Triazene Drug Metabolites. Part 13.[1] The Decomposition of 3-Acyl-3-alkyl-1-aryltriazenes in Aqueous Sulfuric Acid

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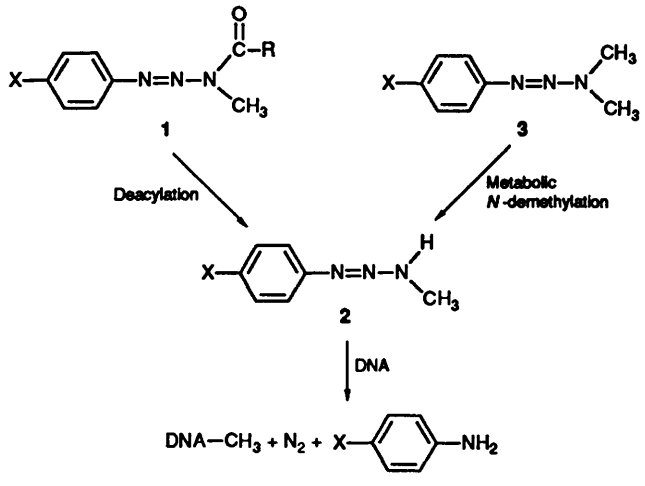
The hydrolysis of 1-aryl-3-acyl-3-methyltriazenes in aqueous sulfuric acid is described. The 3-formyl derivative undergoes an acid-catalysed deacylation reaction, characterised by a monotonic rise in the pseudo-first-order rate constant, k_0 with increasing acidity, solvent deuterium isotope effects, $k^{H,SO_4}/k^{D,SO_4}$, of 0.9 (at 0.95 mol dm^{-3} H_2SO_4) and 0.8 (at 2.85 mol dm^{-3} H_2SO_4) and an entropy of activation of −80 J mol^{-1} K^{-1}. The 3-alkanoyl derivatives also undergo acid-catalysed decomposition involving cleavage of either the N^3–C acyl bond or the N^2–N^3 triazene bond. Below 3 mol dm^{-3} H_2SO_4, only acyl bond cleavage is observed. At higher acidities the extent of N^2–N^3 bond cleavage increases. The reaction is characterised by (i) solvent deuterium isotope effects of *ca.* 0.6 at 2 and 5 mol dm^{-3} H_2SO_4 and *ca.* 0.4 at 8 mol dm^{-3} H_2SO_4, (ii) $\Delta S^{\ddagger}$ values of −6.7 and −51 J mol^{-1} K^{-1} at 2 and 6.1 mol dm^{-3} H_2SO_4, respectively, (iii) Hammett ρ values for the substituent in the triazene *N*-aryl ring of −0.7 and −0.9 at 3 and 9 mol dm^{-3} H_2SO_4, respectively, and (iv) an increase in reactivity with electron donating ability of the alkyl substituent of the acyl group. The 3-trifluoroacetyl triazenes are subject to solvolysis of the neutral, as well as the protonated, substrate. The hydrolysis of the neutral substrate involves N–acyl bond cleavage and is characterised by a solvent deuterium isotope effect, $k^{H,O}/k^{D,O}$, of 2.4, and a Hammett ρ value of +0.8 for the substituent in the N-aryl ring. The reactivity of the neutral substrate diminishes with increasing acidity until 6 mol dm^{-3} H_2SO_4, beyond which acid-catalysed N–acyl bond cleavage predominates, for which the solvent isotope effect, $k^{H,SO_4}/k^{D,SO_4}$, is 0.8 and the Hammett ρ value −0.5. The 3-aroyl substrates suffer acid-catalysed decomposition, the extent of the N^2–N^3 bond cleavage process being greater than for the N-alkanoyl counterparts. The reactions are rationalised in terms of a process that involves pre-equilibrium protonation of the substrate either at the N^1 triazene atom or the amide oxygen atom, followed by subsequent decomposition of the protonated substrate *via* either N^3–C bond cleavage, involving attack of water at the amide carbonyl, or unimolecular N^2–N^3 bond cleavage. The relative extents of the N^3–C and N^2–N^3 bond cleavage processes depend on the reactivity of the acyl group and the water activity; the higher the water activity and the more reactive the acyl group, the more deacylation is favoured.

