

Kinetic Study on the Alkaline Hydrolysis of 1-Aryl-2-phenyl-2-imidazolines. Basicity-Rate of Hydrolysis and Structure Relationships

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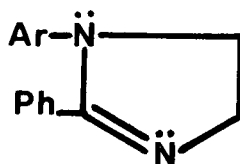
Rate constants (k_{obs}) of hydrolysis in boiling alkaline ethanolic solution for six 1-aryl-2-phenyl-2-imidazolines were determined. The influence of substituents in the phenyl group at N-1 upon rate of hydrolysis was studied. When the imidazoline ring is considered to be a substituent of the benzene ring at N-1, a good correlation with the Hammett equation is found. It was observed that reaction rates were enhanced by electron-releasing phenyl substituents of N-1 and reduced by electron-withdrawing groups, providing a change in the mechanism of the reaction in the first case that was not observed in the second. Agreement with the Hammett equation allowed comparison between experimental and "calculated" rate constants which are nearly equal. An equation relating the rate constants with the ionization constants of imidazolinium ions is given.

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In continuation of our study on the properties of cyclic amidines (1), the stability to alkaline hydrolysis of 1-aryl-2-phenyl-2-imidazolines (2) has been studied. Kinetic studies were performed with six imidazolines in boiling 95% ethanolic solutions of potassium hydroxide in order to determine the influence of substituents at N-1 upon the rates of hydrolysis. A molar ratio of alkali to imidazoline of 50:1 was used and the reactions were followed by uv spectrophotometry, selecting a wavelength at which the absorptivity of the imidazoline **A** (Scheme I) and its corresponding reaction product **B** differed appreciably (0.4-0.7 absorbance units). Control experiments indicated that Beer's law was valid at the selected wavelength. In order to establish that hydrolysis of **A** followed only the degradative pathway **B**, under the conditions employed in the runs, it was necessary to verify that **C** (Scheme I) was not produced in the reaction and also that **B** did not

undergo subsequent hydrolysis. This was investigated by hptlc. For compounds **1-5** (Table I) no trace of degradation products from **A**, except **B**, was detected throughout the reactions. At constant pH the rates of disappearance of the imidazolines were found to be first order. Plots of log (absorbance) against time were linear for at least 80% of the reaction for all the samples except for compound **6** for which linearity held up to 40% of the reaction. Pseudo-first-order rate constants are given in Table I. The earlier deviation from first-order kinetics observed for compound **6** is explained by the decreased stability of **B** to alkaline hydrolysis when $Ar = 2,4-(NO_2)_2C_6H_3-$ and consequently appearance of the corresponding *N*-(2,4-dinitrophenyl)-ethylene-diamine before one half-life has elapsed. This fact, corroborated by hptlc and the formation of resinous products may account for our failure to determine an exact rate constant for compound **6**.

Table I
Rates of the Alkaline Hydrolysis of 1-Aryl-2-phenyl-2-imidazolines at 80.7°



Compound No.	Ar	$\lambda_{selected}(nm)$	$10^4 k_{obs}/min^{-1}(a)$	Relative Rate	$t_{1/2}(h)$
1	C_6H_5-	290	4.95 (b)	1.00	23.3
2	$4-HO-C_6H_4-$	300	6.20	1.25	18.6
3	$3,4-(MeO)_2C_6H_3-$	300	5.30 (b)	1.07	21.7
4	$4-Cl-C_6H_4-$	290	4.20	0.85	27.5
5	$4-NO_2-C_6H_4-$	290	3.70	0.75	31.2
6	$2,4-(NO_2)_2C_6H_3-$	350	~ 2.4	~ 5	~ 48

(a) The degree of certainty of the rate constants obtained from duplicate experiments was ± 0.1 . (b) Average of five runs.

