

## INVESTIGATION OF SOME OF THE KINETIC PARAMETERS OF THE HYDROLYSIS OF N-ARYLMALEAMIC ACIDS

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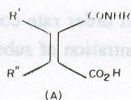
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The hydrolysis of seven substituted N-arylmaleamic acids in acidic medium has been investigated. The reaction follows typical first order kinetics. The rate depends on concentration of substrate and on the basicity of the leaving group. The rate was inversely proportional to the pH of the solution. A free energy relationship has been obtained when  $\log k/k_0$  was plotted against substituted constants ( $\sigma^*$ ).

**Key words:** Kinetics of substituted maleamic acids, Free energy relationship.

### INTRODUCTION

Hydrolysis of amides has been studied quite extensively by various workers, who failed to advance a general and unambiguous mechanism [1-8]. However, two independent investigators Bender [9] and Bruylants [10] have pointed out that carboxylic group adjacent to an amide group increased its rate of hydrolysis. Moreover, Kirby and Lancaster [11] observed that the efficiency of intramolecular catalysis of amide hydrolysis by the undissociated carboxylic group of the N-methylmaleamic system (A), (R = Me, R = alkyl, R = H) was very sensitive to the size of the alkyl groups, R, and increased with increasing size of the substituent.



The corresponding half amide from dimethylmaleamic acid (R', R'' = Me) was found to be even more reactive. Similar findings were reported in later studies on N-substituted maleamic acids derived from a variety of aliphatic amines [12, 13]. Even effect of basicity of leaving group on the hydrolysis of aryl substituted maleamic acids (R', R'' = H; R = 4-NO<sub>2</sub>, 3-NO<sub>2</sub>, 4-C1 and 4-OCH<sub>3</sub>) has been reported [14]. Acid dissociation constants of some maleamic acids have been studied as well [15].

In view of the importance of such a work in understanding the mechanism of enzymic hydrolysis in proteins [16-18] in which we are currently involved, we have reinvestigated some of the earlier observations using procedure outlined by Kluger and Lam [14]. In the present investigations the effects of pH and concentration of substrate on the

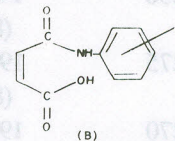
rate constants of hydrolysis of seven aryl substituted maleamic acids (R', R'' = H; R = H, 2-OCH<sub>3</sub>, 2-C1, 3-C1, 3-CH<sub>3</sub>, 4-CH<sub>3</sub> and 4-Br) have been discussed.

### EXPERIMENTAL

All melting points were determined on Kofler block and the chemical used were of the analytical grade. Spectroscopic determination were made on PYE-UNICAM SP8-400 Ultraviolet Spectrophotometer and pH adjustments were monitored on the CORNING-EEL model-5 pH-meter.

**General method for the preparation of N-arylmaleamic acids.** *N-(m-Methyl)-phenylmaleamic acid:* A solution of *m*-toluidine (11.8g; 0.11 mole) in isopropyl ether (25ml) was added dropwise at 20° to the stirred solution of maleic anhydride (9.8g; 0.10 mole) in isopropyl ether (100ml) over a period of 30 minutes. The reaction mixture was further stirred for about half an hour. The crystalline solid separated out was collected on a Buchner funnel and washed with isopropyl ether (3 x 20ml) to furnish the product, 8.12g (yield 79.0%); which was recrystallised from ethanol, m.p. 163-164°.

All the other N-arylmaleamic acids (B) were prepared by the same procedure as described above.



I. R = H; II. R = 2 - OCH<sub>3</sub>; III. R = 2 - C1; IV. R = 3 - C1; V. R = 4 - Br  
VI. R = 4 - CH<sub>3</sub>; VII. R = 3 - CH<sub>3</sub>

**Kinetic Procedure:** The required concentrations of different N-arylmaleamic acids were prepared in distilled water using appropriate amount of buffering agents. Buffers of pH-1 and 2.1 were prepared from HCl, while that of pH-3.5 and 4.1 from HCl/CH<sub>3</sub>CO<sub>2</sub>Na. The ionic strength of

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0.5 $\mu$  was maintained with potassium chloride. The hydrolysis of substituted N-arylmaleamic acids was conducted in the thermostated sample holder at  $25 \pm 0.5^\circ\text{C}$ , followed by monitoring the decrease in absorbance of amide (B) with passage of time at various wavelengths ( $\lambda_{\text{max}}$ ) as given in Table 1.

