

Nucleophilic Substitution Reactions of α -Chloroacetanilides with Pyridines in Dimethyl Sulfoxide

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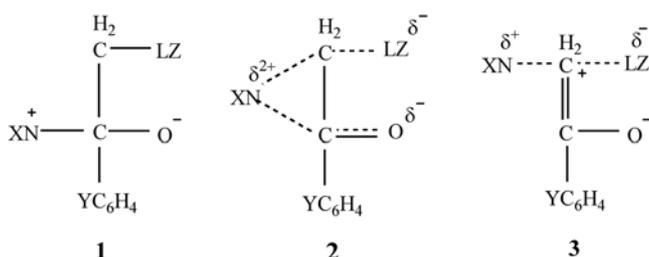
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The kinetic studies of the reactions of α -chloroacetanilides ($\text{YC}_6\text{H}_4\text{NRC}(=\text{O})\text{CH}_2\text{Cl}$; $\text{R}=\text{H}$ (**4**) and CH_3 (**5**)) with pyridines have been carried out in dimethyl sulfoxide at 95 °C. The pyridinolysis rates are faster with **4** than with **5** whereas the aminolysis rates with benzylamines are faster with **5** than with **4**. The Brønsted β_X values are in the range from 0.30 to 0.32 and the cross-interaction constants, ρ_{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 α -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 (T^\pm) followed by a bridged type transition state to expel the leaving group.

Key Words : Pyridinolyses of α -chloroacetanilides, Cross-interaction constants, Stepwise mechanism

Introduction

The nucleophilic substitution reactions of α -halocarbonyl compounds have attracted considerable attention of theoretical¹ as well as experimental organic chemists,² mainly because of the rate-enhancing effect of the α -carbonyl group.^{2a,b,c,3} Although a variety of mechanism has been proposed for α -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 (XN) to the carbonyl group, **1**, (ii) bridging of the nucleophile between the α -carbon and the carbonyl carbon in the transition state (TS),^{3,4c,1a,b} **2**, (iii) concerted displacement with an enolate-like TS,⁵ **3**.

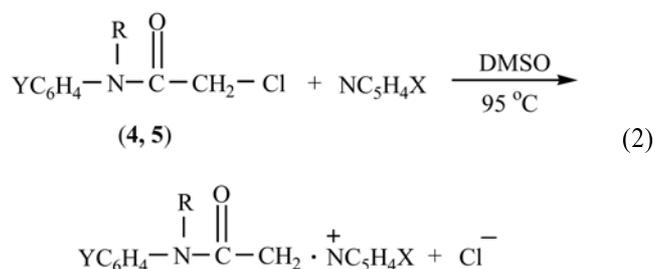


In a series of works, we reported an unified mechanism in which the reaction proceeds through an addition intermediate (**1**) with bridged type TS (**2**)⁶ in the expulsion of the leaving group, LZ^- . In a previous work,^{6d} the aminolyses of α -chloroacetanilides ($\text{YC}_6\text{H}_4\text{NRC}(=\text{O})\text{CH}_2\text{Cl}$; $\text{R}=\text{H}$ and 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, T^\pm , with a bridged type transition state (**2**) for which the cross-interaction constants,⁷ ρ_{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 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 ρ_{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, T^\pm (**1** with XN^+ = pyridinium ion) as the pyridine basicity is increased.^{6c} To gain further evidence in support of our unified mechanism (**1+2**) for the α -halocarbonyl systems, we carried out kinetic studies of the pyridinolysis of α -chloroacetanilides (**4** and **5** with $\text{R}=\text{H}$ and CH_3 , respectively in eq. 2) in dimethyl sulfoxide at 95 °C.



$\text{R} = \text{H}$ (**4**) and CH_3 (**5**).

