Structure-Reactivity Correlation in the Aminolysis of 4-Fluorophenyl Acetate in Aqueous Medium

D. RAJARATHNAM,[1] T. JEYAKUMAR,[2] P. ANANTHAKRISHNA NADAR[2]

[1] *Department of Chemical and Environmental Engineering, The National University of Singapore,*
4 Engineering Drive 4, Singapore 117576
[2] *Department of Chemistry, Annamalai University, Tamil Nadu, India 608002*

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ABSTRACT: The reaction of the title substrate with a series of amines of varying pK_a, viz. ammonia, ethanolamine, glycine, 1,2-diaminopropane, 1,3-diaminopropane, *n*-butylamine, piperidine, hydrazine, imidazole, and hydroxylamine is subjected to a kinetic study in aqueous medium, 25°C, ionic strength 0.1 M (KCl). Pseudo-first-order rate coefficients (k_{obs}) are found throughout under amine excess at various pH values for each amine. For amines, excluding hydrazine, ammonia, and hydroxylamine the reaction follows clean second-order kinetics and the plots of ($k_{obs} - k_H$) against free amine concentration are linear at constant pH. The macroscopic nucleophilic substitution rate coefficients (k_N) are obtained as the slopes of these plots and found to be pH independent. For hydrazine, ammonia, and hydroxylamine, a rate dependence on more than first power of the amine is observed, accordingly, the rate constants for the assisted paths have been disseminated for these amines besides k_N. The Brönsted-type plot (logk_N against amine pK_a) is linear with a slope value of $\beta = 1.02$. The magnitude of the slope value is consistent with a stepwise mechanism through a zwitterionic tetrahedral addition intermediate whose breakdown to products is rate-determining (k_2 step). A remarkable reactivity difference is observed among the diamines, the reason for which is discussed in detail. © 2002 Wiley Periodicals, Inc. Int J Chem Kinet 34: 366–373, 2002

INTRODUCTION

The aminolysis reactions of phenyl acetate in aqueous medium have been studied extensively. The mechanism of these reactions has been well established through structure-reactivity correlations, especially Brönsted-type plots, in which a zwitterionic tetrahedral intermediate ($T^{\pm}$) in the reaction path has always been postulated [1,2]. The stability of $T^{\pm}$ and the rate-determining step have been found to be dependent on the nature and basicity of the amine moiety as well as the phenoxy group. For simple nucleophilic attack of amine (with no significant second-order term on amine), the reaction can be depicted as shown in Scheme 1, where, either the formation of $T^{\pm}$ is the rate-determining step

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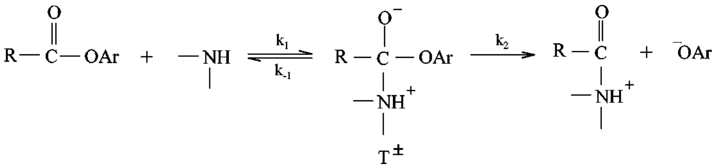
Correspondence to: D. Rajarathnam; e-mail: chedr@nus.edu.sg.



Scheme 1

(k_1 step) with $\beta_{nuc} \cong 0.1 \sim 0.3$ or the breakdown of $T^{\pm}$ to the products is the rate-determining step (k_2 step) with $\beta_{nuc} \cong 0.8 \sim 1.0$ as the basicity of the amine nucleophile varies [3–16].

Though a great deal of information is available on the aminolysis of phenyl acetates in aqueous medium with various substituents [1,4,9–21] that of fluoro substituent is given less attention. In order to clarify the mechanism of the aminolysis of fluoro-substituted phenyl acetate and to assess the influence of amine basicity, in this work we investigate the kinetics of the title reactions in aqueous medium with amines of varying basicity. Through the Brönsted-type plot and the kinetic data a plausible mechanism is deduced.

EXPERIMENTAL

Materials

The 4-fluorophenyl acetate was prepared from corresponding phenol by procedure from the literature [22]. Amines, with the exception of reagent grade imidazole (Fluka) and glycine (BDH), were redistilled from KOH or recrystallized shortly before use. Ethanolamine was simply redistilled. Ammonium chloride (Merck), potassium chloride (Merck), and potassium hydroxide (BDH) were reagent-grade and used as such. Water was double-distilled.

