Pathways for the Decomposition of Alkylaryltriazenes in Aqueous Solution

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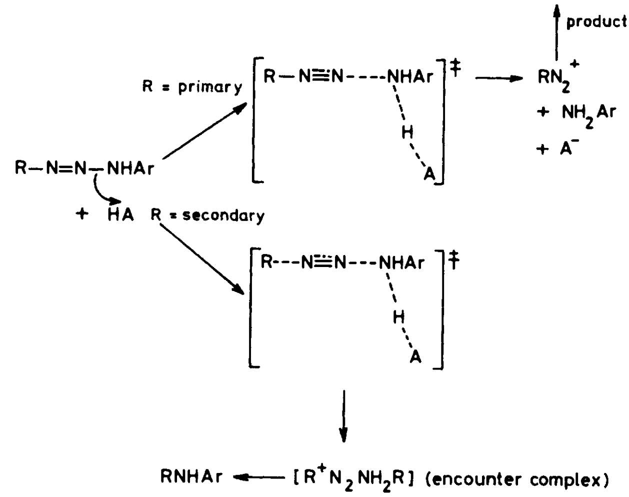
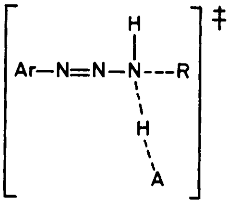
Primary alkylaryltriazenes give solvent-equilibrated alkanediazonium ions and anilines in aqueous solution at 25 °C by two processes. The first, an A–S_E2(N) reaction, involves immobilisation of a molecule of catalysing acid, and a transition state in which the proton is essentially completely transferred and little breakage of the N–N bond has occurred. The structure of this transition state varies with the strength of the catalysing acid and the pK_a of the liberated aniline in a way interpretable in terms of a More O'Ferrall–Jencks diagram. The second process is the departure of aniline anion without acid assistance. The first process is governed by positive, the second by negative, β_{lg} values.

Alkylaryltriazenes are deamination precursors,[1] and the products derived from the alkyl fragment have been extensively studied with a view to characterising carbonium ion reactions.[2] Less attention has been paid to those processes which precede the generation of the carbocationoid centre. Early work by Maskill *et al.*[3] indicated that when primary alkylaryltriazenes were decomposed in glacial acetic acid, only small quantities of internal return products RNHAr were formed, whereas secondary alkylaryltriazenes gave substantial amounts of them. This was held to indicate the occurrence of synchronous fragmentation in the second case: secondary, but not primary alkanediazonium ions are too unstable to exist in glacial acetic acid. The pathway for triazene decomposition was in all the work so far cited reasonably assumed to involve proton-donation to the unconjugated triazene tautomer.

Isaacs and Rannala,[4] in a study of the kinetics of decomposition of methylaryltriazenes by substituted benzoic acids in chloroform, confirmed that proton transfer was rate limiting [k(PhCOOH)/k(PhCOOD) = 2.47 for the *p*-tolyl compound], but, on the basis of modest increases in rate in the series of methyl-, ethyl-, and 1-methylethyl-*p*-tolyltriazenes (ratios 1 : 1.76 : 7.4) proposed a transition state (I) which we find unconvincing for two reasons. It fails to explain both why triazene decomposition has all the features of a deamination reaction,[1,2] and also their own observation of a moderate Hammett ρ value (−0.92) governing the effect of substituents in the aryl group. Their subsequent observation [5] of a strong inverse dependence of rate on solvent donor character is also difficult to reconcile with rate-limiting generation of a powerful electrophile. Some work on the decomposition of methyl substituted phenyl triazenes in 50% aqueous dioxan was reported by Zvěřina *et al.*; [6] they considered the reaction to be A-1, and on this assumption calculated a ρ value of −2.85.



Scheme



(I)

The pathways for the decomposition of alkylaryltriazenes in aqueous solution are of interest since effective k_{cat} inactivators for glycosidases, which work both *in vitro* and *in vivo*, are obtained when the alkyl group is a glycosylmethyl residue.[7] In particular, the lability of these triazenes to acid pH seriously limits their use, and we wished to find ways of minimising this.

A preliminary account of part of this work has been published.[8]

Experimental

Materials.—Propylaryltriazenes were made by the method of White and Scherrer,[1] and were recrystallised from light petroleum. In our hands this method failed to produce benzylaryltriazenes, and substituted benzylphenyltriazenes, and we adopted substantially the original method of Goldschmidt and Holm,[9] of coupling in aqueous solution. To a slurry of the arenediazonium tetrafluoroborate [10] (5 mmol) in ice–water (50 ml) was added the benzylamine (10 mmol), and the mixture was stirred at 0 °C for 30 min. The solids were filtered off, taken up in methanol, filtered, and reprecipitated by addition of ice-water. They were then kept over P_2O_5 *in vacuo* at 4 °C in the dark. Where necessary, further purification was accomplished by recrystallisation from light petroleum or ether–light petroleum. If the reaction mixture produced an insoluble oil, this was extracted with ether or a large volume of light petroleum, concentrated, and the solid recrystallised. Characterisation data are given in Table 1. In general, manipulation of both propyl- and benzyl-triazenes resulted in their progressive contamination with decomposition products, so isolated yields (*ca.* 10%) were sacrificed to speed and ease of work-up. Glycosylmethylaryltriazenes were made as

Table 1. Characterisation data for alkylaryltriazenes

		M.p. (°C) (generally with decomp.)		Required (%)				Found (%)			
Alkyl group	Aryl group		Formula	C	H	N	Hal	C	H	N	Hal
n-Propyl	*p*-Nitrophenyl	82—83	$C_9H_{12}N_4O_2$	52.0	5.8	26.9		52.0	5.6	26.75	
n-Propyl	*p*-Cyanophenyl	64—66	$C_{10}H_{11}N_4$	64.05	5.9	30.0		64.1	6.25	29.5	
n-Propyl	3,4-Dichlorophenyl	60—62	$C_9H_{11}N_3Cl_2$	46.55	4.75	18.1	30.55	46.35	4.7	17.8	30.45
n-Propyl	3,5-Dichlorophenyl	68—70	$C_9H_{11}N_3Cl_2$	46.55	4.75	18.1		45.75	4.4	17.5	
n-Propyl	*p*-Chlorophenyl	36—38	$C_9H_{12}N_3Cl$	54.7	6.1	21.25		54.0	6.0	20.8	18.55
n-Propyl	Phenyl	oil	$C_9H_{13}N_3$	66.25	8.05	25.75		66.2	8.3	25.55	
n-Propyl	*p*-Methoxyphenyl	28—30	$C_{10}H_{15}ON_3$	62.15	7.8	21.75		61.85	8.15	21.8	
n-Propyl	*p*-Methylphenyl	~20	$C_{10}H_{15}N_3$	67.75	8.55	23.7		67.4	8.9	23.8	
p-Methoxybenzyl	Phenyl	89—91	$C_{14}H_{15}N_3O$	69.7	6.25	17.4		70.05	6.0	17.05	
p-Methylbenzyl	Phenyl	62—63.5	$C_{14}H_{15}N_3$	74.65	6.7	18.65		74.35	7.15	18.45	
Benzyl	Phenyl	71—73 (lit.,[9] 72°)	$C_{13}H_{13}N_3$	73.9	6.2	19.9		73.65	6.3	19.35	
p-Chlorobenzyl	Phenyl	65—67	$C_{13}H_{12}ClN_3$	63.55	4.9	17.1	14.45	63.25	5.05	16.95	
p-Nitrobenzyl	Phenyl	56—63	$C_{13}H_{12}N_4O_2$	60.95	4.7	21.85		60.3	4.6	21.2	
Benzyl	*p*-Nitrophenyl	95—97	$C_{13}H_{12}N_4O_2$	60.95	4.7	21.85		60.25	4.8	21.65	
Benzyl	*p*-Chlorophenyl	86—87	$C_{13}H_{12}ClN_3$	63.55	4.9	17.1	14.45	63.55	4.8	17.1	15.15
Benzyl	*p*-Bromophenyl	87—88	$C_{13}H_{12}BrN_3$	53.8	4.15	14.5	27.55	53.55	4.0	14.25	27.75
Benzyl	*p*-Methylphenyl	75—77 (lit.,[9] 77°)	$C_{14}H_{15}N_3O$	74.65	6.7	18.65		74.75	6.85	18.45	
Benzyl	*p*-Methoxyphenyl	89—91	$C_{14}H_{15}N_3O$	69.7	6.25	17.4		70.1	6.25	16.95	

