

Kinetics and Mechanism for the Reaction of 4-Nitrophenyl 2-Furoate with Secondary Alicyclic Amines

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Second-order-rate constants (k_N) have been measured spectrophotometrically for the reactions of 4-nitrophenyl 2-furoate (**1**) with a series of secondary alicyclic amines in H₂O containing 20 mole % DMSO at 25.0 °C. **1** is about 5–8 times more reactive than 4-nitrophenyl benzoate (**2**), although **1** is expected to be less reactive than **2** based on MO calculations and ¹³C NMR study. The Brønsted-type plots for the aminolysis reactions of **1** and **2** are linear with β_{nic} values of 0.78 and 0.85, respectively. The replacement of the CH–CH group by an O atom in the acyl moiety (**2** → **1**) does not cause any mechanism change. The reaction of piperidine with a series of substituted phenyl 2-furoates gives a linear Hammett plot with a large ρ^- value ($\rho^- = 2.88$) when σ^- constants are used. The linear Brønsted and Hammett plots with a large ρ^- value suggest that the aminolysis reaction of **1** proceeds via rate-determining break-down of the addition intermediate to the products.

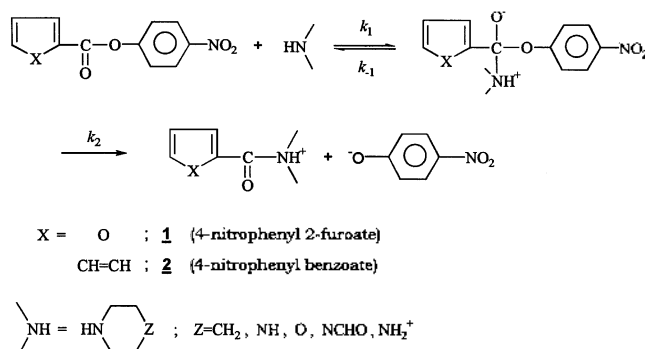
Introduction

Aminolyses of carboxylic esters have intensively been investigated due to importance in chemistry and in biological processes, and their reaction mechanisms are fairly well known.^{1–5} Linear free energy relationships such as Brønsted and Hammett equations have been most frequently used to investigate the reaction mechanism.⁶ A break or curvature in Brønsted-type plots has often been observed for aminolyses of esters with a good leaving group, *i.e.*, from a large slope ($\beta = 0.8 \pm 0.1$) to a small one ($\beta = 0.2 \pm 0.1$) as the amine basicity increases significantly.^{3,4} The break has been attributed to a change in rate-determining step (RDS) for a step-wise reaction. The position of the break in Brønsted-type plots ($\text{p}K_a$) for ester aminolyses has been reported to occur when the amine becomes more basic than the leaving group by 4–5 $\text{p}K_a$ units.^{3,4}

Until recently, most studies have been focused on the effect of leaving group and incoming amines. The effect of acyl moiety on reaction rates and mechanism has been rarely investigated.^{7,9} We recently have performed aminolyses of carboxylic esters with various acyl moiety, such as acetyl, phenylacetyl and substituted benzoyl groups.⁷ In order to expand our study on the effect of acyl moiety on rates and reaction mechanism, we replaced the CH=CH group by an O atom in the acyl moiety as shown in Scheme 1, and performed aminolysis reactions with a series of secondary alicyclic amines. We also investigated the effect of leaving group on reaction rates in order to get further information about the reaction mechanism.

Experimental Section

Materials. Aryl 2-furoates were easily prepared from the reaction of 2-furoyl chloride and corresponding phenols in the presence of triethylamine in methylene chloride.¹⁰



Scheme 1

Other chemicals including the amines used were of the highest quality available from Aldrich. Doubly glass distilled water was further boiled and cooled under a nitrogen atmosphere just before use.

Kinetics. The reactions were followed by monitoring the appearance of the leaving group (substituted phenoxides or phenols) using a Hewlett Packard 8452A Diode UV-vis Spectrophotometer with a Shimadzu TB-85 model constant temperature circulating bath to keep the temperature in the reaction cell at 25.0 ± 0.1 °C. All the reactions were performed under pseudo-first-order conditions in which the amine concentrations were in much excess of the substrate concentration (at least 20 times). The amine solutions were prepared by dissolving equivalent amount of free amine and the conjugate acid of the amine to keep the pH constant. The reaction medium was water containing 20 mole % dimethyl sulfoxide (DMSO) in order to eliminate solubility problems. All the solutions were prepared freshly just before use under a nitrogen atmosphere and transferred by Hamilton gas-tight syringes. The effect of ionic strength on rates was observed to be negligible in the present system. Other details in kinetic methods were similar to the ones described previously.⁷

