Nucleophilic Substitution Reactions of *N*-Methyl α-Bromoacetanilides with Benzylamines in Dimethyl Sulfoxide

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Kinetic studies of the reactions of *N*-methyl-Y-α-bromoacetanilides with substituted X-benzylamines have been carried out in dimethyl sulfoxide at 25.0 °C. The Hammett plots for substituent X variations in the nucleophiles (log k_N *vs* σ_X) are slightly biphasic concave upwards/downwards, while the Brönsted plots (log k_N *vs* pK_a) are biphasic concave downwards with breakpoints at X = H. The Hammett plots for substituent Y variations in the substrates (log k_N *vs* σ_Y) are biphasic concave upwards/downwards with breakpoints at Y = H. The cross-interaction constant ρ_{XY} values are all negative: ρ_{XY} = –0.32 for X = Y = electron-donating; –0.22 for X = electron-withdrawing and Y = electron-donating; –1.80 for X = electron-donating and Y = electron-withdrawing; –1.43 for X = Y = electron-withdrawing substituents. Deuterated kinetic isotope effects are primary normal (k_H/k_D > 1) for Y = electron-donating, while secondary inverse (k_H/k_D < 1) for Y = electron-withdrawing substituent. The proposed mechanisms of the benzylaminolyses of *N*-methyl-Y-α-bromoacetanilides are a concerted mechanism with a five membered ring TS involving hydrogen bonding between hydrogen (deuterium) atom in N-H(D) and oxygen atom in C = O for Y = electron-donating, while a concerted mechanism with an enolate-like TS in which the nucleophile attacks the α-carbon for Y = electron-withdrawing substituents.

Key Words : Benzylaminolysis, *N*-Methyl-α-bromoacetanilides, Cross-interaction constant, Deuterium kinetic isotope effect, Biphasic nonlinear free energy correlation

Introduction

In a series of the nucleophilic substitution reactions of α-halocarbonyl compounds,[1] a unified mechanism was reported in which the reaction proceeds through an addition intermediate (T$^\pm$-type) with a bridged TS I-type in the expulsion of the leaving group, LG$^-$. The benzylaminolyses of α-chloroacetanilides [YC$_6$H$_4$NRC(=O)CH$_2$Cl; 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$^\pm$-type) with a bridged TS I-type.[1e] 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 a zwitterionic tetrahedral intermediate (T$^\pm$-type) followed by a bridged TS I-type to expel the leaving group.[1g]
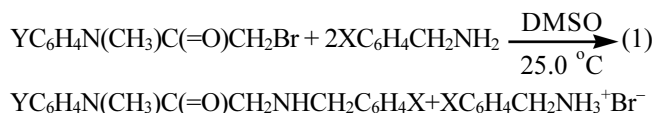

T$^\pm$ **TS I**
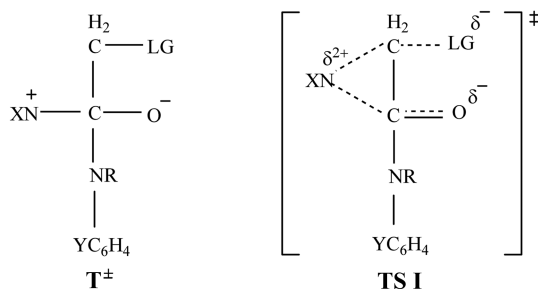
In the benzylaminolyses of α-bromoacetanilides [YC$_6$H$_4$NHC(=O)CH$_2$Br] in DMSO at 35.0 °C,[1h] the Hammett plots for

substituent Y variations in the substrates were biphasic concave upwards/downwards with breaks at Y = 4-Cl (σ_Y = 0.23). Thus, two different mechanisms were proposed: (i) $\sigma_Y \leq 0.23$; a stepwise mechanism through rate-limiting expulsion of the bromide leaving group from a zwitterionic tetrahedral intermediate (T$^\pm$-type) with a bridged TS I-type; (ii) $\sigma_Y \geq 0.23$; a concerted mechanism with an enolate-like TS II-type.
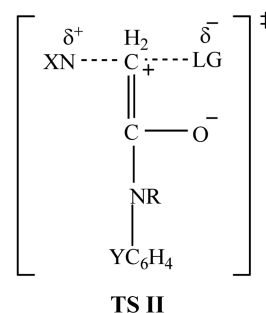
TS II

To gain further understanding of the mechanism for the α-halocarbonyl systems, kinetic studies of the benzylaminolyses of *N*-methyl-Y-α-bromoacetanilides are carried out in DMSO at 25.0 ± 0.1 °C (eq. 1).

