# Structure-Reactivity Relationships in the Pyridinolysis of N-Methyl-N-arylcarbamoyl Chlorides in Dimethyl Sulfoxide

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Nucleophilic substitution reactions of N-methyl-N-arylcarbamoyl chlorides (YC<sub>6</sub>H<sub>4</sub>N(CH<sub>3</sub>)COCl) with pyridines ( $XC_5H_4N$ ) have been investigated in dimethyl sulfoxide at 45.0 °C. A striking trend in the selectivity parameters is that they are constant within experimental errors,  $\rho_{\rm X}=-2.25\pm$ 0.03,  $\beta_{\rm X} = 0.42 \pm 0.01$ , and  $\rho_{\rm Y} = 1.10 \pm 0.06$ , with changing reactivities of the electrophiles ( $\delta \sigma_{\rm Y}$ ) and nucleophiles ( $\delta \sigma_X$ ), respectively, and this leads to a vanishingly small cross-interaction constant,  $ho_{XY} pprox 
ho_{XY} pprox 0$ . The rate data can be expressed in the Ritchie  $N_+$  type equation. Based on this and other results, the mechanism of nucleophile (pyridine) addition to the resonance- stabilized carbocation is proposed. It has been shown from the definition of  $\beta_{XY}$  (and  $\rho_{XY}$ ) together with the Marcus equation that the high intrinsic barrier,  $\Delta G_0^{\dagger}$ , in the intrinsic-barrier controlled reaction series is a prerequisite for such reactions in which the cross-interaction vanishes and the  $N_{+}$ relationship holds.

## Introduction

The mechanism of the nucleophilic substitution reactions of N,N-disubstituted (1, N,N-dimethyl: 2, N,Ndiphenyl: 3, N-methyl-N-phenyl) carbamoyl chlorides has long been controversial ranging from an  $S_N 1^{1,2a}$  to  $S_N 2^2$ including an  $S_N 2$  (intermediate)<sup>3</sup> type. However there does seem to exist a general consensus that the mechanism for solvolysis is primarily  $S_{\rm N}\mathbf{1}$  in character, favored by a strong resonance electron donation from nitrogen. For some systems, a weak nucleophilic participation by solvent and/or amine nucleophile has been observed in a predominantly S<sub>N</sub>1 reaction.<sup>1h</sup>

For reactions of strongly resonance-stabilized systems, e.g., carbocations, that follow the Ritchie  $N_{+}$  relationship,<sup>4</sup> eq 1 where  $N_{+}$  is a parameter characteristic of

$$\log k_{\rm Nu} = N_+ + \log k_0 \tag{1}$$

nucleophile reactivity and  $k_0$  is a constant dependent solely on the identity of the cation, essentially constant nucleophile selectivities are observed with changing electrophile (carbocation) reactivity. Although originally such relationship is reported to apply for ring-substituted diarylmethyl (D<sup>+</sup>), triarylmethyl (T<sup>+</sup>), and the aryl tropylium ions (Tp<sup>+</sup>), it has since been extended to other highly resonance-stabilized systems such as quinon methide.<sup>5</sup> **4**.



In this work, we report structure-reactivity relationships observed in the pyridinolysis of N-methyl-N-arylcarbamoyl chlorides 3 in dimethyl sulfoxide, eq 2. One

 $NC_{5}H_{4}X + YC_{6}H_{4}N(CH_{3})C(O)CI \xrightarrow{DMSO} YC_{6}H_{4}N(CH_{3})C(O)NC_{5}H_{4}X + CI$ (2)

X = p-CH<sub>3</sub>O, p-CH<sub>3</sub>, p-C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>, H, m-C<sub>6</sub>H<sub>5</sub>, m-CH<sub>3</sub>CO, m-Cl, p-CH<sub>3</sub>CO, p-CN or m-CN Y = p-CH<sub>3</sub>O, H, *p*-Cl or *p*-NO<sub>2</sub>

of the principal objectives was to investigate how selectivity changes as the substituents in the nucleophile (X) and substrate (Y) are varied and to determine the crossinteraction constant,  $\rho_{XY}$  and  $\beta_{XY}$  in eq 3<sup>6</sup> where  $\Delta p K_X =$  $pK_X - pK_H$  etc. and  $\rho_{XY} = \beta_{XY} \cdot \rho_X^e \cdot \rho_Y^e$  with  $\rho_i^e = \Delta pK_i / \sigma_i$ , etc. Thus,  $\beta_{XY} = c \cdot \rho_{XY}$  where *c* is a constant. This study