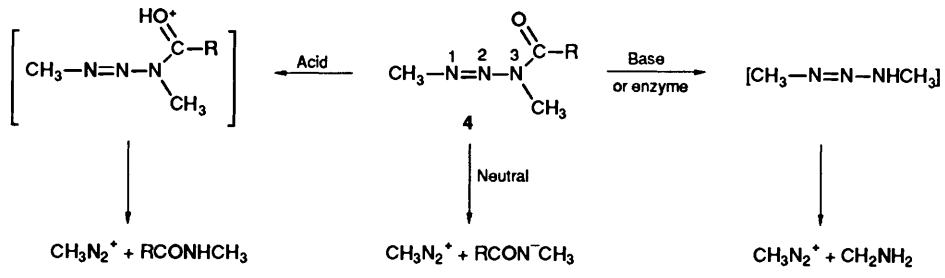
3-Acyl-1-aryl-3-methyltriazenes, **1**, are potential prodrugs of the cytotoxic methylating agents 1-aryl-3-methyltriazenes, **2**, which are thought to be the active metabolite of the anticancer agents 1-aryl-3,3-dimethyltriazenes, **3** (Scheme 1).[2,3] We have previously studied the deacylation of the compounds **1** in basic ethanolic media and showed that they decompose by a general base-catalysed pathway to give **2**, an observation consistent with the possibility that they indeed may be prodrugs of **2**.[4]

3-Acyl-1,3-dialkyltriazenes, **4**, are also known to be anti-neoplastic alkylating agents, diethylphosphoryl-, carbethoxy-, *N*-methylcarbamoyl- and 3-acetyl-1,3-dimethyltriazenes being cytotoxic against certain cell lines, particularly those deficient in methylation repair, and having *in vivo* activity against several tumours.[5] The decomposition of these compounds in aqueous buffers has been studied,[6] and they were found to decompose by acyl bond cleavage, a process that could be catalysed by base or enzyme (esterase). However, at neutral pH or in acidic solutions such compounds were found to decompose by N^2–N^3 bond fission (Scheme 2). *Ab initio* calculations at the 3-21G level for the protonation of 3-acetyltriazene were carried out in order to provide an insight into the mechanism of the acid-catalysed decomposition of the 3-acyl-1,3-dialkyltriazenes.[7] These calculations suggest that, in general, N^3-protonation is a much higher energy process than either O or N^1-protonation.† From product analyses, the authors infer that N^1-protonation is not important as a productive pathway for hydrolysis, and propose that the acid-catalysed hydrolytic decompositon of the 3-acyl-1,3-dialkytriazenes, and possibly other acyltriazenes, must involve O-protonation. Such protonation brings about a lengthening of the N^2–N^3 bond but not an increase of the N^3–C bond length. Thus the acid-catalysed hydrolysis of acetyl-



Scheme 1

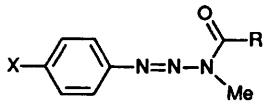
† The numbering system for triazenes is shown in compound **4** (Scheme 2).



Scheme 2

triazene, and, by extension, other 3-acyltriazenes is expected to involve N^2–N^3 bond cleavage rather than N^3–C bond cleavage.

If these predictions are valid for 3-acyl-1-aryl-3-methyltriazenes, **1**, then such compounds will not provide the cyto-



1

	R	X
a;	–H	–CN
b;	$-CH_3$	$-NO_2$
c;	$-CH_3$	–CN
d;	$-CH_3$	$-CO_2C_2H_5$
e;	$-CH_3$	$-CONH_2$
f;	$-CH_3$	$-CH_3$
g;	$-(CH_2)_4CH_3$	–CN
h;	$-(CH_2)_7CH_3$	–CN
i;	$-CF_3$	$-NO_2$
j;	$-CF_3$	–CN
k;	$-CF_3$	$-CO_2C_2H_5$
l;	$-CF_3$	$-CH_3$
m;	$-C_6H_4$-4-NO_2	–CN
n;	$-C_6H_5$	–CN
o;	$-C_6H_4$-4-CH_3	–CN
p;	$-C_6H_4$-4-OCH_3	–CN

toxic methylating agents **2** under acid, and possibly neutral, conditions, and will not be prodrugs of **2**. In order to verify these predictions experimentally, we have carried out a study of the decomposition of compounds **1a–p** in acidic and neutral aqueous media and herein report our results.

Experimental

Substrates and Reagents.—The 3-acyl-1-aryl-3-methyltriazenes **1** were prepared as reported previously.[4,8,9] The following are new compounds.

1b: m.p. 116–118 °C; ν_{max}/cm^{-1} 1690, 1040, 1000 and 860; $\delta_H(CDCl_3)$, 2.47 (3 H, s), 3.47 (3 H, s), 7.8 (2 H, d) and 8.4 (2 H, d) (Found: C, 48.4; H, 4.5; N, 24.9. Calc. for $C_9H_{10}N_4O_3$: C, 48.64; H, 4.5; N, 25.2%).

1d: m.p. 125–126 °C; ν_{max}/cm^{-1} 1700, 1290, 1110 and 1000; $\delta_H(CDCl_3)$ 1.34 (3 H, t), 2.49 (3 H, s), 3.34 (3 H, s), 4.33 (2 H, q), 7.4 (2 H, d) and 7.83 (2 H, d) (Found: C, 57.3; H, 6.1; N, 16.6. Calc. for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86%).

