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Nucleophilic substitution reactions of α-chloroacetanilides with benzylamines in dimethyl sulfoxide

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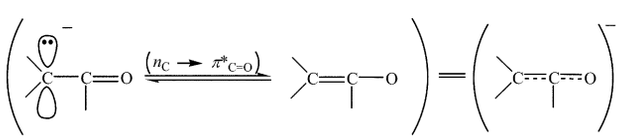
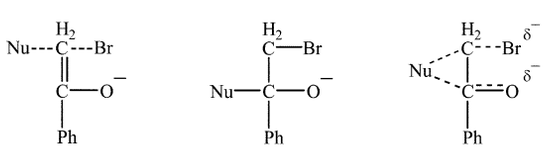
Kinetic studies of the reactions of α-chloroacetanilides ($YC_6H_4NRC(=O)CH_2Cl$; R = H (**5**) and CH_3 (**6**)) with benzylamines ($NH_2CH_2C_6H_4X$) were carried out in dimethyl sulfoxide at 55.0 °C. The Brønsted β_X values were in the range from 0.6 to 0.9 and cross-interaction constants ρ_{XY} were positive: $\rho_{XY} = +0.21$ and $+0.18$ for **5** and **6**, respectively. The rates were faster with **6** than with **5** and inverse secondary kinetic isotope effects involving deuterated benzylamine ($ND_2CH_2C_6H_4X$) nucleophiles, $k_H/k_D < 1.0$, were obtained. Based on these and other results, a stepwise mechanism with rate-limiting expulsion of the chloride leaving group from a zwitterionic tetrahedral intermediate, $T^{\pm}$, is proposed. In this mechanism, a prior carbonyl addition to $T^{\pm}$ is followed by a bridged type transition state to expel the chloride. An enolate-like transition state in which the developing negative charge on C_α delocalizes toward the carbonyl group ($n_C \longrightarrow \pi^*_{C=O}$ interaction) is not feasible for the present series of reactions due to a stronger charge transfer involving the lone pair on the anilino nitrogen ($n_{AN} \longrightarrow \pi^*_{C=O}$ interaction).

Introduction

The nucleophilic substitution reaction of α-halocarbonyl compounds is known to have high reactivity.[1] It has been suggested that an adjacent carbonyl group accelerates the reaction by delocalizing the negative charge developed on the reaction center carbon in the transition state (TS), analogous to the enolate-like structure, **1**[2] (Scheme 1), an α-acylcarbanion,[2a] due to vicinal charge transfer delocalization of the anionic lone pair (n_C) toward the antibonding π orbital of the carbonyl group ($\pi^*_{C=O}$), an $n_C \longrightarrow \pi^*_{C=O}$ interaction.[3] This process is a concerted nucleophilic displacement (an S_N2 type) at the α-carbon not at the carbonyl carbon. The high reactivity of α-halocarbonyl systems, *e.g.*, phenacyl bromide ($YC_6H_4COCH_2Br$), has also been explained by proposing (i) enolate-like TS, **2**,[2c] (ii) prior addition of the nucleophile (Nu) to the carbonyl group, **3**[4] and (iii) bridging of the nucleophile between the α-carbon and the carbonyl carbon, **4**.[1b,4c,5]



Scheme 1



2 **3** **4**

In a previous work on the pyridinolysis of phenacyl bromide,[6] we observed a typical biphasic rate dependence on the amine basicity with a breakpoint at $pK_a^o \cong 3.5$, which was taken to indicate a mechanistic change at the breakpoint from breakdown to formation of a zwitterionic tetrahedral intermediate, $T^{\pm}$ (**3** with Nu = pyridinium ion), as the pyridine basicity is increased. In the rate-limiting step, expulsion of the leaving group, Br^-, occurs by formation of a bridged structure **4**. Thus, in this type of nucleophilic substitution mechanism of phenacyl halides we can nicely accommodate the two mechanisms **3** and **4**, proposed earlier separately by several authors, in one. Additional evidence for the proposed unified mechanism was the clear-cut change in the cross-interaction constant,[7] ρ_{XY} (eqns. (1a) and (1b), where X and Y are the substituents in the nucleophile and the substrate) from a large positive ($\rho_{XY} = +1.4$) to a small positive ($\rho_{XY} \cong +0.1$) value at the breakpoint.

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

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

In view of the unresolved controversy surrounding the nucleophilic substitution mechanism of phenacyl systems (**2**, **3** and **4**), we explore further our unified mechanism presented in the previous work by conducting kinetic studies on the aminolysis of α-chloroacetanilides (**5** and **6** with R = H and CH_3, respectively in eqn. (2)) with benzylamines in dimethyl sulfoxide at 55.0 °C (eqn. (2)).

R = H (**5**) and CH_3 (**6**). X = *p*-CH_3O, *p*-CH_3, H, *p*-Cl and *m*-Cl. Y = *p*-CH_3O, *p*-CH_3, H, *p*-Cl, *m*-Cl (only for **5**) and *p*-NO_2.

