



Kinetic and Mechanistic Investigation of the Alkaline Hydrolysis of Ethyl Isonicotinate in Aqueous Dimethyl Sulfoxide

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ABSTRACT

The present study investigates the influence of aqueous dimethyl sulfoxide (DMSO) on the kinetics and thermodynamic activation parameters associated with the alkaline hydrolysis of ethyl isonicotinate. The reaction was investigated conductometrically in aqueous DMSO media containing 10–50% (v/v) DMSO over the temperature range of 20–50°C. The hydrolysis reaction exhibits second-order kinetics. The specific rate constant decreases progressively with increasing DMSO content, indicating a significant influence of the solvent composition on the reaction rate. The iso-composition activation energy decreases with increasing DMSO concentration, whereas the iso-dielectric activation energy shows a systematic dependence on the dielectric constant of the reaction medium. The thermodynamic activation parameters further indicate changes in the solvation environment of the reacting species and transition state with variation in solvent composition. These observations demonstrate that solvent polarity, dielectric properties, and preferential solvation play important roles in governing the reaction rate and activation process. The study provides useful kinetic and mechanistic insight into the role of aqueous DMSO as a mixed solvent medium for alkaline ester hydrolysis.

Keywords: Ethyl isonicotinate, Alkaline hydrolysis, Aqueous DMSO, Second-order kinetics, Thermodynamic activation parameters.

INTRODUCTION

The alkaline hydrolysis of esters is one of the most extensively studied reactions in organic chemistry, with particular emphasis on its mechanistic and kinetic aspects, because it provides valuable insights into reaction mechanisms, solvent effects, and transition-state formation. The reaction generally proceeds through nucleophilic attack of the hydroxide ions on the electrophilic carbonyl carbon of the ester, forming a tetrahedral intermediate followed by elimination of the alkoxide group giving the corresponding carboxylate group and alcohol (Scheme-1 and 2).^{1,2} A thorough survey of existing literature,³⁻⁷ suggest that the use of mixed aqueous-organic solvents systems particularly water combined with different polar organic solvents alters the dielectric constant and some other physicochemical properties of the solvent system which influence the kinetics of the reaction. This study extends solvent-effect investigations to ethyl isonicotinate by presenting a comprehensive kinetic analysis in aqueous DMSO over different solvent compositions and temperatures, providing mechanistic insights not previously reported for this reaction system.

Ethyl isonicotinate, the ethyl ester of isonicotinic acid, is a pyridine-based ester of considerable pharmaceutical and synthetic importance. It is widely employed as an intermediate in the synthesis of biologically active heterocyclic compounds and pharmaceutical derivatives.^{8,9} Owing to its medicinal relevance and industrial

applications, understanding its hydrolytic behaviour is essential for optimizing synthetic processes and evaluating its chemical stability. Dimethyl sulfoxide (DMSO), a polar aprotic solvent, low-toxicity, completely miscible with water, is extensively used in kinetic studies because of its excellent solvating ability. In aqueous mixtures, DMSO modifies the dielectric constant and preferential solvation of reactants, thereby influencing reaction rates and activation parameters. However, systematic kinetic and mechanistic studies on the alkaline hydrolysis of ethyl isonicotinate in aqueous DMSO remain limited, providing the motivation for the present investigation.

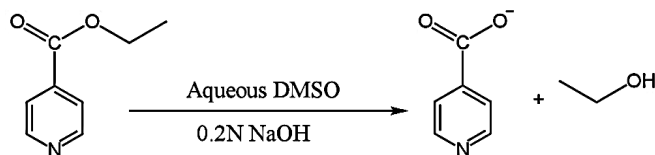
MATERIAL AND METHODS

Materials

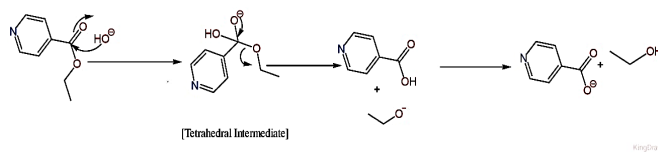
Ethyl isonicotinate (TCI), dimethyl sulfoxide (DMSO, Spectrochem, analytical reagent grade), sodium hydroxide (NaOH, Nice Chemicals), oxalic acid (Nice Chemicals), and potassium chloride (KCl, Loba Chemie) were used. Freshly prepared Double-distilled water was used for the preparation of all aqueous solutions.

