The Geometry of *N*-Hydroxymethyl Compounds. Part 4.[1] Studies on Ground-state Geometry and Decomposition of *N*-(Hydroxymethyl)-triazenes using MNDO Calculations and Kinetic Studies

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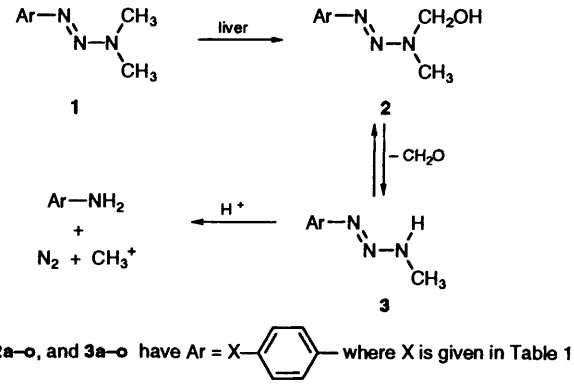
MNDO calculations of the most favoured conformations of antitumour 3-(hydroxymethyl)-3-methyl-1-(4-X-phenyl)triazenes (**2**) indicate N–CH_2OH bond lengths of over 1.49 Å (lengthened by electron-withdrawing groups), correlated with high lability under physiological conditions ($t_{1/2}$ under 1 s). Hydrolysis rates of **2o** (X = NO_2) in methanol/acetonitrile containing water were determined using high performance liquid chromatography (HPLC) and extrapolated to give a $t_{1/2}$ of 43 s at 100% water. Modelling of decomposition pathways of **2d** (X = CH_3) using MNDO predicts that concerted loss of formaldehyde is not favoured. Loss of $[H_2COH]^+$ from nitrogen protonated **2d** is also a high energy process, but loss of formaldehyde from deprotonated **2d** seems feasible under basic conditions. Under acidic conditions the energetically preferred process is loss of water from protonated **2d** to give an iminium ion, even though the required initial *O*-protonation is disfavoured over protonation on nitrogen.

Experimental[2-6] and theoretical[7-8] studies of the selective *in vivo* antitumour effects of 1-aryl-3,3-dimethyltriazenes (**1**) have led to several suggested mechanisms to explain their mode(s) of action but none accounts for all the data. The dimethyltriazenes are inactive *in vitro* and one popular hypothesis is that monomethyltriazenes (**3**), which are known antitumour agents, are produced by liver-mediated oxidative demethylation and are responsible[2] for the dimethyltriazenes' *in-vivo* activity. However, biological results suggest[3] that another metabolite is responsible, at least in part, for the antitumour effect. 1-Aryl-3-methyl-3-(hydroxymethyl)triazenes (**2**), long recognized[4] as intermediates in the oxidative demethylation of 1-aryl-3,3-dimethyltriazenes to monomethyltriazenes might be responsible[10] for the additional affects. Synthetic routes have recently been developed for the preparation[5,6] of these *N*-(hydroxymethyl)triazenes and they have been shown[6] to have antitumour properties and to react[9,10] with nucleophiles under electrophilic catalysis (which might account for the antitumour effect).

N-(Hydroxymethyl)triazenes are reasonably stable in non-polar solvents but rapidly decompose under normal physiological conditions in a pseudo-first-order kinetic process, accelerated by electron donating groups, to give formaldehyde and anilines. Since the half lives for this complete decomposition are only slightly greater than those for the presumed intermediate monomethyltriazenes it was concluded[6] that hydroxymethyl derivatives decompose rapidly to monomethyltriazenes which then hydrolyse to anilines (Scheme 1) but it remained to be shown whether *N*-(hydroxymethyl)triazenes are sufficiently stable under physiological conditions to possess antitumour activity of their own.

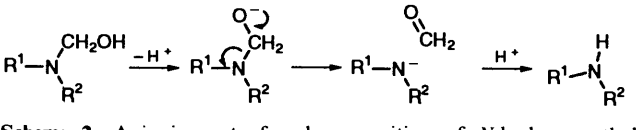
The stability under physiological conditions of *N*-(hydroxymethyl)amides, $RCONHCH_2OH$, correlates[1] well with their MNDO-calculated N–CH_2OH bond lengths. Electron withdrawing R groups on the *N*-(hydroxymethyl)amide reduce negative charge on nitrogen, increase calculated N–CH_2OH bond lengths, and increase rates of hydrolysis. Since there may be a correlation of the antitumour activity of *N*-(hydroxymethyl) compounds with physiological half life, it thus becomes feasible to assess potential antitumour properties from calculated N–CH_2OH bond lengths, or from other parameters related to the stability. We have studied quantum mechanically



Scheme 1 Metabolism of *N*-(hydroxymethyl)triazenes

the structures of fifteen 3-(hydroxymethyl)-3-methyl-1-(*p*-substituted phenyl)triazenes with the main objective of identifying easily obtained molecular parameters which could be used to estimate reactivities. If this series of triazenes behaves similarly to the amides electron withdrawing groups are expected to decrease negative charge on N(3) and increase N–CH_2OH bond lengths and hydrolysis rates in a smooth manner which might correlate with Hammett σ_p values for the substituents.

