

## Nucleophilic Substitution Reactions of $\alpha$ -Chloroacetanilides with Pyridines in Dimethyl Sulfoxide

Shuchismita Dey, Keshab Kumar Adhikary, Chan Kyung Kim, Bon-Su Lee,\* and Hai Whang Lee\*

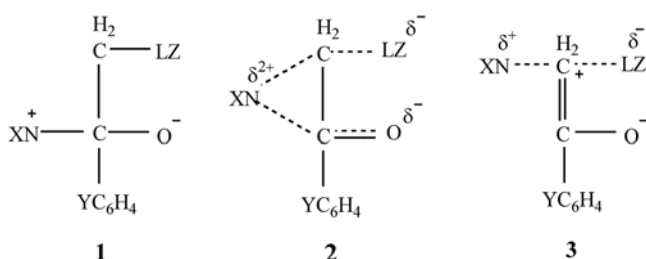
Department of Chemistry, Inha University, Incheon 402-751, Korea. \*E-mail: bslee@inha.ac.kr; hwlee@inha.ac.kr  
Received February 11, 2005

The kinetic studies of the reactions of  $\alpha$ -chloroacetanilides ( $\text{YC}_6\text{H}_4\text{NRC}(=\text{O})\text{CH}_2\text{Cl}$ ;  $\text{R}=\text{H}$  (**4**) and  $\text{CH}_3$  (**5**)) with pyridines have been carried out in dimethyl sulfoxide at 95 °C. The pyridinolysis rates are faster with **4** than with **5** whereas the aminolysis rates with benzylamines are faster with **5** than with **4**. The Brønsted  $\beta_X$  values are in the range from 0.30 to 0.32 and the cross-interaction constants,  $\rho_{XY}$ , are small negative values;  $\rho_{XY} = -0.06$  and  $-0.10$  for **4** and **5**, respectively. Based on these and other results, the pyridinolyses of  $\alpha$ -chloroacetanilides are proposed to proceed *via* a stepwise mechanism with rate-limiting addition of the nucleophile to the carbonyl group to form zwitterionic tetrahedral intermediate ( $\text{T}^\pm$ ) followed by a bridged type transition state to expel the leaving group.

**Key Words** : Pyridinolyses of  $\alpha$ -chloroacetanilides, Cross-interaction constants, Stepwise mechanism

### Introduction

The nucleophilic substitution reactions of  $\alpha$ -halocarbonyl compounds have attracted considerable attention of theoretical<sup>1</sup> as well as experimental organic chemists,<sup>2</sup> mainly because of the rate-enhancing effect of the  $\alpha$ -carbonyl group.<sup>2a,b,c,3</sup> Although a variety of mechanism has been proposed for  $\alpha$ -carbonyl system, by different group of authors, especially in case of phenacyl derivatives, three types among them are considered to be worthy of note: (i) stepwise mechanism with a prior addition of the nucleophile ( $\text{XN}$ ) to the carbonyl group, **1**, (ii) bridging of the nucleophile between the  $\alpha$ -carbon and the carbonyl carbon in the transition state (TS),<sup>3,4c,1a,b</sup> **2**, (iii) concerted displacement with an enolate-like TS,<sup>5</sup> **3**.

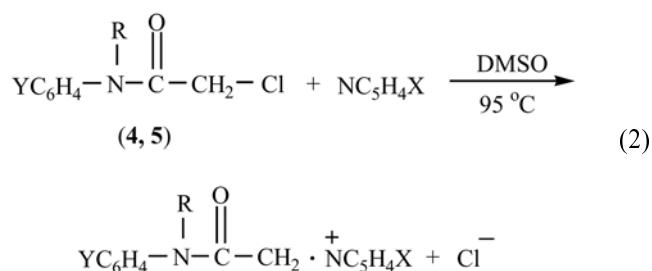


In a series of works, we reported an unified mechanism in which the reaction proceeds through an addition intermediate (**1**) with bridged type TS (**2**)<sup>6</sup> in the expulsion of the leaving group,  $\text{LZ}^-$ . In a previous work,<sup>6d</sup> the aminolyses of  $\alpha$ -chloroacetanilides ( $\text{YC}_6\text{H}_4\text{NRC}(=\text{O})\text{CH}_2\text{Cl}$ ;  $\text{R}=\text{H}$  and  $\text{CH}_3$ ) with benzylamines in dimethyl sulfoxide are found to proceed through a stepwise mechanism with rate-limiting expulsion of the chloride leaving group from a zwitterionic tetrahedral intermediate,  $\text{T}^\pm$ , with a bridged type transition state (**2**) for which the cross-interaction constants,<sup>7</sup>  $\rho_{XY}$  in eqs. 1, where X and Y denote substituents in the nucleophile and substrate, are positive;  $\rho_{XY} = +0.21$  and  $+0.18$  with  $\text{R}=\text{H}$  (**4**) and  $\text{CH}_3$  (**5**), respectively.

$$\log(k_{XY}/k_{\text{HH}}) = \rho_X \sigma_X + \rho_Y \sigma_Y + \rho_{XY} \sigma_{XY} \quad (1a)$$

$$\rho_{XY} = \partial \rho_X / \partial \sigma_Y = \partial \rho_Y / \partial \sigma_X \quad (1b)$$

