Aminolysis of 2,4-Dinitrophenyl 2-Furoate and 2-Thiophenecarboxylate: Effect of Modification of Nonleaving Group from Furoyl to Thiophenecarbonyl on Reactivity and Mechanism

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Second-order rate constants have been determined spectrophotometrically for reactions of 2,4-dinitrophenyl 2-thiophenecarboxylate (**2**) with a series of alicyclic secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The Brønsted-type plot exhibits a downward curvature, *i.e.*, the slope decreases from 0.74 to 0.34 as the amine basicity increases. The pK_a at the center of the Brønsted curvature, defined as pK_a^o, has been determined to be 9.1. Comparison of the Brønsted-type plot for the reactions of **2** with that for the corresponding reactions of 2,4-dinitrophenyl 2-furoate (**1**) suggests that reactions of **1** and **2** proceed through a common mechanism, although **2** is less reactive than **1**. The curved Brønsted-type plot has been interpreted as a change in RDS of a stepwise mechanism. The replacement of the O atom in the furoyl ring by an S atom (**1** → **2**) does not alter the reaction mechanism but causes a decrease in reactivity. Dissection of the apparent second-order rate constants into the microscopic rate constants has revealed that the k_2/k_{-1} ratio is not influenced upon changing the nonleaving group from furoyl to thiophenecarbonyl. However, k_1 has been calculated to be smaller for the reactions of **2** than for the corresponding reactions of **1**, indicating that the C=O bond in the thiophenecarboxylate **2** is less electrophilic than that in the furoate **1**. The smaller k_1 for the reactions of **2** is fully responsible for the fact that **2** is less reactive than **1**.

Key Words : Aminolysis, Mechanism, Brønsted-type plot, Rate-determining step, Nonleaving group

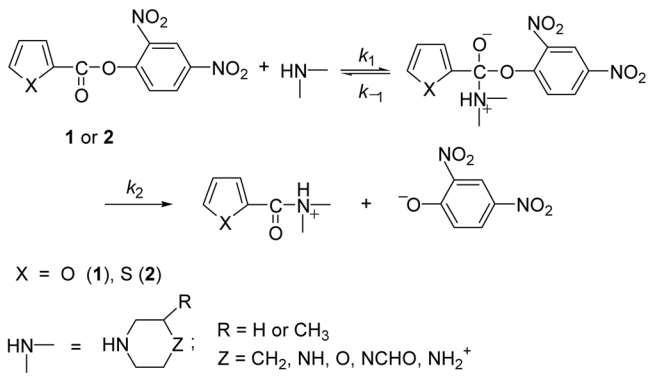
Introduction

Aminolysis of carboxylic esters with a weakly basic leaving group often results in a curved Brønsted-type plot, which has been taken as evidence for a stepwise mechanism.[1-5] The rate-determining step (RDS) has been reported to be dependent on the basicity of the attacking amine and the leaving group, *i.e.*, the RDS changes from breakdown of a zwitterionic tetrahedral intermediate ($T^{\pm}$) to its formation as the attacking amine becomes more basic than the leaving group or the leaving group becomes less basic than the amine by 4 to 5 pK_a units.[1-5]

The pK_a at the center of the Brønsted curvature has been defined as pK_a^o, where a change in the RDS occurs.[6,7] An intriguing question is that whether pK_a^o is dependent on the nature of the nonleaving group or not. Gresser and Jencks have found that the pK_a^o for reactions of diaryl carbonates with a series of quinuclidines increases as the substituent in the nonleaving group changes from an electron-donating group (EDG) to an electron-withdrawing group (EWG).[7] This has been rationalized on the basis that departure of the amine from $T^{\pm}$ is favored, over that of the leaving group, as the substituent in the nonleaving group becomes a stronger EWG.[7] A similar result has been reported 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 = 4-Cl, 4-CN, or 4-NO_2, and for aminolysis of *S*-2,4-dinitrophenyl X-substituted thiobenzoates, pK_a^o increases from 8.5 to 8.9 and 9.9 as X is changed from 4-CH_3 to H and 4-NO_2, in turn.[8,9] Thus, pK_a^o has been suggested to increase upon changing the substituent in the nonleaving group from an EDG to an EWG.[6-9]

However, we have shown that the pK_a^o value is independent of the electronic nature of the substituent X in the nonleaving group for aminolysis of 2,4-dinitrophenyl X-substituted benzoates[10] and benzenesulfonates.[11] A similar result has been found for reactions of Y-substituted phenyl X-substituted benzoates with piperidine and pyridines, *i.e.*, the pK_a^o remains nearly constant as the substituent X in the benzoyl moiety is progressively modified from an EWG to an EDG.[5e,5g]