Results and Discussion

All the reactions in the present study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obs}) were obtained from the slope of the plot of $\ln(A-A_t)$ vs. time. The kinetic results are summarized in Table 1 together with reaction conditions. As shown in Figure 1, the plots of k_{obs} vs. amine concentration are linear, indicating that general base catalysis is absent. Second-order rate constants (k_N) were calculated from the slope of the plots of k_{obs} vs. amine concentrations. Generally five different amine concentrations were used to calculate k_N values. Correlation coefficient of the plot was usually higher than 0.9995. It is estimated from replicate runs that the error in any particular measured rate constant is less than $\pm 3\%$. The k_N values obtained in this way are summarized in Table 2 together with the data for the corresponding reactions with **2** for a comparison purpose.

As shown in Table 2, **1** appears to be more reactive than **2** by 5–8 fold toward all the amines studied. This is consistent with their reactivity order in absolute ethanol, *i.e.*, **1** was reported to be about 2 fold more reactive than **2** toward EtO^- in absolute ethanol.¹¹ Recently MO calculations have shown

Table 1. Experimental Conditions and Pseudo-First-Order Rate Constants (k_{obs}) for Aminolyses of 4-Nitrophenyl 2-Furoate (**1**) in H_2O Containing 20 mole % DMSO at 25.0 °C

Amine (<i>Z</i>)	[>NH]/10 ⁻³ , M	$k_{\text{obs}}/10^{-3} \text{ s}^{-1}$
1. piperidine (CH_2)	.799~3.93	17.4~98.0
2. piperazine (NH)	.799~3.93	3.71~20.7
3. morpholine (O)	3.93~18.2	1.90~9.80
4. 1-formylpiperazine (NCHO)	3.93~18.2	0.100~1.25
5. piperazinium ion (NH_2^+)	3.93~18.2	0.010~0.0510

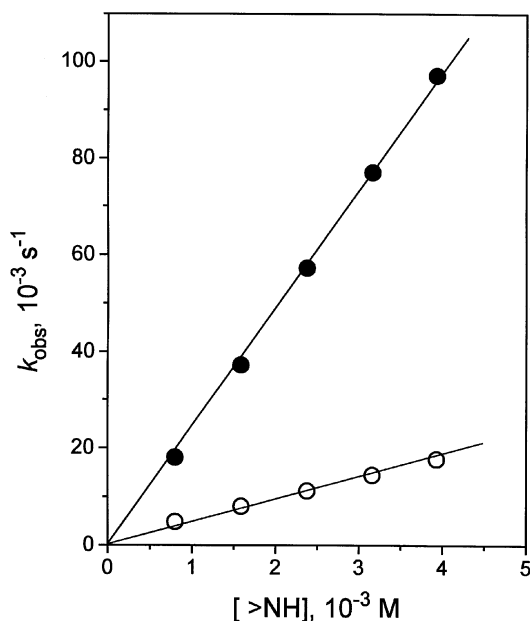


Figure 1. Plots showing dependence of k_{obs} on amine concentrations for the reaction of 4-nitrophenyl 2-furoate (**1**) with piperidine (●) and piperazine (○) in 20 mole % DMSO- H_2O at 25.0 °C.

Table 2. Summary of Second-Order Rate Constants (k_N) for Aminolysis of 4-Nitrophenyl 2-Furoate (**1**) and Benzoate (**2**) in 20 mole % DMSO- H_2O at 25.0 °C

Amine	$\text{p}K_a^a$	$10^3 k_N (\text{M}^{-1} \text{s}^{-1})$	
		1	2
1. piperidine	11.02	253	52.9
2. 3-methyl piperidine	10.8	-	35.5
3. piperazine	9.85	41.1	8.41
4. morpholine	8.65	5.30	.841
5. 1-formyl piperazine	7.98	.733	-
6. piperazinium ion	5.95	.0290	.00466

^aData taken from reference 15.

that the delocalizability of ring electrons in the acyl moiety to the carbonyl group is more significant for **1** than **2**, and the positive charge on the carbonyl carbon of **1** has been calculated to be lower than that of **2**.¹³ Our ^{13}C NMR study is consistent with the result of the MO calculation, *i.e.*, the ^{13}C chemical shift of the carbonyl carbon of **1** and **2** is 163.4 and 163.8 ppm, respectively, indicating that the positive charge of the carbonyl carbon of **2** is slightly higher than that of **1**. Therefore, one would expect **1** is less reactive than **2**, if the initial state stability and the positive charge on the carbonyl group were mainly important for the reactivity of **1** and **2**. However, this argument has been suggested to be only valid when the aminolysis proceeds by rate-determining attack of amine to the carbonyl group of **1** and **2**.¹² In fact, **1** is more reactive than **2**, indicating that the attack of amine to the carbonyl group does not occur at the rate determining step (RDS).

