# Aminolyses of 2,4-Dinitrophenyl 2-Furoate and Benzoate: Effect of Nonleaving Group on Reactivity and Mechanism

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Second-order rate constants ($k_N$) have been determined spectrophotometrically for reactions of 2,4-dintrophenyl 2-furoate (**2**) with a series of alicyclic secondary amines in 80 mol % $H_2O$/20 mol % dimethyl sulfoxide (DMSO) at 25.0 °C. The furoate **2** is more reactive than 2,4-dintrophenyl benzoate (**1**) toward all the amines studied. The higher acidity of 2-furoic acid ($pK_a = 3.16$) compared with benzoic acid ($pK_a = 4.20$) has been suggested to be responsible for the reactivity order, at least in part. The Brønsted-type plots for the reactions of **1** and **2** are curved downwardly, indicating that the aminolyses of both **1** and **2** proceed through a zwitterionic tetrahedral intermediate ($T^\pm$) with a change in the rate-determining step on changing the amine basicity. Dissection of the $k_N$ values into their microscopic rate constants has revealed that the $pK_a^o$ and $k_2/k_{-1}$ ratios for the reactions of **1** and **2** are identical, indicating that the nature of the nonleaving group (*i.e.*, benzoyl and 2-furoyl) does not affect the reaction mechanism. The $k_1$ values have been found to be larger for the reactions of **2** than for those of **1**, which is fully responsible for the fact that the former is more reactive than the latter.

**Key Words :** Aminolysis, Nonleaving group, Yukawa-Tsuno plot, Rate-determining step, Reaction mechanism
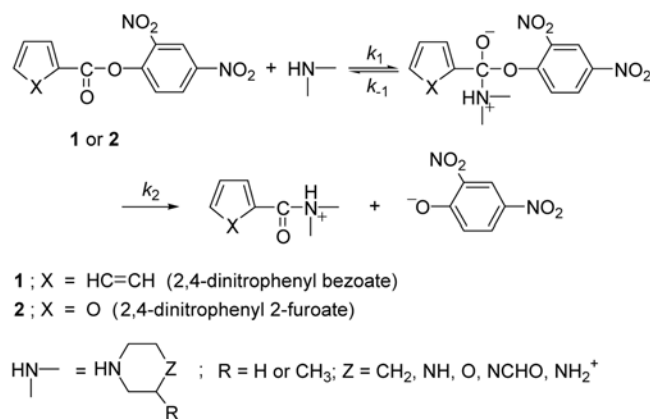
## Introduction

Aminolysis of esters with a good leaving group has often resulted in a curved Brønsted-type plot, *i.e.*, a large slope ($\beta_2 = 0.8 \pm 0.2$) for reactions with weakly basic amines but a small one ($\beta_1 = 0.3 \pm 0.1$) for reactions with strongly basic amines.[1-11] Accordingly, aminolyses of esters have generally been understood to proceed through a zwitterionic tetrahedral intermediate ($T^\pm$) with a change in the rate-determining step (RDS).[1-11]

It has been reported that the RDS changes at $pK_a^o$ (*i.e.*, the curvature center of the curved Brønsted-type plot) from breakdown of $T^\pm$ to its formation as the attacking amine becomes more basic than the leaving group by 4 to 5 $pK_a$ units.[6-11] Gresser and Jencks have found that the $pK_a^o$ value increases as the substituent in the nonleaving group becomes a stronger electron withdrawing group (EWG) for quinuclidinolysis of diaryl carbonates in water.[6] This result has been explained through the argument that an EWG in the nonleaving group favors the departure of amine from $T^\pm$ ($k_{-1}$) than that of the leaving group ($k_2$) as the electron withdrawing ability of the substituent in the nonleaving group increases.[6] Castro et al. have obtained a similar result for pyridinolysis of 2,4-dinitrophenyl X-substituted benzoates (*i.e.*, $pK_a^o = 9.5$ when X = H but $pK_a^o > 9.5$ when X = Cl, CN, or $NO_2$)[7] and *S*-2,4-dinitrophenyl X-substituted thiobenzoates (*i.e.*, $pK_a^o$ increases from 8.5 to 8.9 and 9.9 as substituent X changes from 4-Me to H and 4-$NO_2$, respectively)[8] in aqueous ethanol. Thus, it has been concluded that an EWG in the nonleaving group increases the $pK_a^o$ value by increasing the $k_2/k_{-1}$ ratio.[6-8]