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Table 1. Second-Order Rate Constants,  $k_2$  (×10<sup>4</sup> M<sup>-1</sup> s<sup>-1</sup>), for the Reactions of Y–Substituted N-Methyl-N-arylcarbamoyl Chlorides with X-Pyridines in Dimethyl Sulfoxide at 45.0 °C

Х	pKa <sup>b</sup>	Y = p-CH <sub>3</sub> O	Н	<i>p</i> -Cl	p-NO <sub>2</sub>	$ ho_{ m Y}{}^{-} d$
p-CH <sub>3</sub> O	6.58	56.2	132	191	3090	$1.12\pm0.04$
<i>p</i> -CH <sub>3</sub>	6.03	33.9	74.1	115	1690	$egin{array}{c} (0.999)^c \ 1.11 \pm 0.03 \ (0.999) \end{array}$
p-C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	5.59	20.4	42.7	77.6	1200	$1.15\pm0.01$
Н	5.21	15.8	31.6	56.2	724	$(1.00) \\ 1.08 \pm 0.01 \\ (1.00)$
m-C <sub>6</sub> H <sub>5</sub>	4.87	11.2	22.9	44.6	561	$1.10\pm0.02$
<i>m</i> -CH <sub>3</sub> CO	3.17	2.00	3.98	6.03	97.7	$\begin{array}{c}(1.00)\\1.04\pm0.04\\(0.999)\end{array}$
<i>m</i> -Cl	2.81	1.51	2.63	4.90	72.4	$1.11\pm0.03$
<i>p</i> -CH <sub>3</sub> CO	2.30	1.00	2.09	3.39	52.5	$egin{array}{c} (0.999) \ 1.12 \pm 0.02 \ (1.00) \end{array}$
<i>p</i> -CN	1.86	0.603	1.26	2.24	28.8	$1.08\pm0.02$
<i>m</i> -CN	1.35	0.417	0.871	1.51	17.8	$\begin{array}{c} (1.00) \\ 1.05 \pm 0.02 \\ (1.00) \end{array}$
$\rho_X^a$		$-2.22 \pm 0.08$	$-2.27 \pm 0.11$	$-2.24 \pm 0.11$	$-2.27 \pm 0.08$	$\rho_{\rm XY} = -0.02$
$\beta_{\mathbf{X}}$		$(0.996)^c$ $0.41 \pm 0.01$ $(1.00)^c$	$\begin{array}{c} (0.993) \\ 0.42 \pm 0.01 \\ (0.999) \end{array}$	$(0.992) \\ 0.41 \pm 0.01 \\ (0.998)$	$\begin{array}{c} (0.996) \\ 0.42 \pm 0.01 \\ (0.999) \end{array}$	(0.997) <sup>c</sup>

<sup>a</sup> Excluding *m*-CN. The σ values were taken from: Hansch, C.; Leo, A.; Taft, R. W. Chem. Rev. **1991**, 91, 165. <sup>b</sup> 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. <sup>c</sup> Correlation coefficients. <sup>d</sup> The  $\sigma$  and  $\sigma$ <sup>-</sup> values from the same source as footnote a.

reveals that the  $\rho_{XY}$  (and  $\beta_{XY}$ ) value is practically zero and the Ritchie  $N_+$ -type relationship holds for the present series of reactions, eq 2. We discuss the mechanistic implications of such relationships in the nucleophilic substitution reactions of *N*,*N*-disubstituted **1**–**3** carbamoyl chlorides.

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

$$\log(k_{XY}/k_{HH}) = \beta_X \Delta p K_X + \beta_Y \Delta p K_Y + \beta_{XY} \Delta p K_X \Delta p K_Y$$
(3b)

#### **Results and Discussion**

The pseudo-first-order rate constants observed  $(k_{obs})$ obeyed eq 4, for all the reactions with negligible  $k_0$  ( $\approx$ 0) in DMSO. The second-order rate constants for pyridinolysis,  $k_2$  (M<sup>-1</sup> s<sup>-1</sup>) summarized in Table 1, were obtained as the slopes of the plots of  $k_{obs}$  against pyridine concentrations, [Py], eq 4. No third-order or higher-order terms were detected, and no complications were found in the determination of  $k_{obs}$  or in the linear plots of eq 4.