The amines were employed as buffers to maintain constant pH. The amine–amine hydrochloride buffers were prepared shortly before the kinetic run by the addition of calculated amounts of standardized hydrochloric acid or potassium hydroxide to the solutions of known concentrations of amine-free base or amine hydrochloride as the case may be. At any fixed pH value, the concentration of free amine was evaluated using Eq. (1).

$$[N]_F = \frac{[N]_T K_a}{K_a + a_{H^+}} \tag{1}$$

where, $[N]_T$ is the total amine concentration, K_a is the dissociation constant of the conjugate acid of the amine, and a_{H^+} is the hydrogen ion activity. The pK_a of the conjugate acid of amines were determined from measurements of the pH of partially neutralized solutions under identical conditions to those of the kinetic experiments [4,8].

Kinetic Measurements

These were carried out in aqueous medium, ionic strength 0.1 M (KCl), using a JASCO UVIDEC 340 UV–VIS spectrophotometer equipped with a thermostatted cell holder. The reactions were initiated by adding a solution of 30 μl of the ester stock solution (in dioxan) to 3 ml of thermally equilibrated (25.0 ± 0.1°C) amine–amine hydrochloride buffer. The reactions were followed by monitoring the release of the fluorophenolate ion at regular intervals of time at $\lambda_{max} = 272$ nm. The initial ester concentration was (5–6) $\times 10^{-5}$ M, and the amine concentration was kept at several times excess over the substrate. The pH values of the kinetic solutions were determined using ITL digital pH meter both prior to and at the completion of reactions. The glass electrode was calibrated using standard procedures [23].

All the reactions in the present study fitted good pseudo-first-order kinetics up to greater than 90% of the total reaction. Pseudo-first-order rate coefficients (k_{obs}) were found throughout by means of the Guggenheim method employing least squares technique [24]. The correlation coefficients of the linear regressions were always $\geq$0.999. The experimental conditions of aminolysis and the rate coefficients are given in Table I.

In order to evaluate the results, the alkaline hydrolysis of the ester was also followed spectrophotometrically using known concentrations of potassium hydroxide at 25.0 ± 0.1°C and ionic strength 0.1 M (KCl). The second-order rate coefficient, k_{hyd}, (where, $k_{hyd} = k_{obs}/[OH^-]$), for the ester is 2.46 ± 0.07 s^{-1} M^{-1}.

Product Studies

The product studies were carried out according to the procedure already reported [25], based on the method of Katz et al. [26]. The aminolysis of the ester was allowed to go to completion and the acetamide formed was determined by conversion to acetylhydroxamic acid – ferric ion complex. The absorbance of the complex was determined spectrophotometrically at $\lambda_{max} = 540$ nm and the concentration of acetamide was

Table I Summary of Experimental Conditions and Rate Coefficients for the Aminolysis of 4-Fluorophenyl Acetate[a]

