Triazinines: Synthesis and Proteolytic Decomposition of a New Class of Cyclic Triazenes

Brigitte F. Schmidt,[†] Emily J. Snyder,[†] Robin M. Carroll,[‡] David W. Farnsworth,*[,†] Christopher J. Michejda,[†] and Richard H. Smith, Jr.[†,‡]

Molecular Aspects of Drug Design Section, ABL-Basic Research Program, NCI-Frederick Cancer Research and Development Center, Frederick, Maryland 21702, and Department of Chemistry, Western Maryland College, Westminster, Maryland 21157

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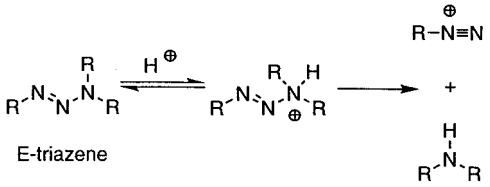
The reaction of 1-azido-3-chloropropane with various Grignard reagents and subsequent treatment with anhydrous isopropylamine results in the formation of the corresponding azimine. If the initial magnesium−triazene complex is first hydrolyzed with Dowex resin and then concentrated, the resultant linear triazene begins self-catalyzed cyclization to form the six-membered-ring triazenes as the major product, with HCl as the byproduct. Addition of an amine, at reduced temperature, allows for the neutralization of the byproduct, HCl, which would otherwise react with the linear triazene and the cyclic six-membered-ring triazene to form hydrolysis products. We have assigned the trivial name of triazinines to this new class of cyclic triazenes. The hydrolytic decomposition of these compounds in mixed acetonitrile−aqueous buffers predominantly forms 3-(alkylamino)-1-propanol and lesser amounts of the rearranged alcohol 1-(alkylamino)-2-propanol and *N*-alkyl-2-propenamine. The rate of hydrolysis of 1-alkyltriazinines is approximately equal to that of the analogous 1,3,3-trialkyltriazenes, about three times slower than that of the analogous 1-alkyltriazolines, and varies in the order ethyl > butyl > 3,3-diethoxypropyl > benzyl. As was true for other triazenes, the mechanism of the decomposition was found to be specific acid-catalyzed (A1), involving rapid reversible protonation followed by rate-limiting formation of a 3-(alkylamino)propyldiazonium ion. The slopes of the log k_{obs} versus pH plots were near −1.0. The solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}, was in all cases <1.0 and ranges from 0.82 for 1-benzyltriazinine to 0.89 for 1-ethyltriazinine. The activation parameters of the proteolytic decomposition of a series, 1-ethyltriazinine, 1-ethyltriazoline, 1,3,3-triethyltriazene, and 1-ethyl-3-methyltriazene, had similar values for $\Delta H^{\ddagger}$ (+9 → 12 kcal/mol) and $\Delta S^{\ddagger}$ (+7 → 15 eu), respectively.

Introduction

We have been interested in the chemistry and biological properties of triazenes for over a decade. The chemistry of acyclic 1,3-dialkyl- and 1,3,3-trialkyltriazenes has been studied extensively. Efficient methods were developed for their synthesis from alkyl azides,[1,2] and their hydrolytic decomposition in aqueous buffers was shown to be specific acid-catalyzed.[3,4] In general, the mechanism of proteolytic decomposition of all of the triazenes studied involves a rapid and reversible protonation at N(3) followed by N(2)−N(3) heterolysis which leads to the formation of a diazonium ion[5] intermediate, as indicated in Scheme 1.

Recently we reported on the chemistry of simple triazolines[6,7] and a related class of high nitrogen compounds, the azimines.[8] Preparation of triazolines can be accomplished by either base-catalyzed decomposition of 1,3-dialkyl-3-acyltriazenes[6] or by a slight modification of a previously reported synthesis involving the reaction of alkyl azides with dimethylsulfoxonium methylide.[7] The reaction of 1-azido-3-chloropropane followed by treatment with anhydrous isopropylamine results in the smooth formation of azimines.[8]

Scheme 1



Numerous cyclic triazenes, where the ring system contains a carbonyl or imine group and is fused to an aromatic moiety, have been reported.[9] Chemical and biological studies[10] of these triazinones lead to derivatives containing an imidazole ring.[11−13] These compounds have been studied as prodrugs which upon hydrolysis ring open to linear triazenes[14] analogous to the antitumor drug DTIC.[15]

Small to medium-sized cyclic triazenes constrain the triazene group to a *Z*-configuration (as opposed to the

