Kinetics and Mechanism of the Aminolysis of Phenacyl Bromides in Acetonitrile. A Stepwise Mechanism with Bridged Transition State

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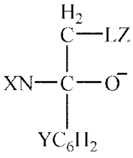
In the aminolysis of phenacyl bromides ($YC_6H_4COCH_2Br$) with benzylamines ($XC_6H_4CH_2NH_2$) in acetonitrile, the Brönsted β_X (β_{nuc}) values observed are rather low ($\beta_X = 0.69$-0.73). These values are similar to those ($\beta_X \cong 0.7$) for other aminolysis reactions of phenacyl compounds with anilines and pyridines, but are much smaller than those ($\beta_X = 1.1$-2.5) for the aminolysis of esters with benzylamines which are believed to proceed stepwise with rate-limiting expulsion of the leaving group. The relative constancy of the β_X values ($\beta_X \cong 0.7$) irrespective of the amine, leaving group and solvent can be accounted for by a bridged type transition state in the rate-limiting expulsion of the leaving group. Thus the aminolysis of phenacyl derivatives are proposed to proceed stepwise through a zwitterionic tetrahedral intermediate ($T^\pm$), with rate-limiting expulsion of the leaving group from $T^\pm$. In the transition state, the amine is bridged between the carbonyl and α-carbons, which leads to negligible effect of amine on the leaving group expulsion rate.

Key Words : Brönsted β values, Aminolysis of phenacyl bromides, Stepwise mechanism, Cross-interaction constant

Introduction

The nucleophilic substitution reactions of phenacyl derivatives have attracted considerable attention of theoretical[1] as well as experimental organic chemists.[2] Although a variety of mechanism has been proposed for the reaction by different groups of authors, 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,[3] **1**, (ii) single step process with bridging of the nucleophile between the α-carbon and the carbonyl carbon in the transition state (TS),[1a,b,3b,4] **2**, and (iii) concerted displacement with an enolate-like TS,[5] **3**. Recently we proposed a unified mechanism in which the reaction proceeds through an addition intermediate (**1**) with bridged type TS[6] (**2**) in the expulsion of the leaving group, LZ^-. In the pyridinolysis of phenacyl bromides,[6a] the change in the β_X ($= \beta_{nuc}$) values from a large ($\beta_X = 0.7$-0.8) to a small ($\beta_X \cong 0.4$) at a breakpoint $pK_a^o = 3.5$ in a biphasic Brönsted plot was observed providing evidence for the stepwise phenacyl transfer through a zwitterionic tetrahedral intermediate, $T^\pm$, with rate-limiting expulsion of the leaving group. Another important piece of evidence for the stepwise mechanism was the positive cross-interaction constant ρ_{XY} (> 0) in eq. 1, where X and Y denote substituent in the nucleophile and substrate, respectively. It has been shown that in a stepwise carbonyl substitution mechanism with a rate-limiting breakdown of the intermediate, the sign of ρ_{XY} is *positive*.[7] This is in contrast to *negative* ρ_{XY} values observed in the concerted nucleophilc substitution reactions of benzyl, benzenesulfonyl and carbonyl compounds.[8]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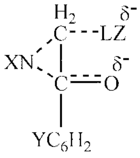
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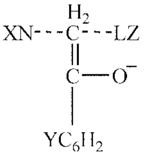
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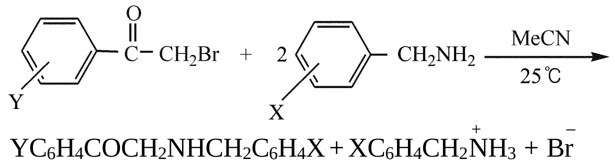
$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \qquad (1a)$$

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

In the present work, we extend our studies on the phenacyl transfer mechanism to the aminolysis of phenacyl bromides with benzylamines in acetonitrile, eq. 2. The purpose of this work is to provide further evidence in support of our unified mechanism (**1** + **2**) for the phenacyl transfer reactions.



$$YC_6H_4COCH_2NHCH_2C_6H_4X + XC_6H_4CH_2\overset{+}{N}H_3 + \overset{-}{Br}$$

X = 4-OMe, 4-Me, H, 4-Cl or 3-Cl
Y = 4-OMe, 4-Me, H, 4-Cl or 3-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

$$d[Br^-]/dt = k_{obsd}\,[YC_6H_4COCH_2Br] \qquad (3)$$

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

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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-phenacyl bromides with X-benzylamines in MeCN at 25 °C

