Reactions of Aryl Acetates with Secondary Alicyclic Amines in Ethanol/Water Mixtures: Effect of the Solvent Composition on the Kinetics and Mechanism

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ABSTRACT: We report a kinetic study on the reactions of secondary alicyclic amines toward 4-nitrophenyl, 2,4-dinitrophenyl, and 2,4,6-trinitrophenyl acetates (**1**, **2**, and **3**) in ethanol/water mixtures of different compositions. It is found that (i) the intermediate in the reaction of **1** is stabilized in a mixture of 90 vol% ethanol; (ii) for the reaction of **2**, the mechanism is stepwise in water but concerted in the mixtures; (iii) For the reaction of **3**, the mechanism is concerted along the whole range of composition; (iv) the effect of $-NO_2$ outweighs the solvent effect; (v) preferential solvation in the core of reaction can be ruled out. © 2011 Wiley Periodicals, Inc. Int J Chem Kinet 43: 687–693, 2011

INTRODUCTION

The aminolysis reactions of aryl esters in solution have been studied by several groups, and there is now considerable data on the kinetics and mechanisms of these processes [1–31]. Aryl esters are compounds that depending on the nature of the nucleophile, the leaving group, and other factors can react by two possible mechanisms: (i) A concerted pathway [7–14], where the nucleophile attack at the electrophilic carbon in the carbonyl group occurs simultaneously with the leaving group departure within a single step. (ii) A stepwise mechanism where the interaction of the nucleophile with the electrophilic carbon may lead to the formation of a tetrahedral intermediate, $T^{\pm}$, from which the leaving group detaches [1–11,15–31]. In these reactions, as well as in other related ones, several factors have been described as affecting the

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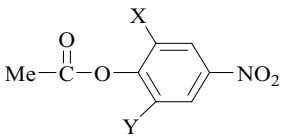


1 X = Y = H
2 X = H; Y = NO_2
3 X = Y = NO_2

Figure 1 General structures of the aryl acetates considered in this study.

kinetics and mechanisms, such as nucleophile nature [12,13,15,16,32–34], leaving-group ability (nucleofugality) [14–31,35–38], nonleaving-group effect [22–24,39,40], nucleophile–electrophile interaction [41], and solvent effects [14,42–47]. Most of these works involve experimental investigations, and there have also been theoretical studies of these factors [14,27,48]. However, concerning the solvent effects on the kinetics and mechanisms, there have been no systematic studies in the literature but only scattered results [14,42–47]. Therefore, the solvent effects in acylation reactions have not been completely documented up to date. Our group has systematically studied the aminolysis of aryl esters in both aqueous solution [17–21,34] and 44 wt% ethanol/water [22–24]. On the contrary, other groups have been studying acylation reactions in pure organic solvents, such as acetonitrile, dimethylsulfoxide, and also in their aqueous mixtures [25,26,28–31,42–47]. Based on these results, it is possible to argue that the interactions between solvent and intermediate $T^{\pm}$, reactants, and transition state (TS) change the reaction mechanism [25,26,28–31,34].

In this work, we report on the kinetics of the reactions of 4-nitrophenyl, 2,4-dinitrophenyl, and 2,4,6-trinitrophenyl acetates (**1, 2**, and **3**, respectively; see Fig. 1) with a series of secondary alicyclic (SA) amines in ethanol/water mixtures of different compositions. The aim of this study is twofold: First, the kinetic measurements are used to obtain Brønsted-type plots (log of rate coefficients vs. pK_a values) and gain useful information about the reaction mechanism. A second goal of this work is to investigate the effects of the solvent and the nucleofuge nature on the kinetics and reaction mechanism.

EXPERIMENTAL

Materials

SA amines were purified by recrystallization or distillation. Acetates **1, 2**, and **3** were prepared as described [49].

