Triazene Drug Metabolites. Part 4.[1] Kinetics and Mechanism of the Decomposition of 1-Aryl-3-benzoyloxymethyl-3-methyltriazenes in Mixed Aqueous–Organic Solvents

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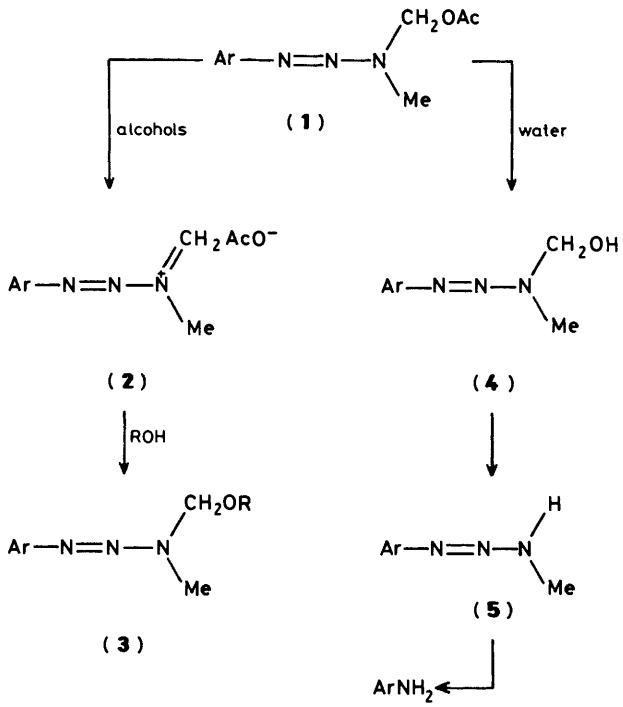
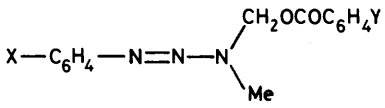
Kinetic studies for the hydrolysis of 1-aryl-3-benzoyloxymethyl-3-methyltriazenes to 1-aryl-3-hydroxymethyl-3-methyltriazenes in mixed aqueous–organic media are reported. Reactions are first-order in the benzoyloxymethyltriazene, and are independent of pH above pH 8. Below pH 8, specific acid catalysis is observed. No nucleophilic catalysis is detected at any pH. The observed first-order rate constants, k_{obs}, vary with the substituent in both the 1-aryl and benzoyl rings. Hammett σ values of 1.28 and 1.41 are obtained for substituents in the benzoyl group in 50% MeCN–H_2O and 60% dioxane–H_2O respectively. A Hammett ρ value of −1.84 is obtained in 50% MeCN–H_2O for substituents in the 1-aryl ring. Observed first-order rate constants also vary with the composition of aqueous dioxane mixtures and a linear correlation between log k_{obs} and the Grunwald–Winstein Y parameter is found to give a slope of 0.99. The solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}, is 1.26 for the 4-methoxybenzoyl derivative. Values of the activation parameters are $\Delta H^{\ddagger}$ *ca.* 80 kJ mol^{-1} and $\Delta S^{\ddagger}$ *ca.* −5 J K^{-1} mol^{-1}. The data are best interpreted in terms of a unimolecular ionisation of the benzoyloxymethyltriazene to form a iminium cation and a benzoate anion. Hydroxymethyltriazene formation results from the capture of the intermediate iminium ion by water. Consistent with this mechanism, a common ion effect of the benzoate anion is observed, and the benzoate ion is *ca.* 75 times more effective than water at trapping the iminium ion.

1-Aryl-3-acetoxymethyl-3-methyltriazenes, (**1**), are possible pro-drugs of the 1-aryl-3-hydroxymethyl-3-methyltriazenes (**4**)[2] which are central intermediates in the metabolic activation of the cancer chemotherapeutic dimethyltriazenes.[3] Vaughan and co-workers recently studied the solvolysis of some of these acetyl derivatives in alcohols and proposed, on the basis of limited kinetic evidence, that the reaction proceeds through an intermediate iminium ion (**2**) which then reacts with the alcohol present giving the corresponding alkyl ether (**3**) (Scheme 1).[4] They also reported that, in aqueous solutions, the hydrolysis of the acetate (**1**) occurs rapidly to give a hydroxymethyltriazene (**4**) which decomposes to give the corresponding arylamine *via* the monomethyltriazene (**5**) (Scheme 1). However, no spectroscopic evidence could be observed for these intervening reactions and the decomposition of (**1**) to the arylamine was cleanly first-order. Comparing rates of hydrolysis of (**1**), (**4**) and (**5**) (Ar = 4-CNC_6H_4 or 4-$MeOCOC_6H_4$ in each case), Vaughan *et al.* found that (**1**) and (**4**) decompose at a similar rate, but that (**5**) decomposes at a faster rate.[4]