In this connection 5-25  $\mu\text{l}$  of the required maleamic acid solution (0.0125-0.625M) in dioxane was taken in the quartz cell (10 mm) and buffer solution was added to make up a total volume of 3 ml. The values of absorbance ( $A_t$ ) were recorded after regular intervals, usually of 5 minutes and absorbance ( $A_\infty$ ) of the solution was recorded after 24 hours. Thus decrease in the absorbance of the respective amide band of the maleamic acid was noted at each interval of time.

When  $\log(A_t - A_\infty)$  versus (t) were plotted, straight lines were obtained. The slopes when multiplied by 2.303 afforded first order rate constants  $k \text{ min}^{-1}$ , which when divided by 60 gave rate constants  $k \text{ sec}^{-1}$ .

The measurements for the effects of change of concentration of the substance, maleamic acid, were observed at pH-1.

## RESULTS AND DISCUSSION

Trial and error plots of the rate data for the runs with all the maleamic acids at different concentration (ranging from 0.0125 to  $6.25 \times 10^{-2}\text{M}$ ) indicate that the first order rate constant,  $k_{\text{obs}}$ , increases with increase in the concentration of the substance and reaches a limiting value at about  $6.25 \times 10^{-2}\text{M}$ . Thus  $k_{\text{obs}}$  depends upon the concentration of

the substance particularly below  $6.25 \times 10^{-2}\text{M}$ . The results have been shown in Fig. 1.

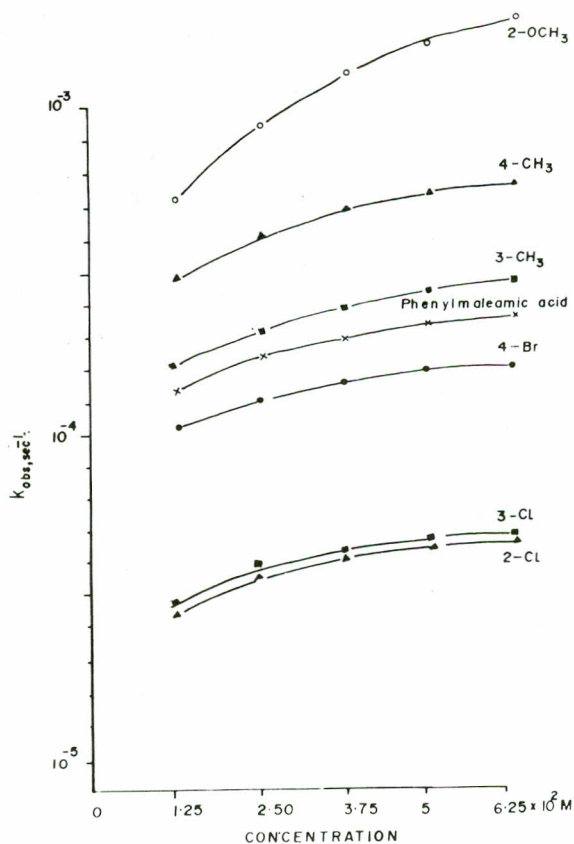


Fig. 1. Dependence of first order rate constants ( $k_{\text{obs}}$ ) for hydrolysis of compounds (I-VII), on concentration of substrate.

Table 1. Substituted N-arylmaleamic acids.