Although *N*-(hydroxymethyl) compounds are important both pharmacologically (for anticancer[12] agents, prodrugs,[13] and animal feedstuffs[14]) and chemically (as intermediates in the production of amine/formaldehyde resins, for example) there are only a few literature studies of their mechanisms of reaction. Johansen and Bundgaard[11] studied the rates of decomposition of *N*-(hydroxymethyl)amides to produce formaldehyde and amides and concluded that the decomposition occurs (Scheme 2, R^1 = RCO) through an anionic intermediate undergoing



Scheme 2 Anionic route for decomposition of *N*-hydroxymethyl compounds

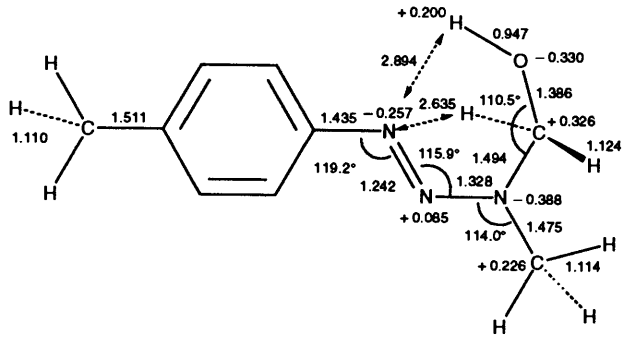


Fig. 1 Optimized structure of **2d** showing atomic charges (signed), bond angles, and bond lengths (Å)

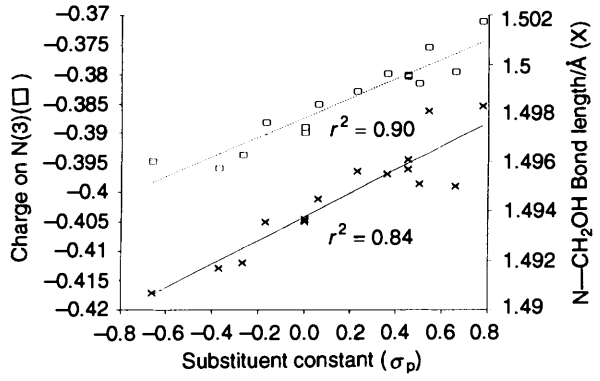
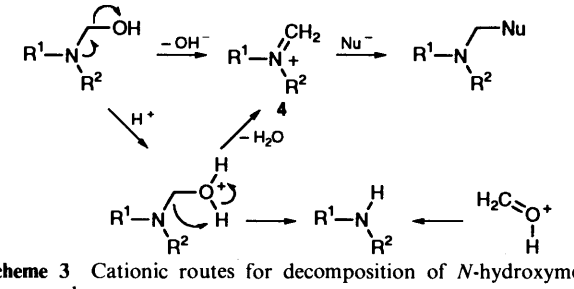


Fig. 2 MNDO calculated charges on N(1) and N–CH_2OH bond lengths (Å) for hydroxymethyltriazenes (**2**) plotted against Hammett substituent constants

rate determining N–CH_2OH bond cleavage. Iley *et al.*[15] showed that nucleophile-induced decomposition of 3-alkyl-3-hydroxymethyl-1-pyridyltriazenes is first-order in the concentration of both substrate and added nucleophile and suggested a six-membered cyclic transition state.

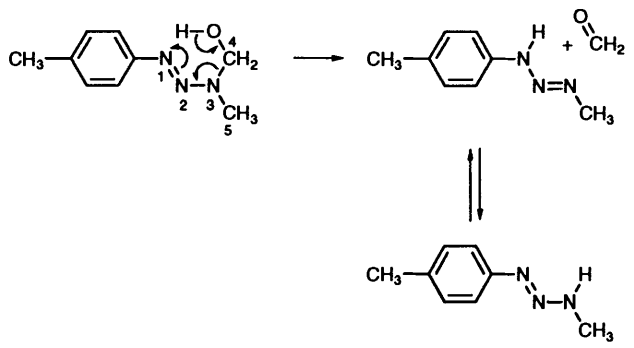
We have made a study of the nature of the energy profile for solvolyses of *N*-(hydroxymethyl)triazenes through three possible routes referred to as the anionic, cationic and concerted mechanisms. The anionic mechanism (Scheme 2, R^1 = Ar–N=N–) is analogous to the solvolysis of hydroxymethylamides. The cationic route has been suggested[12] to account for antitumour properties of hydroxymethyltriazenes and involves elimination of OH^- to generate an iminium ion (**4**, Scheme 3).