As shown in Table 2, the reactivity of amines increases with increasing amine basicity for both **1** and **2** systems. In

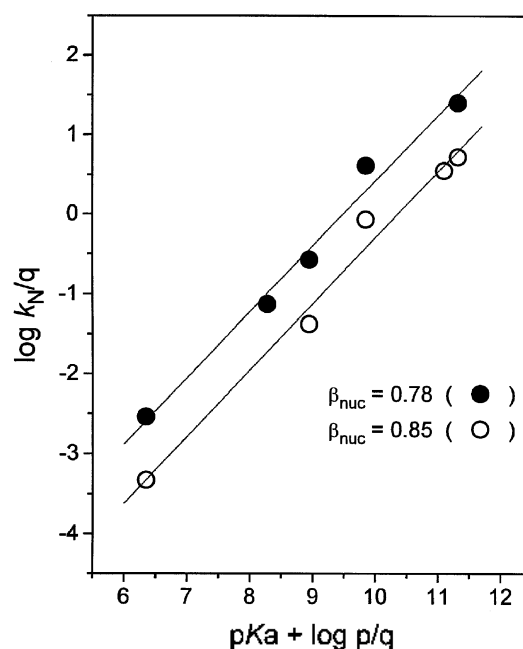


Figure 2. Brønsted-type plots for the reaction of 4-nitrophenyl 2-furoate (**1**) (●) and benzoate (**2**) (○) with a series of secondary alicyclic amines in 20 mole % DMSO- H_2O at 25.0 °C.

order to see the effect of amine basicity on the reactivity of **1** and **2**, Brønsted-type plots have been constructed in Figure 2. Linear Brønsted-type plots have been obtained. Such a linear Brønsted-type plot suggests that there is no mechanism change for the present aminolysis reactions of **1** and **2**.

A break or nonlinear Brønsted-type plot has often been observed for aminolysis reactions of esters with a good leaving group (e.g., 2,4-dinitrophenoxide and 4-nitrothiophenoxide) as the amine basicity increases significantly, and been used as evidence of a change in the RDS from the breakdown of the addition intermediate to the products (the k_2 step in Scheme 1) to the formation of the intermediate (the k_1 step in Scheme 1).^{3,4} A break or curvature in a Brønsted-type plot has been reported to occur when the incoming amine becomes about 4-5 pKa units more basic than the leaving group.^{3,4} The pKa of the conjugate acid of the leaving group (4-nitrophenoxide) is 7.14, and the most basic amine used in the present system is piperidine whose pKa is 11.02. Since the difference in pKa between the leaving group and the most basic amine is smaller than 4 pKa units, a break in the Brønsted-type plot for the present aminolysis would not be expected to occur.

Jencks¹³ and Castro⁸ have suggested that the position of a break (pK^0) in Brønsted-type plot is dependent on the electronic nature of the substituent in the acyl moiety of esters, i.e., an electron donating group (EDG) in the acyl moiety decreases pK^0 by favoring the expulsion of aryloxide relative to amine, while an electron withdrawing group (EWG) increases pK^0 by favoring the expulsion of amine from the addition intermediate. Since O atom is more electronegative than C atom, it would behave as an EWG in a system in which resonance of the nonbonding electrons on O atom is absent. However, delocalization of the nonbonding electrons of the O atom in the acyl moiety of **1** is possible by direct resonance. Therefore, the O atom would behave as an EDG in **1**. This argument is consistent with the result of MO calculations¹² and ¹³C NMR study which supports that the positive charge on the carbonyl carbon is less significant for **1** than **2**. Therefore, one might have observed a break in the Brønsted-type plot for the aminolysis of **1**, if pK^0 is governed by the electronic nature of the acyl moiety. In fact, one can not see any break in the Brønsted-type plot for the reaction of **1** as shown in Figure 2. The present result is consistent with our recent proposal that pK^0 is independent on the electronic nature of the acyl substituent for aminolysis of 2,4-dinitrophenyl substituted benzoates.¹⁴