$$YC_6H_4N(CH_3)C(=O)CH_2Br + 2XC_6H_4CH_2NH_2 \xrightarrow[25.0\ ^oC]{DMSO} \quad (1)$$

$$YC_6H_4N(CH_3)C(=O)CH_2NHCH_2C_6H_4X + XC_6H_4CH_2NH_3^+Br^-$$

X = 4-MeO, 4-Me, H, 4-Cl, 3-Cl
Y = 4-MeO, 4-Me, H, 4-Cl, 4-NO$_2$

Table 1. Second-order rate constants ($k_N \times 10^2/M^{-1}\,s^{-1}$) and selectivity parameters[a] (ρ_X, ρ_Y, β_X, and ρ_{XY}) for the reactions of *N*-Methyl-Y-α-bromoacetanilides with X-benzylamines in DMSO at 25.0 °C

X\Y	4-MeO	4-Me	H	4-Cl	4-NO$_2$	$\rho_Y{}^b$	$\rho_Y{}^c$
4-MeO	15.8	17.4	21.4	32.2	76.8	0.49 ± 0.03	0.71 ± 0.02
4-Me	14.9	16.2	18.1	25.1	49.0	0.31 ± 0.02	0.55 ± 0.02
H	13.3	14.7	16.9	20.4	25.7	0.38 ± 0.02	0.22 ± 0.04
4-Cl	10.6	11.2	11.7	10.9	9.80	0.15 ± 0.03	0.10 ± 0.01
3-Cl	9.07	10.1	11.2	9.22	6.39	0.33 ± 0.05	0.31 ± 0.02
$-\rho_X{}^d$	0.28 ± 0.01	0.27 ± 0.02	0.36 ± 0.15	0.71 ± 0.15	1.75 ± 0.08	$\rho_{XY}{}^{b,d,f}=-0.32 \pm 0.35$	$\rho_{XY}{}^{c,d,g}=-1.80 \pm 0.21$
$\beta_X{}^d$	0.50 ± 0.26	0.51 ± 0.20	0.77 ± 0.05	1.41 ± 0.36	3.23 ± 1.38		
$-\rho_X{}^e$	0.45 ± 0.02	0.45 ± 0.05	0.50 ± 0.15	0.96 ± 0.18	1.65 ± 0.13	$\rho_{XY}{}^{b,e,h}=-0.22 \pm 0.38$	$\rho_{XY}{}^{c,e,i}=-1.43 \pm 0.22$
$\beta_X{}^e$	0.45 ± 0.03	0.45 ± 0.04	0.51 ± 0.13	0.96 ± 0.15	1.65 ± 0.08		

[a]The σ values were taken from Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. The pK_a values of benzylamines in water at 25.0 °C were taken from Blackwell, L. F.; Fischer, A.; Miller, J.; Topsom, R. D.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588. [b]Y = (4-MeO, 4-Me, H). [c]Y = (H, 4-Cl, 4-NO$_2$). [d]X = (4-MeO, 4-Me, H). [e]X = (H, 4-Cl, 3-Cl). [f]Correlation coefficient, *r* = 0.971. [g]*r* = 0.993. [h]*r* = 0.967. [i]*r* = 0.980.

Results and Discussion

The observed pseudo-first-order rate constants (k_{obsd}) were found to follow Eq. (2) for all of the reactions under pseudo-first-order conditions with a large excess of X-benzylamine nucleophile. The k_0 values were negligible ($k_0 = 0$) in DMSO. The second-order rate constants (k_N) were determined with at least five X-benzylamine concentrations. The linear plots of Eq. (2) suggest that there is no base-catalysis or noticeable side reactions and that the overall reaction is described by Eq. (1).

$$k_{obsd} = k_0 + k_N\,[XC_6H_4CH_2NH_2] \qquad (2)$$

The second-order rate constants ($k_N/M^{-1}\,s^{-1}$) are summarized in Table 1, together with the Hammett constants (ρ_X and ρ_Y), Brönsted coefficients (β_X), and cross-interaction constants (ρ_{XY}). Although the Brönsted β_X values are obtained by the plots of log k_N(DMSO) *vs* pK_a(H$_2$O), they are considered to provide reasonable guides, as has been shown for the β_X values in the pyridinolyses of *N*-methyl-*N*-aryl carbamoyl chlorides [YC$_6$H$_4$N(CH$_3$)C(=O)Cl] in DMSO.[2] Spillane and his coworkers have also reported that the Brönsted coefficients (β_X) for the reactions of *N*-aryl sulfamoyl chlorides (YC$_6$H$_4$NHSO$_2$Cl) with anilines in DMSO are similar when determined using pK_a values of anilines measured in water ($\beta_X = 0.69$) and in DMSO ($\beta_X = 0.62$).[3]

The rate is faster with a stronger nucleophile ($\rho_X < 0$) as normally observed for a typical nucleophilic substitution reaction. The Hammett plots (Figure 1) for substituent X variations in the nucleophiles are slightly biphasic concave upwards for Y = (4-MeO, 4-Me, H, 4-Cl) while slightly biphasic concave downwards for Y = 4-NO$_2$ with breakpoints at X = H. However, the Brönsted plots (Figure 2) for substituent X variations are unusually biphasic concave downwards for all Y substituents with breakpoints at X = H.