described previously;[7] these compounds were, except glucosylmethyl-*p*-nitrophenyltriazene, labile, hydrophilic syrups characterised by u.v. spectroscopy, their decomposition in acid, and where possible, their ability to inactivate β-galactosidase: details are given in the following paper[11] except for β-D-galactopyranosylmethylphenyltriazene, $\lambda_{max.}$ 280 nm.

[1-$^2H_2$]Benzyl-*p*-nitrophenyltriazene, m.p. 94—97 °C (decomp.), containing 0.09$_5$ protons at C-1, as estimated by ^1H n.m.r. integration in CD_3CN solution at 200 MHz, was made from [1-$^2H_2$]benzylamine in the normal way. The labelled benzylamine was made by reaction of $LiAlD_4$ (1 g) with benzonitrile (2.5 g) in ether (50 ml) for 30 min under gentle reflux. The excess $LiAlD_4$ was destroyed with ethanol and then water, and the ethereal layer was washed with a 1 : 1 mixture of aqueous ammonia (*d* 0.88) and water. Hydrogen chloride gas was then bubbled through the dried ($MgSO_4$) ether solution. The solid (2.1 g) was filtered off and dissolved in water, the cloudy solution was extracted with ether, the extracts being discarded. The aqueous layer, now clear, was then made alkaline, and extracted with ether. These ether extracts were dried ($MgSO_4$) and the ether evaporated off through a Vigreux column on a steam-bath.

Analytical reagent grade acetonitrile, salts, and buffer components and doubly distilled water were used for the production of all solutions used for kinetics. 1,1-Dimethylethylphosphonic acid, m.p. 188—189 °C (lit.,[12] 191.5—192 °C), equivalent weight (NaOH) 134.3 (theory 138.1), was made by the method of Crofts and Kosalapoff.[12]

Kinetic Methods.—First-order rate constants were measured, either on a Unicam SP 1800 spectrometer fitted with a thermostatted cell block through which water, maintained at 25.0 °C by a Tecam Tempunit device, was passed, or a Unicam SP 8-200 spectrophotometer, fitted with the manufacturer's thermostatting system. Some measurements were also carried out on a Unicam SP 1700 system described elsewhere.[13] First-order rate constants were calculated from linear least squares treatment of Guggenheim[14] or log $(A - A_\infty)$ *versus* time plots. For slow reactions, the Guggenheim method was always used, to minimise possible problems due to air oxidation of aniline products. Decrease of absorbance was monitored in all cases, the wavelengths depending on the aryl group: *p*-nitrophenyl, 362; *p*-cyanophenyl, 300; 3,4-dichlorophenyl and 3,5-dichlorophenyl, 280; *p*-chlorophenyl 280 (maximum) or 316; *p*-bromophenyl, 332; phenyl, 280; *p*-tolyl, 280; *p*-methoxyphenyl, 339 nm.

Catalytic constants were estimated from linear least squares treatment of the variation of k_{obs} with the concentration of a buffer made by mixing equal quantities of acid and basic forms of the buffer components, at total buffer concentrations of 25, 50, 100, and 200 mM, it being confirmed visually that the first three points defined essentially the same catalytic constant and buffer-independent rate as the four. The conformity of pH measurements of these 1 : 1 buffers with literature pK_a values provides some reassurance that our pH measurements with a glass-calomel combination electrode were not overly inaccurate.[15] This electrode was standardised with BDH standard buffers before use, with either a Philips PW 9414 pH-ion meter, or a Radiometer PHM 62 pH meter.

Product Analysis.—Zero, first, and second differentials of the u.v. spectrum of reaction mixtures were recorded on a Perkin-Elmer 555 spectrophotometer. More direct analysis of products from decomposition of benzylphenyltriazene at pH 7, benzyl-*p*-methoxyphenyltriazene at pH 7, and benzyl-*p*-nitrophenyltriazene at pH 11 was attempted by extraction of solutions of the triazenes decomposed under ‘ kinetic ’ conditions, or in 5% aqueous acetonitrile, with ether. Concentration and t.l.c. analysis [silica gel G, 1 : 1 ethyl acetate–light petroleum (b.p. 60—80 °C) as eluent] failed to detect any benzylamine or phenol. Isolated products from the decomposition of benzylaryltriazenes in 1.0M-KCl cannot answer questions about the presence of internal return products, since benzyl chloride reacts with anilines during concentration of the products: in fact g.l.c.–m.s. (on an MS30 instrument with a 170 cm × 0.2 cm i.d. column of SE33) revealed substantial quantities of monobenzylated and dibenzylated anilines.

The products from decomposition of β-D-galactopyranosyl-[1-^{14}C]methyl-p-nitrophenyltriazene [7] in water were examined by t.l.c. on silica gel using butan-1-ol–acetic acid–water (4 : 1 : 1) as eluent. Two main radioactive peaks, R_F 0.59 and 0.44, the former running with β-D-galactopyranosylmethanol,[16] the latter broad, were observed when the plate was examined in a Berthold LB2723 plate-scanner. These were clearly separated from the p-nitroaniline spot at R_F 0.82, and were not coloured. Internal return products are therefore absent in this reaction. The carbohydrate products from decomposition [G-^{3}H]-β-D-galactopyranosylmethyl-p-nitrophenyltriazene were examined by g.l.c.–m.s. of their trimethylsilyl ethers. A 13.9mM solution of triazene [7] in distilled water was allowed to decompose at room temperature for 3 days, diluted to 5 ml with water, extracted with CH_2Cl_2 (5 ml), passed through a 2.5 × 1.3 cm i.d. mixed bed ion exchange column of Amberlite IR-120 (H^+) and Dowex 1 × 8 (OH^-), evaporated, and dried over P_2O_5 *in vacuo* for 1 week before derivatisation with hexamethyldisilazane (4 vol.) and trimethylchlorosilane (2 vol.) in pyridine (10 vol.). This solution was analysed on a Pye 104 gas chromatograph using a 3 ft column of SE33, with nitrogen elution (at a rate of 25 ml min^{-1}) and a temperature program of 1 min at 150 °C and 10 °C min^{-1} to 200 °C. The retention time of β-D-galactopyranosylmethanol in this system was 9.4 min. A similar column was used for g.l.c.–m.s. on an AEI MS 30 system.