In the pyridinolysis of phenacyl bromides ( $\text{YC}_6\text{H}_4\text{C}(=\text{O})\text{CH}_2\text{Br}$ ) in MeCN, a change of  $\rho_{XY}$  from a large positive ( $\rho_{XY} = +1.36$ ) to a small positive ( $\rho_{XY} = 0.09$ ) value indicates a rate-determining step change at the breakpoint ( $\text{p}K_a^0 = 3.2 - 3.6$ ) from breakdown to formation of a zwitterionic intermediate,  $\text{T}^\pm$  (**1** with  $\text{XN}^+$  = pyridinium ion) as the pyridine basicity is increased.<sup>6c</sup> To gain further evidence in support of our unified mechanism (**1+2**) for the  $\alpha$ -halocarbonyl systems, we carried out kinetic studies of the pyridinolysis of  $\alpha$ -chloroacetanilides (**4** and **5** with  $\text{R}=\text{H}$  and  $\text{CH}_3$ , respectively in eq. 2) in dimethyl sulfoxide at 95 °C.



$\text{R} = \text{H}$  (**4**) and  $\text{CH}_3$  (**5**).

$\text{Y} = p\text{-CH}_3\text{O}$ ,  $p\text{-CH}_3$ ,  $\text{H}$ ,  $p\text{-Cl}$  and  $p\text{-NO}_2$ .

$\text{X} = p\text{-CH}_3\text{O}$ ,  $p\text{-CH}_3$ ,  $m\text{-CH}_3$  (only for **5**),  $\text{H}$ ,  $m\text{-C}_6\text{H}_5$  and  $m\text{-COCH}_3$ .

### Results and Discussion

The reactions followed the clean second-order rate law given by eqs. 3 and 4, where  $[\text{Py}]$  is the pyridine concentration. The pseudo-first-order rate constants observed ( $k_{\text{obsd}}$ )

$$d[\text{Cl}^-] / dt = k_{\text{obsd}} [\text{substrate}] \quad (3)$$

$$k_{\text{obsd}} = k_0 + k_{\text{N}} [\text{Py}] \quad (4)$$

obeyed eq. 4, for all reactions with negligible  $k_0$  ( $\cong 0$ ) in DMSO. The second-order rate constants for pyridinolysis,  $k_N$  ( $M^{-1}s^{-1}$ ), summarized in Table 1 and Table 2 for **4** and **5**, respectively, were obtained as the slopes of the plots of  $k_{\text{obsd}}$  against pyridine concentrations, [Py], in eq. (4). No third-order or higher order terms were detected, and no complications were found in the determination of  $k_{\text{obsd}}$  or in the linear plots of eq. 4. The rate is faster with a stronger nucleophile and with a stronger electron withdrawing group in the substrate, **4** and **5** as normally observed for a typical nucleophilic substitution reaction. The rate constants for the pyridinolysis of  $\alpha$ -chloroacetanilides are found to be smaller than those for the aminolysis with benzylamines *e.g.* for Y=H, (**4**);  $k_N = 7.63 \times 10^{-3} M^{-1}s^{-1}$  for benzylamine ( $pK_a = 9.38$  in water) in DMSO at 55 °C<sup>6d</sup> and  $k_N = 1.02 \times 10^{-3} M^{-1}s^{-1}$  for pyridine ( $pK_a = 5.21$  in water) in DMSO at 95 °C as the basicity (nucleophilicity) of pyridine is smaller than that of benzylamine. The Brønsted coefficients  $\beta_X$  ( $\beta_{\text{nuc}}$ ), Hammett constants  $\rho_X$  ( $\rho_{\text{nuc}}$ ) and  $\rho_Y$  values and the cross-interaction constants  $\rho_{XY}$  values are also shown in Table 1 and 2 for **4** and **5**, respectively. The  $pK_a$  values of pyridines used in the Brønsted plots were those determined in water as shown in Figures 1 (**4**) and 2 (**5**), respectively.

The Brønsted coefficients in Tables 1 and 2 could be in error since the rate data in Tables (in DMSO) should be plotted using  $pK_a$  values measured in DMSO. However the  $\beta_X$  values, determined by the  $pK_a$  values in water, are

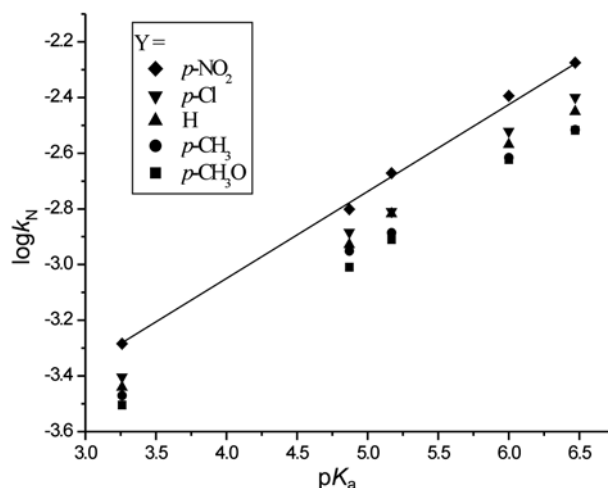


Figure 1. Brønsted plots of  $\log k_N$  vs.  $pK_a(X)$  for the pyridinolysis of Y- $\alpha$ -chloroacetanilides (**4**) in DMSO at 95 °C.