$\text{Y} = p\text{-CH}_3\text{O}$, $p\text{-CH}_3$, 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**), 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_{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_{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_{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 α -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^{6d} 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 β_X (β_{nuc}), Hammett constants ρ_X (ρ_{nuc}) and ρ_Y values and the cross-interaction constants ρ_{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 β_X values, determined by the pK_a values in water, are

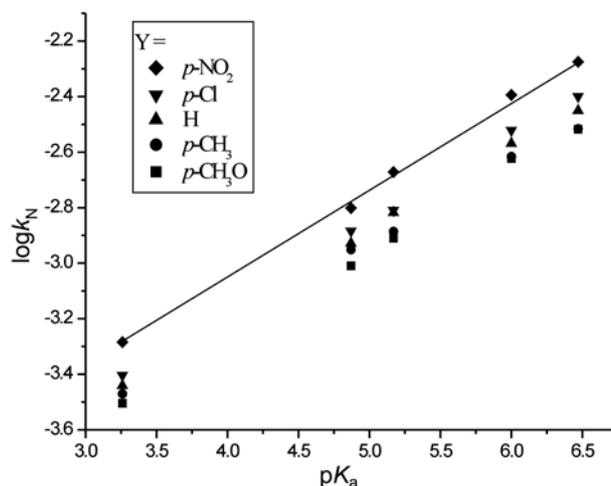


Figure 1. Brønsted plots of $\log k_N$ vs. $pK_a(X)$ for the pyridinolysis of Y- α -chloroacetanilides (**4**) in DMSO at 95 °C.

considered to provide reasonable guides, as has been shown for the β_X values in the pyridinolysis of *N*-methyl-*N*-aryl carbamoyl chloride ($YC_6H_4N(CH_3)C(=O)Cl$) in DMSO.^{10a} The plots of $pK_a(\varepsilon)$ (in five solvents including water) vs. σ 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.*¹¹ reported that the Brønsted coefficients (β_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^a for the pyridinolysis of Y- α -chloroacetanilides in DMSO at 95 °C

X \ Y	Y						ρ_Y^b
	<i>p</i> -OCH ₃	<i>p</i> -CH ₃	H	<i>p</i> -Cl	<i>p</i> -NO ₂		
<i>p</i> -CH ₃ O	30.3	30.5	35.4	39.9	53.1		0.24 ± 0.01
<i>p</i> -CH ₃	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 ₆ H ₅	9.80	11.2	11.8	13.1	15.8		0.18 ± 0.01
<i>m</i> -COCH ₃	3.13	3.39	3.62	3.95	5.20		0.20 ± 0.01
ρ_X^c	-1.55 ± 0.04	-1.49 ± 0.05	-1.54 ± 0.04	-1.56 ± 0.03	-1.58 ± 0.05		
β_X^d	0.31 ± 0.01	0.30 ± 0.01	0.31 ± 0.01	0.32 ± 0.01	0.32 ± 0.01		$\rho_{XY}^e = -0.06 \pm 0.05$

^a σ values were taken from ref. 8. The β_X values were determined using pK_a values in water. The pK_a values were taken from ref. 9. ^bCorrelation coefficients, r , were better than 0.990 in all cases. ^c $r \geq 0.998$. ^d $r \geq 0.999$. ^e $r = 0.997$

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

X \ Y	Y						ρ_Y^b
	<i>p</i> -OCH ₃	<i>p</i> -CH ₃	H	<i>p</i> -Cl	<i>p</i> -NO ₂		
<i>p</i> -CH ₃ O	21.0	22.8	26.7	35.0	52.6		0.40 ± 0.04
<i>p</i> -CH ₃	15.7	16.7	18.6	23.2	33.0		0.32 ± 0.03
<i>m</i> -CH ₃	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 ₆ H ₅	7.51	7.72	8.46	10.8	15.1		0.30 ± 0.02
<i>m</i> -COCH ₃	2.29	2.33	2.58	3.21	4.67		0.31 ± 0.02
ρ_X^c	-1.48 ± 0.05	-1.52 ± 0.04	-1.56 ± 0.02	-1.58 ± 0.02	-1.60 ± 0.05		
β_X^d	0.30 ± 0.01	0.30 ± 0.01	0.31 ± 0.01	0.32 ± 0.01	0.32 ± 0.01		$\rho_{XY}^e = -0.10 \pm 0.05$

^aSame as Table 1. ^b $r \geq 0.990$. ^c $r \geq 0.998$. ^d $r \geq 0.996$. ^e $r = 0.997$

