Kinetics and Mechanism of the Pyridinolysis of Phenacyl Bromides in Acetonitrile

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Kinetic studies of the reactions of substituted phenacyl bromides ($YC_6H_4COCH_2Br$) with pyridines (XC_5H_4N) are carried out in acetonitrile at 45.0 °C. A biphasic Brønsted plot is obtained with a change in slope from a large ($\beta_X \cong 0.65-0.80$) to a small ($\beta_X \cong 0.36-0.40$) value at $pK_a° = 3.2-3.6$, which can be attributed to a change in the rate-determining step from breakdown to formation of a tetrahedral intermediate in the reaction path as the basicity of the pyridine nucleophile increases. This mechanism is supported by the faster rates with pyridines than with anilines and the change of cross-interaction constant ρ_{XY} from a large positive ($\rho_{XY} = +1.4$) to a small positive ($\rho_{XY} \cong +0.1$) value. The large magnitude of Hammett ρ_X ($= -5.5$ to -6.9) values for the pyridines with electron-withdrawing substituents and positive deviations of the π-acceptors, p-CH_3CO and p-CN, are quite similar to those for the pyridinium ion formation equilibria. The activation parameters are also in line with the proposed mechanism.

Introduction

The nucleophilic substitution reactions of α-halocarbonyl compounds, e.g., $YC_6H_4COCH_2Br$, have attracted considerable attention mainly because of the rate-enhancing effect of the α-carbonyl group[1] and the variety of suggested geometries of the transition state (TS) to explain such rate acceleration.[2] The high reactivity has been explained in many conflicting ways.[2] Although an electrostatic rate enhancement[3] and a complex mechanism[4] with intermediate epoxide have been proposed, they received less support than the mechanisms involving (i) a prior addition of the nucleophile (Nu) to the carbonyl group, **1**,[2e,5] (ii) bridging of the nucleophile between the α-carbon and the carbonyl carbon in the TS, **2**,[1b,2b,5,6] and (iii) enolate-like TS, **3**.[7] Theoretical studies predicted that

1   **2**   **3**
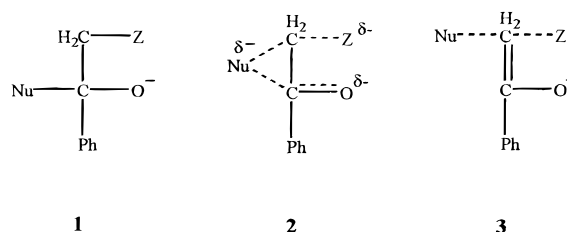
(i) resonance delocalization occurs into the carbonyl group of the electrons in the TS analogous to that in an α-acylcarbanion[2b,8] and (ii) the enolate-like contribution decreases as the nucleophile becomes weaker.[7a,8b] In our previous work, we proposed the mechanism very similar to that involving enolate-like TS; in these works we used anilines,[9] benzylamines,[10] and *N,N*-dimethylanilines (DMA)[11] as nucleophiles but the pK_a values of the amines within a series were limited to narrow range.

In view of mechanistic changes observed in the nucleophilic substitutions of carbonyl compounds from a rate-limiting expulsion of the leaving group from a tetrahedral intermediate, $T^\pm$, with a large β_{nuc} ($\cong 0.8-1.0$) to a rate-limiting formation of $T^\pm$ with a small β_{nuc} ($\cong 0.1-0.3$), we extend in this work the pK_a range of the nucleophile (pyridines, $\Delta pK_a \geq 5$) in the nucleophilic substitution reactions of phenacyl bromides in acetonitrile, eq 1. The objective of this work is to elucidate the mechanism by applying various mechanistic criteria such as (i) the change in the β_X ($= \beta_{nuc}$) values, from a large to

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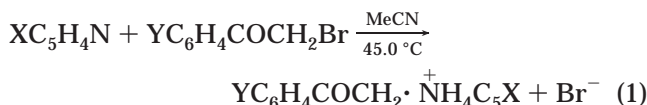
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$$XC_5H_4N + YC_6H_4COCH_2Br \xrightarrow[45.0\,°C]{MeCN}$$

$$YC_6H_4COCH_2 \cdot \overset{+}{N}H_4C_5X + Br^- \quad (1)$$

a small in a biphasic Brφnsted plot as observed in the stepwise acyl transfer mechanism,[12] and (ii) the sign and magnitude of the cross-interaction constant,[13] ρ_{XY} in eqs 2 where X and Y denote substituents in the nucleophile and substrate, respectively.

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_{XY} \quad (2a)$$

$$\rho_{XY} = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X \quad (2b)$$

We have previously shown that in a stepwise carbonyl substitution mechanism the sign of ρ_{XY} is positive and the magnitude is large (≥ 0.5) in a rate-limiting breakdown of the intermediate, $T^{\pm}$.[14] For a concerted nucleophilic substitution reactions of benzyl, benzenesulfonyl and carbonyl compounds, the ρ_{XY} was invariably negative.[13b,15]

In this work we present evidence in support of the stepwise mechanism involving an intermediate of the type **1** for the nucleophilic substitution reactions of phenacyl compounds.

