Triazene Drug Metabolites. Part 10.[1] Metal-ion Catalysed Decomposition of Monoalkyltriazenes in Ethanol Solutions

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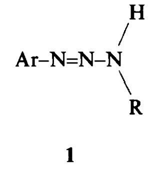
The metal ions Fe^{2+}, Zn^{2+} and Cu^{2+} bring about the rapid decomposition of 1-aryl-3-alkyltriazenes to the corresponding anilines. For Fe^{2+}, a linear dependence of the pseudo-first-order rate constant, k_0, on $[Fe^{2+}]$ was observed, while for Zn^{2+} and Cu^{2+} plots of k_0 *versus* [metal ion] were curved and indicative of complex formation. For Fe^{2+}, second-order rate constants $k_2^{Fe^{2+}}$ for substituted 1-aryl-3-methyltriazenes follow a Hammett relationship giving rise to a ρ value of -3.0. For Zn^{2+} and Cu^{2+}, the data were analysed in terms of an equilibrium constant, $K^{M^{2+}}$, for the dissociation of a metal-ion–triazene complex and the first-order rate constant for the collapse of this complex to products, $k_2^{M^{2+}}$. Hammett ρ values of 1.0 for both $K^{Zn^{2+}}$ and $K^{Cu^{2+}}$ are found, and the corresponding ρ values for $k_2^{Zn^{2+}}$ and $k_2^{Cu^{2+}}$ are -1.3 and -1.9. There is reasonable correlation between the Taft E_s parameter for the alkyl group and $K^{Cu^{2+}}$, giving a δ value of -1.6. The dependence of $k_2^{Cu^{2+}}$ on the alkyl group is not simple: $k_2^{Cu^{2+}}$ decreases in the order $Pr > Et \neq PhCH_2$ *ca.* $4\text{-}MeOC_6H_4CH_2 > CD_3$ *ca.* Me. The reactions catalysed by Cu^{2+} are inhibited by added nucleophilies *e.g.* Br^- and *N*-methylimidazole.

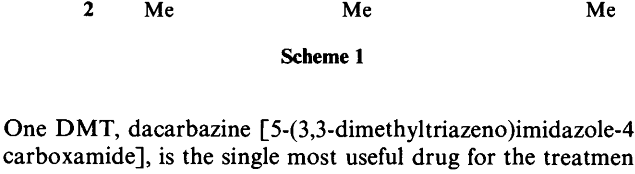
A mechanism is proposed in which the triazene complexes to the metal ion *via* the N(1) nitrogen atom of the *E–cis* conformer, then undergoes a fast proton transfer to form a complex involving the unconjugated tautomer which subsequently decomposes *via* unimolecular scission of the N(2)–N(3) bond to form an alkyldiazonium ion and an aniline–metal complex. The observed products then arise from rapid solvolysis of the metal–aniline complex and the alkyl diazonium ion.

Monoalkyltriazenes **1**, particularly monomethyltriazenes **1** (R = Me), have been the subject of much research due, in large part, to their cytotoxic, mutagenic and anti-cancer activity.[2] These effects result from the alkylating ability of the monoalkyltriazene,[3] and the monomethyl derivatives **1** (R = Me) are known to methylate DNA and RNA.[4,5] Substantial evidence now exists that monomethyltriazenes (MMTs) are the ultimate alkylating species generated by metabolic oxidative activation of the anti-cancer dimethyltriazenes (DMTs) **2** (Scheme 1).[6]



1

	Ar	R
a	$4\text{-}MeC_6H_4$	Me
b	$4\text{-}BrC_6H_4$	Me
c	$4\text{-}EtOCOC_6H_4$	Me
d	$4\text{-}EtOCOC_6H_4$	CH_2CF_3
e	$4\text{-}EtOCOC_6H_4$	CH_2Ph
f	$4\text{-}AcC_6H_4$	Me
g	$4\text{-}AcC_6H_4$	Et
h	$4\text{-}AcC_6H_4$	Pr^n
i	$4\text{-}AcC_6H_4$	CH_2Ph
j	$4\text{-}AcC_6H_4$	$CH_2C_6H_4\text{-}4\text{-}OMe$
k	$4\text{-}AcC_6H_4$	CD_3
l	$4\text{-}CNC_6H_4$	Me
m	$4\text{-}NO_2C_6H_4$	Me
n	3-pyridyl	Me

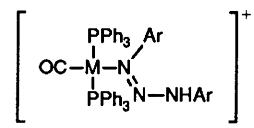


Scheme 1

One DMT, dacarbazine [5-(3,3-dimethyltriazeno)imidazole-4-carboxamide], is the single most useful drug for the treatment of malignant melanoma.[7] A knowledge of the chemistry of MMTs is therefore of relevance to an understanding of their *in vivo* stability and, in particular, their ability to act as transport metabolites in the blood.

