buffer.

Scheme IV



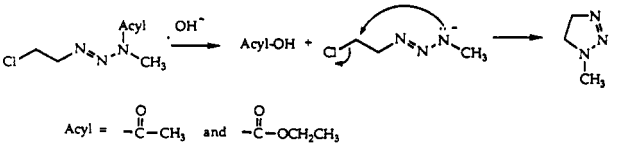
Discussion

The hydrolysis of 1,3-dialkyl-3-acyltriazenes in aqueous buffers in general proceeds by three distinct mechanisms depending upon the pH of the medium. As previously reported, the acid-catalyzed and uncatalyzed decomposition pathways follow the same general mechanistic pattern, heterolysis of the N(2)–N(3) bond, over the entire range of various substituents studied.[4] The present study demonstrates that the base-catalyzed decomposition follows a different route, deacylation, as illustrated in Scheme IV.

The products of the base-catalyzed hydrolysis at pH 13.0, summarized in Table II, show that, with the exception of CMM, all of the 1,3-dialkyl-3-acyltriazenes studied decompose by initial removal of the acyl group. This conclusion is most clearly evident in the case of the 3-acetyl- and 3-carbethoxytriazenes. For each of these compounds, the sole products are the parent 1,3-dialkyltriazene, byproducts derived from the acyl group, and products formed from varying amounts of hydrolysis of the 1,3-dialkyltriazene. An important consequence of this latter reaction is the competitive generation of alkyldiazonium ions from both the N(1) and N(3) alkyl groups. This is in contrast to the acid-catalyzed and uncatalyzed decompositions which yield diazonium ions derived only from the N(1) alkyl group (Scheme I).

The products derived from DMM, HMM, and MHM likewise support the contention that the base-catalyzed mechanism proceeds via deacylation. The presence of additional products associated with N(2)–N(3) heterolysis simply indicate a competitive partitioning of the starting material between the uncatalyzed and base-catalyzed pathways. This competition exists because, even at high pH, the base-catalyzed reaction is slow relative to the uncatalyzed reaction. In Figures 2 and 3, only a slight rate enhancement with increasing pH is observed for these carbamoyltriazenes. Further, comparison of the k_u and k_{OH^-} values (Table IV) gives quantitative evidence of this

Scheme V



competition. Thus, even at pH 13.0, a significant amount of these triazenes decomposes by the uncatalyzed, N(2)–N(3) heterolysis pathway. Clearly, the base-catalyzed deacylation of (methylcarbamoyl)triazenes is a very inefficient reaction.

The base-catalyzed hydrolysis of two of the chloroethyltriazenes, CMA and CMC, gave rise to an unexpected product, 1-methyltriazoline. This result, however, is also consistent with a deacylation reaction. The initial product expected from the deacylation of CMA and CMC is 1-(2-chloroethyl)-3-methyltriazene (CMT). Cyclization of CMT or possibly its anion (triazene $pK_a = \sim 10$)[13] by intramolecular displacement of chloride ion would lead to the formation of 1-methyltriazoline, as shown in Scheme V. This reaction of 1-(2-chloroethyl)-3-acyl-3-alkyltriazenes represents a new route to the formation of 1-alkyltriazolines. It does, however, share some similarities to the methods used by Gaudiano[9] and Heine[14] in their preparations of 1-alkyl- and 1-aryltriazolines, respectively.

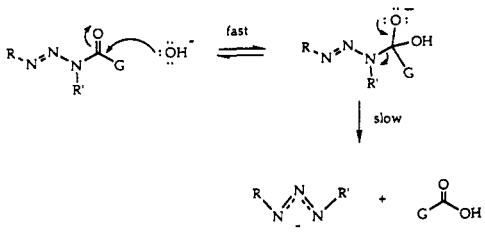
In aqueous solutions at pH 13.0, 1-methyltriazoline (MT) is relatively stable and can be isolated. It is, however, acid labile and would be expected to hydrolyze at pH levels below 10.0. As we have previously reported,[15] the major product of the proton-induced decomposition of MT is predicted on theoretical grounds to be 1-methylaziridine. We have now confirmed this prediction experimentally and the results of that work will be published in the near future.