Scheme 1. Modes of reaction of acetoxymethyltriazenes in alcoholic and aqueous media



(**6**) **a**; X = 4-EtOCO, Y = 4-MeO
b; X = 4-EtOCO, Y = 4-Me
c; X = 4-EtOCO, Y = H
d; X = 4-EtOCO, Y = 4-Cl
e; X = 4-EtOCO, Y = 4-NO_2
f; X = 4-Ac, Y = H
g; X = 4-CN, Y = H
h; X = 4-$CONH_2$, Y = H
i; X = 4-CF_3, Y = H
j; X = 4-Br, Y = H

In the course of examining the chemistry of the analogous benzoate esters (**6**), we observed that such compounds underwent hydrolysis in mixed aqueous–organic buffers by more complex kinetic processes than those described for the acetates (**1**) and we have been able to study the hydrolysis of 1-aryl-3-aroyloxymethyl-3-methyltriazenes (**6**) to the corresponding hydroxymethyltriazene (**4**) in greater kinetic detail than hitherto possible. Herein we report our results.

Experimental

Syntheses.—Benzoyloxymethyltriazenes (**6**) were made by one of two methods. *Method A* involved reaction of the hydroxymethyltriazene (1 mmol) with the appropriate benzoyl chloride (1.2 mmol) in pyridine (2 ml) at 0 °C. The benzoyloxymethyltriazene was isolated by pouring the reaction mixture onto ice–water, and the precipitated solid filtered, dried under reduced pressure, and recrystallised from a mixture of ether–light petroleum.

Method B involved reaction of the hydroxymethyltriazene (1 mmol) with a mixture of dicyclohexylcarbodi-imide (1.2 mmol) and the appropriate benzoic acid (1 mmol) in CH_2Cl_2 in the presence of a small amount (less than 0.1 mol equiv.) of 4-dimethylaminopyridine. After filtration of the precipitated urea, the organic phase was washed (water), dried, the solvent evaporated off, and the product recrystallised as in Method A.

In this way the following compounds were synthesised: (**6a**), m.p. 68—69 °C; $\nu_{max.}$ 1 712 and 1 610 cm^{-1}; δ ($CDCl_3$) 1.40 (3 H, t), 3.34 (3 H, s), 3.85 (3 H, s), 4.38 (2 H, q), 6.05 (2 H, s), and 6.86—8.11 (8 H, 2 × AA′BB′) (Found: C, 61.4; H, 5.8; N, 10.8. Calc. for $C_{19}H_{21}N_3O_5$: C, 61.44; H, 5.7; N, 11.31%).

(**6b**), m.p. 85—87 °C; $\nu_{max.}$ 1 720, 1 710, 1 605, 1 275, 1 172, 1 162, and 1 100 cm^{-1}; δ ($CDCl_3$) 1.40 (3 H, t), 2.40 (3 H, s), 3.34 (3 H, s), 4.38 (2 H, q), 6.06 (2 H, s), 7.18—8.13 (8 H, 2 × AA′BB′) (Found: C, 64.5; H, 6.0; N, 11.9. Calc. for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 6.0; N, 11.82%).

(**6c**), m.p. 67—68 °C (lit.,[2] 66—68 °C); $\nu_{max.}$ 1 725, 1 700, 1 603, 1 270, 1 109, 1 050, 1 022, and 710 cm^{-1}; δ ($CDCl_3$) 1.40 (3 H, t), 3.35 (3 H, s), 4.37 (2 H, q), 6.08 (2 H, s), and 7.26—8.14 (9 H, m) (Found: C, 63.6; H, 5.7; N, 12.1. Calc. for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31%).

(**6d**), m.p. 75—78 °C; $\nu_{max.}$ 1 722, 1 715, 1 605, and 1 050 cm^{-1}; δ ($CDCl_3$) 1.40 (3 H, t), 3.36 (3 H, s), 4.38 (2 H, q), 6.08 (2 H, s), and 7.20—8.26 (8 H, m) (Found: C, 57.5; H, 4.8; N, 11.3. Calc. for $C_{18}H_{18}ClN_3O_4$: C, 57.53; H, 4.83; N, 11.18%).