Instrumentation

Conductometric measurements were carried out using a Systronics Conductivity–TDS Meter (Model 308). The reaction temperature was maintained at 0.1 with a thermostatically controlled constant-temperature water bath (Unicorn Thermostat, Instrumentation and



Scheme 1: Alkaline Hydrolysis of Ethyl isonicotinate in aqueous DMSO



Scheme 2: Proposed mechanism for the alkaline hydrolysis of ethyl isonicotinate in aqueous DMSO

Refrigeration of India, Madras S.no.-0329). Prior to each experiment, the conductivity meter was calibrated using 0.01 N KCl solution. The conductivity cell was thoroughly rinsed with double-distilled water before every measurement to eliminate contamination and ensure reliable conductivity readings.

Kinetic Measurements

The alkaline hydrolysis of ethyl isonicotinate was investigated by the conductometric technique in aqueous DMSO mixtures containing 10–50% (v/v) DMSO over the temperature range of 20–50. Equimolar solutions of ethyl isonicotinate and NaOH were used. Aqueous DMSO mixtures of the required compositions were prepared by mixing appropriate volumes of DMSO and double-distilled water while maintaining a constant final reaction volume. The reactant solutions were equilibrated at the required temperature before mixing. The reaction was initiated by mixing the reactants, and conductivity readings were recorded at regular time intervals until the reaction approached completion. The corresponding data were used to determine the specific second-order rate constants for each DMSO composition and temperature.

RESULTS AND DISCUSSION

Effect of Solvent Composition on the Specific Rate Constant

Table 1 presents the specific rate constants for the alkaline hydrolysis of ethyl isonicotinate in aqueous DMSO, the logarithmic values of the rate constants are listed in Table-2, while their variation with mol% of DMSO is illustrated in Fig. 1.

The gradual decrease in the specific rate constant with increasing DMSO content may be attributed to change in solvation, leading to modification in stability of the transition state and decrease in the concentration of water leading to a lower observed reaction rate. The observed behaviour agrees with the theory of Hughes and Ingold¹⁰ and also with previous studies by.¹¹⁻¹³

The linear decrease in $\log k$ with increasing DMSO mol% suggests that the reaction mechanism remains unchanged over the investigated solvent composition range. These observations are consistent with earlier reports.^{14,15}

Iso-composition activation energy values were calculated with the help of slope of the graph between $\log k$ vs $10^3/T$ listed in Table 3 and Fig. 2. The E_c values calculated are listed in Table 4

Arrhenius Plot and Iso-composition Activation Energy (E_c)

The Arrhenius plots of $\log k$ versus $10^3/T$ (Fig. 2) were linear over the investigated temperature range, suggested that the alkaline hydrolysis of ethyl isonicotinate proceeds through the same reaction mechanism across the investigated aqueous DMSO compositions. The linear relationships also confirm the applicability of the Arrhenius equation for evaluating the activation energy.

As shown in Table 4, the iso-composition activation energy decreased from $56.63 \text{ kJ mol}^{-1}$ at 10% DMSO to $44.30 \text{ kJ mol}^{-1}$ at 50% DMSO. This decrease suggests that increasing the DMSO content modifies the energetic barrier of the reaction.¹⁶⁻²⁰

Iso-dielectric Activation Energy (E_D)

The iso-dielectric activation energy (E_D) was evaluated to assess the influence of the solvent dielectric constant on the alkaline hydrolysis

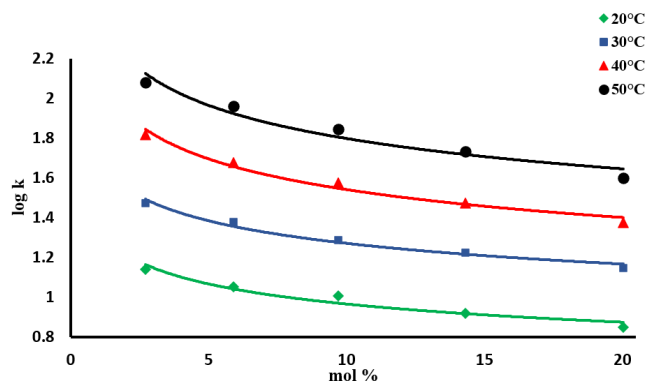


Fig. 1: Variation of $\log k$ value with mol % of DMSO at different temperatures

Table 1: Specific rate constant (k) for alkaline hydrolysis of ethyl isonicotinate in aqueous DMSO media at different compositions and temperatures.