The proton-catalysed decomposition of monoalkyltriazenes **1** has been well studied.[8–10] In aqueous solution, such compounds undergo reaction to form alkanediazonium ions and the corresponding aniline *via* an $A\text{-}S_E2(N)$ mechanism in which, in the transition state, a proton is essentially completely transferred but with little N–N bond cleavage.[8] As well as an acid catalysed reaction, monoalkyltriazenes decompose in aqueous solution *via* a pH-independent pathway. This involves N–N bond cleavage and departure of the aniline anion without assistance by acid.[8] In non-aqueous solutions, acid catalysis is also observed and proton transfer is rate limiting.[10]

Of as much relevance as proton catalysis to the *in vivo* stability of monoalkyltriazenes, is the possibility that Lewis acids, *e.g.* Fe^{n+}, Cu^{2+} and Zn^{2+} can also catalyse their decomposition. For example, the blood concentration of H^+ is *ca.* 10^{-7} mol dm^{-3}, whereas the concentrations of Fe^{n+}, Cu^{2+} and Zn^{2+} are 7×10^{-3}, 1.5×10^{-5} and 10^{-4} mol dm^{-3}, respectively.[11] Thus, it is clear that if such ions do catalyse the decomposition of MMTs, they could be the major factor in determining MMT stability *in vivo*. The interaction of *neutral* 1,3-disubstituted triazenes such as **1** with metal ions has been reported only once, the complexes having structure **3**.[12] Significantly, the triazenes involved are 1,3-diaryltriazenes **1** (R = aryl), which are much more stable than the corresponding 1-aryl-3-alkyltriazenes. In contrast, anions of 1,3-disubstituted triazenes are well-known ligands for a variety of metal ions; triazenes with 1,3-dialkyl,[13] 3-alkyl-1-aryl,[14] and 1,3-diaryl[12,15] substitution patterns have all been reported. Monodentate,[16] chelating bidentate[17,18] and bridging bidentate[19,20] modes of binding are all observed. Interestingly, protonation of a triazenido rhodium complex gives rise to the protonated triazene



3 M = Rh, Ar = 4-MeC_6H_4 or 4-FC_6H_4
M = Ir, Ar = Ph

species **3**, whereas protonation of the corresponding iridium complex involves the formation of an Ir–H bond. There appears to be no previous report, however, upon the interaction of *neutral* 3-alkyl-1-aryl-triazenes with simple metal ions like Zn^{2+}. Herein we address that deficiency, and have studied the decomposition of compounds **1a–n** in ethanol solutions catalysed by Zn^{2+}, Cu^{2+} and Fe^{2+}.

Experimental

The methyl-, ethyl- and propyl-triazenes were synthesised from the corresponding hydroxymethyltriazenes.[21] The 2,2,2-trifluoroethyl- and benzyl-triazenes were synthesised from the parent amine and the appropriate aryldiazonium salt.[22] Coupling constants *J* are given in Hz.

1d: m.p. 87–88 °C; ν_{max}/cm^{-1} 3190, 3160, 1710 and 1605; $\delta_H(CDCl_3)$ 1.35 (3 H, t, *J* 7), 4.25 (2 H, q, *J* 9.5), 4.33 (2 H, q, *J* 7) and 7.45–8.25 (4 H, AA′BB′) (Found: C, 47.9; H, 4.3; N, 15.4. Calc. for $C_{11}H_{12}F_3N_3O_2$: C, 48.0; H, 4.36; N, 15.3%).

1e: m.p. 81–82 °C; ν_{max}/cm^{-1} 3190, 3165, 1715 and 1610; $\delta_H(CDCl_3)$ 1.40 (3 H, t), 4.35 (2 H, q), 4.90 (2 H, s) and 7.25–8.15 (9 H, m) (Found: C, 67.7; H, 6.3; N, 14.6. Calc. for $C_{16}H_{17}N_3O_2$: C, 67.8; H, 6.01; N, 14.8%).

1i: m.p. 96–97 °C; ν_{max}/cm^{-1} 3180, 1360, 1665 and 1550; $\delta_H(CDCl_3)$ 2.55 (3 H, s), 4.85 (2 H, s) and 7.25–8.15 (9 H, m) (Found: C, 71.2; H, 5.7; N, 16.6. Calc. for $C_{15}H_{15}N_3O$: C, 71.1; H, 5.92; N, 16.6%).

1j: m.p. 94–95 °C; ν_{max}/cm^{-1} 3190, 1660 and 1590; $\delta_H(CDCl_3)$ 2.55 (3 H, s), 3.8 (3 H, s), 4.80 (2 H, s) and 6.85–7.95 (8 H, m) (Found: C, 68.0; H, 6.0; N, 14.9. Calc. for $C_{16}H_{17}N_3O_2$: C, 67.8; H, 6.0; N, 14.8%).

1k: m.p. 89–91 °C; ν_{max}/cm^{-1} 3175, 3140, 1670 and 1510; $\delta_H(CDCl_3)$ 2.55 (3 H, s) and 7.30–8.10 (4 H, AA′BB′) (Found: C, 59.7; H/D, 6.0; N, 23.3. Calc. for $C_9H_8D_3N_3O$: C, 60.0, H/D, 6.15; N, 23.3%).