(**6e**), m.p. 103—105 °C; $\nu_{max.}$ 1 720, 1 705, 1 608, 1 525, and 1 058 cm^{-1}; δ ($CDCl_3$) 1.40 (3 H, t), 3.39 (3 H, s), 4.39 (2 H, q), 6.12 (2 H, s), 7.43—8.20 (4 H, AA′BB′), and 8.24 (4 H, s) (Found: C, 55.9; H, 4.3; N, 14.6. Calc. for $C_{18}H_{18}N_4O_6$: C, 55.96; H, 4.7; N, 14.5%).

(**6f**), m.p. 67—69 °C (lit.,[2] 65—69 °C); $\nu_{max.}$ 1 725, 1 695, and 1 600 cm^{-1}; δ ($CDCl_3$) 2.61 (3 H, s), 3.36 (3 H, s), 6.09 (2 H, s), and 7.43—8.15 (9 H, m) (Found: C, 65.4; H, 5.5; N, 13.4. Calc. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.5; N, 13.5%).

(**6g**), m.p. 75—76 °C (lit.,[2] 74—78 °C); $\nu_{max.}$ 2 222, 1 720, and 1 600 cm^{-1}; δ ($CDCl_3$) 3.36 (3 H, s), 6.08 (2 H, s), and 7.42—8.14 (9 H, m) (Found: C, 65.3; H, 4.7; N, 19.4. Calc. for $C_{16}H_{14}N_4O_2$: C, 65.31; H, 4.76; N, 19.05%).

(**6h**), m.p. 139—141 °C; $\nu_{max.}$ 3 410, 3 190, 1 719, 1 658, 1 612, and 1 050 cm^{-1}; δ ($CDCl_3$) 3.35 (3 H, s), 6.08 (2 H, s), 5.9—6.2 (2 H, br exch), and 7.33—8.11 (9 H, m) (Found: C, 61.0; H, 5.1; N, 18.2. Calc. for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94%).

(**6i**), m.p. 45—49 °C; $\nu_{max.}$ 1 729, 1 612, 1 322, 1 263, 1 209, 1 164, 1 128, and 1 049 cm^{-1}; δ ($CDCl_3$) 3.35 (3 H, s), 6.08 (2 H, s), and 7.43—8.11 (9 H, m) (Found: C, 56.8; H, 5.0; N, 12.4. Calc. for $C_{16}H_{14}F_3N_3O_2$: C, 56.80; H, 4.43; N, 12.42%).

(**6j**), m.p. 53—55 °C (lit.[2] 43—50 °C); $\nu_{max.}$ 1 729, 1 268, and 1 066 cm^{-1}; δ ($CDCl_3$) 3.35 (3 H, s), 6.06 (2 H, s), and 7.33—8.10 (9 H, m) (Found: C, 51.9; H, 3.9; N. 12.1 Calc. for $C_{15}H_{14}BrN_3O_2$: C, 51.87; H, 4.03; N, 12.10%).

Kinetics.—A small aliquot (20 μl) of a solution of the benzoyloxytriazene (5×10^{-3} mol l^{-1}) in dioxane was injected into a thermostatted cuvette containing 3 ml of the required buffer solution. The final concentration of (**6**) was therefore *ca.* 3×10^{-5} mol l^{-1}. The u.v. spectrum of the solution was monitored with time, *t* [Figure 1(a)]. Two consecutive reactions were observed: the first, the decomposition of (**6**) to the corresponding hydroxymethyltriazene (**4**); the second, the decomposition of (**4**) to the aniline. By monitoring the solution at the isosbestic point of the second reaction, it is possible to independently study the first reaction. Thus, the reactions were