Results and Discussion

The rate law followed in the present reactions, eq 1, is given by eqs 3 and 4, where [XPy] is X-substituted pyridine concentration and k_2 is the rate constant for aminolysis of the substrates, $YC_6H_4COCH_2Br$. The second-

$$d[Br^-]/dt = k_{obs}[YC_6H_4COCH_2Br] \quad (3)$$

$$k_{obs} = k_2[XPy] \quad (4)$$

order rate constants for pyridinolysis (k_2) were obtained as the slopes of plots of eq 4. The k_2 values, together with the pK_a values of the pyridinium ions in water at 25.0 °C are summarized in Table 1.

The rate constants for the pyridinolysis of phenacyl bromides are greater than those for the aminolysis with isobasic anilines, e.g., for Y = H; $k_2 = 11.4 \times 10^{-3}$ M^{-1} s^{-1} for pyridine with X = H (pK_a = 5.21) in MeCN at 45.0 °C, and $k_2 = 8.07 \times 10^{-3}$ M^{-1} s^{-1} for aniline with X = p-MeO (pK_a = 5.34) in MeOH at 45.0 °C.[9a] The rate of the anilinolysis of phenacyl bromide was found to decrease as the acetonitrile content of the MeCN–MeOH mixtures increases: $k_2 = 5.46 \times 10^{-3}$ M^{-1} s^{-1} (80%

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MeOH) and 3.41×10^{-3} M^{-1} s^{-1} (50% MeOH) for X = p-MeO at 45.0 °C.[9b] This means that the k_2 value (8.07×10^{-3} M^{-1} s^{-1}) will be smaller in acetonitrile (approximately by a factor of 3), k_2 (MeCN) $\cong 2.7$ M^{-1} s^{-1}, which leads to ca. one-fourth of the k_2 for pyridinolysis. The rate decrease with increasing acetonitrile content was also observed in the aminolysis of phenacyl arenesulfonates with anilines in MeOH–MeCN mixtures.[9a] The addition of acetonitrile to the aqueous solvent is known to increase the fraction of amine expulsion from $T^{\pm}$ to form ester in the aminolysis of unsymmetrical carbonate esters.[16] Thus, the rate of leaving group expulsion (rate-limiting step) decreases relative to that in aqueous solution. The greater k_2 value for the reaction of phenacyl bromide with pyridine nucleophile than that with aniline is at variance with the results of Forster et al.[7b] Their interpolated rate constants using Arrhenius parameters at 310 K gave the rate sequence, aniline > pyridine. The errors in the Arrhenius activation energy (E_a) ranged from 0.8 to 1.4 kcal mol^{-1} so that their results may not be reliable.

Correlations of rate constants, k_2, obtained in acetonitrile with pK_a values of the pyridinium ions in water, eq 5, are justified,[17] since the pK_a values in acetonitrile are linearly related with those in water with essentially

$$\log k_2(\text{MeCN}) = \beta_X p K_a(H_2O) + \text{constant} \quad (5)$$

unity slopes, $S = 1.02$ (theoretical at the B3LYP/6-31G* level)[17] and $S = 1.05$ (experimental)[17,18] with constant $\cong 7.0$ in eq 6. The Brønsted β_X (β_{nuc}) values determined by eq 5 are collected in Table 2 together with ρ_X (ρ_{nuc}) and

$$pK_a(\text{MeCN}) = SpK_a(H_2O) + \text{constant} \quad (6)$$

ρ_Y values. The Brønsted plots are shown in Figure 1. The curved lines consist of two linear parts, with the Brønsted slopes $\beta_X = 0.65–0.80$ and $\beta_X = 0.36–0.40$. The break point, pK_a°, occurs at p$K_a \cong 3.5$. The Brønsted break may be interpreted to result from a change in the rate-determining step from breakdown of the intermediate, $T^{\pm}$, to products to $T^{\pm}$ formation as the amine basicity increases.[12] The intermediate, $T^{\pm}$, should be of the form **1**,[2e,5] and the pyridinolysis of phenacyl bromides in acetonitrile is consistent with the mechanism depicted by eq 7, where the k_b step is rate limiting. In this k_b step, the pyridine molecule shifts to the α-carbon with simultaneous expulsion of Br$^-$.

$$\xrightarrow{k_b} YC_6H_4COCH_2 \cdot \overset{+}{N}C_5H_4X + Br^- \quad (7)$$
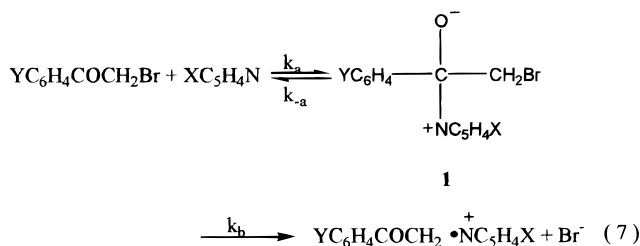
The TS is proposed to have a bridged type structure, **2**,[5,6] with Nu = pyridine and Z = Br (vide infra).

