Kinetic Study of the Solvolysis Reactions of 1-Aryl-3-acetoxymethyl-3-alkyltriazenes: Evidence for Iminium Ion Intermediates and the S_N1 Mechanism

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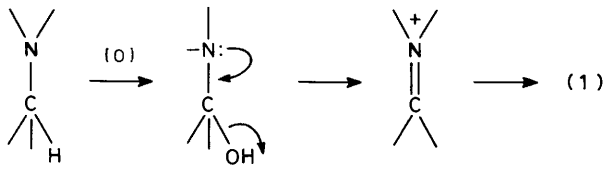
The first-order rate constants of the reactions of acetoxymethyltriazenes with nucleophiles have been measured. Acetoxymethyltriazenes undergo hydrolysis in phosphate buffer to give the corresponding arylamines, presumably *via* the hydroxymethyl- and monomethyl-triazenes. The acetoxymethyltriazenes undergo solvolysis in alcohols and in mixtures of alcohols and other solvents; the rate of solvolysis has been correlated with the Grunwald–Winstein parameter (Y) for solvent ionising power, thus supporting the hypothesis of an S_N1 mechanism and the intermediate formation of iminium ions during the solvolysis. The hypothesis is further supported by the non-common-ion effect; the presence of lithium chloride in the solvent greatly increases the rate of reaction, whereas lithium acetate causes a slight decrease in rate, attributable to a common-ion effect. Reaction of the acetoxymethyltriazene with sodium azide in aqueous acetone affords the α-azidomethyltriazene (a new type of triazene not previously reported) and provides supporting evidence for the iminium ion hypothesis. On the other hand, the acetoxymethyltriazene did not react with neat ethanethiol, providing further evidence for an S_N1 mechanism; and S_N2 reaction would be expected to proceed more quickly in the thiol than in the alcohol. It is shown that hydroxymethyltriazenes do not react *via* iminium ions and that functionalisation to a derivative such as the acetate is necessary for iminium ion generation. The implications of these results for the metabolism of xenobiotic *N*-alkyl compounds are discussed.

The 1-aryl-3-alkyl-3-hydroxymethyltriazenes (ArN=N–NR–CH_2OH) are an important class of compound, both because of their chemical significance as rare examples of stable α-carbinolamines and for their pharmacological properties as antitumour agents.[1] In a previous paper,[2] the synthesis of a series of acetate (ArN=N–NR–CH_2OAc) and methyl ether (ArN=N–NR–CH_2OMe) derivatives of the hydroxymethyltriazenes was described. The acetates were converted smoothly into the methyl ethers by solvolysis in methanol, and it was suggested that these methanolysis reactions took place *via* the iminium ion intermediate ArN=N–$^+$NR=CH_2. This paper describes a study of the kinetics of the nucleophilic substitution reactions of acetoxymethyltriazenes, undertaken to test the iminium ion hypothesis.

The importance of iminium ion intermediates extends beyond their chemical significance. Several studies[3] of the metabolism of *N*-alkyl xenobiotic molecules have suggested that iminium ions are involved as electrophilic metabolites. It has been suggested that iminium ions are generated by enzymic oxidation of the *N*-alkyl compounds to α-carbinolamines [equation (1)], which then eject hydroxide ion to generate the iminium ion.



This hypothesis has an obvious chemical drawback, *i.e.* the poor leaving-group character of the hydroxide ion, and the theory deserves severe chemical scrutiny. However, virtually all the α-carbinolamines which have been suggested as intermediates in metabolism are too unstable to be isolated, so that a direct test of the iminium ion hypothesis is difficult. The hydroxymethyltriazene derivatives represent an ideal model system to test these hypotheses.

