Nucleophilic Substitution Reactions of α-Bromoacetanilides with Benzylamines

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

*Department of Chemistry, Inha University, Incheon 402-751, Korea. *E-mail: hwlee@inha.ac.kr*
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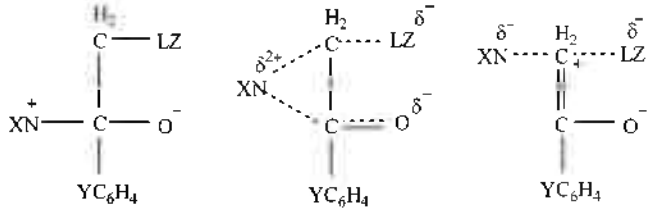
Kinetic studies of the reactions of α-bromoacetanilides [$YC_6H_4NHC(=O)CH_2Br$] with substituted benzylamines ($XC_6H_4CH_2NH_2$) have been carried out in dimethyl sulfoxide at 35.0 °C. The Hammett plots for substituent (Y) variations in the substrate (log k_{XY} *vs.* σ_Y) are biphasic concave upwards/downwards with breaks at Y = 4-Cl (σ_Y = 0.23). The Hammett coefficients ρ_Y and the cross-interaction constant ρ_{XY} (= +0.16) are positive for $\sigma_Y \leq 0.23$, while the ρ_Y values are positive/negative [$\rho_Y > 0$ for X = (4-MeO and 4-Me) and $\rho_Y < 0$ for X = (H, 4-Cl and 3-Cl)] and the ρ_{XY} (= −1.51) value is negative for $\sigma_Y \geq 0.23$. Based on these and other results, the benzylaminolyses of α-bromoacetanilides are proposed to proceed through rate-limiting expulsion of the bromide leaving group from a zwitterionic tetrahedral intermediate, $T^{\pm}$, with a bridged transition state for $\sigma_Y \leq 0.23$, while the reaction proceeds through concerted mechanism with an enolate-like TS in which the nucleophile attacks the α-carbon for $\sigma_Y \geq 0.23$.

Key Words : Aminolysis, α-Bromoacetanilides, Cross-interaction constants, Concave and convex Hammett plots

Introduction

The nucleophilic substitution reactions of α-halocarbonyl compounds have been studied extensively. A variety of mechanisms have been proposed for the α-carbonyl system, especially for phenacyl derivatives, among which three types are considered noteworthy: (i) stepwise mechanism with prior addition of the nucleophile (XN) to the carbonyl carbon,[1] **1**; (ii) bridging of the nucleophile between the α-carbon and the carbonyl carbon in the transition state (TS),[2,1c] **2**; and (iii) concerted displacement with an enolate-like TS,[3] **3**.



1 **2** **3**

In a series of works,[4-10] we reported a unified mechanism in which the reaction proceeds through an addition intermediate (**1**) with a bridged TS (**2**) in the expulsion of the leaving group, LZ^-. In previous reports,[8,10] the benzylaminolyses of α-chloroacetanilides [$YC_6H_4NRC(=O)CH_2Cl$; R = H and CH_3] in DMSO were 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 TS (**2**). In contrast, the pyridinolyses of α-chloroacetanilides in DMSO were proposed to proceed through a stepwise mechanism with rate-limiting addition of the nucleophile to the carbonyl carbon to form zwitterionic tetrahedral intermediate ($T^{\pm}$) followed by a bridged TS to expel the leaving group. This mechanism change was interpreted mainly on the basis of the reactivity (benzylaminolysis rate: R = CH_3 > H; pyridinolysis rate: R = H > CH_3), and the cross-interaction constants.[11] ρ_{XY} values, [eqs. (1)]: positive for benzylaminolysis [ρ_{XY} = +0.21 (R = H) and +0.18 (R = CH_3)][8] and negative for pyridinolysis [ρ_{XY} = −0.06 (R = H) and −0.10 (R = CH_3)].[10] Thus, we knew that the aminolysis of α-chloroacetanilides is one of the typical models that explicitly shows the sequence of the amine expulsion rate from $T^{\pm}$.