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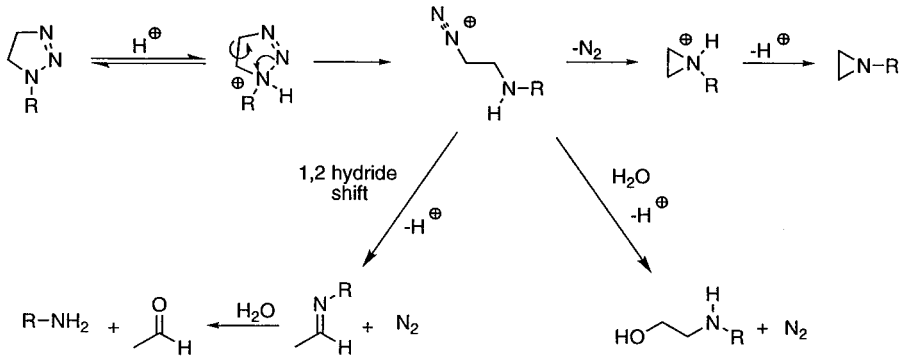
Scheme 2



E-form found in acyclic triazenes), and therefore cyclic triazenes present an opportunity to explore the chemistry of the *Z*-triazene moiety.[6,7] Triazolines, 4,5-dihydro-1,2,3-triazoles, are perhaps the best known simple cyclic triazenes. Their chemistry has been dominated by the study of thermolysis reactions[16] with several reports of acid-induced decompositions, generally involving bi- and tricyclic-1-aryltriazolines.[17] The hydrolysis of triazolines involves the protonation of the triazoline N(1),[18] followed by heterolytic cleavage of the N(1)−N(2) bond to generate the 2-(methylamino)ethyldiazonium ion, which undergoes further transformations to the final products, Scheme 2.

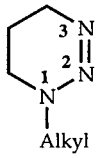
In the present work, we describe the synthesis of a new class of cyclic triazenes,1-alkyltriazinines. In addition, we report the results of an investigation of the products and mechanism of their acid-catalyzed decomposition in aqueous buffers. The compounds discussed in this paper are listed in Table 1.

Results

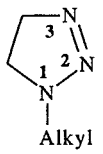
Product Studies. The decomposition reaction of each triazinine was followed periodically by ^{1}H NMR analysis, typically at times of 0, 0.5, 5, 24, 48, and 72 h. Product yield data are recorded in Table 2 for the earliest time at which all of the triazinine had disappeared, for **1** this was 5 h (no further change in product distribution was observed up to 72 h) and 5 h for **3**. Values are reported as a percentage of the total *N*-ethyl- or *N*-benzyl-containing products, respectively. Each triazinine compound contained a small amount of azimine. Because this compound is stable to the reaction conditions and does not appear to influence the reaction, it served as a convenient internal standard for product peak integration. The identity of each product was determined by the addition of standard compounds or by comparison with spectra of authentic material.

pH Dependence of the Rate of Triazinine Decomposition. The rates of decomposition of representative triazinines, 1-ethyl- and 1-benzyltriazinine, were determined in buffers over a range of pH levels. The data are presented in Table 3. Plots of log k_{obs} versus pH for these data are displayed in Figure 1. The slopes and intercepts

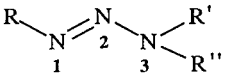
Table 1. Structure and Abbreviations of Compounds Studied



Compound	1-Alkyl
1	ethyl
2	butyl
3	benzyl
4	3,3-diethoxypropyl



Compound	1-Alkyl
5	ethyl
6	benzyl



Compound	R
7	R = R' = R'' = ethyl
8	R=methyl, R'=ethyl, R''=H

for the lines in Figure 1 are as follows: **1**, −0.833, 6.06; **3**, −0.840, 5.56. The coefficient of determination (r^2) are 0.996 and 0.999, respectively.

Relative Rates of Decomposition of 1-Alkyltriazinines. The rate of decomposition of the series of 1-alkyltriazinines was determined in pH 10.00, 0.10 M lysine buffer at 25 °C. Added to this study was an acyclic triazene, 1,3,3-triethyltriazene **7**, and two cyclic triazenes, 1-ethyl- and 1-benzyltriazolines **5** and **6**, for comparison purposes. The rate constants obtained from these studies are included in Table 4, which shows that 1-alkyltriazinines are approximately as reactive as the analogous trialkyltriazenes but less reactive than the analogous 1-alkyltriazolines under the reaction conditions.

Solvent Deuterium Isotope Effect. The rates of decomposition of all of the simple 1-alkyltriazinines were measured in D_2O buffers of p*D* equivalent to the pH (10.00) of the analogous H_2O buffers used in the relative rate studies. In preparing the D_2O buffers, the nominal pH readings were 9.60, corrected according to the rela-

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(18) The numbering for cyclic triazenes is different than that for the acyclic. The saturated nitrogen in cyclics is designated as N(1), while in acyclics it is designated as the N(3) nitrogen.