Table II

Compound No.	Observed and Calculated Rate Constants of Alkaline Hydrolysis for 1-Aryl-2-phenyl-2-imidazolines at 80.7°						
	σ (a)	σ_{im}	$10^4 k_{obs}/\text{min}^{-1}$	$10^4 k'_{calc}/\text{min}^{-1}$	$10^4 k''_{calc}/\text{min}^{-1}$	$\log(k''_{calc}/10^4/\text{min}^{-1})$	pK_a (b)
1	0.00	0.00	4.95	4.95	4.95	-3.305	9.26
2	-0.519	-0.281	6.20	6.12	6.11	-3.214	9.62
3	-0.117 (c)	-0.117	5.30	5.20	5.41	-3.267	9.55
4	+0.227	+0.219	4.20	4.51	4.21	-3.376	8.98
5	+0.778	+0.40	3.70	3.59	3.67	-3.435	7.65

(a) Hammett substituent constants (4). (b) Experimental values obtained in an earlier paper (1). (c) σ_{found} which gives a better fit to the regression than the $\Sigma\sigma$ value (9).

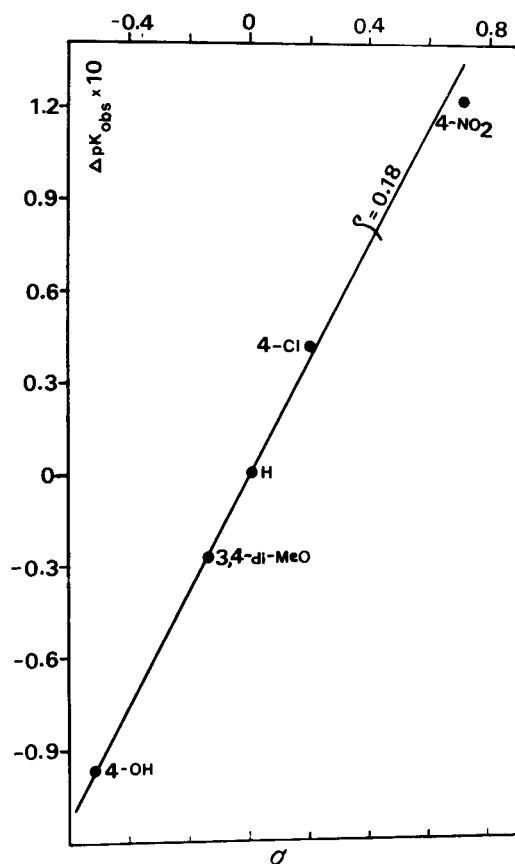


Figure 1: Hammett approach for the influence of substituents at N-1 in the alkaline hydrolysis of 1-aryl-2-phenyl-2-imidazolines.

If compound **1** is taken as a reference, relative rates in Table I indicate that electron-withdrawing substituents in the benzene ring at N-1 retard hydrolysis while electron-releasing groups accelerate it. These results agree with the generally accepted mechanism for this type of reaction (3) in which initial attack on C-2 is performed by hydroxide ion (D). The electron-deficient N-1 that results from the contribution of mesomeric structures (Scheme II) decreases the possibility of activation of the C=N bond. This effect will be more important in the case of those substituents which have -I and -M effects (Compounds **5**

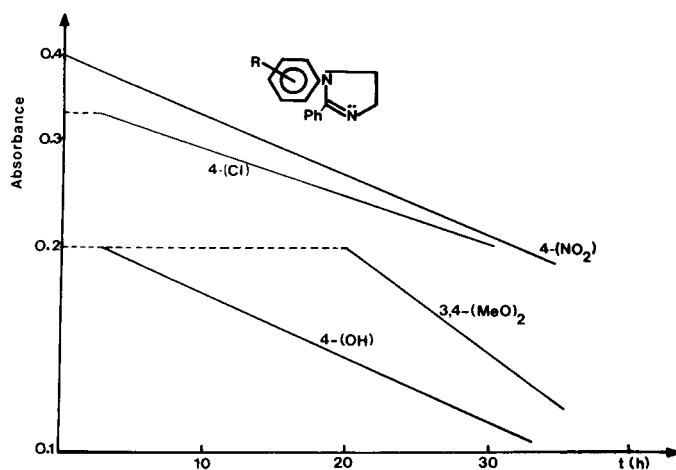


Figure 2: Dependence of rate constants of alkaline hydrolysis of 1-aryl-2-phenyl-2-imidazolines on alkali concentration.