The pK_a of β-D-galactopyranosylmethylamine was measured by titration of a 1% solution of the material with 0.5M standard HCl solution (B.D.H.) in a Radiometer TTT 60 automatic titrator at 25—26 °C. The pH meter was standardised at pH 7.00 and 9.00 using B.D.H. standard buffers. A value of 9.03 was obtained. A similar titration with tris * gave a pK_a of 8.08 (lit.,[17] 8.08).

Results and Discussion

The tautomerisation of alkylaryltriazenes with electron-withdrawing substituents in the aryl group is slow on the n.m.r. timescale; [17] it is therefore a possibility that tautomerisation might be kinetically significant in the decomposition of these compounds. However, those triazenes with slower tautomerisation rates are also those in which comparable quantities of the two forms exist at equilibrium.[18] Therefore, if interconversion of tautomers (II) and (III) were kinetically significant in the decomposition process, clean first-order kinetics would not be observed, as they are.

$$\underset{\text{(II)}}{\text{R—N=N—NHAr}} \rightleftharpoons \underset{\text{(III)}}{\text{R—NH—N=N—Ar}}$$

Figures 1—3 show the dependence on pH-meter reading of the first-order rate constants for the decomposition of propyl-, benzyl-, and glycosylmethyl-aryltriazenes at 25.0 °C in 1.0M-KCl solutions, containing 1%, 5%, and no acetonitrile, respectively. The constants for decomposition of the propyl-, and to some extent also the benzyl- and glycosylmethyl-triazenes are dependent on the concentration of oxygen acid buffers (the nitrogen acid buffers tris-HCl and ethanolamine-HCl have no detectable effect), and the constants displayed in Figure 1—3 represent either rates measured directly in nitrogen acid buffers, or rates measured in oxygen acid buffers and extrapolated to zero buffer concentration. It is clear that (in addition to the buffer-catalysed pathway) there are two routes for triazene decomposition: a pH-independent pathway, accelerated by electron-withdrawing substituents in the aryl group and an acid-catalysed reaction accelerated by electron-donating substituents in the aryl group. The rates of both processes increase in the order glycosylmethyl < benzyl <

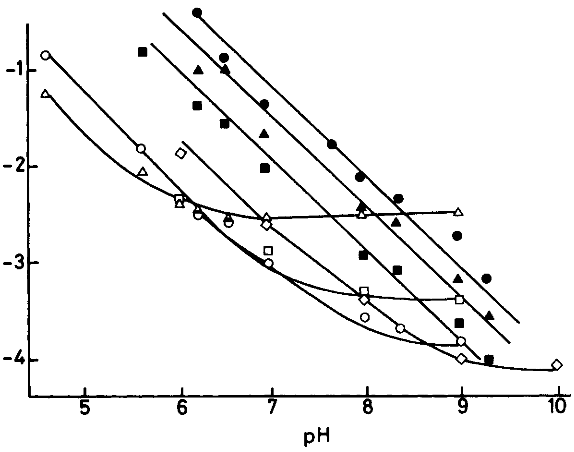


Figure 1. Dependence on pH of first-order rate constant for decomposition of 1-propylaryltriazenes in 1.0M aqueous KCl, 1% in acetonitrile at 250 °C. Buffers were 0.1M-tris(hydroxymethyl)aminomethane–HCl or ethanolamine–HCl. Points extrapolated to zero buffer concentration with the oxygen acid buffers of Table 3 are also plotted. ●, p-Methoxyphenyl; ▲, phenyl; ■, p-chlorophenyl; ◇, 3,4-dichlorophenyl; ○, 3,5-dichlorophenyl; □, p-cyanophenyl; and △, p-nitrophenyl. The lines are the theoretical lines described by the values of $k_{H_3O^+}$ and k_0 in Table 3

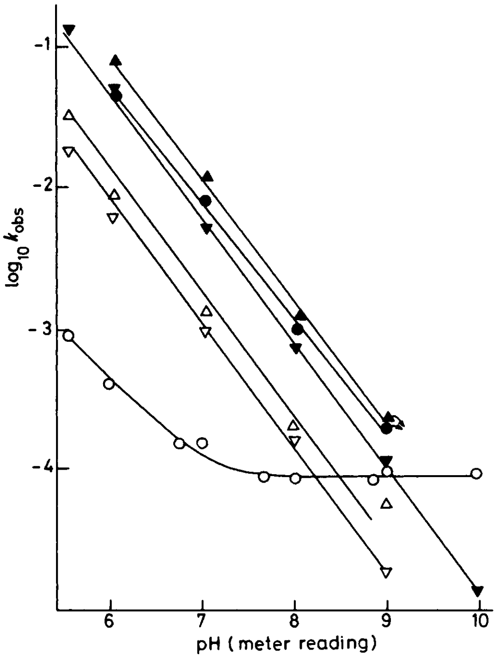


Figure 2. Dependence on pH-meter reading of the first-order rate constants for decomposition of benzylaryltriazenes in 1.0M aqueous KCl, 5% in acetonitrile at 25.0 °C. Buffers as for Figure 1. ▲, p-Methoxyphenyl; ●, p-methylphenyl; ▼, phenyl; △, p-chlorophenyl; ▽, p-bromophenyl; ○, p-nitrophenyl (pH-independent rate 9 × 10^{-5} s^{-1}). The lines are empirical. The arrows on the pH 9 points indicate the effect of changing the electrolyte to 1.0M-NaN_3

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* tris = tris(hydroxymethyl)aminomethane.

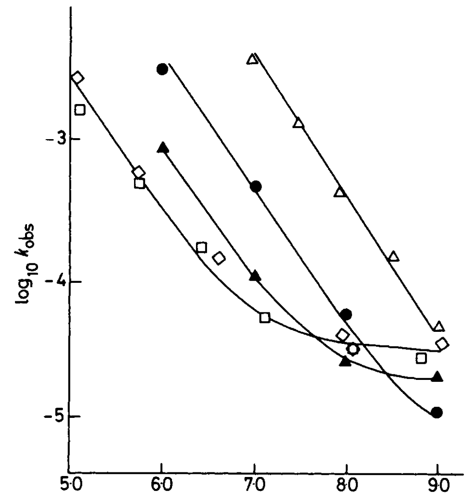


Figure 3. Dependence on pH of the first-order rate constants for decomposition of glycosylmethylaryltriazenes in 1.0M-KCl at 25.0 °C. Buffers as for Figure 1. The lines are theoretical. △, β-D-Galactopyranosylmethylphenyltriazene, $k_{obs} = 3.4 \times 10^4 [H_3O^+]$; ●, β-D-galactopyranosylmethyl-3,4-dichlorophenyltriazene, $k_{obs} = 4 \times 10^3 [H_3O^+] + 7 \times 10^{-6}$; ▲, β-D-galactopyranosylmethyl-*p*-cyanophenyltriazene, $k_{obs} = 8 \times 10^2 [H_3O^+] + 1.8 \times 10^{-5}$; ◇, β-D-glucopyranosylmethyl-; □, β-D-galactopyranosylmethyl-*p*-nitrophenyltriazene, $k_{obs} = 2.8 \times 10^2 [H_3O^+] + 3.1 \times 10^{-5}$