X	Y					ρ_Y[d]
	4-OMe	4-Me	H	4-Cl	3-NO2	
4-OMe	9.55	10.8	12.8	15.8	26.6	0.45 ± 0.01
4-Me	8.91	9.90	11.4	15.1	24.5	0.45 ± 0.01
H	6.76	7.59	8.71	11.2	19.1	0.46 ± 0.01
4-Cl	4.20	4.67	5.62	7.27	12.0	0.47 ± 0.01
3-Cl	3.31	3.66	4.23	5.64	9.77	0.48 ± 0.01
ρ_X[b]	−0.75 ± 0.05	−0.76 ± 0.04	−0.76 ± 0.03	−0.73 ± 0.05	−0.71 ± 0.04	ρ_{XY}[e] = 0.05
$ß_X$[c]	0.73 ± 0.06	0.74 ± 0.06	0.74 ± 0.05	0.71 ± 0.06	0.69 ± 0.05	

[a] The σ values were taken from Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. 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 Blackwell, L. F.; Fischer, A.; Miller, J.; Topsom, R. D.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588. The p*K*a = 9.67 was used for 4-methoxy benzylamine. [b] Correlation coefficients (r) are better than 0.993. [c] r = 0.991. [d] r = 0.999 (all). [e] r = 0.994.

concentration. The second-order rate constants (k_N) were obtained as the slopes of plots of eq. 4 with more than five excess benzylamine concentrations. The k_N values are summarized in Table 1 together with the Hammett (ρ_X and ρ_Y) and Brönsted (β_X) coefficient and cross-interaction constant, ρ_{XY}. The β_X values determined by plotting logk_N (MeCN) *vs* pK_a(H_2O) in Figure 1 are considered reliable since the pK_a values in MeCN are linearly related with those in water with essentially a unity slope.[9]

The β_X values in Table 1 are within narrow range of 0.69-0.73, which are quite similar to those for other phenacyl transfer reactions. For example, the reactions of phenacyl benzenesulfonates ($YC_6H_4COCH_2SO_2C_6H_4Z$ where Z is a substituent in the leaving group) with benzylamines in MeOH gave β_X values of 0.61-0.76[10] with ρ_{XY} = 0.02-0.04 and ρ_{XZ} = 0.09-0.12. The β_X values for the reaction of α-chloroacetanilides ($YC_6H_4N(R)COCH_2Cl$; R=H and CH_3) with benzylamines in DMSO were 0.56-0.87 (ρ_{XY} = 0.21)[6b] for R=H and 0.61-0.87 (ρ_{XY} = 0.18) for R=CH_3. For the reactions of phenacyl benzenesulfonates with anilines in MeOH-MeCN mixtures the β_X values obtained were 0.61-0.76[11] (ρ_{XY} = 0.05-0.14 and ρ_{XZ} = 0.19-0.32). Likewise, for the pyridinolysis of phenacyl bromides in MeCN the β_X values were 0.65-0.78[6a] (ρ_{XY} = 1.36). All These phenacyl transfer reactions have nearly constant β_X values of 0.7 ± 0.1 and positive ρ_{XY} and ρ_{XZ} values despite the fact that the phenacyl transfer reactions quoted above involve different nucleophiles, (benzylamines, anilines or pyridines), different leaving groups (benzenesulfonate, chloride or bromide) and different solvents (MeOH, MeCN or DMSO). This is in quite 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 leaving group: aminolysis with benzylamines exhibited much larger β_X values (1.06-2.80)[12] than those with anilines (0.79-1.20)[13] and/or pyridines (0.64-0.94)[14] in acetonitrile.