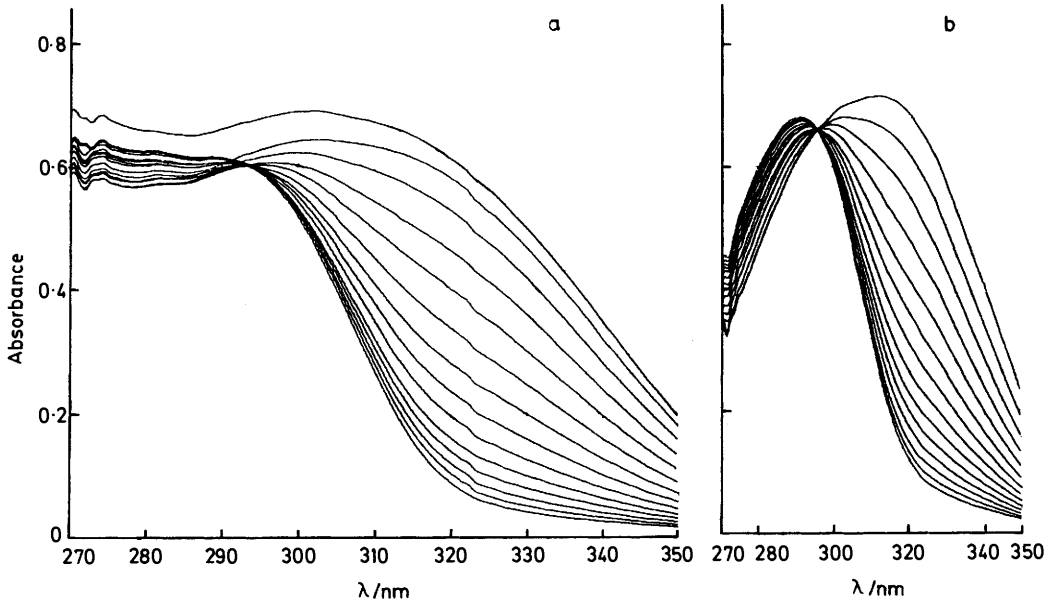


Figure 1. U.v. spectra recorded during the hydrolysis of (a): (**6a**) and (b): (**4b**) in 50% MeCN–H_2O morpholine buffers

Table 1. The effect of acetonitrile concentration on the pH meter reading of various buffers at 25 °C. [B]/[BH$^+$] = 1

	pH reading		
% MeCN	pyridine	morpholine	piperidine
0	4.67	7.85	10.93
10	4.63	7.73	10.81
20	4.50	7.64	10.75
30	4.31	7.52	10.64
40	4.30	—	10.59
50	4.18	7.42	10.50

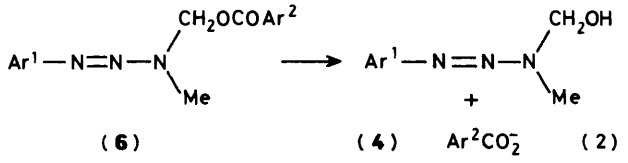
monitored at the wavelength of the second reaction and first-order rate constants, k_{obs}, determined from plots of ln $(A_t - A_\infty)$ *versus* time. Good straight lines were obtained up to at least five half-lives. Values of k_{obs} determined in this way were reproducible to ± 5%.

pH Measurements.—It is important to determine whether or not the presence of acetonitrile has a differential effect on the pH reading in the pH regions used in this work. Therefore we recorded the meter pH reading as a function of the percentage of acetonitrile in three different buffer systems. The values are collected in Table 1. It is clear that the change in pH with percentage composition of acetonitrile in the solvent system is fairly constant across the pH range, and that in 50% MeCN–H_2O the pH reading is some 0.45 pH units *less* than the corresponding reading in a purely aqueous system. We have made no attempt, therefore, to correct the pH values obtained for each solution and pH values reported throughout this paper are those recorded directly from the pH meter using an ordinary combination pH electrode.

Results and Discussion

In purely aqueous buffers we found that, like the acetoxymethyltriazenes, the benzoyloxymethyltriazenes (**6**) have similar rates of hydrolysis to the corresponding hydroxymethyltriazene (**4**) and monomethyltriazene (**5**). However, we were not able to detect a difference between the rates of hydrolysis of (**4**) and (**5**) as observed for (**1**) by Vaughan.[4] However, in contrast to (**1**), solvolyses of the benzoates (**6**) in such aqueous media yield first-order plots of ln *A versus* time which have an induction period. This led us to search for conditions where the reaction responsible for the induction period could be observed, and by using mixtures of organic solvents and aqueous buffers we were able to observe two consecutive reactions by u.v. spectroscopy [Figure 1(a)]. This observation is almost certainly due to the liberation of benzoate anion from (**6**) rather than the acetate anion (which does not significantly absorb u.v. radiation in this region) from (**1**). Comparing u.v. spectra of (**6**) with those of the corresponding (**4**) and (**5**) recorded under the same conditions (except for the absence of the benzoate ion) (Figure 1), we conclude that the first reaction corresponds to the decomposition of the ester to the hydroxymethyltriazene (**4**) [equation (2)]. In fact, under

$$\text{Rate} = k_{obs}[(\mathbf{6})] \quad (1)$$



(**6**) (**4**) (**2**)

Table 2. First-order rate constants, k_{obs}, for the hydrolysis of (**6a**) in 50% MeCN–H_2O buffers at 25 °C. μ = 0.5 mol l^{-1} ($NaClO_4$)