Kinetics.—Reactions were initiated by injecting a stock ethanolic solution of the appropriate triazene into a thermostatted UV cuvette containing an ethanolic solution of the metal perchlorate at a known concentration. Ionic strength was maintained at 0.15 mol dm^{-3} using $NaClO_4$. Repeated scanning of the UV spectrum showed the presence of an isosbestic point. Observed pseudo-first-order rate constants were then determined by monitoring reactions at a suitably fixed wavelength and plotting ln $(A_t - A_\infty)$ *versus* time. Rate constants, k_{obs}, obtained by this method were reproducible to ±5% or better. Catalytic constants for each metal ion were estimated as discussed in the Results and Discussion section.

Product Analysis.—The UV spectrum of the reaction solution at the end of each reaction was scanned, and this showed that the products were probably the parent anilines, $ArNH_2$. However, since the spectra of $ArNH_2$, ArNHR and $ArNR_2$ are very similar we carried out HPLC analysis of several reaction solutions directly using a C8 reversed-phase system and employing water–acetonitrile–methanol (5:2:3) containing 0.025 mol dm^{-3} $NH_4^+AcO^-$ (pH 6.5) as eluent. For the Cu^{2+}-catalysed decomposition of compounds **1a**, **1c** and **1l** the yields of the corresponding $ArNH_2$ were 97(±4)%, 95(±4)% and 97(±2)%, respectively. We were unable to detect any ArNHMe or $ArNMe_2$ in these solutions. Similar results were obtained for other substrates and metal ions. We did not attempt to identify the product derived from the alkyl group.

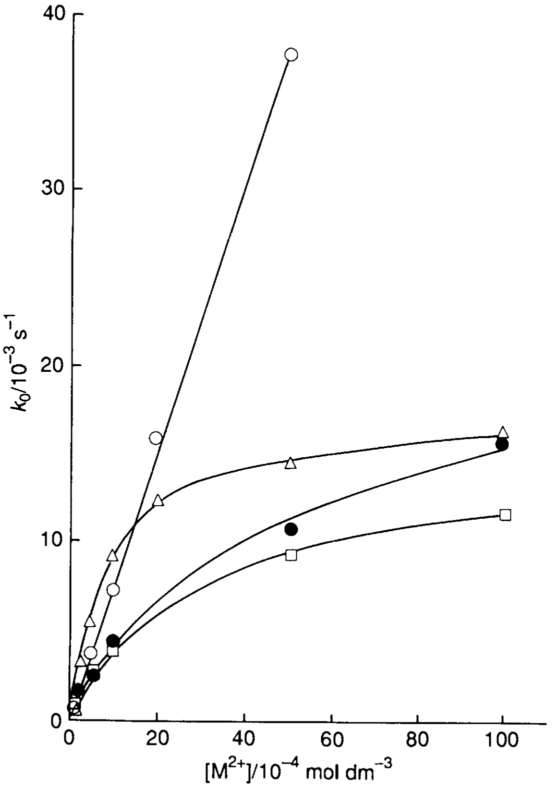


Fig. 1 Typical plots of k_0 *versus* $[M^{2+}]$ for the Fe^{2+}, Cu^{2+} and Zn^{2+} catalysed decomposition of various triazenes: ○ = **1m**, Fe^{2+}; △ = **1n**, Fe^{2+}; ● = **1m**, Cu^{2+}; □ = **1c**, Zn^{2+}

Formation of Zinc Tetrakis(N-*methylimidazole*) *Perchlorate*.—The white precipitate which forms from solutions in which [*N*-methylimidazole]:[zinc perchlorate] > 4 was collected by filtration, washed with ether and dried. Its structure as the tetrakis(*N*-methylimidazole) complex of zinc perchlorate followed from the ^1H NMR spectrum and elemental analysis: $\delta_H(CD_3CN)$ 3.75 (3 H, s), 6.98 (1 H, s), 7.22 (1 H, s) and 7.78 (1 H, s); ν_{max}/cm^{-1} 3120, 1545, 1530, 1375, 1250, 1235, 1100 (vbr), 960, 935, 830, 660 and 610 (Found: C, 38.6; H, 4.8; N, 22.6. Calc. for $C_{16}H_{24}N_8O_4ClZn$: C, 38.98; H, 4.91; N, 22.74%).

Results and Discussion

In the presence of Zn^{2+}, Cu^{2+} and Fe^{2+} perchlorates, 3-alkyl-1-aryltriazenes decompose to the corresponding anilines, eqn. (1).

$$Ar–N=N–NHR \xrightarrow{M(ClO_4)_2} ArNH_2 + N_2 + EtOR \quad (1)$$

This reaction is analogous to the proton-catalysed process. The reactions have a first-order dependence on the monoalkyltriazene as indicated by both the linearity of the ln $(A_t - A_0)$ *versus* time plots and an unchanged observed pseudo-first-order rate constant, k_0, on increasing the concentration of the monoalkyltriazene. The rate of decomposition of the monoalkyltriazenes also varied with the concentration of the metal ion, but in a manner that varied with both the metal ion and the triazene employed (Fig. 1). For Fe^{2+}, a linear correlation between k_0 and $[Fe^{2+}]$ is observed for the substituted phenyltriazenes at all