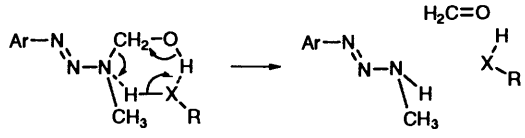
Scheme 3 Cationic routes for decomposition of *N*-hydroxymethyl compounds

The poor leaving group characteristics of the hydroxide ion make this rather unlikely unless preceded by protonation on oxygen allowing elimination of water instead of hydroxide. The concerted mechanism (Scheme 4) is electronically similar to decarboxylation of β-keto-carboxylic acids and to a retro-ene reaction. We have also made a preliminary study of the second-order concerted mechanism of Iley *et al.* (Scheme 5) which involves two hydrogen bonds being converted into single bonds.

In this paper we report the results of this theoretical work



Scheme 4 Concerted mechanism for decomposition of an *N*-(hydroxymethyl)triazene (**2d**)



XR = OR or NR_2

Scheme 5

and also the determination of some rates of decomposition of triazenes by HPLC including the hydrolysis of 3-(hydroxymethyl)-3-methyl-1-(4-nitrophenyl)triazene into 3-methyl-1-(4-nitrophenyl)triazene.

Results and Discussion

Ground State Structures.—Fifteen 1-aryl-3-(hydroxymethyl)-3-methyltriazenes (**2a–o**) were studied by the MNDO method; a summary of important structural parameters is given in Table 1. The preferred conformation of the hydroxymethyltriazenes was found to be as illustrated (Fig. 1) for the methyl derivative. In common with X-ray results[16] for the *p*-carbethoxy derivative (**2k**), our calculations predict that hydroxymethyltriazenes do not exhibit significant intramolecular hydrogen bonding although there is a preference for CH_2OH rather than CH_3 to be near N(1). The preferred conformation shown by the X-ray work has the CH_2OH closer to N(2). Rotating the –N(CH_2-OH)(CH_3) moiety of our 1-(4-methylphenyl)-3-(hydroxymethyl)-3-methyltriazene (**2d**) by 180° about the N=N bond such that the CH_2OH is closer to N(2) gave an optimized structure with a calculated energy increase of 1 kJ mol^{-1} and the N–CH_2OH bond length decreased to 1.4926 Å.

The effect of electron withdrawing groups on the atomic charge on N(3) and on the N–CH_2OH bond length and bond order was examined. Electron withdrawing groups reduced the charge on N(3) as expected but the N–CH_2OH bond length increased accompanied by a decrease in bond order. A reasonably good correlation between these parameters and the Hammett substituent constants was found (Fig. 2). The change in bond order (not plotted) parallels the other lines with r^2 = 0.89 and should be a good measure of the stability of the hydroxymethyltriazenes since it is this bond which must be broken.* However, we concentrated on the N–CH_2OH bond length for comparison with previous work.

In our previous studies[1] on *N*-(hydroxymethyl)amides a correlation was established between the MNDO calculated N–CH_2OH bond length (varying from 1.470 to 1.486 Å) and

* A referee has pointed out that an equally good correlation, r^2 = 0.87, exists between σ_p and the N(3)–C(5) bond length. Thus, the bond length of the bond that isn't broken also correlates with the substituent in the aryl ring. Bond order is therefore a preferable indicator of reactivity but since changes in the N(3)–C(4) bond order parallel the N(3)–C(4) bond length we have used the latter for the reasons stated.

Table 1 Calculated molecular data for 3-(hydroxymethyl)-3-methyl-1-(4-X-phenyl)triazenes