The curved Brønsted type plots have also been interpreted to result from structural variation of the TS in a single step (concerted) mechanism.[19] We think, nevertheless, that the pyridinolyses of phenacyl bromides are

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Table 1. Second-Order Rate Constants, k_2 ($\times 10^3$ M^{-1} s^{-1}), for the Reactions of Y−Phenacyl Bromides with X-Pyridines in Acetonitrile at 45.0 °C

| | | Y = | | | | | | | |
X	pK_a[a]	*p*-CH$_3$O	*p*-CH$_3$	*p*-C$_6$H$_5$	H	*m*-CH$_3$O	*p*-Cl	*m*-NO$_2$	*p*-NO$_2$
p-CH$_3$O	6.58	31.6	37.3	39.2	39.9	40.4	49.0	61.9	63.1
p-CH$_3$	6.03	17.7	20.8	21.8	22.6	23.2	30.2	38.7	40.3
m-CH$_3$	5.67	14.1	16.6	17.4	17.8	17.9	21.2	27.3	29.9
p-C$_6$H$_4$CH$_2$	5.59	13.8	16.2	16.3	17.4	17.6	20.4	27.0	29.4
H	5.21	9.64	10.9	11.2	11.4	12.1	14.8	19.6	19.9
m-C$_6$H$_5$	4.87	6.73	7.35	7.98	8.00	8.18	10.5	13.1	15.4
m-CH$_3$CO	3.10	1.23	1.33	1.45	1.48	1.50	1.78	2.34	2.45
m-Br	2.85	0.837	0.905	0.986	1.01	1.02	1.21	1.59	1.67
p-CH$_3$CO	2.30	0.286	0.295	0.308	0.355	0.399	0.409	0.560	0.630
p-CN	1.86	0.120	0.123	0.142	0.156	0.175	0.179	0.272	0.301
m-CN	1.35	0.0565	0.0577	0.0676	0.0698	0.0866	0.0977	0.177	0.196

[a] In water at 25.0 °C. Fischer A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3591. Hong, S. W.; Koh, H. J.; Lee, I. *J. Phys. Org. Chem.* **1999**, 12, 425.

Table 2. Brønsted (β_X) and Hammett Coefficients (ρ_X and ρ_Y) for the Pyridinolysis of Phenacyl Bromides (YC$_6$H$_4$COCH$_2$Br) in Acetonitrlie at 45.0 °C[a]

| | | | X = *p*-CH$_3$O−*m*-C$_6$H$_5$ (pK_a = 6.58−4.87) | | X = *m*-CH$_3$CO−*m*-CN (pK_a = 3.10−1.35) | |
X	ρ_Y	Y	ρ_X	β_X	ρ_X[b]	β_X
p-CH$_3$O	0.27 ± 0.02(0.984)	*p*-CH$_3$O	−1.97 ± 0.16 (0.987)	0.38 ± 0.02(0.996)	−6.76 ± 0.17	0.78 ± 0.02(0.999)
p-CH$_3$	0.33 ± 0.03(0.983)	*p*-CH$_3$	−2.06 ± 0.18 (0.985)	0.40 ± 0.02(0.995)	−6.89 ± 0.18	0.80 ± 0.03(0.998)
m-CH$_3$	0.28 ± 0.02(0.987)	*p*-C$_6$H$_5$	−2.06 ± 0.16 (0.988)	0.40 ± 0.02(0.996)	−6.72 ± 0.16	0.78 ± 0.03(0.998)
p-C$_6$H$_4$CH$_2$	0.29 ± 0.02(0.990)	H	−2.07 ± 0.16 (0.988)	0.40 ± 0.02(0.996)	−6.70 ± 0.16	0.77 ± 0.02(0.999)
H	0.31 ± 0.02(0.988)	*m*-CH$_3$O	−2.04 ± 0.16 (0.988)	0.39 ± 0.02(0.996)	−6.23 ± 0.09	0.72 ± 0.02(0.999)
m-C$_6$H$_5$	0.33 ± 0.03(0.982)	*p*-Cl	−2.02 ± 0.11 (0.994)	0.39 ± 0.01(0.999)	−6.35 ± 0.11	0.75 ± 0.04(0.996)
m-CH$_3$CO	0.29 ± 0.01(0.994)	*m*-NO$_2$	−2.01 ± 0.13 (0.992)	0.39 ± 0.01(0.998)	−5.61 ± 0.01	0.67 ± 0.05(0.991)
m-Br	0.29 ± 0.01(0.994)	*p*-NO$_2$	−1.88 ± 0.10 (0.995)	0.36 ± 0.01(0.999)	−5.48 ± 0.01	0.65 ± 0.05(0.992)
p-CH$_3$CO	0.33 ± 0.02(0.985)					
p-CN	0.38 ± 0.02(0.994)					
m-CN	0.54 ± 0.02(0.996)					