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

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

In the pyridinolysis of phenacyl bromides [$YC_6H_4C(=O)CH_2Br$] in MeCN, a change of ρ_{XY} from a large positive (ρ_{XY} = +1.36) value to a small positive (ρ_{XY} = 0.09) value indicates a rate-determining step change at the breakpoint (pK_a° = 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.[7] To gain further information of the mechanism for the α-halocarbonyl systems, we performed kinetic studies of the benzylaminolysis of α-bromoacetanilides in DMSO at 35.0 °C, eq. (2).

$$YC_6H_4NHC(=O)CH_2Br + 2XC_6H_4CH_2NH_2 \xrightarrow[35.0\ ^\circ C]{DMSO} YC_6H_4NHC(=O)CH_2NHCH_2C_6H_4X + {}^{+}NH_3CH_2C_6H_4X - Br^- \quad (2)$$

X = 4-MeO, 4-Me, H, 4-Cl, 3-Cl
Y = 4-MeO, 4-Me, H, 4-Cl, 3-Cl, 4-NO_2

Results and Discussion

The reactions followed the clean second-order rate law given by eqs. (3) and (4), where [BnA] is the benzylamine

Table 1. Second-Order Rate Constants, k_N ($\times 10^3/M^{-1}\,s^{-1}$), and Selectivity Parameters[a] for the Reactions of Y-α-Bromoacetanilides with X-Benzylamines in DMSO at 35.0 °C

X\Y	4-MeO	4-Me	H	4-Cl	3-Cl	4-NO_2	ρ_Y[b]	ρ_Y[c]
4-MeO	237	259	306	369	463	916	0.39 ± 0.01 (0.999)[d]	0.72 ± 0.01 (0.999)
4-Me	194	204	250	309	347	490	0.42 ± 0.03 (0.995)	0.36 ± 0.01 (0.999)
H	176	187	219	270	257	231	0.38 ± 0.02 (0.998)	−0.13 ± 0.01 (0.999)
4-Cl	124	136	159	199	191	153	0.41 ± 0.01 (0.999)	−0.21 ± 0.02 (0.995)
3-Cl	85.5	97.5	113	159	135	106	0.53 ± 0.04 (0.994)	−0.31 ± 0.05 (0.986)
$-\rho_X$	0.64 ± 0.08 (0.980)	0.61 ± 0.07 (0.982)	0.63 ± 0.06 (0.987)	0.55 ± 0.03 (0.995)	0.78 ± 0.05 (0.993)	1.38 ± 0.19 (0.974)	ρ_{XY}[b] = 0.16 ± 0.14 (0.976)	ρ_{XY}[c] = −1.51 ± 0.26 (0.960)
β_X	0.84 ± 0.06 (0.993)	0.79 ± 0.06 (0.992)	0.82 ± 0.06 (0.992)	0.71 ± 0.05 (0.993)	0.99 ± 0.14 (0.972)	1.70 ± 0.40 (0.927)		

[a]The σ values were taken from ref 12 and the pK_a values of benzylamines in water at 25.0 °C were taken from ref 13. [b]Y = 4-MeO-4-Cl. [c]Y = 4-Cl-4-NO_2. [d]Correlation coefficient.

concentration. The observed pseudo-first-order rate constants (k_{obsd}) obeyed eq. (4). for all reactions with negligible k_0 (≅ 0) in DMSO.

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

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

The second-order rate constants for benzylaminolysis, k_N ($M^{-1}s^{-1}$), summarized in Table 1, were obtained as the slopes of the plots of k_{obsd} against benzylamine concentration, [BnA], 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 Bronsted coefficients β_X (β_{nuc}), Hammett coefficients ρ_X (ρ_{nuc}) and ρ_Y, and the cross-interaction constants ρ_{XY} are also shown in Table 1. The rate is faster with a stronger nucleophile, *i.e.*, $\rho_X < 0$, as normally observed for a typical nucleophilic substitution reaction. However, the rate is not always faster with a stronger electron withdrawing group in the substrate, *i.e.*, $\rho_Y > 0$ or $\rho_Y < 0$ depending on the substituents in the substrate.

The Hammett plots for substituent (Y) variations in the substrate (log k_N *vs.* σ_Y) are biphasic concave upwards and downwards with breaks at Y = 4-Cl (σ_Y = 0.23) as shown in Figure 1. The Hammett plots gradually change from concave upwards for X = 4-MeO, to almost linear for X = 4-Me, to concave downwards for X = H, 4-Cl and 3-Cl. When $\sigma_Y \leq 0.23$, the Hammett coefficients ρ_Y and the cross-interaction constant ρ_{XY} (= +0.16) are positive. But when $\sigma_Y \geq 0.23$, the ρ_Y values are positive for X = (4-MeO and 4-Me), and negative for X = (H, 4-Cl and 3-Cl) and the ρ_{XY} (= −1.51) value is negative.

