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Effect of Pressure on the Reaction between 3-Methyl-1-*p*-tolyl-triazene and Benzoic Acid; A Kinetic Study

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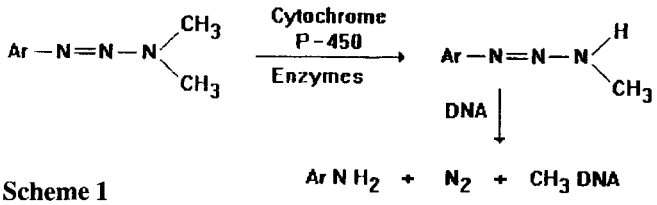
Abstract. Rates of reaction between 3-methyl-1*p*-tolytriazene and benzoic acid were measured with variation of pressure in chloroform and acetonitrile. Activation volumes were found to be −15 and −4 $cm^3\ mol^{-1}$, respectively. The reaction mechanism is discussed in the context of these values.

3-Alkyl-1-aryl triazenes are considered as antitumours [1]. Their pharmacological activity has been attributed to the diazo compounds resulting from the rapid dissociation of the triazenes under physiological conditions [2]. Toxicities, carcinogenic characteristics, the anticonvulsant and antileukemic activities of some triazenes have been studied [3–5]. The cytotoxic monomethyltriazenes (**1**) are known as alkylating agents, capable of alkylating DNA and RNA. (**1**) is an intermediate in the metabolic oxidation of dimethyltriazenes by cytochrome P-450 enzymes [6, 7] (scheme 1). Triazenes (**1**) were reported in treating malignant melanoma [8].



Scheme 1

Triazenes are known to decompose in a variety of solvents under acidic conditions [9, 10]. In principle the three nitrogen atoms can be protonated. Although quantum chemical calculations indicate the same probability of protonation at N-1 and N-3 [11], other authors showed that protonation at N-1 is preferred [12].

$$\overset{1\ \ 2\ \ 3}{\text{Ar-N=N-NH(CH}_3\text{)}} \qquad (1)$$

Previous studies of a wide variety of triazenes showed that protonation occurs at N-3 with subsequent or simultaneous splitting of N-2 and N-3 bond [13]. In literature records there is no unequivocal conformity in view of the mechanistic pathway of the decomposition of triazenes in acidic medium. Some papers show that the decomposition is subjected to general acid catalysis and mechanistically is a bimolecular one denoted $A\text{-}S_E2$, which represent an electrophilic substitution at nitrogen atom [14]. While others prefer the idea of specific catalysis by the mechanism of A1 type, which involves a pre-equilibrium protonation with spontaneous decomposition of the protonated triazene in a rate-determining step [15].

In the work presented here, the effect of pressure on the rate of reaction between 3-methyl-1-*p*-tolytriazene and benzoic acid has been studied in order to obtain more information on the reaction mechanism where mechanistic inferences may be confidently drawn from the volume of activation parameters [16].

Experimental

Materials: 3-Methyl-1-*p*-toyltriazene was prepared according to the reported procedure [17], purified by sublimation *in vacuo*, *m.p.* 80.5–81°C. Chloroform (BDH) was shaken several times with water, then dried over anhydrous magnesium sulphate and then distilled. Acetonitrile (BDH) was dried over anhydrous magnesium sulphate then distilled. Benzoic acid was recrystallized from boiling water and dried.

Products analysis: The reaction products were determined qualitatively and quantitatively by g.l.c. and it was established that the reactions was clean [14].

Kinetic Procedure: The kinetic measurements were completed under pseudo-first order conditions by keeping a large excess of benzoic acid over the triazene. The initial concentration of the later was in the order of 10^{-5} M, while the acid concentrations were 3.80×10^{-3} M and 1.84×10^{-2} M in chloroform and acetonitrile, respectively. Mixtures of reagents in the concentrations specified above were placed in a 1cm-path length cell (spectrocil) so as to fill it completely. A stopper having an open top connecting the cell by a capillary was then inserted, filled to above the capillary with the reaction mixture, and a quantity of mercury was inserted into the stopper reservoir. In this way pressure could be transmitted without damage to cell while the reaction solution remained isolated from the surrounding medium. The apparatus was then placed in a thermostatted stainless steel pressure vessel equipped with two sapphire windows and filled with hexane as a pressure-transmitting medium. The vessel fitted into the spectrophotometer so that the beam passed through the windows and the cuvette within. After attaching the threaded closure the pressure was applied by means of a hand pump delivering hexane to the top of the pressure vessel (Fig.1). Progress of reaction was then monitored at 340 nm by observing disappearance of the triazene at 29.8 ± 0.1°C.