Results and discussion

The reactions obeyed the kinetic law given by eqns. (3) and (4), where BnA is a benzylamine nucleophile. The second-order rate constants for aminolysis (k_N) were obtained as the slopes of plots of eqn. (4) with more than five excess benzylamine concentrations. The k_N values are summarized in Tables 1 and 2 for **5** and **6**, respectively, together with Hammett constants (ρ_X and

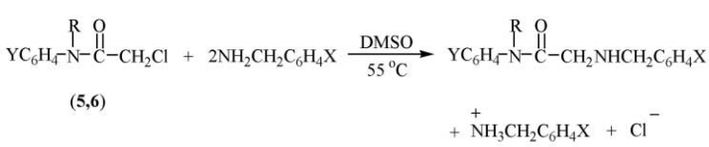


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Table 1 The second-order rate constants, k_N (10^{-2} M^{-1} s^{-1}), and selectivity parameters[a] for the reactions of Y-α-chloroacetanilides (**5**) with X-benzylamines in dimethyl sulfoxide at 55.0 °C

	Y						
X	*p*-CH_3O	*p*-CH_3	H	*p*-Cl	*m*-Cl	*p*-NO_2	ρ_Y[b]
p-CH_3O	0.641	0.704	0.979	1.04	1.43	2.08	0.49 ± 0.04
p-CH_3	0.467	0.533	0.821	0.898	1.20	1.90	0.57 ± 0.05
H	0.420	0.455	0.763	0.845	1.09	1.73	0.59 ± 0.06
p-Cl	0.299	0.345	0.517	0.580	0.793	1.32	0.61 ± 0.04
m-Cl	0.219	0.253	0.435	0.460	0.653	1.09	0.65 ± 0.06
ρ_X[c]	−0.66 ± 0.07	−0.63 ± 0.06	−0.54 ± 0.05	−0.54 ± 0.06	−0.51 ± 0.04	−0.43 ± 0.04	ρ_{XY}[e] = 0.21 ± 0.06
β_X[d]	0.87 ± 0.08	0.81 ± 0.09	0.71 ± 0.02	0.71 ± 0.02	0.66 ± 0.03	0.56 ± 0.03	

[a] The σ values were taken from ref. 8. The β_X values were determined using pK_a values in water. The pK_a values of benzylamines in water at 25 °C were taken from ref. 9. [b] Correlation coefficients, r, were better than 0.981 in all cases. [c] $r \geq 0.984$. [d] $r \geq 0.981$. [e] $r = 0.972$.

Table 2 The second-order rate constants, k_N (10^{-2} M^{-1} s^{-1}), and selectivity parameters[a] for the reactions of *N*-methyl-Y-α-chloroacetanilides (**6**) with X-benzylamines in dimethyl sulfoxide at 55.0 °C

	Y					
X	*p*-CH_3O	*p*-CH_3	H	*p*-Cl	*p*-NO_2	ρ_Y[b]
p-CH_3O	0.691	0.931	1.07	1.71	2.65	0.54 ± 0.07
p-CH_3	0.599	0.755	0.981	1.58	2.47	0.58 ± 0.08
H	0.487	0.647	0.838	1.30	2.21	0.61 ± 0.07
p-Cl	0.301	0.426	0.536	0.834	1.49	0.63 ± 0.07
m-Cl	0.264	0.371	0.475	0.776	1.40	0.67 ± 0.07
ρ_X[c]	−0.68 ± 0.04	−0.62 ± 0.04	−0.59 ± 0.05	−0.58 ± 0.05	−0.47 ± 0.05	ρ_{XY}[e] = 0.18 ± 0.12
β_X[d]	0.87 ± 0.08	0.80 ± 0.09	0.75 ± 0.02	0.75 ± 0.02	0.61 ± 0.03	

[a] Same as in Table 1. [b] $r \geq 0.982$. [c] $r \geq 0.977$. [d] $r \geq 0.978$. [e] $r = 0.968$.

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

$$k_{obsd} = k_N [BnA] \quad (4)$$

ρ_Y), Brønsted (β_X) coefficients and cross-interaction constants (ρ_{XY}).

Brønsted plots, log k_N(DMSO) *vs.* pK_a(H_2O), are shown in Fig. 1 for the aminolysis of **5**. Although the β_X (= β_{nuc}) values are based on the plots of log k_N(DMSO) *vs.* pK_a(H_2O), they are considered to provide reasonable guides, as has been shown for the β_X values in the pyridinolysis of *N*-methyl-*N*-arylcarbamoyl chloride ($YC_6H_4N(CH_3)C(=O)Cl$) in DMSO.[10] Spillane *et al.*[11] have also 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 pK_a values of anilines measured in water (β_X = 0.69) and in DMSO (β_X = 0.62).