Determination of pK_a

The pK_a values for the conjugate acids of the SA amines in different aqueous/ethanol mixtures were determined potentiometrically by the reported method [50]. The experimental conditions used were the same as those used for the kinetic measurements (see below). The pK_a values obtained for the conjugate acids of amines, under these conditions, are shown in Table I.

Kinetic Measurements

The kinetics of the reactions was measured through a diode-array spectrophotometer (at the 300–500 nm wavelength range) in different ethanol/water mixtures at 25.0 ± 0.1°C and an ionic strength of 0.2 M (maintained with KCl). The reactions were studied under at least 10-fold amine excess over the substrate, the initial concentration being 2.5×10^{-5} M. Under these conditions, pseudo-first-order rate coefficients (k_{obs}) were found throughout, the reactions being followed for at least five half-lives by the absorbance increase at the wavelength corresponding to 4-nitrophenoxide (400 nm), 2,4-dinitrophenoxide (350 nm), or 2,4,6-trinitrophenoxide (350 nm) anions. For all the reactions, the pH was maintained constant by the buffer formed by partial protonation of the nucleophile or by addition of an external buffer. Some of the reactions with piperazine and piperazinium ion were studied at several pH values, where mixtures of both amines are present. In these cases, the k_N values were obtained through Eqs. (1) and (2). In these equations, k_{Nobs} is an overall nucleophilic rate constant (corresponding to the mixture of nucleophiles), $[N]_{tot}$ is the total piperazine (piperazine + piperazinium ion) concentration, F_N and F_{NH} are the molar fractions of piperazine and piperazinium ion, respectively, and k_N and k_{NH} are their corresponding nucleophilic rate constants. The values of k_{Nobs} were obtained as the slopes of linear plots of k_{obs} vs. $[N]_{tot}$ at constant pH. The nucleophilic rate constants for the reactions with piperazine (k_N) and piperazinium ion (k_{NH}) were determined through Eq. (2), as described [51].

$$k_{obs} = k_0 + k_{Nobs}[N]_{tot} \quad (1)$$

$$k_{Nobs} = F_N k_N + F_{NH} k_{NH} \quad (2)$$

Reaction Product Studies

For the reactions of **1, 2** and **3**, one of the products was identified as 4-nitrophenoxide, 2,4-dinitrophenoxide, and 2,4,6-trinitrophenoxide anions, respectively. This

Table I Values of pK_a for the Conjugate Acids of SA Amines and k_N Values for the Reactions of SA Amines with Acetates **1**, **2**, and **3** in Different Aqueous/Ethanol Mixtures[a]

Substrate	Ethanol (Vol%)	SA Amine	pK_a	$k_N/(s^{-1}\ M^{-1})$
1	90	Piperidine	10.0	2.50
		Piperazine	9.13	0.82
		1-(2-Hydroxyethyl)piperazine	8.65	0.20
		Morpholine	7.98	0.075
		1-Formylpiperazine	6.96	0.0086
1	25	Piperidine	11.02	15.9
		Piperazine	9.86	3.20
		1-(2-Hydroxyethyl)piperazine	9.16	0.636
		Morpholine	8.56	0.253
		1-Formylpiperazine	7.71	0.041
		Piperazinium ion	5.41	0.000222
2	75	Morpholine	8.23	16.6
2	50	Piperidine	10.82	194
		Piperazine	9.71	129
		1-(2-Hydroxyethyl)piperazine	9.09	38.0
		Morpholine	8.48	30.0
		1-Formylpiperazine	7.63	6.0
		Piperazinium ion	5.37	0.67
2	25	Piperidine	11.02	423
		Piperazine	9.86	275
		1-(2-Hydroxyethyl)piperazine	9.16	72.2
		Morpholine	8.56	39.8
		1-Formylpiperazine	7.71	9.13
		Piperazinium ion	5.41	0.84
2	10	Piperidine	11.15	789
		Piperazine	9.90	275
		1-(2-Hydroxyethyl)piperazine	9.29	110
		Morpholine	8.71	70.3
		1-Formylpiperazine	7.57	15.3
		Piperazinium ion	6.65	0.879
3	50	Piperidine	10.82	1814
		Piperazine	9.71	1241
		1-(2-Hydroxyethyl)piperazine	9.09	129
		Morpholine	8.48	214
		1-Formylpiperazine	7.63	29.8
		Piperazinium ion	5.37	3.5