[a] Values in parentheses are correlation coefficients. [b] Calculated only for X = *m*-CH$_3$CO, *m*-Br, and *m*-CN.
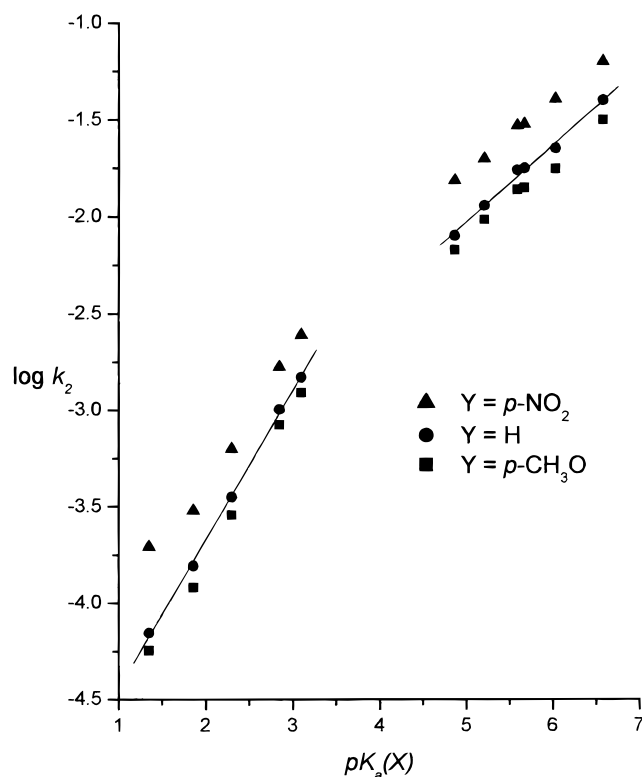
Figure 1. Brφnsted plots (β_X) for the X-pyridinolysis of Y-phenacyl bromides (for Y = *p*-CH$_3$O, H, and *p*-NO$_2$) in MeCN at 45.0 °C.

stepwise for the following reasons, although a concerted mechanism with an enolate type TS, **3**, cannot be rigorously excluded.

(1) The faster rate of the aminolysis of phenacyl

bromide with pyridine than with aniline (vide supra) is consistent with carbonyl addition mechanism (through **1**), rather than with simple S$_N$2 displacement at the α-carbon (**3**). For example, in the aminolysis of phenyl chloroformate (PhOC(=O)Cl) with pyridines (XC$_5$H$_4$N)[12h] and anilines (X'C$_6$H$_4$NH$_2$)[20] in acetonitrile at 25.0 °C the second-order rate constant, k_2, were 2.52 M^{-1} s^{-1} (X = *m*-CONH$_2$, pK_a = 3.33) and 1.82 M^{-1} s^{-1} (X' = *p*-Cl, pK_a = 3.98), respectively. Also in the aminolysis of ethyl S-2,4-dinitrophenylthiocarbonate (DNPTC) with pyridines[21] and anilines[22] in water at 25.0 °C gave the k_2 values of 18 × 10^{-3} M^{-1} s^{-1} (X = H, pK_a = 5.37) and 6.1 × 10^{-3} M^{-1} s^{-1} (X' = *p*-Me, pK_a = 5.56), respectively. Note that we used more basic anilines than pyridines under the same experimental conditions in the comparison.

In contrast, however, in the simple S$_N$2 reactions at softer reaction centers than the carbonyl carbon the aminolysis rates are faster with aniline nucleophiles than with pyridines. For example, in the aminolysis of benzyl bromide the rate constants, k_2, with pyridine (XC$_5$H$_4$N)[23] and aniline (X'C$_6$H$_4$NH$_2$)[24] in methanol were 1.35 × 10^{-3} M^{-1} s^{-1} (X = H, pK_a = 5.21) at 50.0 °C and 4.48 × 10^{-3} M^{-1} s^{-1} (X' = p-CH$_3$, pK_a = 5.10) at 35.0 °C, respectively. The k_2 value for aniline is greater than that for pyridine although lower temperature and basicity are used for

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aniline. Similarly, in the aminolysis of benzenesulfonyl chloride with pyridines[25] and anilines[26] in methanol at 35.0 °C the k_2 values were 15.9×10^{-2} M^{-1} s^{-1} (X = H, pK_a = 5.21) and 26.6×10^{-2} M^{-1} s^{-1} (X' = p-CH$_3$, pK_a = 5.10), respectively. These comparisons of rates clearly demonstrate that nucleophilic substitution at a carbonyl carbon is enhanced by hard nucleophiles whereas those at a saturated carbon (benzyl carbon) and sulfonyl center are facilitated by softer nucleophiles (anilines). Therefore, the faster rates found with pyridines than with anilines support the stepwise carbonyl addition mechanism.