Amine	pH	$[N]_F$ (10^{-2} M)[b]	$k_{obsd} - k_H$ (10^{-3} s^{-1})	k_2' (10^{-2} s^{-1} M^{-1})
Ammonia	8.73	12.44–22.39	1.12–2.69	0.90–1.20
	8.90	16.44–29.59	1.34–3.23	0.82–1.10
	9.10	21.85–39.33	1.61–4.32	0.74–1.10
	9.32	28.15–50.67	1.83–4.70	0.65–0.93
Ethanolamine	9.30	7.74–17.02	1.59–3.31	1.97 ± 0.02
	9.51	10.11–22.25	1.83–4.31	1.90 ± 0.09
	9.81	13.42–29.53	2.29–5.20	1.73 ± 0.07
	10.15	16.34–35.95	2.79–6.19	1.72 ± 0.06
Glycine	9.13	10.41–15.41	2.39–4.61	2.65 ± 0.04
	9.34	14.95–22.13	3.49–6.15	2.56 ± 0.06
	9.56	20.72–30.67	3.79–7.55	2.13 ± 0.09
	9.75	26.15–38.70	4.96–9.42	2.15 ± 0.03
1,2-Diaminopropane	9.75	13.93–27.85	3.27–6.80	2.42 ± 0.05
	9.90	16.96–33.93	3.94–8.02	2.33 ± 0.05
	10.20	23.04–46.08	4.53–9.97	2.13 ± 0.07
	10.40	26.57–53.14	5.54–12.00	2.17 ± 0.02
1,3-Diaminopropane	9.90	0.321–0.964	2.33–6.47	70.8 ± 0.5
	10.15	0.494–1.48	3.07–8.30	59.3 ± 0.8
	10.42	0.727–2.18	3.62–11.64	52.1 ± 0.6
	10.71	0.990–2.97	6.43–18.08	63.2 ± 0.8
n-Butylamine	9.52	0.154–1.08	0.491–3.33	30.2 ± 0.2
	9.73	0.238–1.66	0.810–5.32	34.1 ± 0.4
	9.94	0.359–2.51	1.15–7.69	25.9 ± 0.4
	10.15	0.524–3.67	1.62–11.58	31.6 ± 0.3
Piperidine	10.10	0.144–1.01	1.28–7.86	82.2 ± 0.4
	10.35	0.243–1.70	2.04–13.24	80.8 ± 0.6
	10.55	0.359–2.51	2.84–19.35	78.8 ± 0.4
	10.70	0.472–3.30	3.78–26.01	79.7 ± 0.9
Hydrazine	6.90	4.49–6.25	2.49–4.62	5.54–7.40
	7.20	8.29–11.55	5.51–10.06	6.65–8.71
	7.50	14.42–20.08	8.58–15.63	5.95–7.78
	7.90	26.07–36.31	14.50–29.25	5.56–8.06
Imidazole	7.21	7.62–22.85	1.06–3.17	1.40 ± 0.04
	7.41	8.80–26.41	1.23–3.77	1.40 ± 0.02
	7.62	9.80–29.41	1.60–4.61	1.61 ± 0.03
	7.80	10.45–31.36	1.82–4.89	1.65 ± 0.05
Hydroxylamine	6.10	7.93–23.80	1.75–8.92	2.21–3.75
	6.30	9.07–27.20	2.09–10.80	2.30–3.97
	6.55	10.15–30.46	2.78–15.25	2.74–5.01
	6.87	11.04–33.12	3.45–18.72	3.12–5.65

[a] In aqueous solution at 25.0 ± 0.1°C, ionic strength 0.1 M (KCl). At least five runs were carried out at each pH. The errors shown are standard deviations.

[b] Concentration of free amine.

determined from a calibration plot obtained through the standard solutions of acetamide, which showed in all the cases at least 90% of the formation of amide product under the experimental conditions.

RESULTS AND DISCUSSION

The k_{obs} values for the aminolysis of the ester were converted to the apparent second-order rate coefficients, k_2', where $k_2' = (k_{obs} - k_H)/[N]_F$, where k_H is the product of k_{hyd}, the second-order rate coefficient for the alkaline hydrolysis of esters and the concentrations of hydroxide ion present in the system for aminolysis, calculated from a_{OH^-} and the activity coefficient of hydroxide ion [27]. For amines ethanolamine, glycine, 1,2-diaminopropane, 1,3-diaminopropane, *n*-butylamine, piperidine, and imidazole k_2' values are almost constant within a given pH and are independent of free amine concentration (Table I). The plots of $\log(k_{obs} - k_H)$ against $\log[N]_F$ for these amines are

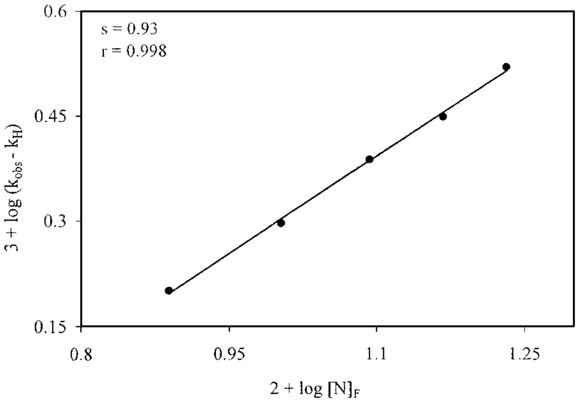


Figure 1 Plot of $\log(k_{\text{obs}} - k_{\text{H}})$ against $\log\,[\text{N}]_{\text{F}}$ for the aminolysis of 4-fluorophenyl acetate by ethanolamine at pH 9.30.

linear with unit slope. A representative plot of ethanolamine at pH 9.30 is shown in Fig. 1. Thus, the aminolysis by these amines depends only upon the first power of free amine concentration and the reaction proceeds by simple nucleophilic attack on ester.