Base	10^3(Base)/mol l^{-1}	10^3(HCl)/mol l^{-1}	pH	$10^3 k_{obs}$ /s^{-1}
Pyridine	2.0	0.5	5.10	9.76
	4.0	1.0	5.08	9.60
	6.0	1.5	5.08	9.71
	8.0	2.0	5.08	9.56
	3.0	1.0	4.81	10.19
	4.5	1.5	4.96	9.88
	6.0	2.0	4.79	9.94
	3.0	0.5	5.40	8.62
	4.8	0.4	5.8	7.32
Imidazole	2.0	0.5	7.17	5.29
	4.0	1.0	7.18	5.74
	6.0	1.5	7.21	5.43
	8.0	2.0	7.19	5.29
	3.0	1.2	6.60	6.39
	6.0	2.0	6.90	5.64
	4.8	0.4	7.90	4.91
Morpholine	4.0	1.0	9.31	4.48
	6.0	1.5	9.34	4.63
	8.0	2.0	9.45	4.58
	8.8	0.8	9.70	4.76
	1.5	1.0	8.14	4.78
Piperidine	4.0	1.0	11.26	4.65
	6.0	1.5	11.39	4.60
	8.0	2.0	11.48	4.62
	4.8	0.4	11.62	4.31
Tetramethyl-guanidine	2.0	1.0	10.02	4.57
	8.8	0.8	12.44	4.71

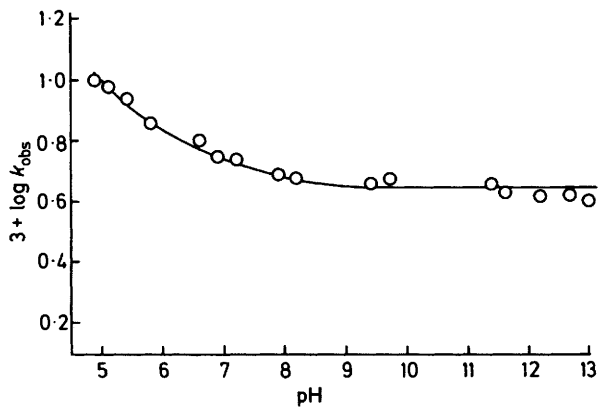


Figure 2. pH–Rate profile for the hydrolysis of (**6a**) at 25 °C

these conditions, at 300 nm it is possible to observe the decomposition of the hydroxymethyltriazene (**4**) to the monomethyltriazene (**5**) prior to decomposition of the latter to the corresponding arylamine and we shall report on this reaction in a subsequent publication. Monitoring the decrease in absorbance of the reaction of (**6a**) at 290 nm, the wavelength of the isosbestic point of the second reaction, we obtained good first-order plots of ln *A versus* time. Thus reactions follow equation (1). Other benzoyloxymethyltriazenes (**6b**—**j**) behave similarly.

pH–Rate Profile.—First-order rate constants, k_{obs}, at various pH values were obtained for the decomposition of (**6a**) to (**4a**) in mixed aqueous–acetonitrile (1:1) buffers. Below pH 4.75, the reaction of (**6a**) to (**4a**) was too fast to be monitored. Above pH 4.75, the reaction is essentially acid- and base-independent, though there is some acid catalysis between pH 5—8 (Figure 2). This acid catalysis is specific in nature, there being no general acid catalysis (Table 2). A striking feature of this pH profile is

Table 3. Substituent effects on the values of k_{obs} for the hydrolysis of (**6**) to (**4**) in aqueous organic buffers at 25 °C. [Morpholine] = 8×10^{-3}M, [HCl] = 2×10^{-3}M, pH = 9.27, μ = 0.5 mol l^{-1} ($NaClO_4$)

	$10^3 k_{obs}/s^{-1}$	
	50% acetonitrile	60% dioxane
(**6a**)	4.58	0.69
(**6b**)	6.70	
(**6c**)	10.70	1.56
(**6d**)	20.4	4.14
(**6e**)		20.1
(**6f**)	10.2	
(**6g**)	3.85	
(**6h**)	19.7	
(**6i**)	6.60	
(**6j**)	38.9	

Table 4. Rates of hydrolysis of (**6a**) in aqueous 1,4-dioxane of varying composition at 25 °C. μ = 0.5 mol l^{-1}

% dioxane	$10^3 k_{obs}/s^{-1}$	Y^a
30	22.31	2.46
40	6.85	1.95
50	1.30	1.36
60	0.455	0.72

[a] Grunwald–Winstein Y value.