Table 2. Products and Yields[a] from the Hydrolysis of 1-Ethyl- and 1-Benzyltriazinine at 25 °C in Aqueous Buffers[b]

1-ethyltriazinine[c]	% product [5 h][d]
3-(ethylamino)-*n*-propanol	44.7
N-ethyl allylamine	11.1
3-(ethylamino)-2-propanol	11.0
propionaldehyde[e]	9.2
ethylamine	19.0
1-benzyltriazinine[c]	**% product [5 h][d]**
3-(benzylamino)-*n*-propanol	56.2
N-benzyl allylamine	13.3
3-(benzylamino)-2-propanol	16.8
propionaldehyde[e]	12.3
benzylamine	24.3

[a] Yields were determined by ^{1}H NMR analysis and are based on the percent of total *N*-Et or *N*-benzyl signals present in the spectra as compared to the internal standard. [b] The buffer was 25% (v/v) CD_3CN in D_2O containing 0.05 M sodium phosphate. [c] The initial triazinine concentration was 0.5 M for each study. [d] The value in the brackets represents the time at which all triazinine was first noted to be absent from the ^{1}H NMR and also represents the time at which product yields were determined. [e] Reported propionaldehyde yield is the total combined yield of propionaldehyde and its hydrate, present in approximately equal amounts.

Table 3. pH Profile for Rate[a] of Decomposition of 1-Alkyltriazinines[b] in 0.1 M Lysine Buffers[c] at 25° C

	compd	
pH	**1**	**3**
10.00	5.25	1.45
10.25	3.34	0.875
10.50	2.02	0.529
10.75	1.37	0.346
11.00	0.745	0.206

[a] k (s^{-1}) $\times 10^3$, average of two independent runs (<3% variablity). [b] Triazinine initial concentration was 3×10^{-5} M. [c] 0.25 M ionic strength, maintained with added Na_2SO_4.

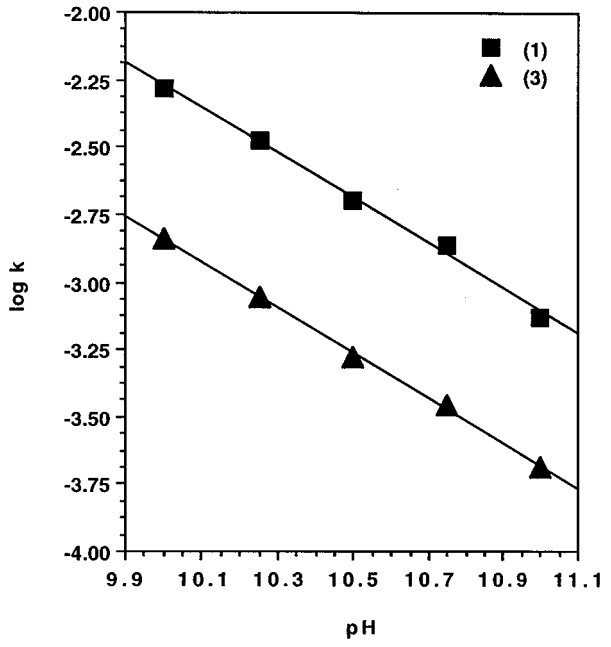

Figure 1. Plots of log k_{obs} vs pH for the decomposition of 1-alkyltriazinines in 0.1 M lysine buffers at 25 °C.

tionship $pD = pH_{nominal} - 0.4$.[19] The measured rates of decomposition in D_2O buffers and the calculated values for the solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}, are recorded in Table 4. The solvent isotope effects varied somewhat with triazinine structure, but in all cases k_{H_2O}/k_{D_2O} was < 1.0. Ethyltriazoline **5**, included in the study as a control, produced a value, 0.58, comparable to that previously reported, 0.62.[7]

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Table 4. Solvent Isotope Effects on the Rate[a] of Decomposition of 1-Alkyltriazinines[b] in Aqueous Buffers[c]

comps	relative rate[d]	k_{H_2O}	k_{D_2O}	k_{H_2O}/k_{D_2O}
1	1.00	6.02	6.74	0.89
2	0.49	2.94	3.38	0.87
3	0.25	1.53	1.86	0.82
4	0.27	1.63	1.92	0.85
5	2.70	16.18	27.90	0.58
6	0.97	5.86		
7	1.02	6.13		

[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] Triazinine initial concentration 3.0×10^{-5} M. [c] 0.1 M lysine buffer, pH 10.00, 0.25 M ionic strength (maintained with Na_2SO_4). Nominal pH reading of 9.60 for D_2O buffer. [d] Rates based on the lead compound, 1-ethyltriazinine, normalized to 1.00.