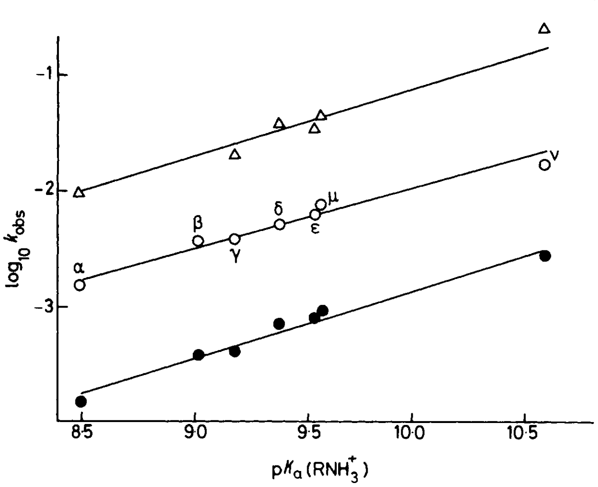


Figure 4. Effect of alkyl substituents on rate of decomposition of *p*-alkylphenyltriazenes, 1.0M-KCl, 25.0 °C. △, pH reading 6.0; ○, pH reading 7.0; ●, pH reading 8.0. (0.1M-Tris–HCl buffers), α, *p*-nitrobenzyl; β, β-D-galactopyranosylmethyl; γ, *p*-chlorobenzyl; δ, benzyl; ε, *p*-methylbenzyl; μ, *p*-methoxybenzyl; ν, propyl. The data for the substituted-benzyl phenyltriazenes were obtained in 5% acetonitrile (see text)

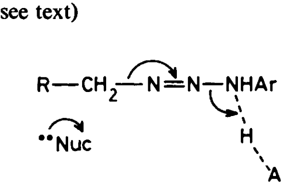
propyl. There is no indication of complete protonation of any triazene, in contrast to a previous report.[6]

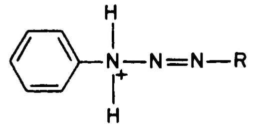
It was not possible to obtain even moderately consistent data for benzylaryltriazenes without the presence of an organic co-solvent. Some justification for our desire to avoid this if at all possible comes from the failure of the log *k*–pH meter reading plots of Figure 2 to have a gradient of 1.0 in the clearly acid catalysed region (gradients of *ca.* 0.9 are observed), which we attribute to the effect of acetonitrile on the pH electrode.

It is convenient to consider in turn the proton-catalysed reaction, the buffer catalysed reaction, and the pH-independent reaction.

A *The Proton-catalysed Reaction*.—This does not involve any cleavage of the alkyl carbon–nitrogen bond. Figure 4 displays first-order rate constants for decomposition of various primary alkylphenyltriazenes at pH meter readings of 6.0, 7.0, and 8.0 as a function of the pK_a of the alkylamine (Figures 1—3 indicate that the pH-independent reaction is not important for alkylphenyltriazenes at any of the pH values studied). It is clear that this parameter alone governs the rate. If second-order rate constants for the H_3O^+-catalysed reactions of the benzylphenyltriazenes are taken as 10^7 times the first-order rate constant at a pH-meter reading of 7.0 in 5% acetonitrile (a procedure which has some justification since the electrode was of the E_07 type [19]), then decomposition of primary alkyl phenyl triazenes is described by equation (1), where pK_a refers to that of the primary alkylammonium ion.

$$\log k_{H_3O^+} = (-1.03 \pm 0.01) + (0.614 \pm 0.015)\,\mathrm{p}K_a \qquad (1)$$
$$(r\ 0.9986)$$





(IV)

This linear free energy relationship was displayed in the preliminary communication.[8] It is remarkable for two things, first that it exists at all, and secondly the high sensitivity of the reaction to inductive effects in the alkyl group. Simply interpreted, the β value of 0.6 implies that the charge on nitrogen in the transition state is 0.6 of what it is in a primary alkylammonium ion. This high sensitivity to inductive effects could well account for the modest rate increase in the series methyl < ethyl < 1-methylethyl which led Isaacs and Rannala [4] to formulate a non-deaminative transition state for acid-catalysed triazene decomposition.

The conformity of points for substituted benzylphenyltriazenes, particularly with strongly conjugatively electron-donating substituents such as *p*-methoxy, to the relationship of equation (1) indicates synchronous fragmentation in an S_N1 sense is not taking place. The small, and rate-retarding, effect of replacing 1.0M-KCl by 1.0M-NaN_3 as 'inert electrolyte' (Figure 2) makes synchronous fragmentation in an S_N2 sense unlikely also.*

Therefore the reaction is either *A*-1 or *A*-S_E2(N), in both cases with the alkanediazonium ion as a real intermediate, or protonated triazene (IV) as a discrete intermediate whose formation is rate-determining, and about whose subsequent

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* This process lacks precedent, although it has been advanced by White *et al.* (E. H. White, L. W. Jelinsky, I. R. Politzer, B. R. Branchini, and D. F. Roswell, *J. Am. Chem. Soc.*, 1981, **103**, 4231) to explain our affinity labelling results.[7] Such a process however necessitates a 100% capture of the alkylating species, which is not found.[7]

Table 2. Zero, first, and second derivative spectra of triazene decomposition products compared with the corresponding aniline or triazene decomposed in 200mM-cacodylate buffer

Triazene decomposed or aniline	ε		$d\varepsilon/d\lambda$			$d^2\varepsilon/d\lambda^2$		
	max.	min.	max.	min.	intercept	max.	min.	intercept
PhNHMe	230, 282	214, 265	249, 292	220, 271	229, 281	253, 294	242, 280	248, 290
$PhNH_2$	222, 278	214, 257	241, 287	214, 264	226, 278	244, 290	236, 274	240, 282
$C_3H_7N_3HC_6H_5$	227, 274	218, 254	238, 288	222, 266	228, 276	242	225	232
p-$ClC_6H_4NH_2$	236, 284	218, 266	246, 296	226, 274	239, 284	252, 304	236, 286	244, 294
$C_3H_7N_3H$-*p*-C_6H_4Cl	237, 284	217, 266	246, 302	227, 276	237, 284	248, 303	236, 280	241, 290
p-$MeOC_6N_4NH_2$	226, 290	216, 262	238, 304	218, 282	225, 290	244, 310	230, 290	237, 300
$C_3H_7N_3H$-*p*-C_6H_4OMe	244, 292	218, 262	238, 304	220, 282	223, 289	244	230	238
3,5-$Cl_2C_6H_3NH_2$	238, 288	224, 266	248, 298	234, 276	238, 288	255, 308	240, 288	247, 296
$C_3H_7N_3H$-3,5-$C_6H_3Cl_2$	238, 286	232, 268	246, 296	233, 276	240, 284	252, 300	238, 284	243, 292
p-$NO_2C_6H_4NH_2$	376	294	408	330	370			
$C_3H_7N_3H$-*p*-$C_6H_4NO_2$	378	293	408	332	372			
* $PhCD_2N_3H$-*p*-$C_6H_4NO_2$	380	298	410	340	377			

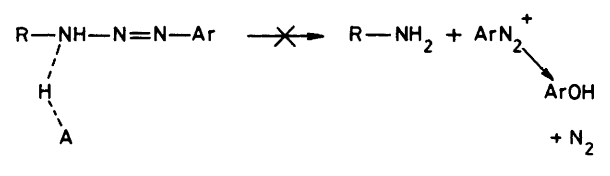
* In 50mM-cacodylate buffer.

fate nothing can be said. The magnitude of the β value makes this last possibility unlikely. The inductive effect of R, which has no effect on the position of tautomeric equilibrium of alkylaryltriazenes,[18] and so cannot exert a kinetic effect that way, is attenuated by two atoms, if the equilibrium protonation of (IV) is compared with the equilibrium protonation of $R-NH_3^+$. Hammett ρ values governing the pK_a values of ArCOOH, $ArCH_2COOH$, and $ArCH_2CH_2COOH$ are 1.0, 0.49, and 0.21, respectively.[20] Therefore, one would expect the pK_a of (IV) to be correlated with the pK_a of RNH_3^+ with a β value of the order of 0.2. But if the inductive effect of R is to be exerted on the rate of protonation, rather than its equilibrium position, it would be still further attenuated.