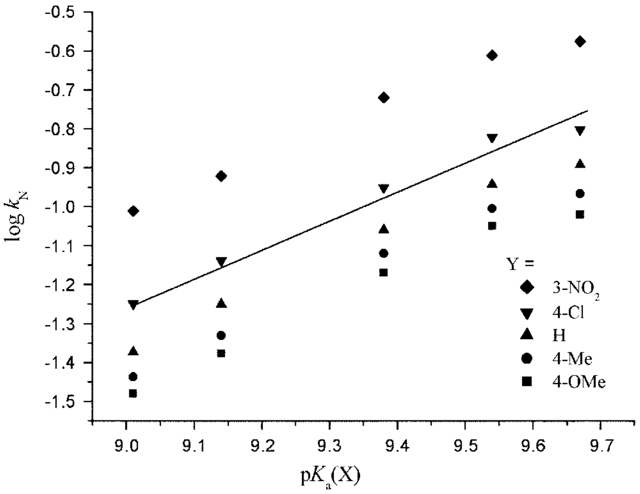
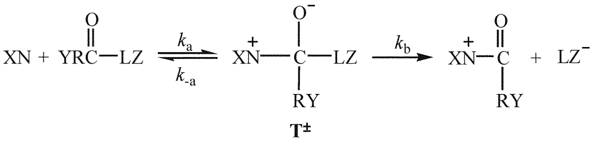


Figure 1. Brönsted plots for the reactions of Y-phenacyl bromides with X-benzylamines in MeCN at 25 °C.

To rationalize the relative constancy of β_X (≅ 0.7) in the phenacyl transfers and the large differences in the magnitude of β_X values between the stepwise aminolysis of esters with benzylamines (primary amines) and those with anilines and pyridines, we consider MO theoretical aspects of relative expulsion rate of the amine (NX) and leaving group (LZ) from the zwitterionic tetrahedral intermediate, $T^{\pm}$, involved in the stepwise aminolysis of carbonyl esters, eq. 5, where X, Y and Z represent substituents in the amine nucleophile, substrate and leaving group, respectively. The cationic product in eq. 5 undergoes deprotonation in a fast step when NX is primary or secondary amine.



$$XN + YRC(=O){-}LZ \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \overset{+}{X}N{-}C(O^-)(RY){-}LZ \xrightarrow{k_b} \overset{+}{X}N{-}C(=O)RY + LZ^- \quad (5)$$

$T^{\pm}$

For the stepwise mechanism with rate-limiting breakdown of $T^{\pm}$ in eq. 5, the overall rate constant k_N can be simplified as eq. 6.

$$k_N = (k_a/k_{-a})k_b = Kk_b \quad (6)$$

Thus, dependence of the rate (log k_N) on amine basicity (pK_X) can be given as eqs. 7.

$$\mathrm{dlog}k_N/\mathrm{dp}K_X = \mathrm{dlog}k_a/\mathrm{dp}K_X - \mathrm{dlog}k_{-a}/\mathrm{dp}K_X + \mathrm{dlog}k_b/\mathrm{dp}K_X \tag{7a}$$

$$\beta_X = \beta_a - \beta_{-a} + \beta_b \tag{7b}$$

Primary amines (*e.g.* benzylamines) will have strong localized cationic charge on the amine nitrogen ($-N^+X$ in $T^{\pm}$) whereas secondary and/or tertiary amines (*e.g.* pyridines) should have relatively weak positive charge on $-N^+X$ due to delocalization of the positive charge.[15] In general, secondary and tertiary amines stabilize $T^{\pm}$ by delocalizing cationic charge on the amine nitrogen atom.[15,16] The strength of the localized cationic charge will decrease therefore roughly in the order of decreasing rate of expulsion from $T^{\pm}$,[12i,14c] benzylamines > secondary amines > anilines > pyridines. Within a given series of amine, *e.g.*, substituted benzylamines or pyridines, an electron withdrawing substituent, $\delta\sigma_X > 0$, leads to a stronger localized cationic charge on $-N^+X$ in $T^{\pm}$ than an electron donating substituent, $\delta\sigma_X < 0$. The cationic center on N constitutes a strong electron acceptor which will depress σ^* level[17] of the $C-N^+$ bond orbital in $T^{\pm}$. The stronger the cationic charge, the stronger is the electron accepting ability, and hence the lower will become the σ^* level. The depression of the σ^* level, therefore, depends on the electron accepting ability of $-N^+X$ in $T^{\pm}$, not on the absolute basicity of NX. Thus the σ^* level will be the lowest in $T^{\pm}$ with benzylamines and the highest with pyridines for the amine series considered above. This will in turn lead to the strongest vicinal charge transfer of the oxygen lone pair electron in $T^{\pm}$ (n_O) to $\sigma^*_{C\text{-}N^+}$ orbital ($n_O \to \sigma^*_{C\text{-}N^+}$) for benzylamines since the second-order perturbation energy, $\Delta E^{(2)}_{n\to\sigma^*}$, due to the charge transfer is inversely dependent on the energy gap, $\Delta\varepsilon = \varepsilon_{\sigma^*} - \varepsilon_n$, eq. 8,[17-19] where $F_{n\sigma^*}$ is the Fock matrix element, $F_{n\sigma^*} = \langle n \mid F \mid \sigma^* \rangle$, which is proportional to the overlap ($S_{n\sigma^*}$) between the two