It is common for both the Hammett and Brönsted plots for substituent X variations to show the same free energy correlation for the aminolysis of the substrates: (i) a linear Hammett plot leads to a linear Brönsted plot; (ii) a biphasic concave upward Hammett plot leads to a biphasic concave
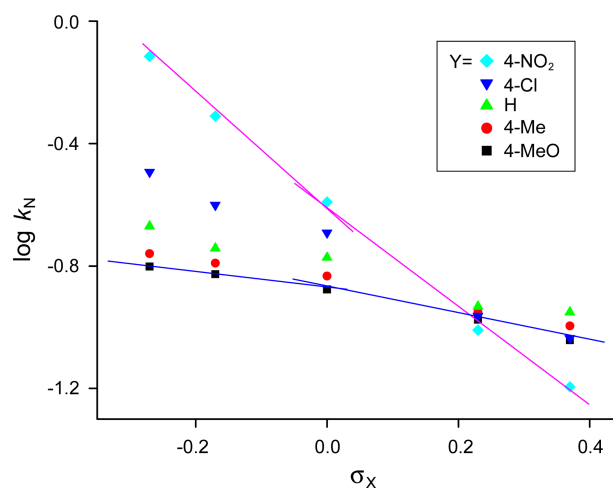

Figure 1. Hammett plots (log k_N *vs* σ_X) for the reactions of *N*-methyl-Y-α-bromoacetanilides with X-benzylamines in DMSO at 25.0 °C.

Figure 2. Brönsted plots [log k_N *vs* pK_a(H$_2$O)] for the reactions of *N*-methyl-Y-α-bromoacetanilides with X-benzylamines in DMSO at 25.0 °C.

upward Brönsted plot; (iii) a biphasic concave downward Hammett plot leads to a biphasic concave downward

Figure 3. Hammett plots (log k_N *vs* σ_Y) for the reactions of *N*-methyl-Y-α-bromoacetanilides with X-benzylamines in DMSO at 25.0 °C.
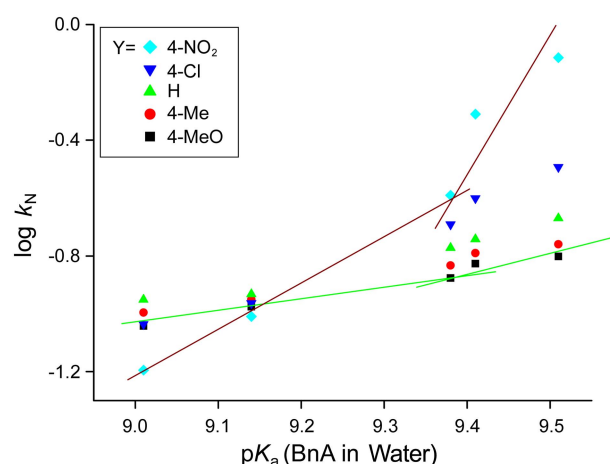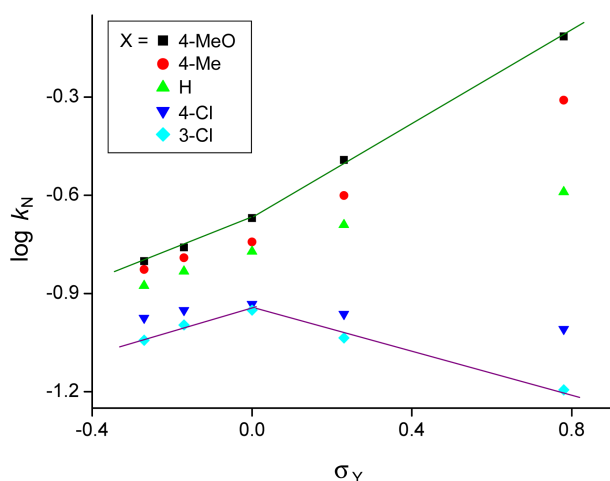
Brönsted plot. Thus, in general, the nonlinear free energy correlation is interpreted as follows: a biphasic concave upward plot is diagnostic of a change in the reaction mechanism, such as parallel reactions where the reaction path is changed depending on the substituents, while the concave downward plot is diagnostic of a rate-limiting step change from bond breaking with less basic nucleophiles to bond formation with more basic nucleophiles.[4] As seen in Figures 1 and 2, both diagnoses are not appropriate to interpret the mechanism of the studied reaction system, since the Hammett plots are dominantly biphasic concave upwards whereas the Brönsted plots are biphasic concave downwards.