considered to provide reasonable guides, as has been shown for the  $\beta_X$  values in the pyridinolysis of *N*-methyl-*N*-aryl carbamoyl chloride ( $YC_6H_4N(CH_3)C(=O)Cl$ ) in DMSO.<sup>10a</sup> The plots of  $pK_a(\varepsilon)$  (in five solvents including water) vs.  $\sigma$  gave the slopes,  $\rho_S(\varepsilon)$ , which is linear with Onsager dielectric function  $(\varepsilon-1)/(2\varepsilon+1)$  with  $r = 0.999$ . Spillane *et al.*<sup>11</sup> reported that the Brønsted coefficients ( $\beta_X$ ) for the reaction of *N*-phenylsulfamoyl chloride ( $YC_6H_4NHSO_2Cl$ ) with anilines in DMSO are similar when determined using

Table 1. Second-order rate constants, ( $k_N \times 10^4/M^{-1}s^{-1}$ ) and selectivity parameters<sup>a</sup> for the pyridinolysis of Y- $\alpha$ -chloroacetanilides in DMSO at 95 °C

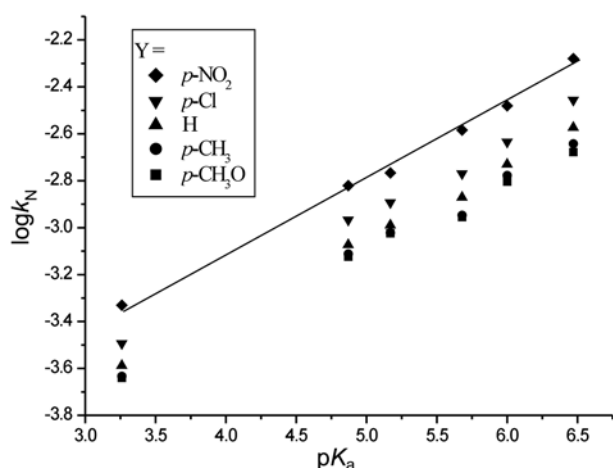
X \ Y	Y						$\rho_Y^b$
	<i>p</i> -OCH <sub>3</sub>	<i>p</i> -CH <sub>3</sub>	H	<i>p</i> -Cl	<i>p</i> -NO <sub>2</sub>		
<i>p</i> -CH <sub>3</sub> O	30.3	30.5	35.4	39.9	53.1		0.24 ± 0.01
<i>p</i> -CH <sub>3</sub>	23.8	24.2	27.0	30.1	40.4		0.22 ± 0.01
H	12.3	13.0	15.2	15.5	21.3		0.22 ± 0.01
<i>m</i> -C <sub>6</sub> H <sub>5</sub>	9.80	11.2	11.8	13.1	15.8		0.18 ± 0.01
<i>m</i> -COCH <sub>3</sub>	3.13	3.39	3.62	3.95	5.20		0.20 ± 0.01
$\rho_X^c$	-1.55 ± 0.04	-1.49 ± 0.05	-1.54 ± 0.04	-1.56 ± 0.03	-1.58 ± 0.05		
$\beta_X^d$	0.31 ± 0.01	0.30 ± 0.01	0.31 ± 0.01	0.32 ± 0.01	0.32 ± 0.01		$\rho_{XY}^e = -0.06 \pm 0.05$

<sup>a</sup> $\sigma$  values were taken from ref. 8. The  $\beta_X$  values were determined using  $pK_a$  values in water. The  $pK_a$  values were taken from ref. 9. <sup>b</sup>Correlation coefficients,  $r$ , were better than 0.990 in all cases. <sup>c</sup> $r \geq 0.998$ . <sup>d</sup> $r \geq 0.999$ . <sup>e</sup> $r = 0.997$

Table 2. Second-order rate constants, ( $k_N \times 10^4/M^{-1}s^{-1}$ ) and selectivity parameters<sup>a</sup> for the pyridinolysis of *N*-methyl-Y- $\alpha$ -chloroacetanilides in DMSO at 95 °C

X \ Y	Y						$\rho_Y^b$
	<i>p</i> -OCH <sub>3</sub>	<i>p</i> -CH <sub>3</sub>	H	<i>p</i> -Cl	<i>p</i> -NO <sub>2</sub>		
<i>p</i> -CH <sub>3</sub> O	21.0	22.8	26.7	35.0	52.6		0.40 ± 0.04
<i>p</i> -CH <sub>3</sub>	15.7	16.7	18.6	23.2	33.0		0.32 ± 0.03
<i>m</i> -CH <sub>3</sub>	11.1	11.3	13.4	17.0	26.1		0.40 ± 0.05
H	9.46	9.51	10.2	12.8	17.1		0.23 ± 0.03
<i>m</i> -C <sub>6</sub> H <sub>5</sub>	7.51	7.72	8.46	10.8	15.1		0.30 ± 0.02
<i>m</i> -COCH <sub>3</sub>	2.29	2.33	2.58	3.21	4.67		0.31 ± 0.02
$\rho_X^c$	-1.48 ± 0.05	-1.52 ± 0.04	-1.56 ± 0.02	-1.58 ± 0.02	-1.60 ± 0.05		
$\beta_X^d$	0.30 ± 0.01	0.30 ± 0.01	0.31 ± 0.01	0.32 ± 0.01	0.32 ± 0.01		$\rho_{XY}^e = -0.10 \pm 0.05$

