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Spectrophotometric and Polarographic Studies on the Kinetics of Hydrolysis of N-(6-methyl-5-nitropyridin-2-yl methylidene)-N′-(substituted thiazol-2-yl)hydrazines

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The kinetics of the hydrolysis of hydrazone derived from nitropyridine 2-carboxaldehyde and 2-hydrazino-4-substituted thiazoles Ia-e in 10% (v/v) DMF-buffer mixture has been investigated by applying two independent and different techniques viz UV-spectrophotometry and differential pulse, polarography (DPP). The hydrolysis has been found to follow general acid-base catalysis. Mechanism for the hydrolysis in acidic medium has been postulated. The observed rate constants, activation and thermodynamic parameters for the hydrolysis have been calculated. The effects of pH, molecular structure, temperature and change in percentage of water in the DMF-buffer mixture on the rate of hydrolysis have been discussed.

INTRODUCTION

Hydrazino compounds and hydrazones[1,2] have been extensively studied for their potentiality as therapeutic agents for the treatment of hypertension and CNS depression. Several research projects were directed to study the hydrolysis of hydrazone derived from aliphatic and aromatic amines.[3-14] The preparation of heterocyclic hydrazines and hydrazides has received considerable attention since iproniazide demonstrated in vitro activity.[15,16] However, a literature survey revealed the absence of hydrolysis of hydrazone derived from biologically active nitropyridine[17,18] and 4-substituted aminothiazole. The resulting hydrazones have more potent monoamine oxidase inhibitory activity.[19]

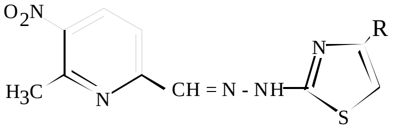
The present investigation is concerned with the hydrolysis kinetics of (6-methyl-5-nitropyridine-2-yl methylidene)-4-(substituted thiazol-2-yl)hydrazines in acidic buffer solutions. Such type of investigation has been followed by spectrophotometric (UV-spectra) and differential pulse polarographic (DPP) techniques. Thus, the evaluation of reaction rate, activation energy and thermodynamic parameters (ΔG^*, ΔH^* and ΔS^*) for the hydrolysis process with the two independent techniques, i.e. UV-spectra and DPP, can give additional information on the effect of polar substituents on the rate of hydrolysis. Moreover our aim is to explore the potentialities of UV-spectrophotometry for studies on the hydrolysis process of the compounds investigated in comparison with DPP.

EXPERIMENTAL

Materials

(6-Methyl-5-nitropyridine-2-yl methylidene)-4-(substituted thiazol-2-yl)hydrazines (I_{a-e}) were prepared and purified by the conventional method.[19] The purity of the compounds was checked by elemental analysis and m.p. determination.

The structures of the compounds under investigation are represented as follows:



I

(a) R = C_6H_4-OCH_3(p) (b) R = C_6H_4-CH_3(p) (c) R = -C_6H_5 (d) R = C_6H_4-Cl(p) (e) R = C_6H_4-NO_2(p)

Stock 10^{-3} M solutions of the hydrazone compounds were prepared in DMF. The modified universal buffer series of Britton and Robinson[20] has a dual function: one as a supporting electrolyte in polarographic measurements and the other as a hydrolysis medium. The measured values of pH's were obtained using a digital Radiometer pH (M 64). The pH-meter accuracy lies within ± 0.005 units.

Instrumentation

Electronic spectra were scanned on a CECIL CE 599 recording spectrophotometer equipped with a temperature controlled cell holder and matched 1 cm quartz cell. The temperature in the cell holder was controlled by means of a Julabo FP 40 thermostat with an accuracy of ± 0.01 °C where temperature of the sample was measured directly in the cell within the wavelength range 250-550 nm.