Compound	X	σ_p	Heat of formation /kJ mol^{-1}	Bond lengths				N3–C4 Bond order	Charge density	
				N1–N2	N2–N3	N3–C4	N3–C5		N3	C4
a	NH_2	−0.66	92.30	1.2411	1.3319	1.4907	1.4733	0.8431	−0.3948	0.3273
b	OH	−0.37	22.20	1.2410	1.332	1.4917	1.4734	0.8422	−0.3960	0.3280
c	OCH_3	−0.268	14.93	1.2415	1.3311	1.4919	1.4736	0.8417	−0.3937	0.3272
d	CH_3	−0.17	39.37	1.2422	1.3283	1.4936	1.4750	0.8384	−0.3881	0.3262
e	$NHCOCH_3$	0	−65.25	1.2419	1.3290	1.4937	1.4742	0.8388	−0.3900	0.3267
f	H	0	70.76	1.2420	1.3287	1.4936	1.4751	0.8393	−0.3890	0.3240
g	F	0.006	−122.33	1.2433	1.3268	1.4945	1.4761	0.8368	−0.3850	0.3240
h	Cl	0.232	38.70	1.2433	1.3256	1.4956	1.4761	0.8355	−0.3828	0.3240
i	$CONH_2$	0.36	−14.67	1.2440	1.3248	1.4955	1.4765	0.8348	−0.3799	0.3251
j	$COOCH_3$	0.45	−255.49	1.2440	1.3247	1.4957	1.4765	0.8344	−0.3801	0.3252
k	$COOC_2H_5$	0.45	−273.69	1.2440	1.3249	1.4961	1.4764	0.8344	−0.3803	0.3253
l	$COCH_3$	0.502	−71.06	1.2438	1.3253	1.4951	1.4764	0.8352	−0.3815	0.3255
m	CF_3	0.54	−550.25	1.2451	1.3226	1.4981	1.4773	0.8313	−0.3754	0.3244
n	CN	0.66	201.05	1.2440	1.3246	1.4950	1.4766	0.8347	−0.3794	0.3249
o	NO_2	0.778	141.66	1.2459	1.3211	1.4983	1.4784	0.8295	−0.3711	0.3241

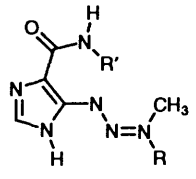
Table 2 MNDO calculated heats of formation of molecules and ions

Compound	Heat of formation /kJ mol^{-1}	Compound	Heat of formation /kJ mol^{-1}
H_2O	−255[a]	ArN=N–N(CH_3)CH_2OH (**2d**)	39
HCHO	−138[a]	ArN=N–NHCH_3 (**3d**)	240.9
NH_3	−27[a]	ArNH–N=NCH_3	241.2
H^+	1366[a]	ArN=N–N(CH_3)CH_2^+ (**4d**)	1027
H_3O^+	561[a]	ArN=N–N(CH_3)$CH_2OH_2^+$	802
$H_2C{=}OH^+$	651	ArN=N–NH(CH_3)CH_2OH^+	779
NH_4^+	165[a]	ArNH=N–N(CH_3)CH_2OH^+	756
OH^-	−33[a]	ArN=N–N(CH_3)CH_2O^-	20
		ArN=N–N(CH_3)$^-$	100

[a] Value given by J. J. P. Stewart.[18]

physiological half-lives (ranging from 6×10^5 s to 0.23 s). The N–CH_2OH bond lengths for all the hydroxymethyltriazenes (**2a–o**) were calculated by MNDO to be in the range 1.492–1.499 Å. Extension of our correlation for hydroxymethylamides to these hydroxymethyltriazenes thus predicts physiological half lives of under one second—too low for biological activity of their own. Additionally electron-withdrawing groups increase the NCH_2OH bond length and are therefore predicted to decrease the stability of the hydroxymethyltriazenes. In practice decomposition to the aniline is accelerated[6] by electron-donating groups but this is probably due to accelerated irreversible decomposition of the monomethyltriazene formed by the initial reversible loss of formaldehyde from the hydroxymethyltriazene.

Interestingly HMIC **5a**, the presumed first metabolite from the anti-tumour drug DTIC, **5b** has a predicted N–CH_2OH bond length of 1.497 Å but its isomer **6** in which the CH_2OH is transferred to the amido side-chain had a heat of formation only 3 kJ mol^{-1} greater but a calculated N–CH_2OH bond length of 1.471 Å indicating a much decreased lability to hydrolysis. In view of these results it seems likely that the compound claimed as HMIC from reaction[17] of the monomethyltriazene **5c** with formaldehyde is in fact its isomer **6**.



5;	R	R′
5a;	CH_2OH	H
5b;	CH_3	H
5c;	H	H
6;	H	CH_2OH

Modelling of Decomposition Pathways.—For each of the four possible decomposition pathways simple protonation and deprotonation steps were not considered in detail because of the difficulty of assessing the large changes in solvation energy involved. Each pathway was studied for 3-(hydroxymethyl)-3-methyl-1-(4-methylphenyl)triazene (**2d**) decomposing to 3-methyl-1-(4-methylphenyl)triazene (**3d**) and formaldehyde with an overall enthalpy change of 64 kJ mol^{-1}. A detailed study of the complete potential energy surfaces was not attempted.