The reactions for these amines are governed by the kinetic law under the experimental conditions given by Eqs. (2) and (3),

$$\frac{d[\text{ArO}^-]}{dt} = (k_{\text{obs}} - k_{\text{H}})[\text{Ester}] \tag{2}$$

$$(k_{\text{obs}} - k_{\text{H}}) = k_0 + k_{\text{N}} F_{\text{N}} [\text{N}]_{\text{T}} \tag{3}$$

where Ar represents 4-fluorophenyl, k_{obs} is the pseudo-first-order rate coefficient, k_0 is the coefficient of assisted paths comprising general acid, general base, and specific base assisted attack of amines, k_{N} is the macroscopic nucleophilic substitution rate coefficient, F_{N} is the free-amine fraction and $[\text{N}]_{\text{T}}$ is the concentration of total amine (free-amine plus protonated form). Since, $F_{\text{N}} = [\text{N}]_{\text{F}}/[\text{N}]_{\text{T}}$, Eq. (3) becomes,

$$(k_{\text{obs}} - k_{\text{H}}) = k_0 + k_{\text{N}} [\text{N}]_{\text{F}} \tag{4}$$

The values of k_0 and k_{N} were obtained as the intercept and slope, respectively, of linear plots of $(k_{\text{obs}} - k_{\text{H}})$ against $[\text{N}]_{\text{F}}$ at constant pH. For the reactions by these amines, the value of k_0 was negligible compared to the aminolysis term in Eq. (4) and k_{N} values obtained were pH-independent. These plots are exemplified for the case of ethanolamine at various pH values in Fig. 2. The mean k_{N} values are given in Table II.

An increase in $k_2{}'$ values is observed for hydrazine, ammonia, and hydroxylamine by varying the concentration of free amine within a given pH (Table I). The plots of $\log(k_{\text{obs}} - k_{\text{H}})$ against $\log[\text{N}]_{\text{F}}$ for this group of amines give slope value more than 1, for which a representative plot is shown in Fig. 3 by hydrazine at pH 6.90. For these amines which show dependence on second-molecule of amine, Eq. (5) governs the reaction:

$$(k_{\text{obs}} - k_{\text{H}})/[\text{N}]_{\text{F}} = k_{\text{N}} + (k_{\text{gb}} + k_{\text{ga}}\, a_{\text{H}}{}^{+}/K_{\text{a}})[\text{N}]_{\text{F}} \tag{5}$$

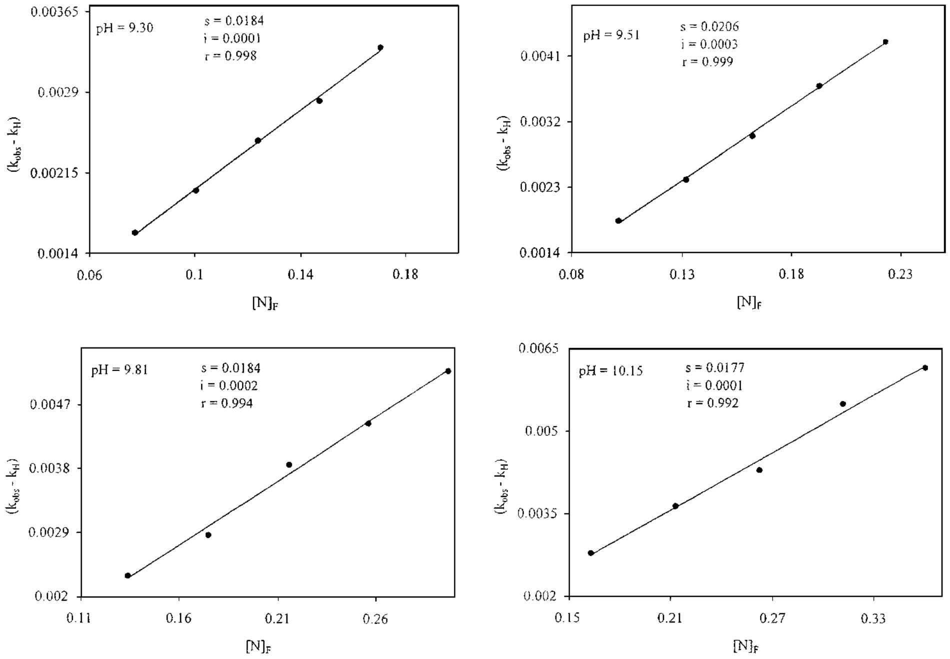


Figure 2 Plots of $(k_{\text{obs}} - k_{\text{H}})$ against $[\text{N}]_{\text{F}}$ for the aminolysis of 4-fluorophenyl acetate by ethanolamine at various pH values.