1g: m.p. 60–62 °C; ν_{max}/cm^{-1} 2220, 1705, 1050 and 860; $\delta_H(CDCl_3)$ 0.8–1.88 (9 H, m), 2.84 (2 H, t), 3.47 (3 H, s) and 7.79 (4 H, s) (Found: C, 65.2; H, 7.0; N, 22.0. Calc. for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69%).

1l: m.p. 60–62 °C; ν_{max}/cm^{-1} 1725, 1255, 1170, 1095 and 820; $\delta_H(CDCl_3)$ 2.4 (3 H, s), 3.48 (3 H, s) and 7.32–7.68 (4 H, m) (Found: C, 51.7; H, 4.3; N, 14.4. Calc. for $C_{10}H_{10}F_3N_3O$: C, 48.97; H, 4.08; N, 17.30%).

1m: m.p. 204–206 °C; ν_{max}/cm^{-1} 2240, 1700, 1360, 1200, 1050 and 855; $\delta_H(CDCl_3)$ 3.68 (3 H, s) and 7.39–7.83 (8 H, m) (Found: C, 58.2; H, 3.5; N, 22.5. Calc. for $C_{15}H_{11}N_5O_3$: C, 58.25; H, 3.55: N, 22.65%).

1n: m.p. 162–164 °C; ν_{max}/cm^{-1} 2210, 1690, 1200, 1035 and 840; $\delta_H(CDCl_3)$ 3.55 (3 H, s), 7.16 (5 H, s) and 7.33–7.36 (4 H, m) (Found: C, 67.8; H, 4.5; N, 21.4. Calc. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.57; N, 21.19%).

1o: m.p. 142–144 °C; ν_{max}/cm^{-1} 2220, 1675, 1365 and 1040; $\delta_H(CDCl_3)$ 2.49 (3 H, s), 3.66 (3 H, s), 7.16–7.38 (4 H, m) and 7.53 (4 H, s) (Found: C, 69.0; H, 5.0; N, 19.9. Calc. for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.06; N, 20.13%).

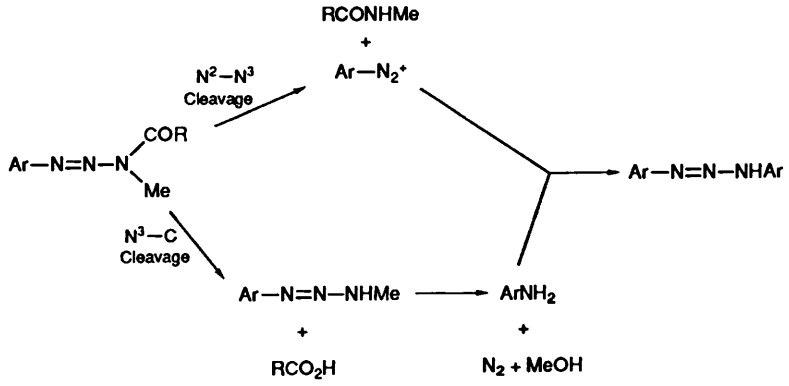
1p: m.p. 133–135 °C; ν_{max}/cm^{-1} 2208, 1720, 1035 and 830; $\delta_H(CDCl_3)$ 3.66 (3 H, s), 3.87 (3 H, s), 7.06 (2 H, d) and 7.71 (2 H, d) (Found: C, 65.5; H, 4.71; N, 18.9. Calc. for $C_{16}H_{14}N_4O_2$: C, 65.20; H, 4.79; N, 19.02%).

Kinetics.—The decompositon of **1** was followed by monitoring the decrease in UV absorbance of the substrate, at an appropriate wavelength, using a Perkin-Elmer Lambda 3 spectrophotometer. For solubility reasons, acetonitrile (20% v/v) was necessary as a co-solvent. Reaction solutions were monitored continuously in cells thermostatted to ±0.1 °C. Initial substrate concentrations were *ca.* 3×10^{-6} mol dm^{-3}. At the conclusion of each experiment the acidity of the solution was determined by titration against standard alkali. Values of the pseudo-first-order rate constants, k_0 were obtained from plots of ln $(A_t - A_\infty)$ *versus* time, and were reproducible to ± 5%.

Product Analysis.—We were unable to perform satisfactory quantitative product analyses on dilute solutions at the end of kinetic runs. This precluded the partitioning of the overall rate constants between the competing reactions. However, at the end of each kinetic reaction a UV spectrum of the products was recorded from which the presence of the diaryltriazenes could be detected, and this was confirmed by TLC analysis of the reaction mixtures. We were, however, able to isolate and quantify the products of some large scale hydrolysis reactions. For example, 4-aminobenzonitrile was isolated by extraction from larger scale hydrolysis reactions of **1c** in 2.8 and 4 mol dm^{-3} solutions of H_2SO_4. The same compound, in 10.7 mol dm^{-3} H_2SO_4, yielded 4-aminobenzonitrile and 1,3-di(4-cyanophenyl)triazene. The hydrolysis of **1n** in 10.7 mol dm^{-3} H_2SO_4 yielded 4-aminobenzonitrile, *N*-methylbenzamide, 1,3-di(4-cyanophenyl)triazene and benzoic acid.