(2) A similar biphasic dependence of log k_2 on the pyridine basicity was obtained for acetyl chloride (CH$_3$-COCl) in aqueous solution[27] and for methyl chloroformate (CH$_3$OCOCl) in aqueous[12d] and acetonitrile solutions[12h] with a breakpoint at p$K_a°$ $\cong$ 3.6 where the rate constants for expulsion of the attacking (pyridines) and leaving groups (Cl), k_{-a} and k_b, are equal. This very low breakpoint ($\sim$3.6) is a characteristic of very good leaving group (Cl$^-$), since the stepwise reactions exhibit a decrease of p$K_a°$ as the basicity of the leaving group decreases.[12g,28] This is due to the larger k_b for the less basic nucleofuge, which requires a less basic amine (lower pK_a) to satisfy the relation $k_{-a} = k_b$.[12d,27] The slope changes from β_X (= β_{nuc}) = 0.80 to 0.25 as the pyridine basicity increases. This trend with chloride leaving group is very similar to that found with the present system with bromide leaving group, which is also a very good leaving group, except that the β_X values are slightly lower for the weak bases (β_X (= β_{nuc}) = 0.7–0.8) and slightly higher for the strongly basic pyridines ($\beta \cong 0.4$). In fact, the pyridinolysis of methyl chloroformate in acetonitrile had very similar value of $\beta_X \cong 0.7$ for the weak bases.[12h] However, these somewhat lower slopes, β_X, can be ascribed to the use of pK_a's in water, as the correlations, eqs 5 and 6, indicate; the observed β_X values must be lower by a factor of 1.05 (experimental S in eq 6) than the true values in acetonitrile. The biphasic Brønsted plots for CH$_3$COCl and CH$_3$OCOCl have been interpreted as mechanistic changes occurring at p$K_a°$ $\cong$ 3.6 from breakdown to formation of the tetrahedral intermediate, T$^\pm$, as pyridine basicity increases. However, Jencks and co-workers interpreted a larger slope of β_X = 0.7 for the reactions of methyl chloroformate with acetate and phenolate anions as a rate-limiting attack but they could not give reasons why this value is larger than that for nitrogen nucleophiles (β_X = 0.25).[27]

In our previous works on the aminolysis of phenacyl bromides and arenesulfonates, we obtained β_X = 0.6–0.8 with anilines and benzylamines,[9,10] but β_X = 0.3–0.4 with *N,N*-dimethylanilines (DMA).[11] In these works we used bases of very narrow pK_a ranges [they were pK_a = 9.54 (*p*-MeO) − 9.14 (*p*-Cl), 5.34 (*p*-MeO) − 3.98 (*p*-Cl) and 5.16 (*p*-MeO) − 2.82 (*p*-Br) for the conjugate acids of benzylamine, aniline, and DMA, respectively] so that no breakpoint was found. In case of the reactions of phenacyl arenesulfonates with DMAs, the slope of 0.3–0.4 is reasonable since the putative T$^\pm$ with DMA should be very unstable and probably cannot exist with a

significant lifetime due to steric hindrance of the two methyl groups on N, and the formation of T$^\pm$ should be the rate-limiting step.

It has been shown that the sequence of amine expulsion rate from the tetrahedral intermediate is benzylamines > secondary alicyclic amines > anilines > pyridines,[12g,29] which should give the same p$K_a°$ sequence, and the p$K_a°$ should be the lowest with pyridines.[12g] This is another reason no breakpoints were found with benzylamines[10] and anilines,[9] but was found in this work with pyridines (p$K_a°$ $\cong$ 3.5). For example, the aminolysis of 2,4,6-trinitrothiophenyl acetates, CH$_3$C(=O)SC$_6$H$_2$-(NO$_2$)$_3$, with secondary alicyclic amines gave p$K_a°$ = 7.8, whereas those with pyridines gave p$K_a°$ = 4.9 under the same experimental conditions.[30] For 2,4-dinitrophenyl thioacetates they are p$K_a°$ = 8.9 (alicyclic amines) and 6.6 (pyridines).[30]

The partitioning of the intermediate to reactants and products has been shown to be dependent on substituents on the acyl group,[31] since the rate of expulsion of anions is decreased ($\delta\rho_Z < 0$) more than that of amines by electron-withdrawing from the acyl group ($\delta\sigma_Y > 0$).[28,31] This causes a small increase of the p$K_a°$ value upon the increase of the electron-withdrawing power of the acyl group,[16,28] which is in accord with our results of slight increase in p$K_a°$ from ca. 3.2 to 3.4 and to 3.6 as the substituent in the acyl group, Y, is changed from Y = *p*-MeO, to H and to *p*-NO$_2$. This change in the position of the breakpoint, p$K_a°$, with different substituents on the acyl group also supports the stepwise carbonyl addition mechanism[16,28] in which expulsion of bromide ion from an addition intermediate, **1**, is rate-limiting.