Table II Macroscopic Nucleophilic Substitution Rate Coefficients for the Aminolysis of 4-Fluorophenyl Acetate[a]

No.	Amine	pK_a	k_N (10^{-2} s^{-1} M^{-1})
1	Ammonia[b]	9.21 ± 0.02	0.41 ± 0.01
2	Ethanolamine	9.50 ± 0.03	1.88 ± 0.05
3	Glycine	9.71 ± 0.05	3.83 ± 0.09
4	1,2-Diaminopropane	9.95 ± 0.07	2.39 ± 0.07
5	1,3-Diaminopropane	10.50 ± 0.09	58.8 ± 0.2
6	*n*-Butylamine	10.60 ± 0.08	31.4 ± 0.5
7	Piperidine	11.21 ± 0.09	77.4 ± 0.8
8	Hydrazine[b]	7.96 ± 0.04	1.01 ± 0.02
9	Imidazole	6.97 ± 0.05	1.46 ± 0.02
10	Hydroxylamine[b]	5.81 ± 0.03	1.62 ± 0.03

[a] Values of both pK_a and k_N in aqueous solution, at $25.0 \pm 0.1^\circ$C, ionic strength 0.1 M (KCl). The errors shown are standard deviations.

[b] For these amines k_N values are determined using Eq. (5).

where, k_{gb}, k_{ga}, and K_a are the rate constants for general base assisted attack of amine, the general acid assisted attack of amine, and the dissociation constant of aminium ion respectively. The values of k_N and $(k_{gb} + k_{ga}a_{H^+}/K_a)$ are obtained as the intercepts and slopes from the plots of $(k_{obs} - k_H)/[N]_F$ against $[N]_F$ for each pH of the medium. Further plot of these slope values against a_{H^+}/K_a should give k_{gb} and k_{ga} as the intercept and slope, respectively. For ammonia and hydroxylamine the slope values of the plots of Eq. (5) are almost constant over the pH range employed and hence taken as k_{gb}. The k_N and k_{gb} values thus derived for ammonia and hydroxylamine are $0.41 \pm 0.01 \times 10^{-2}$ s^{-1} M^{-1}, $1.62 \pm 0.03 \times 10^{-2}$ s^{-1} M^{-1} and $2.07 \pm 0.07 \times 10^{-2}$ s^{-1} M^{-2}, $3.71 \pm 0.03 \times 10^{-2}$ s^{-1} M^{-2}, respectively. For hydrazine the slope values of the plots of Eq. (5) are not constant and decrease with the pH of the medium (Fig. 4). Thus, a further plot of these slope values against a_{H^+}/K_a is drawn for hydrazine as shown in Fig. 5, and the derived k_N, k_{gb}, and k_{ga} values are $1.01 \pm 0.02 \times 10^{-2}$ s^{-1} M^{-1}, 13.27×10^{-2} s^{-1} M^{-2}, and 7.9×10^{-2} s^{-1} M^{-2} respectively. These results are consistent to that observed earlier for the aminolysis of phenyl acetate by these amines in aqueous medium [3,8,17,18].

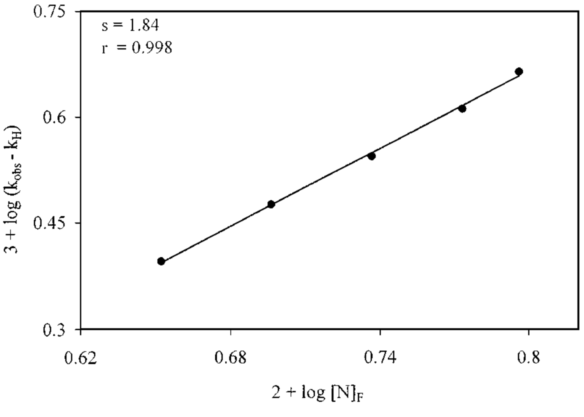


Figure 3 Plot of log $(k_{obs} - k_H)$ against log $[N]_F$ for the aminolysis of 4-fluorophenyl acetate by hydrazine at pH 6.90.