Pseudo-first order rate constants were calculated using the Guggenheim method [18]. The slope values for the effect of pressure on rate were calculated by a least-squares method. The correlation coefficient in both solvents is 0.9964. Duplicate kinetic runs showed that the rates were reproducible within ± 2%, in chloroform and 1% in acetonitrile.

Results and Discussion

Rates of decomposition of 3-methyl-1-p-tolyltriazene with benzoic acid in solvents chloroform and acetonitrile with pressure variation from 1 bar to 1 000 bar and up to 1 200 bar, respectively, are presented in tables 1 and 2. The data enable values for volumes of activation to be calculated from equation (**1**). A plot of In $k_{rel.}$ against P was found to be linear over the experimental range (Fig. 2).

$$\Delta V^* = -RT\, \mathrm{d}\ln k/\mathrm{d}p \qquad (1)$$

The volumes of activation were –15 and – 4 $cm^3\ mol^{-1}$ in $CHCl_3$ and CH_3CN, respectively. Volumes of activation are fairly negative in both solvents and remarkably small in acetonitrile. The observed values may be accounted for as follows: The proposed mechanisms can be represented by equations A and B [14, 15].

$$R + HA \xrightarrow{\kappa} P \qquad (A)$$

$$R + H^+ \rightleftharpoons RH^+ \longrightarrow P \qquad (B)$$

ΔV^* Values are more characteristic of a concerted process [14], where a slow proton transfer is believed to be

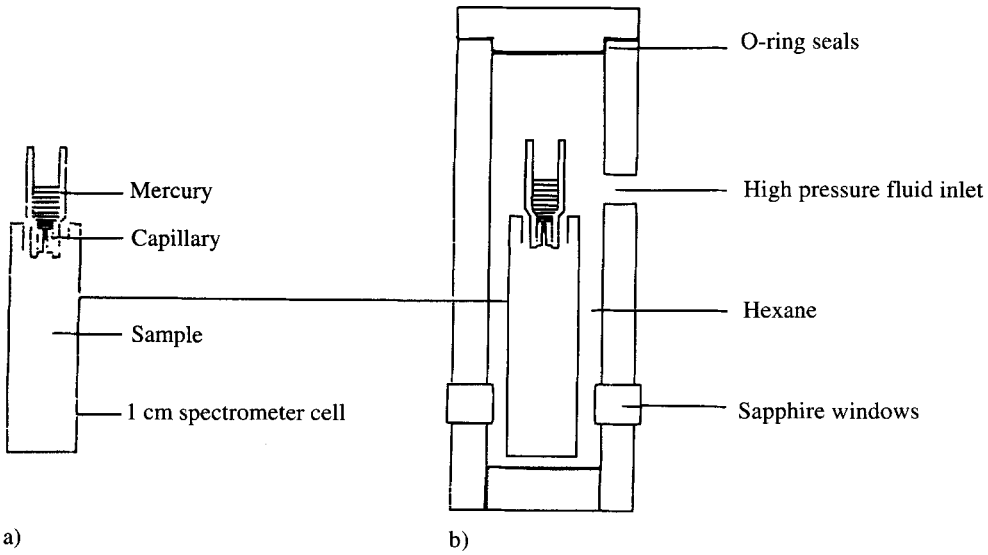


Fig. 1 Schematic diagram for the high pressure equipment: a) pressure spectrophotometer cell; b) the pressure vessel.

Table 1 Pseudo-first order rate constants of 3-methyl-1-*p*-tolyltriazene with benzoic acid in chloroform at 29.8 °C

p/bar	av. $k_1 \times 10^4$ s^{-1}	SD % [a])	$k_{1\,rel.}$
1	2.510	2	1
210	2.900	2	1.155
300	3.050	2	1.215
420	3.370	2	1.343
600	3.540	1	1.410
700	3.880	4	1.546
820	4.160	2.5	1.657
1000	4.700	2	1.872

[a]) SD: Standard deviation.

Table 2 Pseudo-first order constants of 3-methyl-1-*p*-tolyltriazene with benoic acid in acetonitrile at 29.8 °C

p/bar	av. $k_1 \times 10^4$ s^{-1}	SD % [a])	$K_{1\,rel.}$
1	2.515	2	1
400	2.660	3	1.058
620	2.795	2	1.183
700	2.835	1.5	1.127
980	2.950	1	1.173
1200	3.080	1.5	1.225