The Hammett plots (Figure 3) for substituent Y variations in the substrates are biphasic concave upwards/downwards with the breakpoint at Y = H: (i) biphasic concave upwards for X = (4-MeO, 4-Me); (ii) biphasic concave downwards for X = (H, 4-Cl, 3-Cl). Thus, the rate is not always faster with a stronger electron-withdrawing group in the substrate for X = (4-Cl, 3-Cl), and unusual negative ρ_Y values are observed for Y = (H, 4-Cl, 4-NO$_2$).

Cross-interaction constants (CICs: ρ_{XY}), Eqs. (3), can be a strong tool to provide the mechanistic criteria for the nucleophilic substitution reactions.[5] Here, X and Y are the substituents of the nucleophiles and substrates, respectively. The sign and magnitude of the CICs have made it possible to correctly interpret the reaction mechanism and the degree of tightness of the transition state (TS), respectively. The sign of ρ_{XY} is normally negative in a concerted S$_N$2 reaction (or in a stepwise reaction with rate-limiting bond formation), whereas it is positive for a stepwise reaction with a rate-limiting leaving group departure from the intermediate. The magnitude of ρ_{XY} is inversely proportional to the distance between X and Y in the TS.[5] The calculated values of ρ_{XY} depending on the substituents X and Y are summarized in Table 1.[6]

$$\log(k_{XY}/k_{HH}) = \rho_X \sigma_X + \rho_Y \sigma_Y + \rho_{XY} \sigma_X \sigma_Y \qquad (3a)$$

$$\rho_{XY} = \partial \rho_X / \partial \sigma_Y = \partial \rho_Y / \partial \sigma_X \qquad (3b)$$

The deuterium kinetic isotope effects (DKIEs) have provided a useful means to determine the TS structures in nucleophilic substitution reactions, and how the reactants, especially through changes in substituents, alter the TS structures. Incorporation of deuterium in the nucleophile has an advantage in that the α-DKIEs reflect only the degree of bond formation. When partial deprotonation of the benzylamine occurs in a rate-limiting step by hydrogen bonding, the k_H/k_D values are greater than unity.[7] The greater the strength of the hydrogen bonding, the greater the k_H/k_D value becomes. In contrast, DKIEs can only be inverse ($k_H/k_D < 1.0$) in a normal S$_N$2 reaction, since the N–H(D) vibrational frequencies invariably increase upon going to the TS because of an increase in steric congestion in the bond-making process.[7] The greater the extent of the bond formation, the smaller the k_H/k_D value becomes. Thus, the real primary normal DKIEs due to the hydrogen bond is greater than the observed value, since the other hydrogen (deuterium) of the N–H(D) moiety yields the secondary inverse DKIE.

The DKIEs (k_H/k_D) are summarized in Table 2, together with the ρ_{XY} values for substituent X and Y variations, and the substituent effects of X and Y on ρ_{XY} are divided into four blocks *a*, *b*, *c*, and *d* for convenience. The DKIEs involving deuterated benzylamines (XC$_6$H$_4$CH$_2$ND$_2$) are primary normal ($k_H/k_D > 1$) for Y = 4-Me (electron-donating), while secondary inverse ($k_H/k_D < 1$) for Y = 4-NO$_2$ (electron-withdrawing substituent). The k_H/k_D values decrease with decrement of the electron-donating ability of substituent X.

Second-order rate constants ($k_N/M^{-1} s^{-1}$), selectivity parameters (β_X and ρ_{XY}), and DKIEs (k_H/k_D) for the benzylaminolyses of six phenacyl derivatives are summarized in Table 3. Taking into account the solvent effects and temperature dependence on the reaction rate constant, the sequence of benzylaminolysis rates is PhCOCH$_2$Br > PhN(CH$_3$)COCH$_2$Br > PhNHCOCH$_2$Br > PhCOCH$_2$OSO$_2$Ph > PhN(CH$_3$)COCH$_2$Cl > PhNHCOCH$_2$Cl which is consistent with the sequence of leaving group mobilities, Br > OSO$_2$Ph > Cl.[8]

The benzylaminolyses of phenacyl bromides were proposed to proceed *via* a stepwise mechanism through a zwitterionic tetrahedral intermediate (T$^\pm$) with rate-limiting expulsion of the leaving group from T$^\pm$ on the basis of a positive ρ_{XY} (= 0.05) value, the relative constancy of the β_X values ($\beta_X \approx 0.7$), and the secondary normal β-DKIEs ($k_H/k_D = 1.02$-1.09).[1f] The secondary normal β-DKIEs ($k_H/k_D > 1$) involving the rate-limiting expulsion of the leaving group from the intermediate were reported by the authors as follows: $k_H/k_D = 1.03$-1.11 for the reactions of phenylacetyl chlorides with deuterated anilines in MeCN,[9a] $k_H/k_D = 1.04$-1.12 for the reactions of 4-nitrophenyl *N*-phenylcarbamates with deuterated benzylamines in MeCN.[9b] The obtained order of 1.1 is consistent with the typical value of secondary normal β-DKIEs.[10]