Table 1. Kinetic parameters for the hydrolysis of the 1-aryl-3-acetoxymethyltriazenes in 1.7% (v/v) Me_2SO–0.01M-phosphate buffer, pH 7.5, at 37 °C, measured by u.v. spectroscopy

Compound	X	k_1/min^{-1}	λ/nm
(4)	CN	1.20×10^{-2}	310
(7)	MeO_2C	1.90×10^{-2}	314
(12)	CH_3CO	2.84×10^{-2}	324

Table 2. Kinetic parameters for the hydrolysis of the 1-*p*-methoxycarbonylphenyl-3-alkyl-3-methyltriazenes in 1.7% (v/v) Me_2SO–0.01M-phosphate buffer, pH 7.5, at 37 °C, measured by u.v. spectroscopy

Compound	R	k_1/min^{-1}	λ/nm
(5)	H	2.58×10^{-2}	315
(6)	CH_2OH	1.97×10^{-2}	312
(7)	CH_2OAc	1.90×10^{-2}	314
(8)	CH_2OMe	(>24 h)	314

Results and Discussion

Acetoxymethyltriazenes undergo hydrolysis in mixtures of aqueous buffer and organic solvent, typically 1% dimethyl sulphoxide; the reaction can be followed spectrophotometrically and first-order rate constants determined from the decrease of absorbance of the reactant with time. The u.v. spectrum of the acetate during hydrolysis undergoes virtually the same change as has been seen previously for the hydrolysis of hydroxymethyl- and monomethyl-triazenes.[1] These three types of triazene have almost identical $\lambda_{max.}$ values in the u.v. spectra and all the solvolyses lead to the same final u.v. spectrum, that of the arylamine $ArNH_2$. Tables 1—3 show the rate constants determined for several of these triazenes, which were chosen in order first to assess the effect of the substituent in Ar on the rates of reaction and second to compare the rates of hydrolysis of the acetoxymethyl-, hydroxymethyl-, and monomethyl-triazenes with the same Ar group.

The results in Table 1 clearly show that the hydrolysis of an

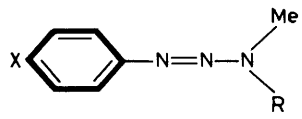
acetoxymethyltriazene is decelerated by an electron-withdrawing substituent. Furthermore, the trend of reactivity shows the same order as for the corresponding hydroxymethyl- and monomethyl-triazenes, *i.e.* electron-withdrawing groups slow down the hydrolysis of all triazenes in this sequence [compare (**1**) with (**5**), and (**3**) with (**6**)]. The significant observation from these data is the comparison of rates of hydrolysis of triazenes with the same Ar group: it is apparent that the rates of hydrolysis of an acetoxymethyltriazene and a hydroxymethyltriazene are virtually equal, whereas the monomethyltriazene hydrolysis has a significantly larger rate constant.

These observations suggest that hydrolysis of the acetate occurs rapidly to give a hydroxymethyltriazene (Scheme), possibly *via* an iminium ion intermediate. However, it is necessary to comment further on the significant difference between the rates of reaction of the hydroxymethyltriazenes and the corresponding monomethyltriazenes, which react *ca.* 25—50% faster under the dilute phosphate buffer conditions used in this study. (In a previous study,[1] these rate constants were measured in more concentrated phosphate buffer and were observed to be identical within the limits of experimental error.) The rate of conversion of hydroxymethyltriazene to monomethyltriazene appears to be close to that for the subsequent fragmentation; if these steps are indeed of similar rate, then the former reaction must feature in the rate-determining process. Furthermore, a rate-determining process involving consecutive reactions of similar rate would follow a complex rate law, and the reaction of the hydroxymethyltriazene would not obey the simple first-order kinetics observed in this study. Further study of this complex system is obviously necessary; not least among the unanswered questions is the role of phosphate ion in the hydrolysis process.

Nevertheless it is clear that the important question of iminium ion involvement in the hydrolysis of the acetoxymethyltriazenes cannot be answered from kinetic measurements of hydrolysis by u.v. spectroscopy. The conversion of acetate into hydroxymethyltriazene appears to occur too readily to be evaluated more fully by this method. Further study of this system by measurement of hydroxymethyltriazene build-up during reaction is made difficult by two factors: (*a*) the similarity of u.v. spectra of the three types of triazene, and (*b*) the unstable nature of hydroxymethyltriazenes which precludes their analysis by h.p.l.c. or t.l.c.[1]