[a]) SD: Standard deviation

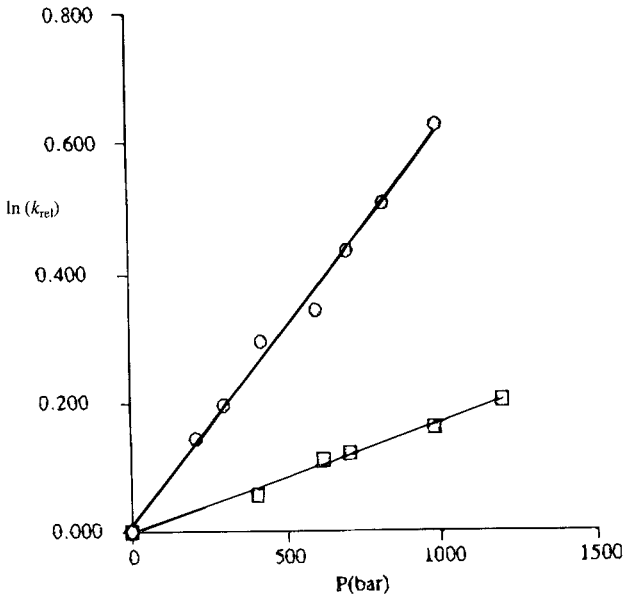


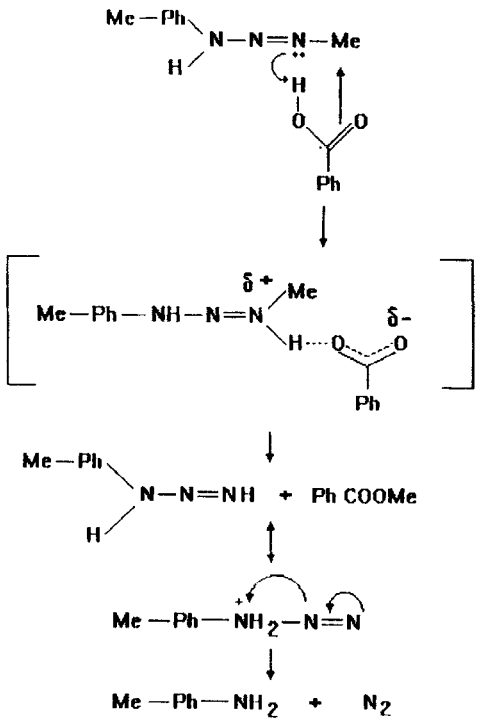
Fig. 2 Effect of pressure on rates of decomposition of 3-methyl-1-*p*-tolyltriazene; o = in chloroform, □ = in acetonitrile

involved in the rate determining step (eq. A). The modest pressure acceleration in acetonitrile is probably a measure of the element of electrostriction due to the formation of the protonated triazene. The electrostrictive volume change ΔV_e, given by Drud-Nernst equation (2) [19], depends upon the dielectric constant function Φ, which would be greater for a less polar solvent.

$$\Delta V_e = L\,q^2/2\gamma\phi \qquad (2)$$

A decrease of pk_A values by 0.2–0.4 units per kbar applied pressure will increase the dissociation of acids, and the effect of pressure on ionization will be even greater in less polar solvents [16]. The volumes of activation are similar to that reported for diphenyldiazomethane decomposition by carboxylic acids [20] ($\Delta V^* = -13$ cm^3 mol^{-1}). The small volumes of activation suggest an early transition state with little relaxation of solvation. The volume of activation in the less polar solvent is more negative, and the difference (11 cm^3 mol^{-1}) may reflect a contribution from pressure favored increased solvation of the transition state.

The results are consistent with a mechanism involving a concerted electrophilic substitution at the nitrogen in which N–H bond making and N–C bond breaking are synchronous, where the proton transfer and the expulsion of the alkyl cation occure in the rate determining step [14, 21] (scheme 2). The ΔV^* values obtained do not support the mechanism proposed in equation (B), where the protonation is in rapid equilibrium and the protonated triazene decomposition to products is the rate limiting step [15], in which the observed volume of activation would be a composite quantity (eq. 3) [22].



Scheme 2

$$\Delta V^*_{obs} = \Delta V_1 + \Delta V_2^* \qquad (3)$$

ΔV_1 is the volume change for the pre-equilibrium proton transfer, and it is assumed that this parameter is quite small, perhaps ± 0–2 $cm^3\ mol^{-1}$. But in the slow step a bond is broken and charge is usually dispersed, making ΔV_2^* positive. Thus if the reaction occurs via this mechanism, ΔV^*_{obs} values are expected to be positive in resemblance to acetic acid catalyzed hydrolysis [22] (ΔV^* =+ 13 $cm^3\ mol^{-1}$) and benzoic anhydride hydrolysis [23] (ΔV^* =+7 $cm^3\ mol^{-1}$), a fact which has not been observed in this work.

In conclusion, the magnitude of ΔV^* observed can be interpreted as a result of a composite value for the protonation being associative and decomposition of the formed complex being dissociative. The results are in agreement with ionic character of an early transition state. This is in accordance to the A-S_E2 mechanism and lend support to it.

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