$$-d[M_i]/dt = k_{inter}[M_i][\sim\!\!\sim CH_2Br] \quad (10a)$$

and

$$-d[M_j]/dt = k_{inter}[M_j][\sim\!\!\sim CH_2Br] \quad (10b)$$

from which

$$d[M_i]/dt = d[M_j]/dt \quad (11)$$

or

$$[M_i] = [M_j] \quad (12)$$

during the whole course of the reaction. Now, since

$$d[C_i]/dt = (k_{intra})_i[M_i] \quad (13a)$$

and

$$d[C_j]/dt = (k_{intra})_j[M_j] \quad (13b)$$

one obtains

$$d[C_i]/d[C_j] = (k_{intra})_i[M_i]/(k_{intra})_j[M_j] \quad (14)$$

from which eq 4 follows, remembering eq 12 and integrating between limits.

Registry No. I, 88083-55-0; II, 88083-56-1; III, 88083-57-2; $BuC(CO_2Et)_2^-$, 14851-09-3; BuBr, 109-65-9; $Br(CH_2)_6C(CO_2Et)_2^-$, 88083-58-3; $Br(CH_2)_7C(CO_2Et)_2^-$, 88083-59-4; $Br(CH_2)_8C(CO_2Et)_2^-$, 88083-60-7; $Br(CH_2)_9C(CO_2Et)_2^-$, 88083-61-8; $Br(CH_2)_{10}C(CO_2Et)_2^-$, 88083-62-9; $Br(CH_2)_{11}C(CO_2Et)_2^-$, 88083-63-0; $Br(CH_2)_{12}C(CO_2Et)_2^-$, 88083-64-1; $Br(CH_2)_{16}C(CO_2Et)_2^-$, 88083-65-2; $Br(CH_2)_{20}C(CO_2Et)_2^-$, 88083-66-3; $Br(CH_2)_4Cl$, 6940-78-9; LiBr, 7550-35-8; diethyl 1,1-cyclobutanedicarboxylate, 3779-29-1; diethyl 1,1-cyclopentanedicarboxylate, 4167-77-5; diethyl 1,1-cyclohexanedicarboxylate, 1139-13-5; diethyl 1,1-cycloheptanedicarboxylate, 6557-83-1; diethyl 1,1-cyclooctanedicarboxylate, 76999-11-6; diethyl 1,1-cyclododecanedicarboxylate, 76999-15-0; diethyl 1,1-cyclotridecanedicarboxylate, 37689-04-6; diethyl 1,1-cycloheptadecanedicarboxylate, 76999-16-1; diethyl 1,1-cycloheneicosanedicarboxylate, 76999-17-2; diethyl dibutylmalonate, 596-75-8; diethyl sodiomalonate, 996-82-7; diethyl (4-chlorobutyl)malonate, 18719-44-3.

Specific Acid Catalysis in the Decomposition of Trialkyltriazenes

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Abstract: The acid-catalyzed decomposition of 1,3-di-*n*-butyl-3-methyltriazene (**1**) in aqueous buffer was investigated. Determination of the kinetics over a pH range of 10.4 to 12 indicated that the reaction is acid catalyzed. Variation of buffer concentration, at constant ionic strength, produced an insignificant variation in the rate constant. The determination of kinetics of the decomposition of **1** in nine different buffers, ranging in pK_a from 9.6 to 12.7, also gave negligible variation in the rate constants. The solvent isotope effect for the reaction, k_H/k_D, was 0.62. These data strongly support the conclusion that the reaction is specific acid catalyzed. This implies that the reaction involves fast, reversible protonation of the triazene followed by the rate-determining heterolysis of the protonated species to *n*-butyldiazonium ion and *n*-butylmethylamine. A product study of the decomposition supported the conclusion that *n*-butyldiazonium ion was formed during the reaction. The kinetics of the reaction of 1,3,3-trimethyltriazene (**2**) in various buffers also supported the notion of specific acid catalysis in the decomposition of that triazene. The decomposition of 1,3-dimethyl-3-acetyltriazene (**3**) was very slow in comparison to the others, requiring strongly acidic solutions for the reaction to occur (k_{obsd} 7.67×10^{-4} s^{-1} at pH 1.05). 1,3-Dimethyl-3-carbethoxytriazene (**4**) decomposed about 7 times more rapidly than **3** at pH 1.80 but was much more stable than the trialkyltriazenes at that pH.