[a] Both pK_a and k_N values were obtained in the corresponding ethanol/water mixture, at 25.0 ± 0.1°C and an ionic strength of 0.2 M.

was achieved by comparison of the UV–vis spectra after completion of the reactions with those of the authentic samples of the corresponding phenoxide ions under the same experimental conditions.

RESULTS AND DISCUSSION

The kinetics of all the studied reactions obeyed Eq. (3), where k_0 and k_N are the rate coefficients for solvolysis (ethanolysis and/or hydrolysis) and aminolysis of the substrates, respectively. The values of k_0 and k_N showed no dependence on pH within the pH range employed. These values were obtained as the intercept and slope, respectively, of linear plots of k_{obs} against the free amine concentration (Eq. (3)) at constant pH. The experimental conditions, the amine concentration, and k_{obs} values for the studied reactions are shown in Tables S-1 to S-32 in the Supporting Information.

$$k_{obs} = k_0 + k_N\,[\text{free amine}] \tag{3}$$

The k_0 values were much smaller than those of the k_N [free amine] term in Eq. (3). The values of k_N for the

reactions of acetates **1, 2**, and **3** with SA amines in different aqueous/ethanol mixtures are shown in Table I.

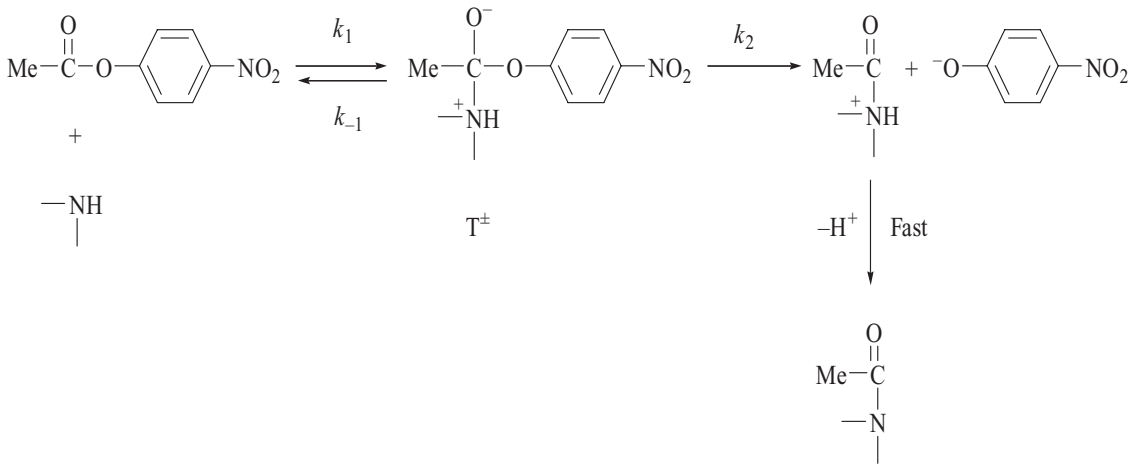
With the k_N and pK_a data of Table I, the statistically corrected Brønsted-type plots ($\log k_N/q$ vs. $pK_a + \log(p/q)$) were obtained with $q = 2$ for piperazine ($q = 1$ for all other amines) and $p = 2$ for all conjugate acids of the amines, except for the piperazinium ion with $p = 4$. The parameter q is the number of equivalent basic sites on the free amine, and p is the number of equivalent dissociable protons on the conjugate acid of the amine [12,13,52]. These plots are shown in Figs. S1–S6 in the Supporting Information. The Brønsted-type plots obtained in different aqueous/ethanol mixtures are linear with slopes, $\beta = 0.8$ and 0.9 for the reactions of **1** at 90 and 25 vol% ethanol, respectively, and $\beta = 0.49$–0.54 for the reactions of **2** and **3** at 10–50 vol% ethanol. The values of the Brønsted slopes for the reactions of **1** are in accordance with a stepwise mechanism where breakdown to products of a tetrahedral intermediate is the rate-determining step. In these cases, the slope values usually vary between 0.8 and 1.1 [1–11,15–25,53,54]. On the contrary, the magnitude of the slopes for the reactions of acetates **2** and **3** is in accordance with a concerted mechanism, which usually exhibits slope values of 0.4–0.7 [7–14,32,33]. The β value measures the effective charge development from reactants to the TS. For stepwise reactions, the amino moiety in the TS for the second step has a full positive charge (full C–N bond formation), and in concerted reactions this charge is smaller (partial C–N bond formation). This is why for the former mechanism β is near unity, whereas for a concerted process, β is smaller than unity.