Differential pulse polarograms were obtained with a PAR 174 A polarographic analyzer equipped with a PAR 1.72 drop time and electrode assembly. Polarograms were recorded with an advanced X-Y recorded (HP 7045 A). A thermostated Metrohm cell with a three electrode system was used.

Spectrophotometric Rate Measurements

The kinetic runs of the investigated compounds were performed in 10% (v/v) DMF-buffer mixtures at 30 °C. After being properly thermostated at the required temperature, aliquots (9 mL) of buffer were transferred to a test tube containing (1 mL) of 5×10^{-4} M I_{a-e}. The mixture was then shaken vigorously and transferred to 1 cm quartz cell, and the change in UV absorption at the selected wavelength was recorded. The disappearance of I_{a-e} was followed to ~65-85% completion.

Polarographic Rate Measurements

The Universal buffer solution (20 mL) containing DMF 10% (v/v) was placed in the polarographic cell and deaerated with nitrogen. After 30 min. of temperature equilibration the required volume of the investigated compounds was added rapidly, and the decay of the differential pulse polarographic beak was recorded at different time intervals. The hydrolysis products do not exhibit any reduction current in the potential range in which the reduction of the investigated compounds occurs.

The reaction is monitored spectrophotometrically or polarographically under pseudo first-order condition by following the disappearance of I_{a-e}. The rate constants were computed from the variation of absorbance (A) and/or beak height (μA) with time. The data were graphically represented as log A or log I_p vs. time. Straight lines were obtained with a correlation coefficient close to unity, which indicates that the hydrolysis strictly follows first-order kinetics. For every run the rate constant was obtained from the slope of the least squares refined linear plot. The reported rate constant is the mean of at least four replicate runs. Activation parameters were obtained from Arrhenius plots and the appropriate kinetic equations.

RESULTS AND DISCUSSION

The hydrolysis of I_{a-e} derivatives in 10% (v/v) DMF-buffer mixtures has been studied spectrophotometrically. UV absorption of the investigated compounds exhibit absorption bands located at (283-410 nm), a phenomena which can be interpreted as charge transfer (CT) bands for the hydrazone compounds investigated.[23] It was found that in acidic buffer solutions the absorption of the CT band decreases while a new band appears at longer wavelength. This new band is due to the absorption of one of the hydrolysed products (Figs. 1A and 1B).

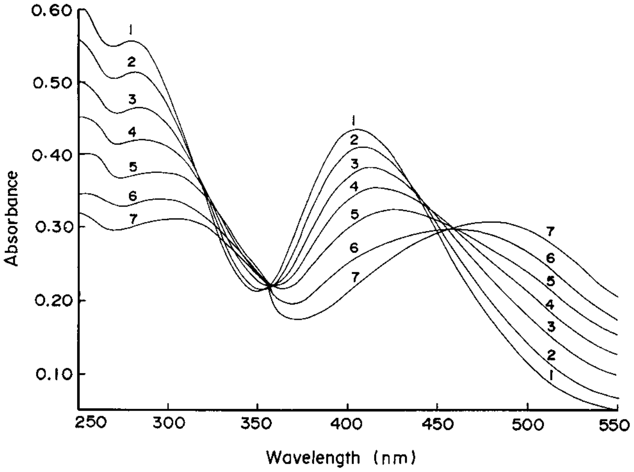


Fig. 1A. Time dependence of absorption spectra of 5×10^{-5} M I_c derivative at 30 °C. (pH 2.25). 1) 10; 2) 15; 3) 20; 4) 25; 5) 32; 6) 40; and 7) 50 min.