The initial product from the concerted pathway (Scheme 4) is 1-methyl-3-(4-methylphenyl)triazene which was calculated to be 0.3 kJ mol^{-1} (Table 2) less stable than its tautomer 3-methyl-1-(4-methylphenyl)triazene. Location of the transition state between the hydroxymethyltriazene and the formaldehyde + monomethyltriazene products was not possible either by stretching the N–CH_2OH bond nor by widening the separation between the mid-points of the C–O and N=N bonds. The latter method is similar to that used to locate transition states in carbocyclic concerted reactions studied by *ab initio* calculations[19] but fails here since the lack of symmetry allows the C–O and N=N bonds to become non-parallel by rotation of the CH_2–OH group putting the OH distant from the nitrogens; increasing the separation of C–O and N=N bonds eventually leads to heterolytic cleavage of the N–CH_2OH bond.

Gradual reduction of the O–H • • • N distance did result in product formation (Fig. 3) and the transition state was located with a heat of formation of 307 kJ mol^{-1} (258 kJ mol^{-1} above the starting materials) by use of the 'saddle calculation', available in MOPAC.[20] The energy of this geometry was highly sensitive to a decrease in O–H • • • N distance but it was confirmed as a transition state by having only one significantly negative force constant. Thus although the energy change for

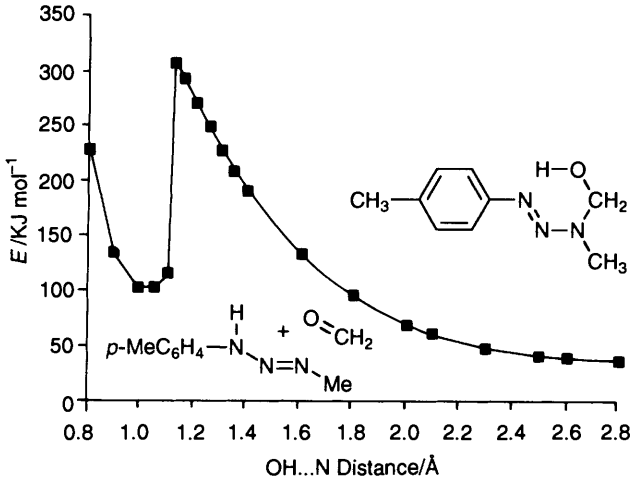


Fig. 3 MNDO calculated heats of formation for optimized geometries on the reaction pathway (gradual reduction of OH · · · N distance) for concerted decomposition of **2d**

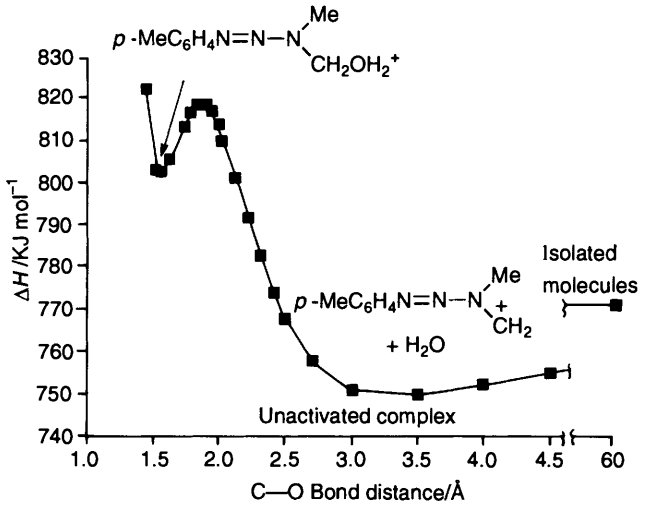


Fig. 4 MNDO calculated heats of formation for optimized geometries on the reaction pathway (gradual increase of NCH_2 · · · OH_2 distance) for cationic decomposition of **2d**

the concerted reaction is quite low at 64 kJ mol^{-1} its high activation energy makes this an unfavourable mechanism at 39 °C. The reaction is not forbidden on steric strain or orbital symmetry grounds and the eigenvalues of the occupied molecular orbitals change smoothly on passing through the transition state. It seems that the high energy results mainly from electrostatic repulsion between nitrogens 1 and 3 and a developing negative charge (−0.60 at the transition state) on the oxygen. We are currently investigating whether MNDO has a tendency to over-estimate the energy of such non-symmetrical concerted transition states.