Table 1 Second-order catalytic rate constants, $k_2^{\mathrm{Fe}^{2+}}$, for the Fe^{2+} catalysed decomposition of various triazenes

Triazene	T/°C	$k_2^{\mathrm{Fe}^{2+}}$/dm^3 mol^{-1} s^{-1}
1b	20	331
1c	20	103
1l	20	13.8
1m	15	4.03
	20	7.02
	25	10.0
	30	13.8
	35	23.2
1n	20	12.6

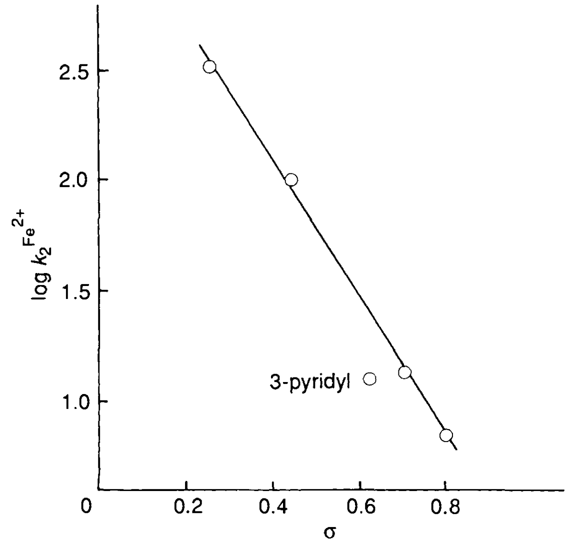


Fig. 2 Hammett plot for the Fe^{2+} catalysed decomposition of monomethyltriazenes

[Fe^{2+}] employed (up to 10^{-2} mol dm^{-3}). At higher values of [Fe^{2+}] the absorbance of the metal ion severely interfered with the UV spectrum of the triazene and reliable kinetic data could not be obtained. For the 3-pyridyltriazene **1n**, a plot of k_0 *versus* [Fe^{2+}] is curved (Fig. 1). For Cu^{2+} and Zn^{2+}, plots of k_0 *versus* [metal ion] also are curved for all triazenes studied. Such behaviour is typical of a pre-equilibrium phenomenon such as that involving a metal ion–substrate complex.

Fe^{2+} *Catalysis.*—Second-order catalytic rate constants, $k_2^{\mathrm{Fe}^{2+}}$, for the Fe^{2+}-catalysed decomposition of triazenes **1b**, **c**, **l** and **m** were obtained from the slopes of plots of k_0 *versus* [Fe^{2+}] such as that in Fig. 1. Values of $k_2^{\mathrm{Fe}^{2+}}$ are given in Table 1. The data give rise to a Hammett ρ value of $-3.0(\pm 0.2)$ (Fig. 2). The temperature variation of $k_2^{\mathrm{Fe}^{2+}}$ yields values of $\Delta S^\ddagger$ $-33(\pm 10)$ J K^{-1} mol^{-1} and $\Delta H^\ddagger$ $58(\pm 4)$ kJ mol^{-1}.

For the heterocyclic triazene **1n**, the curvature of the k_0 *versus* [Fe^{2+}] plot (Fig. 1) suggests that for this compound formation of a metal complex occurs. However, the Hammett σ value for this compound, 0.62,[23] is of similar magnitude to that for 4-CNC_6H_4, 0.7, for which curvature of the k_0 *versus* [Fe^{2+}] plot is not observed. For this reason, we believe that the interaction of compound **1n** with Fe^{2+} differs somewhat from the analogous substituted phenyltriazenes.

We have shown elsewhere that for the corresponding hydroxymethyltriazenes the heterocyclic pyridyltriazene **1n** preferentially binds to lanthanide metal ions through the pyridine nitrogen atom.[24] By analogy, a similar complex **4** may be formed between Fe^{2+} and the pyridyl nitrogen. Such a complex, MT*, is unlikely to be product forming, and the kinetics may be analysed in terms of eqn. (2) where M, T and P are the metal ion, triazene and products, respectively. Using this analysis, K^* and $k_2^{\mathrm{Fe}^{2+}}$ can be obtained from a plot of $1/k_0$ *versus* $1/[Fe^{2+}]$ (Fig. 3). Values of 1.76×10^{-4} mol dm^{-3} and 12.6 dm^3 mol^{-1} s^{-1} for K^* and $k_2^{\mathrm{Fe}^{2+}}$, respectively are determined and, interestingly, the value of $k_2^{\mathrm{Fe}^{2+}}$ for **1n** lies close to that expected from the Hammett plot (Fig. 2) implying that such an analysis is probably correct.