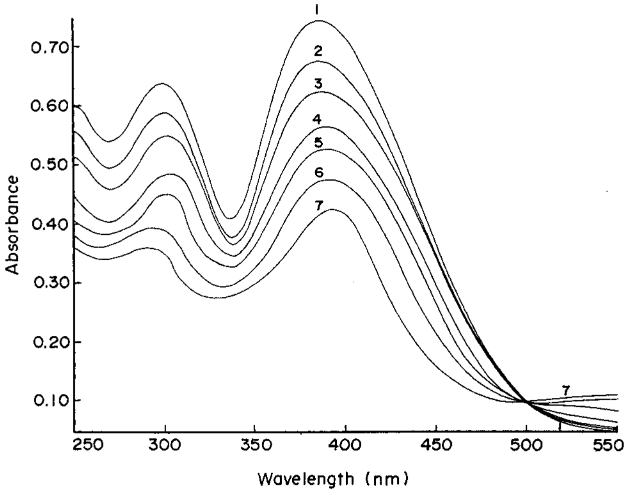
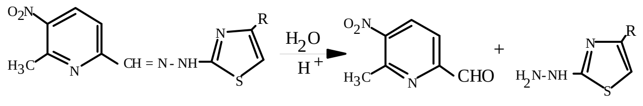


Fig. 1B. Time dependence of absorption spectra of 5×10^{-5} M I_e derivative at 30 °C. (pH 2.25). 1) 10; 2) 18; 3) 25; 4) 33; 5) 42; 6) 50; and 7) 60 min.

The differential pulse currents of a different substitute I_{a-e} has also been recorded as a function of potential in universal buffer solutions containing 10% (v/v) DMF. I_b and I_e derivatives are shown in (Figs. 2A and 2B). The differential pulse peak is related to the reduction of the hydrazone moiety (-CH=N-NH-) which in acidic media undergoes a totally irreversible electrode reaction with a total uptake of 4-electrons and 4-protons per molecule.[21,22] In this context it was found that, in acidic buffer solutions, the reduction peak, which corresponds to the reduction of the C=N bond, decreases with time (Fig. 2A and 2B) while a second differential peak appears at more negative potentials. Closer inspection of the second peak shows the coincidence of E_p of this peak with that corresponding to the reduction of the aldehyde. This indicates that the second peak must be attributed to the reduction of aldehyde formed by hydrolysis of the investigated compounds into their main constituents. Hydrolysis is due to the localization of electrons on the "N" atom of the azomethine center according to the following general reaction:



A comparative kinetic study of the investigated compounds was carried out with UV spectroscopy and DDP. The disappearance of the absorbance of the CT band or of the DDP peak was recorded at different time intervals. The decay of I_{a-e} derivatives in acidic medium (pH 2.25-5.05) is of first order (Figs. 3 and 4).

The observed first order rate constants are plotted as a function of pH for all compounds under investigation. The pH-rate constant profile shows that the rate constant decreases gradually with increasing the pH. At pH < 2.25 the rate of hydrolysis becomes independent on the pH (Fig. 5).

However, in neutral media (pH > 5.05) the hydrolysis process was not observed and has no measurable values. Such behaviour can be observed under conditions in which the substrate exists as a free base and can undergo attack by protons, so that a general acid-base catalysis mechanism is postulated in Scheme I for the hydrolysis of compounds under investigation in universal buffer acidic media which is similar to the mechanism proposed by many workers for similar systems.[24-26] Such mechanism involves the conversion of the hydrazone compound to its conjugate acid ($-CH=\overset{+}{N}H-NH-$) in a rapid pre-equilibrium step followed by the slow attack of H_2O molecule (Scheme I).