Second-order rate constants and selectivity parameters for the aminolyses of several phenacyl derivatives are summarized in Table 2. Considering the effects of solvent and temperature on the reaction rate, the sequence of benzylaminolysis rates is $YPhCOCH_2Br$ > $YPhNHCOCH_2Br$ > $YPhCOCH_2OSO_2Ph$ > $YPhN(CH_3)COCH_2Cl$ > $YPhNHCOCH_2Cl$ which is consistent with the sequence of leaving group mobilities, Br > OSO_2Ph > Cl.[14] The sequences of anilinolysis ($YPhCOCH_2Br$ > $YPhCOCH_2OSO_2Ph$) and pyridinolysis rates [$YPhCOCH_2Br$ > $YPhNHCOCH_2Cl$ > $YPhN(CH_3)COCH_2Cl$] are also consistent with the sequence of leaving group mobilities.

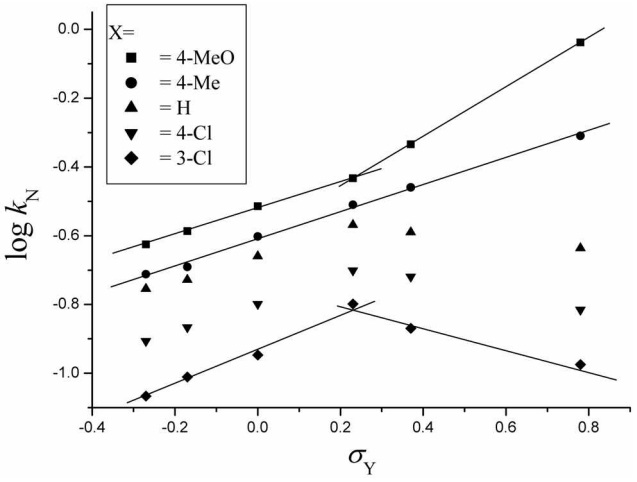


Figure 1. Hammett plots for reactions of Y-α-bromoacetanilides with X-benzylamines in DMSO at 35.0 °C.

1. $\sigma_Y \leq 0.23$ (Y = 4-MeO, 4-Me, H and 4-Cl).

The β_X values with *positive* ρ_{XY} (except phenacyl bromide when X = 4-MeO-3-Ph with ρ_{XY} = +0.09; *vide infra*) in Table 2 are within the narrow range of 0.56-0.87: for the reactions of (i) phenacyl bromides (when X = 3-Ac-3-CN) with pyridines in MeCN, β_X = 0.65-0.80 (ρ_{XY} = 1.36);[7] (ii) phenacyl bromides with anilines in MeOH, β_X = 0.60-0.66 (ρ_{XY} = 0.11);[5] (iii) phenacyl bromides with benzylamines in MeCN, β_X = 0.69-0.73 (ρ_{XY} = 0.05);[9] (iv) phenacyl benzenesulfonates with anilines and benzylamines in MeOH, β_X = 0.66-0.72 (ρ_{XY} = 0.11) and β_X = 0.69-0.74 (ρ_{XY} = 0.03), respectively;[4,6] (v) α-chloroacetanilides [$YC_6H_4N(R)COCH_2Cl$; R=H and CH_3] with benzylamines in DMSO, β_X = 0.56-0.87 (ρ_{XY} = 0.21) for R=H and β_X = 0.61-0.87 (ρ_{XY} = 0.18) for R=CH_3;[8] and (vi) α-bromoacetanilides with benzylamines (when Y = 4-MeO-4-Cl) in DMSO, in the present work, β_X = 0.71-0.84 (ρ_{XY} = 0.16). All of these phenacyl transfer reactions have nearly constant β_X values of 0.7 ± 0.1, despite the fact that these reactions involve different nucleophiles (benzylamine, aniline or pyridine), different leaving groups (benzenesulfonate, chloride or bro-

Table 2. Summary of Second-Order Rate Constants and Selectivity Parameters for the Aminolyses of the Phenacyl Derivatives