$$\Delta E^{(2)}_{n\to\sigma^*} = -2(F_{n\sigma^*})^2/\Delta\varepsilon \tag{8}$$

interacting orbitals. MO models of the intermediate show that the two lone pairs (n_O) on the oxygen atom are antiperiplanar[15,20] to the two σ^* bonds, $\sigma^*_{C\text{-}N^+}$ and $\sigma^*_{C\text{-}LZ}$, which should give optimum $n_O \to \sigma^*$ interactions[18,19] as shown in Figure 2. The vicinal $n_O \to \sigma^*$ charge transfer interaction stabilizes ($\Delta E^{(2)}_{n\to\sigma^*} < 0$) the intermediate, but weakens σ^* bond and strengthens the bond in between the two interacting orbitals.[19] Thus as the results of $n \to \sigma^*$ interactions, the $C-N^+$ bond is weakened (easily broken and hence k_{-a} is large) but the C–O bond is strengthened (contracted) leading to a greater degree of double bond character for the carbonyl group ($\mathrm{C}\overset{\cdots}{-}\mathrm{O}$) and renders a larger negative charge on the carbonyl carbon.

In nucleophilic substitution reactions, effects of substituents in the nucleophile (σ_X) and leaving group (σ_Z) on the progress of reaction (the TS position) along the reaction coordinate can be predicted using a model based on relative thermodynamic stability of products (or reactants), *e.g.*, Hammond postulate, Bell-Evans-Polanyi principle etc.[21,22] These models predict that a substituent ($\delta\sigma_X < 0$ and/or $\delta\sigma_Z > 0$) which stabilizes product (and hence leads to a greater thermodynamic driving force, $\delta\Delta G^o < 0$, with a greater reactivity) results in an earlier TS with a smaller extent of bond making ($\delta\beta_X < 0$, $\delta\mid\rho_X\mid < 0$) and bond cleavage ($\delta\mid\beta_Z\mid < 0$, $\delta\rho_Z < 0$). Thus, a greater reactivity leads to a lower selectivity, *i.e.*, reactivity-selectivity principle[23] (RSP) holds.

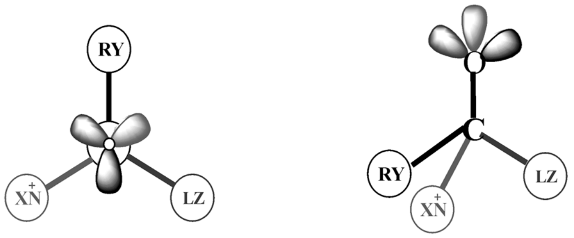
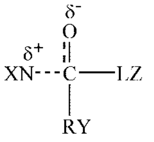
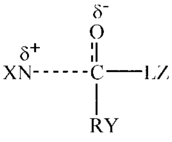


Figure 2. Antiperiplanar lone pairs on the oxygen atom to the three bonds, $C-N^+X$, C–LZ and C–RY, in a zwitterionic tetrahedral intermediate, $T^{\pm}$.