Results and Discussion

In neutral solutions, except for compounds **1i–l**, it was found that the acyltriazenes are exceptionally stable. However, product analyses reveal that 3-acyl-1-aryl-3-methyltriazenes decompose in H_2SO_4 solutions by two competing pathways: (i) N–acyl bond cleavage to give 1-aryl-3-methyltriazenes, which themselves rapidly decompose to the corresponding anilines, and (ii) N^2–N^3 bond cleavage with formation of a diaryltriazene and *N*-methylamide (Scheme 3). Depending upon the acidity,



Scheme 3 Pathways of product formation from 3-acyl-1-aryl-3-methyltriazenes

Table 1 The relative extent of bond cleavage reactions for the acid-catalysed decomposition of acyltriazenes **1a**, **1c** and **1n**

	Percentage reaction[a]		
Bond cleavage	**1a**	**1c**	**1n**
N^3–C[b]	100[d]	100,[e] 89,[f] 71[d]	40[d]
N^2–N^3[c]	0[d]	0,[e] 11,[f] 29[d]	60[d]

[a] ±5%. [b] Calculated from the amounts of 4-aminobenzonitrile and 1,3-diaryltriazene formed. [c] Calculated from the amounts of 1,3-diaryltriazene formed for **1a** and **1c**, or the amount of *N*-methylbenzamide formed for **1n**. [d] In 10.7 mol dm^{-3} H_2SO_4. [e] In 2.8 mol dm^{-3} H_2SO_4. [f] In 8 mol dm^{-3} H_2SO_4.

products of both reactions are observed for most compounds studied. Generally, at low acidities N–acyl bond cleavage products predominate, in some cases exclusively, but at higher acidities both reactions are observed.

Decomposition of 1-(4-*Cyanophenyl*)-3-*formyl*-3-*methyltriazene* **1a**.—Compound **1a** decomposes in H_2SO_4 solutions (0.5–10 mol dm^3) giving 4-aminobenzonitrile as the only product (Table 1), although, at $[H_2SO_4]$ = 12 mol dm^{-3} and in concentrated H_2SO_4, small amounts of 1,3-di(4-cyanophenyl)-triazene could be detected. Therefore, for **1a** the preferred pathway of decompositions is N–acyl bond fission. The hydrolysis of **1a** is strongly acid catalysed, even at low acidity, and the pseudo-first-order rate constants exhibit a monotonic increase with increasing acidity and no rate maximum (Fig. 1). The deuterium solvent isotope effect $k_0^{H_2SO_4}/k_0^{D_2SO_4}$ is effectively independent of acidity and its mean value is 0.8 (Table 2). This value is consistent with a fast pre-equilibrium protonation of the substrate with a higher concentration of the conjugate acid in D_2SO_4 than in H_2SO_4. The entropies of activation in 0.95 and 4.85 mol dm^{-3} H_2SO_4 for **1a** can be calculated from the results in Table 3, and are, respectively, −76 and −88 J mol^{-1} K^{-1} (Table 4). These values are typical of bimolecular processes. Therefore we conclude that the hydrolysis of **1a** proceeds *via* a rate-determining attack of water on the protonated substrate, with formation of a tetrahedral intermediate that rapidly breaks down to products (Scheme 4). The deuterium solvent isotope effect thus comprises a contribution for the pre-equilibrium protonation and one for the attack of water on the protonated substrate. The former results in an inverse isotope effect whereas the latter produces a normal isotope effect, since D_2O is a poorer nucleophile than H_2O. These combine to yield a small inverse solvent deuterium isotope effect.

The site of protonation of the substrate is uncertain. Although Michejda and co-workers discounted protonation of N^1 because it was unproductive for their system,[7] here it clearly could lead to product formation. Indeed, inspection of the data of Michejda and co-workers[7] reveals that protonation at N^1 in 3-acetyltriazene lengthens the N^3–CO bond considerably, owing to delocalisation of the nitrogen non-bonding electron pair on N^3 into the protonated triazene, rather than amide, system.[7] This lengthening of the C–O bond is associated with increased reactivity of the acyl group.