As seen in Table 3, the β_X values are consistently 0.7 ± 0.1 and the ρ_{XY} values are positive except for *N*-methyl-Y-α-bromoacetanilides and Y-α-bromoacetanilides (only when

Table 2. Deuterium kinetic isotope effects (k_H/k_D) involving deuterated benzylamines and the ρ_{XY} values for variations in substituents X and Y for the reactions of *N*-Methyl-Y-α-Bromoacetanilides with X-Benzylamines in DMSO at 25.0 °C

X\Y	4-MeO	4-Me	H	4-Cl	4-NO₂
4-MeO 4-Me		(*a*) X = Y = (4-MeO, 4-Me, H) $\rho_{XY} = -0.32$ $k_H/k_D = 1.23$ (X = 4-MeO; Y = 4-Me)		(*c*) X = (4-MeO, 4-Me, H) Y = (H, 4-Cl, 4-NO₂) $\rho_{XY} = -1.80$ $k_H/k_D = 0.99$ (X = 4-MeO; Y = 4-NO₂)	
H		$k_H/k_D = 1.24$ (X = H; Y = 4-Me)		$k_H/k_D = 0.60$ (X = H; Y = 4- NO₂)	
4-Cl 3-Cl		(*b*) X = (H, 4-Cl, 3-Cl) Y = (4-MeO, 4-Me, H) $\rho_{XY} = -0.22$ $k_H/k_D = 1.33$ (X = 4-Cl; Y = 4-Me)		(*d*) X = (H, 4-Cl, 3-Cl) Y = (H, 4-Cl, 4-NO₂) $\rho_{XY} = -1.43$ $k_H/k_D = 0.47$ (X = 4-Cl; Y = 4-NO₂)	

Table 3. Summary of second-order rate constants ($k_N{}^a \times 10^4$/M^{-1} s^{-1}), selectivity parameters (β_X and ρ_{XY}), and deuterium kinetic isotope effects (k_H/k_D) for the benzylaminolyses of the phenacyl derivatives

Substrate	solv	$k_N{}^a \times 10^4$ (°C)	β_X	ρ_{XY}	k_H/k_D	ref
YC₆H₄COCH₂Br	MeCN	871 (25.0)	0.69-0.73	0.05	1.02-1.09	1f
YC₆H₄N(CH₃)COCH₂Br	DMSO	1,690 (25.0)	0.49-0.77^b	−0.32^b	1.23-1.24^b	This
			0.44-0.51^c	−0.22^c	1.24-1.33^c	work
			0.77-3.23^d	−1.80^d	0.60-0.99^d	
			0.51-1.65^e	−1.43^e	0.47-0.60^e	
YC₆H₄NHCOCH₂Br	DMSO	2,190 (35.0)	0.71-0.84^f	0.16^f	–	1h
			0.71-1.70^g	−1.51^g	–	
YC₆H₄COCH₂OSO₂C₆H₅	MeOH	112 (45.0)	0.69-0.74	0.03	–	1c
YC₆H₄N(CH₃)COCH₂Cl	DMSO	83.8 (55.0)	0.61-0.87	0.18	0.83-0.90	1e
YC₆H₄NHCOCH₂Cl	DMSO	76.3 (55.0)	0.56-0.87	0.21	0.87-0.97	1e

^{a}X = Y = H. ^{b}X = Y = (4-MeO, 4-Me, H). ^{c}X = (H, 4-Cl, 3-Cl) and Y = (4-MeO, 4-Me, H). ^{d}X = (4-MeO, 4-Me, H) and Y = (H, 4-Cl, 4-NO₂). ^{e}X = (H, 4-Cl, 3-Cl) and Y = (H, 4-Cl, 4-NO₂). ^{f}Y = (4-MeO, 4-Me, H, 4-Cl). ^{g}Y = (4-Cl, 3-Cl, 4-NO₂).

$\sigma_Y \geq 0.23$). These results strongly suggest that the reaction mechanism of the present work is somewhat complicated and different from earlier works. There is no doubt that the studied reactions proceed through a concerted mechanism or a stepwise mechanism with a rate-limiting bond formation step, since all the ρ_{XY} values are negative.