In contrast to the ready hydrolysis of the acetate (**7**), the analogous methoxymethyltriazene (**8**) is stable to hydrolysis at pH 7.5 and is similar in stability to a typical dimethyltriazene [*e.g.* (**2**) Table 3]. This result is entirely expected, in view of the poor leaving-group character of the methoxide group, as compared with the acetate group in (**7**). Methoxymethyltriazenes are obtained readily by methanolysis of the corresponding acetoxymethyltriazenes,[2] which could occur *via* the iminium ion intermediate (Scheme). Since the methoxymethyltriazene is stable, and methanolysis is significantly slower than hydrolysis, it seemed that a more meaningful kinetic analysis could be undertaken with a study of the methanolysis, and solvolysis, of the acetoxymethyltriazenes.

The kinetics of the methanolysis reactions were measured by two independent methods: (*a*) h.p.l.c. and (*b*) n.m.r. spectroscopy. In the former method, liquid chromatographic analysis of the reaction mixture allowed convenient measurement of the relative amounts of the acetate and methyl ether at frequent intervals. The relative amounts of reactant and product could



	X	R
(**1**)	CN	H
(**2**)	CN	CH_3
(**3**)	CN	CH_2OH
(**4**)	CN	CH_2OAc
(**5**)	CO_2Me	H
(**6**)	CO_2Me	CH_2OH
(**7**)	CO_2Me	CH_2OAc
(**8**)	CO_2Me	CH_2OMe
(**9**)	CO_2Me	CH_2OEt
(**10**)	CO_2Me	CH_2N_3
(**11**)	CH_3CO	CH_2OH
(**12**)	CH_3CO	CH_2OAc

Table 3. Kinetic parameters for the hydrolysis of 1-*p*-cyanophenyl-3-alkyl-3-methyltriazenes in 1.7% (v/v) Me_2SO–0.01M-phosphate buffer, pH 7.5, at 37 °C, measured by u.v. spectroscopy

Compound	R	k_1/min^{-1}	λ/nm
(**1**)	H	1.67×10^{-2}	310
(**2**)	CH_3	(>24 h)	324
(**3**)	CH_2OH	1.33×10^{-2}	310
(**4**)	CH_2OAc	1.20×10^{-2}	310

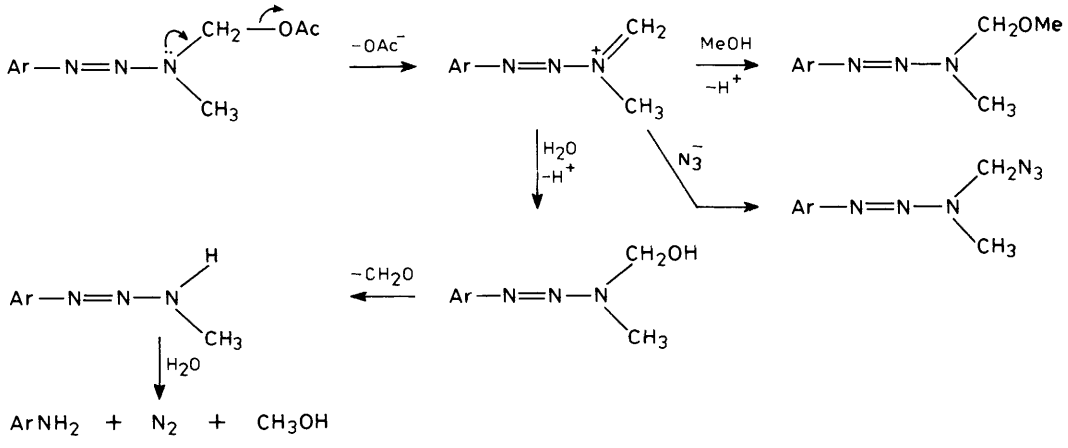


Table 4. Kinetic parameters for the solvolysis of 1-*p*-cyanophenyl-3-acetoxymethyl-3-methyltriazene (**4**) in alcohols