The study of the chemistry of triazenes has been confined almost entirely to 1-aryl-3,3-dialkyltriazenes. These substances have been shown to be potent carcinogens[2] while some members of the series have been shown to be useful in chemotherapy of cancer.[3] Trialkyltriazenes, however, have not been studied, primarily because no reliable methods for their synthesis have been devised. This is no longer the case since general synthetic methods have been developed by our laboratory.[4,5] These new substances have been shown to have substantially different characteristics from their aryldialkyl analogues. Thus, while trialkyltriazenes are stable in nonhydroxylic solvents, they have been found to be very unstable in aqueous solution. In contrast to the aryldialkyltriazenes, which require metabolic activation, the trialkyltriazenes are potent, directly acting bacterial mutagens.[6] Moreover, some of these substances have been found to be highly selective cytotoxic agents against human tumor cells which are deficient in DNA alkylation repair systems. They are much less toxic toward normal human cells.[7] These data hold promise that suitably substituted members of this series might be useful in chemotherapy. The biological data suggest strongly that trialkyltriazenes decompose to alkylating agents capable of reacting with DNA. It is reasonable to suppose that these agents are alkyldiazonium ions.

In an earlier paper we suggested that the trialkyltriazenes decomposed in aqueous buffers by a general acid catalyzed re-

† 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.

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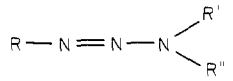
action.[8] This paper reports data on a more comprehensive kinetic and product study of the decomposition of trialkyltriazenes and also of a novel group of compounds, 1,3-dialkyl-3-acyltriazenes. It is shown that trialkyltriazenes follow specific acid catalyzed decomposition kinetics.

The present study involved the decomposition of triazenes **1–4**.



1, R = R′ = 1-C_4H_9; R″ = CH_3 3, R = R′ = CH_3; R″ = $COCH_3$
2, R = R′ = R″ = CH_3 4, R = R′ = CH_3; R″ = $CO_2CH_2CH_3$

Experimental Section

Synthesis of Triazenes. The preparation of 1,3-di-1-butyl-3-methyltriazene (**1**) was carried out as described earlier.[4] The product was purified by vacuum distillation, bp 109–111 °C (33 mmHg). Examination of NMR, IR, and mass spectra and GLC chromatograms indicated purity >99%. The other triazenes, 1,3,3-trimethyltriazene (**2**) and 1,3-dimethyl-3-acetyltriazene (**3**), were prepared according to the procedures of Smith and Michejda.[5] The (ethoxycarbonyl)triazene **4** was prepared according to the procedure for the acetyltriazene **3**[5] except that ethyl chloroformate was substituted for acetyl chloride. Triazene **4**, bp 89–90 °C (15 mm), was formed in 52% yield. Its IR spectrum (CCl_4) had bands at 1720 and 1160 cm^{-1}, the UV showed a λ_{max} of 232 nm (ϵ 12 770, MeCN), and the ^1H and ^{13}C NMR spectra and the mass spectrum were consistent with the structure.

Buffers. The buffer concentration variation was accomplished by using a ((cyclohexylamino)propanesulfonic acid) buffer.[9] Caps (Sigma) was dried in an Abderhalden apparatus using refluxing acetone. Sodium perchlorate (Fisher) was similarly dried for 2 days using refluxing xylene (138 °C). A buffer of a specific ionic strength and measured pH was obtained by mixing two solutions containing the proper final concentrations of total Caps (ionized and un-ionized) and sodium perchlorate. For example, in order to prepare a solution of 0.01 M Caps buffer of pH 10.8 and ionic strength of 0.2 M, 0.055 g of Caps and 0.59 g of $NaClO_4$ were dissolved in water, which had been distilled from $KMnO_4$, to a volume of 25.0 mL. Another lot of the buffer components, containing the same amount of Caps and $NaClO_4$, was dissolved in about 20 mL of water, the pH of this solution was adjusted to about 11 with concentrated sodium hydroxide solution, and this solution was diluted to 25.0 mL with distilled water. The first solution was then treated with the second until the observed pH was close to 10.8. At that point the solution was filtered 3 times through a 0.45 nm Millipore filter. The final adjustment to pH 10.8 ± 0.02 was made on the filtrate. All buffers were prepared similarly and were used within 24 h. The pH was checked frequently before, during, and after the reaction. The value never varied more than ±0.02 unit. However, it should be pointed out that absolute pH readings in relatively concentrated salt solutions are probably not reliable beyond ±0.1 pH unit. Thus, while reproducibility of observed pH within a given set of experiments was within the ±0.02 unit range, the absolute pH readings were probably not better than ±0.1 unit. The pH measurements were made with an Orion Model 701 digital pH meter using a Fisher combination electrode with a calomel reference.