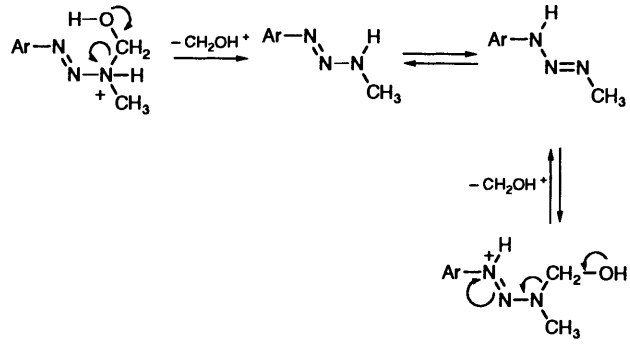
Starting from the hydroxymethyltriazene (**2d**) protonated on oxygen, loss of water proceeds (Fig. 4) with a low activation energy (16 kJ mol^{-1}) to give the iminium ion (**4**) with evolution of 30 kJ mol^{-1} (for production of isolated product molecules). Both the protonated triazene and the iminium ion have high energies of formation (Table 2) but protonation of the triazene has a heat of reaction of −603 kJ mol^{-1}—more favourable than protonation of an isolated water molecule to H_3O^+ at −550 kJ mol^{-1} and so it seems a reasonable mechanism in aqueous solution under acidic catalysis. This supports the idea of *in vivo* generation of the iminium ion which could react with nucleophiles leading, in biological systems, to alkylated biomolecules.

There is some experimental support for this—the OH of 3-(hydroxymethyl)-3-methyl-1-(3-pyridyl)triazenes may be replaced[9] by *S*-cysteinyl or alkoxy[21] groups under acidic conditions. On the other hand acid may be more likely to protonate nitrogen rather than oxygen as required for this mechanism.

We performed similar calculations on hydroxymethyltriazene protonated on nitrogen and determined that protonation on N(1) is thermodynamically favoured over protonation on N(3) or on oxygen (Table 2). The cationic route (generation of iminium ion) appears viable with the reasonably low energy gap between N- and O-protonation, especially since the gap would be reduced by correction of the known tendency of MNDO calculations to under-estimate the energetic disadvantage of loss of conjugation [which occurs on N(3)-protonation of the triazene].

Another possibility is S_N2 displacement of OH^- or H_2O by nucleophiles and, using arguments analogous to those used for the S_N1 (cationic) route, the latter appears reasonable under aqueous acidic conditions. However, competition between thiols and alcohols for reaction with acidified hydroxymethyltriazenes favours[21] the alcohol which would not be expected for an S_N2 mechanism. Being a three-component system the S_N2 process is also more difficult to model and we have not attempted calculations of activation energies to test its viability.

Loss of $[H_2C{=}OH]^+$ from the N(3)-protonated *N*-(hydroxymethyl)triazene would lead to monomethyltriazene (**3d**) (Scheme 6) but the calculated energy increase of 113 kJ mol^{-1}



Scheme 6

for the reaction makes it an unlikely decomposition mechanism compared to formation of water and iminium ion. This energy increase is associated with the high energy of protonated formaldehyde compared to the iminium ion, whose positive charge is extensively delocalised. Loss of $[H_2C{=}OH]^+$ from the N(1)-protonated *N*-(hydroxymethyl)triazene gives the tautomer of **3d** but is even less favoured energetically.

Deprotonation of the hydroxymethyltriazene and transfer of the proton to water involves a calculated enthalpy change of +797 kJ mol^{-1} but under basic conditions the proton may transfer to OH^- with a calculated enthalpy release of 241 kJ mol^{-1}. The resulting triazenylmethoxide anion may expel formaldehyde to give a triazenyl anion $[ArN{=}N{-}NCH_3]^-$. This decomposition was calculated to have an activation barrier of only 0.7 kJ mol^{-1} and released 71 kJ mol^{-1} (for production of the unactivated complex of products, Fig. 5) indicating that the triazenylmethoxide ion has such kinetic instability that it will not have real existence at room temperature.

The second-order concerted mechanism (Scheme 5) was studied for both water and ammonia as nucleophiles but no low-energy pathway for the postulated mechanism could be located. The only transition state identified started from the hydroxymethyltriazene in the conformation having OH *anti* to N(3) and hydrogen bonded to ammonia. Decrease of the ammonia hydrogen to N(1) distance brought about the desired

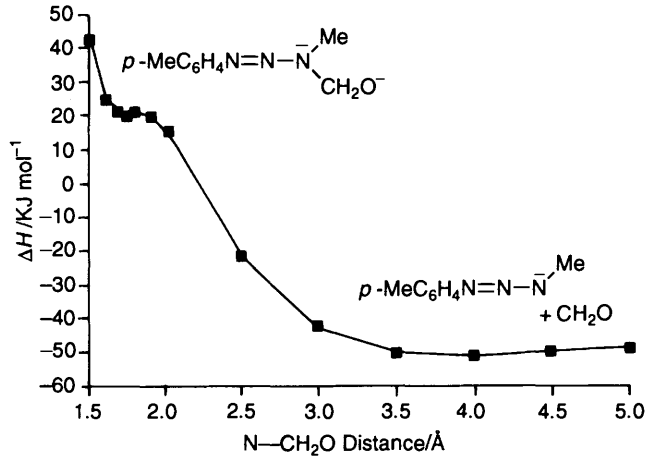


Fig. 5 MNDO calculated heats of formation for optimized geometries on the reaction pathway (gradual increase of N · · · CH_2O distance) for anionic decomposition of **2d**