(3) The Hammett plots for variations of substituent Y and X are shown in Figures 2 and 3, respectively. The ρ_Y values (Table 2) are all positive, indicating that the reaction center becomes more negative in the TS, reactant → **5**. This is consistent with the negative charge development on the carbonyl carbon in the development of the C=O bond which is partially offset by expulsion of pyridinium ion from the intermediate shifting toward a more remote α-carbon in the TS, **5**. The relatively small positive ρ_Y values (0.3–0.5 in Table 2) suggest that the negative charge development on Cα----C----O moiety is relatively small compared to that on the carbonyl carbon in the S$_N$2[13b] processes involving benzoyl halides with aniline nucleophiles ($\rho_Y \cong 2.0$).

4   **5**
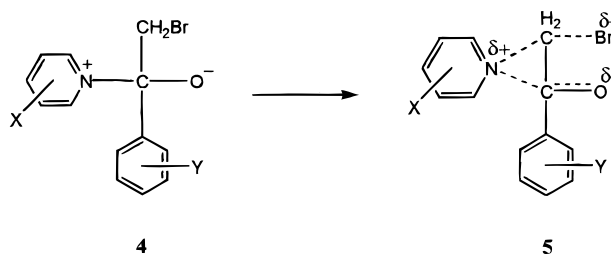
Examination of Figure 3 reveals that the Hammett plots are also biphasic just as we obtained in the Brønsted plots (Figure 1). A notable difference between the two is that all the electron acceptor groups including *p*-CH$_3$CO and *p*-CN fall on a straight line of steeper slope (β_X =

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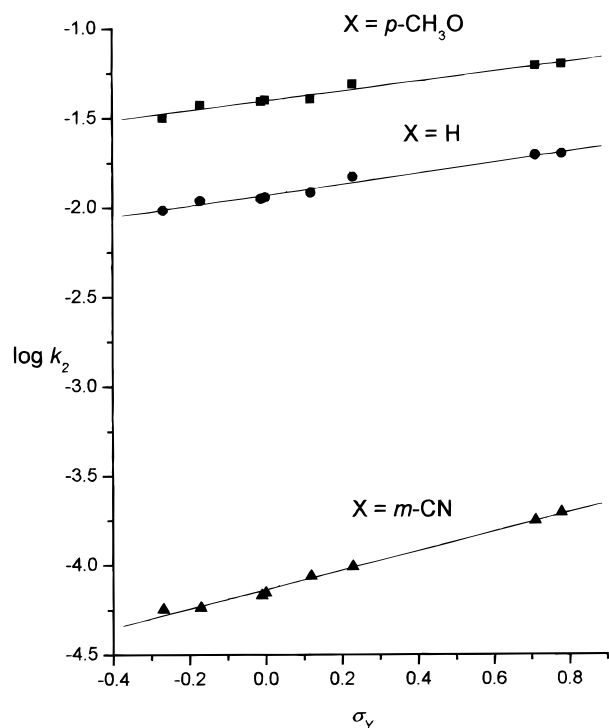(31) Lee, I.; Lee, D.; Kim, C. K. *J. Phys. Chem. A* **1997**, *101*, 879.

Figure 2. Hammett plots (ρ_Y) for the X-pyridinolysis (X = p-CH₃O, H, and m-CN) of Y-phenacyl bromides in MeCN at 45.0 °C.
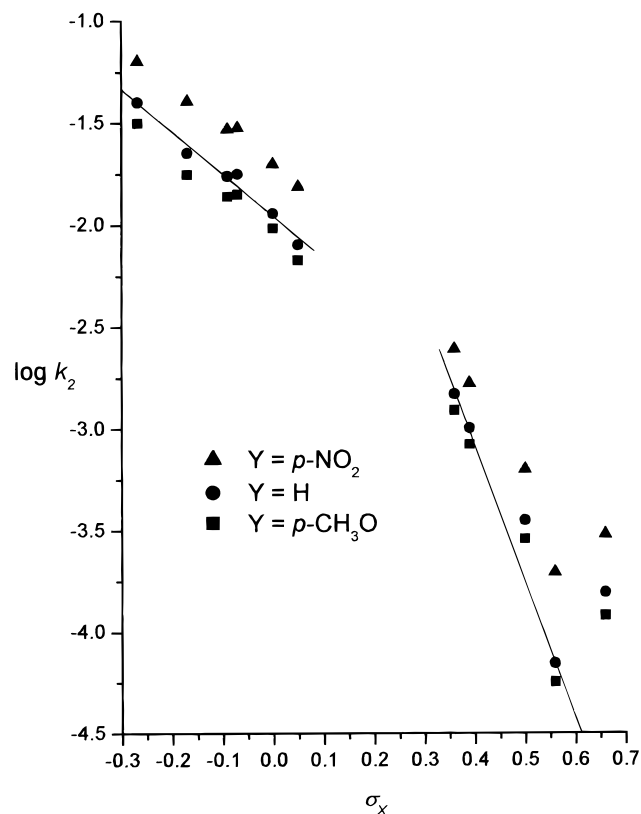

Figure 3. Hammett plots (ρ_X) for the X-pyridinolysis of Y-phenacyl bromides (for Y = p-CH₃O, H, and p-NO₂) in MeCN at 45.0 °C.