Determination of Kinetics. The rates were followed spectrophotometrically using a Cary Model 17 UV-visible spectrophotometer. The reaction solutions were contained in thermostated 1-cm cells, and the temperature was held constant at 25 ± 0.2 °C in all experiments. The decomposition was followed by monitoring the absorbance at the maximum absorption of each triazene for at least 3 half-lives (λ_{max} **1** 243 nm (ϵ 9860); λ_{max} **2** 243 nm (ϵ 9040); λ_{max} **3** 235 nm (ϵ 15 600); λ_{max} **4** 232 nm (ϵ 12 770)). The reaction cuvette was charged with the appropriate prethermostated buffer (1.49 mL) and the reaction was initiated by injection of 10.0 μL of 0.003 M triazene in acetonitrile. The final concentration was 2.0×10^{-5} M. The reference blank contained the same buffer and 10 μL of acetonitrile. The absorbance vs. time data were recorded on a strip chart. At the end of a run 30 points were determined from the chart and the data were analyzed by a computer program which employed the Guggenheim approximation[11] to determine the A_∞ values and the first-order rate constants by a linear least-squares method. The rate plots were generally linear for at least 3 half-lives.

Product Studies. The products of decomposition of **1** were determined on solutions which were 2.0×10^{-2} M in triazene dissolved in a 0.1 M, pH 10.8 Caps buffer, and an ionic strength of 0.2 M. The reaction was allowed to proceed for 24 h. The decomposition solution was analyzed by GC using two columns. The alcohols were separated on a 6 ft × 2 mm ID glass column packed with Ultrabond 20 M (100/120 mesh) and operated at 40 °C, while the amines were separated on a 6 ft × 2 mm ID glass column packed with Chromasorb 103 (60/80 mesh) operated at 140 °C and at 200 °C. The separations were carried out on a Perkin Elmer sigma II chromatograph equipped with an FID and N-P detector, the outputs of which were interfaced to a Hewlett-Packard Model 3354 computer through a Hewlett-Packard 18652A A/D converter. Standard curves were constructed using known concentrations of 1-butanol, 2-butanol, *N*-methylbutylamine, and *N*-methyl-*N*,*N*-dibutylamine, using six points for each and spanning a concentration range of 2.0×10^{-2} M to 5×10^{-4} M. At least five 2-μL injections of unknown solutions were used to obtain the peak areas of each component. The concentrations of the components were read from the standard curves.

Table I. Observed First-Order Rate Constants[a] for the Disappearance of 1,3-Di-1-butyl-3-methyltriazene from pH 10.4 to 12.0 in Aqueous Buffer at 25 °C

pH[b]	$k_{obsd} \times 10^4$, s^{-1} (std dev × 10^4)
10.4	9.75 (0.55)
10.8	3.68 (0.033)
11.2	1.38 (0.033)
11.6	0.443 (0.0033)
12.0	0.190 (0.017)

[a] Average of three independent determinations. [b] Caps ((cyclohexylamino)propanesulfonic acid) buffer was used at a concentration of 0.10 M and the ionic strength held constant with sodium perchlorate at 0.20 M.

Table II. Experimental Conditions for Determinations of the Rate Constants and k_{obsd} for the Decomposition of Various Triazenes in Aqueous Buffers at 25 °C, Ionic Strength 0.2 M[a]

triazene	[triazene], M	pH (buffer)	$k_{obsd} \times 10^4$, s^{-1}
2	2.0×10^{-5}	10.8 (0.01 M Caps)	1.13
3	2.0×10^{-5}	1.80 (0.10 M H_3PO_4)	1.15
		1.05 (0.10 M HCl)	7.67
4	2.0×10^{-5}	1.80 (0.10 M H_3PO_4)	7.67
		7.50 (0.10 M NaH_2PO_4)	0.13
		11.50 (0.10 M Na_2HPO_4)	0.32[b]

[a] Ionic strength maintained with sodium perchlorate. [b] Uncorrected for absorbance due to 1,3-dimethyltriazene.