Table 5. Temperature Profile for Rate[a] of Hydrolysis of Cyclic[b] and Acyclic Triazenes[b] in 0.1 M Lysine Buffers[c] and Their Associated Activation Parameters[d]

	compd			
temperature (°C)	**1**	**5**	**7**	**8**
20.0	3.82	11.12	3.81	0.11[e]
22.5	4.51	12.93	4.71	0.14[e]
25.0	5.36	14.67[e]	5.65	0.17
27.5	6.04	16.59[e]	6.46[e]	0.20
30.0	7.03	18.46[e]	7.55	0.24
	activation parameters			
$\Delta H^{\ddagger}$, kcal/mol	10.10	8.32	11.28	12.47
$\Delta S^{\ddagger}$, cal/°C mol	10.64	6.72	14.71	11.73
$\Delta G,^{\ddagger}$ kcal/mol[f]	6.93	6.32	6.90	8.97

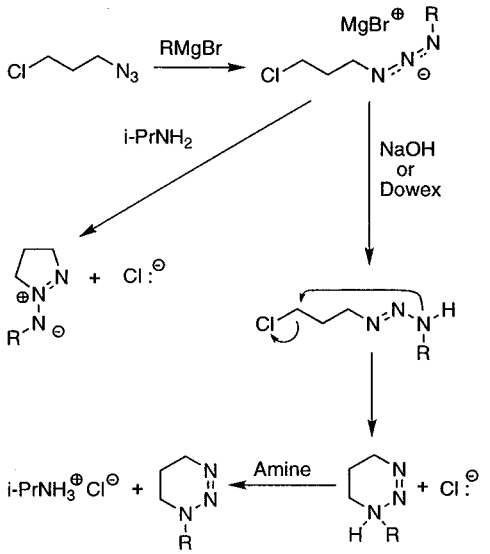
[a] k_{obs} (s^{-1}) $\times 10^3$ average of two independent runs (<3% variability). [b] Initial concentration was 3×10^{-5} M. [c] 0.25 M ionic strength, maintained with added Na_2SO_4. [d] Calculated by using values of $k_{obs} \times [H_3O^+]^{-1}$; $[H_3O^+] = 1.0 \times 10^{-10}$. Least-squares analysis of each line gave a correlation coefficient of a least 0.993. [e] Average of three independent runs (<3% variability). [f] Calculations performed at 25 °C.

Activation Parameters of 1-Alkyltriazenines. The dependence of the rate of decomposition upon temperature was determined for 1-ethyltriazinine **1** and, for comparison purposes, three additional triazenes, 1-ethyltriazoline, **5**, 1,3,3-triethyltriazene, **7**, and 1-ethyl-3-methyltriazene **8** [which exists as a mixture of two tautomers[5]]. The data, shown in Table 5, were determined in a pH 10.0, 0.10 M lysine buffer. Values for k_{obs} were obtained at five different temperatures ranging from 20 to 30 °C. Duplicate and, in some cases, triplicate runs were performed. Adjustments for pH were made by dividing the averaged k_{obs} by the $[H_3O^+]$ to give k_{spec}. Plots of log $[k_{spec}/T$ (K)] versus $1/T$ (K) gave slopes and intercepts used to calculate the activation parameters, $\Delta H^{\ddagger}$ (kcal/mol) and $\Delta S^{\ddagger}$ (cal/deg mol eu). The values calculated are for **1**, [10.10, 10.64]; for **5**, [8.32, 6.72]; for **7**, [11.28, 14.71]; and for **8**, [12.47, 11.73], respectively. The values for **8** are in good agreement with those previously reported [12.67, 11.36].[5] The $\Delta H^{\ddagger}$ values favor the reactivity order: **5** > **1** > **7** > **8**, but the $\Delta S^{\ddagger}$ values appear to predict a different order.

Discussion

We report herein the preparation of a new class of cyclic triazenes, one in which the triazene moiety is incorporated in a six-membered ring. By analogy with the five-membered analogues, triazolines, we have chosen the trivial name triazinine for the members of this class.

Scheme 3



We had previously reported that the reaction of 1-azido-3-chloropropane with alkyl Grignard reagents, followed by the addition of isopropylamine, leads to the formation of *N*-alkylazimines.[8] In that publication we noted that hydrolysis of the initial magnesium salt with aqueous NH_4OH/NH_4Cl buffers permits the isolation of the linear triazene, 1-alkyl-3-(3-chloropropyl)triazene.