Solvent	Temp (°C)	Method of analysis	k_1/h^{-1}
MeOH	20	N.m.r.	6.63×10^{-2}
MeOH	20	H.p.l.c.	6.82×10^{-2}
MeOH	37	H.p.l.c.	2.5×10^{-1}
MeOH–MeCN (50:50 v/v)	20	N.m.r.	1.35×10^{-2}
EtOH	20	N.m.r.	6.82×10^{-3}
CH_3CN	20	N.m.r.	0
Bu^{t}OH	25	N.m.r.	$< 5.3 \times 10^{-4}$
MeOH–Bu^{t}OH (50:50 v/v)	20	N.m.r.	2.6×10^{-3}

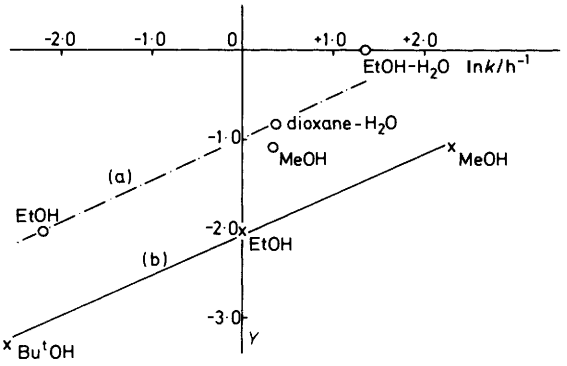


Figure. Plot of the Grunwald–Winstein parameter (Y)[4] for solvent ionising power against (*a*) ln k_1 from the solvolysis of the acetate (**7**) at 37 °C; (*b*) ln (k_{solv}/k_{EtOH}) from the solvolysis of the acetate (**4**) at 20 °C. Data for compound (**4**) were normalised to the rate of ethanolysis to permit easier comparison of the data for the two compounds

also be obtained from the ^{1}H n.m.r. spectrum of the reaction mixture; the N–CH_2 signals of the acetate and methyl ether are sufficiently well resolved to permit the calculation of relative concentrations. The relative concentrations of the methyl ether and the acetate in a reaction mixture at any time, t, gives an accurate measure of the percentage (x%) of starting material in the mixture. The ratio $100/x$ is equal to the ratio of concentrations $[A_0]/[A]$; the slope of the plot of ln $(100/x)$ against t is equal to the rate constant. Rate constants for the same reaction were determined from both h.p.l.c. and n.m.r. data, giving excellent agreement within the limits of experimental error.

Tables 4 and 5 show the first-order rate constants for the solvolysis of the acetoxymethyltriazenes (**4**) and (**7**) in a variety of solvents. Several significant trends can be observed.

(*a*) The rate of solvolysis is strongly dependent on the solvent; the order of rates is EtOH–H_2O (fastest) > MeOH ≡ dioxane–H_2O > MeOH–MeCN ≡ EtOH > Bu^{t}OH (slowest). This sequence is in good correlation with the solvent ionising power as measured by the Grunwald–Winstein parameter (Y).[4] A plot of ln k against Y (Figure) for the two substrates is approximately linear.

(*b*) The rate of solvolysis is influenced by the substituent in Ar. The methanolysis of (**7**), with the less strongly electron-withdrawing substituent, occurs ten times faster than that of (**4**). Indeed the low reactivity of (**4**) became a minor problem owing to the length of time required to complete some of the kinetic runs. Compound (**7**) was selected for a more detailed study of the solvent effect because of its greater reactivity.

(*c*) Solvolysis of (**7**) by a 1:1 molar mixture of MeOH and EtOH proceeds at a rate intermediate between the rates of reaction with the pure alcohols; the product was a mixture of the two ethers with a small but significant predominance of the methyl ether.