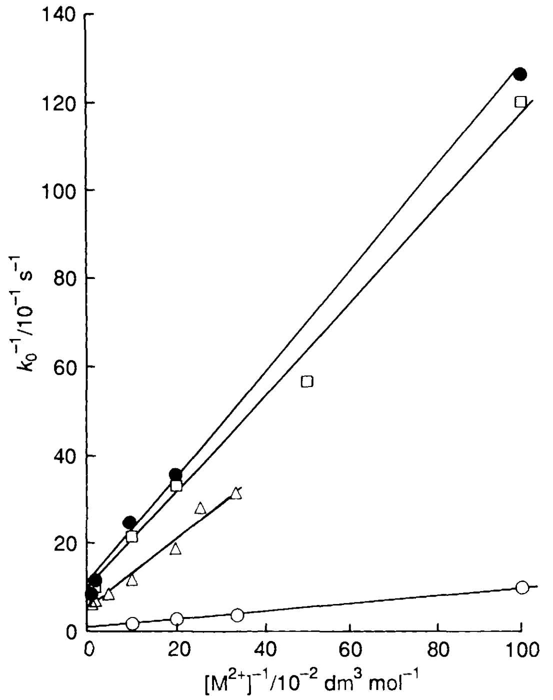
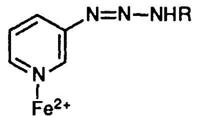


Fig. 3 Plots of $1/k_0$ *versus* $1/[M^{2+}]$ for the metal-ion catalysed decomposition of various triazenes: ○ = **1h**, Cu^{2+}; △ = **1n**, Fe^{2+}; □ = **1m**, Cu^{2+}; ● = **1c**, Zn^{2+}



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$$\mathrm{MT^*} \underset{}{\overset{K^*}{\rightleftharpoons}} \mathrm{T} + \mathrm{M} \xrightarrow{k_2^{\mathrm{Fe}^{2+}}} \mathrm{P} + \mathrm{M} \qquad (2)$$

Catalysis by Cu^{2+} *and* Zn^{2+}.—Curvature of the plots of k_0 *versus* [Cu^{2+}] or [Zn^{2+}] is indicative of a complexation phenomenon and is best rationalised in terms of a pre-equilibrium formation of a triazene–metal ion complex [eqn. (3)]. Defining $[M]_t$ and [M] as the total metal ion and free

$$\mathrm{M} + \mathrm{T} \underset{K^{\mathrm{M}^{2+}}}{\rightleftharpoons} \mathrm{MT} \xrightarrow{k_2^{\mathrm{M}^{2+}}} \mathrm{M} + \mathrm{P} \qquad (3)$$

metal ion concentrations, $[T]_t$ and [T] as the analogous triazene concentrations, [MT] as the concentration of the complex, and making use of the relationships in eqns. (4) and

$$[\mathrm{T}]_t = [\mathrm{T}] + [\mathrm{MT}] \qquad (4)$$

$$K^{\mathrm{M}^{2+}} = \frac{[\mathrm{M}][\mathrm{T}]}{[\mathrm{MT}]} \qquad (5)$$

Table 2 Catalytic constants, $k_2^{M^{n+}}$ and $K^{M^{n+}}$, for the Cu^{2+} and Zn^{2+} catalysed decomposition of various monoalkyltriazenes in ethanol

Triazene	T/°C	$k_2^{Cu^{2+}}/10^{-2}$ s^{-1}	$K^{Cu^{2+}}/10^{-4}$ mol dm^{-3}	$k_2^{Zn^{2+}}/10^{-3}$ s^{-1}	$K^{Zn^{2+}}/10^{-3}$ mol dm^{-3}
1a	20	—	—	8.36	0.65
	24	—	—	10.9	0.67
	31	—	—	32.4	0.43
	35	—	—	40.4	0.59
1b	35	17.2	4.07	15.5	0.94
1c	35	5.42	4.93	10.1	1.18
	35	53.8[a]	6.97[a]		
1d		*b*	*b*	—	—
1e	35	57.5	329	—	—
1f	35	6.20	7.65	—	—
1g	35	17.8	15.4	—	—
1h	35	27.8	26.5	—	—
1i	35	13.6	46.7	—	—
1j	35	16.5	58.9	—	—
1k	35	7.75	3.5	—	—
1l	20	0.41	22.5	—	—
	25	0.85	34.0	—	—
	30	1.63	30.8	—	—
	35	2.33	11.6	3.84	3.27
	40	7.97	53.2	—	—
1m	35	1.29	14.3	2.13	45.9

[a] In Pr^iOH. [b] See text.

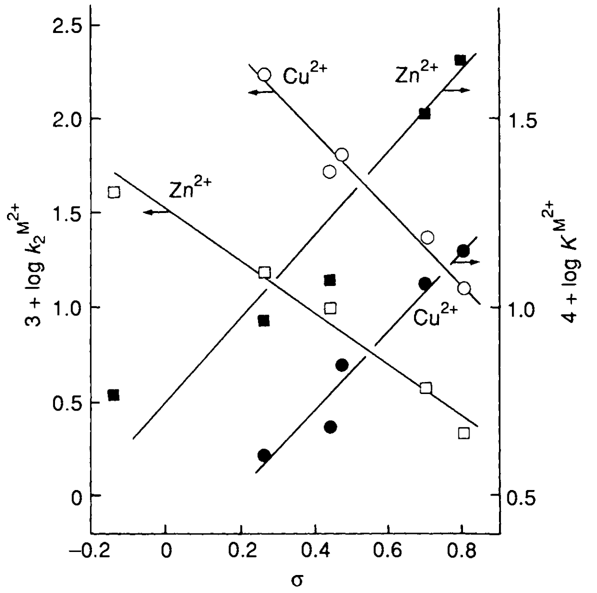


Fig. 4 Hammett plots of $k_2^{M^{2+}}$ and $K^{M^{2+}}$ for the Cu^{2+} and Zn^{2+} catalysed decomposition of monomethyltriazenes