$0.7 \sim 0.8$) in the Brønsted plots (log k_2 vs pK_a), but the two strong π-acceptors, p-CH₃CO and p-CN, deviate positively in the Hammett plots (log k_2 vs σ).[32]

These two acceptor substituents are known to have weak π-donor effect under the strong cationic charge of

pyridinium ion (azonium ion, $>N^+=$) and deviate positively from the log k_2 vs σ (Hammett) plots.[17,32] This is evident from the much enhanced rates for the two substituents in the plots. However, these deviations are absent in the log k_2 vs pK_a (Brønsted) plots, since the basicity enhancing π-donor effect of the two acceptors is correctly reflected in the pK_a measurement in contrast to the lack of such π-donor effect (due to the lack of strong cationic functional center) in the determination of the σ constants.[32] The negative slope of the electron donor segment (including X = m-CH₃CO) is smaller ($\rho_X = -1.9$ to -2.2) than that of the electron-acceptor part ($\rho_X = -5.5$ to -6.9) which excludes p-CH₃CO and p-CN. The magnitude of this latter ρ_X is comparable to that for the plots of the pK_a values of substituted pyridines versus σ ($\rho = 6.01$).[32b]

Since the slope of the plots of pK_a vs σ for the dissociation of pyridinium ions, eq 8, is $+6.01$, that for the reverse process of eq 8 should be -6.01. In the
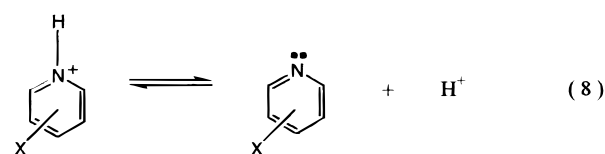
stepwise pyridinolysis mechanism, eq 7 where $k_2 = (k_a/k_{-a})k_b = Kk_b$, the similar pyridinium ion (**4**) equilibria are involved and our Hammett ρ_X values of -5.5 to -6.9 are very similar to that for the reverse process of eq 8. Moreover, the positive deviations of the π-acceptors, p-CH₃CO and p-CN, from the Hammett plots are also the same in the two processes, the pyridinium ion formation equilibria (reverse of eq 8) and the pyridinolysis of phenacyl bromides. Thus, the large negative ρ_X values and deviations from linearity of p-CN and p-CH₃CO provide another piece of evidence in support of the proposed mechanism through a tetrahedral intermediate.

(4) One of the most puzzling results obtained in the aminolysis of phenacyl bromides (and arenesulfonates) has been that the cross-interaction constant, ρ_{XY} in eq 2, is invariably positive,[9−11] which is not consistent with the bond formation process ($\rho_{XY} < 0$) in a concerted reaction.[13b,15] In fact, we predicted that the positive ρ_{XY} is a necessary condition for a stepwise mechanism through a tetrahedral intermediate.[14] For the normal bond formation of amines in a concerted or S_N2 process at saturated and carbonyl carbon center, a stronger electron-acceptor substituent in the substrate ($\delta\sigma_Y > 0$) leads to a greater degree of bond formation ($\delta\rho_X < 0$) so that ρ_{XY} is always negative.[13b,15] However, as we noted above, in the partitioning of tetrahedral intermediate the rate of expulsion of amines is increased ($\delta\sigma_X > 0$) by a stronger electron-acceptor substituent in the acyl group ($\delta\sigma_Y > 0$)[16,28,31] so that ρ_{XY} should be positive (eq 2b). We believe that the magnitude of ρ_{XY} is larger for the breakdown than the formation of T$^{\pm}$, as we obtained ($\rho_{XY} = 0.09$ and $\rho_{XY} = 1.36$ for formation and breakdown of **1**, respectively) in the present work. In the TS proposed, **5**, the pyridine is bridged to C$_\alpha$ and carbonyl carbon so that the interaction between X and Y should be large as reflected in the large positive cross-interaction constant, $\rho_{XY} \cong 1.4$.[13b] Addition-

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Table 3. Activation Parameters[a] for the Reactions of Y-Phenacyl Bromides with X-Pyridines in Acetonitrile