Blocks *a* and *b*: The primary normal DKIEs for blocks *a* and *b* imply that partial deprotonation of the benzylamine occurs in the TS. Two possible TS structures can be proposed: (i) the TS III involving hydrogen bond between a hydrogen (deuterium) atom in N-H(D) and an oxygen atom in C=O; (ii) the TS IV involving hydrogen bond between a hydrogen (deuterium) atom in N-H(D) and a leaving group Br. The TS III has a five membered ring, while the TS IV has a four membered ring. Regarding the ring strain energy, a five membered ring is energetically more favorable compared to a four membered ring. The TS III is a backside nucleophilic attack, while the TS IV is a frontside nucleophilic attack. It is well known that a backside attack is energetically much more favorable compared to a frontside attack, when there is no severe steric hindrance in the TS for backside nucleophilic attack. Thus, it is our suggestion that the TS III is more plausible compared to TS IV for blocks *a* and *b*.

The greater k_H/k_D value for a weaker nucleophile (X = 4-Cl: $k_H/k_D = 1.33$) than for a stronger one (X = 4-MeO: k_H/k_D

TS III

TS IV
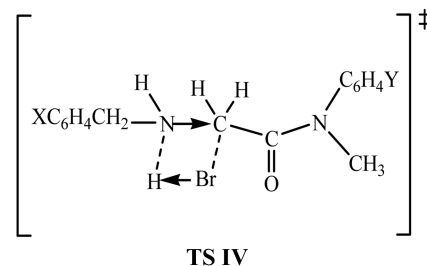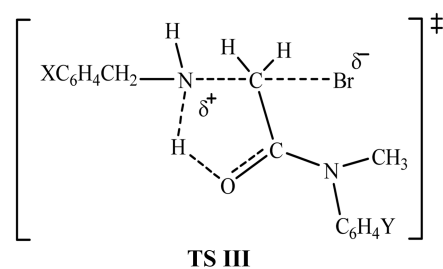
= 1.23) means that the hydrogen bond strength for X = electron-withdrawing is greater than that for X = electron-donating substituent. In other words, the k_H/k_D value should be greater for the stronger nucleophile than for the weaker nucleophile, when the degree of bond formation is proportional to the nucleophilicity. This implies that block *b* has earlier TS compared to block *a*, resulting in biphasic linear free energy correlation for variations of X and a somewhat

greater ρ_{XY} value for block $\underline{a}$ (later TS with a greater degree of bond formation: $\rho_{XY} = -0.32$) than for block $\underline{b}$ (earlier TS with a lesser degree of bond formation: $\rho_{XY} = -0.22$).

For a stepwise reaction with rate-limiting formation of the tetrahedral intermediate ($T^{\pm}$), the sign of ρ_{XY} (<0) will be the same for the forward reaction of concerted S_N2 processes.[5] However, 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 ($\partial\sigma_Y > 0$) so that $\rho_{XY} = \partial\rho_X/\partial\sigma_Y$ should be positive. Then, the sign and the magnitude of ρ_{XY} would be compensated for by these two factors, $\rho_{XY} < 0$ for the bond formation step and $\rho_{XY} > 0$ for the amine expulsion from $T^{\pm}$.[1d] As a result of the compensatory effects of the opposite signs, the ρ_{XY} values for the reactions of the rate-limiting formation of $T^{\pm}$ are very slightly negative or even very slightly positive: $\rho_{XY} = -0.06$ and -0.10 for the pyridinolysis of $YC_6H_4NHCOCH_2Cl$ and $YC_6H_4N(CH_3)COCH_2Cl$, respectively;[1g] $\rho_{XY} = +0.09$ for the rate-limiting formation in the pyridinolysis of phenacyl bromide.[1d] Thus, the values of $\rho_{XY} = -0.22$ and -0.32 for blocks $\underline{a}$ and $\underline{b}$, respectively, imply that the studied reactions proceed through a concerted mechanism involving the TS III.

Blocks $\underline{c}$ and $\underline{d}$: The secondary inverse DKIEs for blocks $\underline{c}$ and $\underline{d}$ imply that the hydrogen (deuterium) atoms in N-H(D) experience steric congestion in the TS. The degree of steric congestion steeply increases as the substituent X changes from an electron-donating to an electron-with-drawing substituent: $k_H/k_D = 0.99(X = 4\text{-MeO}) > 0.60(X = H) > 0.47(X = 4\text{-Cl})$. The k_H/k_D value of 0.47 for X = Cl is exceptionally small,[11] indicating extremely severe steric crowding in the TS. It is evident that the bond formation is extensively advanced in the TS. The smallest k_H/k_D value of 0.367 was observed for the reaction of Y-*O*-aryl methyl phosphonochloridothioate with deuterated X-anilines in MeCN when X = 4-Cl and Y = 4-CN.[12]