The k_N values thus obtained and the pK_a values were statistically corrected [28–30] before plotting the Brönsted-type equation. The plot is linear for the nucleophiles ammonia, ethanolamine, glycine, 1,3-diaminopropane, *n*-butylamine, and piperidine with a slope value of $\beta = 1.02$ ($r = 0.995$). The plot is shown in Fig. 6. The numbers given in the plot are according to the order of amines given in Table II. Expectedly, hydroxylamine and hydrazine deviate from the plot owing to the "α-effect" [13,31] and imidazole because of its reactivity towards the ester as a tertiary amine [3]. The deviation of 1,2-diaminopropane from the plot and its lesser reactivity are discussed in the later part.

The value of the slope is consistent with a stepwise mechanism, where a $T^{\pm}$ is found on the reaction pathway and its breakdown to products is rate-determining. Larger Brönsted slope values ($\beta_{nuc} = 0.8$–1.0) have been found in the aminolysis of phenyl acetates [14], 2-nitrophenyl acetate [15], 4-nitrophenyl acetate [12], 2,4-dinitrophenyl acetate [9], and other reactive carbonyl compounds [32–38]. In all these studies a stepwise mechanism has been proposed with the breakdown of $T^{\pm}$ to products being the rate-determining step. Contrarily, smaller Brönsted slope values ($\beta_{nuc} = 0.1$–0.3) have been found in the aminolyses of these esters when the formation of $T^{\pm}$ is rate determining [19,39,40].

According to the results and rate law obtained, the analysis of products and the Brönsted-type plot found for the reactions under study, the mechanism of these reactions can be assumed to adopt Scheme I with k_2 step being rate-limiting. Since, for the present reactions $k_{-1} \gg k_2$, it follows that $k_N = K_1k_2$ through the rate

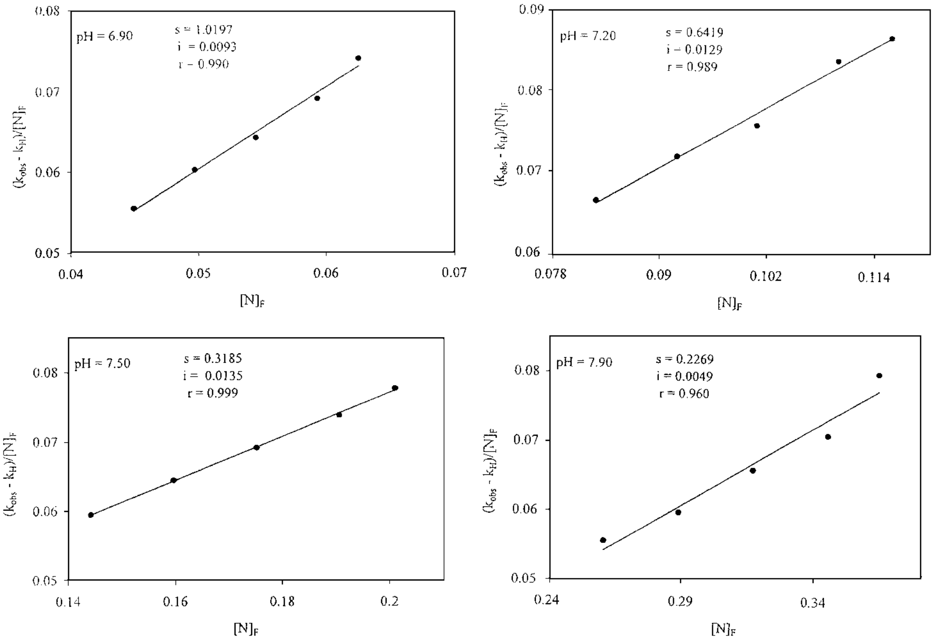


Figure 4 Plots of $(k_{\text{obs}} - k_{\text{H}})/[\text{N}]_{\text{F}}$ against $[\text{N}]_{\text{F}}$ for the aminolysis of 4-fluorophenyl acetate by hydrazine at various pH values.

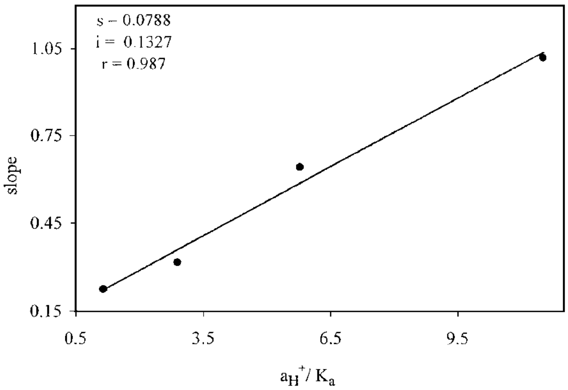


Figure 5 Plot of slope values (from Fig. 4) against $[\text{N}]_{\text{F}}$ for the aminolysis of 4-fluorophenyl acetate by hydrazine.