Table 5. Kinetic parameters for the solvolysis of 1-*p*-methoxycarbonylphenyl-3-acetoxymethyl-3-methyltriazene (**7**) in alcohols

Solvent	Temp (°C)	Method of analysis	k_1/h^{-1}
MeOH	25	H.p.l.c.	6.24×10^{-1}
MeOH	37	H.p.l.c.	1.40
MeOH–MeCN (50:50 v/v)	37	N.m.r.	1.12×10^{-1}
EtOH	37	N.m.r.	1.17×10^{-1}
MeOH–EtOH[a] (1:1 molar)	37	H.p.l.c.	4.45×10^{-1}
EtOH–H_2O (80:20 v/v)	37	H.p.l.c.	3.86
Dioxane–H_2O (80:20 v/v)	37	U.v.	1.44
MeOH	0	H.p.l.c.	4.00×10^{-2}
0.1M-LiCl–MeOH	26	N.m.r.	*b*
0.1M-LiCl–MeOH	0	N.m.r.	> 8.32
0.1M-LiOAc–MeOH	0	N.m.r.	6.67×10^{-3}
NaOMe–MeOH	0	N.m.r.	*b*

[a] N.m.r. analysis of the final product gives the composition: 58% methyl ether (**8**), 42% ethyl ether (**9**). [b] Too fast to be measured by n.m.r. or h.p.l.c. as used in this study.

(*d*) Solvolysis of (**7**) in aqueous ethanol (20:80) proceeds much faster than in pure ethanol. This observation is consistent with the greater ionising power of the mixed solvent system, and in both cases the product was the pure ethyl ether (**9**).

(*e*) The solvolysis of (**7**) in methanol was accelerated greatly by the presence of 0.1M-lithium chloride; the reaction was too fast to be measured at room temperature. At 0 °C the reaction was still very fast, but a lower limit for k_1 was determined. In contrast, the presence of 0.1M-lithium acetate in the methanol caused a six-fold decrease in rate of methanolysis. Reaction of (**7**) with sodium methoxide in methanol at 0 °C was too rapid to be measured.

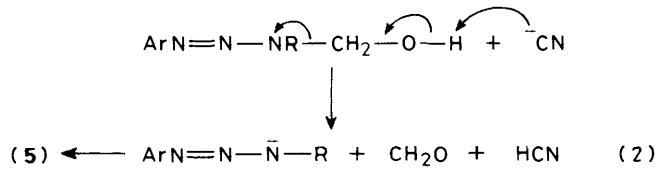
Some of the observations made here may point towards an S_N2 mechanism for the displacement of the acetate group in an acetoxymethyltriazene by a solvent molecule or other nucleophile. For example, the variation of rates of reaction in different alcohols could be at least partly attributable to the change in bulk of the nucleophilic solvent. The apparent salt effect caused by the addition of LiCl could indicate direct substitution by Cl^-, *i.e.* nucleophilic catalysis; however, we see no evidence in the product analyses for an intermediate chloromethyltriazene, which should certainly survive the methanolysis conditions for a measurable time. The rate enhancement by sodium methoxide could well indicate a change of mechanism to S_N2 due to the greatly increased nucleophilicity.

However, we feel that the evidence leans much more heavily towards an S_N1 mechanism for the solvolysis of acetoxymethyltriazenes. The correlation of rate of solvolysis with solvent ionising power appears to us to be convincing evidence for an iminium ion mechanism, reinforced by the salt effect[5] caused by LiCl and the pronounced common-ion effect seen in the presence of LiOAc. The effect of the substituent in the aryl group on the rate of methanolysis is also evidence of a unimolecular dissociation since the effect of an electron-withdrawing group in Ar is to decrease the electron density at N-3 of the triazene, thereby decreasing the propensity of the nitrogen lone-pair to offer anchimeric assistance to the acetate leaving group.

In the reaction of (7) with MeOH–EtOH, a slight preference for the methyl ether was observed in the products; this result is consistent with an S_N1 mechanism in which the iminium ion is formed within a solvent cage of MeOH and EtOH molecules. The overall rate is determined by the rate of formation of the iminium ion, but the subsequent reaction with methanol is faster than with ethanol presumably because the smaller alcohol molecule can diffuse more quickly through the solvent cage. Thus the reaction of the iminium ion with this solvent is diffusion-controlled and gives a predominance of the methyl ether in the product mixture. However there is no obvious explanation for the apparent preference for ethanolysis in the reaction of (7) with EtOH–H_2O (80%); certainly there is no evidence in the product analysis for the formation of a hydroxymethyltriazene (or of a product derived from its degradation).