The magnitudes of the ρ_{XY} values of -1.80 (block $\underline{c}$) and -1.43 (block $\underline{d}$) are considerably large and comparable to that of -1.51 for the benzylaminolysis of Y-α-bromoacetani-lides when $\sigma_Y \geq 0.23$.[1h] The large magnitude of the ρ_{XY} value implies that the bond making is extensively advanced in the TS, which is consistent with the results of the DKIEs. Comparing the benzylaminolyses of *N*-methyl-Y-α-bromo-acetanilides with those of Y-α-bromoacetanilides for Y = electron-withdrawing substituents, the kinetic results are almost similar [except the location of break points, $\sigma_Y = 0$ (Y = H) for *N*-methyl-Y-α-bromoacetanilides and $\sigma_Y = 0.23$ (Y = 4-Cl) for Y-α-bromoacetanilides]: (i) biphasic concave upward/downward Hammett plots for substituent Y vari-ations, resulting in a negative σ_Y for X = electron-withdraw-ing substituents; (ii) large magnitudes of ρ_{XY}, -1.80 (block $\underline{c}$) and -1.43 (block $\underline{d}$) for *N*-methyl-Y-α-bromoacetanilides and -1.51 for Y-α-bromoacetanilides; (iii) exceptionally large values of β_X, 0.77-3.23 (block $\underline{c}$) and 0.51-1.65 (block $\underline{d}$) for *N*-methyl-Y-α-bromoacetanilides and 0.71-1.70 for Y-α-bromoacetanilides, indicating advanced bond making in the TS.[1h] These results suggest that both two reaction systems proceed through a concerted mechanism with an enolate-like TS II-type in which the nucleophile attacks the α-carbon with a great degree of bond formation. The sign inversion of ρ_Y can be interpreted as a charge reversal at the reaction center of the substrate from dominant bond formation ($\rho_Y > 0$; block $\underline{c}$), *via* equivalent degree of bond formation and breaking ($\rho_Y = 0$; calculate value of $\rho_X = 0.17$), to dominant bond breaking ($\rho_Y < 0$; block $\underline{d}$ except for X = H) in the TS as previously described.[1h] Huge secondary inverse DKIE [$k_H/k_D = 0.47$ (X = 4-Cl and Y = 4-NO$_2$) in block $\underline{d}$] is consistent with dominant bond breaking in which the extent of bond formation in the TS is almost as great as product. As a result, the nucleophile experience enormous steric congestion in the TS, resulting in huge secondary inverse DKIE. At a glance, the smaller magnitude of $\rho_{XY} = -1.43$ for block $\underline{d}$ compared to that of $\rho_{XY} = -1.80$ for block $\underline{c}$ is opposite to the obtained DKIEs, since the greater magnitude of ρ_{XY} leads to smaller value of secondary inverse DKIE i.e., greater secondary inverse one. This seems to be attributed to dominant bond breaking for block $\underline{d}$ where the negative charge is distorted to the leaving group (enough to give negative ρ_Y), resulting in smaller interaction between X and Y in block $\underline{d}$ compared to that in block $\underline{c}$.

Experimental Section

Materials. GR grade DMSO 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. GR grade toluidine, benzylamins, and D$_2$O were used without further purification. Deuterated benzylamines were prepared by benzylamines with D$_2$O in ethyl ether. The mixture was stirred for 24 hr at room temperature. The organic layer was separated and dried over anhydrous MgSO$_4$. Deuterated benzylamines were isolated by solvent evaporation under reduced pressure. After numerous attempts, the benzylamines were deuterated more than 98%, as confirmed by ^{1}H-NMR.

Preparation of Substrates. *N*-Methyl-Y-α-bromoacetanilides were prepared according to the literature methods of esterification. Aniline derivatives and bromoacetic anhydride were dissolved in dry ether. The reaction mixture was worked-up with water, and dried over anhydrous MgSO$_4$, and the product was isolated by column chromatography with ethylacetate/*n*-hexane. The solvent was removed under reduced pressure, and the substrate was finally isolated. Analysis of the substrates gave the following results.

***N*-Methyl-4-methoxy-α-bromoacetanilide:** Light yellow oily liquid; ^{1}H-NMR (400 MHz, CDCl$_3$), δ 3.26 (s, 3H), 3.66 (s, 2H), 3.83 (s, 3H), 6.93 (d, $J = 2.2$ Hz, 2H), 7.19 (d, $J = 2.1$ Hz, 2H); ^{13}C-NMR (100 MHz, CDCl$_3$), δ 26.69 (s, 1C), 38.23 (s, 1C), 55.49 (s, 1C), 114.99-159.33 (s, 6C arom.), 167.07 [s, 1C (C=O)]; IR (KBr disk) ν_{max} 3007 cm^{-1} (C-H str. Aromatic), 2840 cm^{-1} (C-H str.), 1743 cm^{-1} (C=O str.), 841 cm^{-1} (C-N str.); *m/z* (EI) 257 (M$^+$), 259 (isotope, M$^+$).