Compound	$\lambda_{\text{max}}$ , nm	m.p. $^\circ\text{C}$ (Yield %)	Formula	Calculated/(Found)			
				% C	% H	% N	% Hal
I	264	205-207* (89.9)	—	—	—	—	—
II	230	145-147 (88.3)	$\text{C}_{11}\text{N}_2\text{NO}_4$	59.73 (59.80)	4.98 (5.06)	6.33 (6.27)	—
III	275	190-191 (84.0)	$\text{C}_{10}\text{H}_9\text{ClNO}_3$	52.98 (52.88)	3.97 (3.78)	6.18 (6.34)	15.67; Cl (15.81)
IV	270	193-194 (90.4)	$\text{C}_{10}\text{H}_9\text{ClNO}_3$	52.98 (52.74)	3.97 (4.13)	6.18 (6.02)	15.67; Cl (15.49)
V	284	196-199 (94.0)	$\text{C}_{10}\text{H}_9\text{BrNO}_3$	44.44 (44.63)	3.33 (3.48)	5.19 (5.37)	29.26; Br (29.12)
VI	300	189-192 (84.7)	$\text{C}_{11}\text{H}_{12}\text{NO}_3$	64.08 (64.25)	5.82 (5.69)	6.80 (6.71)	—
VII	296	163-164 (79.0)	$\text{C}_{11}\text{H}_{12}\text{NO}_3$	64.08 (64.31)	5.82 (5.74)	6.80 (6.92)	—

\*Ref. (14) gives m.p.  $206^\circ\text{C}$ .

The plots of  $\log (A_t - A_\infty)$  versus  $(t)$  gave straight lines in all cases and  $k_{obs}$  were also calculated from the slope.

The dependence of the observed first order rate constants for the hydrolysis of various maleamic acids on the solution acidity (pH) has been presented in Fig. 2. It is

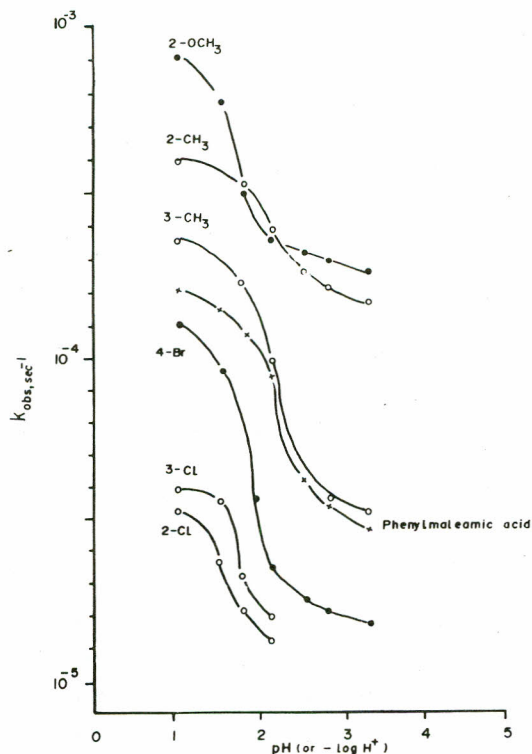


Fig. 2. Dependence of first order rate constants ( $k_{obs}$ ) for hydrolysis of *N*-substituted arylmaleamic acids on solution acidity at  $25 \pm 0.5^\circ$

quite obvious that the rate of all compounds showed a decrease with increase in pH. This is suggestive of the increasing tendency for dissociation of the carboxyl moiety with increasing pH, and with consequent decrease in the hydrolysis of the amide group. Moreover, it may be noted that compounds with the most basic amine as its leaving group, gave the highest  $k_{obs}$ .

Thus at pH 1-3.25 arylmaleamic acids having electron donating groups ( $\text{CH}_3$ ;  $\text{OCH}_3$ ) showed higher  $k_{obs}$  values than those having electron withdrawing groups (Cl; Br). This indicates that the electron donating groups probably make the reaction site "electron rich" suitable for attack by the "hydronium ion". A linear relationship was observed when rate constants were plotted against the basicity ( $\text{pK}_a$ ) of leaving amines. Representative results obtained at pH-1 have been shown (Fig. 3).