Therefore the reaction is either *A*-1 or *A*-S_E2, with generation of an alkanediazonium ion.

If such species are discrete, solvent-equilibrated intermediates, then no internal return products RNHAr should be formed. They are absent from the decomposition products of β-D-galactopyranosylmethyl-*p*-nitrophenyltriazene in water, and cannot be detected by t.l.c. of the decomposition products of benzylaryltriazenes in water (In 1.0M-KCl solution benzyl chlorides are possible products: these were shown to be capable of alkylating anilines during work-up.) Since the u.v. spectra of *N*-alkylated anilines are significantly different from those of simple anilines, the differential u.v. spectral data in Table 2 indicate that at least substantial quantities of *N*-alkylated anilines are absent. These data also show conclusively that alkylaryltriazenes do not decompose by a reversal of their method of formation.

There is other evidence that alkanediazonium ions are more stable in water than was once thought: the methanediazonium ion has been observed at 25.0 °C directly and has a lifetime of 0.3 s.[21] The evidence for synchronous fragmentation of secondary alkylaryltriazenes obtained by Maskill *et al.*[3] is plausibly attributed to the effect of solvent polarity: an alkanediazonium ion carries a large concentration of positive charge next to carbon, which is stabilised in polar solvents: decrease of solvent polarity will thus destablise it with respect to the transition state for the S_N1 departure of nitrogen in which charge is dispersed, to the extent of reducing the lifetime of the secondary alkanediazonium ions to below that of an encounter complex.



Distinction between an *A*-1 reaction and an *A*-S_E2(N) reaction for the proton catalysed reaction can be made on two grounds. First, if ion (IV) were a discrete intermediate, *i.e.* if the reaction were *A*-1, then true general acid catalysis would not be observed, which it is. (Formal general acid catalysis, arising from nucleophilic attack of the anion of the buffer on protonated triazene is unlikely because of the absence of an effect of other nucleophiles.) Secondly, *A*-1 reactions exhibit inverse D_2O solvent isotope effects of 2—3.[22] The decomposition of propyl-*p*-methoxyphenyltriazene at pH or pD 7.68 in 0.1M-tris–HCl buffer, 1.0M in KCl at 25.0 °C (pD being taken as pH-meter reading +0.4 [23]) gave a solvent isotope effect, k_{H_2O}/k_{D_2O}, of 1.0_8. Thus an *A*-1 reaction is not observed with the leaving group with which it is most likely, the most basic one.[24]

Given that proton transfer is synchronous with N–N bond cleavage, it is possible to estimate the degree of proton transfer and N–N bond cleavage at the rate-determining transition state. The β_{lg} value for H_3O^+-catalysed decomposition of propylaryltriazenes, corrected for substituent effects on the tautomeric equilibrium, is 0.83 ± 0.05; for β-D-galactopyranosylmethyl- and benzyl-aryltriazenes the corresponding values are 0.76 ± 0.02 and 0.75 ± 0.06, respectively. (For phenyl- and *p*-bromophenyl-triazenes tautomerisation constants were estimated by interpolation in the linear free energy relationship described in the previous paper.[18]) In all cases reaction is assumed to take place *via* the unconjugated tautomer. These β_{lg} values are high; simply interpreted, a β_{lg} value of 1.0 implies that the leaving group is completely protonated and the N–N bond not cleaved at all at the transition state. Therefore, even with essentially complete proton transfer, little N–N cleavage can be taking place.

The β value of 0.6, obtained with the H_3O^+-catalysed decomposition of alkylphenyltriazenes then presents an apparent paradox, since it indicates substantial build-up of charge on the nitrogen atom next to the alkyl carbon and hence at first sight a high degree of N–N bond cleavage. However, the positive charge on an alkylammonium ion can be dispersed by hydrogen bonding, a process not available to a diazonium ion, and it is reasonable to expect that the generation of diazonium ions will be exceptionally sensitive to inductive effects. There is some additional evidence for this with the pH-independent reaction.

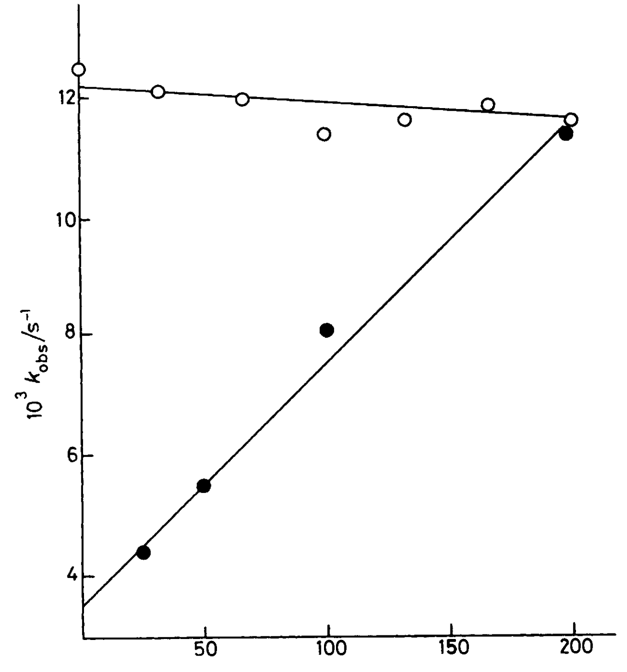


Figure 5. Effect of addition of solute on k_{obs} for decomposition of propyl-*p*-methoxyphenyltriazene at 25.0 °C, 1.0M-KCl, 1% in acetonitrile: ●, 1 : 1 t-butyl phosphonate buffer; ○, K_2SO_4 (to 0.1M-tris HCl buffer pH 7.68)

There are thus no qualitative differences between catalysis by H_3O^+ and true general acid catalysis by other acids.

B *The Buffer Catalysed Process.*—The buffer catalysis of a number of propylaryltriazene decompositions was examined. We were conscious of instances of specific salt effects on glycosyl [25] and phosphoryl [26] transfer, and on the hydrolysis of an iminium ion,[27] and elected to use a swamping electrolyte (1.0M-KCl), and keep added buffer concentrations below 0.2M. Figure 5 shows the contrasting effect of increasing K_2SO_4 concentration and buffer concentration on the hydrolysis of propyl-*p*-methoxyphenyltriazene. A similar control experiment was performed at the other extremum of leaving group ability: 10^3 k_{obs}/s^{-1} in 25mM-phosphate buffer for propyl-*p*-nitrophenyltriazene (4.09) increased with increasing concentrations of Na_2SO_4 as follows: 25mM (4.27), 75mM (4.24), 125mM (4.38), and 1.75mM (4.55). It is clear that, provided only substantial increases in rate are attributed to buffer catalysis, catalytic constants can be obtained without keeping the ionic strength accurately constant.