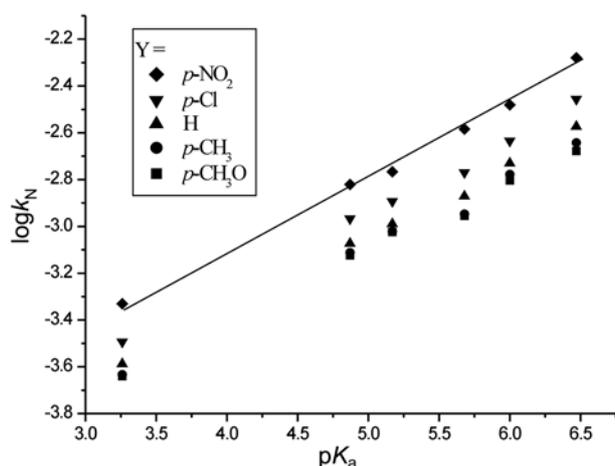
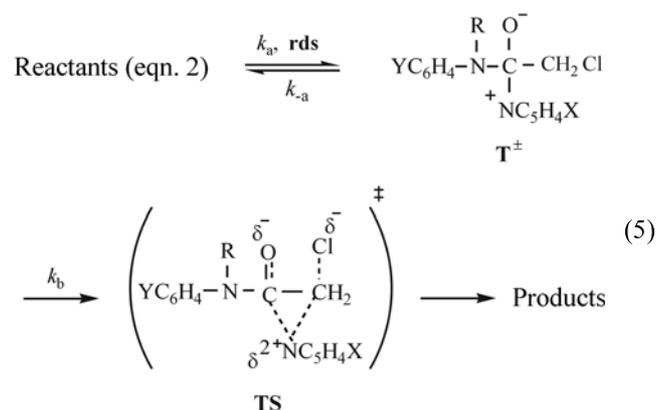


Figure 2. Brønsted plots of $\log k_N$ vs. pK_a (X) for the pyridinolysis of *N*-methyl-*Y*- α -chloroacetanilides (**5**) in DMSO at 95 °C.

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 α -carbon) to form the zwitterionic intermediate, T^\pm , in eq. 5 in the rate-determining step. In a previous work,^{6d} we have explained that nucleophile initially interacts more strongly with carbonyl carbon ($\pi^*_{\text{C=O}}$) than with α -carbon ($\sigma^*_{\text{C-Cl}}$) on MO theoretical approach.¹² In the second step, the departing pyridine molecule shifts to the α -carbon with simultaneous expulsion of 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 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 α -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.¹³ The aminolysis of α -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 α -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 α -chloroacetanilides. For the aminolysis of α -chloroacetanilides with benzylamines, the leaving group expulsion from T^\pm is enhanced by a stronger electron donating R (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 ρ_{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,^{6d} respectively. The very small magnitude of ρ_{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.⁷ 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 ρ_{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 ρ_{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 ($\text{YC}_6\text{H}_4\text{C}(=\text{S})\text{SC}_6\text{H}_4\text{Z}$) with anilines in MeCN. In contrast, all of the $\text{S}_{\text{N}}2$ displacement reactions of various substrates with amines are reported to give negative ρ_{XY} values.⁷ A stronger electron-acceptor substituent in the substrate ($\partial\sigma_{\text{Y}} > 0$) leads to a greater degree of bond formation ($\partial\rho_{\text{X}} < 0$) so that $\rho_{\text{XY}} = \partial\rho_{\text{X}}/\partial\sigma_{\text{Y}}$ is negative. For a stepwise reaction with the rate-limiting formation of tetrahedral intermediate, T^{\pm} , the sign of ρ_{XY} will be same for the forward reaction of concerted $\text{S}_{\text{N}}2$ processes,^{7c,15c,16} i.e., $\rho_{\text{XY}} < 0$, as shown in the present work. However, as discussed previously,^{6c} in the partitioning of tetrahedral intermediate the rate of expulsion of amines is increased ($\partial\rho_{\text{X}} > 0$) by a stronger electron-acceptor substituent in the acyl group ($\partial\sigma_{\text{Y}} > 0$)¹⁷ so that $\rho_{\text{XY}} = \partial\rho_{\text{X}}/\partial\sigma_{\text{Y}}$ should be positive. Thus the sign and magnitude of ρ_{XY} would be compensated by the two factors, i.e., $\rho_{\text{XY}} < 0$ for bond formation step and $\rho_{\text{XY}} > 0$ for amine expulsion from T^{\pm} . As a result of compensation effects of opposite signs, the ρ_{XY} values for the reactions of the rate-limiting formation of T^{\pm} are very small negative or positive: $\rho_{\text{XY}} = -0.06$ and -0.10 for the pyridinolysis of **4** and **5** (this work) in DMSO, respectively; $\rho_{\text{XY}} = +0.09$ for the rate-limiting formation part of pyridinolysis of phenacyl bromide in MeCN^{6c}; $\rho_{\text{XY}} = +0.05$ for the aminolysis of aryl dithiobenzoates with benzylamines in MeCN.¹⁸