The rate of the hydrolysis reaction follows the equations,

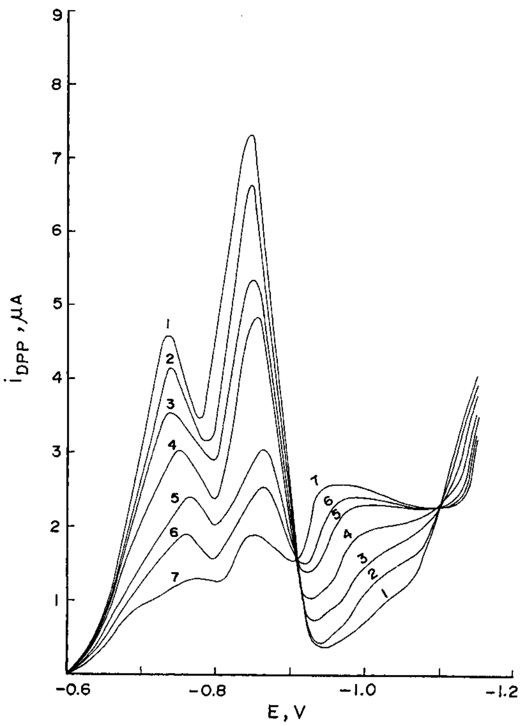


Fig. 2A. Time dependence of differential pulse polarograms of 5× 10^{-5} M I_c derivative at 30 °C. (pH 2.25). 1) 10; 2) 16; 3) 22; 4) 30; 5) 38; 6) 45; and 7) 55 min.

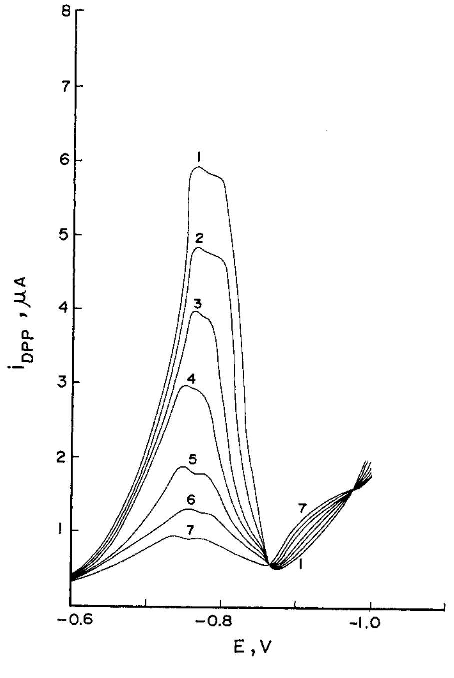


Fig. 2B. Time dependence of differential pulse polarograms of 5× 10^{-5} M I_e derivative at 30 °C. (pH 2.25). 1) 10; 2) 18; 3) 27; 4) 35; 5) 43; 6) 52; and 7) 65 min.

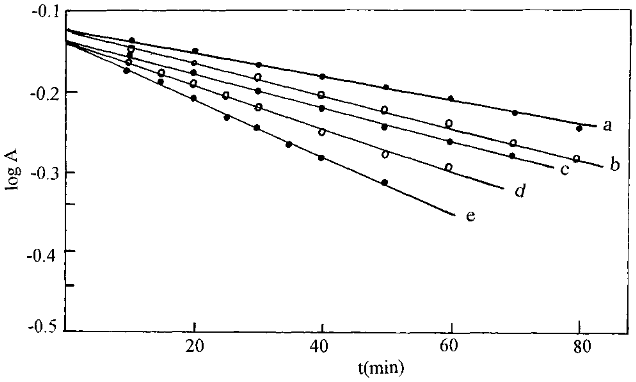


Fig. 3. First-order plots of log A vs t (min) at different temperatures for the hydrolysis of I_c derivative at pH 2.25. a) 20 °C, b) 25 °C, c) 30 °C, d) 35 °C and e) 40 °C.

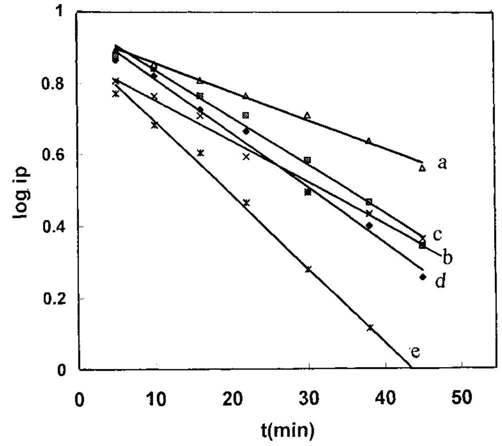


Fig. 4. First-order plots of log i_p vs t (min) at different temperatures for the hydrolysis of I_c derivative at pH 2.25. a) 20 °C, b) 25 °C, c) 30 °C, d) 35 °C and e) 40 °C.