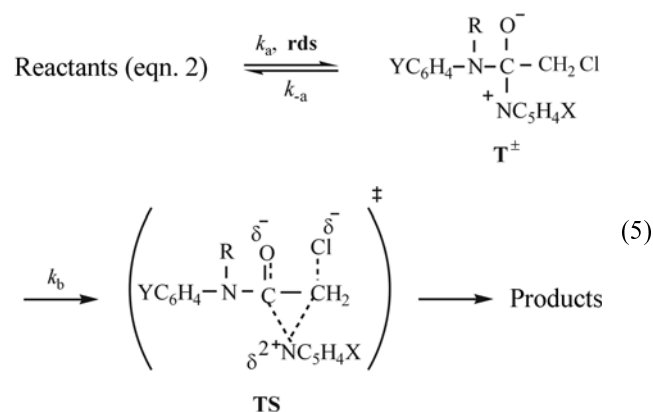
<sup>a</sup>Same as Table 1. <sup>b</sup> $r \geq 0.990$ . <sup>c</sup> $r \geq 0.998$ . <sup>d</sup> $r \geq 0.996$ . <sup>e</sup> $r = 0.997$



**Figure 2.** Brønsted plots of  $\log k_N$  vs.  $pK_a$  (X) for the pyridinolysis of *N*-methyl-*Y*- $\alpha$ -chloroacetanilides (**5**) in DMSO at 95 °C.

$pK_a$  values of anilines measured in water ( $\beta_X = 0.69$ ) and in DMSO ( $\beta_X = 0.62$ ). This provides evidence in support of correlating the rate data determined in DMSO with the  $pK_a$  values measured in water.

We propose for the present series of reactions, the stepwise mechanism with rate limiting formation of  $T^\pm$ , followed by bridged type transition state to expel the chloride leaving group, in eq. 5 where  $k_N = k_a$  since  $k_{-a} \ll k_b$ . Nucleophile of pyridine attacks



firstly on carbonyl carbon (not  $\alpha$ -carbon) to form the zwitterionic intermediate,  $T^\pm$ , in eq. 5 in the rate-determining step. In a previous work,<sup>6d</sup> we have explained that nucleophile initially interacts more strongly with carbonyl carbon ( $\pi^*_{\text{C=O}}$ ) than with  $\alpha$ -carbon ( $\sigma^*_{\text{C-Cl}}$ ) on MO theoretical approach.<sup>12</sup> In the second step, the departing pyridine molecule shifts to the  $\alpha$ -carbon with simultaneous expulsion of  $\text{Cl}^-$  leaving group, in a bridging type (2) transition state structure. This is reasonable, since in the intermediate there is only one LUMO ( $\sigma^*_{\text{C-Cl}}$ ) left for the amine to attack. The proposed mechanism for the present work can be justified on the following grounds.

(1) In the present system, we observed faster rates with **4** than with **5**, comparing  $k_N$  values in Table 1 and 2. This is reasonable, because  $\text{CH}_3$  group is a stronger electron donor

(compare to H), which donate electron to the anilino nitrogen. As a result, electron density on carbonyl carbon increases in **5** ( $\text{R}=\text{CH}_3$ ) rather than in **4** ( $\text{R}=\text{H}$ ) and nucleophile attacks less strongly in the former, *i.e.*, the initial rate-limiting carbonyl addition step ( $k_a$ ) is retarded. In contrast, the reaction rates of  $\alpha$ -chloroacetanilides with benzylamines in DMSO are faster with **5** ( $\text{R}=\text{CH}_3$ ) than with **4** ( $\text{R}=\text{H}$ ) which was taken to imply the rate-limiting expulsion of the leaving group from  $T^\pm$ . This is in accord with the sequence of amine expulsion rate from  $T^\pm$ ; benzylamines > secondary alicyclic amines > anilines > pyridines.<sup>13</sup> The aminolysis of  $\alpha$ -chloroacetanilides is one of the typical models to show the sequence of the amine expulsion rate from  $T^\pm$  explicitly. In case of the aminolysis of  $\alpha$ -chloroacetanilides with benzylamines, the benzylamine expulsion rate ( $k_{-a}$ ) from  $T^\pm$  is faster than the leaving group expulsion rate ( $k_b$ ),  $k_{-a} \gg k_b$ , and the leaving group expulsion is rate-determining step. On the other hand, the pyridine expulsion rate from  $T^\pm$  is slower than the leaving group expulsion rate,  $k_b \gg k_{-a}$ , and the bond formation step is rate-determining one for the pyridinolysis of  $\alpha$ -chloroacetanilides. For the aminolysis of  $\alpha$ -chloroacetanilides with benzylamines, the leaving group expulsion from  $T^\pm$  is enhanced by a stronger electron donating R ( $\text{CH}_3$  relative to H) which leads to faster rates with **5** ( $\text{R}=\text{CH}_3$ ) than with **4** ( $\text{R}=\text{H}$ ).