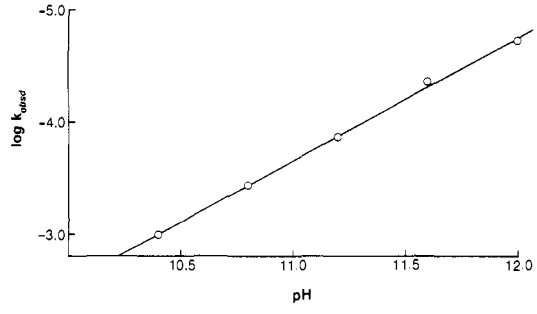


Figure 1. pH Dependence on the rate of decomposition of 1,3-di-1-butyl-3-methyltriazene in aqueous buffer.

Results

pH Dependence on the Rate of Decomposition of Triazenes. The rate of decomposition of **1** was studied over the pH range of 10.4

(8) Sieh, D. H.; Michejda, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 442–445.
(9) The zwitterionic Caps buffer was used in this study rather than the more commonly used phosphate buffer because we tried to minimize salt effect by keeping the ionic strength as low as possible. At the pH used in this study, the ionic strength of the phosphate buffer would have to be around 1 M if the buffer concentration was varied up to 0.25 M. Moreover, at high salt concentrations the activities of the phosphate species are profoundly influenced by the concentration of the added salt.[10] This effect makes it difficult to calculate the amount of the salt to be added and the ionic strength contributions of the buffer components. In this work an assumption was made that Caps behaves as a neutral species, i.e., the charges do not behave independently. The consistency of the kinetic data supports this assumption.
(10) Bates, R. G. "Determination of pH"; Wiley: New York, 1964; pp 52–53.
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Table III. Influence of Caps Buffer Concentration[a] on the Rate of Decomposition of 1,3-Di-1-butyl-3-methyltriazene[b] at pH 10.8 and 25 °C

[buffer], M	k_{obsd}[c] × 10^4, s^{-1} (std dev × 10^4)
0.01	4.38 (0.13)
0.05	4.43 (0.033)
0.10	4.58 (0.15)
0.15	4.13 (0.033)
0.20	3.90 (0.083)
0.25	3.77 (0.033)
	slope -3.03×10^{-4}

[a] Ionic strength held constant at 0.20 M with $NaClO_4$. [b] Initial concentration 2×10^{-5} M. [c] Average of three determinations.

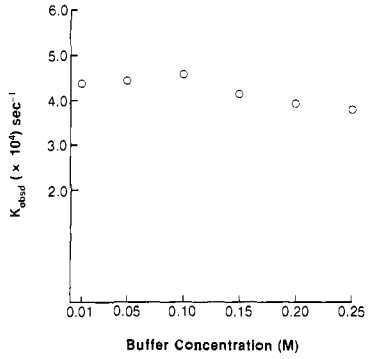

Figure 2. Effect of Caps buffer concentration on the rate of decomposition of 1,3-di-1-butyl-3-methyltriazene at pH 10.8.

to 12.0. The observed rate constants are listed in Table I. The rates were cleanly first order and the plot of log k_{obsd} vs. pH, Figure 1, indicated that the reaction rate was inversely proportional to pH. Thus, the reaction is acid catalyzed in spite of the alkaline pH range used. Below pH 10 the reaction was too rapid for convenient measurement. The rates of decomposition of 1,3,3-trimethyltriazene (**2**), 1,3-dimethyl-3-acetyltriazene (**3**), and 1,3-dimethyl-3-carbethoxytriazene (**4**) are indicated in Table II. It is interesting to note that the methyl triazene **2** is roughly twice as stable at pH 10.8 as triazene **1**. The acylated triazene **3** was completely stable under the conditions where the alkyltriazenes decomposed rapidly. It required strongly acidic conditions before any decomposition was detected. Triazene **4** is about 7 times more reactive than **3** at pH 1.80 but is much more stable than the trialkyltriazenes.

Dependence of the Rate of Decomposition of 1 on Buffer Concentration. The dependence of rate on buffer concentration at constant ionic strength is a diagnostic tool for detection of general acid catalysis. Triazene **1** was decomposed at pH 10.8 in Caps buffer ranging in concentration from 0.01 M to 0.25 M. The ionic strength was held constant at 0.2 M with sodium perchlorate. The rate constants are listed in Table III. These data are shown graphically in Figure 2. Although there appears to be a slight variation in the rate constants and a linear least-squares line through these points gives a negative slope of 3.03 × 10^{-4}, this variation is not considered to be significant.