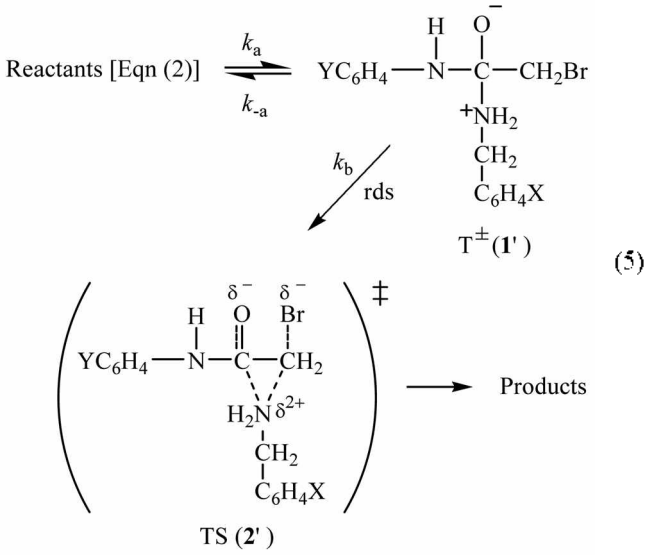
substrate	nuc	solv	$k_N^a \times 10^4$ (°C)	$-\rho_X$	β_X	ρ_Y	ρ_{XY}	ref
$YPhCOCH_2Br$	Py	MeCN	114 (45.0)	1.88-2.07[b]	0.30-0.40[b]	0.27-0.33[b]	0.09[b]	7 (biphasic)
				5.48-6.89[c]	0.65-0.80[c]	0.29-0.54[c]	1.36[c]	
$YPhCOCH_2Br$	An	MeOH	25.1 (45.0)	1.67-1.82	0.60-0.66	0.56-0.63	0.11	5
$YPhCOCH_2Br$	BnA	MeCN	871 (25.0)	0.71-0.75	0.69-0.73	0.45-0.48	0.05	9
$YPhCOCH_2OSO_2Ph$	An	MeOH	6.16 (45.0)	1.81-1.99	0.66-0.72	0.57-0.63	0.11	4
$YPhCOCH_2OSO_2Ph$	BnA	MeOH	112 (45.0)	0.70-0.76	0.69-0.74	0.53-0.55	0.03	6
$YPhNHCOCH_2Cl$	Py	DMSO	15.2 (95.0)	1.49-1.58	0.30-0.32	0.18-0.24	−0.06	10
$YPhNHCOCH_2Cl$	BnA	DMSO	76.3 (55.0)	0.43-0.66	0.56-0.87	0.49-0.65	0.21	8
$YPhN(CH_3)COCH_2Cl$	Py	DMSO	10.2 (95.0)	1.48-1.60	0.30-0.32	0.23-0.40	−0.10	10
$YPhN(CH_3)COCH_2Cl$	BnA	DMSO	83.8 (55.0)	0.47-0.68	0.61-0.87	0.54-0.67	0.18	8
$YPhNHCOCH_2Br$	BnA	DMSO	2190 (35.0)	0.55-0.64[d]	0.71-0.84[d]	0.38-0.53[d]	0.16[d]	This work
				0.55-1.38[e]	0.71-1.70[e]	−0.31-0.72[e]	−1.51[e]	(biphasic)

[a]X = Y = H. [b]X = 4-MeO, 4-Me, 3-Me, 4-Bn, 3-Ph. [c]X = 3-Ac, 3-Br, 4-Ac, 4-CN, 3-CN. [d]Y = 4-MeO, 4-Me, H, 4-Cl. [e]Y = 4-Cl, 3-Cl, 4-NO_2.

mide) and different solvents (MeOH, MeCN or DMSO). Moreover, all of the ρ_{XY} values are positive as required by the stepwise mechanism with rate-limiting expulsion of the leaving group.[11] This is quite in contrast to the large difference in magnitude of the β_X values involved in the stepwise aminolysis of carbonyl and thiocarbonyl esters with rate-limiting expulsion of the leaving group: aminolysis with benzylamines exhibited much larger β_X values (1.06-2.80)[15] than those with anilines (0.79-1.20)[16] and/or pyridines (0.64-0.94)[17] in MeCN.