(5), the rate expression in eqn. (6) can be obtained. Thus, the pseudo-first-order rate constant, k_0, is given by eqn. (7), and a

$$\text{Rate} = \frac{k_2^{M^{2+}}[M]_t[T]_t}{[M]_t + K^{M^{2+}}} \qquad (6)$$

$$k_0 = \frac{k_2^{M^{2+}}[M]_t}{[M]_t + K^{M^{2+}}} \qquad (7)$$

double reciprocal plot of $1/k_0$ *versus* $1/[M]_t$ should yield a straight line of slope $K^{M^{2+}}/k_2^{M^{2+}}$ with an intercept of $1/k_2^{M^{2+}}$. Some typical plots for Cu^{2+} and Zn^{2+} catalysed reactions are shown in Fig. 3. Values of $k_2^{M^{2+}}$ and $K^{M^{2+}}$ obtained from such plots are given in Table 2. Comparing the catalytic constants for Cu^{2+} and Zn^{2+}, it may be said that $K^{Zn^{2+}}$ is 2–10 times greater than $K^{Cu^{2+}}$, *i.e.* more extensive metal-ion–triazene complex formation is apparent for Cu^{2+} than for Zn^{2+}. Further, $k_2^{Cu^{2+}}$ is 5–10 times greater than $k_2^{Zn^{2+}}$. Thus, catalysis by Cu^{2+} is more efficient than by Zn^{2+}.

For Cu^{2+}, Hammett plots (Fig. 4) using compounds **1b, c, f, l** and **m** of $k_2^{Cu^{2+}}$ and $K^{Cu^{2+}}$ yield ρ values of −1.9 and +1.0, respectively; the corresponding plots for Zn^{2+} using compounds **1a–c, l** and **m** (Fig. 4) give rise to ρ values of −1.3 for $k_2^{Zn^{2+}}$ and 1.0 for $K^{Zn^{2+}}$. Since $K^{M^{2+}}$ is defined as a dissociation constant, the positive sign of ρ for both Cu^{2+} and Zn^{2+} indicates that, as expected, electron-donating substituents *increase* the extent of formation of metal-ion–triazene complex. However, the sign of ρ for $k_2^{M^{2+}}$ for both Cu^{2+} and Zn^{2+} is negative which indicates that electron-donating substituents also increase the rate at which the metal-ion–triazene complex decomposes to products.

The effect of the alkyl group was studied for Cu^{2+} using compounds **1c–k**. Inspection of the data for these compounds (Table 2) enables the following observations to be made. First, increasing the size of the alkyl group increases $K^{Cu^{2+}}$, *i.e.* increasing steric bulk diminishes the extent of formation of the metal-ion–triazene complex. There is a reasonable correlation (r = 0.94) with the Taft E_s parameter giving a value for δ of −1.6. Second, for R = Me, Et and Pr, $k_2^{Cu^{2+}}$ increases along the series. However, this is not a simple dependence on steric or electronic effects, since $k_2^{Cu^{2+}}$ values for R = $PhCH_2$ and 4-$MeOC_6H_4CH_2$ are similar to that for R = Et. Nonetheless, it is clear from these data that formation of an alkyl carbocation in

Table 3 Effect of Br^- and *N*-methylimidazole on the rate of the Cu^{2+} catalysed decomposition of **1c** in ethanol at 35 °C. $[Cu^{2+}] = 10^{-4}$ mol dm^{-3}; $\mu = 0.15$ mol dm^{-3}

$[Br^-]$/ 10^{-4} mol dm^{-3}	k_0/ 10^{-3} s^{-1}	[*N*-methylimidazole]/ 10^{-6} mol dm^{-3}	k_0/ 10^{-3} s^{-1}
0	9.14	0	9.14
0.1	5.74	0.1	5.98
—	—	1.0	5.59
2.0	2.37	2.0	5.21
3.0	1.98	5.0	3.91
5.0	1.91	10.0	3.75
10.0	1.24	50.0	2.11
800	0.20	100.0	0.85

Table 4 Effect of added water on k_0 for the Cu^{2+} catalysed decomposition of **1l**

Water content/% (v/v)	$k_0/10^{-3}$ s^{-1}
0	2.33
10	0.289
20	0.259
30	0.207

the step represented by k_2 is precluded; in such a situation $k_2^{Cu^{2+}}$ for compound **1j** would be expected to be about an order of magnitude larger than that for **1i**, which it is not. Electronic effects must play a part, however, as compound **1d** is stable at all $[Cu^{2+}]$ employed. Further comparison of the data for **1f** and **1k** clearly indicate that C–H bond cleavage is not important in the decomposition of monoalkyltriazenes.