Figure 6 illustrates the dependence of k_{obs} for decomposition of propyl-*p*-nitrophenyltriazene on the composition and concentration of phosphate buffers. It is clear that the observed buffer catalysis is due overwhelmingly to the acid component of the buffer, and that it is subject to a solvent isotope effect of 1.6.* On the assumption that the change in acid from H_3O^+ to undissociated, weaker acid does not invalidate the conclusions about the intermediacy of alkanediazonium ions, then this change in solvent isotope effect could be interpreted as a change in the structure of the transition state (if secondary effects are neglected), although isotope effects for catalysis by H_3O^+ are commonly lower than those for other, undissociated general acids, because of the different fractionation factor of the solvated proton.†[28]

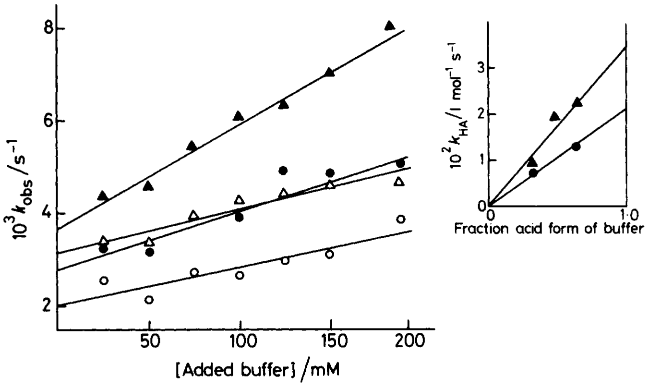


Figure 6. Dependence of rate of decomposition of propyl-*p*-nitrophenyltriazene in 1.0M aqueous KCl, 1% in acetonitrile, at 25.0 °C on the composition and concentration of phosphate buffers, in H_2O and D_2O. Full symbols, 2 : 1 $H_2PO_4^-$-HPO_4^{2-}; open symbols, 1 : 2 $H_2PO_4^-$-HPO_4^{2-}; triangles, H_2O; circles, D_2O. Inset: plot of apparent catalytic constant against fraction of acid component of the buffer. The plot for H_2O also includes a point for a 1 : 1 buffer obtained from the usual four points

The data in Table 3 do indeed show the presence of a slight variation in transition state structure as the acidity of the aniline and of the catalysing acid changes. As the catalysing acid changes from H_3O^+ to the general acids studied, β_{lg} decreases: as the aniline becomes less basic, and decreases. This effect is observed only with oxygen acids (neutral, anionic, and cationic), not with cationic nitrogen acids, which do not act as detectable general acids. Steric hindrance could well be the cause of the inertness of the tris cation in this way, but the absence of catalysis by ethanolamine might be a reflection of some intrinsically lower catalytic effectiveness: nitrogen-to-nitrogen proton transfer is characterised by large negative entropies of activation.[29]

The precision of the data does not warrant other than a qualitative discussion of the changes in transition state structure, which are best discussed in terms of the More O'Ferrall [30]-Jencks diagram of Figure 7. The changes have the following manifestations. (i) As the aniline basicity increases, the Brønsted α increases: this represents movement of the transition state perpendicular to the reaction co-ordinate.

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* The value of 3.0, reported in the preliminary communication,[8] was the result of an arithmetical blunder.

† The acid-catalysed decomposition of trialkyltriazenes is another deamination reaction, which should closely parallel the decomposition of alkylaryltriazenes. Sieh and Michejda (D. H. Sieh and C. J. Michejda, *J. Am. Chem. Soc.*, 1981, **103**, 442) observed buffer catalysis, implying an A-S_E2(N) pathway, similar to alkylaryltriazenes, but report a solvent deuterium isotope effect, at pH or pD 7.8, in 0.5M-phosphate buffer, of k_{D_2O}/k_{H_2O} = 2.05. Their statement that this ' suggests that the concentration of the conjugate acid of the triazene is higher in D_2O than H_2O ' is however mistaken since their data indicate that in 0.5M-phosphate buffer >95% of the reaction goes through the buffer-catalysed pathway. Since the pK_a of $H_2PO_4^-$ in H_2O is lower by *ca.* 0.58 units than the pK_a of D_2PO_4 in D_2O (R. Gary, R. G. Bates, and R. A. Robinson, *J. Phys. Chem.*, 1964, **68**, 3806), at constant pL there will be a higher proportion of the catalytically active form of the buffer in D_2O than in H_2O. Their solvent isotope effect on the $H_2PO_4^-$ catalysed decomposition of 1,3-di-t-butyl-3-methyltriazene is thus in the same region as ours for the same acid catalysing the decomposition of propyl-*p*-nitrophenyltriazene (if p$K_a \gg 7.8$ in their system, $k_{H_2PO_4}/k_{D_2PO_4}$ 1.9).

Table 3. Second-order rate constants (l mol^{-1} s^{-1}) for catalysis of the decomposition of propylaryltriazenes in 1M-KCl at 25 °C

Catalysing acid	H_3O^+ [a]	CH_3COOH	$^-O_2CCH{=}CHCO_2H$	$\underset{\substack{\|\\O}}{(CH_3)_2As{-}OH}$ Me_2AsO_2H	$H_2PO_4^-$	$Bu^tPHO_3^-$	(H_2O) [a] (Primary constant, s^{-1})	α No parentheses, value without H_2O but with H_3O^+ Square brackets: Value without H_3O^+ but with H_2O, parentheses: neither H_2O nor H_3O^+
Measured (literature) pK_a in 1M-KCl	−1.74	4.60 (4.60) [b]	5.60	6.18 (6.15) [c]	6.55 (6.50) [d]	8.36 (8.35) [e]	15.74	
p, q	3,1	1,2	1,4	1,2	2,3	1,3	2,1	
Liberated aniline(pK_a) [f]								
p-$MeOC_6H_4NH_2$ (5.36)	7.2 × 10^5			3.26 ± 0.4	2.34 ± 0.13	(8.1 ± 0.5) × 10^{-2}		0.699 ± 0.015 (0.80 ± 0.06)
$C_6H_5NH_2$ (4.60)	3.0 × 10^5			1.2 ± 0.15	2.28 ± 0.16	(1.38 ± 0.22) × 10^{-2}		0.71 ± 0.06 (1.0 ± 0.27)
p-$ClC_6H_4NH_2$ (3.98)	1.0 × 10^5		0.74 ± 0.12	0.59 *	0.54 ± 0.08	(1.27 ± 0.07) × 10^{-2}		0.688 ± 0.036 (0.64 ± 0.15)
3,4-$Cl_2C_6H_3NH_2$ (2.97)	1.9 × 10^4						5.0 × 10^{-5}	
3,5-$Cl_2C_6H_3NH_2$ (2.37)	5.9 × 10^3	0.49 ± 0.15	0.124 ± 0.008	0.088 *	0.108 *	(1.8 ± 0.3) × 10^{-3}	9.1 × 10^{-5}	(0.635 ± 0.035) [0.52 ± 0.03] (0.63 ± 0.10)
p-CNC_6HNH_2 (1.71)	5.03 × 10^3						2.9 × 10^{-4}	
p-$NO_2C_6H_4NH_2$ (1.02)	2.2 × 10^3	0.151 ± 0.015	(6.1 ± 0.8) × 10^{-2}	(3.74 ± 0.012) × 10^{-2}	(3.3 ± 0.1) × 10^{-2} (2.0 ± 0.1 in D_2O)		2.3 × 10^{-3}	0.615 ± 0.031 [0.29 ± 0.02] (0.43 ± 0.06)
β_{lg} †	0.83 ± 0.05	~0.6	0.53 ± 0.07	0.67 ± 0.06	0.66 ± 0.05	0.77 ± 0.13	−0.68 ± 0.15 −0.24 ± 0.01 ‡	

