

Solvent effects on ester linkage of 4-nitrophenyl acetate in aqueous and ethanol solutions with imidazole and hydroxide ion as nucleophiles

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The reaction of 4-nitrophenyl acetate in aqueous and ethanol solutions with imidazole as a nucleophile has been monitored spectrophotometrically. The second order rate constants of these reactions are 10 times higher in water than in alcoholic solutions. This is attributed to better solvation of the initial state and less solvation of the excited state in the alcohol medium. The entropy of activation in water is more negative indicating the greater structuredness of the excited state in water. In addition to the above, the base hydrolysis reaction of the ester using OH^- as a nucleophile in buffered aqueous solutions has been followed spectrophotometrically as a function of pH . The observed pseudo first order rate constant obeys the relationship $k_{\text{obs}} = k_0 + k_{\text{OH}} [\text{OH}^-]$ where k_0 represents the water reactions and the buffer dependent rate constant, and k_{OH} is the rate constant for the OH^- catalyzed (specific base) reaction. For both cases, a mechanism involving a tetrahedral intermediate and in which the nucleophile attacks at the electrophilic carbon of the ester $\text{C}=\text{O}$ is proposed.

Nucleophilic attack of a variety of nucleophiles on substrates belonging to a number of organic classes of compounds can be explained by either a general catalysis type mechanism or by specific and general acid-base mechanism¹⁻⁶. Both types of mechanism are hard to differentiate in the absence of ability to chemically or spectroscopically trap the intermediate or knowledge of the transition state. In nucleophilic catalysis, however, the solvent is not directly involved in the formation of the reactive intermediate. This is contrary to general acid-base catalysis in which the solvent plays an important role. It is thus essential that solvent effects should be taken into consideration in any study of the kinetics of nucleophilic attacks. In the present study we report the solvent effects on nucleophilic attack at ester linkage with a view to establish the role of solvent in an attempt to elucidate the mechanism for such system.

Materials and Methods

Reagent grade chemicals were used in all preparations except when mentioned otherwise. Doubly distilled water was used throughout. Perchloric acid (70%), lithium perchlorate, potassium hydrogen phthalate and sodium hydroxide were all reagent grade (AR) and obtained from Fluka or BDH Chemicals. 2-Amino-2-(hydroxymethyl)-propane-1,3-diol (tris buffer) (AR) was obtained from BDH Chemicals. Imidazole (pure) was supplied by Koch-

Light Laboratories Ltd as yellowish crystals and was recrystallized from dichloromethane as white crystals (m. pt. 90-91°C). 4-Nitrophenol was obtained commercially from BDH or Aldrich and purified before use by standard techniques.

Synthesis of 4-nitrophenyl-acetate was done according to standard literature methods. In a typical preparation 12 mmol of 4-nitrophenol (1.66 g) and 12 mmol of triethylamine (1.22 g) were dissolved in 20 ml dichloromethane. The mixture was cooled to 0°C. Slow addition of acetyl chloride (14 mmol, 1.10 g) yielded a white precipitate of $\text{Et}_3\text{NH}^+\text{Cl}^-$. The reaction mixture was allowed to reach room temperature and then filtered. The filtrate was extracted with dil. HCl and dried over anhydrous sodium sulfate. Evaporation of dichloromethane yielded the ester as an oily material which was separated in the form of a white crystalline solid from petroleum ether (60-80°C), ethanol or ethyl acetate. The purity of the final product was established by recrystallization from absolute ethanol as white crystals with m.pt. 93-94°C.

UV-vis spectra were recorded on a UV spectrophotometer (Cecil CE 7200) equipped with thermostated ($\pm 0.1^\circ\text{C}$) cell compartment. The temperature inside the cell was kept at the desired temperature by circulating water through the thermostated cell holder with constant temperature circulator (Grant LTD6G temperature bath).

The pH of the solution in all buffered experiments was measured using Jenco pHmeter (model 6072) at controlled temperature and calibrated using standard buffers at two pH values. For the kinetic experiments, all pH values were determined at the beginning and end of the reaction.