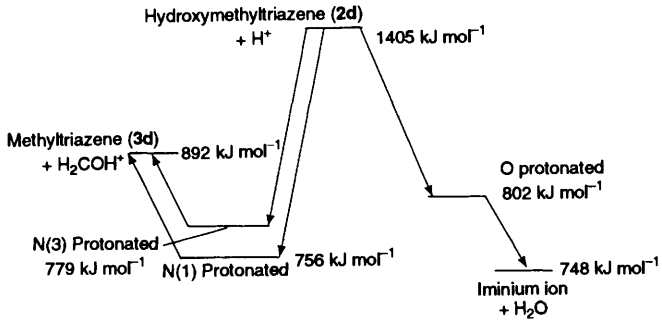


Fig. 6 Energy diagram (not to scale) for decomposition of the hydroxymethyltriazene (**2d**) under acidic conditions

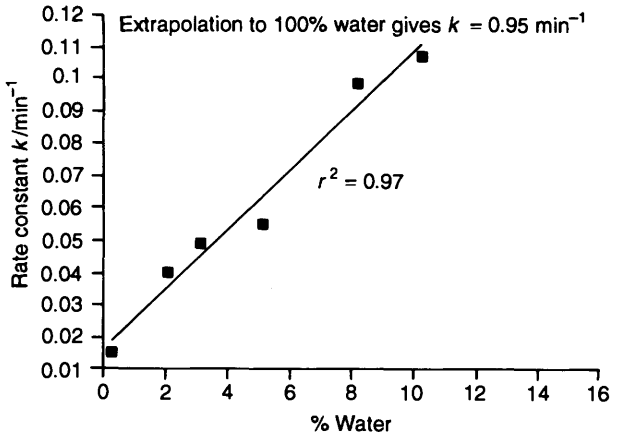


Fig. 7 Effect of variation of water concentration on the pseudo-first-order rate constant for hydrolysis of 3-(4-nitrophenyl)-3-methyl-3-(hydroxymethyl)triazene (**2o**) in methanol/acetonitrile (1:1)

reaction with an activation energy of 343 kJ mol^{-1}. This suggests that the proposed mechanism is unlikely compared to deprotonation by OH^- but we have not examined all the possibilities in this rather flexible system. A full investigation was not attempted since geometry specification in MOPAC of this sytem is very difficult and the results might not be conclusive since MNDO modelling of hydrogen bonds is poor.

In summary our calculations indicate that decomposition of hydroxymethyltriazenes is unlikely to occur by the concerted process or by loss of protonated formaldehyde from protonated triazene. Loss of OH^- from the hydroxymethyltriazene to give an iminium ion seems similarly unlikely because of the relatively high energy of both the hydroxide and iminium ions. Production of an iminium ion by loss of water from protonated triazene appears favourable under acidic catalysis, even though the required initial protonation on oxygen is disfavoured relative to protonation on nitrogen (Fig. 6). Base-catalysed deprotonation to a transient triazenylmethoxide ion which loses formaldehyde to give a monomethyltriazene *via* its anion seems to be a reasonable alternative, although this mechanism does not explain the observation[21] that primary and secondary, but not tertiary amines catalyse the decomposition of hydroxymethylpyridyltriazenes.

Solvolysis and Hydrolysis of Hydroxymethyltriazenes.—The solvolysis of four hydroxymethyltriazenes (**2j**, **2l**, **2n** and **2o**) in methanol/acetonitrile (1:1) was followed by HPLC and each decomposed rapidly ($t_{\frac{1}{2}}$ 27, 55, 75 and 23 min respectively at room temperature) to the monomethyltriazenes (**3j**, **l**, **n** and **o**). The pseudo-first-order rates give a curved Hammett plot suggesting that a different mechanism operates when a strongly electron-withdrawing group is attached. Although pyridyltriazenes have been studied similarly, we believe this is the first reported quantitative analysis of the medically used 1-(4-X-phenyl)-3-hydroxymethyltriazenes in the presence of their initial decomposition products.