The relative constancy of β_X (≅ 0.7) in the aminolysis of phenacyl derivatives has been rationalized theoretically.[9] Prior addition of the nucleophile to form a zwitterionic tetrahedral intermediate, $T^{\pm}$ (**1**), should occur, and the leaving group is expelled in the rate-determining step. In this step, the TS is formed by bridging of the amine between the carbonyl and α-carbons, **2**. In the TS **2** structure, the susceptibility of rate ($d\log k_b$) for the leaving group expulsion step to the basicity of the amine (dpK_X), *i.e.*, β_b (= $\partial\log k_b/\partial pK_X$), should be insignificant ($\beta_b \cong 0$) since the two opposing effects of pK_X (one on the carbonyl carbon and the other on the α-carbon) will be compensatory or will cancel each other out. In the former, electrons are transferred to the amine from the carbonyl carbon, whereas in the latter, electrons are transferred from the amine to the α-carbon.[9] In fact, only a meager change in ρ_Z ($\Delta\rho_Z = 0.05$) was observed for a pK_X change of 0.36 (4-OMe→4-Cl benzylamine) in the aminolysis of phenacyl benzenesulfonates ($YPhCOCH_2OSO_2PhZ$) with X-benzylamines in MeOH[9] for Y = 4-NO_2, in contrast to a large change in ρ_Z ($\Delta\rho_Z = 1.21$) for the aminolysis of thiophenyl methylacetate ($C_2H_5COSC_6H_4Z$) with X-benzylamines ($\Delta pK_X = 0.36$) in MeCN.[15b] This means that, in the phenacyl transfers, the overall β_X is grossly independent of the amine nature: hence, the β_X value becomes practically constant, *i.e.*, $\beta_X \cong 0.7$ irrespective of the amine, leaving group, or solvent, as experimentally observed.

Therefore, we conclude that the relative constancy of the β_X value provides evidence for a unified mechanism (**1** + **2**) of phenacyl transfers.[9] We propose, for the present reaction when $\sigma_Y \leq 0.23$, a stepwise mechanism with rate-limiting expulsion of the bromide leaving group from a zwitterionic tetrahedral intermediate, $T^{\pm}$ (**1'**), with a bridged TS (**2'**), eq. (5), based on the β_X (= 0.71-0.84) and positive ρ_{XY} (= 0.16) values.



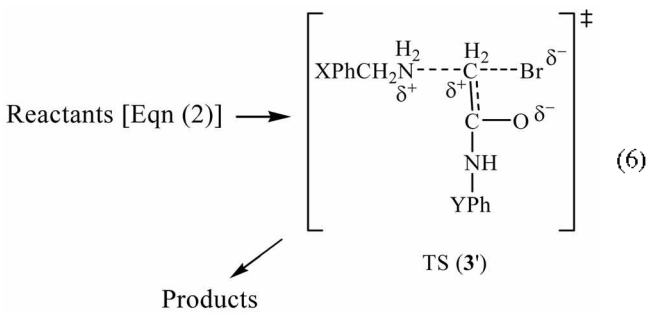
2. $\sigma_Y \geq 0.23$ (Y = 4-Cl, 3-Cl and 4-NO_2).

The cross-interaction constant ρ_{XY} (= −1.51) is *negative* for $\sigma_Y \geq 0.23$, but is positive (= +0.16) for $\sigma_Y \leq 0.23$ in the present work. A stronger electron-withdrawing substituent in the substrate ($\partial\sigma_Y > 0$) leads to a greater degree of bond formation ($\partial\rho_X < 0$ or $\partial|\rho_X| > 0$) so that $\rho_{XY} = \partial\rho_X/\partial\sigma_Y$ is negative. For a stepwise reaction with rate-limiting formation of the tetrahedral intermediate, $T^{\pm}$, the sign of ρ_{XY} will be the same for the forward reaction of concerted S_N2 processes,[11,16c,17] *i.e.*, $\rho_{XY} < 0$. However, as discussed previously,[7] in the partitioning of the tetrahedral intermediate, the rate of expulsion of amines is increased ($\partial\rho_X > 0$) by a stronger electron-withdrawing substituent in the acyl group ($\partial\sigma_Y > 0$)[20] so that $\rho_{XY} = \partial\rho_X/\partial\sigma_Y$ should be positive. Thus the sign and the magnitude of ρ_{XY} would be compensated for by these two factors, *i.e.*, $\rho_{XY} < 0$ for the bond formation step and $\rho_{XY} > 0$ for the amine expulsion from $T^{\pm}$. As a result of

compensatory effects of the opposite signs. the ρ_{XY} values for the reactions of the rate-limiting formation of $T^{\pm}$ are very small negative or positive: ρ_{XY} = −0.06 and −0.10 for the pyridinolysis of $YPhNHCOCH_2Cl$ and $YPhN(CH_3)COCH_2Cl$, respectively;[10] ρ_{XY} = +0.09 for the rate-limiting formation in the pyridinolysis of phenacyl bromide[7] (*vide supra*); ρ_{XY} = +0.05 for the aminolysis of aryl dithiobenzoates with benzylamines in MeCN.[21]