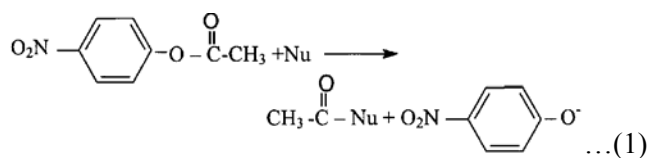
Kinetic studies

The reactions were followed spectrophotometrically. All reactions were carried out under pseudo-first order conditions in which the concentration of the nucleophile was at least 100 times as large as that of the ester. The concentration of the ester was in the range $3\text{--}8 \times 10^{-4} \text{ M}$ whereas that of imidazole varied between 1×10^{-3} and $2.4 \times 10^{-2} \text{ M}$. All reactions were carried at four temperatures, viz., 5, 10, 15 and 20°C . The kinetic experiment was initiated by the addition of 0.1 ml of the ester (dissolved in spectroscopic grade ethanol) to an aqueous or alcoholic solution containing the desired concentration of imidazole in a 10 ml flask and thermostated at the desired temperature. The reaction mixture was transferred to the spectrophotometer quartz cell placed in the cell holder. Initially as well as in a number of experiments, full spectral scans between $\lambda=500 \text{ nm}$ and $\lambda=200 \text{ nm}$ were made. In the rest of the experiments, the reaction was monitored at a fixed wavelength of $\lambda=398 \text{ nm}$ representing the maximum wavelength for the appearance of 4-nitrophenolate ion. In all buffered experiments the reaction was initiated by the addition of 0.1 ml of the ester to a thermostated aqueous solution of tris- HClO_4 mixture adjusted to an ionic strength of 0.2 M with LiClO_4 . The pH of the buffered solutions was in the range 3.7–8.9. The reactions were carried out at four temperatures, viz., 15, 20, 25 and 30°C .

Results and Discussions

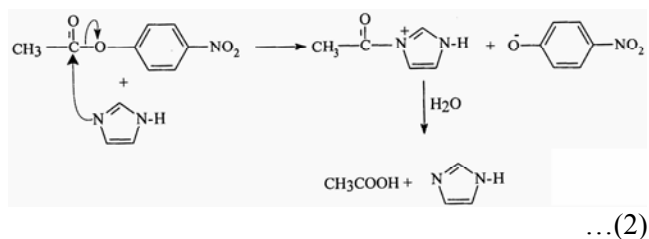
The present work describes a kinetic and mechanistic study of the reaction of 4-nitrophenylacetate ester with the nucleophiles, imidazole and hydroxide ion. In the first study the reaction was carried out in aqueous and alcoholic solutions. In the second case only the aqueous reaction is reported. In all cases the reactions were studied at four temperatures, viz., 5, 10, 15 and 20°C in the case of imidazole as a nucleophile and at 15, 20, 25 and 30°C for the hydroxide reaction.

The reactions of imidazole with the ester in ethanol were carried out at two temperatures only, i.e., 20 and 25°C . The reactions studied may be represented by the reaction (1).



Reaction of 4-nitrophenyl acetate with imidazole in aqueous solutions

An aliquot of 0.1 ml of a stock solution of the ester dissolved in ethanol was diluted with 10 ml of an aqueous solution of imidazole. The use of non-aqueous solvents is necessary for dissolving the ester, which is insoluble in aqueous solutions. The concentration of the ester was maintained at about $7.5 \times 10^{-4} \text{ M}$ and the imidazole varied between 1.2×10^{-3} and $4.7 \times 10^{-3} \text{ M}$. Under these conditions first order plots were obtained. The reactions were followed spectrophotometrically by scanning the spectra at 500–200 nm as a function of time or at a fixed wavelength of $\lambda = 398 \text{ nm}$. The overall reactions is represented by Eq. (2).