The effect of temperature on the catalytic constants, $k_2^{M^{n+}}$ and $K_2^{M^{n+}}$, for the Cu^{2+} and Zn^{2+} catalysed reactions was studied using triazenes **1l** and **1a** respectively. The data show (Table 2) that, as anticipated, $k_2^{M^{2+}}$ is much more sensitive to temperature than $K^{M^{2+}}$. Indeed for Zn^{2+}, no clear change in $K^{Zn^{2+}}$ over the temperature range studied was observed. The temperature variation in $k_2^{Cu^{2+}}$ gives rise to values for $\Delta S^‡$ and $\Delta H^‡$ of +54(±10) J K^{-1} mol^{-1} and 100(±5) kJ mol^{-1}, respectively; similarly, for Zn^{2+}, values for $\Delta S^‡$ and $\Delta H^‡$ are +6(±10) J K^{-1} mol^{-1} and 85(±5) kJ mol^{-1}.

Since the metal-ion catalysed reactions constitute dealkylation of the triazene and, moreover, dealkylation of monoalkyltriazenes has been observed to involve nucleophile alkylation,[2,4,5] it was of interest to study whether or not the decomposition of the metal-ion–triazene complex is catalysed by added nucleophiles. Thus, we carried out reactions in the presence of Br^-, a non-basic nucleophile and the basic *N*-methylimidazole. Both types of nucleophile bring about a significant reduction in the observed pseudo-first-order rate constants (Table 3), which can almost certainly be ascribed to a reduction in the M^{2+} concentration as a result of complexation between the nucleophile and the metal ion. Indeed, at elevated concentrations of *N*-methylimidazole it was possible to isolate the complex, tetrakis(*N*-methylimidazole) zinc perchlorate. Metal-ion catalysed decomposition is therefore not subject to nucleophilic catalysis.

Mechanism of the Metal-ion Catalysed Decomposition of Monoalkyltriazenes.—Thus far we have analysed the observed rate data in terms of eqn. (3). Before discussing the mechanism in more detail, it is worth commenting on an alternative process, outlined in eqns. (8) and (9), which involves solvolysis of the metal ion to liberate a proton, followed by a proton-catalysed process analogous to eqn. (3). Saturation of TH^+ in eqn. (9) could account for the curvature seen for the plots of k_0 *versus* $[Zn^{2+}]$ and $[Cu^{2+}]$ except that such saturation has never before been observed for the reaction of monomethyltriazenes with the proton either in aqueous or non-aqueous solvents.[8–10] Moreover, curvature of this nature would then be expected for Fe^{2+} which is the most acidic of the metal ions studied here.[25] Our results clearly show a linear dependence on the concentration of Fe^{2+} up to 10^{-2} mol dm^{-3}, while curvature is apparent for the less acidic Zn^{2+} and Cu^{2+} metal ions at similar concentrations. Thus, curvature for a proton-catalysed mechanism must reside in an alternative explanation, and it can be shown that the pseudo-first-order rate constant for eqns. (8) and (9) may be given by eqn. (10) (assuming that, as discussed above, saturation of TH^+ does not occur).

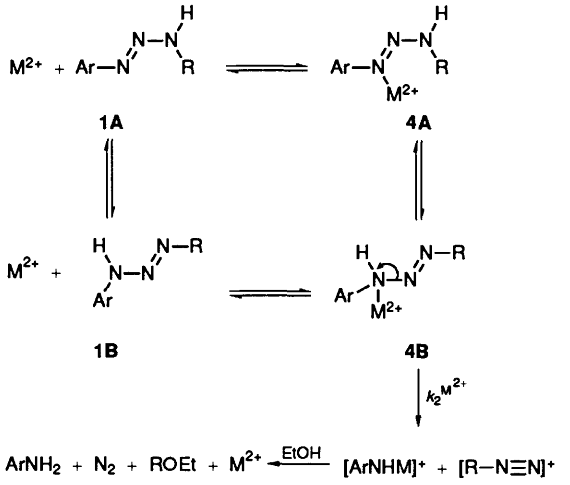
$$M + SH \underset{}{\overset{K_m}{\rightleftharpoons}} MS + H^+ \tag{8}$$

$$T + H^+ \underset{K^{H^+}}{\rightleftharpoons} TH^+ \xrightarrow{k_2^{H^+}} H^+ + P \tag{9}$$

$$k_0 = \frac{k_2^{H^+}}{K^{H^+}} \{(K_m^2 + 4K_m[M]_T)^{\frac{1}{2}} - K_m\} \tag{10}$$

At high $[M]_T$ k_0 has a dependence on $[M]_T^{\frac{1}{2}}$, and at low $[M]_T$ series expansion shows that k_0 has a linear dependence on $[M]_T$. This is not the type of curvature found, and we infer that proton catalysis is not responsible for the reactions observed here. To provide further evidence for this conclusion, we studied the effect of added water on the decomposition of compounds **1b** by Cu^{2+}. The results in Table 4 show that k_0 decreases as the water content increases (at least up to 30% v/v). Moreover, in water none of the metal ions are able to provide a concentration of H^+ of greater than 10^{-7} mol dm^{-3}.[25] In ethanol, the H^+ concentration is likely to be somewhat less than this. At such H^+ concentrations, monomethyl- and monobenzyl-triazenes have half-lives that range from 12.5 to 210 min depending on the aryl substituent.[8,26] For any particular triazene the half-lives for the metal-ion catalysed reactions observed here are much shorter than the corresponding values for the H^+-catalysed reaction.