As expected, each of the hydroxymethyltriazenes decomposed so rapidly in aqueous solution at pH 7.4 at room temperature that only monomethyltriazenes and anilines were detected on the first injection (about 1 min after mixing). The hydrolysis rate for lower water concentrations was studied for a methanol/acetonitrile solution of 1-(*p*-nitrophenyl)-3-(hydroxymethyl)-3-methyltriazene (**2o**) containing added phosphate buffer. A direct correlation between the pseudo-first-order rates of hydrolysis and water concentration was established (see Fig. 7) and extrapolation to 100% water gives a half-life of 43 s at room temperature. This is consistent with either a rate-limiting protonation step by water in the cationic route or a rate-limiting deprotonation step by water in the anionic route. Attempts were made to repeat this half-life determination using the other three triazenes but peak resolution deteriorated so badly in the presence of water that no reliable results were obtained. However, the relative stabilities in methanol/acetonitrile and our theoretical studies indicate that none of the other triazenes is likely to be significantly more stable than the nitro derivative. The determined half-life is longer than expected, compared with < 1 s predicted for physiological conditions from the studies on hydroxymethylamides. It therefore seems that the correlation established for *N*-(hydroxymethyl)amides gives less precise agreement with experiment when applied to decomposition of the more labile triazenes. This is not surprising given that both the experimental evidence[15] and our calculations suggest that more than one reaction mechanism is operative across this range of compounds.

In conclusion *N*-(hydroxymethyl)triazenes are much too easily hydrolysed to be antitumour agents in their own right. Even if confined to lipophilic sites their half-lives are likely to be less than a few minutes. The possibility that they react with nucleophiles to give more stable derivatives which could be hydrolysed to *N*-(hydroxymethyl)triazenes after transportation to the active site remains, however.

Experimental

Calculation Methods.—Triazene structures were optimized using the semi-empirical-MNDO method[22] by means of the MOPAC program package[20] on a VAX 11/750 and subsequently on a DEC 5830 computer at the University College of Wales, Aberystwyth. Only the *trans*-isomer about the –N=N– bond, which is clearly the sterically preferred one, was

considered. It has been shown [7] that a planar conformation for the main skeletal structure, –Ph–N=N–N<, of dimethylaryltriazenes is the most stable and this portion was constrained to be planar in all our calculations except for the concerted mechanisms and for N(3) protonation in which the carbons attached to N(3) were allowed any orientation. In addition the benzenoid CCC and CCH bond angles were fixed at 120°; the C=C bond lengths were fixed at 1.407 Å, the MNDO calculated value [18] for benzene; the four benzenoid C–H bonds were optimized while constrained to be of equal length; and hydrogen atoms in CH_3 groups were considered to be equivalent.

In the study of the decomposition through the anionic route, the $N–CH_2O^-$ bond length was gradually increased from its equilibrium value for the anion to that for complete dissociation and the structure re-optimized for each chosen $N–CH_2OH$ bond length with respect to all the other parameters. The cationic route was similarly studied, except the C–O bond was gradually stretched instead of the $N–CH_2O^-$ bond; the starting conformation was obtained by addition of a proton to the most stable conformation of **2d** followed by an energy minimization. The concerted mechanisms were studied by stretching the $N–CH_2OH$ bond, by bringing the products closer together and by the methods outlined in the discussion.

Determination of the Half-lives of N-*Hydroxymethyltriazenes by HPLC.*—An LDC/Milton Roy Constametric 111 chromatograph fitted with a UV detector (254 nm) was used to assay the changing composition of triazene solutions. Filtered samples of the triazene solution (4–5 10^{-4} mol dm^{-3}) in acetonitrile/methanol (1:1; HPLC grade) containing 0–10% Na/K-Phosphate buffer (0.06 mol dm^{-3}; pH 7.4) were injected at suitable intervals onto a 25 cm C_{18} reverse phase column of 5 μm particles (Merck 100RP) and eluted with acetonitrile/methanol (1:1) at 0.4 cm^3 min^{-1}. Detector readings were converted into relative concentrations of the various components using their absorbances at 254 nm measured for standard solutions in acetonitrile/methanol (1:1). Pseudo-first-order rate constants were obtained from the gradients of plots of ln(mole fraction of triazene) against time.

Synthesis of Triazenes.—**WARNING**: Alkyltriazenes are cancer causing agents. Hydroxymethyltriazenes (**2j**, **l**, **n**, **o**) were synthesised [6] from the corresponding diazonium salt, methylamine and formaldehyde and purified by recrystallisation. Monomethyltriazenes (**3j**, **l**, **n**, **o**) were synthesised [23] by adding a solution of the diazonium salt to aqueous methylamine and purified by recrystallisation. The identity of each was confirmed by its melting point and its ^1H NMR spectrum; purity was confirmed using TLC and HPLC.

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