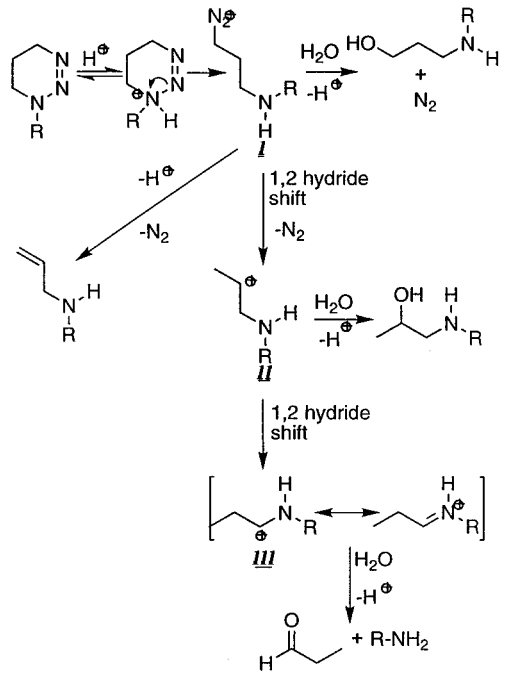
We now report that, in the workup, replacement of isopropylamine with Dowex or NH_4OH/NH_4Cl buffer at 0 °C leads to the immediate formation of the 1-alkyl-3-(3-chloropropyl)triazenes. Upon concentration this linear triazene undergoes self-catalyzed cyclization to triazinine, with small amounts of azimine and much decomposition. If, on the other hand, concentration is followed immediately by the addition with cooling of an amine, a less rapid, more controlled formation of the triazinine occurs with little decomposition. Presumably, the amine stabilizes the formation of 1-alkyltriazinines by neutralizing the byproduct of the displacement reaction, HCl. In the procedure described herein, the linear triazene was not purified, but simply formed through Grignard hydrolysis with Dowex-resin or NH_4OH/NH_4Cl buffers and immediately reacted with isopropylamine. The presumed mechanism for this reaction involves intramolecular displacement of the chloro group by the more distant of the three nitrogens of the triazene moiety (Scheme 3). In this mechanism we have chosen to use the 3-alkyl-1-(3-chloropropyl) tautomer of the linear triazene as the reactant and its N3 as the nucleophile. It is also possible that the reaction could occur by N1 of the 1-alkyl-3-(3-chloropropyl) tautomer functioning as the nucleophile.

As mentioned above, for the purposes of preparing the compounds, we did not isolate the linear triazene intermediate but rather carried out the cyclization step as rapidly as possible (to minimize degradation of the intermediate and product triazenes by the HCl formed). We did, however, want to better understand the mechanism for triazinine formation. This study required the formation of the linear triazene, which was prepared as described above but not concentrated. The resulting solution was dried and kept cold. Determinations by NMR and thin-layer chromatography showed the linear triazene to be stable in solution for as long as the study was carried out, ~3 weeks. [Note: when kept in ether or THF, the linear triazene was only stable when the solution was very dry; absorbed moisture caused bubbling and the appearance of a white precipatate, indications of cyclization and decomposition.] To study the mechanism of cyclization, aliquots of the linear triazene solution were concentrated and immediately taken up in various amines and then cooled to −20 °C. These were compared with concentrated linear triazene, which was cooled but had no amine added. The reactions were followed by TLC, which after several days indicated that all of the amine-containing reactions formed substantial amounts of the cyclic triazinine. For several amines, a small amount of the corresponding azimine was observed. These experiments showed that (1) all amines tested [isopropyl, diisopropyl, diethyl, triethyl, and pyridine] allowed the formation of triazinines, with minimal amounts of decomposition, as compared to the reaction with no amine present, and (2) concentration alone caused initial cyclization, with subsequent decomposition of the product triazinine and the starting linear triazene to give final products which contain only a small amount of the azimine and mainly non-triazene-containing hydrolysis products.

In principle, it might be expected that the chemistry of 1-alkyltriazinines would be similar to that of the five-membered analogues, 1-alkyltriazolines. Previously reported work[7] on the hydrolytic decomposition of triazolines in the presence of acids found the major product to be an *N*-alkylaziridine, the result of acid-catalyzed ring opening followed by loss of molecular nitrogen and reclosure of the ring, as shown in Scheme 2. Lesser amounts of 2-(alkylamino)ethanols, acetaldehyde, and alkylamines were also observed.