In contrast, we have recently shown that the $pK_a^o$ value and the $k_2/k_{-1}$ ratio are not influenced by the electronic nature of the substituent X in the nonleaving group for aminolyses of 2,4-dinitrophenyl X-substituted benzoates and benzenesulfonates.[9-11] We have argued that an electron donating group (EDG) in the nonleaving group would increase $k_2$ and $k_{-1}$, while an EWG would decrease $k_2$ and $k_{-1}$, since both the leaving group and amine depart from $T^\pm$ with the bonding electrons. Thus, it has been concluded that the $k_2/k_{-1}$ ratio is independent of the electronic nature of the substituent X in the nonleaving group.

We have extended our kinetic study to reactions of 2,4-dinitrophenyl 2-furoate (**2**) with a series of alicyclic secondary amines as shown in Scheme 1. The kinetic data in the current study have been compared with those for the corresponding reactions of 2,4-dinitrophenyl benzoate (**1**) to



**1** ; X = HC=CH  (2,4-dinitrophenyl bezoate)
**2** ; X = O  (2,4-dinitrophenyl 2-furoate)

**Scheme 1**

investigate the effect of changing the nonleaving group from benzoyl to 2-furoyl on reactivity and reaction mechanism, particularly on $pK_a^o$ and $k_2/k_{-1}$ ratio.
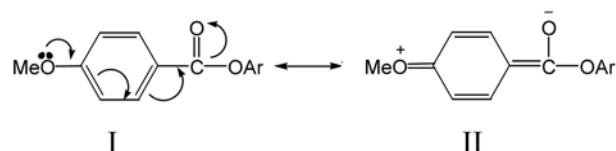
## Results and Discussion

Reactions of **2** with all the amines studied proceeded with quantitative liberation of 2,4-dinitrophenoxide ion. The reactions were followed by monitoring the appearance of 2,4-dinitrophenoxide ion at 400 nm. Kinetic study was performed under pseudo-first-order conditions; the amine concentration was always in excess over that of the substrate **2**. All reactions obeyed first-order kinetics over 90% of the total reaction. Pseudo-first-order rate constants ($k_{obsd}$) were determined from the equation, $\ln(A_\infty - A_t) = -k_{obsd}\,t + C$. The plots of $k_{obsd}$ *vs.* the amine concentration were linear passing through the origin, indicating that general base catalysis by a second amine molecule is absent and the contribution of $OH^-$ ion from the hydrolysis of amines to $k_{obsd}$ is negligible. Thus, the rate equation can be expressed as eq (1). The second-order rate constants ($k_N$) were determined from the slope of these linear plots. Generally five different amine concentrations were used to determine $k_N$ values. It is estimated from replicate runs that the uncertainty in the rate constants is less than 3%. The $k_N$ values determined in this way are summarized in Table 1.

$$\text{rate} = k_N[\mathbf{2}][\text{amine}] \tag{1}$$

**Effect of Nonleaving Group on Reactivity.** As shown in Table 1, the $k_N$ value for the reaction of **2** decreases as the basicity of amines decreases, *i.e.*, it decreases from 427 $M^{-1}s^{-1}$ to 43.5 and 1.47 $M^{-1}s^{-1}$ as the $pK_a$ of amines decreases from 11.02 to 8.65 and 5.95, respectively. A similar result is shown for the corresponding reactions of **1**. However, the furoate **2** is more reactive than the benzoate **1** for all the amines studied.