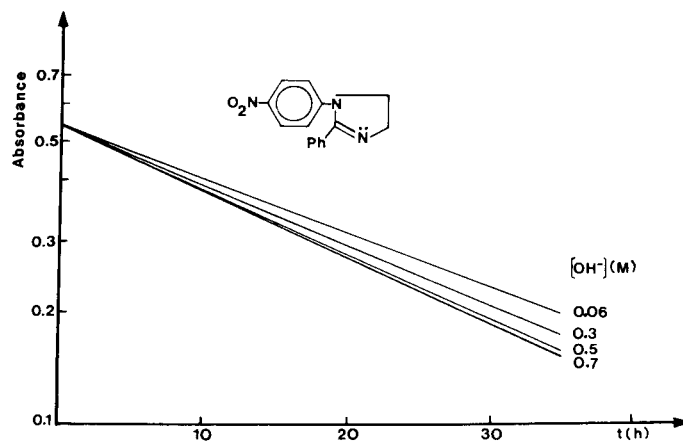


Figure 3

and **6**). In fact, the nitroderivatives are the most stable compounds.

Contributions by mesomeric structures in Scheme II manifest themselves in compounds **5** and **6**, the uv absorption at 358 nm and 354 nm, respectively, undergoing a hypsochromic effect to 310 nm and 240 nm (Scheme III).