4a

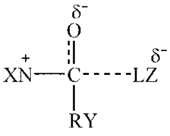
(later TS)



4b

(earlier TS)

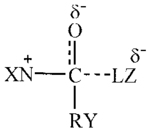
According to the principle of microscopic reversibility,[24] the TSs for the reversible steps, k_a and k_{-a}, should be identical. Thus, the TSs for the two steps (one TS since k_a and k_{-a} have identical structure) can be represented schematically for benzylamines (stronger $n_O \to \sigma^*$ interaction leads to lager k_{-a} with smaller negative β_{-a}) and pyridines (weaker $n_O \to \sigma^*$ interaction leads to smaller k_{-a} with lager negative β_{-a}) as **4a** and **4b**, respectively. These structures tell us that for the nucleophile with a strong cationic charge (**4a**) β_a is large but β_{-a} is numerically small (small negative) since TS **4a** shows that bond formation has progressed to a large degree (β_a = large positive) but expulsion of amine from $T^{\pm}$ has progressed to a small degree (β_{-a} = small negative). For the nucleophile with a weak cationic charge (**4b**) the situation is exactly opposite, *i.e.*, β_a is small positive but β_{-a} is large negative. In effect the two, β_a and β_{-a}, are *complementary* so that $\beta_a - \beta_{-a}$ portion of the β_X (eq. 7b) is practically constant, $\beta_a - \beta_a \cong$ constant, irrespective of the amine nature. According to eq 7b the nearly constant ($\beta_a - \beta_{-a}$) is supplemented by β_b, which means that the different size of overall β_X is primarily dependent on the β_b (> 0) value. The sign of β_b (= $\mathrm{dlog}k_b/\mathrm{dp}K_X$) is positive[25] since *for a given amine nucleophile* the expulsion rate of leaving group from $T^{\pm}$ increases ($\mathrm{dlog}k_b > 0$) with the basicity of amine ($\mathrm{dp}K_X > 0$).[15] This is due to a greater *push* provided by a basic amine with the weak delocalized cationic charge on $-N^+X$ (and acyl group)[15] in $T^{\pm}$ than by a weakly basic amine with the strong localized cationic charge on $-N^+X$. Conversely, a stronger localized cationic charge on $-N^+X$ in $T^{\pm}$ exerts a stronger *pull* than a more delocalized cationic charge because of the greater electron demand. Thus a primary amine (*e.g.* benzylamine) with the strongly localized cationic charge in $T^{\pm}$ leads to the slower leaving group expulsion than a secondary or tertiary amine (*e.g.* pyridine) with delocalized cationic charge in $T^{\pm}$. On the other hand, the greater β_X ($= \beta_a - \beta_{-a} + \beta_b$) values for the aminolysis with benzylamines (**5a**) than with anilines and pyridines (**5b**) are resulted from the larger size of β_b for benzylamines. This means that the rate of leaving group expulsion from $T^{\pm}$ is small but selectivity is large for benzylamine nucleophile. The greater selectivity accompanying the lower reactivity is also evident in the observation that a greater degree of bond cleavage ($\delta\rho_Z > 0$; greater selectivity) is obtained by a nucleophile with a stronger electron acceptor ($\delta\sigma_X > 0$; weaker nucleophile) in the aminolysis of various esters.[12-14] In these cases, ρ_Z is the selectivity parameter representing susceptibility of the total rate ($d\log k_N$) to the substituent, Z, in the leaving group ($\delta\sigma_Z$). Adherence to the RSP is one of the criteria for the stepwise nucleophilic substitution of esters with rate-limiting breakdown of the tetrahedral intermediate, $T^{\pm}$.[7b,26]



$\overset{+}{\mathrm{XN}}\text{—}\underset{\mathrm{RY}}{\overset{\overset{\delta^-}{\mathrm{O}}}{\mathrm{C}}}\text{-----}\overset{\delta^-}{\mathrm{LZ}}$

5a

(later TS)



$\overset{+}{\mathrm{XN}}\text{—}\underset{\mathrm{RY}}{\overset{\overset{\delta^-}{\mathrm{O}}}{\mathrm{C}}}\text{---}\overset{\delta^-}{\mathrm{LZ}}$

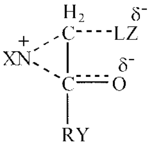
5b

(earlier TS)