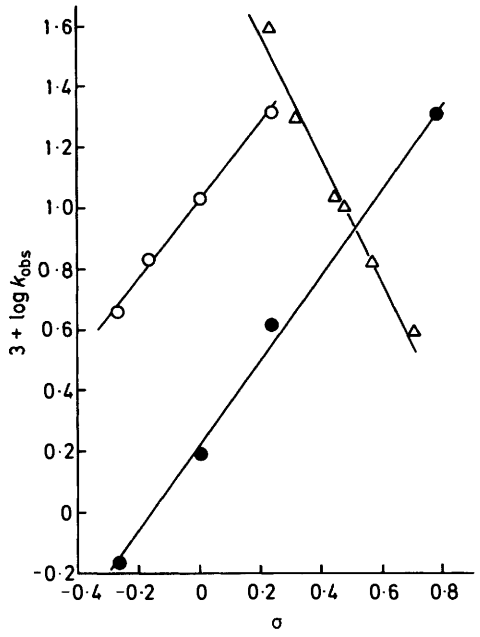
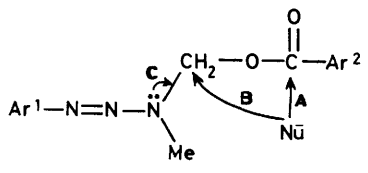


Figure 3. Hammett plots for the hydrolyses of (**6a**—**j**) in 50% MeCN–H_2O (open symbols) and 60% dioxane–H_2O (solid symbols). Circles represent the effect of group Y, and triangles the effect of group X

the lack of any nucleophilic catalysis by OH^-, even at pH 13. Ester hydrolyses generally show such nucleophilic catalysis around pH 6—7.[5] Moreover, the data in Table 2 also indicate that there is no nucleophilic catalysis from the buffer materials such as piperidine or morpholine and in none of these reactions were we able to isolate *N*-(4-methoxybenzoyl)piperidine, *N*-(4-methoxybenzoyl)morpholine, or *N*″-(4-methoxybenzoyl)-*N*,*N*,*N*′,*N*′-tetramethylguanidine. Ester hydrolyses, particularly of those in which the alcohol leaving group has a $pK_a < 11$, generally display nucleophilic buffer catalysis.[5,6] We have shown elsewhere that hydroxymethyltriazenes have pK_a *ca.* 10—11.[1]

Substituent Effects.—Observed first-order rate constants measured in the acid-independent region of the pH profile (pH 9.27) vary with the substituents both in the benzoate group and also in the aryl group of the triazene (Table 3). The k_{obs} values for the substituent in the aromatic ring of the benzoate group correlate with the Hammett σ values (Figure 3), giving values for ρ of 1.28 in 50% MeCN and 1.41 in 60% dioxane. The positive sign of the ρ values is consistent with the increasing nucleofugacity of the leaving group.

While a positive ρ value for the correlation of rates with the substituent in the benzoate group is to be expected whatever the mechanism of solvolysis, the sign and magnitude of ρ for substituents in the *N*-1 aryl group should be more sensitive to mechanistic events. Thus, either nucleophilic attack at the ester carbonyl carbon (**7**; **A**) or S_N2 attack at the acyloxymethyl carbon (**7**; **B**) would be expected to show positive ρ values, whereas ionisation (**7**; **C**) would be expected to show a negative ρ value since the *N*-3 lone pair of electrons which facilitate such a process are conjugated with the aromatic ring.



(**7**)

The first-order rate constants for compounds (**6 c**, **f**—**j**), collected in Table 3, correlate with Hammett σ constants (Figure 3), giving a ρ value of −2.0. The rate constants for the intermolecular methylation of substituted *N*,*N*-dimethylanilines, which correlate with σ^+, have a ρ value of −3.3 which is somewhat larger than that for the intramolecular alkylation described here.[7] Presumably the extra double bond between the nitrogen atom and the aromatic ring in the triazenes attenuates the substituent effect.

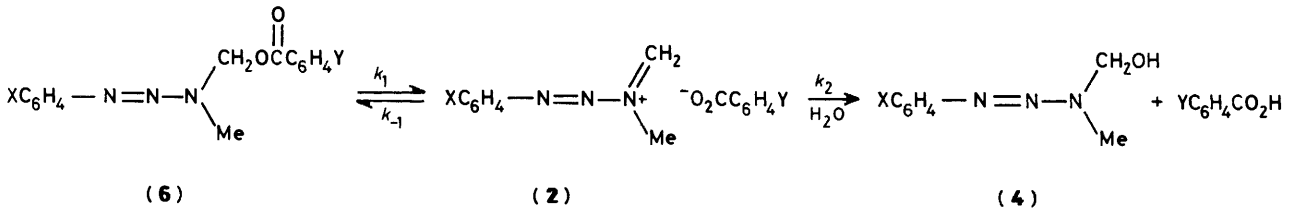
Solvent Effects.—Rates for the solvolysis of (**6b**) in aqueous dioxane vary with the solvent composition (Table 4). The data correlate well with the Grunwald–Winstein Y parameter, giving equation (3) (r = correlation coefficient).