Alternatively, the most basic site in amides is the carbonyl oxygen atom. The theoretical calculations identify the amide oxygen atom as an equally probable site as the triazene N^1 atom for protonation. Protonation of the amide carbonyl oxygen atom results in a lengthening of the N^2–N^3 bond but a

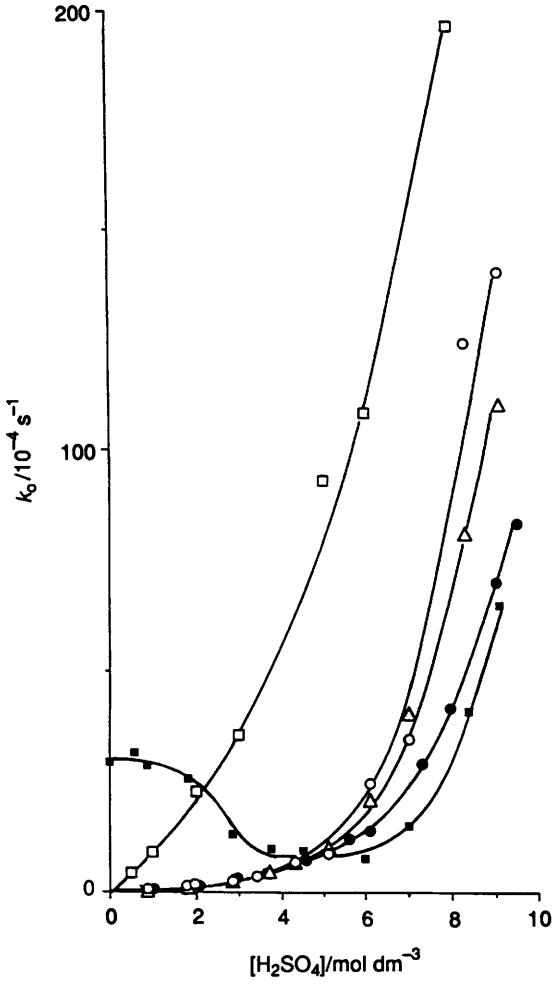


Fig. 1 Variation of k_0 with $[H_2SO_4]$ for 3-alkanoyltriazenes **1a** □, **1c** ○, **1g** △, **1h** ● and **1j** ■, at 25 °C

Table 2 Solvent deuterium isotope effects ($k_0^{H_2SO_4}/k_0^{D_2SO_4}$) for **1a**, **1c** and **1j** in L_2SO_4 solutions at 25 °C (L = H or D)

	$k_0^{H_2SO_4}/k_0^{D_2SO_4}$[a]		
$[L_2SO_4]$/mol dm^{-3}	**1a**	**1c**	**1j**
0.58	—	—	2.4
0.95	0.9	—	—
2.00	—	0.6	—
2.85	0.8	—	—
5.00	—	0.7	1.3
5.80	0.8	—	—
8.00	—	0.4	0.8

[a] ±0.1.

Table 3 Effect of temperature on the pseudo-first-rate order rate constants for the decomposition of **1a**, **1c** and **1j** in H_2SO_4

		$k_0/10^{-4}$ s^{-1}		
$[H_2SO_4]$/mol dm^{-3}	T/°C	**1a**	**1c**	**1j**
0.58	21.3	—	—	24.6
	23.0	—	—	26.9
	25.1	—	—	30.9
	29.7	—	—	43.5
0.95	18.0	4.8	—	—
	24.9	8.4	—	—
	29.9	14.5	—	—
	35.3	22.5	—	—
	39.5	35	—	—
2.09	24.9	—	1.56	—
	29.8	—	2.50	—
	35.1	—	4.40	—
	40.1	—	6.94	—
4.90	12.2	25.9	—	—
	16.7	40.2	—	—
	21.2	59.2	—	—
	25.5	81.4	—	—
	30.6	126.1	—	—
5.0	20.2	—	—	5.32
	25.2	—	—	8.60
	30.9	—		13.4
	35.0	—	—	20.0
	40.0	—	—	30.4
6.1	20.0	—	9.00	—
	21.9	—	10.7	—
	25.0	—	15.3	—
	29.3	—	23.1	—
	34.0	—	40.7	—
8.0	20.6	—	—	17.0
	25.0	—	—	24.0
	30.1	—	—	38.8
	35.3	—	—	59.7
9.0	10.4	—	2.28	—
	14.4	—	2.67	—
	22.0	—	5.15	—
	28.8	—	11.1	—
	35.1	—	24.5	—

shortening of the amide C–N^3 bond. Although this might imply that N^2–N^3 bond cleavage is the more favoured of these two processes, protonation of the oxygen atom will of course raise the electrophilic nature of the amide carbonyl atom. The third site for protonation, the triazene N^3 atom is energetically much less favourable, but does lead to a lengthening of both the N^2–N^3 and N^3–CO bonds.[7]

However, further inspection of the theoretical data identifies the N^1 site in the *E*, *syn*, *cis* conformer as that with the highest proton affinity.[7] This is depicted in Scheme 4. It is clear from this that hydrogen bonding to the amide carbonyl is the most plausible explanation for the high proton affinity, in which case

Table 4 Entropies of activation $\Delta S^{\ddagger}$ (±10) for the decompositon of **1a**, **1c** and **1j**

	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}		
$[H_2SO_4]$/mol dm^{-3}	**1a**	**1c**	**1j**
0.58	—	—	−127
0.95	−76	—	—
2.09	—	−67	—
4.85	−88	—	—
5.00	—	—	−92
6.10	—	−51	—
8.00	—	—	−101
9.00	—	−56	—

deciding between protonation of N^1 or O is a difficult, and possibly fruitless, task. Either site will activate the amide carbonyl to rate-limiting nucleophilic attack by water, giving rise to the observed deacylated products (Scheme 4).