We propose, for the present series of reactions, the stepwise mechanism with rate-limiting breakdown of $T^{\pm}$ in eqn. (5)

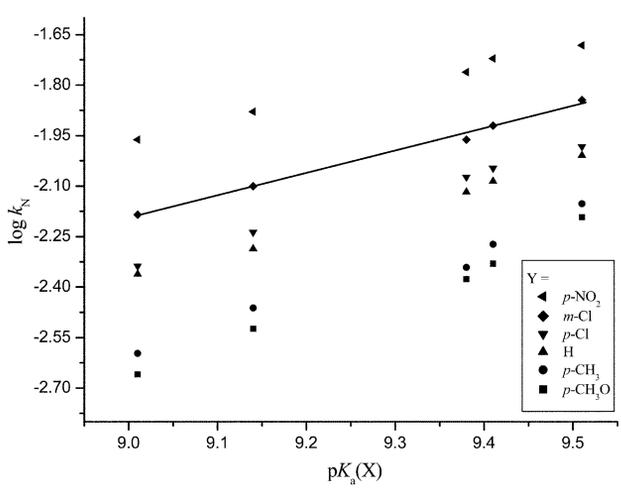
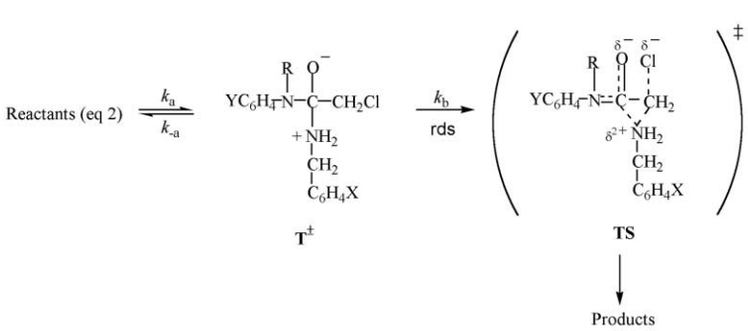


Fig. 1 Brønsted plots (β_X) for the reactions of Y-α-chloroacetanilides (**5**) with X-benzylamines in DMSO at 55.0 °C.



(5)

Table 3 Kinetic isotope effects on the second-order rate constants (k_H/k_D) for the reactions of $YC_6H_4NRC(=O)CH_2Cl$ with $XC_6H_4CH_2ND_2$ in dimethyl sulfoxide at 55.0 °C

R	X	Y	k_H (10^{-2} M^{-1} s^{-1})	k_D (10^{-2} M^{-1} s^{-1})	k_H/k_D
H (**5**)	*p*-CH_3O	*p*-Cl	1.04	1.13	0.92
	p-CH_3O	*p*-NO_2	2.08	2.15	0.97
	H	*p*-Cl	0.845	0.970	0.87
	H	*p*-NO_2	1.73	1.87	0.93
CH_3 (**6**)	*p*-CH_3O	H	1.07	1.25	0.86
	p-CH_3O	*p*-NO_2	2.65	2.93	0.90
	H	H	0.838	1.01	0.83
	H	*p*-NO_2	2.21	2.52	0.88

where $k_N = (k_a / k_{-a})k_b = Kk_b$ based on the following grounds:

(1) MO theory states that it is the lowest unoccupied antibonding orbital (LUMO) that is attacked by a nucleophile.[12] In this respect there are two choices, $\pi^*_{C=O}$ and σ^*_{C-Cl}, the former being much lower than the latter. For example, for formyl chloride (HC(=O)Cl) the two antibonding orbital levels are $\varepsilon(\pi^*_{C=O}) = 0.0795$ and $\varepsilon(\sigma^*_{C-Cl}) = 0.1965$ au at the RHF/6-311++G*** // MP2/6-311+G** level.[13] This means that the lone pair orbital (n_N) on the amine nitrogen atom in the nucleophile interacts much more strongly with $\pi^*_{C=O}$ than with σ^*_{C-Cl} and forms an intermediate $T^{\pm}$ leading to a concerted (S_N2) displacement at the α-carbon; the wider the energy gap between two antibonding orbitals, $\Delta\varepsilon = \varepsilon(\sigma^*) - \varepsilon(\pi^*)$, the stronger the proclivity for formation of a stable carbonyl addition intermediate through $n_N \longrightarrow \pi^*_{C=O}$ interaction.[14] The intermediate $T^{\pm}$ in eqn. (5) is formed in a rapid step (k_a is large) but the expulsion of the benzylamine from $T^{\pm}$ is also fast (k_{-a} is large). It has been shown that the sequence of amine expulsion rate from $T^{\pm}$ is benzylamines > secondary alicyclic amines > anilines > pyridines.[15] The rapidly departing amine (BnA) then attacks the σ^*_{C-Cl} orbital in the rate-determining step with the bridging type structure (type **4**) to expel the leaving group, Cl^-. This is reasonable, since in the intermediate (type **3**) there is only one LUMO (σ^*_{C-Cl}) left for the amine to attack. In the TS (eqn. (5)), the vicinal charge transfer delocalization of the lone pair on the anilino nitrogen (n_{AN}) toward the developing carbonyl $\pi^*_{C=O}$ orbital ($n_{AN} \longrightarrow \pi^*_{C=O}$ interaction) facilitates the expulsion of the leaving group from $T^{\pm}$ by providing an extra stabilization for the TS leading to an increase in k_b. This is why we observed faster rates with **6** than with **5**, comparing k_N values in Tables 1 and 2. The CH_3 group is a stronger electron donor than H so that the n_{AN} level in **6** is raised to a higher level than that in **5** and leads to a smaller inter-frontier energy gap $\Delta\varepsilon = \varepsilon(\pi^*) - \varepsilon(n_{AN})$. The stabilization energy due to a vicinal charge transfer increases as the energy gap between the interacting orbitals becomes narrower.[3b,16] If the reactions proceeded by a direct attack on σ^*_{C-Cl} (S_N2), possibly through an enolate-like TS (type **2**), the electron donor R (= CH_3) should have retarded the rate, since in the TS the reaction center carbon becomes more negative as evidenced by the positive ρ_Y ($\rho_Y > 0$ in Tables 1 and 2).