$$\log k = 0.99Y - 4.12 \quad (r = 0.994) \qquad (3)$$

Grunwald–Winstein correlations having unit slope are generally considered to arise from processes involving unimolecular ionisations.[7]

The solvolysis of (**6a**) in the pH-independent region of the reaction is faster in 50% MeCN–H_2O than in 50% Me_3CN–D_2O. The data in Table 5 give a solvent isotope k_{H_2O}/k_{D_2O} value of 1.26, consistent with an ionisation process being a rate-determining step.[8]

Mechanism of the Hydrolysis of Benzoyloxymethyltriazenes.—The lack of an OH^-- or nucleophile-promoted hydrolysis reaction, the effect of the substituent X in the triazene aryl ring, the dependence of the hydrolysis on the ionising power of the solvent, and the solvent isotope effect all point to a mechanism which involves a unimolecular ionisation of the substrate to form an iminium ion (Scheme 2). Applying the steady-state assumption to the concentration of the iminium ion, the rate



(6) (2) (4)

Scheme 2. Mechanism of the solvolysis of 1-aryl-3-benzoyloxymethyl-3-methyltriazenes (**6**)

Table 5. Rates of solvolysis of (**6a**) in 50% MeCN–H_2O and 50% MeCN–D_2O solutions at 25 °C. μ = 0.5 mol l^{-1}

$[OH^-]$/mol l^{-1}	$[OD^-]$/mol l^{-1}	pH	$10^3k_0/s^{-1}$
0.016		12.2	4.12
0.050		12.7	4.18
0.100		13.0	3.98
	0.01	12.0	3.24
	0.05	12.7	3.42
	0.10	13.0	3.21

Table 6. Rate constants, k_{obs}, for the hydrolysis of (**6g**) at 25 °C in 50% MeCN–H_2O solutions of varying ionic strength

μ/mol l^{-1}	pH	$10^3\ k_{obs}/s^{-1}$
0.05	11.89	2.83
0.10	11.93	2.93
0.20	11.93	3.01
0.50	11.90	2.90

expression for such a mechanism is given by equation (4), and the observed rate constant $k_{obs} = k_1k_2[H_2O]/k_{-1}[ArCO_2^-] + k_2[H_2O]$. A common-ion effect due to $ArCO_2^-$ is thus anticipated and a plot of $1/k_{obs}$ *versus* $[ArCO_2^-]$ should give a straight line of slope $k_{-1}/k_1k_2[H_2O]$ and intercept $1/k_1$. Thus it is possible to determine the ratio k_{-1}/k_2, which is the relative partitioning of the iminium ion between the benzoate anion and water. Such a plot for the hydrolysis of (**6c**) at 25 °C and pH 9.25 in the presence of various benzoate concentrations is shown in Figure 4. The intercept, $1/k_1$, is 111.4 s and the slope 299.2 s l mol^{-1}, from which the a value of k_{-1}/k_1 = 74.5. Thus, the benzoate ion is some seventy times more effective than water at trapping the iminium ion. The effect of benzoate ion is not related to the ionic strength of the medium since, as the data in Table 6 show, the reaction is largely independent of ionic strength. This common ion effect also confirms our original deduction that the reaction we observe is the conversion (**6**) ⟶ (**4**). If the reaction were simply the ionisation process to form the iminium ion (**2**), then an increase in $[PhCO_2^-]$ would *increase* k_{obs} since, in this case, $k_{obs} = k_1 + k_{-1}[PhCO_2^-]$.*

$$\text{Rate} = k_1k_2[(\mathbf{6})][H_2O]/k_{-1}[ArCO_2^-] + k_2[H_2O] \quad (4)$$

Further confirmation for this mechanism comes from the measurement of activation parameters. The data for the hydrolysis of (**6 a**,**c**,**d**, and **g**) in the pH-independent region are contained in Table 7. The values of $\Delta S^‡$ are close to zero, which is indicative of a unimolecular, rather than a bimolecular, process. Winstein showed, many years ago, that $\Delta S^‡$ for the solvolysis of Bu^{t}Cl varied in both sign and magnitude depending on the composition of the solvent; for 50—60% mixed organic–aqueous solvents $\Delta S^‡$ is negative and almost zero.[9]

