

DIAZO COUPLING AT NITROGEN. VII.*

PROTOLYSIS OF SOME *para*-SUBSTITUTED 1-PHENYL-3-METHYLTRIAZENE DERIVATIVES

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Kinetics of protolysis of 1-phenyl-3-methyltriazene and some of its *para*-substituted derivatives have been studied in acid aqueous medium. It has been found, that the reaction is pseudomonomolecular, first order, with antecedent acid-base equilibrium, with activation energy 10.5 kcal/mol. The reaction rate is practically independent of the ionic strength of medium. The rate constants have been satisfactorily correlated with the Hammett σ constants. On the basis of the kinetic data and the protolysis products the reaction mechanism has been suggested.

In our foregoing papers we focused our attention on the formation and synthesis of 1-aryl-3-methyltriazene compounds which are important in the study of chemical carcinogenicity of 1-aryl-3,3-dimethyltriazene compounds¹⁻⁴. They are the presumed intermediates in the metabolism of 1-aryl-3,3-dimethyltriazenes which belong not only to cancerogens⁵ but also to cancerostatics^{6,7}. Within our studies of these compounds⁸⁻¹³ we devoted our attention also to the decomposition of 1-phenyl-3-methyltriazene derivatives in acid aqueous medium. This problem was dealt with by Dimroth^{14,15} as early as at the beginning of this century. He found that even the introduction of carbon dioxide into the solutions of the abovementioned compounds causes their decomposition, aniline and one nitrogen molecule being formed quantitatively. The decomposition took the same course in mineral acids, where the protolysis products involve the methylesters of these acids, too. Recently Preussmann and coworkers¹⁶ described a probable mechanism of the action of 1-aryl-3,3-dimethyltriazenes in living organisms. He found that they undergo enzymatic oxidation with N-demethylation to give 1-aryl-3-methyltriazenes which in turn undergo protolysis by the mechanism described by Dimroth¹⁷.

Therefore, we devoted this work to protolysis of 1-aryl-3-methyltriazene and verified the mechanism proposed not only by identification of the reaction products but also by kinetic study.

EXPERIMENTAL

1-Phenyl-3-methyltriazene and its *para*-substituted derivatives were synthesized, on the one hand, by the method described^{6,7} and, on the other hand, by our previous method¹. 2-Hydroxynaphthalene-3,6-disulfonic acid, 4-ethoxyaniline, aniline, 4-chloroaniline, 4-bromoaniline and dioxane

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(Lachema) were of c.p. purity grade. The other chemicals used were of p.a. and c.p. purity grades (Lachema, Merck). Britton–Robinson buffer solutions with 50% dioxane and precisely adjusted ionic strength were used¹⁸. Gasometric analyses were carried out with the use of usual apparatus for eudiometric determination of aromatic diazo compounds¹⁹. Photometric analyses were carried out with the use of a Spekkol spectrophotometer (Zeiss, Jena). pH was measured by means of a Precision pH-Meter (Radelkis, Budapest) with a glass and a saturated calomel electrodes (Labora). For kinetic measurements of the nitrogen gas evolved we used the manometric apparatus described by Kinley and Benbrook^{20,21} and modified by us for the possibility of a continuous record of the course of analysis²². The protolysis products were identified with the use of a gas chromatograph (Carlo Erba), Chromosorb W silaminated with 10% Versamide 900 at 198°C and Synachrom E5 at 144°C being used for separation of the aromatic amines and identification of methanol, respectively.

Kinetic Measurements of Protolysis

The thermostated reaction vessel of the manometric apparatus was charged with 16 ml Britton–Robinson buffer solution having the requested pH and ionic strength and 8 ml dioxane, and closed. After starting the recorder EZ 2, 1 ml 0.4M standard stock solution of the respective 1-aryl-3-methyltriazene compound was injected by means of a syringe through the rubber stopper ("penicilline" stopper). pH of the reaction solution was measured after finishing the reaction, and the volumes of the measured nitrogen gas evolved on protolysis were read from the record for definite time intervals; the constants were computed from the equation

$$k_1 = (1/t) 2.303 \log (v_\infty / (v_\infty - v_t)),$$

where k_1 is the first-order rate constant and v_∞ and v_t (ml) are the volumes of the nitrogen gas evolved at the end of the reaction and at a time t , respectively (under constant conditions).

Identification of Protolysis (Hydrolysis) Products of 1-Phenyl-3-methyltriazene

0.01 mol 1-phenyl-3-methyltriazene was mixed with 100 ml water and left to stand at the room temperature while any nitrogen gas was evolved. Then the hydrolysis products were extracted in 50 ml ether and the extract was analyzed by gas chromatography.

Gasometric determination of 1-phenyl-3-methyltriazenes. The method was analogous to usual gasometric analysis of diazo compounds. 0.001 mol of the respective triazene compound dissolved in 5 ml dioxane was added to 10 ml 1N-H₂SO₄ and 50 ml water. The nitrogen gas evolved was collected in the gasometric burette and its volume recalculated for normal conditions.

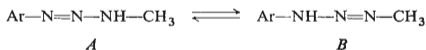
Determination of arenediazonium salts in protolysis products of 1-phenyl-3-methyltriazenes. Three model compounds were chosen for this experiment, viz. 1-(4'-ethoxyphenyl)-3-methyltriazene, 1-phenyl-3-methyltriazene and 1-(4'-bromophenyl)-3-methyltriazene. 0.01 mol triazene was placed in 50 ml calibrated flask and 12 ml 2.5M-HCl was added. After the end of nitrogen gas evolution water was added to make the volume 50 ml. From the mixture obtained three samples (0.5, 1.0 and 2.0 ml) were withdrawn by means of a pipette and added each to 40 ml 0.2M borax and 4.5 ml 0.01M 2-hydroxynaphthalene-3,6-disulfonic acid in a 50 ml calibrated flask. After adjusting the volume with 0.2M borax, the extinction of the solutions was measured at the λ_{\max} of the respective azo dyestuffs. The percentage of the azo compound formed was calculated from calibration lines for each case.