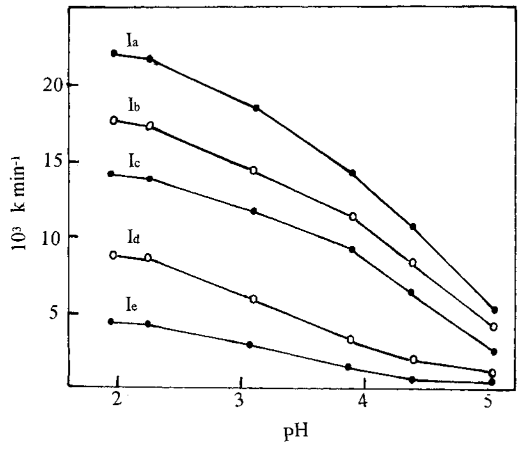
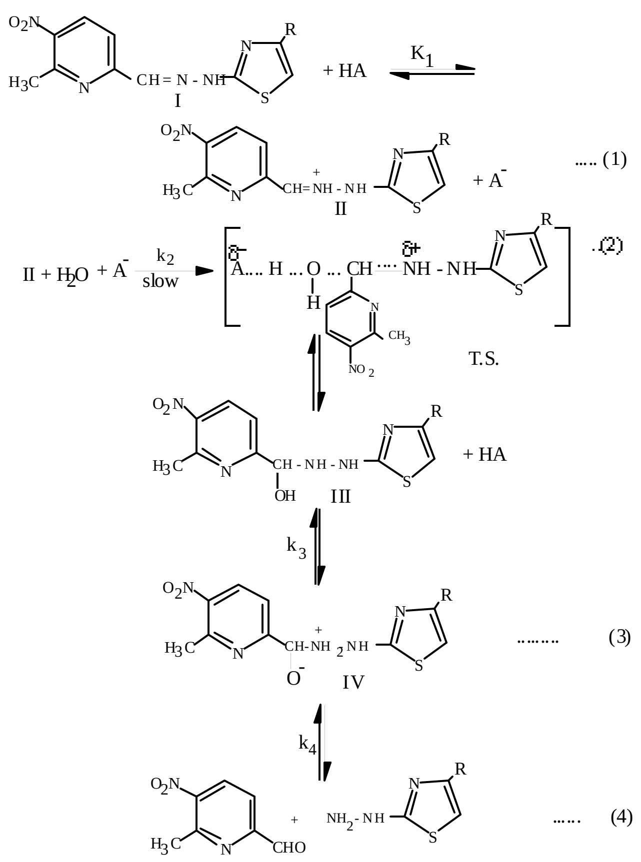


Fig. 5. Effect of pH on the first-order rate constant value of hydrolysis of 5× 10^{-5} M of I_a-I_e at 30 °C.

Scheme I



$$\frac{-d(II)}{dt} = k_2\,[II]\,[A] = k_2\,K_1\,[I]\,[HA],$$

$$\frac{-d(II)}{dt} = K_{obs.}\,[I]\,[HA].$$

Upon increasing the percentage of water content during the hydrolysis process of the compounds under investigation, one can observe an increase in the rate constant values where the activation energy values show a remarkable decrease (Table 1).

Furthermore, it was found that the observed rate constant increases with increasing electron donating power (Table 2) in the thiazole moiety confirming that the attack of water on the protonated hydrazone represents the rate determining step. On the other hand electron withdrawing group (I_d and I_e) decrease k_{obs} and increase the energy of activation.