(2) The sign of cross-interaction constants  $\rho_{XY}$  are *negative* but very small magnitude,  $\rho_{XY} = -0.06$  and  $-0.10$  for the reactions of **4** and **5**, respectively in contrast to the *positive*  $\rho_{XY} = +0.21$  and  $+0.18$  for the reactions of **4** and **5** with benzylamines,<sup>6d</sup> respectively. The very small magnitude of  $\rho_{XY}$  in this work is partly ascribed to the intervening NR group in the substrate between the reaction center carbon and the benzene ring *i.e.*, the fall-off by a factor of 2.4-2.8 due to an intervening group.<sup>7</sup> In all the aminolysis of phenacyl derivatives involving different nucleophiles (benzylamines, anilines or pyridines), different leaving groups (chlorides, bromides or arenesulfonates) and different solvents (MeOH, MeCN or DMSO), the  $\rho_{XY}$  values were positive which were taken to indicate the reactions proceed by a stepwise mechanism with rate-limiting expulsion of the leaving group:  $\rho_{XY} = 0.05^{6c}$  and  $\rho_{XY} = 1.36^{6c}$  for the reactions of phenacyl bromides with benzylamines and with pyridines in MeCN, respectively;  $\rho_{XY} = 0.02$ - $0.04^{6b}$  and  $\rho_{XY} = 0.05$ - $0.14^{6a}$  for the reactions of phenacyl benzenesulfonates ( $\text{YC}_6\text{H}_4\text{C(=O)CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$ ) with benzylamines in MeOH and with anilines in MeOH-MeCN, respectively;  $\rho_{XY} = 0.21$  and  $0.18^{6d}$  for the reactions of **4** and **5** with benzylamines in DMSO, respectively. The acyl transfer reactions with rate-limiting expulsion of the leaving group also give relatively large positive  $\rho_{XY}$  values:  $\rho_{XY} = 0.38$ - $0.42^{14a}$  for the reactions of *p*-nitrophenyl benzoates ( $\text{YC}_6\text{H}_4\text{C(=O)OC}_6\text{H}_4\text{-p-NO}_2$ ) with benzylamines in MeOH;  $\rho_{XY} = 0.53$ - $0.64^{14b}$  for the reactions of benzoic anhydrides ( $\text{YC}_6\text{H}_4\text{C(=O)OC(=O)-C}_6\text{H}_5$ ) with anilines in MeOH;  $\rho_{XY} = 1.35$ - $1.49^{15a}$  and  $0.51$ - $0.61^{15b}$  for the reactions of *S*-phenyl benzoates ( $\text{YC}_6\text{H}_4\text{C(=O)SC}_6\text{H}_4\text{Z}$ ) with anilines in MeOH and with benzylamines in MeCN, respectively;  $\rho_{XY} = 0.61$ - $0.71^{15c}$  for the

reactions of aryl dithiobenzoates (YC<sub>6</sub>H<sub>4</sub>C(=S)SC<sub>6</sub>H<sub>4</sub>Z) with anilines in MeCN. In contrast, all of the S<sub>N</sub>2 displacement reactions of various substrates with amines are reported to give negative  $\rho_{XY}$  values.<sup>7</sup> A stronger electron-acceptor substituent in the substrate ( $\partial\sigma_Y > 0$ ) leads to a greater degree of bond formation ( $\partial\rho_X < 0$ ) so that  $\rho_{XY} = \partial\rho_X/\partial\sigma_Y$  is negative. For a stepwise reaction with the rate-limiting formation of tetrahedral intermediate, T<sup>±</sup>, the sign of  $\rho_{XY}$  will be same for the forward reaction of concerted S<sub>N</sub>2 processes,<sup>7c,15c,16</sup> i.e.,  $\rho_{XY} < 0$ , as shown in the present work. However, as discussed previously,<sup>6c</sup> in the partitioning of tetrahedral intermediate the rate of expulsion of amines is increased ( $\partial\rho_X > 0$ ) by a stronger electron-acceptor substituent in the acyl group ( $\partial\sigma_Y > 0$ )<sup>17</sup> so that  $\rho_{XY} = \partial\rho_X/\partial\sigma_Y$  should be positive. Thus the sign and magnitude of  $\rho_{XY}$  would be compensated by the two factors, i.e.,  $\rho_{XY} < 0$  for bond formation step and  $\rho_{XY} > 0$  for amine expulsion from T<sup>±</sup>. As a result of compensation effects of opposite signs, the  $\rho_{XY}$  values for the reactions of the rate-limiting formation of T<sup>±</sup> are very small negative or positive:  $\rho_{XY} = -0.06$  and  $-0.10$  for the pyridinolysis of **4** and **5** (this work) in DMSO, respectively;  $\rho_{XY} = +0.09$  for the rate-limiting formation part of pyridinolysis of phenacyl bromide in MeCN<sup>6c</sup>;  $\rho_{XY} = +0.05$  for the aminolysis of aryl dithiobenzoates with benzylamines in MeCN.<sup>18</sup>

