Effect of Nonleaving Group on the Reaction Rate and Mechanism: Aminolyses of 4-Nitrophenyl Acetate, Benzoate and Phenyl Carbonate

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Second-order rate constants have been determined spectrophotometrically for the reaction of phenyl 4-nitrophenyl carbonate with a series of primary amines in H_2O containing 20 mol % DMSO at 25.0 °C. The Brønsted-type plot is linear with a β_{nuc} 0.69 ± 0.04, which is slightly smaller than the β_{nuc} values for the reactions of 4-nitrophenyl acetate ($\beta_{nuc} = 0.82 \pm 0.03$) and benzoate ($\beta_{nuc} = 0.76 \pm 0.01$), indicating that the reaction proceeds through a tetrahedral zwitterionic intermediate $T^{\pm}$. The carbonate is more reactive than the corresponding acetate and benzoate. The changing Me (or Ph) to PhO has resulted in a decrease in the β_{nuc} value without changing the reaction mechanism but an increase in the reactivity. The electronic effect of the substituent in the nonleaving group appears to be responsible for the enhanced reactivity of the carbonate compared with the corresponding acetate and benzoate.

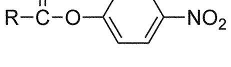
Key Words : Aminolysis, Structure-reactivity relationship, Rate-determining step, Leaving group

Introduction

Ester aminolyses have received much interest due to the importance in biological processes as well as in synthetic applications.[1-5] Reactions of carboxylic esters with amines have been suggested to proceed through a tetrahedral addition intermediate $T^{\pm}$, in which the rate-determining step is dependent on the basicity of the leaving group and the amine nucleophile.[1-5] Aminolyses of esters with a good leaving group have often exhibited nonlinear Brønsted-type plots by changing a β_{nuc} from 0.8 ± 0.2 to 0.3 ± 0.2 as the amine becomes more basic than the leaving group by 4-5 pK_a units.[1-5] Such a nonlinear Brønsted-type plot has been interpreted as a change in the rate-determining step from the breakdown of $T^{\pm}$ to the formation of $T^{\pm}$.[1-5]

Structure-reactivity relationships have provided useful information to investigate the reaction mechanism. However, most studies have focused on the effect of the leaving group and the nucleophile until recently. The effect of the nonleaving group has not been fully understood.[5-8] We have been studying the effect of the nonleaving group on the reaction rate and mechanism for reactions of aryl substituted benzoates and benzenesulfonates with amine and anionic nucleophiles.[5a,b,e,9]

In the present study, we report the result of kinetic studies for the reactions of phenyl 4-nitrophenyl carbonate (**1**) with a series of primary amines in H_2O containing 20 mol % DMSO. The aim is to investigate the effect of the nonleaving group on the reaction rate and mechanism by comparing the kinetic data for the present study with those reported previously for the corresponding reactions of 4-nitrophenyl acetate (**2**) and benzoate (**3**).[10]



1: R = PhO
2: R = Me
3: R = Ph

Experimental Section

Materials. Phenyl 4-nitrophenyl carbonate (**1**) was easily prepared from the reaction of phenyl chloroformate with 4-nitrophenol in anhydrous ether under the presence of triethylamine. The amines used were of the highest quality available from Aldrich. Doubly glass distilled water was further boiled and cooled under nitrogen just before use. DMSO was distilled over CaH_2 at a reduced pressure. All the solutions were prepared fressly just before use, and transferred by Hamilton gas-tight syringes.

Kinetics. The kinetic study was performed with a Scinco S-2100 PDA UV-vis spectrophotometer for the slow reactions ($t_{1/2} \geq 10$ s) or with an Applied Photophysics SX-17 MV stopped-flow spectrophotometer for the fast reactions ($t_{1/2} < 10$ s) equipped with a Leslab RTE-110 constant temperature circulating bath to keep the reaction temperature at 25.0 ± 0.1 °C. All the reactions were performed under pseudo-first-order conditions, *i.e.*, the amine was *ca*. 20-200 times more concentrated than the substrate. The amine stock solution of *ca.* 0.2 M was prepared by dissolving 2 equiv of amine hydrochloride and 1 equiv of standardized NaOH solution to keep the pH constant by making a self-buffered solution. The reaction medium was H_2O containing 20 mol % DMSO to eliminate solubility problems.