The magnitude of β_{mic} has been calculated to be 0.78 and 0.85 for the present aminolysis reactions of **1** and **2**, respectively. Useful information can be obtained from β_{mic} values.⁶ The magnitude of β_{mic} value has been suggested to be as a measure of the effective charge developed at the N atom at the transition state (TS) in the RDS of aminolysis reactions.^{14,15} Therefore, one might consider the positive charge on the N atom at the TS is slightly less significant for the reaction of **1** than that of **2**. The magnitude of β_{mic} has also been suggested to represent a selectivity parameter.¹⁶ Since **1** is more reactive than **2**, and the β_{mic} value for **1** is smaller

Table 3. Summary of Second-Order Rate Constants (k_N) for the Reaction of Y-Substituted Phenyl 2-Furoate with Piperidine in 20 mole % DMSO-H₂O at 25.0 °C^a

Y	σ^-	σ	$k_N, \text{M}^{-1}\text{s}^{-1}$
4-NO ₂	1.27	0.78	25.3
4-CHO	1.13	0.42	4.79
4-COCH ₃	0.87	0.50	1.90
4-Cl	0.23	0.23	0.019

^a σ^- and constants taken from reference 18.

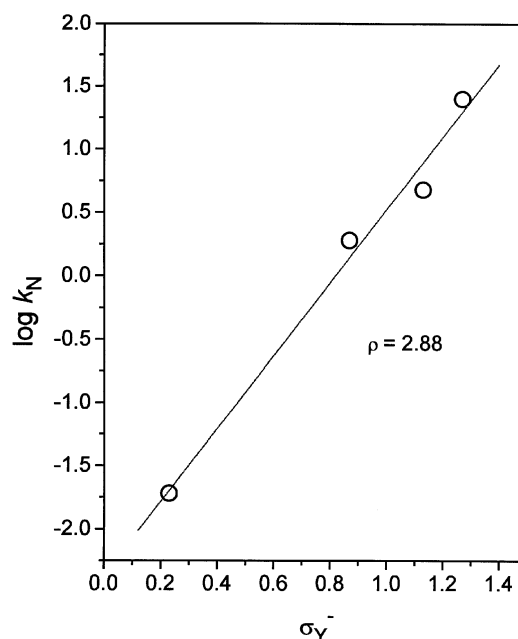


Figure 3. A Hammett plot for the reaction of substituted phenyl 2-furoates with piperidine in 20 mole % DMSO-H₂O at 25.0 °C.

than that for **2**, the reactivity-selectivity principle is operative in the present system.

In order to obtain more information about the reaction mechanism and the TS structure, the effect of leaving group on rates has been investigated by changing the substituent in the leaving group from 4-NO₂ to 4-CHO, 4-COCH₃ and 4-Cl. The kinetic results are summarized in Table 3 and demonstrated graphically in Figure 3.

One can see that the reactivity increases with increasing electron withdrawing ability of the substituent in the leaving group. σ^- constants give much better Hammett correlation than σ constants with a large ρ^- value ($\rho^- = 2.88$) as shown in Figure 3. However, the Hammett plots for the reaction of aryloxides with **2** or its analogues have been reported to give extremely poor correlation when σ^- constants were used.¹⁷ Slightly better but still poor Hammett correlation has been obtained when σ^0 constants were used.¹⁷ The contrasting results clearly imply that there is a difference in the mechanism between the reactions with amines and with aryloxides. If the leaving group departure occurs at the RDS, a partial negative charge would develop at the O atom of the leaving aryloxide. Such a partial negative charge can be delocalized onto the substituent in the leaving group (e.g., 4-NO₂, 4-

CHO, 4-COCH₃) by direct resonance. Therefore σ constants should give better correlation than constants if the leaving group departure occurs at the RDS. The fact that σ constants give better correlation for the present aminolysis suggests that the leaving group departure occurs at the RDS. Besides, the large ρ value obtained in the present system suggests that the degree of leaving group departure is significantly advanced at the rate-determining TS. This argument is consistent with the preceding proposal that the present aminolysis proceeds via an addition intermediate and the collapse of the intermediate to the products is the RDS.

Conclusions

The present study allows us to conclude the following: (1) **1** is more reactive than **2**, although the positive charge on the carbonyl carbon of the former has been suggested to be less significant than that of the latter; (2) The replacement of the CH=CH group by an O atom in the acyl moiety (**2** \rightarrow **1**) increases reactivity but does not cause any mechanism change; (3) The Brønsted-type plots for the aminolysis reactions of **1** and **2** are linear and the Hammett plot with σ constants gives better correlation than the one with σ constants for the reactions of substituted phenyl 2-furoates with piperidine, indicating that the aminolysis of **1** proceeds via a rate determining break-down of the addition intermediate to the products.

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