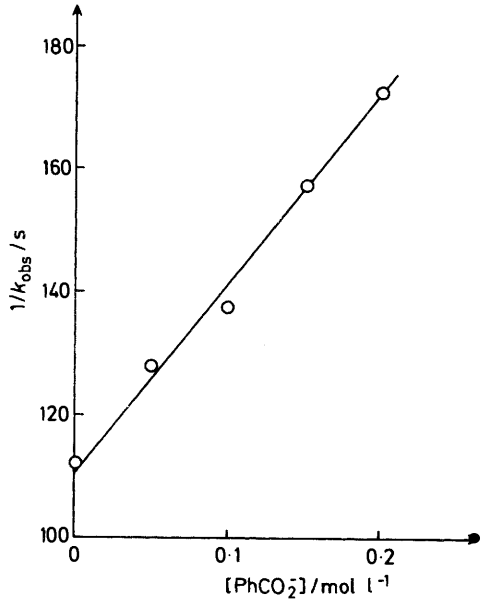


Figure 4. Plot of $1/k_{obs}$ *versus* $[PhCO_2^-]$ for the solvolysis of (**6c**)

Specific acid catalysis of the reaction can be accounted for by the protonation of the ester moiety of the benzoyloxytriazene (**6**). Such protonation will assist the formation of the iminium ion (**2**). The contribution of such catalysis at the pH values used in the present study is, however, small.

* Strictly speaking, if such a situation were operating, then

$$\begin{aligned}\text{Rate} = -\mathrm{d}[(\mathbf{6})]/\mathrm{d}t &= k_1[(\mathbf{6})] - k_{-1}[(\mathbf{2})][PhCO_2^-] \\ &= k_1[(\mathbf{6})] - k_{-1}\{[(\mathbf{6})]_0 - [(\mathbf{6})]\}[PhCO_2^-] \\ &= (k_1 + k_{-1}[PhCO_2^-])[(\mathbf{6})] - \\ &\qquad k_{-1}[(\mathbf{6})]_0[PhCO_2^-]\end{aligned}$$

However, $[PhCO_2^-]$ is effectively constant throughout the reaction so the last term can be considered a constant. The integrated form of this equation is thus

$$\log\{(k_1 + k_{-1}[PhCO_2^-])[(\mathbf{6})] - k_{-1}[(\mathbf{6})]_0[PhCO_2^-]\}/k_1[(\mathbf{6})]_0 = (k_1 + k_{-1}[PhCO_2^-])\,t$$

As the reaction follows first-order kinetics, it follows that the $k_{-1}[(\mathbf{6})]_0[PhCO_2^-]$ term contributes little to the left-hand side of the above equation. This then simplifies to

$$\log\{k_1 + k_{-1}[PhCO_2^-]\}/k_1[(\mathbf{6})]_0 + \log[(\mathbf{6})] = (k_1 + k_{-1}[PhCO_2^-])\,t$$

from which it follows that a first-order plot of log [(**6**)] *versus* t gives an observed rate constant, k_{obs}, which can be expressed as

$$k_{obs} = k_1 + k_{-1}[PhCO_2^-]$$

Table 7. Rate constants, k_{obs}, and activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, for the hydrolysis of (**6 a, c, d,** and **g**) at 25 °C in pH 9.5, 50% MeCN–H_2O morpholine buffers. $[Morpholine]_{total} = 8 \times 10^{-3}$ mol l^{-1}, $\mu = 0.5$ mol l^{-1}

	$10^3 k_{obs}/s^{-1}$ / T/K							
	283	288	293	298	303	308	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}
(6a)		1.68	2.87	4.58	8.29	14.3	80.5	−19.0
(6c)			3.88	7.26	12.7	21.1	85.0	+4.0
(6d)	5.07	8.86	15.4	27.6			79.5	−7.2
(6g)		1.31	2.23	3.85	8.28	12.0	87.5	+2.2

The results reported here for the benzoates (**6**), together with those described elsewhere for the corresponding acetates (**1**), indicate that acyloxymethyltriazenes in general undergo solvolysis *via* iminium ion formation. However, the reactivity of these compounds is such that unless stabilised in some as yet unknown way, they are unlikely to be anything but transitory intermediates *in vivo*. Vaughan has suggested that they may have a role in the activation of hydroxymethyltriazenes (**4**) for biological conjugation. Compounds such as (**4**) do not form iminium ions directly. Elsewhere, however, we have found that a simpler activation process is achieved by H^+.[10]

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