The data presented in Table 2 show that the decomposition of a representative 1-alkyltriazinine, **1**, in 25% acetonitrile−75% aqueous phosphate buffer leads to a mixture of ring-opened products. At no time during the decomposition did product studies show the presence of either an azetidine or an aziridine. It had been shown previously[7] that under the same reaction conditions the aziridine would be quite stable. As little as ~2.5% yield of aziridine could be detected by NMR. These facts appear to rule out any aziridines as possible products of, or intermediates in, the decomposition of 1-alkyltriazinines. The major product, formed in 45% yield, is 3-(ethylamino)-1-propanol. In addition, lesser amounts of 3-(ethylamino)-2-propanol, *N*-ethyl-2-propenamine, ethylamine, and propionaldehyde are also formed. The latter two products presumably result from the initial formation and subsequent hydrolysis of *N*-propylideneethanamine. A proposed mechanism to explain the formation of the above products is shown in Scheme 4. By analogy with 1-alkyltriazolines, protonation at N(1) is the likely step that initiates decomposition. Heterolysis of the N(1)−N(2) bond generates 3-(alkylamino)-propyldiazonium ion, species *I* in Scheme 4, a common intermediate for the formation of all of the observed products. Nucleophilic displacement of molecular nitrogen followed by transfer of a proton to solvent would account for the major product, 3-(alkylamino)-1-propanol. Removal of a proton from carbon-2, concerted with loss of nitrogen, leads to the formation of the elimination product *N*-alkyl-2-propenamine. As has been observed for the proteolysis of 1-alkyltriazolines[7] and acyclic 1,3-dialkyltriazenes,[4] loss of nitrogen can also be accompanied by a 1,2-hydride shift to form a secondary carbocation, *II*. Reaction with water produces 3-(alkylamino)-2-propanol. Alternatively, a second 1,2-hydride shift would produce the stabilized cation *III*. Reaction of this species with water would then account for the formation of alkylamine and propionaldehyde. The yields of prod-

Scheme 4



ucts derived from the unrearranged (*I*) and rearranged (*II*) cationic species favor the former, a pattern reminiscent of that found both in 1-alkyltriazolines[7] and acyclic 1,3-dialkyltriazenes.[4]

The products of the acid-mediated decomposition of **3** in mixed acetonitrile−buffer solutions are in general similar to those observed from **1**. 1-Benzyltriazinine gives rise to 3-(benzylamino)-1-propanol, 3-(benzylamino)-2-propanol, benzylamine, and propionaldehyde. The latter two products again suggest the formation and subsequent hydrolysis of *N*-propylidenebenzylamine.

Overall, the decomposition of simple 1-alkyltriazinines in aqueous buffers involves the formation of a 3-(alkylamino)propyldiazonium ion and yields the related 3-(alkylamino)-1-propanol as the major product. The nature of the 1-alkyl group had very little influence on the product distribution.

Previous studies of acyclic triazenes[3,4] and 1-alkyltriazolines[7] have shown that the general mode of acid-catalyzed hydrolysis in aqueous buffers follows a specific acid-catalyzed, A1, mechanism. This involves rapid reversible protonation followed by rate-determining formation of an alkyldiazonium ion.

The mechanism of the hydrolytic decomposition of triazinines is acid-catalyzed. The data in Table 3 and Figure 1 show a direct and linear dependence of the rate of decomposition of **1** and **3** on the hydronium ion concentration of the buffer. Consequently, the slopes of the log(k_{obs}) versus pH plots are near −1.0. For all 1-alkyltriazinines studied, hydrolysis is more rapid in D_2O than in H_2O buffers (Table 4). The calculated solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}, varies from 0.89 for **1** to 0.82 for **3**. Taken together, these data again point to a specific acid-catalyzed mechanism, A1, in which rapid reversible protonation of the substrate occurs prior to the rate-limiting N(1)−N(2) heterolysis step. [Note that the numbering of the triazene moiety in cyclic triazenes is the reverse of that in acyclic triazenes.][18]

Rates of decomposition for various simple 1-alkyltriazinines, Table 4, follow the order ethyl > butyl > 3,3-diethoxypropyl > benzyl. This pattern is similar to that seen with 1-alkyltriazolines,[7] ethyl > methyl > propyl > benzyl. It is reasonable to assume that N(1) substituents such as benzyl (and 3,3-diethoxypropyl) exert a rate-retarding effect through inductive electron withdrawl, which destabilizes the conjugate acid form of the substrate. Given a specific acid-catalyzed mechanism, the overall rate for substrate disappearance is $(1/K_a)k_{dissoc}$, where K_a is the acidity of the conjugate acid form of the neutral triazene and k_{dissoc} is the rate of N(1)−N(2) heterolysis. When the basicity of the neutral substrate is reduced, these N(1) substituents retard the overall rate of triazinine proteolysis. The order ethyl > butyl is counter to the inductive effect and suggests that steric inhibition reduces the ability of the solvent to stabilize the conjugate acid of the substrate.

1-Alkyltriazinines decompose about as fast as the analogous 1,3,3-trialkyltriazenes; compare the rates for **1** and **7** in Table 4. It can also be seen (Table 4) that 1-alkyltriazinines decompose approximately three to four times slower (1-ethyl, 6.02×10^{-3} s^{-1}; 1-benzyl, 1.53×10^{-3} s^{-1}) than the analogous 1-alkyltriazolines (1-ethyl, 1.62×10^{-2} s^{-1}; 1-benzyl, 5.86×10^{-3} s^{-1}). We believe these factors to be the result of a rather complex combination of structural effects on both K_a and k_{dissoc}.