There is one further piece of evidence which supports the S_N1 iminium ion mechanism indirectly by throwing considerable doubt on the validity of an S_N2 hypothesis. The acetoxymethyltriazene (7) is totally unreactive towards neat ethanethiol.[6] If the ethanolysis of (7) were proceeding by an S_N2 mechanism then undoubtedly reaction with ethanethiol would go considerably faster.

A logical extension of this study is to determine whether the iminium ion intermediate, derived from the acetoxymethyltriazene, can be trapped by nucleophiles other than an alcohol or water. Such experiments would not only add to the mechanistic study, but might also lead to the synthesis of new α-substituted triazenes not readily available by other routes. A commonly used nucleophile in metabolite-trapping experiments[7] is cyanide ion. However, the reaction of (7) with a saturated sodium cyanide solution (2.3M) afforded an unidentified gum; the i.r. spectrum of the gum showed the absence of the cyanide group. Reaction of (7) with a dilute cyanide solution afforded an identifiable product, the monomethyltriazene (5). It appears that, under these conditions, the acetate undergoes solvolysis by water to give the hydroxymethyltriazene (6) followed by rapid loss of formaldehyde to give (5). The cyanide ion appears to act only as a base catalyst in abstracting the proton from the *N*-hydroxymethyl group [equation (2)].



Although iminium ion trapping by cyanide was not successful, a surprisingly effective trapping agent was found to be the azide ion. Reaction of (7) with sodium azide in aqueous acetone proceeds smoothly to afford a good yield of the α-azidomethyltriazene (**10**), which is the first example of a triazene of this type to be reported. The structure of (**10**) was established from i.r., ^{1}H n.m.r., and mass spectra. The i.r. spectrum shows a strong azide band at 2 120 cm^{-1} and the ^{1}H n.m.r. spectrum gives the expected signals of the NMe, OMe, and aromatic protons. The methylene group situated between the azide group and the triazene group gives a chemical shift at δ 5.2, similar to that of the methylene group of a hydroxymethyltriazene.[1] The ^{13}C n.m.r. spectrum of (**10**) confirms the structure and shows no surprising features.

The mass spectrum of the azidomethyltriazene (**10**) gives further strong structural evidence. The molecular ion is clearly seen at *m/z* 248; the predictable loss of N_2 is evident from a fragment at *m/z* 220, but loss of an N_3 fragment is not observed. However, a fragment at *m/z* 193 does indicate loss of the CHN_3 moiety. Other peaks in the mass spectrum indicate: (*a*) loss of CH_3O (*m/z* 217); (*b*) loss of CO_2Me (*m/z* 189); and (*c*) fragmentation at the N(2)–N(3) bond (*m/z* 163, ArN_2^+). The base peak is at *m/z* 135, corresponding to breakage of the C–N bond linking the aryl and triazene moieties.

The mechanistic implication of the formation of (**10**) is clear: the iminium ion can be trapped by an ionic nucleophile if the nucleophile is able to compete with the nucleophilic solvent successfully. The apparent superiority of azide ion over cyanide ion is not readily explained; however, further studies are being undertaken to establish the generality of the synthesis of α-azidomethyltriazenes analogous to (**10**).

An important question, both for the elucidation of the mechanism of the reactions and for the potential pharmacological implications of this study, is the extent to which the hydroxymethyltriazene itself might undergo nucleophilic displacement. There remains the possibility that a hydroxymethyltriazene might dissociate unimolecularly under appropriate conditions in a protic, polar solvent such as methanol. However, it was found that reaction of (**6**) in methanol alone at 37 °C is very slow and leads only to the monomethyltriazene (**5**), which in turn breaks down slowly under these conditions to give the arylamine, methyl *p*-aminobenzoate.