$$k_{\rm obs} = k_0 + k_2 \,[\rm Py] \tag{4}$$

The rate is faster with a stronger nucleophile and with a stronger electron-withdrawing group in the substrate 3 as normally observed for a nucleophilic substitution reaction in which negative charge develops at the reaction center, carbonyl carbon, i.e.,  $\rho_{\rm Y} > 0$ , in the transition state (TS). The Brønsted  $\beta_X$  ( $\beta_{nuc}$ ) and Hammett  $\rho_X$  ( $\rho_{nuc}$ ) and  $\rho_{\rm Y}$  values are also shown in Table 1. The p*K*<sub>a</sub> values of pyridines used in the Brønsted plots were those determined in water. Thus, the Brønsted coefficients in Table 1 ( $\beta_{\rm X} \approx 0.42$ ) could be in error since the rate data in Table 1 (in DMSO) should be plotted using  $pK_a$  values measured in DMSO. However our recent theoretical studies of solvent effects on the basicity of substituted

pyridines at the IPCM/B3LYP/6-31 G\* level<sup>7</sup> have shown that there is a constant  $pK_a$  difference of  $\Delta pK_a$  =  $pK_a(MeCN) - pK_a(H_2O) = 7.7$  due mainly to the H<sup>+</sup> ion solvation free energy difference of 10.5 kcal mol<sup>-1</sup> between acetonitrile and water. The plot of  $pK_a(MeCN)$  vs  $pK_a(H_2O)$  exhibited a straight line of near unity (1.02) slope so that the Brønsted coefficients determined by the plot of log  $k_2$ (MeCN) against p $K_a$ (H<sub>2</sub>O) should be almost the same as those against  $pK_a$ (MeCN).

A similar invariance of Brønsted coefficient for the reactions of 4-nitrophenylsulfamate in chloroform with eight pyridines has been reported using  $pK_a(H_2O)$  and  $pK_a(CH_3CN)$  values with  $\beta = 0.31 \pm 0.02$  (r = 0.985) and  $\beta = 0.30 \pm 0.02$  (r = 0.994), respectively.<sup>8</sup> Moreover, the plots of p $K_a(\epsilon)$  (in five solvents including water) vs  $\sigma$  gave the slopes,  $\rho_{s}(\epsilon)$ , which is linear with Onsager dielectric function  $(\epsilon - 1)/(2\epsilon + 1)$ , eq 5, with correlation coefficient of 0.999 (n = 5).<sup>7</sup> This means that the specific

$$\rho_{\rm s} = 14.6 \left(\frac{\epsilon - 1}{2\epsilon + 1}\right) - 16.1\tag{5}$$

hydrogen bonding solvation component is not important in the solvation effect on the ionization equilibria of pyridinium ions in water. The slope,  $\rho_s$  , is thus solely dependent on the bulk solvent effect ( $\epsilon$ ) and for  $\epsilon = 78.3^9$ (water) and  $\epsilon = 37.9^9$  (acetonitrile) the  $\rho_s$  values are quite similar being -8.9 and -9.1, respectively. Since the  $\epsilon$ value for DMSO is 46.5,<sup>9</sup> the  $\rho_s$ , value of -9.0 is obtained in DMSO from eq 5. This indicates that the Brønsted coefficients determined by plotting  $\log k_2$  (DMSO) against  $pK_a$  (H<sub>2</sub>O) should be practically the same as those by plotting log  $k_2$  (DMSO) against p $K_a$  (DMSO). Spillane et

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**Figure 1.** Brønsted plots ( $\beta_X$ ) for the (X)-pyridinolysis of Y-substituted *N*-methyl-*N*-arylcarbamoyl chlorides (for Y = p-CH<sub>3</sub>O, H, p-Cl, and p-NO<sub>2</sub> in DMSO at 45 °C).

al.<sup>10</sup> reported that the Brønsted coefficients ( $\beta_X$ ) for the reaction of *N*-phenylsulfamoyl chlorides (YC<sub>6</sub>H<sub>4</sub>NHSO<sub>2</sub>-Cl) with anilines (XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>) in acetonitrile are similar when determined using p $K_a$  values of anilines measured in water ( $\beta_X = 0.685$ ) and in DMSO ( $\beta_X = 0.62$ ). This provides evidence in support of correlating the rate data determined in DMSO (and in MeCN) with the p $K_a$  values measured in water.

The excellent linearities found in the Brønsted plots using 10 nucleophlies ( $r \ge 0.998$ , standard deviation  $\le 0.01$ ) in Figure 1 lend further credence to our procedure. We therefore think that our  $\beta_X$  values in Table 1 represent reasonable and meaningful values. The Hammett plots for variation of substituent Y in the substrates showed better correlation with  $\sigma_p^-$  ( $\rho_Y^-$ )<sup>11</sup> rather than with the normal  $\sigma_p$  ( $\rho_Y$ ) constants. In the Hammett plots for substituent (X) changes in pyridines, a negative deviation was observed with X = m-CN (Figure 2) so that nine pyridines, excluding the *m*-CN, are used in the  $\rho_X$  determination.