X	Y	T (°C)	k_2 (×10³) M⁻¹ s⁻¹	$\Delta H^{\ddagger}$ (kcal mol⁻¹)	$-\Delta S^{\ddagger}$ (cal mol⁻¹ K⁻¹)
m-CH$_3$	p-CH$_3$O	35	6.21		
		45	14.1	1.6 ± 0.3	17 ± 1
		55	32.0		
m-CH$_3$	p-NO$_2$	35	15.1		
		45	29.9	13.1 ± 0.4	25 ± 1
		55	59.2		
m-CN	p-CH$_3$O	35	0.0355		
		45	0.0565	8.7 ± 0.3	51 ± 1
		55	0.0898		
m-CN	p-NO$_2$	35	0.131		
		45	0.196	7.5 ± 0.2	52 ± 2
		55	0.294		

[a] Calculated by Eyring equation. Errors shown are standard deviations.

ally, we postulated that in the stepwise mechanism ρ_{YZ} is negative while ρ_{XZ} is positive, where Z is the substituent in the leaving group,[14] and a greater reactivity leads to a smaller selectivity, i.e., the reactivity-selectivity principle (RSP) holds.[14] In the present reaction, we did not vary the leaving group, and the sign of ρ_{YZ} and ρ_{XZ} cannot be examined. However, we reported previously that $\rho_{YZ} = -0.62$ and $\rho_{XZ} = +0.32$ for the reactions of anilines (XC$_6$H$_4$NH$_2$) with phenacyl arenesulfonates (YC$_6$H$_4$COCH$_2$OSO$_2$C$_6$H$_4$Z) in methanol at 45.0 °C.[9a] The RSP was found to hold in all of the aminolysis of phenacyl bromides and arenesulfonates.[9–11] In the present work, the RSP is held in general, but there are some anomalies. The sign and magnitude of ρ_{XY} in the present work, therefore, support the stepwise mechanism for the pyridinolysis of phenacyl bromides, eq 7.

(5) The activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, are also in line with the proposed mechanism. For example, the pyridinolysis of thiophenyl 4-nitrobenzoates in acetonitrile (T = 35, 45, and 55 °C) was found to proceed by rate-limiting breakdown of T$^{\pm}$; the $\Delta H^{\ddagger}$ (= 7.5–7.6 kcal mol⁻¹) and $\Delta S^{\ddagger}$ (−39 to −55 eu) values obtained[12h] are very similar to our $\Delta H^{\ddagger}$ (= 7.5 and 8.7 kcal mol⁻¹) and $\Delta S^{\ddagger}$ (−51 and −52 eu) values in Table 3 for the reactions with weakly basic pyridine (X = m-CN). Similar activation parameters are reported also for other carbonyl addition reactions.[33]

It should be also mentioned that the kinetic isotope effects involving deuterated nucleophiles (XC$_6$H$_4$ND$_2$ + C$_6$H$_5$COCH$_2$OSO$_2$C$_6$H$_5$ in MeCN), k_H/k_D (= 1.01–1.10), reported earlier are also consistent with the stepwise mechanism through the addition intermediate, T$^{\pm}$.[34]

Experimental Section

Materials. Merck GR acetonitrile was used after three distillations. The pyridine nucleophiles, Aldrich GR, were used without further purification. Aldrich phenacyl bromide substrates were used, which were recrystallized before use.

Rate Constants. Rates were measured conductometrically at 45.0 ± 0.05 °C. The conductivity bridge used in this work was a self-made computer automatic A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obs}, were determined by the curve fitting analysis of the diskette data with a modified version of the origin program, which fits conductance vs time data to the equation $A = A_{\infty} + (A_0 - A_{\infty})\exp(-k_{obs}t)$, where A_{∞}, $A_0 - A_{\infty}$, and k_{obs} are iteratively optimized to achieve the best possible least-squares fit with a large excess of pyridine (Py); [phenacyl bromide] ≅ 1 × 10⁻³ M and [Py] = 0.03–0.24 M. Second-order rate constants, k_2, were obtained from the slope of a plot of k_{obs} vs [Py] with more than five concentrations of pyridine, eq 4. The k_2 values in Table 1 are the averages of more than three runs and were reproducible to within ±3%.

Product Analysis. p-Methylphenacyl bromide (CH$_3$C$_6$H$_4$C-(O)CH$_2$Br) was reacted with an excess of pyridine (C$_5$H$_5$N) with stirring for more than 15 half-lives at 45.0 °C in acetonitrile, and the products were isolated by evaporating the solvent under reduced pressure. The product mixture was treated by column chromatography (silica gel, 15% ethyl acetate/n-hexane). Analysis of the product gave the following results.

C$_5$H$_5$N$^+$–CH$_2$C(O)C$_6$H$_4$CH$_3$Br$^-$: mp 208–210 °C; δ_H, NMR (250 MHz, CDCl$_3$), 1.91 (2H, s, CH$_2$), 2.32 (3H, s, CH$_3$), 7.1–7.3 (4H, m, benzene), 8.0–9.0 (5H, m, pyridine); EIMS m/z 212 (M$^+$). Anal. Calcd for C$_{14}$H$_{14}$NOBr: C, 79.2; H, 6.6. Found: C, 79.1; H, 6.7.

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