The correlation between σ_X ($\partial\sigma_X > 0$) and ρ_Z ($\partial\rho_Z > 0$) *requires* that the cross-interaction constant ρ_{XZ} ($= \partial\rho_Z/\partial\sigma_X = \partial\rho_X/\partial\sigma_Z$) should be positive[10,11,12-14] for the stepwise mechanism with rate-limiting breakdown of $T^{\pm}$. By the same token, an increase in σ_X ($\partial\sigma_X > 0$) resulted in a larger positive ρ_Y ($\partial\rho_Y > 0$) value (Table 1) with a stronger negative charge development on the carbonyl carbon.[6,10,11,12c,13c,15] Thus the sign of ρ_{XY} ($= \partial\rho_Y/\partial\sigma_X = \partial\rho_X/\partial\sigma_Y$) is also positive. These two, $\rho_{XZ} > 0$ and $\rho_{XY} > 0$, are necessary conditions for the stepwise aminolysis with rate-limiting breakdown of $T^{\pm}$.[6b,13c,27]

Now let us examine the mechanism of phenacyl transfers. Frontier molecular orbital (FMO) theory predicts that the lowest unoccupied antibonding orbital (LUMO) is the most likely orbital that is attacked by an incoming nucleophile in the nucleophilic substitution reactions. Among the two types of LUMOs, $\pi^*_{C=O}$ and $\sigma^*_{C\text{-}LZ}$,[17b] in the phenacyl derivatives, the former ($\pi^*_{C=O}$) is much lower than the latter ($\sigma^*_{C\text{-}LZ}$). This means that interaction of lone pair orbital (n_N) on the nitrogen atom of the amine nucleophile is much stronger with $\pi^*_{C=O}$ and forms an intermediate, $T^{\pm}$, rather than with $\sigma^*_{C\text{-}LZ}$ leading to a concerted (S_N2) displacement at the α-carbon.[17b] It has been shown that due to the wide energy gap, $\Delta\varepsilon = \varepsilon_{\sigma^*} - \varepsilon_{\pi^*}$, the proclivity for the stable carbonyl addition intermediate formation is much stronger than the concerted S_N2 displacement in the nucleophilic substitution of carbonyl compounds.[17b] This means that in the aminolysis of phenacyl derivatives, a prior addition of the nucleophile to form a zwitterionic tetrahedral intermediate, $T^{\pm}$ (**2**), should occur. In fact a biphasic Brönsted plot is obtained in the pyridinolysis of phenacyl bromides[6a] in MeCN indicating that a change in the rate-limiting step from breakdown to formation of $T^{\pm}$ occurs as the basicity of pyridine nucleophile increases. Once an addition intermediate (**2**) is formed, the leaving group (LZ) 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.[6b]

This unified mechanism, **1** + **2**, differs from the stepwise carbonyl transfer mechanism, eq. 5, in the rate-limiting expulsion, k_b.; the leaving group is expelled by the amine which bridges over the two carbon centers, α- and carbonyl carbons, **6**. In this TS structure (**6**) for the leaving group expulsion step, k_b, the susceptibility of rate ($d\log k_b$) to the basicity of amine (dpK_X), *i.e.*, β_b, should be insignificant ($\beta_b \cong 0$) since the two effects of pK_X, (one, on the carbonyl carbon and the other, on the α-carbon) will be *compensatory* or cancels out each other. 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. As a result the effect of amine on the stability of TS **6** will become negligible. In fact only a meager change in ρ_Z ($\Delta\rho_Z = 0.05$) was observed for the pK_a(X) change of 0.36 (4-OMe → 4-Cl benzylamine) in the aminolysis of phenacyl benzenesulfonates with benzylamines in MeOH[10] for Y = 4-NO_2 at 45.0 °C, in contrast to a large change in ρ_Z ($\Delta\rho_Z = 1.21$) for the aminolysis of $C_2H_5C(=O)SC_6H_5$ with benzylamines ($\Delta pK_a(X) = 0.36$) in MeCN at 45.0 °C.[12b] This means that in the phenacyl transfers, the overall β_X will be grossly independent of the amine nature and hence the β_X value becomes practically constant, eq. 9, *i.e.*, $\beta_X \cong 0.7$ irrespective of the amine, leaving group, or solvent, as experimentally observed (vide supra).