(3) The initial rate-limiting formation of T^{\pm} is also supported by the smaller magnitude of β_{X} (0.30-0.32 for both **4** and **5**), indicating the degree of bond formation, than those of the aminolysis with benzylamines ($\beta_{\text{X}} = 0.56$ -0.87).^{6d} In case of acyl transfer reactions of aryl dithiobenzoates with benzylamines in MeCN for which the rate-limiting attack on the thiocarbonyl, $\beta_{\text{X}} = 0.19$ -0.26¹⁸ are found. A biphasic dependence of $\log k_{\text{N}}$ on the pyridine basicity was obtained for aryl dithiobenzoates,¹⁹ aryl dithioacetates²⁰ and aryl furan-2-carbodithioates ($\text{c-C}_4\text{H}_3\text{OC}(=\text{S})\text{SC}_6\text{H}_4\text{Z}$)²¹ in MeCN with a breakpoint at $\text{p}K_{\text{a}}^{\circ}$ where the rate-limiting step is changed from bond breaking to bond formation as the basicity of pyridine is increased. The β_{X} values are also small for the rate-limiting formation parts of the acyl transfer reactions of pyridinolysis of aryl dithiobenzoates ($\beta_{\text{X}} = 0.16$ -0.18),¹⁹ aryl dithioacetates ($\beta_{\text{X}} = 0.37$ -0.39)²⁰ and aryl furan-2-carbodithioates ($\beta_{\text{X}} = 0.16$ -0.17)²¹ in MeCN. In contrast, the β_{X} values are within narrow range of 0.7 ± 0.1 for the aminolysis of phenacyl derivatives which proceed stepwise through a zwitterionic tetrahedral intermediate with rate-limiting expulsion of the leaving group; $\beta_{\text{X}} = 0.69$ -0.73^{6c} and $\beta_{\text{X}} = 0.65$ -0.80^{6c} for the reactions of phenacyl bromides with benzylamines and with anilines in MeCN, respectively; $\beta_{\text{X}} = 0.63$ -0.76^{6b} and $\beta_{\text{X}} = 0.65$ -0.76^{6a} for the reactions of phenacyl benzenesulfonates with benzylamines in MeOH and with anilines in MeOH-MeCN, respectively; $\beta_{\text{X}} = 0.56$ -0.87^{6d} and $\beta_{\text{X}} = 0.61$ -0.87^{6d} 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 $\beta_{\text{X}} = 0.71$ -0.78,¹⁹ 0.83-0.94²⁰ and 0.73-0.81,²¹ respectively. The large magnitudes of

Brønsted coefficients, β_{X} (β_{nucl}) ≥ 0.8 ^{15b,c,17a,22} 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 ($\beta_{\text{X}} = 0.85$)^{13c} and methyl 4-nitrophenyl carbonate ($\beta_{\text{X}} = 0.86$),²³ a stepwise mechanism with rate-limiting breakdown of T^{\pm} is proposed.