We have recently shown that the effect of substituent in the nonleaving group on reactivity is significant for nucleophilic substitution reactions of aryl X-substituted benzoates and benzensulfonates with primary and secondary amines[9-11] as well as with anionic nucleophiles such as $OH^-$. $CN^-$, and $N_3^-$.[12] In all cases, the reactivity of these esters increased as

**Table 1**. Summary of Second-order Rate Constants ($k_N$, $M^{-1}s^{-1}$) for the Reactions of 2,4-Dinitrophenyl Benzoate (**1**) and 2-Furoate (**2**) with Alicyclic Secondary Amines in 80 mol % $H_2O$/20 mol % DMSO at $25.0 \pm 0.1$ °C

| No. | Amines | $pK_a$ | $k_N/M^{-1}s^{-1}$ | |
| --- | --- | --- | --- | --- |
| | | | **1** | **2** |
| 1 | piperidine | 11.02 | 174[a] | 427 |
| 2 | 3-methyl piperidine | 10.80 | 167[a] | 402 |
| 3 | piperazine | 9.85 | 82.1[a] | 224 |
| 4 | morpholine | 8.65 | 19.6[a] | 43.5 |
| 5 | 1-formyl piperazine | 7.98 | 5.43[a] | 12.3 |
| 6 | piperazinium ion | 5.95 | 0.467[a] | 1.47 |

[a]Data taken from ref. 9b.

the substituent X in the benzoyl or the sulfonyl moiety becomes a stronger EWG.[9-12] We have found that the Yukawa-Tsuno plots for these reactions are linear with *r* values ranging from 0.4 to 1.6.[9-12] Since the *r* value in the Yukawa-Tsuno plot represents a relative extent of resonance contribution between the electron donating substituent (*e.g.*, 4-MeO) and the reaction center (*e.g.*, the carbonyl or sulfonyl group),[13,14] the ground state has been suggested to be stabilized through resonance as illustrated by resonance structures I $\leftrightarrow$ II.



The effect of delocalizability of ring electrons to the carbonyl group (*i.e.*, resonance structures III $\leftrightarrow$ IV, where R = benzoyl, 2-furoyl, and 2-thiophenecarboxyl) has also been studied theoretically.[15] Lee *et al.* have reported that the delocalizability of ring electrons decreases in the order 2-furoyl > 2-thiophenecarboxyl > benzoyl on the basis of the ab initio calculations at the MP2/6-31G*//MP2/6-31G* level.[15] Furthermore, the natural bond orbital (NBO) positive charge on the carbonyl carbon has been computed to be in the reverse order, *i.e.*, 2-furoyl (0.328) < 2-thiophenecarboxyl (0.351) < benzoyl (0.376),[15] indicating that the benzoate **1** is more electrophilic than the furoate **2**. Accordingly, one might expect that **1** is more reactive than **2**. However, Table 1 shows that **2** is more reactive than **1** toward all the amines studied. Thus, one can suggest that the delocalizability of ring electron (or the NBO positive charge) cannot determine the reactivity of **1** and **2** toward the amines in the current study.



2-Furoic acid ($pK_a$ = 3.16) is 1.04 $pK_a$ units more acidic than benzoic acid ($pK_a$ = 4.20).[16] Thus, one might suggest that the high acidity of 2-furoic acid is responsible, at least in part, for the fact that **2** is more reactive than **1**. This argument is consistent with our recent reports that an acid strengthening substituent X in the benzoyl or benzene-sulfonyl moiety increases the reactivity of aryl X-substituted benzoates or benzenesulfonates toward various nucleophiles.[9-12]