A quantitative evaluation of the influence of substi-

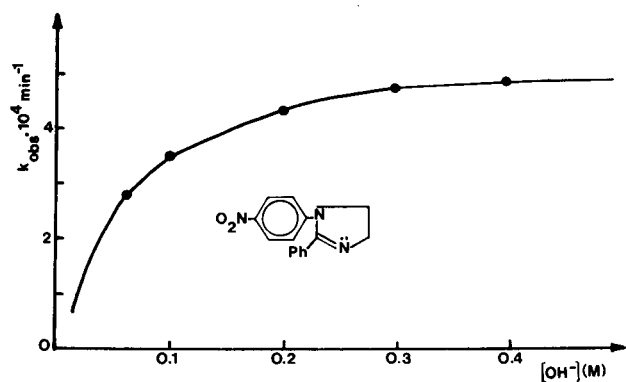


Figure 4

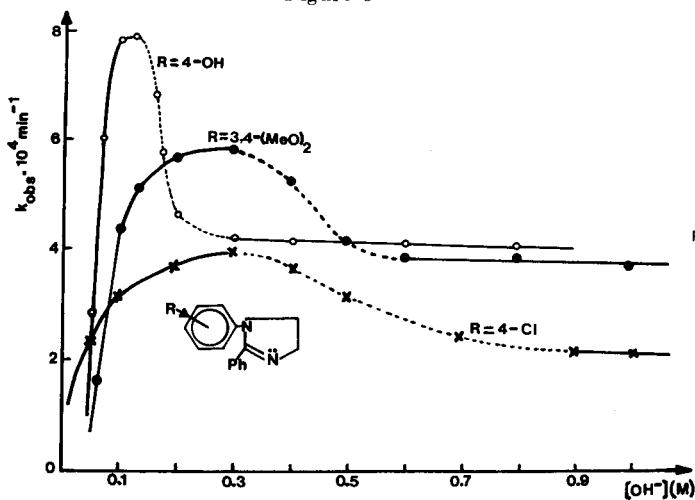


Figure 5

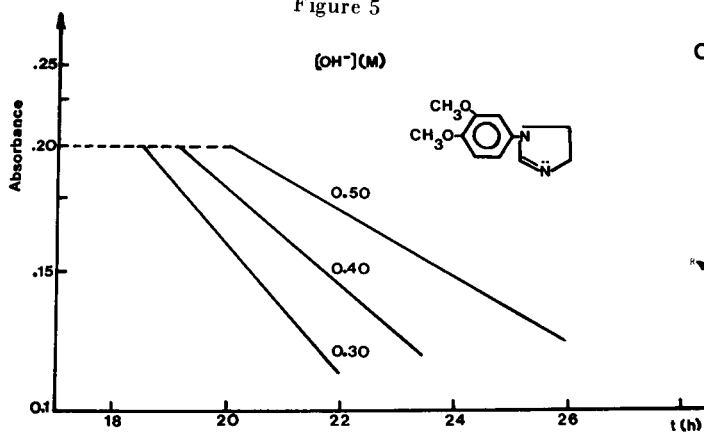
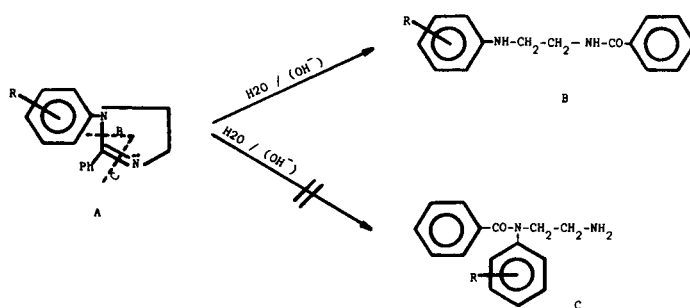


Figure 6

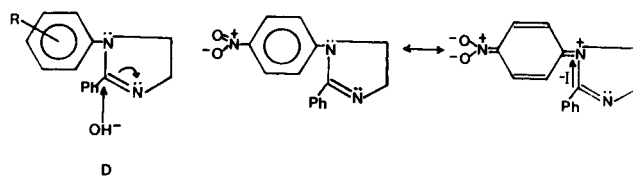
tents upon the reaction rates of hydrolysis was made through the Hammett approach (4). A plot of ΔpK_{obs} for compounds 1-5 against Hammett σ -constants gave good correlation with $\rho = 0.18$, ($r = 0.9799$; $s = 0.037$), (Figure 1). The small value of the slope indicates that the phenyl substituents at N-1 have very low influence. This fact is explained considering that imidazolines are rigid molecules (5,6), in which the N-C-N system cannot remain planar due

to the high repulsion determined by the eclipsed conformation of the methylene groups. The Hammett equation allowed us to obtain "calculated" rate constants (k') which are presented in Table II. Though k'_{calc} values are close to k_{obs} values, especially for compound 4, better agreement is obtained (k''_{calc}) when new effective substituent constants.

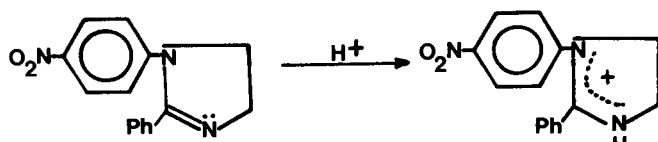
Scheme I



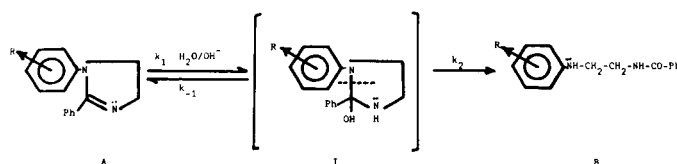
Scheme II



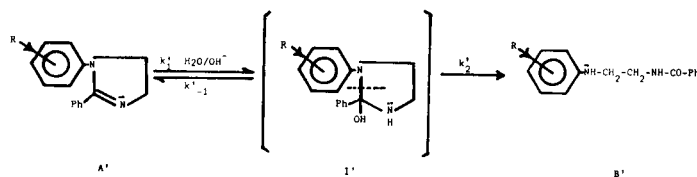
Scheme III



Scheme IV



Scheme V



denoted by σ_{im} (Table II), are used in the Hammett equation. These σ_{im} values were calculated from the ionization of the imidazolium hydrochlorides (1) using the cor-