(2) The sign of cross-interaction constant ρ_{XY} is positive, $\rho_{XY} = +0.21$ and $+0.18$ for the reactions of **5** and **6**, respectively. This mechanistic criteria for the acyl transfer reactions has provided a useful means to distinguish between stepwise reactions *via* an intermediate ($\rho_{XY} > 0$) and concerted (S_N2) reactions ($\rho_{XY} < 0$) *via* a single TS. For example, all the S_N2 displacement reactions of benzyl ($YC_6H_4CH_2$–),[7b] benzoyl (YC_6H_4CO–),[7b] benzenesulfonyl ($YC_6H_4SO_2$–),[7b] 1-phenylethyl (YC_6H_4-$CH(CH_3)$–),[17] 2-phenylethyl ($YC_6H_4CH_2CH_2$–),[18] and 1-phenyl-2-propyl ($YC_6H_4CH_2CH(CH_3)$–)[19] derivatives with amines ($XC_6H_4NH_2$, $XC_6H_4CH_2NH_2$, and XC_5H_4N) are reported to give negative ρ_{XY} values. Also in the concerted (S_N2) aminolyses of phenyl chloroformates (YC_6H_4OCOCl)[20] and aryl phenyl chlorophosphates ($YC_6H_4O(C_6H_5O)P(=O)Cl$)[21] with anilines in MeCN, the sign of ρ_{XY} was negative. In contrast, for the stepwise aminolysis reactions of: *p*-nitrophenyl benzoates ($YC_6H_4C(=O)OC_6H_4$-*p*-NO_2)[22] with benzylamines in MeCN ($\rho_{XY} = +0.4$), cinnamoyl chlorides ($YC_6H_4CHCHCOCl$)[23] with anilines in MeCN ($\rho_{XY} = +0.88$), benzoic anhydrides (YC_6H_4-$COOCOC_6H_5$)[24] with anilines in MeOH ($\rho_{XY} = +0.5$), phenyl dithiobenzoates ($YC_6H_4C(=S)SC_6H_5$)[25] with anilines in MeCN ($\rho_{XY} = +0.66$), *p*-nitrophenyl *N*-phenylcarbamates (YC_6H_4-$NHCOOC_6H_4$-*p*-NO_2)[26] with benzylamines in MeCN ($\rho_{XY} = +1.10$), phenyl chloroformates[27] with pyridines in MeCN ($\rho_{XY} = +0.31$), and phenacyl bromide[6] with pyridines in MeCN ($\rho_{XY} = +1.4 \longrightarrow +0.1$), the sign of ρ_{XY} was always positive.[28] In the last example,[6] the ρ_{XY} values changed from a large positive ($\rho_{XY} = +1.4$) to a small value ($\rho_{XY} = +0.1$) as the mechanism changed at a pyridine basicity of 3.5 from breakdown to formation of $T^{\pm}$ with the increase in basicity of pyridines. In all the aminolysis reactions of phenacyl derivatives[6,7b] the ρ_{XY} values were positive indicating that the reaction proceeded by a stepwise mechanism with prior formation of the carbonyl addition intermediate (type **3**).