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$$\begin{aligned}\beta_X \cong \beta_a - \beta_{-a} &\cong \text{constant } (\beta_b \cong 0)\\ &\cong 0.7\end{aligned} \tag{9}$$

The relative constancy of the β_X value, therefore, provides evidence for our unified mechanism (**1**+**2**) of phenacyl transfers. As noted above, other pieces of evidence for the unified mechanism are (i) the sign of cross-interaction constants, $\rho_{XY} > 0$, $\rho_{XZ} > 0$ (and $\rho_{YZ} < 0$),[25] which are exactly opposite to those for the concerted (S_N2) type reactions ($\rho_{XY} < 0$, $\rho_{YZ} > 0$ and $\rho_{XZ} < 0$),[8] and (ii) adherence to the RSP.[7b,26]

The kinetic isotope effects (k_H/k_D) involving deuterated benzylamines ($XC_6H_4CH_2ND_2$) in Table 2 reveal that the k_H/k_D values are all near unity. This is in accord with the

Table 2. Kinetic isotope effects on the second-order rate constants (k_N) for the reactions of Y-phenacyl bromides with deuterated X-benzylamines ($XC_6H_4CH_2ND_2$) in acetonitrile at 25 °C

X	Y	k_H (10^{-2} M^{-1} s^{-1})	k_D (10^{-2} M^{-1} s^{-1})	k_H/k_D
H	4-OMe	6.76	6.58	1.03
H	H	8.71	8.58	1.02
H	3-NO_2	19.1	18.5	1.03
4-Cl	4-OMe	4.20	4.01	1.05
4-Cl	H	5.62	5.20	1.08
4-Cl	3-NO_2	12.0	11.0	1.09

stepwise mechanism with rate-limiting breakdown of the intermediate.[12e,13c,28] As noted above, in the two TSs corresponding to the reversible steps ($k_a + k_{-a}$) and the k_b step the effects of TS structure on N–H (N–D) vibrations will be compensatory and hence will be small.

The activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$, summarized in Table 3 show that the activation enthalpies are relatively low and the entropies of activation have small negative values. Characteristically, they are rather insensitive to the variation of substituents in the nucleophile, X, and in the substrate, Y. This should result from the relatively loose TSs as indicated by a small cross-interaction constant, ρ_{XY} (= 0.05), albeit the intervening groups in the nucleophile (–CH_2–) and in the substrate (–C(=O)–) should make the distance from X and Y to the reaction center (α-carbon) far apart and lead to fall-off of both substituent effects on the rate.

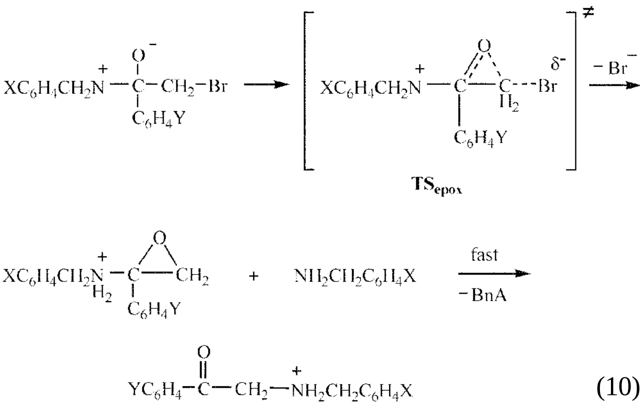
Another notable feature is the relatively small $-\Delta S^{\neq}$ values ($\Delta S^{\neq} \approx -10$ eu) which are in contrast to much larger negative entropies of activation (–20 to –60 eu)[12a-b,d-e,j,13b-14] found for other aminolysis of esters in which the breakdown of $T^{\pm}$ is rate-limiting. Inspection of the TS structure (**6**) reveals that partial cleavage of C–N^+ and C–LZ bonds in the phenacyl transfer gives a relatively loose structure in contrast to partial bond cleavage of C–LZ alone in the carbonyl transfers (**5a** or **5b**).

Table 3. Activation parameters[a] for the reactions of Y-phenacyl bromides with X-benzylamines in acetonitrile

X	Y	t (°C)	k_N (10^{-2} M^{-1} s^{-1})	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (cal mol^{-1} K^{-1})
H	4-OMe	15	3.87	9.1 ± 0.2	10 ± 1
		25	6.76		
		35	11.6		
H	3-NO_2	15	11.1	9.1 ± 0.1	9 ± 1
		25	19.1		
		35	32.3		
4-Cl	4-OMe	15	2.47	8.9 ± 0.2	10 ± 1
		25	4.20		
		35	7.21		
4-Cl	3-NO_2	15	7.14	8.7 ± 0.2	10 ± 1
		25	12.0		
		35	20.4		

[a] Calculated by the Eyring equation. The maximum errors calculated (by the method of Wiberg, K. B. *Physical Organic Chemistry*; Wiley: New York, 1964; p 378) are ± 0.5 kcal mol^{-1} and ± 2 eu for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, respectively.