The dependence of the rate of decomposition upon temperature was determined for 1-ethyltriazinine **1**, 1-ethyltriazoline **5**, 1,3,3-triethyltriazene **7**, and 1-ethyl-3-methyltriazene **8** (data shown in Table 5). Several conclusions can be extracted from the results: (1) the form of the triazene [cyclic or acyclic] seems to have little effect on stability of the triazene moiety, (2) the small positive values for the entropy of activation implies little ordering in the transition state, and (3) the enthalpy order **5** > **1** ≥ **7** > **8** suggests that the higher reactivity of the triazoline is reflected in the enthalpy of activation, rather than in the entropy. The behavior of triazinines is very similar to that of acyclic trialkyltriazenes.

In summary, 1-alkyltriazinines can be prepared in good yield by an amine-mediated cyclization of linear (3-chloropropyl)triazenes, though the latter substances cannot be isolated in pure form due to spontaneous cyclization accompanied by decomposition. The general pattern by which 1-alkyltriazinines undergo hydrolysis in aqueous buffers involves a specific acid-catalyzed (A1) mechanism, rapid reversible protonation of N(1) followed by rate-limiting heterolysis of the N(1)−N(2) bond. This is very similar to the mechanisms previously reported for acyclic triazenes[3,4] and 1-alkyltriazolines.[7] The key intermediate generated is the 3-(alkylamino)propyldiazonium ion, a species which is then partitioned among several different pathways, with direct displacement of molecular nitrogen dominating. The rates of reaction, due to the alkyl substituents, follow that of their closely related cyclic analogues, 1-alkyltriazolines, as opposed to their linear analogues.

Experimental Section

Safety Note. Because acyclic triazenes are potent biological alkylating agents, it is only prudent to assume that 1-alkyltriazinines are also potentially toxic and carcinogenic. At all times, efficient hoods and protective clothing should be used in working with these substances. Further, 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 alkyl azide used in the preparation of 1-alkyltriazinines has been reported previously.[2,4,5] The preparation of buffers and the UV determina-

tions for both chemical analysis and kinetic studies have been reported.[4−7] NMR spectra were obtained on a Varian XL-200 spectrometer. All samples submitted for exact mass determination were shown to be of >92% purity by ^{1}H NMR analysis. The major impurity in these samples was found to be the corresponding azimine. Removal of final traces of this impurity is extremely difficult due to the extreme sensitivity of 1-alkyltriazinines to hydrolytic decomposition.

Because of the above-stated reactivity of 1-alkyltriazinines, we determined that combustion analysis is not an appropriate method of establishing purity or identity. An alternative method, high-resolution mass spectrometric molecular formula determination, was instead chosen. Exact mass measurements were determined on either a VG 70-250 mass spectrometer using a peak matching technique or on a ZAB-2F, using fast atom bombardment (FAB) and peak matching. (See Supporting Information for availability of these spectra.)

1-Ethyltriazinine (1). To a 2.4 g (20 mmol) solution of chloropropyl azide in 30 mL of dry THF was added, dropwise, 21 mmol of ethylmagnesium chloride under N_2 at −30 °C. Over the next 30−45 min the reaction warmed to −10 °C and was hydrolyzed with 5 g of DOWEX (RG 501-X8, 20−50 mesh, fully generated). The magnesium salt was precipitated with 30 mL of diethyl ether and filtered, and the filtrate was concentrated in vacuo. The yellowish oil was immediately diluted with 8.5 mL of isopropylamine and refrigerated overnight. The precipitate was filtered off and the filtrate concentrated. The resultant oil was purified by column chromatography, using basic Al_2O_3 eluted with (90:10) diethyl ether/isopropylamine [$R_f = 0.7$] to yield 735.9 mg (31%): UV (CH_3CN) λ_{max} 243 nm (log ϵ 3.90); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.25 (3H, t, $J = 7.21$ Hz), 1.79 (2H, dt, $J = 5.84$ Hz, $J = 6.60$ Hz), 3.22 (2H, dt, $J = 6.60$ Hz, $J = 1.54$ Hz), 3.47 (2H, dt, $J = 5.84$ Hz, $J = 1.54$ Hz), 3.61 (2H, q, $J = 7.21$ Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.0, 15.7, 43.3, 47.0, 50.9; exact mass calcd *m/z* for M^+, $C_5H_{11}N_3$ 113.0953, found 113.0977 (by EI).

Preparation of Other Triazinines. The above reaction procedure was used in the synthesis of each of the following triazinines.