These observations have significant implications for the proposed role of iminium ions in the metabolism of *N*-alkyl xenobiotic molecules, [equation (1)]. Evidently in the case of triazenes, the formation of the iminium ions directly by loss of a hydroxide ion does not take place. However, if the hydroxymethyl group is converted into an acetate, then the more favourable character of the leaving group, *i.e.* acetate, encourages the formation of an intermediate iminium ion in unimolecular S_N1 process. In a biological context, it appears likely that certain xenobiotic molecules with structural similarity to triazenes, such as the ubiquitous nitrosamines, must go through a 'conjugation' step wherein the oxidative metabolite, the carbinolamine, undergoes further metabolism to a derivatised form, such as a glucuronide or an acetate, prior to the generation of an electrophilic iminium ion.

The reluctance of the hydroxymethyltriazene to form iminium ions directly is undoubtedly related to the electron density at N-3, which determines the availability of the electron lone-pair for anchimeric assistance. The resonance present in all triazenes of this type reduces the electron density at N-3 and thus severely affects the ability to provide anchimeric assistance to the leaving group. Saunders[8] has clearly defined the two extreme types of carbinolamine, which differ in behaviour as a result of variation in the basicity of the nitrogen bearing the hydroxymethyl group. Carbinolamines with strongly basic nitrogen give evidence of iminium ion formation, whereas those with weakly basic nitrogen break down by loss of formaldehyde. Hydroxymethyltriazenes clearly fall into the second group, and undergo solvolysis by loss of formaldehyde rather than *via* iminium ions. The effect of the nitrogen basicity is not as evident in the reactions of the acetoxymethyltriazenes, which do clearly undergo nucleophilic solvolysis in protic media to afford intermediate iminium ions.

Experimental

^{1}H N.m.r. spectra were recorded with a Varian EM360 60 MHz instrument.

Syntheses.—Monomethyl- [(**1**) and (**5**)] and dimethyl- (**2**) triazenes were prepared by diazonium coupling with methylamine[9] or dimethylamine.[10] Hydroxymethyltriazenes [(**3**), (**6**) and (**11**)] were synthesised by diazonium coupling with formaldehyde–methylamine mixtures as described in ref. 1, and the acetoxymethyl- [(**4**), (**7**), and (**12**)] and methoxymethyl- (**8**)

triazenes were prepared from the corresponding hydroxymethyltriazenes.[2]

3-Ethoxymethyl-1-p-methoxycarbonylphenyl-3-methyltriazene (**9**). This triazene was prepared by reaction of the acetoxymethyltriazene (**7**) (0.5 g) in ethanol (10 ml) at 37 °C for 16 h; yield 0.27 g, m.p. 59—60 °C (from ether), $\nu_{max.}$ 1 730 and 1 610 cm^{-1}; $\delta(CDCl_3)$ 1.23 (3 H, t, *J* 7 Hz), 3.25 (3 H, s), 3.53 (2 H, q, *J* 7 Hz), 3.90 (3 H, s), 5.20 (2 H, s), and 7.4—8.2 (4 H, AA'BB').

H.p.l.c. Analysis.—Reaction mixtures consisting of an acetate and its solvolysis product, the alkoxymethyltriazene, in the appropriate alcohol, were analysed quantitatively by high-pressure liquid chromatography using a Varian LC 5000 instrument with two-solvent gradient capability. Triazenes were separated by normal phase chromatography on a Brownlee Polar Bond Phase NH_2 column (10 μm; 30 cm), with hexane–methylene dichloride as the eluant at a flow rate of 1.7 ml min^{-1}. Detection was carried out with a u.v. detector with fixed wavelength (254 nm).

In a typical kinetic run, the acetate (50 mg) was dissolved in the solvent (5 ml) and incubated at the required temperature with stirring, using a water-powered magnetic stirrer in the controlled temperature bath. Samples (30 μl) were removed by syringe and injected directly into the chromatograph injection loop. Relative concentrations of the reactant and product were determined from the areas of peaks on the chromatogram.