Comparing the magnitudes of the ρ_{XY} (= −0.10 to +0.09) values in the reactions above with that in the present work for $\sigma_Y \geq 0.23$. the obtained ρ_{XY} (= −1.51) value has an exceptionally large negative magnitude and the β_X (= 0.71-1.70) values also have relatively large magnitudes, which strongly suggest that the present reaction proceeds through a different reaction path from than the reactions above. Moreover, with electron-withdrawing Y (= 4-NO_2, 3-Cl and 4-Cl; $\sigma_Y \geq 0.23$) substituents. *negative* ρ_Y values are obtained for electron-withdrawing X (= 3-Cl, 4-Cl and H) substituents. while positive ρ_Y values are obtained for electron-donating X (= 4-MeO and 4-Me) substituents. The negative slope ($\rho_Y < 0$) may imply either development of positive charge or, alternatively, reduction of negative charge at the reaction center in the TS due to more advanced bond breaking of the bromide ion than bond making for benzylamine. The closer approach of the nucleophile is made possible by developing a stronger positive charge center through expulsion of the leaving group to a greater extent. Thus. the tighter bond making in the TS is assisted by the greater degree of bond breaking in a concerted process.

These results cannot be rationalized by a stepwise mechanism with rate-limiting addition of the nucleophile to the carbonyl carbon to form a zwitterionic tetrahedral intermediate (**1'**) followed by a bridged TS (**2'**) to expel the leaving group, but can be substantiated by concerted displacement with an enolate-like TS (**3'**), eq. (6).



(6)

The large magnitude of the cross-interaction constant. ρ_{XY} (= −1.51). suggests that bond making is extensively advanced in the TS since the magnitude of the cross-interaction constant is inversely proportional to the distance between the substituents X and Y.[11] The large β_X (= 0.71-1.70) values are also consistent with advanced bond making in the TS.

The sign inversion of ρ_Y can be interpreted as a charge reversal at the reaction center of the substrate from dominant bond formation ($\rho_Y > 0$) to dominant bond breaking ($\rho_Y < 0$) in the TS at the isokinetic point. $\sigma_{X,ISOKINETIC}$. ($\rho_Y = 0$).[22]

$$\log (k_{XY}/k_{HH}) = \rho_X^H\sigma_X + \rho_Y^H\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (7)$$

$$= \rho_X^H\sigma_X + (\rho_Y^H + \rho_{XY}\sigma_X)\sigma_Y \quad (8)$$

Let $\rho_Y = \rho_Y^H + \rho_{XY}\sigma_X$ (9). and substitute eq. (9) into eq. (8), to get eq. (10)

$$\log (k_{XY}/k_{HH}) = \rho_X^H\sigma_X + \rho_Y\sigma_Y \quad (10)$$

In eq. (9). when $\sigma_X = \sigma_{X,ISOKINETIC} = -(\rho_Y^H/\rho_{XY}) = -(-0.13)/(-1.51) = -0.09$. at which $\rho_Y = \rho_Y^H + \rho_{XY}\sigma_X = 0$. the reaction rate is constant regardless of the substituent Y in the substrate.

$$\log (k_{XY}/k_{HH}) = \rho_X^H\sigma_{X,ISOKINETIC} = -(\rho_X^H\rho_Y^H/\rho_{XY}) = \text{constant} \quad (11)$$