[a] To estimate precision of these data, see Figures. [b] A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 7031. [c] M. I. Page and W. P. Jencks, *J. Am. Chem. Soc.*, 1972, **94**, 8828. [d] A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 7045. [e] J. O. Knipe and J. K. Coward, *J. Am. Chem. Soc.*, 1979, **101**, 4339 (at 40 °C). [f] Ref. 16.

* Three points only on plot; error ±20%. † Corrected for fraction of reactive tautomer using data in previous paper. The correction for unsubstituted phenyl is estimated by interpolation at pK_a 4.60. ‡ Correlated with the pK_a of the aniline: R. A. Cox and R. Stewart, *J. Am Chem. Soc.*, 1976, **98**, 488. The correlation coefficients are *versus* pK_a($ArNH_3^+$), −0.953; *versus* pK_a($ArNH_2$), −0.997.

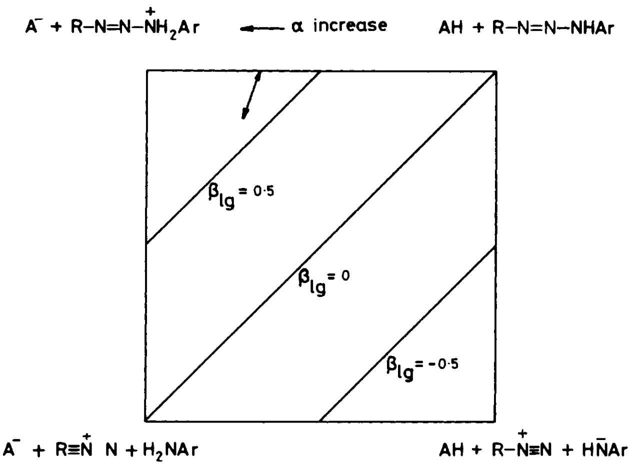


Figure 7. More O'Ferrall–Jencks diagram showing the approximate position of the transition state and direction of the reaction co-ordinate for the acid-catalysed decomposition of alkylaryltriazenes. Contours are omitted

(ii) As the Brønsted acid gets more acidic, the β_{lg} value increases. (iii) As the diazonium ion is made less stable, by inductively electron-withdrawing groups in the alkyl moiety, buffer catalysis becomes harder to observe (α increases). (iv) The change in (ii) has little effect on the β_{lg} value.

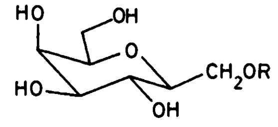
The direction of the reaction co-ordinate can be rigorously deduced from inter-related changes of the type described above:[31] in this case it is in a ‘ NNE–SSW ’ direction. Given the location of the transition state given by the β_{lg} and α values, right on the ‘ northern ’ edge of the diagram, and the characterisation of the reaction as A-S_E2(N), this is entirely reasonable. (The fact that $\beta_{lg} > \alpha$ for some of these reactions, impossible on the simple picture, could represent imbalance in the various parameters describing the transition state.[32])

C *The pH-Independent Reaction.*—This mode of decomposition was entirely unexpected. The following pieces of evidence constrain us to formulate it as a simple unimolecular heterolysis of a nitrogen–nitrogen bond, with anilide anion departing from an alkanediazonium ion.

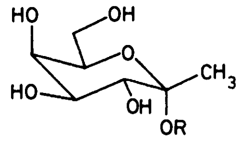
(i) The products of the reaction are those of a deamination reaction. *p*-Nitroaniline is the chromophoric product of the decomposition of propyl-*p*-nitrophenyltriazene, and the carbohydrate products from the decomposition of β-D-galactopyranosylmethyl-*p*-nitrophenyltriazene in water are typical deamination products similar to those obtained by Coxon and Fletcher[16] using nitrous acid deamination of β-D-galactopyranosylmethylamine or by Brockhaus *et al.*[33] using decomposition of β-D-galactopyranosyldiazomethane in methanol containing sodium methoxide [compounds (v)—(x)].

G.l.c of the trimethylsilyl ethers from the decomposition of the carbohydrate triazene in water revealed 4 main peaks A—D, relative retention times 1.00, 0.82, 0.79, and 0.75, and relative area 1 : 0.20 : 0.21 : 0.15. A was identified as trimethylsilylated (V), *m/e* 554(M^+), 539(M^+ − Me), 464(M^+ − Me_3SiOH), and 451(M^+ − CH_2OSiMe_3), by co-injection with a genuine sample, and identity of the mass spectral fragmentation pattern.

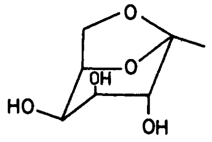
After treatment with 20% aqueous acetic acid overnight, material D was converted into C (relative intensities of peaks 1.0 : 0.18 : 0.37 : 0.07).C is probably the trimethylsilyl derivative of (VII) [*] [prominent ions *m/e* 449(M^+ − Me − Me_3SiOH), 407(M^+ − $SiMe_2OSiMe_3$), 361(M^+ − CH_2OSiMe_3 − Me_3SiOH), 359(M^+ − $2Me_3SiOH$ − Me), 374(M^+ − $2Me_3SiOH$), 375(M^+ − $SiMe_3O$ − $SiMe_3OH$?)]. (Fragmentation patterns of related compounds are discussed by Mononen.[34]) D is then probably the internal glycoside (IX), on the basis of its conversion to (VII) with mild acid, and a mass spectral peak at 319(M^+ − Me_3Si ?). The identification of products apart from β-D-galactopyranosylmethanol is necessarily tentative, but it is clear that the triazene is decomposing *via* precedented deamination routes, which suffices for the present purposes.



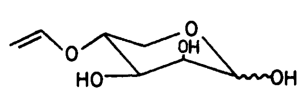
(V) R = H
(VI) R = Me



(VII) R = H
(VIII) R = Me



(IX)



(X)

(ii) The sensitivity of the process to the pK_a of the aniline is in the opposite sense to that for the proton and general acid catalysed reaction: electron-withdrawing substituents are strongly acceleratory. Moreover, the rates for four propyltriazenes correlate better with the pK_a values of the anilines than with those of the anilinium ions. The β_{lg} value in the former case (−0.24) indicates comparatively little negative charge build-up on the aniline. (In correcting for the tautomerisation equilibrium, for this process too we assume the reactive tautomer to be the unconjugated one.)