Finally an alternative reaction path through an epoxide type TS, eq. 10, may be envisaged. However this path with TS_{epox} is not consistent with the experimental results:



(10)

Firstly in the TS_{epox} the –NH_2 (–ND_2) moiety becomes more crowded than in $T^{\pm}$ so that (i) k_H/k_D should be less than one[29] in contrast to the observed values of k_H/k_D = 1.0 and (ii) the $-\Delta S^{\neq}$ value should have been much larger ($\Delta S^{\neq} \approx -20$ to –60 eu). Secondly, the β_b cannot be insignificantly small and independent of the amine nature (Table 2) since the expulsion rate of the leaving group, Br^-, depends on push (or pull) provided by the amine in $T^{\pm}$. This means that the β_X values (= $\beta_a - \beta_{-a} + \beta_b$) should differ depending on the amine nature as we found with the aminolysis of esters.[12-14] Lastly in order to break the CH_2–Br bond in TS_{epox} there should be substantial proximate charge transfer from oxygen lone pairs (n_O) toward the $\sigma^*_{CH_2\text{-}Br}$ bond, *i.e.*, $n_O \rightarrow \sigma^*_{CH_2\text{-}Br}$ interaction should occur. However, this is rather difficult since $\sigma^*_{CH_2\text{-}Br}$ orbital is neither vicinal nor geminal to the oxygen lone pair (see Figure 2) so that the overlap between the two orbitals is very small.[18,19] The $n_O \rightarrow \sigma^*_{CH_2\text{-}Br}$ interaction should therefore be very weak and hence the TS_{epox} should form a rather high barrier, *i.e.*, the activation energy for the process (eq. 10) should be much higher than the path through the amide bridge TS (in the form of **6**). In this TS (**6** with LZ = Br, NX = BnA, and RY = C_6H_4Y) the strong $n_O \rightarrow \sigma^*_{C-N^+X}$ vicinal charge transfer interaction facilitate C–N^+ bond rupture so that the bridge formation becomes much easier.

Experimental Section

Materials. GR grade phenacyl bromides and benzylamines were used after recrystallization. HPLC grade MeCN (water content is less than 0.005%) was used without further purification, except drying over molecular sieve, storing under nitrogen atmosphere, and then distilled before use.

Kinetic Measurement. Rates were measured conductometrically at 25.0 °C for the reactions of phenacyl bromides with benzylamines in MeCN using a computer controlled conductivity bridge constructed in this laboratory. Pseudo-first-order rate constants, $k$obsd, were measured by using curve fitting method in ORIGIN program (version 5.1). Pseudo-first-order rate constants were determined with large excess of nucleophiles, [substrate] = 1 × 10^3 M and [nucleophile] = 0.1-0.5 M. Pseudo-first-order rate constant values were average of two (or three) runs which were reproducible to ± 3%.

Product Analysis. 4-Methoxy phenacyl bromide (0.15 M) was reacted with an exess of benzylamine (3 M) for 24 hr at 25 °C in MeCN. The product mixture was treated for workup with ether and water. The product mixture was separated by column chromatography (silica gel, 10% MeOH/MC). Analysis of the product gave the following results.

$4\text{-}\mathrm{CH_3OC_6H_4COCH_2NHCH_2C_6H_5}$. liquid; Anal. Found: C, 75.4; H, 6.6; N, 5.3. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. δ_H, NMR (200 MHz, $CDCl_3$), 7.93-6.91 (9H, m, aromatic), 4.08 (2H, s, CH2), 3.89 (2H, s, CH2). 3.87 (3H, s, OCH_3). 1.22 (1H, s, NH); MS (EI) *m/z* 255 (M+).

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25. Note that β_b is different from β_Z (= β_{lg}) which is negative and represents the susceptibility of the overall rate (logk_N) to the change in pK_a values of the leaving group (Z).
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