Table II shows the β values and the mechanisms associated with the studied reactions. Also included are the reported values for the reactions in water [13,15,20].

The following three important observations can be drawn from Table II:

1. The reactions of **1** with SA amines proceed by a stepwise mechanism through a zwitterionic tetrahedral intermediate ($T^{\pm}$), as that shown in Scheme 1, regardless of the aqueous ethanol composition. According to the Brønsted slopes found, expulsion of 4-nitrophenoxide from the $T^{\pm}$ intermediate is the rate-determining step. Therefore, it can be concluded that the $T^{\pm}$ intermediate is stabilized even in the 90 vol% ethanol mixture.
2. The SA aminolysis of **2** is stepwise in water, but concerted in aqueous ethanol mixtures. The concerted process is shown in Scheme 2 (with X = H).
3. The reactions of **3** with SA amines are governed by a concerted mechanism, as that of Scheme 2 ($X = NO_2$), in the whole range of the solvent mixtures studied.

The incorporation of a second NO_2 group in the nucleofuge of the substrate (compound **2**) does not change the stepwise mechanism in water solution, but the incorporation of a third NO_2 group (compound **3**) in this solvent destabilizes the $T^{\pm}$ intermediate, changing the mechanism to a concerted one [13]. Nevertheless, in 10 vol% ethanol, the incorporation of the second nitro group is sufficient to destabilize the $T^{\pm}$ intermediate. This fact can be attributed to the decreasing stability of the intermediate due to not only the



Scheme 1 Stepwise reaction mechanism for the acetylation reactions of SA amines with compound **1** in different aqueous/ethanol mixtures.

Table II Values of Brønsted Slopes (β) and Associated Mechanisms (Concerted or Stepwise) for the Reactions of **1**, **2**, and **3** with SA Amines in Different Aqueous Ethanol Mixtures[a]

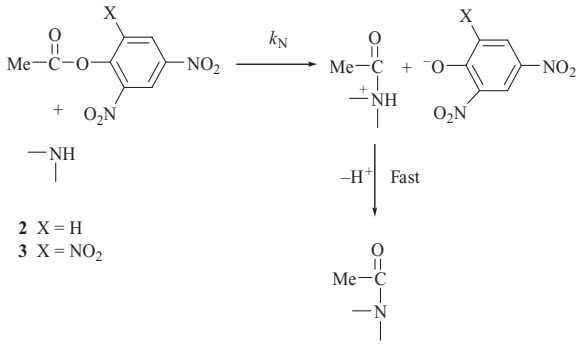
	β Values and Associated Reaction Mechanisms in Ethanol (Vol%)				
Substrate	0	10	25	50	90
1	0.82 stepwise [15]		0.91 stepwise		0.81 stepwise
2	0.2 and 0.85 stepwise [20]	0.54 concerted	0.50 concerted	0.49 concerted	
3	0.41 concerted [13]			0.52 concerted	