We have recently performed reactions of 2,4-dinitrophenyl 2-furoate (**1**) with a series of alicyclic secondary amines and



Scheme 1

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concluded that the reactions proceed through a stepwise mechanism with a change in the RDS as the amine becomes more basic than the leaving aryloxide or the leaving aryloxide becomes less basic than the amine by *ca.* 5 pK_a units.[10d] We have extended our study to aminolysis of 2,4-dinitrophenyl 2-thiophenecarboxylate (**2**) to investigate the effect of modification of the nonleaving group from 2-furoyl to 2-thiophenecarbonyl on reactivity and mechanism, particularly on the k_2/k_{-1} ratio (see Scheme 1).

Results and Discussion

Reactions of **2** with alicyclic secondary amines proceeded with quantitative liberation of 2,4-dinitrophenoxide. The kinetic study was performed spectrophotometrically under pseudo-first-order conditions, *e.g.*, the amine concentration was at least 20 times greater than the substrate concentration. All reactions obeyed first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln (A_\infty - A_t) = -k_{obsd}t + C$. The plot of k_{obsd} versus amine concentration was linear and passed through the origin, indicating that general base catalysis by a second amine molecule is absent and the contribution of H_2O and/or HO^- from hydrolysis of amine to k_{obsd} is negligible. Thus, the rate equation can be given as eq. (1). The apparent second-order rate constants (k_N) were determined from the slope of the linear plots of k_{obsd} versus amine concentration and are summarized in Table 1. It is estimated from the replicate runs that the uncertainty in the rate constants is less than ±3%.

$$\text{Rate} = k_{obsd}[\mathbf{2}], \text{ where } k_{obsd} = k_N[\text{amine}] \quad (1)$$

Effect of Modification of Nonleaving Group from Furoyl to Thiophenecarbonyl on Reactivity and Mechanism. As shown in Table 1, the second-order rate constant k_N for the reactions of **2** decreases as the basicity of amines decreases, *e.g.*, from 145 $M^{-1}s^{-1}$ to 15.3 and 0.397 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of amines decreases from 11.02 to 8.65 and 5.95, in turn. A similar result is shown for the corresponding reactions of 2,4-dinitrophenyl 2-furoate (**1**) although the furoate **1** is *ca.* 3 times more reactive than the thiophenecarboxylate **2**.

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

Entry		pK_a	$k_N/M^{-1}s^{-1}$	
			1 [a]	**2**
1	piperidine	11.02	427	145
2	3-methylpiperidine	10.80	402	139
3	piperazine	9.85	224	68.2
4	morpholine	8.65	43.5	15.3
5	1-formylpiperazine	7.98	12.3	4.04
6	piperazinium ion	5.95	1.47	0.397

[a]Data taken from ref. 10d.

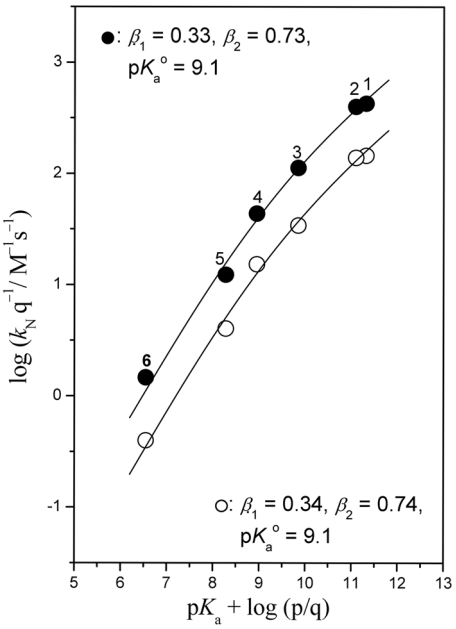

Figure 1. Brønsted-type plots for the reactions of 2,4-dinitrophenyl 2-Furoate (**1**, ●) and 2,4-dinitrophenyl 2-thiophenecarboxylate (**2**, ○) with alicyclic secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1. The plots are statistically corrected using *p* and *q*.[16]