The kinetic data were analyzed at the wavelength of maximum change ($\sim 400 \text{ nm}$). In all cases good linear plots were obtained for $\ln(A-A_0)$ versus t over the range of at least five half lives. The values for the observed rate constants, k_{obs} , were obtained from linear least squares treatment of the data. The plots of k_{obs} versus the concentration of imidazole at the four temperatures were linear with zero intercept (Fig. 1), indicating a very slow water reaction in comparison to the reaction with the nucleophile. The slopes of the lines were obtained from linear least squares fit of the data. The second-order rate constants and the corresponding activation parameters are given in Table 1. The overall rate of the reaction can thus be represented by the rate law given by Eq. (3).

$$\text{Rate} = k[\text{Ester}][\text{Im}] \quad \dots(3)$$

Activation parameters obtained from linear fit of $\ln(k/T)$ with $1/T$ and are also given in Table 1.

Reaction of imidazole with 4-nitrophenyl acetate in ethanol

The nucleophilic attack by imidazole on the ester linkage of 4-nitrophenylacetate was studied in 96%

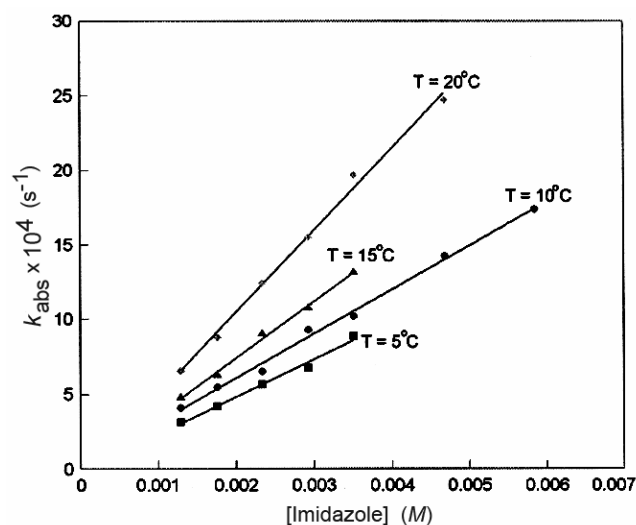


Fig. 1 — Dependence of k_{obs} on imidazole concentration for the reaction of imidazole with 4-nitrophenyl acetate in aqueous solutions.

Table 1 — Second order rate constants and activation parameters for the reaction of imidazole with 4-nitrophenyl acetate in aqueous and ethanol medium

Temp (°C)	Aq. medium k ($M^{-1} s^{-1}$)	Ethanol medium	
		$10^5 k_s$ (s^{-1})	$10^3 k$ ($M^{-1} s^{-1}$)
5	0.25±0.01		
10	0.31±0.01		
15	0.38±0.02		
20	0.54±0.01	5.27±0.10	4.2±0.6
25		5.15±0.08	6.3±0.7
ΔH^\ddagger (kJ mol ⁻¹)	30.7 ± 4		56.9
ΔS^\ddagger (J mol deg ⁻¹)	-109 ± 16		-62.1
ΔG^\ddagger_{298} (kJ mol ⁻¹)	63.3 ± 5		75.4

ethanol as a solvent at 20 and 25°C. The experiments were carried out in exactly the same manner as for the aqueous reaction. The imidazole concentration ranged from $4.7\text{--}23.4 \times 10^{-3} M$ whereas that of the ester was maintained at $3.07 \times 10^{-4} M$. In all the cases good linear plots of $\ln(A - A_\infty)$ versus time were obtained over five half-lives. The final k_{obs} values were obtained from linear least squares fit of the data to the equation of first order kinetics. The dependence of k_{obs} on the concentration of imidazole was linear (Fig. 2) and followed the relationship,

$$k_{\text{obs}} = k_s + k_{\text{Im}} [\text{Im}] \quad \dots(4)$$

where k_s is the rate constant for solvent nucleophilic attack and k_{Im} is the second order rate constant for the reaction of imidazole as a nucleophile. The second order rate constants as well as the activation parameters are given in Table 1.