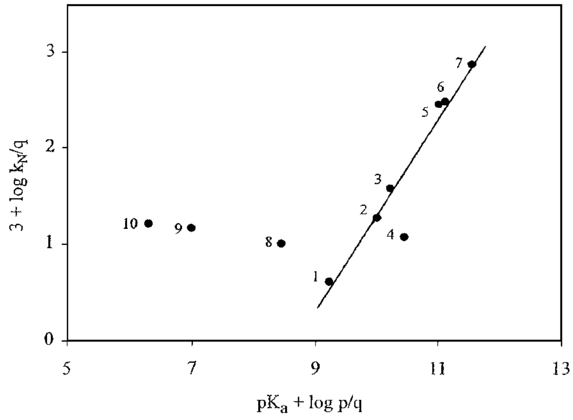
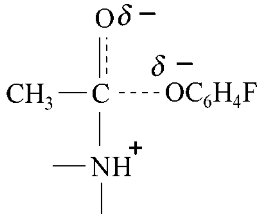


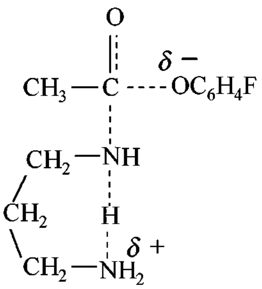
Figure 6 Brönsted-type plot (statistically corrected) obtained in the aminolysis of 4-fluorophenyl acetate in water, 25°C, ionic strength 0.1 M KCl.



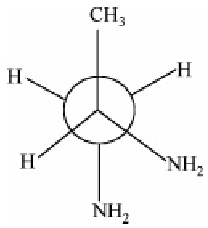
Structure I

expression $k_{\text{N}} = k_1 k_2/(k_{-1} + k_2)$, for the formation of $\text{T}^{\pm}$ assumed under steady-state conditions. Where K_1 is the equilibrium constant for the first step.

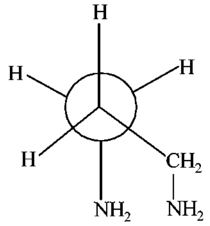
The transition state for the aminolysis of this ester may exist as shown in Structure I. Analogue transition state and a similar rate equation with a preequilibrium step has been proposed in the pyridinolysis of 2,4-dinitrophenyl 4-nitrobenzoate ($\beta_{\text{nuc}} = 0.9$) [34] and, in the aminolysis of 4-acetyl-1-naphthyl acetate ($\beta_{\text{nuc}} = 0.74$) and of 6-acetyl-2-naphthyl acetate ($\beta_{\text{nuc}} = 0.94$) [41] in aqueous medium.



Structure II



Structure III



Structure IV

Among the diamines, the reactivity of 1,3-diaminopropane is higher than 1,2-diaminopropane. Enhanced reactivity was observed in the reactions of diamines with phenyl acetate [7] and acetylimidazole [42] when compared to simple primary amines, which has been attributed to the existence of intramolecular general base catalysis. In the present case, the reaction of 1,3-diaminopropane proceeds in a similar manner with a transition state as shown as Structure II, similar to the one already proposed (7).

However, no such comparable reactivity is observed for 1,2-diaminopropane and also it shows a negative deviation from the plot owing to its decreased reactivity. It has been proposed that for 1,2-disubstituted ethane, XCH_2–CH_2X or XCH_2–CH_2Y (X, Y = polar substituents), molecules prefer "*gauche*" conformation in solution, wherein the structure has the maximum number of gauche interactions between adjacent electron pairs or polar bonds, and is termed as "*gauche effect*" [43–50]. This effect was ascribed to nuclear electron attractive forces between the groups or unshared pair. The diaminopropane can be considered as disubstituted ethane and the "*gauche*" conformations for 1,2-diaminopropane and 1,3-diaminopropane are shown as Structures III and IV, respectively, where for the former "*gauche effect*" can be expected to operate between two adjacent amino groups thereby reducing its nucleophilicity compared to latter for which the amino groups are apart and also the assistance by one amine moiety to other is more probable regardless of the conformation of the C—C bond.

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