responding equation $\sigma_{im} = (pK_a^\circ - pK_a) / 1.28$. Accordingly, a plot of the $\log (k_{obs}/k_{obs}^\circ)$ against σ_{im} for compounds **1-5** gave $\rho = 0.32$ ($r = 0.9978$; $s = 0.158$). The fact that k_{obs} and k_{calc}'' are nearly equal makes evident the close linear relationship between rate and ionization constants, given by the expression $\log k_h = 0.25 pK_a - 5.66$. This equation allowed us to correct our experimental pK_a value for compound **3**, from 9.55 (1) to an adjusted value of 9.40 which now fits well into the Hammett structure-basicity relationship presented in our earlier paper (1).

According to our results, substituents in the benzene ring at N-1 influence the electronic density at N-1 by inductive and mesomeric effects. These changes only inductively (7) alter the electronic density at the site of nucleophilic attack (C-2), an effect which is quantitatively reflected in the imidazolium ionization constants.

Influence of Aryl Groups at N-1 on the Mechanism of the Reactions.

Kinetics of the reactions were carried out at different alkali concentrations (0.05-1.3 M). The application of the differential method showed a first-order dependence of all the reactions on the imidazoline concentrations for the range $5 \times 10^{-3} - 1 \times 10^{-4} M$, and a complex dependence on the alkali concentration for a fixed molarity of substrate $1 \times 10^{-3} M$. Thus, reactions follow the rate law $v = k [A] a_{OH^-}$, with $k = k_{obs}/a_{OH^-}$. Experimental values of k_{obs} are presented in Tables I and II.

Plots of \log (absorbance) versus time at different alkali concentrations showed an unusual behavior according to the nature of the aryl substituent at N-1 (Figure 2). This was assumed to be produced by a change in the mechanism of the reaction when strong electron-releasing groups are present at N-1. Thus, we tried to gain further insight into the nature of both mechanisms.

Electron-Withdrawing Groups at N-1.

Plots of \log (absorbance) vs. time for 0.06-1.3M concentrations of alkali showed the instantaneous cleavage of the heterocyclic ring to give the open product **B** (Figure 3), and the reaction was found to be irreversible. However, the opening does not occur directly. A tetrahedral addition intermediate **I** (Scheme IV), similar to that observed for other reactions (8), could be detected by hptlc. It was observed that imidazoline and intermediate coexist throughout the reaction to give finally **B**.

Chromatographic experiments point out that the imidazoline is not completely converted into the intermediate during the slow step of the reaction, (*i.e.*, $k_{-1} \neq 0$). However, experimental data in Figure 3 indicate that the equilibrium $A \rightleftharpoons I$ is immediately attained, which implies that $k_{-1} \gg k_1$, especially at low alkali concentrations, so that $k_1/k_{-1} + k_{-2} \ll 1$. With $k_{obs} = k_1 k_2 / (k_{-1} + k_2)$, and taking into account the observed dependence

of k_{obs} values on the hydroxide concentration, it is concluded that, when -I and -M electron-attracting groups are present at N-1, reactions exclusively involve rate-determining catalysed formation of the tetrahedral addition intermediate ($v = k [A] a_{OH^-}$). Figure 4 illustrates the case.

Electron-Releasing Groups at N-1.

In this case a different variation of the rate constants on increasing the alkali concentration is observed (Figure 5). The attainment of bell-shaped curves indicates a change in the mechanism of the reaction on going to higher $[OH^-]$.

Lower ranges of alkali reactions present a similar behavior to that revealed in the above case, resembling the plots of \log (absorbance) against time observed in Figure 3 (*i.e.*, the catalysed formation of the intermediate (k'_1/k'_{-1}) is rate-determining and $v = k' [A'] a_{OH^-}$ (Scheme V)).