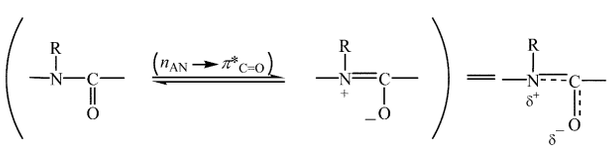
(3) The kinetic isotope effects on the rate, k_H/k_D, involving deuterated benzylamines ($ND_2CH_2C_6H_4X$) are less than unity ($k_H/k_D < 1.0$).[29] In the expulsion of leaving group Cl^- from $T^{\pm}$, the amine approaches at the α-carbon so that the N–H (on benzylamine) vibrational modes are compressed and lead to the inverse secondary kinetic isotope effect, $k_H/k_D < 1.0$.[29,30] Smaller k_H/k_D values (Table 3) are obtained for an electron acceptor or a weaker electron donor X ($\partial\sigma_X > 0$) than a stronger donor X indicating that the amine with $\partial\sigma_X > 0$ approaches closer to the α-carbon in the TS, *i.e.*, bond making between benzylamine and α-carbon is greater with a more positive ρ_Y value, $\partial\rho_Y > 0$. This is, of course, in line with the positive ρ_{XY} (eqn. (1b)) obtained in this work, but does not conform to a direct displacement (S_N2) mechanism at α-carbon for which the ρ_{XY} is negative, since $\rho_{XY} = (\partial\rho_Y) / (\partial\sigma_X) = (-) / (+) < 0$ in eqn. (1b) requires a less positive ρ_Y value ($\partial\rho_Y < 0$) for benzylamine with an electron acceptor X ($\partial\sigma_X > 0$). Thus, the trends of changes in the inverse secondary kinetic isotope effects ($k_H/k_D < 1.0$) are consistent with our proposed mechanism,[30] eqn. (5).

(4) A stronger acceptor Y (= *p*-NO_2) leads to a relatively large k_H/k_D value with a lower activation enthalpy, $\Delta H^{\ddagger}$.[31] This suggests that the TS is at an earlier stage with a lower degree of $N \cdots C_\alpha$ bond making (larger k_H/k_D) and $C_\alpha \cdots Cl$ bond cleavage (lower $\Delta H^{\ddagger}$ value).[31] This is, however, an opposite trend to that expected from the S_N2 type reactions for which ρ_{XY} is negative: $\rho_{XY} = \partial\rho_X / \partial\sigma_Y < 0$ requires that $\partial\sigma_Y > 0$ should lead to $\partial\rho_X < 0$, *i.e.*, a more negative ρ_X with a greater degree of bond making in the TS. For example, the anilinolysis of 2-phenylethyl benzenesulfonates in MeOH[18] is reported to proceed by an S_N2 mechanism with $\rho_{XY} = -0.12$. In this case, ρ_X changes to a more negative value ($\rho_X = -1.14$ to -1.33, $\partial\rho_X < 0$, indicating a greater degree of bond formation) and ρ_Z changes to a more positive value ($\rho_Z = 0.99$ to 1.10, $\partial\rho_Z > 0$, indicating a greater extent of leaving group expulsion) in the TS as the substituent Y is changed from an electron donor, *p*-OCH_3, to an acceptor, *p*-NO_2, ($\partial\sigma_Y > 0$).

(5) The β_X values range from 0.6 to 0.9 (in Tables 1 and 2). The lower end value, 0.6, seems somewhat smaller than that

normally considered to represent a stepwise mechanism with rate-limiting expulsion of the leaving group ($\beta_X \geq 0.8$).[32] Nevertheless the β_X values are well within the range ($\beta_X \geq 0.7$–0.8 in water, and 0.6–0.7 in MeCN) of those reported to be stepwise mechanisms. In the aminolysis of ethyl *S*-aryl thiolcarbonates ($C_2H_5OC(=O)SC_6H_4Z$) with secondary alicyclic amines in water the slopes were β_X = 0.7–0.8[33] and in the pyridinolysis of *S*-phenyl *p*-nitrobenzoates (*p*-$NO_2C_6H_4C(=O)SC_6H_4Z$) and aryl furan-2-carbodithioates ($C_4H_3OC(=S)C_6H_4Z$) in MeCN the slopes were β_X = 0.6–0.7[34] and 0.7–0.8,[35] respectively. All these reactions were consistent with a stepwise mechanism where breakdown of $T^{\pm}$ is rate-limiting. In the present work, the breakpoint, pK_a^o, at which $k_{-a} \cong k_b$ and the rate-limiting step changes from breakdown to formation of $T^{\pm}$, was not observed. This is because the expulsion rate of benzylamine (k_{-a}) from $T^{\pm}$ is so large that the ratio $k_{-a} : k_b$ becomes large, leading to a breakpoint that is higher than the pK_a values of benzylamine used in the rate measurements ($pK_a^o \geq 9.7$; the upper limit of the pK_a of *p*-methoxybenzylamine employed). The pK_a^o value can only be observable when the expulsion rate of the amine from $T^{\pm}$ (k_{-a}) is low and the ratio $k_{-a} : k_b$ becomes small.[32,36] Such examples are reported for the pyridinolysis of phenacyl bromide[6] and aryl furan-2-carbodithioates[35] in MeCN at pK_a^o = 3.5 and 5.2, respectively.