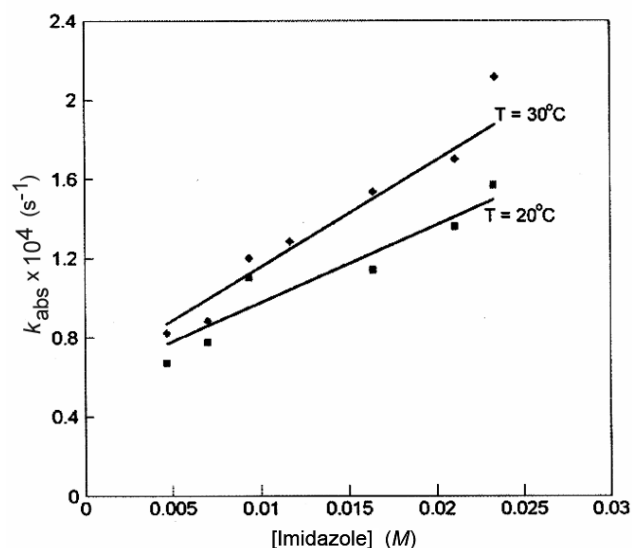


Fig. 2 — Dependence of k_{obs} on imidazole concentration for the reaction of imidazole with 4-nitrophenyl acetate in ethanol.

Table 2 — Values of k_w and k_{OH} and activation parameters for the reaction of OH^- with 4-nitrophenyl acetate at various temperatures

Temp. (°C)	$10^5 k_w$ (s^{-1})	k_{OH} ($M^{-1} s^{-1}$)
15	2.07 ± 0.5	13.0 ± 2
20	2.63 ± 0.3	22.3 ± 2
25	2.33 ± 0.7	43.0 ± 0.3
30	3.83 ± 0.7	69.2 ± 5
ΔH^\ddagger (kJ mol ⁻¹)	84.69	22.58
ΔS^\ddagger (J mol deg ⁻¹)	46.48	-164.62
ΔG^\ddagger_{298} (kJ mol ⁻¹)	75.95	71.64

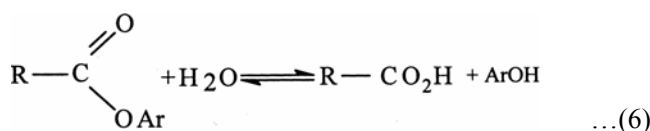
Reaction of hydroxide ion with 4-nitrophenyl acetate

The reaction of OH^- with 4-nitrophenyl acetate was studied at 15, 20, 25, 30°C. The concentration of the ester was maintained at $7.5 \times 10^{-3} M$. The OH^- ion concentration was kept constant by using Tris buffer. A mixture of Tris and HClO_4 was used to give the desired pH value. The concentration of Tris in all solutions was 0.05 M whereas that of perchloric acid varied between 0.01–0.04 M. The pH was varied between 7.3–8.9. For all reactions ionic strength was maintained at a fixed value of 0.2 M, LiClO_4 . Plots of k_{obs} versus OH^- were linear and obeyed the following equation:

$$k_{\text{obs}} = k_w + k_{\text{OH}} [\text{OH}^-] \quad \dots(5)$$

The final least squares values and the corresponding activation parameters are given in Table 2.

The hydrolysis of an ester in an aqueous solution can be represented by Eq. (6).

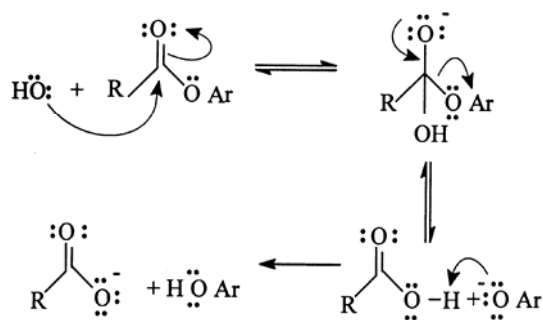


The equilibrium constants for simple ester formation at normal temperatures is of the order of 0.1-10. Hence in principle, Eq. 3 can be driven in either direction by the choice of appropriate experimental conditions. In fact such reactions are quite slow and equilibrium cannot be attained in reasonable time without the use of catalysts. The interaction of esters with nucleophiles, however, is irreversible. Thus the reaction of esters with hydroxide ions in buffered alkaline solutions is irreversible. The reason may be attributed to the fact that no free carboxylic acid is generated, and its removal from the reaction medium drives the reaction to completion. Such a situation is true for all nucleophilic attacks on esters.