Various steps involved during the hydrolysis of *N*-arylmaleamic acids has been shown in Scheme-1. Present investigations support the previous work in which the hydrolysis of amide group of the maleamic acids follows typi-

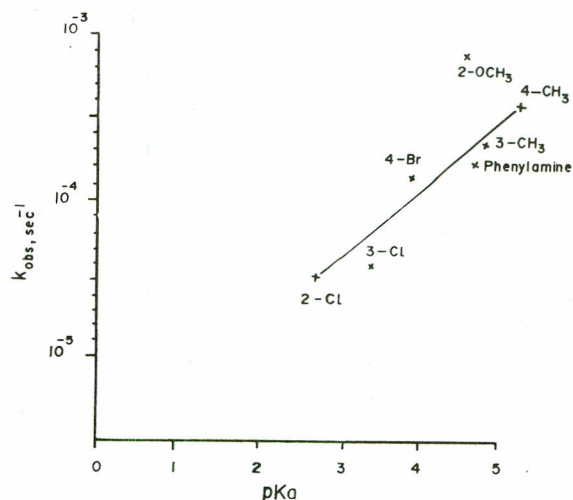
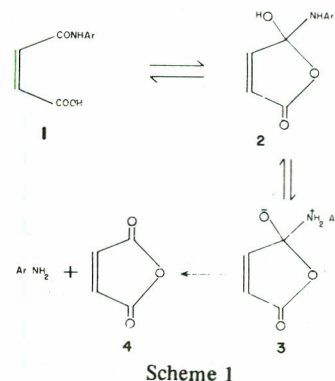


Fig. 3. Variation in first order rate of hydrolysis of *N*-substituted arylmaleamic acid with change in  $\text{pK}_a$  of substituents at  $25 \pm 0.5$  at pH-1.



Scheme 1

cal unimolecular process and is facilitated by the proximity of the carboxyl group [9-10]. In this connection, the rate determining step is considered to be the cleavage of the C-N bond in strongly acidic media [19]. Moreover, the rate increased with increase in the basicity ( $\text{pK}_a$ ) of the amine (Fig. 3). This indicates that in the rate determining step of such hydrolysis, which involves the formation of a zwitter ionic state, the basicity of the leaving group is more important than the bond strength. This suggestion is again in conformity with earlier observations [14]. A linear free energy relationship is obtained when  $\log k/k_0$  is plotted against substituent constants ( $\sigma^*$ ) as shown in Fig 4. This suggests

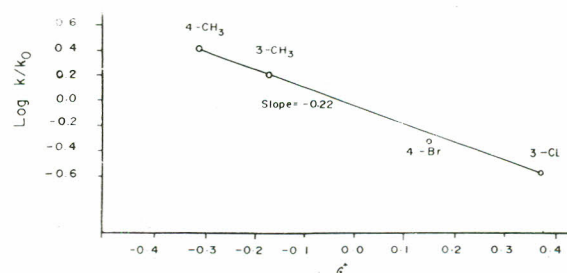


Fig. 4. Plot of  $\log K/k_0$  against substituent constants ( $\sigma^*$ ).



that a thorough resonance exists between the reaction site (amide group) and the para substituents. The slope of the plot yields reaction constant ( $\rho = -0.22$ ). A negative value of this constant shows that electron donating groups increase the rate constant of the hydrolysis of N-arylmaleamic acids. Moreover, a small value suggests that in this reaction the mechanism involves a cyclic transition state with little charge separation [20]. Such a transition state may be zwitter ionic in nature, formed by the transfer of a proton from oxygen to nitrogen, which subsequently decomposes to yield an amine and cyclic anhydride. This proposal is in agreement with two groups of workers [12, 21].

### CONCLUSION

The kinetics of the hydrolysis of seven N-arylmaleamic acids, out of which six have been synthesised for the first time, have been investigated. It may be inferred from the kinetic data that the reaction depends upon the concentration of the substrate (below  $5.25 \times 10^{-2}M$ ) and the basicity of the leaving group. It obeys typical first order kinetics. The rate of the reaction has been observed to be inversely proportional to the pH of the reaction medium. Moreover, the acids having electron-donating groups ( $CH_3$ ,  $OCH_3$ ) gave higher  $K_{obs}$  values than those having electron withdrawing groups (Cl, Br). Consequently a free energy relationship has been obtained for this reaction and even the reaction constant ( $\rho = 0.22$ ) calculated for it. A generalised mechanism involving participation of the carboxylic group at the adjacent amide has been postulated for the hydrolysis of the maleamic acid. This mechanism supports the present investigations and conforms to the earlier work.

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