**Effect of Nonleaving Group on Reaction Mechanism.** In Figure 1 is demonstrated the effect of amine basicity on reactivity. The Brønsted-type plots exhibit downward curvature for reactions of **1** and **2**. Such a nonlinear Brønsted-type plot has often been found for aminolysis of esters with a good leaving group and suggested as evidence of a stepwise mechanism with a change in the RDS. In fact, we have
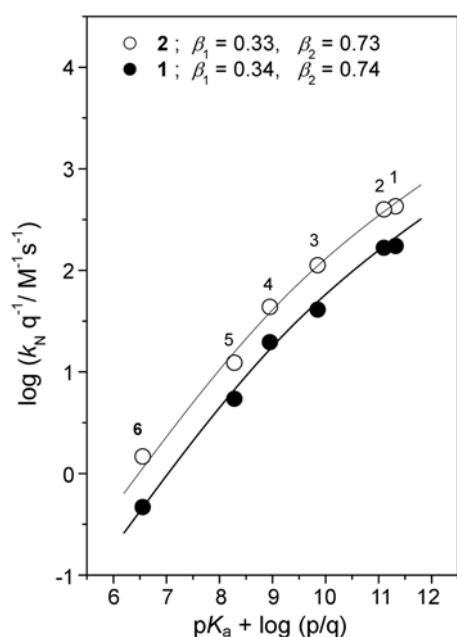
**Figure 1**. Brønsted-type plots for the reactions of **1** ( ● ) and **2** ( ○ ) with alicyclic secondary amines in 80 mol % $H_2O$/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.
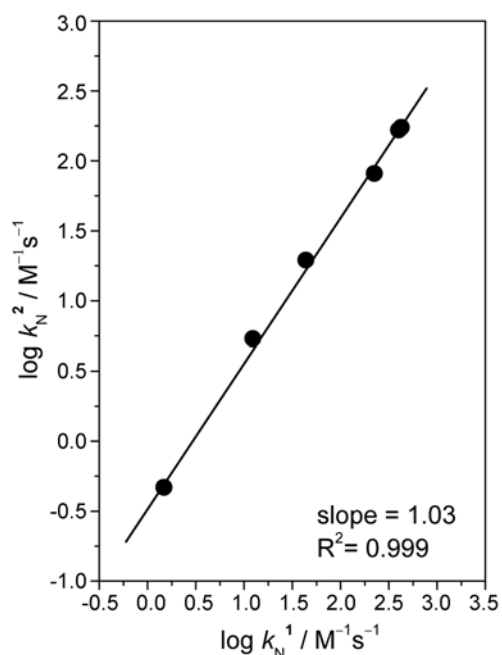


**Figure 2**. Plot of log $k_N$ for the reactions of **1** versus log $k_N$ for the reactions of **2** in 80 mol % $H_2O$/20 mol % DMSO at 25.0 ± 0.1 °C.

recently reported that the reactions of **1** with all the amines employed in this study proceed through $T^{\pm}$ with a change in the RDS from the breakdown of $T^{\pm}$ to its formation as the amine becomes more basic than the leaving 2,4-dinitro-phenoxide ion by *ca.* 5 p$K_a$ units.[5a,9a] Thus, one can suggest that the aminolysis of **2** proceeds also through $T^{\pm}$ on the basis of the nonlinear Brønsted-type plot as shown in Figure 1. This argument can be supported from the linear corre-lation between the logarithmic second-order rate constants

for the reactions of **1** and **2**. As shown in Figure 2, the log $k_N$ for the reactions of **2** exhibits a good linear correlation with that for the corresponding reactions of **1** with a slope close to unity.

The nonlinear Brønsted-type plot shown in Figure 1 for the aminolysis of **2** has been analyzed using a semiempirical equation (eq 2)[6,17] on the basis of the proposed mechanism shown in Scheme 1. The parameters $\beta_1$ and $\beta_2$ represent the slope of the curved Brønsted plots in Figure 1 for the reactions with strongly basic and weakly basic amines, respectively. Here $k_N^{\circ}$ refers to the $k_N$ value at p$K_a^{\circ}$ where $k_2/k_{-1} = 1$. The parameters determined from the fitting of eq (2) to the experimental points are $\beta_1 = 0.33$, $\beta_2 = 0.73$, and p$K_a^{\circ}$ = 9.1. Although the $\beta_1$ and $\beta_2$ values are slightly smaller for the reactions of **2** than for those of **1** (*i.e.*, $\beta_1 = 0.34$ and $\beta_2 = 0.74$), the p$K_a^{\circ}$ value is the same, *i.e.*, p$K_a^{\circ}$ = 9.1 for both reactions of **1** and **2**. This result is consistent with our previous conclusion that the nature of the nonleaving group does not influence the p$K_a^{\circ}$ value.[5,9-11]

$$\log (k_N/k_N^{\circ}) = \beta_2(pK_a - pK_a^{\circ}) - \log (1 + \alpha)/2$$
$$\text{where } \log \alpha = (\beta_2 - \beta_1)(pK_a - pK_a^{\circ}) \qquad (2)$$