(3) The initial rate-limiting formation of T<sup>±</sup> is also supported by the smaller magnitude of  $\beta_X$  (0.30-0.32 for both **4** and **5**), indicating the degree of bond formation, than those of the aminolysis with benzylamines ( $\beta_X = 0.56-0.87$ ).<sup>6d</sup> In case of acyl transfer reactions of aryl dithiobenzoates with benzylamines in MeCN for which the rate-limiting attack on the thiocarbonyl,  $\beta_X = 0.19-0.26$ <sup>18</sup> are found. A biphasic dependence of  $\log k_N$  on the pyridine basicity was obtained for aryl dithiobenzoates,<sup>19</sup> aryl dithioacetates<sup>20</sup> and aryl furan-2-carbodithioates (c-C<sub>4</sub>H<sub>3</sub>OC(=S)SC<sub>6</sub>H<sub>4</sub>Z)<sup>21</sup> in MeCN with a breakpoint at pK<sub>a</sub><sup>o</sup> where the rate-limiting step is changed from bond breaking to bond formation as the basicity of pyridine is increased. The  $\beta_X$  values are also small for the rate-limiting formation parts of the acyl transfer reactions of pyridinolysis of aryl dithiobenzoates ( $\beta_X = 0.16-0.18$ ),<sup>19</sup> aryl dithioacetates ( $\beta_X = 0.37-0.39$ )<sup>20</sup> and aryl furan-2-carbodithioates ( $\beta_X = 0.16-0.17$ )<sup>21</sup> in MeCN. In contrast, the  $\beta_X$  values are within narrow range of  $0.7 \pm 0.1$  for the aminolysis of phenacyl derivatives which proceed stepwise through a zwitterionic tetrahedral intermediate with rate-limiting expulsion of the leaving group;  $\beta_X = 0.69-0.73$ <sup>6c</sup> and  $\beta_X = 0.65-0.80$ <sup>6c</sup> for the reactions of phenacyl bromides with benzylamines and with anilines in MeCN, respectively;  $\beta_X = 0.63-0.76$ <sup>6b</sup> and  $\beta_X = 0.65-0.76$ <sup>6a</sup> for the reactions of phenacyl benzenesulfonates with benzylamines in MeOH and with anilines in MeOH-MeCN, respectively;  $\beta_X = 0.56-0.87$ <sup>6d</sup> and  $\beta_X = 0.61-0.87$ <sup>6d</sup> for the reactions of **4** and **5** with benzylamines in DMSO, respectively. The rate-limiting expulsion parts of pyridinolysis of aryl dithiobenzoates, aryl dithioacetates and aryl furan-2-carbodithioates give  $\beta_X = 0.71-0.78$ ,<sup>19</sup>  $0.83-0.94$ <sup>20</sup> and  $0.73-0.81$ ,<sup>21</sup> respectively. The large magnitudes of

Brønsted coefficients,  $\beta_X$  ( $\beta_{\text{nucl}}$ )  $\geq 0.8$ <sup>15b,c,17a,22</sup> are normally considered to represent a stepwise mechanism with rate-limiting expulsion of the leaving group. Castro *et al.* investigated the quinuclidinolysis of ethyl *S*-4-nitrophenyl thiocarbonate ( $\beta_X = 0.85$ )<sup>13c</sup> and methyl 4-nitrophenyl carbonate ( $\beta_X = 0.86$ ),<sup>23</sup> a stepwise mechanism with rate-limiting breakdown of T<sup>±</sup> is proposed.

(4) The reactivity-selectivity principle (RSP) does not hold to the studied system, i.e., the faster rate ( $\partial k_N > 0$ ) is invariably accompanied by a larger magnitude of selectivity parameters,  $\partial|\rho_X| > 0$ ,  $\partial\rho_X > 0$  and  $\partial\beta_X > 0$  as shown in Tables 1 and 2. The fail of RSP is another criterion for the stepwise mechanism with rate-limiting addition of the nucleophile to the substrate.<sup>24</sup>

The activation parameters for **4** ( $\Delta H^\ddagger = 12-15$  kcal mol<sup>-1</sup> and  $\Delta S^\ddagger = -34$  to  $-37$  cal mol<sup>-1</sup> K<sup>-1</sup>) and **5** ( $\Delta H^\ddagger = 14-16$  kcal mol<sup>-1</sup> and  $\Delta S^\ddagger = -30$  to  $-33$  cal mol<sup>-1</sup> K<sup>-1</sup>) are summarized in Table 3. The activation enthalpies for the pyridinolysis are slightly larger than those for the aminolysis with benzylamines ( $\Delta H^\ddagger = 9-13$  and  $10-15$  kcal mol<sup>-1</sup> for **4** and **5**, respectively)<sup>6d</sup> while the activation entropies for pyridinolysis are smaller than those for aminolysis with benzylamines ( $\Delta S^\ddagger = -20$  to  $-30$  and  $\Delta S^\ddagger = -14$  to  $-28$  cal mol<sup>-1</sup> K<sup>-1</sup> for **4** and **5**, respectively).<sup>6d</sup> These suggest that the degree of bond formation for pyridinolysis is larger than that for aminolysis with benzylamines in the bond formation step.

Finally, we can interpret the pyridinolysis of  $\alpha$ -chloro-

**Table 3.** Activation parameters<sup>a</sup> for the reactions of *N*-R-*Y*- $\alpha$ -chloroacetanilides with X-pyridines in DMSO

R	X	Y	Temp. (°C)	$k_N \times 10^4$ (M <sup>-1</sup> s <sup>-1</sup> )	$\Delta H^\ddagger$ (kcal mol <sup>-1</sup> )	$-\Delta S^\ddagger$ (cal mol <sup>-1</sup> K <sup>-1</sup> )	
<b>(4)</b>	H	<i>p</i> -NO <sub>2</sub>	75	7.79	12.5 ± 0.3 <sup>b</sup>	37 ± 1	
			85	13.1			
			95	21.3			
	<i>p</i> -CH <sub>3</sub> O	H	75	12.4	13.4 ± 0.2	34 ± 1	
			85	22.0			
			95	35.4			
	<i>m</i> -C <sub>6</sub> H <sub>5</sub>	<i>p</i> -Cl	75	4.10	14.6 ± 0.2	32 ± 1	
			85	7.42			
			95	13.1			
H	H	75	4.99	14.0 ± 0.2	34 ± 1		
		85	8.99				
		95	15.2				
<b>(5)</b>	H	<i>p</i> -NO <sub>2</sub>	75	5.58	14.4 ± 0.3	33 ± 1	
			85	10.1			
			95	17.1			
	<i>p</i> -CH <sub>3</sub> O	H	75	8.86	13.8 ± 0.3	33 ± 1	
			85	16.2			
			95	26.7			
	CH <sub>3</sub>	<i>m</i> -C <sub>6</sub> H <sub>5</sub>	<i>p</i> -Cl	75	3.36	14.7 ± 0.2	32 ± 1
				85	6.15		
				95	10.8		
	H	H	75	2.94	15.5 ± 0.2	30 ± 1	
			85	5.61			
			95	10.2			