(6) The substituent effects of Y and R on the rate are twofold: (i) on k_a in the initial intermediate formation step and, (ii) on k_b in the rate-limiting leaving group expulsion step from $T^{\pm}$. The two effects oppose each other. An electron withdrawing substituent Y ($\partial\sigma_Y > 0$) enhances positive charge on the carbonyl carbon, or alternatively lowers the $\pi^*_{C=O}$ level so that k_a is increased.[16] In contrast, k_b will be retarded, since an electron acceptor Y in the nonleaving group decreases the rate of expulsion of anionic leaving group, Cl^-. The enhanced rate observed with electron acceptors ($\partial\sigma_Y > 0$) in Tables 1 and 2 testifies that the effect on k_a is greater than on k_b. This is reasonable since the carbonyl group (effect on k_a) is nearer to Y than the α-carbon (effect on k_b). In contrast, the initial carbonyl addition step (k_a) is retarded while the rate-limiting leaving group expulsion from $T^{\pm}$ (k_b) is enhanced by a stronger electron donating R (CH_3 relative to H). The resonance delocalization of the lone pair on the anilino nitrogen (Scheme 2) raises the $\pi^*_{C=O}$ level (higher for



Scheme 2

CH_3 than for H) leading to a decrease in the initial rate of attack by the amine (k_a is reduced) due to a weaker $n_N \rightarrow \pi^*_{C=O}$ interaction.[16] In contrast, in the expulsion of Cl^- from $T^{\pm}$, a stronger electron donating R (CH_3) will lead to a stronger $n_{AN} \rightarrow \pi^*_{C=O}$ interaction which provides a greater push for the expulsion of Cl^- from $T^{\pm}$ in the TS. The greater rates (k_N) observed with R = CH_3 (Table 2) indicate that the effect of R on k_b is greater than on k_a. This is reasonable since a stronger electron donor in the nonleaving group (R = CH_3) in $T^{\pm}$ provides a greater push in the expulsion of anionic leaving group in the rate-limiting breakdown of $T^{\pm}$.[32]

(7) Reference to Tables 1 and 2 reveals that the faster rate ($\partial k_N > 0$) is invariably accompanied by a smaller magnitude of selectivity parameters, $\partial\beta_X < 0$, $\partial\rho_Y < 0$, and $\partial|\rho_X| < 0$, *i.e.*, the reactivity-selectivity principle (RSP) holds.[37] The adherence of the rate data to the RSP is another criterion for the stepwise mechanism with rate-limiting expulsion of the leaving group from the intermediate[38] and provides additional support for our proposed mechanism in this work.

Finally, it is appropriate here to comment on the aminolysis mechanism with an enolate-like TS (type **2**). The substrate used in this work, $YC_6H_4NRC(=O)CH_2Cl$, has a strong delocalized structure, Scheme 2, due to the vicinal charge transfer interaction involving the lone pair on the anilino nitrogen (n_{AN}), $n_{AN} \rightarrow \pi^*_{C=O}$. This is much stronger than the enolate-like structure in Scheme 1 since development of negative charge on the α-carbon is not strong enough to form an anionic lone-pair which is required for the type of structure shown in Scheme 1. In any case, the $n_{AN} \rightarrow \pi^*_{C=O}$ (Scheme 2) should be much stronger than the $n_C \rightarrow \pi^*_{C=O}$ interaction (Scheme 1), so the enolate-like TS is not feasible in the present work. However, in the nucleophilic substitution reaction of an α-halocarbonyl compound, *e.g.*, phenacyl halides, the enolate-like TS may become competitive with the stepwise carbonyl addition mechanism proposed in the present work, provided the negative charge development on the α-carbon in the TS is strong enough to warrant sizable $n_C \rightarrow \pi^*_{C=O}$ interaction. However, the reactions in which development of such a strong negative charge on the α-carbon is possible in the TS may not be common, and hence reactions proceeding with the enolate-like TS may be rare.

Experimental

Materials

GR grade dimethyl sulfoxide was dried with a 4 Å molecular sieve and then used after three distillations under reduced pressure. The benzylamine nucleophiles, GR grade, were used after recrystallization or distillation.

Preparations of Y-α-chloroacetanilide and *N*-methyl Y-α-chloroacetanilide

The Y-α-chloroacetanilide (**5**) and *N*-methyl Y-α-chloroacetanilide (**6**) were prepared by the literature method[39] of esterification. Aniline derivatives and chloro acetic anhydride were dissolved in dried ether. In the case of **5**, the reaction mixture was extracted with water, and dried over $MgSO_4$ and then recrystallized from *n*-hexane. In the case of **6**, solvent was removed under reduced pressure and the product was isolated by column chromatography (silica gel, 20–50% ethyl acetate–*n*-hexane).

***p*-Methoxy α-chloroacetanilide.** White grey solid; mp 119–121 °C (lit.[39b] 121 °C); ^{1}H NMR (200 MHz, $CDCl_3$), δ 3.80 (s, 3H), 4.18 (s, 2H), 6.89 (d, J = 9.0 Hz, 2H), 7.44 (d, J = 9.2 Hz, 2H), 8.16 (s, 1H); *m*/*z* 198 (M^+).