The $k_N$ values for the reactions of **2** have been dissected into their microscopic rate constants to obtain further infor-mation about the reaction mechanism. The apparent second-order rate constant $k_N$ can be expressed as eq (3) by applying the steady-state conditions to the intermediate on the basis of the proposed mechanism.

$$k_N = k_1 k_2 / (k_{-1} + k_2) \qquad (3)$$

The $k_2/k_{-1}$ ratios associated with the aminolysis of **2** have been determined using eqs (4)-(9). Eq (3) can be simplified to eq (4) or (5). Then, $\beta_1$ and $\beta_2$ can be expressed as eqs (6) and (7), respectively.

$$k_N = k_1 k_2 / k_{-1}, \text{ when } k_2 \ll k_{-1} \qquad (4)$$

$$k_N = k_1, \text{ when } k_2 \gg k_{-1} \qquad (5)$$

$$\beta_1 = d(\log k_1) / d(pK_a) \qquad (6)$$

$$\beta_2 = d(\log k_1 k_2 / k_{-1}) / d(pK_a)$$
$$= \beta_1 + d(\log k_2 / k_{-1}) / d(pK_a) \qquad (7)$$

Eq (7) can be rearranged as eq (8). Integral of eq (8) from p$K_a^{\circ}$ results in eq (9). Since $k_2 = k_{-1}$ at p$K_a^{\circ}$, the term (log $k_2 / k_{-1})_{pKa}^{\circ}$ is zero. Therefore, one can calculate the $k_2/k_{-1}$ ratios for the aminolysis of **2** from eq (9) using p$K_a^{\circ}$ = 9.1, $\beta_1$ = 0.33, and $\beta_2$ = 0.73.

$$\beta_2 - \beta_1 = d(\log k_2 / k_{-1}) / d(pK_a) \qquad (8)$$

$$(\log k_2 / k_{-1})_{pKa} = (\beta_2 - \beta_1)(pK_a - pK_a^{\circ}) \qquad (9)$$

The $k_1$ values have been determined from eq (10) using the $k_N$ values in Table 1 and the $k_2/k_{-1}$ ratios calculated above. The $k_2/k_{-1}$ ratios and $k_1$ values are summarized in Table 2.

$$k_N = k_1 k_2 / (k_{-1} + k_2)$$
$$= k_1 / (k_{-1}/k_2 + 1) \qquad (10)$$

The $k_2$ value has been suggested to be independent of the

**Table 2**. Summary of Microscopic Rate Constants $k_1$ and $k_2/k_{-1}$ Ratios for the Reactions of **2** (and **1** in parentheses) with Alicyclic Secondary Amines in 80 mol % $H_2O$/20 mol % DMSO at 25.0 ± 0.1 °C

| No. | Amines | $pK_a$ | $k_1/M^{-1}s^{-1}$ | $k_2/k_{-1}$ |
|---|---|---|---|---|
| 1 | piperidine | 11.02 | 482 (197)[a] | 7.73 (7.73)[a] |
| 2 | 3-methyl piperidine | 10.80 | 466 (193)[a] | 6.32 (6.32)[a] |
| 3 | piperazine | 9.85 | 336 (123)[a] | 2.00 (2.00)[a] |
| 4 | morpholine | 8.65 | 93.4 (42.1)[a] | 0.872 (0.872)[a] |
| 5 | 1-formyl piperazine | 7.98 | 38.5 (17.0)[a] | 0.470 (0.470)[a] |
| 6 | piperazinium ion | 5.95 | 16.8 (5.36)[a] | 0.096 (0.096)[a] |

[a]Data in the parentheses are for the reactions of **1** taken from ref. 9b.
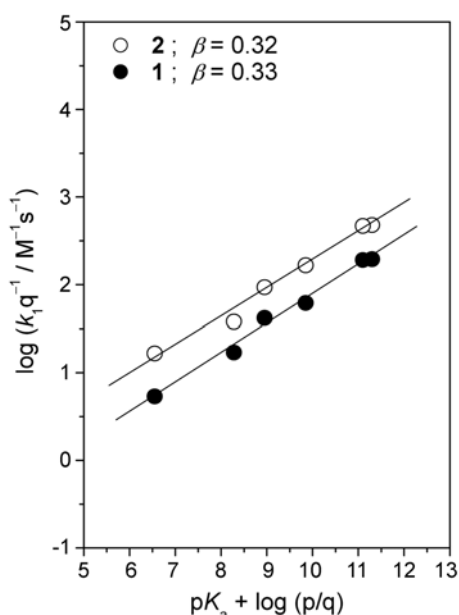