Kinetic Analysis by N.m.r.—In a typical experiment, the acetate (50 mg) was dissolved in the appropriate alcohol or solvent mixture (5 ml) and incubated at the required temperature with stirring. After the appropriate time, the whole mixture was evaporated to dryness under vacuum; the residue was diluted with chloroform (5 ml) and the mixture evaporated again under vacuum to ensure that all the reaction solvent was removed. The residue was taken up in deuteriochloroform and the ^1H n.m.r. spectrum recorded. The relative amounts of the components were calculated from integration of the *N*-methylene signals of the acetate (δ *ca.* 5.80) and the ether (δ *ca.* 5.15). The deuteriochloroform solution was then evaporated to dryness and the residue dissolved in the same amount of the reaction solvent. The incubation was then resumed until the next time point. The time required to record the n.m.r. spectrum was not included in the time of reaction used for each time point.

Kinetics of Hydrolysis of Triazenes.—Buffer solution was prepared by adding a solution of potassium dihydrogen phosphate (1.3609 g l^{-1}) to a solution of dipotassium monohydrogen phosphate (1.7409 g l^{-1}) until the pH was 7.5.

The triazene (2 mg) was dissolved in dimethyl sulphoxide (1 ml); a sample (50 μl) of this solution was added to the cuvette and then diluted with phosphate buffer (3 ml). The cuvette was immediately inserted into the sample beam; the reference cuvette contained 50 μl of pure dimethyl sulphoxide diluted with buffer (3 ml). The spectrum was recorded between 230 and 400 nm in the repetitive scan mode with a 5 min time interval between scans. The spectrophotometer used was a Varian-Cary 219 instrument. The rate of reaction was determined from the decrease of absorbance at $\lambda_{max.}$ of the reactant with time.

Reaction of the Hydroxymethyltriazene (**6**) *with Methanol.*—The hydroxymethyltriazene (**6**) (50 mg) was dissolved in methanol (5 ml) and the mixture stirred for 5 days at 37 °C. T.l.c. analysis from day to day showed that the hydroxymethyltriazene (**6**) was decomposing slowly, and that reaction was virtually complete after 5 days. Evaporation of the methanol under vacuum and analysis of the residue by ^1H n.m.r. showed the presence of the monomethyltriazene (**5**) (40%) [δ 3.43 (br s, NMe), 3.90 (s, OMe), and 7.3 (br) and 8.05 (AA'BB' arom., J_{AB} 8 Hz)] and methyl *p*-aminobenzoate (60%) [δ 3.83 (s, OMe), 4.1 (br s, NH_2), and 6.6 and 7.85 (AA'BB' aromatic, J_{AB} 8 Hz)].

Reaction of the Acetate (**7**) *with Potassium Cyanide in Aqueous Acetone.*—The acetate (**7**) (100 mg) (0.35 mmol) was dissolved in 50% v/v aqueous acetone (3 ml) with potassium cyanide (50 mg, 0.77 mmol) and the mixture was stirred at room temperature for 48 h. The acetone was removed under vacuum and the residue extracted with chloroform. The chloroform extracts were washed with water, dried, and evaporated to afford the monomethyltriazene (**5**) (50 mg), which had i.r. and n.m.r. spectra identical with those of an authentic sample.[9]

Reaction of the Acetate (**7**) *with Sodium Azide in Aqueous Acetone.*—The acetate (**7**) (0.5 g, 1.78 mmol) was dissolved in 50% v/v aqueous acetone (15 ml) saturated with sodium azide (2.5 g, 38.5 mmol) and the mixture was stirred at room temperature for 2 days. The acetone was removed under vacuum and the residue extracted with chloroform. The extracts were washed with water, dried, and evaporated to afford 3-azidomethyl-1-*p*-methoxycarbonylphenyl-3-methyltriazene (**10**) (0.30 g), m.p. 54—57 °C; $\nu_{max.}$ 3 400w, 2 180, 2 120s, 1 730, and 1 610 cm^{-1}; M^+, 248, *m/z* 220, 217, 193, 189, 163, and 135; $\delta_H(CDCl_3)$ 3.2 (3 H, s, NMe), 3.9 (3 H, s, OMe), 5.13 (2 H, s, CH_2), and 7.43, 7.56, 8.0, and 8.13 (4 H, AA'BB' arom., J_{AB} 8 Hz); $\delta_C(CDCl_3)$ 34.2 (br), 52.0 (sh), 71.2 (br), 120.9, 130.5, 153.0, and 166.7 p.p.m.

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