The data for propyl-, benzyl-, and β-D-galactopyranosylmethyl-*p*-nitrophenyltriazenes give some indication of the large effect of the pK_a of the alkylamine: the three points lie on a line described by equation (2). (The line is illustrated in

$$\log k_0 = -15.2 + 1.19\,\mathrm{p}K_{a(\mathrm{RNH_3^+})} \qquad (2)$$

the preliminary communication.[8]) The absence of any special effect with the benzyl compound makes any elimination pathway involving diazo compounds unlikely. The β value in equation (2) indicates a high build-up of charge on the alkyl-bound nitrogen, in contrast to the β_{lg} value, which indicates about a quarter of a charge on the aniline nitrogen, but this apparent paradox, exactly the same as with the acid-catalysed reaction, is resolved if it is accepted that the effective charge next to the alkyl group is much higher in an alkanediazonium ion than in an alkylammonium ion.

$$PhCH_2{-}N{=}N{-}NH{-}p{-}C_6H_4NO_2 \not\longrightarrow PhCH{=}\overset{+}{N}{=}\overset{-}{N} + NH_2C_6H_4NO_2.$$

(iii) The absence of a primary deuterium kinetic isotope effect in the pH-independent decomposition of [1-$^2H_2$]benzyl-*p*-nitrophenyltriazene establishes conclusively that this reaction does not involve eliminative processes leading to phenyl-

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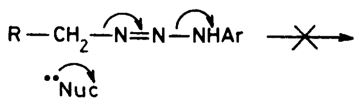
[*] The 3,4-dichlorophenylhydrazone of deoxyheptulose (VII) was prepared according to Coxon and Fletcher[16] but in our hands the syrup produced by their conditions for regeneration of heptulose exhibits n.m.r. signals incompatible with structure (VII). Moreover the hydrazone cannot be regenerated from this syrup.

diazomethane. Moreover, since the labelled triazene was made by coupling [1-$^2H_2$]benzylamine with *p*-nitrobenzenediazonium tetrafluoroborate in alkaline aqueous solution, and still retained its deuterium, the triazene does not exchange its deuterium with solvent at a rate fast compared to its decomposition, and the absence of a primary deuterium kinetic isotope effect is mechanistically meaningful. (The absence of deuterium wash-out during synthesis of this compound also makes the suggested[35] presence of triazene tautomers of the type RCH=N–NH–NH–Ar additionally[36] unlikely).

In fact, if protiated and deuteriated samples are compared directly during the same run (with reversal of positions in the spectrometer cell holder between runs) a small inverse secondary isotope effect can be detected (k_H/k_D 0.9_7 at pH 6.76, 0.9_5 at pH 7.68, and 0.8_9 at pH 8.85). Since $PhCH_2NH_3^+$ is a stronger acid than $PhCD_2NH_3^+$ by 0.054 p*K* units,[37] the observed effect is in the right direction, given the sensitivity of the reaction to the pK_a of the alkylammonium ion.

(iv) The reaction does not involve a bimolecular nucleophilic displacement on carbon by water (or chloride ion) since replacing 1.0M-KCl as swamping electrolyte by 1.0M-NaN_3 has only minimal kinetic effect, rates (10_3 k/s^{-1} in 25mM-tris–HCl buffer) being 5.7, 2.4_9, $2.6,_2$ and 2.5, at pH 6.0, 7.0, 8.0, and 9.0, respectively (*cf.* Table 3, Figure 1).

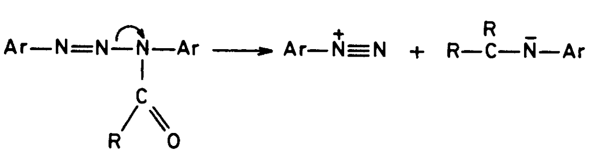


(v) The question of solvent participation by partial proton donation to the leaving anilide anion is, in principle, not as susceptible to unambiguous probes as the above alternative mechanistic hypotheses. If the pH-independent reaction is regarded as general acid catalysis by water, then it falls on the Brønsted line for propyl-*p*-nitrophenyltriazene, but not that for propyl-3,5-dichlorophenyltriazene (Table 3). The two traditional probes of solvent involvement, solvent deuterium isotope effect and entropy of activation, both indicate that solvent is not involved.

The rate of decomposition of propyl-*p*-nitrophenyltriazene in 25mM-tris–HCl buffer, 1.0M in KCl in D_2O is $2.1_8 \times 10^{-3}$ s^{-1} and $2.1_6 \times 10^{-3}$ s^{-1} at ratios of basic to acidic buffer component of 1 : 2 and 2 : 1, respectively. With the pH-independent rate in H_2O (Table 3), these data give k_{H_2O}/k_{D_2O} 1.0_8, well below what is expected for a water reaction in which the water acts as a general acid. For example, a value of k_{H_2O}/k_{D_2O} of 1.61 at 75 °C was reported for the A-S_E2 reaction of benzylidenecatechol with water.[38]

In 100mM-tris–HCl buffer, pH-meter reading 8.0 at 25 °C,* in 1.0M-KCl, 5% in acetonitrile, the rates (10^5 k/s^{-1}) of decomposition of benzyl-*p*-nitrophenyltriazene are 9, 30_8, and 129, at 25.0, 35.1 and 45.9 °C, respectively, giving $\Delta H^‡$ 23.6 ± 1.0 kcal mol^{-1}, $\Delta S^‡$ 2 ± 3 cal mol^{-1} K^{-1}. Near zero entropies of activation of dissociative reactions generally indicate unimolecular pathways: the pH-independent hydrolysis of *p*-nitrophenoxytetrahydropyran, a process which involves simple departure of *p*-nitrophenoxide from the tetrahydropyranyl cation without immobilisation of a solvent molecule as a general acid[39] (or nucleophile[40]) shows $\Delta S^‡$ 2.2 cal mol^{-1} K^{-1} and k_{H_2O}/k_{D_2O} 1.1.

Therefore any kinetically significant proton transfer from the solvent to departing anilide anion does not manifest



itself by traditional criteria. It is common mechanistic experience that kinetically significant proton transfer from water occurs when a stronger base than OH^- acts as a leaving group from a substrate which is a weaker base than H_2O.[41] Conditions for synchronous proton transfer from water are met in this case, but proton transfer does not take place. However, proton donation by water to a leaving group weaker than OH^-, which is contrary to this rule, is also observed in another system.[38] The rule may have only limited validity.

A very similar reaction (with a better leaving group from a more electrophilic diazonium ion) has been investigated by Pytela *et al.*[42] 1-Acyl-1,3-diaryltriazenes of various structures show an acid-catalysed, a base-catalysed, and a pH-independent decomposition mode in water. The pH-independent reaction is considered to involve departure of *N*-acylanilide anion from arenediazonium ion. A solvent deuterium isotope effect is not observed. Activation entropies vary with R, but are generally negative. Pytela *et al.* consider a number of solvent water molecules to be involved in the rate-determining transition state, on the basis of solvent effects and isokinetic temperature studies. (Their use of the Winstein–Grunwald *m* value as a criterion for solvent involvement is however mistaken, since it more properly reflects charge separation at the transition state. Unambiguously S_N1 reactions with highly delocalised anionic leaving groups therefore give low *m* values.[43]) It is difficult, however, to distinguish between solvent involvement in the rather general sense proposed by Pytela *et al.* from normal solvation. The pH-independent reactions of alkylaryltriazenes are best considered as simple S_N1 reactions on nitrogen, with nitrogen as a leaving group. Heterolysis of a homonuclear bond in an S_N1 sense is precedented in carbon chemistry.[44]

Acknowledgements

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