The effect of amine basicity on reactivity is illustrated in Figure 1 for the reactions of **1** and **2**. The Brønsted-type plots are curved downwardly, *i.e.*, as the amine basicity increases, the slope decreases from 0.74 to 0.34 for the reactions of **2** and from 0.73 to 0.33 for those of **1**. The curved Brønsted-type plot obtained for the reactions of the furoate **1** has recently been interpreted as evidence for a change in the RDS of a stepwise mechanism, *i.e.*, from breakdown of $T^\pm$ to its formation as the amine basicity increases.[10d] The stepwise mechanism has been further supported from the contrasting Brønsted-type plots obtained for aminolysis of Y-substituted phenyl 2-furoates, *i.e.*, the plot was linear with a β_{lg} value of 1.19 for the reactions with weakly basic morpholine but curved with decreasing β_{lg} from 1.25 to 0.28 for the reactions with strongly basic piperidine.[12]

The pK_a at the center of the Brønsted curvature, defined as pK_a° where $k_{-1} = k_2$, is 9.1 for the reactions of **2**, which is *ca.* 5 pK_a units higher than the pK_a of the conjugate acid of the leaving 2,4-dinitrophenoxide. The current result is consistent with the report that a change in RDS occurs when the amine becomes more basic than the leaving group by 4 to 5 pK_a units.[1-5] Thus, one can suggest that the current aminolysis of **2** also proceeds through a stepwise mechanism with a change in the RDS.

To examine the above argument that the reactions of **1** and **2** proceed through the same mechanism (*i.e.*, a stepwise mechanism with a change in the RDS), a plot of log k_N for the reaction of **2** versus log k_N for the reaction of **1** has been constructed in Figure 2. One might expect a linear plot if the reactions of **1** and **2** proceed through a common mechanism.

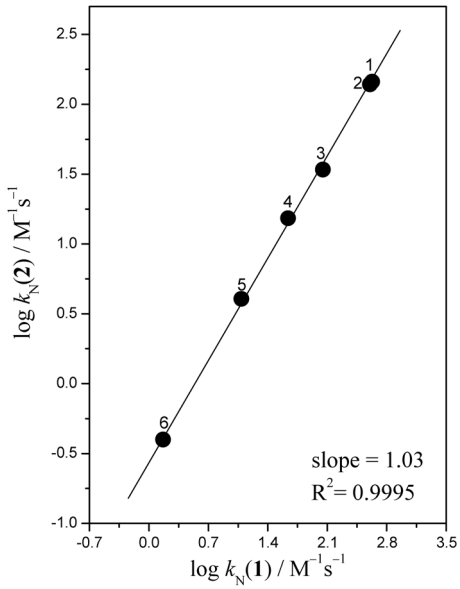

Figure 2. Plot of log k_N for reactions of **1** versus log k_N for the reactions of **2** in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

In fact, Figure 2 exhibits an excellent linearity, indicating that their mechanism is the same. The slope of 1.03 for the linear plot is consistent with the fact that the reactions of **2** exhibit slightly larger slope in the Brønsted-type plot than those of **1**. Thus, one can conclude that the current reactions proceed through a stepwise mechanism with a change in the RDS. Accordingly, the apparent second-order rate constant k_N can be expressed as eq. (2).

$$k_N = k_1k_2/(k_{-1} + k_2) \quad (2)$$

Dissection of k_N into Microscopic Rate Constants. The nonlinear Brønsted-type plot in Figure 1 has been analyzed using a semiempirical equation (eq. 3),[7,13] where β_1 and β_2 represent the slope of the Brønsted-type plot in Figure 1 for the reaction with strongly and weakly basic amines, respectively. The k_N^o refers to the k_N at pK_a^o in which k_{-1}= k_2. The parameters determined for the reactions of **2** are as follows: log k_N^o = 1.20, pK_a^o = 9.1, β_1 = 0.34 and β_2 = 0.74. Therefore, one can suggest that the RDS for the reaction of **2** changes from the k_2 step to the k_1 process as the amine basicity increases on the basis of the magnitude of β_1 and β_2 values.

$$\log (k_N/k_N°) = \beta_2(pK_a - pK_a°) - \log (1 + \alpha)/2$$
$$\text{where } \log \alpha = (\beta_2 - \beta_1)(pK_a - pK_a°) \quad (3)$$

The k_N values for the reactions of **2** have been dissected into their microscopic rate constants to shed more light on the reaction mechanism. The k_2/k_{-1} ratios associated with the reactions of **2** have been determined using eqs. (4)-(9). Eq. (2) can be simplified to eq. (4) or (5). Then, β_1 and β_2 can be expressed as eqs. (6) and (7), respectively.