1-Butyltriazinine (2) was obtained in 10% yield following purification by column chromatography, using neutral alumina eluted with (9:1:0.5) pentane/diethyl ether/isopropylamine [$R_f = 0.4$]: UV (CH_3CN) λ_{max} 243 nm (log ϵ 3.83); ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ 0.95 (3H, t, $J = 7.38$ Hz), 1.37 (2H, m), 1.63 (2H, m), 1.79 (2H, dq, $J = 6.55$ Hz, 5.87 Hz), 3.22 (2H, tt, $J = 6.55$ Hz, 1.51 Hz), 3.37 (2H, dt, $J = 5.87$ Hz, 1.51 Hz), 3.56 (2H, t, 7.3 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.8, 15.7, 19.8, 30.0, 44.0, 46.9, 56.2; exact mass calcd *m/z* for MH^+ $C_7H_{16}N_3$ 142.1344, found 142.1347 (by FAB).

1-Benzyltriazinine (3) was obtained in 47% yield following purification by column chromatography, using neutral alumina eluted with (9:1:0.5) pentane/diethyl ether/isopropylamine [$R_f = 0.3$]: UV (CH_3CN) λ_{max} 244 nm (log ϵ 4.02); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.73 (2H, m), 3.11 (2H, tt, $J = 6.50$ Hz, $J = 1.56$ Hz), 3.48 (2H, tt, $J = 7.86$ Hz, $J = 1.56$ Hz), 4.77 (2H,s), 7.32 (5H, m); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 15.5, 43.3, 46.9, 60.3, 126.9, 127.9, 128.6, 136.9; mass calcd *m/z* for M^+, $C_{10}H_{13}N_3$ 175.1205, found 175.1109 (by EI).

(3,3-Diethoxypropyl)triazinine (4) was obtained in 47% yield following purification by column chromatography, using neutral alumina eluted with (7:5:0.5) pentane/diethyl ether/isopropylamine [$R_f = 0.5$]: UV (CH_3CN) λ_{max} 243 nm (log ϵ 3.84); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.21 (3H, t, $J = 7.05$ Hz), 1.79 (2H, dt, $J = 5.95$ Hz, $J = 6.60$ Hz), 2.0 (2H, dt, $J = 5.67$ Hz, $J = 7.33$ Hz), 3.23 (2H, tt, $J = 6.60$ Hz, $J = 1.56$ Hz), 3.47 (2H, tt, $J = 5.95$ Hz, $J = 1.56$ Hz), 3.58 (2H, q, $J = 7.05$ Hz), 3.64 (2H, t, $J = 7.33$ Hz), 4.58 (1H, t, $J = 5.59$ Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 15.3, 15.8, 32.4, 44.4, 47.1, 52.4, 61.6, 101.1; mass calcd *m/z* for MH^+, $C_{10}H_{22}N_3O_2$ 216.1712, found (relative intensity) 216 (by FAB).

Product Studies. The products of hydrolytic decomposition were determined for 1-ethyl- and 1-benzyltriazinine by carrying out reactions in solutions containing 25% (v/v) acetonitrile-d_3 dissolved in 0.05 M buffers of sodium phosphate in D_2O adjusted to the appropriate pH with a D_2O solution of NaOD. A previous study[7] determined that the formation of products was unaffected by the presence of acetonitrile. The addition of this cosolvent, however, permits the use of more highly concentrated, and thus more easily analyzed, reaction solutions. In a typical experiment, buffer plus acetonitrile-d_3 was added to a weighed amount of the compound. The sample was mixed thoroughly to ensure homogeneity, and 0.5 mL was placed in a capped NMR tube. The reaction course was followed[7] until all of the starting triazinine had been decomposed. The initial triazinine concentration in each reaction was 0.050 M. It was shown that after the triazinine was completely decomposed, the pH had changed by no more than ±0.4 pH unit. Assignment of the NMR peaks arising from the various products was made by comparison with authentic samples and by coincidence of peaks upon the addition of authentic materials. Yields were determined by comparative integration of the product peaks. In the case of 1-benzyltriazinine, several products were confirmed by reports in the literature.[20,21]

Kinetic Studies. The method employed for the preparation of the buffers used in these kinetic studies has been reported previously.[4−7] Rates of triazinine decomposition in aqueous solution were followed spectrophotometrically.[4−7] 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 triazinine was followed by monitoring the change in absorbance at its highest wavelength λ_{max} (see Experimental 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 Na_2SO_4) and the reaction was initiated by the addition of 9 μL of a 4.5×10^{-3} M solution of the 1-alkyltriazinine in acetonitrile; the initial triazinine concentration was thus 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 least-squares method.[22] The rate constants were an average of at least two separate runs with standard errors of less than 3%. In several cases, 100 absorbance vs time readings were unable to be obtained; in those experiments a minimum of at least three independent runs were used with standard errors of less than 3%. Temperature studies were performed in a similar fashion, using 1-cm thermostated cells connected to a circulating waterbath maintaining constant temperature to within ±0.1 °C. Buffers used in these studies were pH adjusted at the temperature at which a particular rate was to be determined.

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Supporting Information Available: Supporting ^{1}H NMR and ^{13}C NMR spectra (12 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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