***p*-Methyl α-chloroacetanilide.** White solid; mp 162–164 °C (lit.[39b] 163 °C); ^{1}H NMR (200 MHz, $CDCl_3$), δ 2.34 (s, 3H), 4.19 (s, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 8.20 (s, 1H); *m*/*z* 183 (M^+).

α-Chloroacetanilide. Brown solid; mp 134–135 °C (lit.[39b] 134 °C); ^{1}H NMR (200 MHz, $CDCl_3$), δ 4.18 (s, 2H), 7.25–7.53 (m, 5H), 8.16 (s, 1H); *m*/*z* 169 (M^+).

***p*-Chloro α-chloroacetanilide.** Light brown solid; mp 168–170 °C (lit.[39b] 169 °C); ^{1}H NMR (200 MHz, $CDCl_3$), δ 4.20 (s, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 9.2 Hz, 2H), 8.22 (s, 1H); *m*/*z* 203 (M^+).

***m*-Chloro α-chloroacetanilide.** Light brown solid; mp 98–100 °C; Anal. Found: C, 46.9; H, 3.5; N, 6.8. Calcd. for $C_8H_7NOCl_2$: C, 47.09; H, 3.46; N, 6.86%. ^{1}H NMR (200 MHz, $CDCl_3$), δ 4.20 (s, 2H), 7.02–7.68 (m, 4H), 8.23 (s, 1H); *m*/*z* 214 (M^+).

***p*-Nitro α-chloroacetanilide.** Greenish yellow solid; mp 181–183 °C (lit.[39b] 183 °C); ^{1}H NMR (200 MHz, $CDCl_3$), δ 4.23 (s, 2H), 7.84 (d, J = 9.2 Hz, 2H), 8.25 (d, J = 9.2 Hz, 2H), 8.89 (s, 1H); *m*/*z* 183 (M^+).

***N*-Methyl *p*-methoxy-α-chloroacetanilide.** Light brown oil; Anal. Found: C, 56.1; H, 5.5; N, 6.4. Calcd. for $C_{10}H_{12}NO_2Cl$: C, 56.22; H, 5.66; N, 6.56%. IR (KBr film) ν_{max} (Neat) 840 (C–N stretching), 1742 cm^{-1} (C=O stretching); ^1H NMR (200 MHz, $CDCl_3$) δ 3.28 (s, 3H), 3.84 (s, 5H), 6.95 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 9.2 Hz, 2H); *m*/*z* (EI) 213 (M^+).

***N*-Methyl *p*-methyl-α-chloroacetanilide.** Brown oil; Anal. Found: C, 60.8; H, 6.3; N, 7.2. Calcd. for $C_{10}H_{12}NOCl$: C, 60.77; H, 6.12; N, 7.09%. IR (KBr film) ν_{max} (Neat) 827 (C–N stretching), 1746 cm^{-1} (C=O stretching); ^1H NMR (200 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.30 (s, 3H), 3.87 (s, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H); *m*/*z* (CI) 198 (M^+).

***N*-Methyl α-chloroacetanilide.** Light brown solid; mp 66–67 °C; Anal. Found: C, 58.7; H, 5.5; N, 7.5. Calcd. for $C_9H_{10}NOCl$: C, 58.87; H, 5.49; N, 7.63%. IR (KBr disk) ν_{max} 801 (C–N stretching), 1686 cm^{-1} (C=O stretching); ^1H NMR (200 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.85 (s, 2H), 7.23–7.47 (m, 5H); *m*/*z* (EI) 183 (M^+).

***N*-Methyl *p*-chloro-α-chloroacetanilide.** Pale brown solid; mp 54–55 °C; Anal. Found: C, 49.4; H, 4.3; N, 6.2. Calcd. for $C_9H_9NOCl_2$: C, 49.57; H, 4.16; N, 6.42%. IR (KBr disk) ν_{max} 850 (C–N stretching), 1681 cm^{-1} (C=O stretching); ^1H NMR (200 MHz, $CDCl_3$) δ 3.30 (s, 3H), 3.86 (s, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H); *m*/*z* (CI) 218 (comp.) (M^+), 184 (base).

***N*-Methyl *p*-nitro-α-chloroacetanilide.** Light brown solid; mp 111–112 °C; Anal. Found: C, 47.1; H, 4.1; N, 12.1. Calcd. for $C_9H_9N_2O_3Cl$: C, 47.28; H, 3.97; N, 12.25%. IR (KBr disk) ν_{max} 861 (C–N stretching), 1681 cm^{-1} (C=O stretching); ^1H NMR (200 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.95 (s, 2H), 7.50 (d, J = 9.2 Hz, 2H), 8.34 (d, J = 10.6 Hz, 2H); *m*/*z* (EI) 228 (M^+).