Activation parameters were obtained from the plot of logarithm of the observed rate constant versus the reciprocal of absolute temperature. Thermodynamic parameters of activation (ΔG*, ΔH* and ΔS*) were calculated from the appro-

Table 1. Effect of Percentages of Water in the DMF-buffer Solution Mixtures on the Values of the Observed Rate Constants for the Hydrolysis of I_c at pH = 2.25 and 30 °C Calculated from UV-spectra and DDP

% water	UV-spectra	DPP
	10^3 k, min^{-1}	10^3 k, min^{-1}
90	12.9 ± 0.6	13.6 ± 0.7
80	11.1 ± 0.7	10.4 ± 0.8
70	7.6 ± 0.4	8.3 ± 0.6
60	4.2 ± 0.2	3.7 ± 0.3

Table 2. Specific Rate Constants for the Hydrolysis of I_{a-e} at pH 2.25, 10% (v/v) DMF-buffer Solutions Calculated from UV-spectra and DPP Measurements at 30 °C

No	R	UV-spectra	DPP
		10^3 k, min^{-1}	10^3 k, min^{-1}
Ia	$C_6H_4OCH_3$(p)	21.6 ± 1.2	22.1 ± 1.4
Ib	$C_6H_4CH_3$(p)	17.1 ± 0.9	18.2 ± 1.1
Ic	C_6H_5	12.9 ± 0.6	13.6 ± 0.7
Id	C_6H_4Cl(p)	8.7 ± 0.4	9.3 ± 0.6
Ie	$C_6H_4NO_2$(p)	5.3 ± 0.2	4.7 ± 0.3

Table 3. Activation Energies and Thermodynamic Activation Parameters for the Hydrolysis of Ia-e at pH 2.25, 10% (v/v) DMF-buffer Solutions Calculated from UV-spectra DDP at 30 °C

Compounds	UV-spectra				DPP			
	E_a* Kcal mol^{-1}	ΔG* Kcal mol^{-1}	ΔH* Kcal mol^{-1}	-ΔS* cal mol^{-1} k^{-1}	E_a* Kcal mol^{-1}	ΔG* Kcal mol^{-1}	ΔH* Kcal mol^{-1}	-ΔS* cal mol^{-1} k^{-1}
Ia	11.1	21.0	10.5	34.7	10.5	20.8	9.9	36.1
Ib	12.4	21.4	11.8	31.8	12.8	21.7	12.2	31.5
Ic	13.7	21.7	13.1	28.4	14.2	22.0	13.6	27.8
Id	16.1	22.9	15.5	24.4	15.8	22.2	15.2	23.0
Ie	19.5	25.0	18.9	20.1	20.4	25.3	19.8	18.2

priate equations derived from transition state theory and are given in Table 3. The parameters indicate that the hydrolysis is decreased with increasing the pH of the hydrolysis medium, but enhanced by an increasing donating power of the substituent. The values of entropy of activation ΔS* indicate a dependence on both the pH and the type of substituent in the thiazole moiety. On comparing the values of ΔS* at the same pH, it becomes apparent that I_e derivative has the lowest activation entropy than the other derivatives (I_{a-d}).

This correlation is due to the strong withdrawing character of the nitro substituent which in turn makes the activated complex less randomly linked to solvent molecules. This behaviour is in agreement with the change of rate constant and E_a* values.

In conclusion, such comparative kinetic studies on the hydrolysis of some substituted pyridinethiazole hydrazones emphasize that more comprehensive and detailed information on the hydrolysis of the compounds investigated is attainable by the combined application of the two methods utilized, i.e. UV-spectrophotometry and DPP taking into consideration their respective sensitivity to charge transfer and to faradic reduction response.

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Key Words

Kinetic studies; Hydrolysis; Nitro-2-pyridine carboxaldehyde-2-thiozolyl hydrazones; UV-spectrophotometry and differential pulse; Polarograph (DPP).

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