$$k_N = k_1k_2 / k_{-1}, \text{ when } k_2 << k_{-1} \quad (4)$$
$$\text{or} \quad k_N = k_1, \text{ when } k_2 >> k_{-1} \quad (5)$$

Table 2. Summary Microscopic Rate Constants k_1 and k_2/k_{-1} Ratios 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

Entry	pK_a	$k_1/M^{-1}s^{-1}$		k_2/k_{-1}	
		1[a]	**2**	**1**[a]	**2**
1 piperidine	11.02	482	164	7.73	7.73
2 3-methylpiperidine	10.80	466	161	6.32	6.32
3 piperazine	9.85	336	102	2.00	2.00
4 morpholine	8.65	93.4	32.9	0.872	0.872
5 1-formylpiperazine	7.98	38.5	12.6	0.470	0.470
6 piperazinium ion	5.95	16.8	4.55	0.096	0.096

[a]Data for the reactions of **1** taken from ref. 10d.

$$\beta_1 = d(\log k_1) / d(pK_a) \quad (6)$$
$$\beta_2 = d(\log k_1k_2/k_{-1}) / d(pK_a)$$
$$= \beta_1 + d(\log k_2/k_{-1}) / d(pK_a) \quad (7)$$

Eq. (7) can be rearranged as eq. (8). Integral of eq. (8) from pK_a^o results in eq. (9). Since $k_2 = k_{-1}$ at pK_a^o, the term $(\log k_2/k_{-1})_{pKa}^o$ is zero. Therefore, one can calculate the k_2/k_{-1} ratios for the reactions of **2** from eq. (9) using pK_a^o = 9.1, β_1 = 0.34 and β_2 = 0.74.

$$\beta_2 - \beta_1 = d(\log k_2/k_{-1}) / d(pK_a) \quad (8)$$
$$(\log k_2/k_{-1})_{pKa} = (\beta_2 - \beta_1)(pK_a - pK_a^o) \quad (9)$$

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 determined above. The k_2/k_{-1} ratios and k_1 values determined are summarized in Table 2.

$$k_N = k_1k_2 / (k_{-1} + k_2) = k_1 / (k_{-1}/k_2 + 1) \quad (10)$$

Effect of Nonleaving Group on Microscopic Rate Constants. It has been reported that the basicity of amines does not influence k_2 since the push provided by aminium moiety of $T^{\pm}$ is absent.[7,14] On the other hand, k_{-1} would increase with decreasing the amine basicity. Thus, one can expect that the k_2/k_{-1} ratio decreases as the amine basicity decreases. In fact, as shown in Table 2, the k_2/k_{-1} ratio decreases as the amine basicity decreases for the reactions of **1** and **2**.

Thiophene-2-carboxylic acid is known to be a weaker acid than 2-furoic acid.[15] Accordingly, one might expect the k_2/k_{-1} ratio would be larger for the reaction of **2** than for the corresponding reaction of **1**, if an acid strengthening substituent in the nonleaving group decreases the k_2/k_{-1} ratio as suggested by Gresser and Jencks[7] and by Castro *et al.*[8,9] However, as shown in Table 2, the k_2/k_{-1} ratio for the reaction of **2** is exactly the same as that for the corresponding reaction of **1**, indicating that modification of the nonleaving group from furoyl to thiophenecarbonyl does not affect the k_2/k_{-1} ratio. The current result is consistent with our previous proposal that the k_2/k_{-1} ratio is independent of the electronic nature of the substituent in the nonleaving group of 2,4-dinitrophenyl X-substituted benzoates (X-C_6H_4CO-OC_6H_3-$(NO_2)_2$) and benzenesulfonates (X-$C_6H_4SO_2$-OC_6H_3-$(NO_2)_2$).[10,11] We have proposed that an EWG in the non-

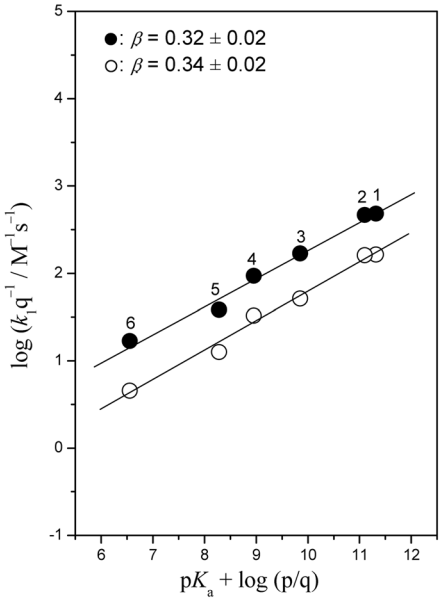

Figure 3. Brønsted–type plots for k_1 for the reactions of **1** (●) and **2** (○) with alicyclic secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

leaving group decreases both k_2 and k_{-1}, while an EDG increases them, since the leaving aryloxide and amine depart from $T^{\pm}$ with the bonding electron pair. This argument can account for the result that the reactions of **1** and **2** result in the same k_2/k_{-1} ratio.[10, 11]