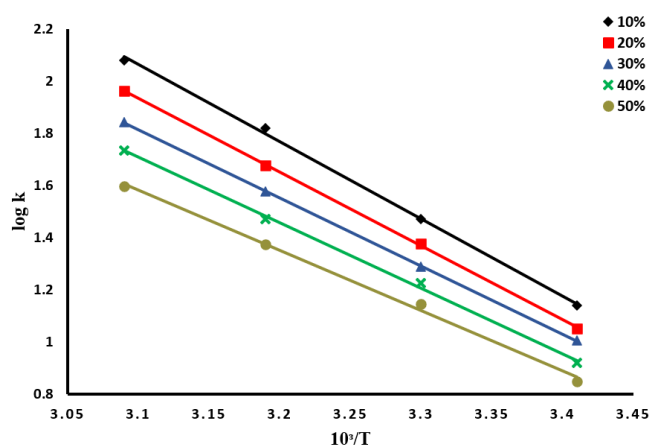
Temperature in	Specific rate constant k at different composition of DMSO				
	10%	20%	30%	40%	50%
20	13.858	11.298	10.176	8.323	7.079
30	29.673	23.877	19.428	16.806	14.025
40	65.832	47.460	37.707	29.691	23.707
50	120.336	91.575	69.735	54.171	39.698

Table 2:Variation of log k of the reaction with mol% of DMSO at different temperatures and compositions.

% of DMSO (v/v)	mol% of DMSO	log k at different Temperature			
		20	30	40	50
10%	2.71	1.141	1.472	1.818	2.080
20%	5.90	1.053	1.377	1.676	1.961
30%	9.70	1.007	1.288	1.576	1.843
40%	14.32	0.920	1.225	1.472	1.733
50%	20.04	0.849	1.146	1.374	1.598

Table 3:Variation of log k values of the reaction with $10^3/T$ in aqueous DMSO media.

Temperature in	$10^3/T$	log k at different composition of DMSO				
		10%	20%	30%	40%	50%
20	3.41	1.141	1.053	1.007	0.920	0.849
30	3.30	1.472	1.377	1.288	1.225	1.146
40	3.19	1.818	1.676	1.576	1.472	1.374
50	3.09	2.080	1.961	1.843	1.733	1.598

**Fig. 2:**Plot of log k vs. $10^3/T$ in aqueous DMSO media

of ethyl isonicotinate in aqueous DMSO. As shown in Table-5, E_D increase with increasing dielectric constant. This trend indicates that solvent polarity significantly influences the activation process by altering the solvation of the reacting species and the transition state. These observations are consistent with the findings.^{7,21-24}

Influence of Water Content on Reaction Kinetics

The relationship between log k and log[H₂O] at different temperatures is summarized in Table-6. A linear dependence of log k on log[H₂O] was observed throughout the investigated temperature range, in agreement with the Robertson equation.²⁵ This behaviour suggests that water molecules participate in the activation process and contribute to stabilization of the transition state. The relationship is expressed as:

$$\log k = \log k_0 + n \log[H_2O]$$

where the slope of the linear plot corresponds to the solvation number (n).

Table-7 presents the slopes obtained from the linear plots of log k versus log[H₂O] at different temperatures. The slope values increase progressively from 1.106 at 20 to 1.851 at 50, indicating enhanced participation of water molecules in the formation and stabilization of the activated complex with increasing temperature.

Thermodynamic Activation Parameters

The thermodynamic activation parameters, namely the enthalpy of activation (ΔH^*), entropy of activation (ΔS^*), and Gibbs free energy of activation (ΔG^*), were evaluated using the Wynne-Jones and Eyring equation.²⁶ The calculated values for different aqueous DMSO compositions are presented in Table 8. These parameters provide valuable information regarding the energetics of the reaction and the nature of the activated complex formed during the alkaline hydrolysis of ethyl isonicotinate.