The base-catalyzed decomposition of CMM follows a pathway which is different from that of all of the other triazenes. The only products formed are VMM, the result of a dehydrohalogenation reaction, and lesser amounts of its subsequent deacylation product, 1-vinyl-3-methyltriazene (VMT). Because no 1-methyltriazoline was observed, there appears to be no significant amount of deacylation of CMM. Dehydrohalogenation is the sole reaction responsible for the base-catalyzed decomposition of CMM. The availability of this relatively efficient alternative to deacylation accounts for the fact that, among the (methylcarbamoyl)triazenes (DMM, HMM, MHM, and CMM), only CMM shows a significant base-catalyzed domain below pH 11.5 (compare Figures 1–3).

The deacylation of 1,3-dialkyl-3-acyltriazenes appears to be specific base-catalyzed. The solvent deuterium isotope effects, k_{H_2O}/k_{D_2O}, measured at pH 12.0 are in general <1 (Table V). The only exceptions are the values obtained for DMM and HMM, a reflection of the mixed mechanisms by which these compounds decompose at pH 12.0. As noted above, even at pH 13.0 the decomposition of these two triazenes involves a significant contribution from the uncatalyzed pathway. The independently measured solvent isotope effects for the uncatalyzed hydrolysis of DMM and HMM are 1.09 and 1.13, respectively.[4] The hydrolysis of esters and amides is normally characterized by general base catalysis with $k_{H_2O}/k_{D_2O} > 1.0$.[16] 3-Formyl-3-alkyl-

(13) McGarrity, J. F.; Smyth, T. *J. Am. Chem. Soc.* **1980**, *102*, 7303–7308.
(14) Heine, H. W.; Tomalia, D. A. *J. Am. Chem. Soc.* **1962**, *84*, 993–995.
(15) Wladkowski, B. D.; Smith, R. H., Jr.; Michejda, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 7893–7897.

Scheme VI



1-aryltriazenes, for example, give a k_{EtOH}/k_{EtOD} of 2.2.[3] There have been reports, however, of specific base catalysis in the hydrolysis of esters and amides.[17]

A deacylation mechanism consistent with specific base catalysis is shown in Scheme VI. It involves rapid reversible attack by hydroxide ion on the carbonyl carbon followed by rate determining heterolysis of the N(3)–acyl bond. This results in the formation of the triazenyl anion, which subsequently can either abstract a proton from solvent or, in the case of the chloroethyltriazenes, cyclize to 1-methyltriazoline. In each of the 3-acyl series, as the substituent on N(1) is varied, the value of k_{OH^-} follows the order: 2-chloroethyl >2-hydroxyethyl > methyl (Table IV). This observation is consistent with inductive electron withdrawal leading to stabilization of both the anionic tetrahedral intermediate, I, as well as the triazenyl anion, II.

The base-promoted dehydrohalogenation of CMM gives a k_{H_2O}/k_{D_2O} of 0.42. This observation suggests an $(E1cB)_R$ mechanism, rapid reversible proton removal followed by rate-limiting loss of chloride. Resonance stabilization of the anion by the adjacent triazene moiety may be responsible for the E1cB type mechanism.

The present work completes the general picture of the hydrolysis of 1,3-dialkyl-3-acyltriazenes in aqueous buffers. Three distinct mechanisms are observed, depending upon the pH of the medium. In acidic solutions, a specific acid-catalyzed pathway dominates. At near-neutral pH, decomposition is by an uncatalyzed route. In both of these mechanisms the same general mechanistic pattern is followed, heterolysis of the N(2)–N(3) bond to generate an alkyldiazonium ion derived solely from the N(1) alkyl group. Hydrolysis in alkaline solutions proceeds by a specific base-catalyzed pathway, which involves initial deacylation and results in the production of the parent 1,3-dialkyltriazene. Subsequent hydrolysis of this triazene can lead to the competitive formation of alkyldiazonium ions from both the N(1) and N(3) alkyl groups.