<sup>a</sup>Calculated by Eyring equation. <sup>b</sup>Standard deviation

acetanilides as a stepwise with rate-limiting formation of zwitterionic tetrahedral intermediate, based on Hammett constants  $\rho_X$  and  $\rho_Y$ , Brønsted coefficients  $\beta_X$ , cross-interaction constants  $\rho_{XY}$ , RSP and activation parameters. The enolate-like transition state and an alternative reaction path through an epoxide type transition state are ruled out based on the previous works.<sup>6d,e</sup>

### Experimental Section

**Materials.** Aldrich GR grade pyridines were used without further purification. All other materials were as reported previously.<sup>6d</sup>

**Kinetic Procedure.** Rate constants were determined as described previously.<sup>6d</sup> For the present work, [Substrate] =  $1 \times 10^{-3}$  and [Py] = 0.13–0.21 M were used.

**Product Analysis.** *p*-Nitro- and *N*-methyl *p*-nitro- $\alpha$ -chloroacetanilides (0.0003 moles) were refluxed with 4-picoline (0.003 moles) in 40 mL acetonitrile at 95 °C. After more than 15 half-lives, solvent was removed under reduced pressure and the product was purified by washing several times with ether. Analytical data of the product gave the following results:

***p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NHC(=O)CH<sub>2</sub>N<sup>+</sup>C<sub>5</sub>H<sub>4</sub>-*p*-CH<sub>3</sub>Cl<sup>-</sup>.** White solid; mp 248 °C;  $\delta_{\text{H}}$  (200 MHz, DMSO-*d*<sub>6</sub>) 2.66 (3H, s, CH<sub>3</sub>), 5.69 (2H, s, CH<sub>2</sub>), 11.7 (1H, s, NH), 7.89 (2H, d, *J* = 9.2 Hz, benzene), 8.05 (2H, d, *J* = 6.6 Hz, pyridine), 8.27 (2H, d, *J* = 9.6 Hz, benzene), 8.90 (2H, d, *J* = 7.0 Hz, pyridine);  $\delta_{\text{C}}$  (50 MHz, DMSO-*d*<sub>6</sub>) 22.3, 62.2, 119.7, 125.8, 128.5, 143.4, 145.1, 146.0, 160.6, 165.3;  $\nu_{\text{max}}$  (nujol mull) 3469, 3389, 1716, 1563, 1258. Anal. Calcd for C<sub>14</sub>H<sub>14</sub>ClN<sub>3</sub>O<sub>3</sub>: C, 54.6; H, 4.6; N, 13.7. Found: C, 54.5; H, 4.7; N, 13.6.

***p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>N(CH<sub>3</sub>)C(=O)CH<sub>2</sub>N<sup>+</sup>C<sub>5</sub>H<sub>4</sub>-*p*-CH<sub>3</sub>Cl<sup>-</sup>.** White solid; mp 242 °C;  $\delta_{\text{H}}$  (200 MHz, DMSO-*d*<sub>6</sub>) 2.62 (3H, s, CH<sub>3</sub>), 3.36 (3H, s, N-CH<sub>3</sub>), 5.70 (2H, bs, CH<sub>2</sub>), 7.82 (2H, d, *J* = 7.0 Hz, benzene), 8.02 (2H, d, *J* = 6.2 Hz, pyridine), 8.35 (2H, d, *J* = 8.4 Hz, benzene), 8.87 (2H, d, *J* = 6.4 Hz, pyridine);  $\delta_{\text{C}}$  (50 MHz, DMSO-*d*<sub>6</sub>) 21.6, 37.0, 60.9, 124.7, 127.8, 129.2, 145.2, 145.4, 147.7, 159.8, 165.1;  $\nu_{\text{max}}$  (nujol mull) 3560, 3397, 1681, 1518, 1295. Anal. Calcd. for C<sub>15</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>3</sub>: C, 56.0 H, 5.0; N, 13.1. Found: C, 55.8; H, 5.2; N, 13.2.