Decomposition of the Alkanoyltriazenes **1c**, **1g** *and* **1h**.—The rate constants for the acid-catalysed decomposition of these compounds are shown in Fig. 1. At $[H_2SO_4] < 4$ mol dm^{-3} only the product of N-acyl bond fission can be observed. However, at $[H_2SO_4] > 4$ mol dm^{-3}, products of the N^2–N^3 bond cleavage reaction are also observed.

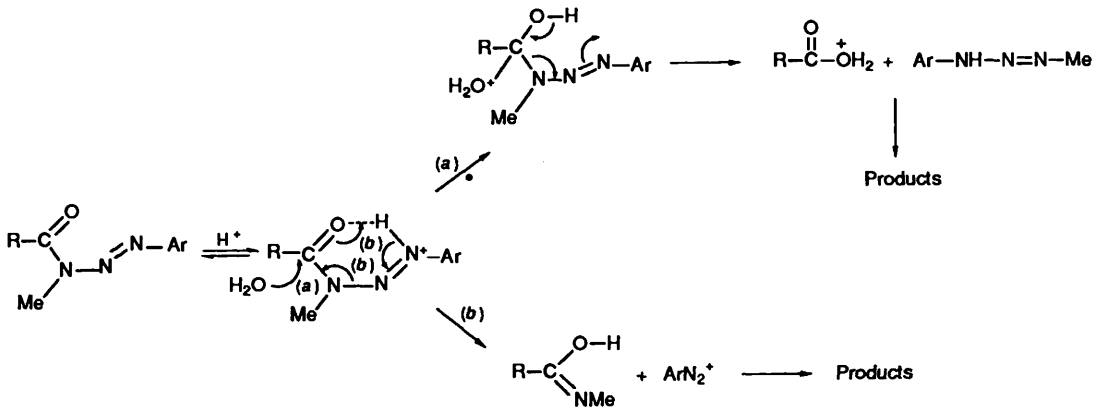
These compounds exhibit much less pronounced acid catalysis at low acidities than the formyl compound **1a**. This probably reflects the difference in reactivity between the alkanoyl and formyl groups towards the nucleophilic attack of water, allowing the N^2–N^3 cleavage reaction to compete much more effectively with the N-acyl fission.

This can be seen from Table 1 where, under identical conditions, the *N*-formyl compound **1a** undergoes exclusive N-acyl bond cleavage, the *N*-acetyl compound **1c** undergoes decomposition with about 70% N-acyl bond cleavage, and the much less reactive *N*-benzoyl compound **1n** (*vide infra*) decomposes with only 40% N-acyl bond cleavage. A similar trend can be observed for **1c** as the acidity increases (Table 1). Thus, as the water activity diminishes, the extent of hydrolysis decreases and the contribution of N^2–N^3 bond cleavage to the overall reaction increases.

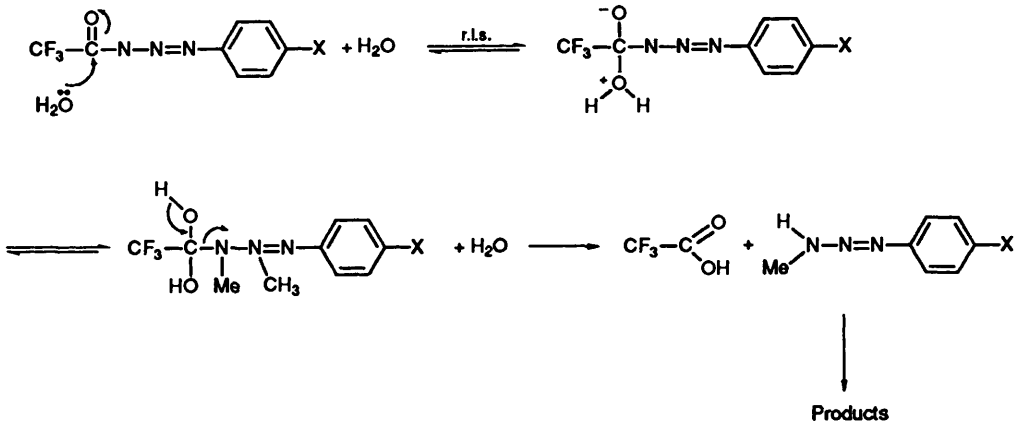
In H_2SO_4 *ca.* 2 mol dm^{-3}, **1c** exhibits a solvent deuterium isotope effect of 0.6 and an entropy of activation of −67 J mol^{-1} K^{-1} (Tables 2 and 4). These values are similar to those obtained for **1a**, so it seems reasonable to propose a similar reaction mechanism for the hydrolysis (Scheme 4). Again, it is difficult to assign the site of protonation, though the larger rate constants observed with the longer chain alkyl groups might suggest protonation at the amide oxygen, which would account for the onset of acid catalysis at lower acidities for compounds **1g** and **1h** as compared to compound **1c**.