Rate of Decomposition as a Function of Buffer pK_a. In general, acid-catalyzed decompositions have an observed rate constant of the form

$$k_{obsd} = k_{H^+}[H^+] + \sum_i k_{HA}[HA]_i$$

The components in the summation refer to the various possible general acid species. When the reaction is catalyzed only by hydronium ions (specific acid), the summation term vanishes. This situation demands that the rate constant for the reaction, at constant pH, be independent of the concentrations and identity of the general acids. Consequently, the rate of decomposition of **1** was determined at pH 10.8 in nine different buffers ranging in pK_a from 9.6 to 12.74. The individual rate constants are listed in Table IV. It is clear from these data that there is no significant

Table IV. Rate Constants for the Decomposition of **1** in Various Buffers[a] at pH 10.8 and 25 °C

buffer[b]	pK_a	k_{obsd} × 10^4, s^{-1}
glycine	9.6	4.50
CO_3^{2-}	10.25	4.73
Caps	10.40	4.77
proline	10.60	4.17
triethylamine	10.76	4.78
diethylamine	10.98	4.58
AsO_4^{3-}	11.53	4.23
PO_4^{3-}	12.32	4.47
$B_4O_7^{2-}$	12.74	5.02

[a] Ionic strength maintained at 0.20 M with sodium perchlorate. [b] The buffer concentration was 0.01 M and the initial concentration of **1** was 2.0×10^{-5} M in all cases.

Table V. Decomposition of Triazene **2** in Various Buffers at pH 10.8 and 25 °C

buffer[a]	pK_a	k_{obsd}[b] × 10^4, s^{-1}
glycine	9.60	1.05
Caps	10.40	1.13
diethylamine	10.98	1.04
AsO_4^{3-}	11.53	1.12

[a] Concentration of buffers was 0.01 M and the ionic strength was maintained at 0.20 M with sodium perchlorate. [b] The initial concentration of **2** was 2.0×10^{-5} M.

variation of the rate with changes in the buffer identity and pK_a. The decomposition of 1,3,3-trimethyltriazene (**2**) was also examined in four different buffer (Table V). Again, no significant variation in the rate constant was observed. These data support the notion that the reaction is catalyzed by specific acid.

Solvent Deuterium Isotope Effect on the Decomposition of 1. The solvent isotope effect on the decomposition of **1** was determined in Caps buffer. A 0.01 M, pH 10.8 buffer was prepared by dissolving Caps in 99.8% deuterium oxide and the ionic strength was adjusted to 0.20 M with sodium perchlorate. The nominal pH meter reading was 10.4, which was equivalent to pD of 10.8, according to the equation,[12] pD = pH_{obsd} + 0.4. The rate constant obtained for decomposition in this buffer was $k_{obsd}^{D_2O} = 7.72 \times 10^{-4}$ s^{-1}. The parallel determination of the rate of decomposition in an aqueous Caps buffer, pH 10.8, yielded a rate constant, $k_{obsd}^{H_2O} = 4.77 \times 10^{-4}$ s^{-1}. Thus the isotope effect for the reaction, k_{H_2O}/k_{D_2O}, was 0.62.

Products of Decomposition of Triazene 1. Decomposition of 2.0×10^{-2} M solutions of **1** in 0.1 M Caps buffer, pH 10.8, gave the following products: methyl-1-butylamine (74% ± 15%), 1-butanol (51% ± 5%), 2-butanol (19% ± 5%), and di-1-butylmethylamine and 1-butyl-2-butylmethylamine (together 5% ± 3%). The butenes were not determined, but by difference they accounted for 25% ± 5% of the 1-*n*-butyl group of the original triazene. The errors quoted here are really confidence limits since the analysis had to be carried out on two separate GC columns. The amines were particularly troublesome to measure accurately in aqueous solution because of poor peak shapes, which made the integration difficult. Nevertheless, the numbers obtained indicate a relatively clean decomposition of the triazene to methyl-1-butylamine and the 1-butyldiazonium ion.

Discussion

The present data provide strong evidence that the decomposition of triazene **1** and also the simplest trialkyltriazene **2** are subject to specific hydronium ion catalysis. The invariance of the rate constant for the decomposition of **1** over a 25-fold variation in buffer concentration (Table III, Figure 2) provides a strong indication that the reaction is not general acid catalyzed. The solvent isotope effect, k_{H_2O}/k_{D_2},O = 0.62, which is close to our original value,[8] is also consistent with specific acid catalysis, since D_3O^+ is a stronger acid than H_3O^+. This conclusion is further supported

(12) Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188–190.