**Figure 3**. Brønsted-type plots for $k_1$ for the reactions of **1** ( ● ) and **2** ( ○ ) with alicyclic secondary amines in 80 mol % $H_2O$/20 mol % DMSO at 25.0 ± 0.1 °C.

basicity of amines, while $k_{-1}$ would decrease as the amine basicity increases.[6-11] Accordingly, one might expect that the $k_2/k_{-1}$ ratio would increase as the amine basicity increases. Table 2 shows that the $k_2/k_{-1}$ ratio increases as the amine basicity increases, which is consistent with the expectation. Table 2 also shows that the $k_2/k_{-1}$ ratios for the reactions of **2** are the same as those for the reactions of **1**. This result supports our previous conclusion that the electronic nature of substituent X in the benzoyl or benzenesulfonyl moiety does not affect the $k_2/k_{-1}$ ratio.[9-11]

As shown in Table 2, $k_1$ increases with increasing amine basicity for both reactions of **1** and **2**. The effect of amine basicity on $k_1$ is illustrated in Figure 3. Both Brønsted-type plots are linear with almost the same slope. It is noted that the $k_1$ value is larger for the reactions of **2** than for those of **1** for a given amine, which is fully responsible for the fact that the former exhibits higher reactivity than the latter.

## Conclusions

The current study has allowed us the following conclu-

sions: (i) The furoate **2** is more reactive than the benzoate **1**. The higher acidity of 2-furoic acid compared with benzoic acid is responsible, at least in part, for the higher reactivity of **2**. (ii) The aminolysis of **2** has been suggested to proceed through $T^{\pm}$ with a change in the RDS on the basis of the nonlinear Brønsted-type plot. (iii) The $pK_a^o$ and $k_2/k_{-1}$ ratios for the reactions of **1** and **2** are identical, indicating that the nature of the nonleaving group (*i.e.*, benzoyl and 2-furoyl) does not affect the reaction mechanism. (iv) The $k_1$ value is larger for the reactions of **2** than for those of **1**, which is fully responsible for the fact that the former is more reactive than the latter.

## Experimental Section

**Materials.** Substrate **2** was readily prepared from the reaction of 2,4-dinitrophenol and 2-furoyl chloride in the presence of triethylamine in anhydrous ether. The purity was confirmed by its melting point and $^1$H NMR spectrum. Amines and other chemicals were of the highest quality available and were generally recrystallized or distilled before use. Due to the low solubility of **2** in pure $H_2O$, aqueous DMSO was used as the reaction medium (*i.e.*, 20 mol % DMSO/80 mol % $H_2O$). Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

**Kinetics.** The kinetic studies were performed at 25.0 ± 0.1 °C with a UV-Vis spectrophotometer equipped with a constant temperature circulating bath for slow reactions (*e.g.*, $t_{1/2} \geq 10$ s) or with a stopped-flow spectrophotometer for fast reactions (*e.g.*, $t_{1/2} < 10$ s). The reactions were followed by monitoring the appearance of 2,4-dinitrophenoxide ion at 400 nm. All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than that of the substrate.

Typically, reaction was initiated by adding 5 $\mu$L of 0.02 M of a substrate solution in MeCN by a 10 $\mu$L syringe into a 10 mm UV cell containing 2.50 mL of the reaction medium and the amine. The amine stock solution of *ca*. 0.2 M was prepared in a 25.0 mL volumetric flask under nitrogen by adding 2 equiv of amine to 1 equiv of standardized HCl solution in order to obtain a self-buffered solution. All the transfers of reaction solutions were carried out by means of gas-tight syringes.

**Products Analysis.** The amount of 2,4-dinitrophenoxide ion was determined quantitatively by comparison of the UV-Vis spectra after the completion of the reactions with those of the authentic samples under the same reaction conditions.

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