[a] β values determined in this work, unless otherwise stated.

electron-withdrawing ability of the NO_2 group in the aromatic ring, leading to a greater nucleofugality but also the effect of the less polar solvent [54]. Another destabilizing factor is the increase in the amine nucleofugality from the $T^{\pm}$ intermediate by the change in solvent from water to aqueous ethanol. It is known that in the aminolysis of esters and diaryl carbonates the amine is expelled faster from the $T^{\pm}$ intermediate by the change to a less polar solvent [54]. Note that for acetate **2**, the change in solvent from water to aqueous 10 vol% ethanol destabilizes the tetrahedral intermediate as well as the incorporation of a third nitro group.

Table I shows that for compounds **1** and **2** the k_N values increase in accordance with the percentage of water in the solvent mixture. On the basis of this observation, we can conclude that the global solvent composition (in the bulk) is the same as that in the solvation shell in the reaction center. This rules out a preferential solvation behavior.

Figure 2 shows the relationship between log k_N and the polarity E_T (30) parameter for the reactions of compound **2** with morpholine and 1-formylpiperazine. The latter was determined using Langhals equation [55] for different vol% of ethanol in the studied mixtures.



Scheme 2 Concerted reaction mechanism for the acetylation reactions of SA amines with compounds **2** and **3** in different ethanol aqueous mixtures.

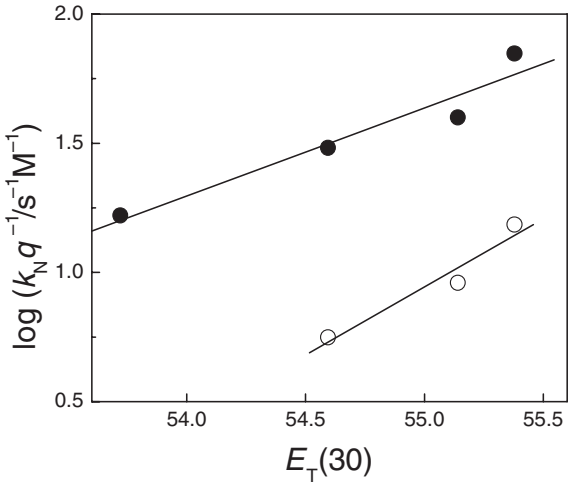


Figure 2 Relationships between log k_N/q values and the E_T (30) parameter for the reactions of compound **2** with morpholine (●) and 1-formylpiperazine (○) in different aqueous/ethanol solvents.

In these cases, linear plots with positive slopes are observed, which can be explained by a greater stabilization of the TS (of the concerted pathway), with respect to reactants, as the solvent mixture becomes more aqueous. It is reasonable that in water media, the putative tetrahedral intermediate would be stabilized favoring the stepwise mechanism.

CONCLUSIONS

The acetylation reactions of a series of aryl acetates toward SA amines are kinetically studied in several aqueous ethanol mixtures. The kinetic data for the reactions of compound **1** are consistent with a stepwise mechanism, with breakdown to products of the tetrahedral intermediate as the rate-determining step for the whole range of solvent mixtures studied. On the

contrary, for the reactions of compounds **2** and **3** the kinetic results are in accordance with a concerted mechanism. From the analysis of the solvent effects on the reaction mechanisms, it is found that (i) for the SA aminolysis of acetate **1**, the tetrahedral intermediate is relatively stable even in 90 vol% ethanol; (ii) the aminolysis of compound **2** is stepwise in water, but concerted in the aqueous/ethanol mixtures studied; (iii) for the aminolysis of compound **2**, the change of solvent from water to aqueous 10 vol% ethanol, as well as the incorporation of a third nitro group, destabilizes the tetrahedral intermediate; (iv) a change of solvent mixture does not change the mechanism of the aminolysis of acetate **3**; and (v) preferential solvation in the core of the reaction can be ruled out for the SA aminolysis of compound **2**.

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