The effect of the substituent in the 1-aryl group for the acetyltriazenes **1b–f** was studied in $[H_2SO_4] = 3.04$ and 9.01 mol dm^{-3} and the results obtained are presented in Table 5. Electron withdrawing substituents decrease the rate of the reaction and the Hammett ρ values are −0.7 (±0.1) and −0.9 (±0.04) respectively. If the rate limiting step for the reaction is the attack of water on the protonated substrate, ρ is a composite value reflecting the effect of the substituent on the protonation of the substrate (favoured by electron donation) and on the attack of water (favoured by electron attraction). The first effect must be stronger since the overall effect results in a negative ρ value.

Decomposition of the 3-*Trifluoroacetyltriazenes* **1i–l**.—At low acidities, the trifluoroacetyl compound **1j** behaves somewhat differently to those compounds described above (Fig. 1).



Scheme 4 Mechanism of the acid-catalysed decomposition of acyltriazenes



Scheme 5 Mechanism of the acid-independent hydrolysis of compounds **1i–l**

Table 5 Substituent effects on the observed first-order rate constants k_0, for the decomposition of **1b–f** and **i–p** in H_2SO_4 at 25 °C

	$k_0/10^{-4}$ s^{-1}						
Compound	0.58[a]	3.04[a]	4.6[a]	6.0[a]	6.1[a]	8.0[a]	9.08[a]
1b		2.60			12.0		65
1c		2.80			14.0		70
1d		3.70			27.0		119
1e		—			—		168
1f		14.3			121		—
1i	44.6					22.5	
1j	30.9					24.0	
1k	22.3					33.1	
1l	7.8					70.0	
1m			0.47	3.0			
1n			6.8	33			
1o			12.8	67			
1p			18.7	230			

[a] Concentration of H_2SO_4 used.

Values of k_0 remain constant to *ca.* 1.5 mol dm^{-3} H_2SO_4, decrease with acidity until *ca.* 4 mol dm^{-3} H_2SO_4, exhibit a plateau until 6.0 mol dm^{-3} H_2SO_4, then increase monotonically above this acidity. The only products of the reaction found in $[H_2SO_4] < 5$ mol dm^{-3} were the corresponding anilines, indicating that the reaction taking place in this region of acidity is N–acyl bond fission. At $[H_2SO_4] = 6$ mol dm^{-3} the 1,3-diaryltriazene product of N^2–N^3 bond cleavage could be detected in small amounts. The rate constants at acidities < 2 mol dm^{-3} H_2SO_4 are identical to those obtained in aqueous buffers extrapolated to zero buffer concentration, and relate to a pH-independent reaction that involves attack of water on the unprotonated substrate (Scheme 5). Consistent with such an interpretation are the solvent deuterium isotope effect (Table 1) of 2.4, and the substituent effect (Table 5), which gives rise to a Hammett ρ value of +0.8 (±0.05) for substituents in the 1-aryl ring. The sign of ρ in this acidity region is the opposite to that seen for compound **1a**, but the same as that seen for the solvent-catalysed deformylation of formyl triazenes in ethanol.[4]

The subsequent *decrease* in k_0 with increasing acidity probably resides in the decreasing availability of water for this deacylation reaction of the neutral substrate. A similar reasoning has been forwarded for the hydrolysis of 1-acetyl-3-methylimidazolium ion in concentrated acids.[10] The subsequent increase of k_0 with acid concentration can then be ascribed to protonation of the substrate. Consistent with this, the solvent deuterium isotope effect reverses, and a value of 0.8 is observed, and the reactivity of compound **1j** is lower compared to **1a**, **c**, **g**, **h** at any given acidity (> 6 mol dm^{-3}). Protonation of **1j** would be expected to be less extensive owing to the electron withdrawing effect of the CF_3 group. The substituent effect in the 1-aryl ring also reverses in this acidity region, giving rise to a Hammett ρ value of −0.5 (±0.02). This is of similar sign, though smaller in magnitude, to those observed for those observed for the acetyl derivative **1c**. Thus, we conclude that in this acidity region the trifluoroacetyltriazenes react like the alkanoyltriazenes.