In other words, when $\sigma_X < \sigma_{X,ISOKINETIC}$. *i.e.*. σ_X = −0.21(4-MeO) and −0.17(4-Me), the degree of bond formation exceeds the degree of bond breaking by enough to give a negative charge at the reaction center in the TS. resulting in $\rho_Y > 0$, as observed in the normal nucleophilic substitution reactions. In contrast, when $\sigma_X > \sigma_{X,ISOKINETIC}$. *i.e.*. σ_X = 0(H), 0.23(4-Cl) and 0.37(3-Cl). the degree of bond breaking exceeds the degree of bond formation by enough to give a positive charge at the reaction center in the TS, resulting in $\rho_Y < 0$. Both electron-withdrawing X and Y groups ($\sigma_X \geq 0$ and $\sigma_Y > 0$) retard the rate of leaving group departure ($\delta \log k_N < 0$). by depleting electrons from the reaction center, α-carbon. and a negative ρ_Y results ($\rho_Y < 0$). Meanwhile, when $\sigma_X = \sigma_{X,ISOKINETIC}$. bond formation and breaking are harmonized to give $\rho_Y = 0$.

Summary

The reactions of α-bromoacetanilides with substituted benzylamines have been studied kinetically in DMSO at 35.0 °C. The Hammett plots for substituent (X) variations in the nucleophile ($\log k_N$ *vs.* σ_X) exhibit linearities. whereas the Hammett plots for substituent (Y) variations in the substrate ($\log k_N$ *vs.* σ_Y) are biphasic concave upwards/downwards with breaks at Y = 4-Cl (σ_Y = 0.23). Based on the relative constancy of the β_X (= 0.71-0.84) and the positive ρ_{XY} (= 0.16) values, when $\sigma_Y \leq 0.23$, we propose a stepwise mechanism through rate-limiting expulsion of the bromide leaving group from a zwitterionic tetrahedral intermediate. $T^{\pm}$. with a bridged TS. Based on the positive/negative ρ_Y and the negative ρ_{XY} (= −1.51) values, when $\sigma_Y \geq 0.23$. we propose a concerted mechanism with an enolate-like TS in which the nucleophile attacks the α-carbon. The mechanistic difference between α-chloroacetanilides and α-bromoacetanilides may be attributed to the greater polarizability of Br leaving group than that of Cl leaving group and to the smaller electronegatity of Br leaving group than that of Cl leaving group. enabling the enolate-like TS for the benzylaminolysis of α-bromoacetanilides.

Experimental Section

Materials. GR grade DMSO was dried with a 4 Å mole-

cular sieve and then used after three distillations under reduced pressure. The benzylamine nucleophiles, GR grade, were used after recrystallization or distillation.

Preparation of Y-α-bromoacetanilides. The Y-α-bromoacetanilides were prepared according to the literature methods for esterification. Aniline derivatives and bromoacetic anhydride were dissolved in dried ether. The reaction mixture was worked up with water and dried over anhydrous $MgSO_4$, and the product was then recrystallized from *n*-hexane.

4-Methoxy-α-bromoacetanilide. Slight reddish solid; mp 131-132 °C; ^{1}H-NMR (200 MHz, $CDCl_3$), δ 3.80 (s, 3H), 4.02 (s, 2H), 6.89 (d, J = 4.4 Hz, 2H), 7.43 (d, J = 4.3 Hz, 2H), 8.07 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$), δ 29.72 (s, 1C), 55.69 (s, 1C), 114.42-157.24 (s, 6C arom.), 163.44 [s, 1C (C=O)]; Anal. Found: C, 44.38; H, 4.14; N, 5.61. Calcd. for $C_9H_{10}NO_2Br$: C, 44.29; H, 4.13; N, 5.74. *m/z* (EI) 243 (M^+), 245 (isotope, M^-).

4-Methyl-α-bromoacetanilide. White solid; mp 158-159 °C; ^{1}H-NMR (200 MHz, $CDCl_3$), δ 2.33 (s, 3H), 4.01 (s, 2H), 7.15 (d, J = 4.2 Hz, 2H), 7.41 (d, J = 4.2 Hz, 2H), 8.07 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$), δ 21.21 (s, 1C), 29.84 (s, 1C), 120.42-135.26 (s, 6C arom.), 163.56 [s, 1C (C=O)]; Anal. Found: C, 47.39; H, 4.42; N, 6.14. Calcd. for $C_9H_{10}NOBr$: C, 47.67; H, 4.49; N, 6.01. *m/z* (EI) 227 (M^+), 229 (isotope, M^-).