Products Analysis. 4-Nitrophenoxide (and/or its conjugate acid) was identified as one of the products of the reactions of **1** with the amines used in the present system by comparison of the UV-vis spectrum at the end of reaction with the authentic sample under the kinetic experimental conditions. The other products, (*e.g.*, phenyl carbamates of ethylamine, glycine, etc.) were found to be stable enough in the kinetic conditions.

Results

The reactions were followed spectrophotometrically by monitoring the appearance of the leaving 4-nitrophenoxide (or its conjugate acid). All the reactions obeyed pseudo-first-order kinetics. The pseudo-first-order rate constants (k_{obs}) were determined from the slope of the linear plots of ln ($A_\infty - A_t$) *vs* t. The kinetic conditions and results are summarized in Table 1. All the plots of k_{obs} *vs* amine concentration were linear passing through the origin as shown in Figure 1, indicating that the contribution of HO^- and/or H_2O to the k_{obs} value is negligible. Thus, the kinetic law obtained can be given as in eqs. (1) and (2), in which [P], [S] and [RNH_2] represent the concentrations of 4-nitrophenoxide, the substrate and the amine, respectively. The second-order rate constants (k_N) were determined from the slope of the linear plots of k_{obs} *vs* [RNH_2]. The k_N values determined in this way are summarized in Table 2 and illustrated in Figure 2.

$$d[P] / dt = k_{obs} [S] \tag{1}$$

Table 1. Experimental conditions and k_{obs} values for the reactions of 4-nitrophenyl phenyl carbonate (**1**) with primary amines in H_2O containing 20 mol % DMSO at 25.0 ± 0.1 °C

RNH_2	pH	10^3 [RNH_2]/M[a]	$10^2 k_{obs}/s^{-1}$	n[b]
Ethylamine	10.67	10.3-51.5	64.1-328	10
Glycine	10.06	10.2-51.8	40.2-199	5
Ethanolamine	9.67	10.3-51.8	18.2-95.9	10
Benzylamine	9.46	1.73-8.42	2.46-12.2	5
Glycylglycine	8.31	9.60-40.5	2.14-9.19	5
Glycineethylester	7.68	9.60-40.5	0.630-2.54	10

[a]Concentration of free amine. [b]Number of runs.

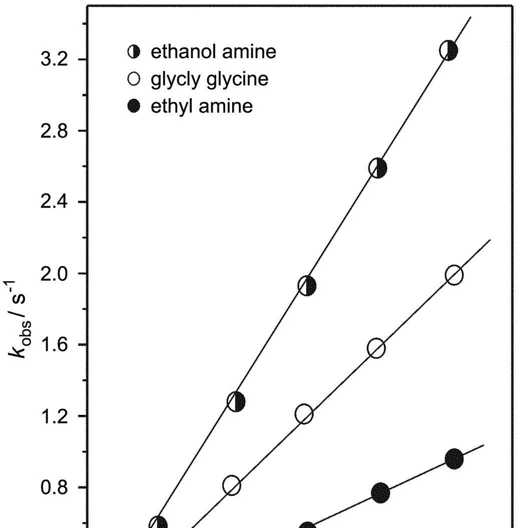


Figure 1. Plots showing dependence of k_{obs} on the amine concentration for the aminolysis of **1** in 20 mol % DMSO at 25.0 °C.

Table 2. Summary of second-order rate constants (k_N, $M^{-1}s^{-1}$) for the aminolyses of **1**, **2** and **3** in H_2O containing 20 mol % DMSO at 25.0 ± 0.1 °C

RNH_2	pK_a	k_N, $M^{-1}s^{-1}$		
		1	**2**[a]	**3**[b]
Ethylamine	10.67	63.9	13.5	1.97
Glycine	10.06	38.1	2.61	0.604
Ethanolamine	9.67	18.8	2.28	0.340
Benzylamine	9.46	14.5	–	0.242
Glycylglycine	8.31	2.30	0.146	0.025
Glycineethylester	7.68	0.620	0.0631	0.0106

[a]Data taken from reference **10(a)**. Data taken from reference **10(b)**.