The enthalpy of activation (ΔH^*) decreases with increasing DMSO content, indicating that the activation barrier becomes lower in solvent mixtures containing higher proportions of DMSO. In contrast, the Gibbs free energy of activation (ΔG^*) shows a slight increase with increasing DMSO content and temperature, suggesting a gradual decrease in reaction feasibility. The increasingly negative entropy of activation (ΔS^*) values with increasing DMSO concentration further support enhanced solvent-solute

Table 4:Value of iso-composition activation energy of alkaline hydrolysis of ethyl isonicotinate with increasing percentage of solvent DMSO

% of DMSO(v/v)	10%	20%	30%	40%	50%
E_c values in kJmol^{-1}	56.63	54.09	50.01	48.05	44.30

Table 5: Iso-dielectric activation energy (E_D) values of the reaction at different dielectric constant D in aqueous DMSO media

Value of D	72	74	76	78	80
E_D values in kJmol^{-1}	106.26	113.40	114.88	121.43	122.52

Table 6: Relationship between log k and log[H₂O] for the alkaline hydrolysis of ethyl isonicotinate in aqueous DMSO at different temperatures.

% of DMSO(v/v)	% of H ₂ O	log [H ₂ O]	log k at different temperature			
			20	30	40	50
10%	90%	1.70	1.141	1.472	1.818	2.080
20%	80%	1.64	1.053	1.377	1.676	1.961
30%	70%	1.56	1.007	1.288	1.576	1.843
40%	60%	1.52	0.920	1.225	1.472	1.733
50%	50%	1.44	0.849	1.146	1.374	1.598

Table 7: Evaluated values of slopes log k with log[H₂O] in DMSO media at different temperatures

Temperature	20	30	40	50
Slope	1.106	1.250	1.692	1.851

Table 8: Thermodynamic activation parameters (ΔH^* , ΔS^* , ΔG^*) of alkaline hydrolysis of ethyl isonicotinate in aqueous DMSO media ΔH^* , ΔG^* in kJmol⁻¹, ΔS^* in Jmol⁻¹K⁻¹.

% of DMSO (v/v)	Thermodynamic Activation Parameters								
	ΔH^*	ΔG^* 20	ΔS^* 20	ΔG^* 30	ΔS^* 30	ΔG^* 40	ΔS^* 40	ΔG^* 50	ΔS^* 50
10%	54.26	75.48	-72.45	76.23	-72.52	76.73	-71.79	77.63	-72.38
20%	51.92	76.00	-82.19	76.76	-82.01	77.57	-81.98	78.36	-81.88
30%	47.86	76.25	-96.90	77.25	-97.00	78.15	-96.80	79.08	-96.67
40%	45.76	76.71	-105.64	77.62	-105.17	78.78	-105.51	79.75	-105.25
50%	41.72	77.07	-120.66	78.03	-119.85	79.35	-120.24	80.58	-120.31

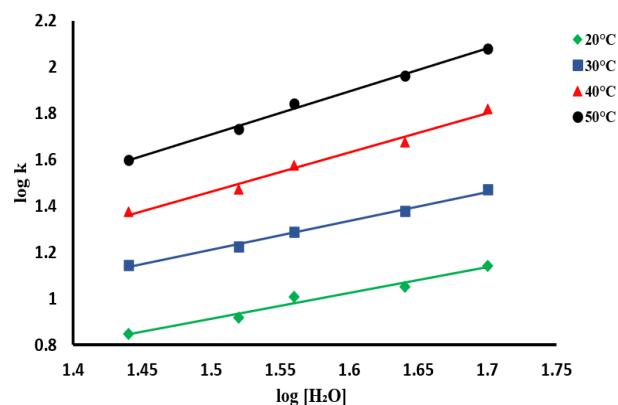
interactions and preferential solvation in the transition state. These thermodynamic parameters demonstrate that both solvent composition and temperature significantly influence the activation process and the kinetics of alkaline hydrolysis. These findings are consistent with previous studies.^{19,27}

CONCLUSION

The present study demonstrates that the alkaline hydrolysis of ethyl isonicotinate in aqueous DMSO obeys second-order kinetics and is strongly influenced by solvent composition and temperature. The systematic decrease in the specific rate constant with increasing DMSO content indicates that changes in solvent polarity and solvation strongly affect the reaction rate. The observed variations in kinetic and thermodynamic activation parameters further support the involvement of solvent-mediated interactions during the activation process. Overall, the results highlight the important role of solvent composition, preferential solvation, and water–solute interactions in controlling the kinetics and mechanistic behavior of ester hydrolysis in aqueous DMSO media.

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**Fig. 3:** Linear variation of log k with log[H₂O] for the alkaline hydrolysis of ethyl isonicotinate in aqueous DMSO at different temperatures.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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