Decomposition of the 3-Aroyltriazenes **1m–p**.—Owing to the low solubilities of these compounds at low acidities, reactions could only be studied at $[H_2SO_4] \geq 3$ mol dm^{-3}. The dependence of the observed first-order rate constants upon acidity are shown in Fig. 2. At these acidities analysis of the reaction mixtures showed the presence of products resulting from both N^3–acyl and N^2–N^3 bond cleavage. Indeed, the data

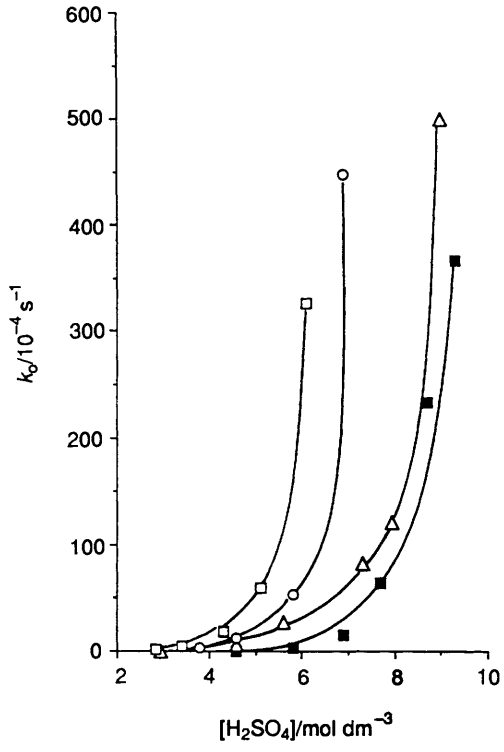


Fig. 2 Variation of k_0 with [H_2SO_4] for 3-aroyltriazenes **1m** □, **1n** ○, **1o** △ and **1p** ■, at 25 °C

of Table 1 indicate that for compound **1n** in 10.7 mol dm^{-3} H_2SO_4 the N^2–N^3 bond cleavage has become the predominant process, almost certainly owing to the lower reactivity of the acyl group in aroyl, as compared with alkanoyl, systems allowing for the incursion of the alternative pathway.

It is obvious from Fig. 2 that electron donating substituents favour acid catalysis. The data in Table 5 at 4.6 and 6.0 mol dm^{-3} H_2SO_4 give rise to a Hammett ρ value of *ca.* −1.5 (±0.2). This is somewhat larger than the values obtained from the substituents in the N^1-aryl ring but is consistent with the mechanism in Scheme 4. It may suggest that protonation occurs at the amide oxygen atom rather than the triazene N^1 atom.

Conclusions

Carboxamides are generally quite resistant to nucleophilic attack at the carbonyl carbon atom. However, the presence of a substituent on the nitrogen atom (*e.g.* NO_2), which involves the nitrogen non-bonding pair in delocalisation away from the carbonyl group, makes the amide much more labile. Such compounds behave like esters with good leaving groups,[11] and exhibit increases in rate with increasing acidity and no rate maxima. Our results show that 3-acyl-3-alkyl-1-aryltriazenes may be considered as reactive amides since the non-bonding electron pair of the amide nitrogen N^3 of the triazene is able to delocalise into the N=N double bond and the aromatic ring. A proton is generally required to activate the substrates, and the protonated substrate can undergo decomposition *via* N^3–C or N^2–N^3 bond cleavage. The relative extents of those bond cleavage reactions depend upon both the acidity of the medium and the structure of the acyl group. Thus, the higher the acidity and the less reactive the acyl group to nucleophilic attack, the greater the extent of N–N bond cleavage. It remains unclear, however, why the *N*-acyl derivatives of the 1-aryl triazenes used in the present study appear to react *via* significant deacylation, whereas *N*-acyl derivatives of the 1-alkyl counterparts only undergo an N^2–N^3 bond cleavage reaction.[6] One possibility, that the 1-alkyl compounds decompose *via* concerted nucleophilic attack by water at the 1-alkyl group, can be discounted by isotopic scrambling experiments which demonstrate that a discrete alkyldiazonium ion is liberated.[6] Neither can the reason lie in the relative stabilities of the two diazonium ions formed, since ArN_2^+ is much more stable than RN_2^+, yet the formation of RN_2^+ is the more favoured. We can only conceive of the possibility that the N^2–N^3 bond cleavage reaction is reversible for the 1-aryl compounds, but is essentially irreversible for the 1-alkyl analogues owing to the instability of the alkyldiazonium ion. As for the possibility that 3-acyltriazenes may be prodrugs of the 3-alkyl-1-aryltriazenes **2**, we have found that the compounds **1** are extremely stable in aqueous solutions around the neutral pH values. At low acidities the only reaction observed is N–acyl bond cleavage. Therefore, it is possible that the *N*-acyltriazenes may provide useful prodrugs of **2**. Nevertheless, to liberate **2** under physiological conditions they will have to be good substrates for hydrolytic enzymes. We are currently undertaking a study of the decomposition of the acyltriazenes **1** and some related compounds in basic media and in blood serum, and shall report our findings in a future paper.

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Paper 3/00426K
Received 22*nd January* 1993
Accepted 11*th February* 1993