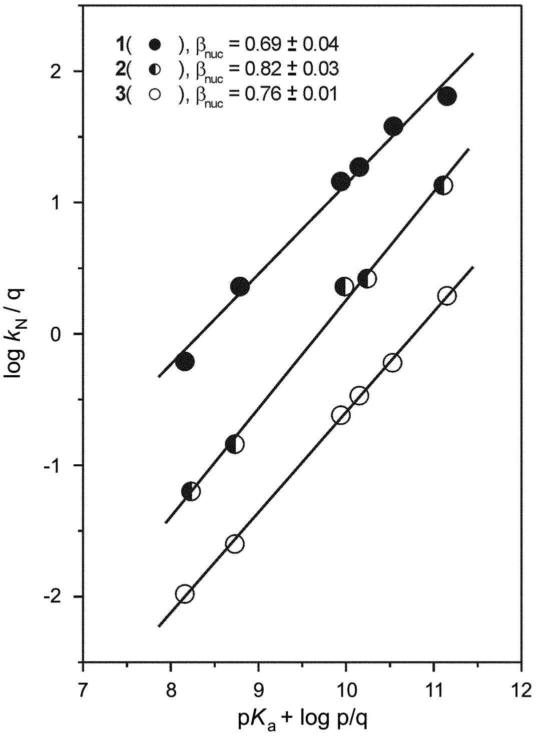
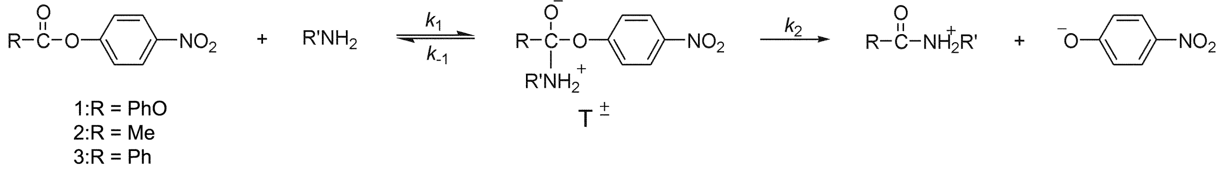


Figure 2. Brønsted-type plots for aminolysis of **1** (●), **2** (◐), and **3** (○) in 20 mol % DMSO at 25.0 °C.

$$k_{obs} = k_N [RNH_2] \tag{2}$$

Discussion

Effect of Nonleaving Group on Mechanism. As shown in Table 2, the second-order rate constant (k_N) increases with increasing the amine basicity for the reactions of the primary amines with **1**. The effect of the amine basicity on the rate constant has been demonstrated in Figure 2. The Brønsted-type plot for the aminolyses of **1** is linear with a β_{nuc} value 0.69 ± 0.04. The Brønsted-type plots for the corresponding reactions of **2** and **3** are also linear with a β_{nuc} value 0.82 ± 0.03 and 0.76 ± 0.01, respectively. The linear Brønsted-type plot with a β_{nuc} value 0.69 ± 0.04 is consistent with a stepwise mechanism as shown in Scheme 1, in which the leaving group departure is the rate-determining step. Therefore, the changing Me (or Ph) to PhO affects the magnitude

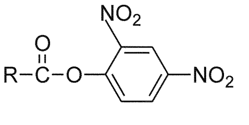


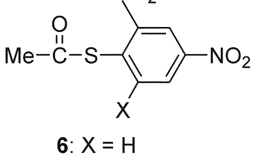
Scheme 1

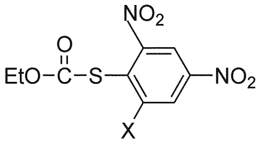
of the β_{nuc} value but not the reaction mechanism in the present system. This argument is consistent with our recent proposal that the effect of the substituent in the nonleaving group of benzoate and benzenesulfonate esters is insignificant on the reaction mechanism.[5a,b,e,9] Therefore, k_N can be expressed as eq. (3).

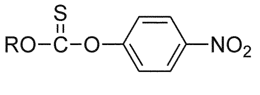
$$k_N = k_1k_2/(k_{-1} + k_2) \qquad (3)$$