α-Bromoacetanilide. Reddish white solid; mp 137-139 °C; ^{1}H-NMR (200 MHz, $CDCl_3$), δ 4.02 (t, 2H), 7.13-7.55 (m, 5H), 8.17 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$), δ 29.48 (s, 1C), 120.04-136.86 (s, 6C arom.), 163.40 (s, 1C (C=O)); Anal. Found: C, 44.52; H, 3.78; N, 6.34. Calcd. for C_8H_8NOBr: C, 44.89; H, 3.77; N, 6.54. *m/z* (EI) 213 (M^+), 215 (isotope, M^-).

4-Chloro-α-bromoacetanilide. Brownish white solid; mp 160-161 °C; ^{1}H-NMR (200 MHz, $CDCl_3$), δ 4.03 (s, 2H), 7.32 (d, J = 4.6 Hz, 2H), 7.50 (d, J = 4.4 Hz, 2H), 8.13 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$), δ 29.33 (s, 1C), 121.25-135.44 (s, 6C arom.), 163.34 [s, 1C (C=O)]; Anal. Found: C, 38.55; H, 2.93; N, 5.56. Calcd. for $C_8H_7NOClBr$: C, 38.67; H, 2.84; N, 5.63. *m/z* (EI) 247 (M^+), 249 (isotope, M^-).

3-Chloro-α-bromoacetanilide. Light yellowish solid; mp 80-81 °C; ^{1}H-NMR (200 MHz, $CDCl_3$), δ 4.01 (s, 2H), 7.12-7.43 (m, 4H), 8.17 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$), δ 29.27 (s, 1C), 117.98-137.95 (s, 6C arom.), 163.65 [s, 1C (C=O)]; Anal. Found: C, 38.74; H, 2.86; N, 5.62. Calcd. for $C_8H_7NOClBr$: C, 38.67; H, 2.84; N, 5.63. *m/z* (EI) 247 (M^+), 249 (isotope, M^-).

4-Nitro-α-bromoacetanilide. Shiny yellow solid; mp 179-180 °C; ^{1}H-NMR (200 MHz, $CDCl_3$), δ 3.98 (s, 2H), 7.83 (d, J = 4.8 Hz, 2H), 8.18 (d, J = 4.5 Hz, 2H), 10.52 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$), δ 28.49 (s, 1C), 118.41-143.83 (s, 6C arom.), 164.92 [s, 1C (C=O)]; Anal. Found: C, 37.44; H, 2.74; N, 10.80. Calcd. for $C_8H_7N_2O_3Br$: C, 37.09; H, 2.72; N, 10.81. *m/z* (EI) 258 (M^-), 260 (isotope, M^+).

Kinetic measurements. The rates were measured conductometrically in dimethyl sulfoxide at 35.0 ± 0.1 °C. A computer connected to an automatic A/D converter conductivity-bridge was used in this work. Pesudo-first-order rate constants, k_{obsd}, were determined with large excesses of benzylamine: [Substrate] = 1-5 × 10^{-3} and [BnA] = 0.04-0.13 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. Pseudo-first-order rate constant values were an average of two (or three) runs that were reproducible to ± 3%.

Product analysis. 4-Methyl-α-bromoacetanilide (0.05 M) was reacted with benzylamine (0.5 M), in DMSO at 35.0 °C. After more than 15 half-lives, the reaction product mixture was isolated by ethyl acetate-water extraction. The ethyl acetate solution was dried over anhydrous $MgSO_4$ for overnight. $MgSO_4$ was removed by filtration. Product was isolated by column chromatography using 10% acetonitrile-ether as the eluent. Solvent was removed under reduced pressure and a light brown solid product was found. Analysis of the product gave the following results:

4-$CH_3C_6H_4NHC(=O)CH_2NHCH_2C_6H_5$. Light brown solid; mp 78.0-79.0 °C.; ^{1}H-NMR (200 MHz, $CDCl_3$), δ 2.08 (brs, 1H, NH), 2.32 (s, 3H), 3.43 (s, 2H), 3.85 (s, 2H), 7.11-7.47 (m, 9H), 9.19 (brs, 1H, NH); ^{13}C-NMR (100 MHz, $CDCl_3$), δ 21.09 (s, 1C), 52.62 (s, 1C), 54.27 (s, 1C), 119.67-139.29 (m, 12C arom.), 169.61 [s, 1C (C=O)]; Anal. Found: C, 74.84; H, 7.13; N, 10.73. Calcd. for $C_{16}H_{18}N_2O$: C, 74.56; H, 7.13; N, 11.02.

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