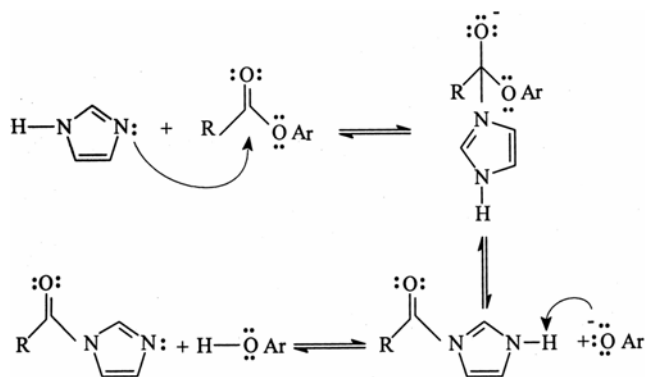
In the present study the reaction of 4-nitrophenylacetate with imidazole as a nucleophile was monitored spectrophotometrically by following the appearance of the generated 4-nitrophenoxide ion. No attempts were made to suppress the formation of H^+ ions resulting from the secondary hydrolysis of acetyl-imidazole. The hydrolysis rate appears to be slow in comparison with the nucleophilic attack on the ester and hence negligible. The second-order nature of the reaction was established by the variation of k_{obs} with the nucleophile concentration.

The base hydrolysis of the ester was followed in buffered aqueous solutions under pseudo-first order conditions. The " k_{obs} " values gave linear dependence on the hydroxide ion concentration as given by Eq. (5), where k_0 represents the water reaction and the buffer dependence rate constant, and k_{OH} is the OH^- catalyzed reaction. All the reactions were carried out in presence of a constant concentration of the buffer and hence no buffer dependence (i.e. general base catalysis path way) is observed. Scheme 1 gives a mechanism for the base hydrolysis of esters. In this mechanism the hydroxide nucleophile attacks at the electrophilic carbon of the ester $\text{C}=\text{O}$, breaking the π bond and forming the tetrahedral intermediate. The intermediate collapses, reforming the $\text{C}=\text{O}$ and results in the loss of the leaving 4-nitrophenyl oxide group and the formation of the carboxylic acid. An acid base reaction results in the deprotonation of the carboxylic acid and the formation of substituted phenol.

The acid base reaction could be assisted by an OH^- attack on the carboxylic acid to form the deprotonated



Scheme 1



Nucleophilic attack of imidazole on the ester

Scheme 2

carboxylic acid and the 4-nitrophenyl oxide which abstracts a proton from a water molecule to form the substituted phenol and regenerate the OH^- ion. The activation parameters for the specific base catalyzed reaction are given in Table 2. The positive value for the entropy of activation indicates that the activated state is less organized than the reactants and supports a concerted mechanism in which simultaneous entering group bond-formation and leaving group bond-breakage is taking place. In addition considerable bond breakage is characteristic of the transition state.

The reaction of imidazole as nucleophile was carried out in aqueous solutions as well as in 96% ethanol-water mixture. The observed pseudo-first-order rate constants in each case gave linear dependencies with the nucleophile concentration. All the lines have zero intercepts within experimental errors and hence it is assumed that the water reaction in both solutions is very small and negligible compared to the nucleophilic attack. The mechanism for the reaction is given in Scheme 2. Here again it is assumed that the imidazole nucleophile attacks at the electrophilic carbon of the ester, $\text{C}=\text{O}$ breaking the π bond and forming the tetrahedral intermediate. The

intermediate collapses, reforming the C=O and results in the loss of the leaving 4-nitrophenyl oxide group and the formation of the protonated alkylimidazole. This is followed by an acid-base reaction in which the 4-nitrophenyl oxide ion abstracts a proton from the imidazole moiety to give the alcohol.

The types of mechanisms discussed above can be viewed as nucleophilic addition elimination or nucleophilic elimination-addition, depending on whether the addition step takes place prior to the elimination step, or vice versa. In the first case the transition state will be characterized by an increase in the coordination of the center of attack and in the second a decrease in coordination will arise. The addition-elimination process can take place at the acyl carbon or at the alkyl carbon of the ester⁷.