***N*-Methyl-4-methyl-α-bromoacetanilide:** Light yellow oily liquid; ^{1}H-NMR (200 MHz, CDCl$_3$), δ 2.33 (s, 3H), 4.01 (s,

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2H), 7.15 (d, *J* = 4.2 Hz, 2H), 7.41 (d, *J* = 4.2 Hz, 2H), 8.12 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃), δ 21.21 (s, 1C), 29.84 (s, 1C), 120.42-135.26 (s, 6C arom.), 163.56 [s, 1C (C=O)]; IR (KBr disk) ν_{max} 3034 cm⁻¹ (C-H str. Aromatic), 2953 cm⁻¹ (C-H str. Aliphatic), 1746 (C=O str.), 828 cm⁻¹ (C-N str.); *m/z* (EI) 241 (M⁺), 243 (isotope, M⁺).

N-Methyl-α-bromoacetanilide: Light bottle-green solid; mp 38-39 °C; ¹H-NMR (200 MHz, CDCl₃), δ 3.31 (s, 3H), 3.67 (s, 2H), 7.27-7.52 (m, 5H); ¹³C-NMR (100 MHz, CDCl₃), δ 26.69 (s, 1C), 38.03 (s, 1C), 126.93-142.96 (s, 6C arom.), 166.53 (s, 1C (C=O)); IR (KBr disk) ν_{max} 3039 cm⁻¹ (C-H str. Aromatic), 2952 cm⁻¹ (C-H str. Aliphatic), 1687 cm⁻¹ (C=O str.), 926 cm⁻¹ (C-N str.); *m/z* (EI) 227 (M⁺), 228 (isotope, M⁺) 229 (isotope, M⁺).

N-Methyl-4-chloro-α-bromoacetanilide: Brownish white solid; mp 70-71 °C; ¹H-NMR (200 MHz, CDCl₃), δ 3.29 (s, 3H), 3.66 (s, 2H), 7.26 (d, *J* = 4.6 Hz, 2H), 7.44 (d, *J* = 4.3 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃), δ 26.36 (s, 1C), 38.04 (s, 1C), 128.40-141.44 (s, 6C arom.), 166.39 [s, 1C (C=O)]; IR (KBr disk) ν_{max} 3055 cm⁻¹ (C-H str. Aromatic), 2952 cm⁻¹ (C-H str. Aliphatic), 1682 cm⁻¹ (C=O str.), 850 cm⁻¹ (C-N str.); *m/z* (EI) 261 (M⁺), 263 (isotope, M⁺).

N-Methyl-4-nitro-α-bromoacetanilide: Light greenish yellow solid; mp 88-89 °C; ¹H-NMR (200 MHz, CDCl₃), δ 3.40 (s, 3H), 3.75 (s, 2H), 7.52 (d, *J* = 4.6 Hz, 2H), 8.33 (d, *J* = 5.9 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃), δ, 26.33 (s, 1C), 38.37 (s, 1C), 125.50-148.78 (s, 6C arom.), 166.38 [s, 1C (C=O)]; IR (KBr disk) ν_{max} 3115 cm⁻¹ (C-H str. Aromatic), 2958 cm⁻¹ (C-H str Aliphatic) 1682 cm⁻¹ (C=O str.), 1524 cm⁻¹ (NO₂ Asym.), 1345 cm⁻¹ (NO₂ sym.), 861 cm⁻¹ (C-N str.); *m/z* (EI) 272 (M⁺), 274 (isotope, M⁺).

Kinetic Measurements. Rates were measured conductometrically as described previously.[1] [Substrate] = 1-5 × 10⁻³ M and [BnA] = 0.04 × 0.13 M. Pseudo-first-order rate constants were reproducible within ± 3%.

Product Analysis. N-Methyl-4-methyl-α-bromoacetanilide (0.05 M) was reacted with benzylamine (0.5 M), in DMSO at 25.0 °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 MgSO₄ overnight. MgSO₄ was removed by filtration. The product was isolated by column chromatography using 10% ethylacetate/*n*-hexane as the eluent. Solvent was removed under reduced pressure and a light brown oily product was found. Analysis of the product gave the following results.

4-CH₃C₆H₄N(CH₃)C(=O)CH₂NHCH₂C₆H₅: Light brown oil; ¹H-NMR (200 MHz, CDCl₃), δ 2.08 (broad, w, 1H, NH), 2.37 (s, 3H), 3.13 (m, 2H), 3.26 (s, 3H), 3.26 (m, 2H), 7.00-7.32 (m, 9H); ¹³C-NMR (100 MHz, CDCl₃), δ 21.07 (s, 1C), 37.35 (s, 1C), 50.27 (s, 1C), 53.45 (s, 1C), 126.86-140.12 (m, 12C arom.), 171.32 [s, 1C (C=O)]; *m/z* 268 (M⁺).

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