It has been shown that 1,3-dialkyl-3-acyltriazenes are potent biological alkylating agents[18] possessing significant antineoplastic properties.[19] The present work demonstrates that the specific mechanism by which these triazenes decompose dramatically influences the nature of the alkylating agent produced. This difference will have a profound influence on the interaction of 1,3-dialkyl-3-acyltriazenes with cellular constituents, particularly DNA.

Acknowledgment. Research sponsored by the National Cancer Institute, DHHS, under Contract No. NO1-CO-74101 with ABL and (R.H.S., in part) by a grants from the National Science Foundation (CHE-8521385 and CHE-8910890). The contents of this publication do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. We are grateful to Mr. John Roman for providing mass spectrometry data.

Supplementary Material Available: Copies of supporting ^1H NMR spectra (6 pages). This material is contained in many 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.

(16) Johnson, S. L. In *Advances in Physical Organic Chemistry*; Gold, V., Ed.; Academic Press: New York, 1967; Vol. 5, pp 237–330. Jencks, W. P. *Catalysis in Chemistry and Enzymology*; Dover: New York, 1987 reprint; p 524.

(17) Pritchard, J. G.; Long, F. A. *J. Am. Chem. Soc.* **1956**, *78*, 6008–6013. Bunton, C. A.; Nayak, B.; O'Connor, C. *J. Org. Chem.* **1968**, *33*, 572–575.

(18) Kroeger-Koepke, M. B.; Michejda, C. J.; Smith, R. H., Jr. *Chem. Res. Toxicol.* **1992**, *5*, 541–547.

(19) Smith, R. H., Jr.; Scudiero, D. A.; Michejda, C. J. *J. Med. Chem.* **1990**, *33*, 2579–2583.

Hydrolyses of 2- and 4-Fluoro N-Heterocycles. 4.[1] Proton Inventories of the Hydrolyses of 2-Fluoro-1-methylpyridinium Iodide, 4-Fluoroquinaldine, and 2-Chloro-1-methylpyrimidinium Triflate

Oliver J. Muscio, Jr.,* Jialun Meng, Haisheng Wang, and Songyuan Shi

Department of Chemistry, Murray State University, Murray, Kentucky 42071-3306

Received March 13, 1991 (Revised Manuscript Received August 21, 1992)

Rate constants for the hydrolyses of 2-fluoro-1-methylpyridinium iodide (**3**), 4-fluoroquinaldine (**4**), and 2-chloro-1-methylpyrimidinium triflate (**5**) in 2×10^{-3} M aqueous sulfuric acid, in D_2O/D_2SO_4, and in mixed H_2O/H_2SO_4–D_2O/D_2SO_4 media are reported. Significant solvent deuterium kinetic isotope effects are evident, with k_H/k_D = 2.07 for **3**, 1.62 for **4**, and 2.12 for **5**. The results of the proton inventories for the hydrolyses of **3** and **5** are best fit by a form of the Gross–Butler equation for three nearly equivalent sites with fractionation factors of 0.78. The proton inventory of **4** does not yield a unique solution to the Gross–Butler equation, but the results are also consistent with three transition state sites with nearly equal fractionation factors of 0.72–0.78, as well as an additional transition-state site with $\phi > 1$ and a reactant site with $\phi \leq 1$. These proton inventories are consistent with mechanisms in which nucleophilic addition of water in the rate-determining step is assisted by proton-transfer to a second water molecule, with development of an "immature hydronium ion" in the transition state. Mechanisms with cyclic proton transfer are also consistent, but are less satisfactory as hydrolysis routes.

In an earlier report[2] on the acid-catalyzed hydrolyses of 2-fluoropyridine (**1**) and 2-fluoropyrimidine (**2**), as well as several other related fluoropyridines and pyrimidines in hydrochloric acid solutions of up to 6 M concentration,

0022-3263/92/1957-6454$03.00/0