by the invariance of the rate constant with changes in the pK_a of various buffers (Table IV). These data indicate that buffer species are not involved in the decomposition reaction and that, therefore, the reaction is catalyzed by specific hydronium ion. Likewise, the invariance of the rate constant for decomposition of triazene **2** with changes in buffer pK_a (Table V) indicates that that triazene behaves similarly to triazene **1**. Consequently, the data for trialkyltriazene decomposition are consistent with the following:

$$RN{=}NNRR^1 + H_3O^+ \underset{K_a}{\overset{\text{fast}}{\rightleftharpoons}} RN{=}NNHRR^{1+} \xrightarrow[k_2]{\text{slow}} RN_2^+ + HNRR^1$$

Scheme I leads to the following expression for the rate of decomposition of the triazenes (T),

$$-d(T)/dt = k_2(H_3O^+)(T)/K_a$$

and hence the observed rate constant is given by $k_{obsd} = k_2(H_3O^+)/K_a$. The logarithmic equivalent for the latter expression[13] is $\log k_{obsd} = \log k_2 + pK_a - pH$. Consequently, the plot of $\log k_{obsd}$ vs. pH should be a line with a slope of −1. The slope in Figure 1 calculated from the data in Table I (−1.08 ± 0.02) is very close to this value. Unfortunately neither k_2 nor the pK_a of the triazene can be obtained independently, since the conjugate acid of the triazene is much too unstable under our conditions. The rate of decomposition of the alkyltriazenes appears to be dominated by their basicity. This is illustrated dramatically by the greatly enhanced stability of the acylated triazene **3**. Here, the presence of the acetyl group would be expected to decrease the basicity of the 3-nitrogen, which is reflected in the requirement for the relatively strongly acidic conditions to affect the decomposition of that triazene. However, it should be pointed out that the mechanistic details for the decomposition of **3** have not been worked out and, in fact, it is possible that the decomposition of **3** involves the initial hydrolysis of the acetyl group. This latter possibility is supported by the behavior of triazene **4**. Data in Table II show that decomposition of this material, which is relatively rapid at acid pH, becomes very slow at neutral pH and increases again in the alkaline range. This is consistent with initial hydrolysis of the carbamate residue and concomitant formation of the dialkyltriazene.

The rate of acid-catalyzed decomposition of a variety of 1,3-diaryltriazenes has been shown to be a function of the basicity of these substances.[14] In fact, these authors also suggest that the aromatic analogues of our triazenes likewise undergo specific acid-catalyzed decomposition. However, Isaacs and Rannala[15] reported that the reaction of 1-aryl-3-alkyltriazenes with carboxylic acids in chloroform involved the synchronous and rate-limiting proton transfer and departure of the alkyl cation. This conclusion was based on the finding of appropriate Hammett correlations which indicated that the reaction rates increased when electron-donating substituents were present on the aryl group of the triazene or electron-attracting substituents were present on the benzoic acids. Also, the reaction exhibited a sizeable isotope effect (k_H/k_D = 2.47) when the reacting acid was labeled with deuterium. Sinnott and co-workers[16] studied the aqueous decomposition of 1-aryl-3-alkyltriazenes and claim to have identified a pH-independent, unimolecular heterolysis of the N–N bond along with a H_3O^+-catalyzed pathway. Their data, however, are difficult to assess.

We had shown earlier[8] that the decomposition of 1,3-bis(cyclopropylcarbinyl) 3-methyltriazene proceeded by a path which was consistent with the formation of the cyclopropylcarbinyl cation. The products of the decomposition of **1** are also consistent with the formation of the 1-butyldiazonium ion, since the product distribution is similar to that observed for deamination of 1-butylamine.[17] Thus, trialkyltriazenes are excellent sources of alkyldiazonium ions. This property should make them very useful for the study of those ions and also explains their mutagenic and also possibly carcinogenic properties.

Warning. Triazenes are strong alkylating agents, and we have shown[6] that, with exception of triazene **3**,[18] they are potent, directly acting bacterial mutagens. Caution should be exercised in their handling because they may also be carcinogenic.

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Registry No. 1, 76387-44-5; **2**, 87031-62-7; **3**, 87031-64-9; **4**, 88211-12-5.

(13) This expression is correct when $K_a >> [H^+]$. In more acidic solutions the correct equation is log

$$\log k_{obsd} = \log k_2 - pH + pK_a - \log (1 + [H^+]/K_a)$$

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(17) Streitwieser, A., Jr.; Schaeffer, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 2888–2893 and references cited therein.

(18) Andrews, A. W.; Michejda, C. J., unpublished data.