Thus, the results are best interpreted in terms of a mechanism that involves the formation of a metal-ion–triazene complex (Scheme 2). The results of the present work are unable to clearly identify which tautomer, **1A** or **1B**, initially or preferentially binds to the metal ion. Sinnott and co-workers have shown that monoalkyltriazenes preferentially exist with the azo group in an *E*-configuration, and that the tautomeric equilibrium involves the *cisoid* form of the conjugated tautomer **1A** and the *transoid*



Scheme 2 Mechanism of the metal-ion catalysed decomposition of monoalkyltriazenes

form of the unconjugated tautomer **1B**.[27] The tautomeric equilibrium between **1A** and **1B** depends mainly upon the aryl group, and is largely independent of the alkyl group, R, and the solvent.[27] Values of the equilibrium constant for the tautomerism **1A** $\rightleftharpoons$ **1B** lie between 2.4 for Ar = $4\text{-NO}_2\text{C}_6\text{H}_4$ and 0.07 for Ar = $4\text{-MeOC}_6\text{H}_4$ at 25 °C. It was noted, however, that the rate of interconversion of **1A** and **1B** is accelerated by the presence of impurities.[27] For this reason, we feel justified in making the assumption that the interconversion of **1A** and **1B** (or **4A** and **4B**) is fast, and does not affect the arguments outlined below.

In principle, complexation of both **1A** or **1B** with the metal ion can occur to form **4A** and **4B** respectively. From the results for **1f–j**, however, we suspect that complexation of **1A** is the major pathway. Interpolation of Sinnott's results[27] using a value[28] of 2.19 for the pK_a of $4\text{-AcC}_6\text{H}_4\overset{+}{\text{N}}\text{H}_3$ gives an equilibrium constant for **1A** $\rightleftharpoons$ **1B** of 1.009. However, the values of $k_2^{M^{2+}}$ obtained for **1f–j** clearly show that complexation of the triazene with the metal is disfavoured as the steric bulk as the alkyl group increases. It is difficult to see how such an effect could be manifest in the complexation of the tautomer **1B**, but complexation of **1A** as shown will clearly involve steric interactions with the R group and the complexed metal ion. This implied mode of complexation is consistent with the known binding modes of the rhodium and iridium complexes of neutral 1,3-diaryltriazenes discussed earlier.[12] Moreover, it has been shown by *ab initio* molecular orbital calculations using a 3-21G basis set that the preferred site of binding of 1,3-dimethyltriazene to the proton is at the N(1) atom, though there appears to be no energetic preference for protonation of the *E-trans* or *E-cis* conformers.[29] Independently, we have found by using MNDO semi-empirical molecular orbital calculations that binding of the triazene N(1) atom to a dipositive metal ion is preferred over binding at N(3) by *ca.* 33 kJ mol^{-1}.[30] As the product of these reactions is the parent aniline, a [1,3]-prototropic shift must occur to form **4B**. This step is fast compared to the subsequent decomposition of **4B**. Such decomposition must involve unimolecular homolytic cleavage of the N(2)–N(3) bond in **4B**: the entropy of activation, $\Delta S^{\ddagger}$, for step $k_2^{M^{2+}}$ is >0 J K^{-1} mol^{-1} for both Cu^{2+} and Zn^{2+}; however, the variation in $k_2^{M^{2+}}$ with R clearly rules out the formation of R^+. Comparison of **1f** with **1k** also rules out diazoalkane formation *via* proton loss. The negative sign for the ρ values obtained for $k_2^{Cu^{2+}}$ and $k_2^{Zn^{2+}}$ can be accommodated by a product-like transition state, in which the effect of electron-releasing groups will stabilise $[\text{ArNHM}]^+$ more than **4B**.

The lack of curvature in the plots of k_0 *versus* $[\text{Fe}^{2+}]_t$ can be contained within this scheme if it is assumed that $K^{Fe^{2+}} > [\text{Fe}^{2+}]_t$. In such a situation, eqn. (7) predicts that k_0 *versus* $[\text{Fe}^{2+}]_t$ will be linear with slope $k_2^{Fe^{2+}}/K^{Fe^{2+}}$. If this is a correct interpretation of events then the results imply $K^{Fe^{2+}} > K^{Zn^{2+}} > K^{Cu^{2+}}$; *i.e.* the extent of complexation diminishes in the order $\text{Cu}^{2+} > \text{Zn}^{2+} > \text{Fe}^{2+}$. This is entirely consistent with the known propensity of these metals to bind the sp^3 nitrogen ligand NH_3 and the sp^2 nitrogen ligand pyridine.[31,32] Moreover, the Hammett ρ value for Fe^{2+} of -3.0 is of a similar magnitude for the *combined* ρ values for $k^{M^{2+}}/K^{M^{2+}}$ for both Zn^{2+} and Cu^{2+}, *viz.* -2.96 and -2.37 respectively.

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