Kinetic measurement

Rates were measured conductometrically in dimethyl sulfoxide at 55.0 ± 0.1 °C (Fig. 2). A computer connected automatic A/D converter conductivity-bridge was used in this work. Pseudo-first-order rate constants, k_{obsd}, were determined with large excess of benzylamine; [Substrate] = 1–5 × 10^{-3} and [BnA] = 0.05–0.12 M. The second-order rate constants, k_N, were obtained from the slopes of plots of k_{obsd} *vs.* [BnA] with more than five concentrations of benzylamine (Fig. 3). Pseudo-first-order rate constant values were average of two (or three) runs which were reproducible to ±3%.

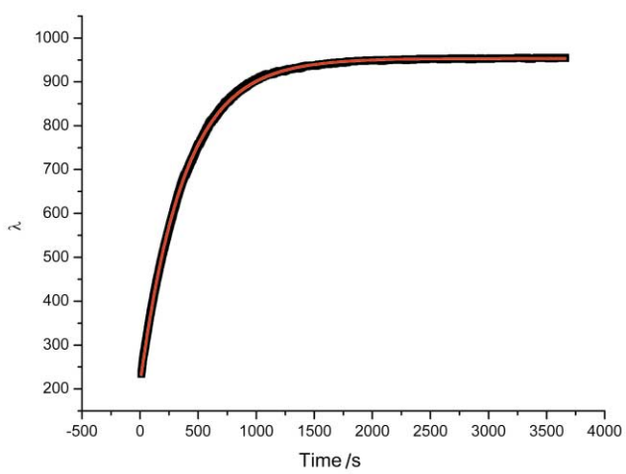


Fig. 2 A typical plot of conductivity (λ × 10^{-6}/S cm^{-1}) *vs.* time (interval 3 s) for the reaction of α-chloroacetanilides with *p*-chlorobenzylamine in DMSO at 55.0 °C. Black line: experimental, red line: curve by Origin method. [α-Chloroacetanilide] ≈ 0.001 M; [*p*-chlorobenzylamine] = 0.1583 M. k_{obsd} = 0.00256/3 = 8.53 × 10^{-4} s^{-1}.

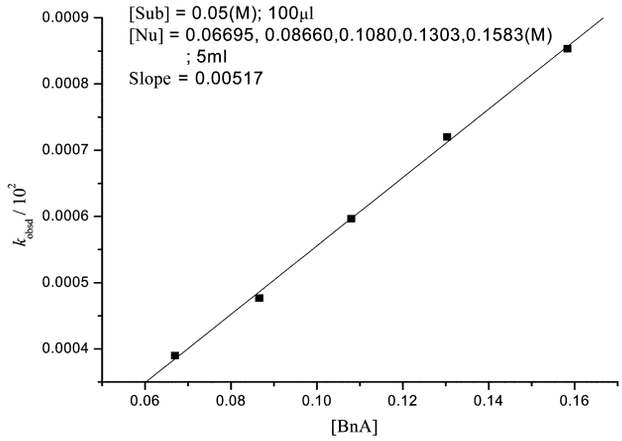


Fig. 3 A plot of k_{obsd} *vs.* concentration of *p*-chlorobenzylamine. Reaction: α-chloroacetanilide (≈ 0.001 M) with *p*-chlorobenzylamine in DMSO at 55.0 °C. Slope = k_N = 5.17 × 10^{-3} M^{-1} s^{-1}; intercept = 4.28 × 10^{-5} ≈ 0; r = 0.9993.

Product analysis

p-Methyl- and *N*-methyl *p*-methyl- α-chloroacetanilide (0.05 M) were reacted with benzylamine (0.5 M), in acetonitrile at 55.0. After more than 15 half-lives, solvent was removed under reduced pressure and the product was separated by column chromatography. Analytical data of the product gave the following results:

***p*-$CH_3C_6H_4NHC(=O)CH_2NHCH_2C_6H_5$.** White solid (silica gel, 10% acetonitrile–diethyl ether, R_f = 0.13); mp 80–81 °C; Anal. Found: C, 75.8; H, 7.2; N, 11.2. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02%. ^1H NMR (200 MHz, $CDCl_3$), δ 1.96 (s, 1H), 2.31 (s, 3H), 3.38 (s, 2H), 3.81 (s, 2H), 7.10–7.47 (m, 9H), 9.20 (s, 1H); *m*/*z* 254 (M^+).

***p*-$CH_3C_6H_4N(CH_3)C(=O)CH_2NHCH_2C_6H_5$.** Brown oil (silica gel, 50% ethyl acetate–*n*-hexane, R_f = 0.23); Anal. Found: C, 75.9; H, 7.4; N, 10.2. Calcd. for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44%. ^1H NMR (200 MHz, $CDCl_3$), δ 2.33 (s, 1H), 2.39 (s, 3H), 3.17 (s, 2H), 3.30 (s, 3H), 3.80 (s, 2H), 7.08–7.27 (m, 9H); *m*/*z* 268 (M^+).

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