On increasing $[OH^-]$ it is observed that the appearance of **B'** is initially delayed (Figure 6, dashed lines) and rate constants become lower. This fact indicates that the equilibrium $A' \rightleftharpoons I'$ is not immediately achieved ($k'_{-1} \sim k'_1$) and reactions do not become first-order until that equilibrium is reached.

At higher hydroxide concentrations chromatographic experiments indicated the instantaneous conversion of **A'** into **I'** ($k'_1 \gg k'_{-1}$). The intermediate accumulates, then undergoes breakdown to give **B'** in the slow step of the reaction (Scheme V). This agrees with our results. Observed rate constants decrease and become nearly $[OH^-]$ independent on the right hand side of the curve (Figure 5) where the reaction exclusively involves the *decomposition of the tetrahedral addition intermediate* ($v = k'_2 [A']$).

It is evident that the major stability of the intermediate is related to its chemical structure. This fact manifest itself in the 4-chloro derivative. The +M effect upon the N-1 contributes to the greater stability of **I'** and in spite of the σ_{Cl}^+ value (greater stability to hydrolysis) the flat bell-shaped curve obtained for this compound (Figure 5) supports this assumption.

EXPERIMENTAL

1-Aryl-2-phenyl-2-imidazolines and N-Aryl-N'-benzoylthylenediamines.

These compounds were synthesized in our laboratory of Organic Chemistry by Dr. I. A. Perillo (2) and conveniently purified to perform the kinetic studies.

Kinetic Measurements.

Ethanol was redistilled, b.p. 78.5°, and distilled water was added to 95% (v/v). The molarity of the alkaline ethanolic solutions varied between 0.05 and 1.3M. The "apparent" pH values of all the reaction mixtures were measured before and after each run and were constant. This value was always above the pH value given by the end point in the neutralization of the imidazolium hydrochlorides with 0.1N potassium hydroxide in 95% ethanol. All "apparent" pH values were determined by a Beckman Zeromatic II pH meter at 20° using a standardized glass

electrode. Entire spectra and absorbances of the acid solutions at 20° were obtained with a Beckman DB-G Grating spectrophotometer.

General kinetic Procedure.

Solutions ($1 \times 10^{-3}M$) of the imidazolines were prepared in the basic hydrolytic solvent. This solution was refluxed (80.7°) in a three-necked flask fitted with a condenser, a thermometer and a port for the insertion of a pipette. No evaporation loss occurred. At known intervals (initially 5, 15, 30 and 60 minutes) the contents of the flask were suddenly cooled to 20° and samples (1.25 ml) were transferred to a volumetric flask (25 ml) containing concentrated hydrochloric acid (0.1 ml) to quench the reaction. The acidified solution was made up to 25 ml with 95% ethanol at 20°, and absorbance at time zero was estimated by extrapolation. The same procedure was followed with the solvent without imidazoline to prepare the blank solution. The long times required for the hydrolysis of all the compounds under our conditions allowed errors due to the reaction mixture being at temperatures different from 80.7° to be neglected.

Pseudo-first-order rate constants were calculated from plots of $\log(A - A_\infty)$ against time on semilogarithmic graph paper and the relationship $k_{obs} = 0.693/t_{1/2}$. Absorbances at $t_{1/2}$ were estimated from $5 \times 10^{-5}M$ control solutions containing different known concentrations of the imidazoline and the corresponding open product at 20°. These standard curves indicated the fulfilment of Beer's law at the selected wavelength.

Chromatographic Experiments.

Simultaneously with the u v kinetic procedures, reactions were followed at the same known intervals on chromatoplates Chptlc Silica gel 60, 10 x 10 cm). 20 μ l of each sample and the corresponding standard dissolved in the same basic medium were run with methanol in a sandwich

chamber. This procedure allowed us to detect the tetrahedral addition intermediate ($R_f \sim 0.4-0.6$), since the imidazolines R_f values are ~ 0.2 and the open products R_f values are > 0.8 . Spots were visualized under the uv light, 254 nm.

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