RESULTS AND DISCUSSION

The following reaction products were found after protolysis of 1-aryl-3-methyltriazenes: the respective substituted aniline, nitrogen gas, methanol and, in the case of the three studied compounds, also arenediazonium ion and methylamine. Hence we presume the protolysis to take the following course (Eqs (A) and (B)), the process



(B) taking place to small extent and being dependent on the nature of *para*-substituent in aryl. We found that the contribution of the reaction (B) was 1.06%, 0.091% and 1.52% in the cases of phenyl-, 4-bromophenyl- and 4-ethoxyphenyl derivatives respectively. It can be presumed that this fact is connected with the tautomerism $A \rightleftharpoons B$ of the 1-aryl-3-methyltriazenes compounds, the forms A and B giving arenediazonium ion (Eq. (B)) and aromatic amine (Eq. (A)), respectively.



It is rather surprising that practically only the form B makes itself felt during protolysis. It does not agree with *e.g.* the behaviour during the reactions of 1-aryl-3-methyltriazenes with phenyl cyanate^{14,15}, during acetylation^{14,15} and diazo coupling at nitrogen atom. Hence it can be considered that the thermodynamically more stable system has preference under given conditions (decomposition into the substituted anilines and nitrogen gas; the aliphatic fragment takes care of itself by rapid coordination with a nucleophilic component).

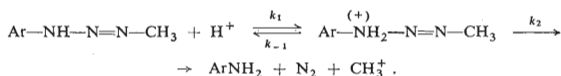
On the basis of kinetic measurements we arrived at a conclusion that the protolysis consists of protonation of triazene and decomposition of the protonated form

TABLE I

Dependence of ($\log k + \text{pH}$) of Protolysis of *p*-Substituted 1-Phenyl-3-methyltriazenes on σ Constants at 25°C and Ionic Strength 0.500

Substituent	$\log k + \text{pH}$	σ	Substituent	$\log k + \text{pH}$	σ
C ₂ H ₅ O	6.19	-0.25	Br	5.02	0.23
CH ₃	5.92	-0.17	I	4.77	0.27
H	6.53	0.00	CH ₃ OCO	4.47	0.45
Cl	5.17	0.23	NO ₂	3.10	0.78

into the aromatic amine, nitrogen gas and methyl cation which reacts rapidly with the nucleophilic components of the medium used:



The proper protolysis is anteceded by an acid-base equilibrium, k_1 being much larger than k_2 . The protolysis rate constant can then be expressed by Eq. (1). This relation

$$k = k_1 k_2 [\text{H}^+] / k_{-1} \quad (1)$$

shows the dependence on hydroxonium ion concentration which is represented graphically for 1-phenyl-3-methyltriazenes in Fig. 1 (the rate constants k are given in min^{-1}). In a certain range of hydroxonium ion concentrations the pH dependence of $\log k$ is linear with the slope equal to unity, which makes it possible (Eq. (1)) to calculate the expression $\log k_2 + pK_a$ and use it for correlation with the Hammett σ constants. The protolysis rate decreases with increasing σ value (Table I) which indicates that *para*-substituents have a greater influence on the equilibrium (k_1/k_{-1}) than on the proper protolysis (k_2). It is interesting that the unsubstituted compound does not fit the correlation, the respective protolysis rate being the highest among the derivatives studied. The reaction constant ρ has the value of -2.85 .

From the results of the kinetic measurements it follows that the protolysis of 1-aryl-3-methyltriazenes compounds is a first-order, pseudomonomolecular reaction, and it is strongly affected by hydroxonium ion concentration, being practically independent of ionic strength. We found the following dependence at pH 7.30 and 25°C:

μ	0.005	0.020	0.073	0.100	0.500	1.000
k, min^{-1}	0.145	0.163	0.178	0.173	0.148	0.161

The influence of temperature on the protolysis rate was studied with all the derivatives of 1-phenyl-3-methyltriazenes and the values obtained fulfilled the Arrhenius relation very well. The activation energy calculated by the least squares method has a value of 10.5 kcal/mol. We give for illustration the temperature dependence of k of the protolysis of the parent substance (pH 7.68, μ 0.500):

$t, ^\circ\text{C}$	25	35	45	55
k, min^{-1}	0.086	0.168	0.252	0.458

In conclusion it is to be stated that a more precise evaluation of the mechanism of the reaction under investigation and of the influence of substituents on the proto-

lysis rate would necessitate to know the equilibrium constant of the antecedent acid-base equilibrium, which is, however, not measurable because of great lability of the protonated forms.

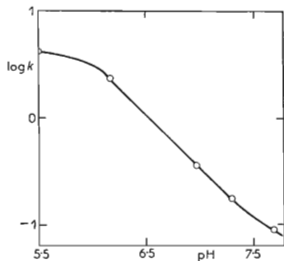


FIG. 1

pH Dependence of $\log k$ of Protolysis of 1-Phenyl-3-methyltriazenes at 25°C and Ionic Strength 0.500

We see the importance of the present work first of all in the obtained information about the conditions of the protolysis, which is connected with formation of methylation, which undoubtedly will play an important role during N-alkylation of biopolymers of the type of nucleic acids and will thus take part in the carcinogenicity of these compounds²³. We are, therefore, going to deal with the problems of N-alkylating action of 1-phenyl-3-methyltriazenes and its *p*-substituted derivatives in some further works.

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