The present result appears to be in contrast to the previous report that the structure of the substrate (*e.g.*, acetate *vs* carbonate ester) affects the reaction mechanism or the position of pK_a^o. Castro *et al.* have reported that pyridinolyses of 2,4-dinitrophenyl acetate (**4**) results in a curved Brønsted-type plots and the center of the curvature (pK_a^o) is at $pK_a = 7.3$,[11] while the Brønsted-type plots for the corresponding reactions of methyl 2,4-dinitrophenyl carbonate (**5**) exhibits a curvature at $pK_a = 7.8$.[12] These results suggest that the changing Me to MeO (*e.g.*, **4** → **5**) increases the pK_a^o value by 0.5 pK_a units. The effect of changing Me to MeO or EtO has also been reported to influence the mechanism of aminolyses. The reactions of *S*-2,4-dinitrophenyl thioacetate (**6**) and *S*-2,4,6-trinitrophenyl thioacetate (**7**) with a series of alicyclic secondary amines have been suggested to proceed stepwisely.[13] However, the same reactions of ethyl *S*-2,4-dinitrophenyl thiocarbonate (**8**) and ethyl *S*-2,4,6-trinitrophenyl thiocarbonate (**9**) have been proposed to occur concertedly.[14] Since MeO is a stronger electron donating group than Me by resonance, the replacement of Me by MeO in the tetrahedral addition intermediate, $T^{\pm}$ has been suggested to increase the instability of $T^{\pm}$ by increasing the expulsion rates of the leaving group (the k_2 value) and the amine nucleophile (the k_{-1} value) from $T^{\pm}$.[15] Therefore, Castro *et al.* have concluded that the enhanced instability of $T^{\pm}$ upon introducing MeO or EtO is responsible for the difference in the reaction mechanism between the aminolyses of the acetates and those of the carbonates.[15]

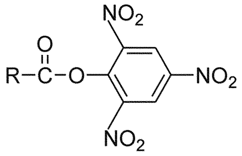

4: R = Me
5: R = MeO

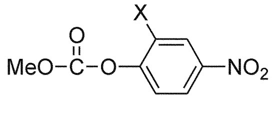

6: X = H
7: X = NO$_2$


8: X = H
9: X = NO$_2$


10: R = Me
11: R = Ph

Effect of Nonleaving Group on Reactivity. As shown in Figure 2, the reactivity decreases in the order **1** > **2** > **3** for a given amine. The lower reactivity of **3** compared with **2** might be attributed to a steric hindrance (*e.g.*, Ph *vs* Me). A similar argument has been reported for the reactions of methyl *O*-4-nitrophenyl thionocarbonate (**10**) and phenyl *O*-4-nitrophenyl thionocarbonate (**11**) with alicyclic secondary amines. The replacement of Me by Ph (*e.g.*, **10** → **11**) has been reported to cause a decrease in reactivity.[3c] If the electronic effect were an important factor which determines the reactivity, one should have expected **10** is less reactive than **11**. Because MeO in **10** has larger electron donating ability by resonance than PhO in **11** ($\sigma_R = -0.56$ and -0.40, respectively).[16] Besides, the former is an inductively weaker electron withdrawing group than the latter ($\sigma_I = 0.29$ and 0.37, respectively).[16] Both of these effects should have resulted in the thionocarbonyl carbon of **10** less positively charged and less susceptible to the amine attack than that of **11**. Therefore, the electronic effect has been suggested to be insignificant based on the result that **10** is more reactive than **11**.[3c] Castro *et al.* have suggested that steric hindrance toward the amine attack by PhO group of **11** is responsible for the decreased reactivity of **11** relative to **10**.[3c]


12: R = Me
13: R = MeO


14: X = H
15: X = NO$_2$

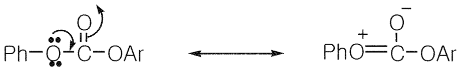
It has been suggested that **4**[17] and 2,4,6-trinitrophenyl acetate (**12**)[3b] are more reactive than **5**[18] and methyl 2,4,6-trinitrophenyl carbonate (**13**)[3b], respectively, toward alicyclic secondary amines. Similar results have been obtained from pyridinolyses of aryl acetates and aryl methyl carbonates, *i.e.*, **2**,[19] **4**[17] and **12**[3b] have been reported to be more reactive than methyl 4-nitrophenyl carbonate (**14**),[20] methyl 2,4-dinitrophenyl carbonate (**15**)[12] and **13**,[3b] respectively. Castro *et al.* have explained the lower reactivity of the carbonates compared with the acetates in two ways, *e.g.*, destabilization of the tetrahedral addition intermediate, $T^{\pm}$ and stabilization of the ground-state of the substrate. Castro *et al.* have suggested that the change of Me to MeO (*e.g.* from acetates to carbonates) in a tetrahedral intermediate destabilizes it by causing an increase in the expulsion rates of both the nucleophile (the k_{-1} value) and the leaving group (the k_2 value) from $T^{\pm}$.[3b] The greater reactivity of the acetates compared with the corresponding methyl carbonates has also been explained by the larger electron releasing effect of the MeO group in the carbonate relative to the Me group in the acetate, since this effect would render the carbonyl carbon of the carbonate less positively charged and less susceptible to the amine attack.[3b] However, the argument suggested by Castro *et al.* can not be applied to the present system, since **1**, which is expected to be least reactive, is more reactive than **2** and **3**.