Williams *et al.*⁸ postulated a concerted mechanism for the reactions of phenyl esters with phenolate ions when the pK_a of the leaving group is in the range 2-11. On the other hand, based on literature results and thermodynamic calculations of the stability of the intermediate, Guthrie⁹ suggested that in the reactions of arylacetates no intermediate of significant lifetime can be expected. These conclusions were based on the small energy barriers for bond formation and bond rupture of the intermediate. Jenckes and Co-workers¹⁰ also reached the same conclusions in support of a concerted mechanism based on Brønsted type analysis. The controversy, however, persists and further evidence from Brønsted type studies supports a two-step mechanism¹¹. Further studies of isotopic effects led Hengge¹² to conclude that the reaction of oxyanion nucleophilicities with *p*-nitrophenylacetate esters occurs by a concerted mechanism. It was thus suggested that the pK_a of the oxyanion nucleophiles is a determining factor for the transition state structure and that aromaticity and the accompanying delocalized nature of the attacking charge do not result in significant alteration in the transition state structure.

In a number of recent studies^{13,14}, Fernandez and de-Rossi attempted to stabilize the postulated tetrahedral intermediate in the two step mechanism by the trifluoromethyl group in the hydrolysis of trifluoroacetate esters. They concluded on the basis of comparison of free energy relationships that the transition state of the reactions studied, have the same degree of bond formation and rupture and that the tetrahedral intermediate, if it exists, has no significant lifetimes, contrary to their previous conclusions¹⁵. In a recent theoretical study on the hydrolysis of methyl

acetate and acetamide, Hori *et al.*¹⁶ found it necessary to include two water molecules as reactants to obtain a tetrahedron intermediate.

The rate constants data in aqueous solution are approximately ten times as large as those obtained in 96% ethanol, indicating a very large solvent effect and the retarding effect of ethanol on the observed rate. It is now a well established fact that solvent physical as well as chemical properties of the solvent play an important role in chemical reactions. Thus properties of solvent such as polarity, hydrogen-bond donation and acceptance ability, dipole moment, dielectric constant, solvation characteristics and solvent structuredness are quite important factors that affect reaction rates in a direct or indirect manner. In addition, a solvent molecule may act in some reactions as reactant acting as a nucleophile or as an electrophile depending on its chemical nature.

Solvent effects have often been rationalized in terms of solvent polarity, summing up all the specific and non-specific interactions of the reaction medium on the initial and transition states. Hence, the thermodynamic properties, (such as enthalpy, entropy and free energy of solvation of the initial and transition states) are used as an important and convenient tool in obtaining quantitative description of solvation and its effects on reaction rates. Thus, considerable efforts have been devoted to the rationalization of kinetic solvent effects of various types of reactions using a thermodynamic approach^{17,18}.

The activation parameters ΔS^\ddagger , ΔH^\ddagger , ΔG^\ddagger_{298} in the two solvent systems are given in Table 1. Data show a 26 kJ increase in ΔH^\ddagger and a 12 kJ increase in ΔG^\ddagger_{298} values whereas the entropy of activation ΔS^\ddagger becomes less negative by 40 J mol deg⁻¹ on going from the aqueous to the alcohol media. The value of -109 J mol deg⁻¹ for ΔS^\ddagger in water when compared to -62 in alcohol indicates the greater structuredness of the transition state in the aqueous medium. This is attributed to the greater hydrogen bonding ability of water. The decrease in ΔH^\ddagger in water is attributed to the greater solvation of the excited state and the lower solvation of the initial state. Alcohol is a better solvent for the reacting species causing a decrease in the energy of the initial state and its solvating ability of the ionic excited state is not as good as that of water. Hence, the energy of the excited state will be higher in alcohol relative to that in water. The combined effect is an increase in the ΔH^\ddagger value in the alcohol medium. The relatively smaller increase in ΔG^\ddagger_{298} value is due the combined enthalpy and entropy effects.

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