(4) The reactivity-selectivity principle (RSP) does not hold to the studied system, i.e., the faster rate ($\partial k_{\text{N}} > 0$) is invariably accompanied by a larger magnitude of selectivity parameters, $\partial|\rho_{\text{X}}| > 0$, $\partial\rho_{\text{X}} > 0$ and $\partial\beta_{\text{X}} > 0$ 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.²⁴

The activation parameters for **4** ($\Delta H^{\ddagger} = 12$ -15 kcal mol⁻¹ and $\Delta S^{\ddagger} = -34$ to -37 cal mol⁻¹ K⁻¹) and **5** ($\Delta H^{\ddagger} = 14$ -16 kcal mol⁻¹ and $\Delta S^{\ddagger} = -30$ to -33 cal mol⁻¹ K⁻¹) 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⁻¹ for **4** and **5**, respectively)^{6d} 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⁻¹ K⁻¹ for **4** and **5**, respectively).^{6d} 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 α -chloro-

Table 3. Activation parameters^a for the reactions of *N*-*R*-*Y*- α -chloroacetanilides with *X*-pyridines in DMSO

R	X	Y	Temp. (°C)	$k_{\text{N}} \times 10^4$ (M ⁻¹ s ⁻¹)	ΔH^{\ddagger} (kcal mol ⁻¹)	$-\Delta S^{\ddagger}$ (cal mol ⁻¹ K ⁻¹)	
4	H	<i>p</i> -NO ₂	75	7.79	12.5 ± 0.3 ^b	37 ± 1	
			85	13.1			
			95	21.3			
	<i>p</i> -CH ₃ O	H	75	12.4	13.4 ± 0.2	34 ± 1	
			85	22.0			
			95	35.4			
	<i>m</i> -C ₆ H ₅	<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				
5	H	<i>p</i> -NO ₂	75	5.58	14.4 ± 0.3	33 ± 1	
			85	10.1			
			95	17.1			
	<i>p</i> -CH ₃ O	H	75	8.86	13.8 ± 0.3	33 ± 1	
			85	16.2			
			95	26.7			
	CH ₃	<i>m</i> -C ₆ H ₅	<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			

^aCalculated by Eyring equation. ^bStandard deviation

acetanilides as a stepwise with rate-limiting formation of zwitterionic tetrahedral intermediate, based on Hammett constants ρ_X and ρ_Y , Brønsted coefficients β_X , cross-interaction constants ρ_{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.^{6d,e}

Experimental Section

Materials. Aldrich GR grade pyridines were used without further purification. All other materials were as reported previously.^{6d}

Kinetic Procedure. Rate constants were determined as described previously.^{6d} For the present work, [Substrate] = 1×10^{-3} and [Py] = 0.13–0.21 M were used.

Product Analysis. *p*-Nitro- and *N*-methyl *p*-nitro- α -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*-NO₂C₆H₄NHC(=O)CH₂N⁺C₅H₄-*p*-CH₃Cl⁻.** White solid; mp 248 °C; δ_H (200 MHz, DMSO-*d*₆) 2.66 (3H, s, CH₃), 5.69 (2H, s, CH₂), 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); δ_C (50 MHz, DMSO-*d*₆) 22.3, 62.2, 119.7, 125.8, 128.5, 143.4, 145.1, 146.0, 160.6, 165.3; ν_{max} (nujol mull) 3469, 3389, 1716, 1563, 1258. Anal. Calcd for C₁₄H₁₄ClN₃O₃: C, 54.6; H, 4.6; N, 13.7. Found: C, 54.5; H, 4.7; N, 13.6.

***p*-NO₂C₆H₄N(CH₃)C(=O)CH₂N⁺C₅H₄-*p*-CH₃Cl⁻.** White solid; mp 242 °C; δ_H (200 MHz, DMSO-*d*₆) 2.62 (3H, s, CH₃), 3.36 (3H, s, N-CH₃), 5.70 (2H, bs, CH₂), 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); δ_C (50 MHz, DMSO-*d*₆) 21.6, 37.0, 60.9, 124.7, 127.8, 129.2, 145.2, 145.4, 147.7, 159.8, 165.1; ν_{max} (nujol mull) 3560, 3397, 1681, 1518, 1295. Anal. Calcd. for C₁₅H₁₆ClN₃O₃: C, 56.0 H, 5.0; N, 13.1. Found: C, 55.8; H, 5.2; N, 13.2.

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