The stabilization of the ground-state of the carbonates and thionocarbonates by introducing the MeO group would cause a decrease in reactivity by decreasing the k_1 value. Such a rate decrease would be significant for the reaction which proceeds through a rate-determining formation of $T^{\pm}$ (*e.g.*, when $k_{-1} << k_2$), since the rate is determined by the k_1 value but not influenced by the k_2/k_{-1} ratio as shown in eq. (4). On the contrary, in the case of the reaction which proceeds through a rate-determining breakdown of $T^{\pm}$ (*e.g.*, when $k_{-1} >> k_2$), the rate is determined by the k_1 value and the k_2/k_{-1} ratio as shown in eq. (5).

$$k_N = k_1 \qquad (4)$$

$$k_N = k_1k_2/k_{-1} \qquad (5)$$

In this case, the effect of changing Me to MeO on rate would be complicated as discussed below. The destabilization of $T^{\pm}$ by changing Me to MeO (*e.g.*, from acetates to carbonates) would result in a decrease in rate by increasing the k_{-1} value as Castro *et al.* suggested.[3b] However, such a destabilization of $T^{\pm}$ would cause also an increase in rate by increasing the k_2 value. Therefore, the rate can be accelerated or retarded depending on the magnitude of the k_2/k_{-1} ratio. Several factors have been suggested to influence the magnitude of the k_2/k_{-1} ratio, *i.e.*, changing (1) the leaving group ability,[13] (2) the amine nature from primary to secondary amines and pyridines,[3b,4d] (3) the substrate from carbonyl to thionocarbonyl ester,[21] (4) the solvent from water to aprotic solvents,[4e,6,22] (5) the substituent on the nonleaving group with a stronger electron donating group.[6,8] However, the factor (5) has not been completely understood.[5a,b,e,6,8,9]



I II

The σ^+ value represents the electron releasing ability by resonance. The σ^+ values are −0.50, −0.31 and −0.18 for PhO, Me and Ph, respectively.[16] Therefore, the ground-state stabilization by resonance (I ↔ II) would be most significant for **1** and the k_1 value would be expected to be smallest for **1**. However, in fact, **1** is more reactive than **2** and **3**. Therefore, the effect of the ground-state stabilization on rate suggested by Castro *et al.* appears to be less significant for the reaction which proceeds through a rate-determining leaving group departure from $T^{\pm}$ as in the present system. Instead, the destabilization of $T^{\pm}$ by changing Me to PhO appears to be more significant, *i.e.*, the increase in the k_2/k_{-1} ratio is larger than the decrease in the k_1 value. The present result clearly suggests that the k_2 value increases more significantly than the k_{-1} value upon changing Me to PhO.

The reactivity order shown in Figure 2 can be explained by an alternative way, *e.g.*, stabilization of the transition-state. When the leaving group begins to depart from $T^{\pm}$, a partial positive charge would develop at the reaction center. Such a positively charged transition-state can be stabilized by an electron-donating substituent such as PhO. Therefore, one can expect that the reactivity would increase with increasing electron donating ability of the substituent in the nonleaving group by stabilizing the transition state. The fact that the order of the reactivity (**1** > **2** > **3**) is identical to the order of σ^+ value (PhO > Me > Ph) is consistent with this argument.

Conclusions

Based on the linear Brønsted-type plots with β_{nuc} 0.69 ± 0.04, one can suggest that aminolyses of **1** proceed through a tetrahedral addition intermediate in which its breakdown is the rate-determining step. The reactivity order decreases in the order **1** > **2** > **3**. Therefore, the changing Me (or Ph) to PhO does not affect the reaction mechanism but results in a decrease in the β_{nuc} value and an increase in the reaction rate. The ground-state stabilization which decreases the k_1 value appears to be less significant than the transition-state stabilization by an electron donating group in the nonleaving group.

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