As mentioned in the previous section, k_N for the reaction of **2** is smaller than that of **1** for a given amine. Since as shown in eq. (10), *i.e.*, $k_N = k_1k_2/(k_{-1} + k_2)$ or $k_N = k_1/(k_{-1}/k_2 + 1)$ in the current aminolysis, the magnitude of k_N for the reactions of **1** and **2** should be dependent on k_1 and/or the k_2/k_{-1} ratio. Table 2 shows that the k_2/k_{-1} ratio is the same for the reactions of **1** and **2**, while k_1 is larger for the reactions of **1** than for the corresponding reactions of **2**. One might expect that the replacement of the O atom in the furoyl ring by a less electronegative S atom causes a decrease in the k_1 value by decreasing the electrophilicity of **2**. Thus, one can suggest that the smaller k_1 for the reactions of **2** is fully responsible for the fact that **2** is less reactive than **1** toward all the amines studied.

The effect of amine basicity on k_1 is illustrated in Figure 3. It is shown that k_1 increases linearly as the amine basicity increases for both reactions of **1** and **2**. The slope of the linear plots is slightly larger for the reactions of **2** ($\beta_1 = 0.34$) than for those of **1** ($\beta_1 = 0.32$), but the difference in β_1 value is within the error range.

Conclusions

The current study has allowed us to conclude the following: (1) Aminolysis of **2** proceeds through a stepwise mechanism with a change in the RDS at $pK_a = 9.1$. (2) Replacement of the O atom in the furoyl ring of **1** by an S atom (**1** → **2**) causes a decrease in reactivity but does not influence the reaction mechanism. (3) The reactions of **1** and **2** result in the same k_2/k_{-1} ratio, indicating that modification of the nonleaving group from furoyl to thiophenecarbonyl does not affect the k_2/k_{-1} ratio. (4) Reactions of **2** result in smaller k_1 than the corresponding reactions of **1**, which is fully responsible for the fact that **2** is less reactive than **1**.

Experimental Section

Materials. Compound **2** was easily prepared from the reaction of 2,4-dinitrophenol with 2-thiophenecarbonyl chloride under presence of triethylamine in anhydrous ether. The purity of **2** was checked by means of the melting point (110-112 °C), ^{1}H NMR δ 9.05 (d, J = 2.5 Hz, 1H), 8.58 (dd. J = 10.0, 2.5 Hz, 1H), 8.06 (dd, J = 5.0, 1.3 Hz, 1H), 7.80 (dd, J = 5.0, 1.3 Hz, 1H), 7.67 (d, J = 10.0 Hz, 1H), 7.25 (t, J = 5.0 Hz, 1H), and anal. calcd for $C_{11}H_6N_2O_6$: C, 44.90; H, 2.06. Found: C, 44.07; H, 2.10. Other chemicals including the amines used were of the highest quality available. The reaction medium was H_2O containing 20 mol % DMSO due to low solubility of the substrate **2** in pure H_2O. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic study was performed with a UV-vis spectrophotometer for slow reactions ($t_{1/2} \geq 10$ s) or with a stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ s) equipped with a constant temperature circulating bath to keep the temperature in the reaction cell at 25.0 ± 0.1 °C. The reaction was followed by monitoring the appearance of the leaving 2,4-dinitophenoxide ion. All the reactions were carried out under pseudo-first-order conditions in which the amine concentrations were at least 20 times greater than the substrate concentration. The amine stock solution of *ca.* 0.2 M was prepared by dissolving two equiv of free amine and one equiv of standardized HCl solution to keep the p*H* constant by making a self buffered solution. Five different amine concentrations were employed to determine second-order rate constants. All the solutions were prepared freshly just before use under nitrogen and transferred by gas-tight syringes.

Product Analysis. 2,4-dinitrophenoxide was liberated quantitatively and identified as one of the products by comparison of the UV-vis spectrum at the end of reaction with the authentic sample under the experimental condition.

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