**Acknowledgement.** This work was supported by Korea Research Foundation Grant (KRF-2002-070-C00061).

### References

- (a) Dewar, M. J. S. *The Electronic Theory of Organic Chemistry*; Oxford University Press: Oxford, 1949; p 73. (b) McLennan, D. J.; Pross, A. *J. Chem. Soc. Perkin Trans. 2* **1984**, 981. (c) Pross, A.; Aviram, K.; Klix, R. C.; Kost, D.; Back, R. D. *New J. Chem.* **1984**, 8, 711. (d) Shaik, S. S. *J. Am. Chem. Soc.* **1983**, 105, 4359. (e) Pross, A.; De Frees, D. J.; Levi, B. A.; Pollack, S. K.; Radom, L.; Hehre, W. J. *J. Org. Chem.* **1981**, 46, 1693. (f) Kost, D.; Aviram, K. *Tetrahedron Lett.* **1982**, 23, 4157. (g) Wolfe, S.; Mitchell, D. J.; Schelegel, H. B. *Can. J. Chem.* **1982**, 60, 1291.
- (a) Conant, J. B.; Kirner, W. R. *J. Am. Chem. Soc.* **1924**, 46, 232. (b) Ross, S. D.; Finkelstein, M.; Petersen, R. C. *J. Am. Chem. Soc.* **1968**, 90, 6411. (c) Halvorsen, A.; Songstad, J. *J. Chem. Soc., Chem. Commun.* **1978**, 327. (d) Bartlett, P. D.; Trachtenberg, E. N. *J. Am. Chem. Soc.* **1958**, 80, 15808. (e) Thorpe, J. W.; Warkentin, J. *Can. J. Chem.* **1973**, 51, 927. (f) Bordwell, F. G.; Brannen, W. T. *J. Am. Chem. Soc.* **1964**, 86, 4645. (g) Lee, I.; Sung, D. D. *Curr. Org. Chem.* **2004**, 8, 557.
- Streitwieser, Jr., A. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962.
- (a) Baker, J. W. *Trans Faraday Soc.* **1951**, 37, 643. (b) Bunton, C. A. *Nucleophilic Substitution at a Saturated Carbon Atom*; Elsevier: New York, 1963; p 5. (c) Winstein, S.; Grunwald, E.; Jones, H. W. *J. Am. Chem. Soc.* **1951**, 73, 2700.
- (a) Yousaf, T. I.; Lewis, E. S. *J. Am. Chem. Soc.* **1987**, 109, 6137. (b) Forster, W.; Laird, R. M. *J. Chem. Soc., Perkin Trans. 2* **1982**, 135.
- (a) Lee, I.; Shim, C. S.; Chung, S. Y.; Lee, H. W. *J. Chem. Soc., Perkin Trans. 2* **1988**, 975. (b) Lee, I.; Shim, C. S.; Lee, H. W. *J. Phys. Org. Chem.* **1989**, 2, 484. (c) Koh, H. J.; Han, K. L.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2000**, 65, 4706. (d) Lee, K. S.; Adhikary, K. K.; Lee, H. W.; Lee, B.-S.; Lee, I. *Org. Biomol. Chem.* **2003**, 1, 1989. (e) Lee, I.; Lee, H. W.; Yu, Y.-K. *Bull. Korean Chem. Soc.* **2003**, 24, 993.
- (a) Lee, I. *Chem. Soc. Rev.* **1990**, 19, 317. (b) Lee, I. *Adv. Phys. Org. Chem.* **1992**, 27, 57. (c) Lee, I.; Lee, H. W. *Collect. Czech. Chem. Commun.* **1999**, 64, 1529.
- Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, 91, 165.
- Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, ch. 8, 1987.
- (a) Lee, I.; Hong, S. W.; Koh, H. J.; Lee, Y.; Lee, B.-S.; Lee, H. W. *J. Org. Chem.* **2001**, 66, 8549. (b) Kim, T.-H.; Huh, C.; Lee, B.-S.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2257. (c) Koh, H. J.; Kim, T. H.; Lee, B.-S.; Lee, I. *J. Chem. Res. (S)* **1996**, 482.
- Spillane, W. J.; Hogan, G.; McGrath, P.; King, J.; Brack, C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2099.
- (a) Fukui, K. *Theory of Orientation and Stereoselection*; Springer-Verlag: Berlin, 1975. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976. (c) Li, H. G.; Kim, C. K.; Lee, B.-S.; Kim, C. K.; Rhee, S. K.; Lee, I. *J. Am. Chem. Soc.* **2002**, 123, 2326.
- (a) Castro, E. A.; Sales, M. J.; Santos, J. G. *J. Org. Chem.* **1994**, 59, 30. (b) Castro, E. A.; Leandro, L.; Millan, P.; Santos, J. G. *J. Org. Chem.* **1999**, 64, 1953. (c) Castro, E. A.; Munoz, P.; Santos, J. G. *J. Org. Chem.* **1999**, 64, 8298. (d) Oh, H. K.; Kim, S. K.; Cho, I. H.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2306.
- (a) Koh, H. J.; Lee, H. C.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **1995**, 16, 839. (b) Lee, B. C.; Yoon, J. H.; Lee, C. G.; Lee, I. *J. Phys. Org. Chem.* **1994**, 7, 273.
- (a) Lee, I.; Shim, C. S.; Lee, H. W. *J. Chem. Res. (S)* **1992**, 90. (b) Lee, I.; Koh, H. J. *New J. Chem.* **1996**, 20, 131. (c) Oh, H. K.; Shin, C. H.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1169.
- (a) Lee, I. *Bull. Korean Chem. Soc.* **1994**, 15, 985. (b) Yew, K. H.; Koh, H. J.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2263.
- (a) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, 99, 6970. (b) Castro, E. A.; Steinfort, G. B. *J. Chem. Soc., Perkin Trans. 2* **1983**, 453. (c) Song, B. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, 111, 8479.
- Oh, H. K.; Shin, C. H.; Lee, I. *Bull. Korean Chem. Soc.* **1995**, 16, 657.
- Oh, H. K.; Lee, J. M.; Lee, H. W.; Lee, I. *Int. J. Chem. Kinet.* **2004**, 36, 434.
- Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2002**, 67, 3874.
- Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2002**, 67, 8995.
- Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, 96, 7018.
- Castro, E. A.; Aliaga, M.; Compodonico, P.; Santos, J. G. *J. Org. Chem.* **2002**, 67, 8911.
- (a) Pross, A. *Adv. Phys. Org. Chem.* **1977**, 14, 69. (b) Buncl, E.; Wilson, H. J. *Chem. Edu.* **1987**, 64, 475.