A striking trend in the selectivity parameters,  $\rho_X$ ,  $\beta_X$ , and  $\rho_Y$  in Table 1, is that they are all constant, within the experimental errors, with changing reactivities of the reacting partners (electrophiles and nucleophiles)  $\rho_X =$  $-2.25 \pm 0.03$ ,  $\beta_X = 0.42 \pm 0.01$  and  $\rho_Y = 1.10 \pm 0.06$ . As a result, the cross-interaction constant,  $\rho_{XY}$  in eq 3a, becomes vanishingly small ( $\rho_{XY} \approx -0.02$  with r = 0.997and n = 36) and the rate constant represents a simple sum of the two substituent effects without the last term of eq 3a,<sup>6a-c</sup> eq 6a.

$$\log(k_{XY}/k_{\rm HH}) \simeq \rho_X \sigma_X + \rho_Y \sigma_Y \tag{6a}$$

This means naturally that the Ritchie  $N_+$  relationship, eq 1, holds since for a given substrate (i.e., for a given Y



**Figure 2.** Hammett plots ( $\rho_X$ ) for the pyridinolysis of Y-substituted *N*-methyl-*N*-arylcarbamoyl chlorides (for Y = p-CH<sub>3</sub>O, H, p-Cl, and p-NO<sub>2</sub> in DMSO at 45.0 °C).

 $(\sigma_{\rm Y})) \rho_{\rm Y} \sigma_{\rm Y}$  in eq 6 is a constant so that eq 6a can now be rearranged to eq 6b, which is the same form as eq 1. In the present reaction series, a similar relation also holds for log  $k_{\rm Y(X)}$ , since for a given X ( $\sigma_{\rm X}$ ) the rates are solely

$$\log k_{X(Y)} = \rho_X \sigma_X + (\log k_{HH} + \rho_Y \sigma_Y) = N_+ + \text{constant}$$
(6b)

dependent on Y ( $\sigma_{\rm Y}$ ) in eq 6a. This result is at variance with the results of McClelland et al.,<sup>12</sup> that there is a clear trend for  $\beta_{\rm X}$  ( $\beta_{\rm nuc}$ ) observed with primary amines to decrease with increasing triarylmethyl cation reactivity. For the  $\Delta\sigma_{\rm Y} \approx +1.5$  change they obtained  $\Delta\beta_{\rm nuc}$  ( $\Delta\beta_{\rm X}$ )  $\leq$ -0.15; i.e.,  $\beta_{\rm XY}$  is distinctly nonzero, which is in contrast to our value of  $\Delta\beta_{\rm X} \approx 0$ , i.e.,  $\beta_{\rm XY} \approx 0$  for the similar increase in  $\Delta\sigma_{\rm Y}$ ; for change in  $\sigma_{\rm Y}$  from Y = *p*-MeO to *p*-NO<sub>2</sub>, ( $\Delta\sigma_{\rm Y} = 1.27 - (-0.27) = 1.54$ ),  $\Delta\beta_{\rm X} \approx 0$  in Table 1. This shows that the present results obey the Ritchie  $N_+$  relationship better than their laser flash photolysis results in aqueous acetonitrile solution.

Originally, the  $N_+$  equation was introduced for addition of nucleophiles to the resonance-stabilized carbocations such as substituted triarylmethyl carbocations and the aryl tropylium ions.<sup>4</sup> In view of the relatively strong resonance stabilization of the *N*,*N*-disubstituted carbamoyl cations,<sup>1h,13</sup> Scheme 1, a possibility of such a mechanism, i.e., nucleophile (pyridine) addition to the resonance-stabilized acylium ion **5**, cannot be excluded. In fact, an S<sub>N</sub>1 mechanism has been proposed for the solvolysis of *N*,*N*-dimethyl **1** and *N*,*N*-diphenyl **2** carbamoyl chlorides in various aqueous solutions by many investigators in this field.<sup>1</sup> However it has been well established that there is a weak nucleophilic participa-

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<sup>(12)</sup> McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.;
Steenken, S. J. Am. Chem. Soc. 1992, 114, 1816.
(13) Li, H. G.; Kim, C. K.; Lee, B.-S.; Kim, C. K.; Rhee, S. K.; Lee,

<sup>(13)</sup> Li, H. G.; Kim, C. K.; Lee, B.-S.; Kim, C. K.; Rhee, S. K.; Lee, I. *J. Am. Chem. Soc.* **2001**, *123*, 2326. The acylium ion is known to be strongly stabilized by the electron-donating substituent theoretically.

Table 2. Second-Order Rate Constants,  $k_2$  (× 10<sup>4</sup> M<sup>-1</sup> s<sup>-1</sup>),<sup>*a*</sup> for the Reactions of Y-Substituted N-Methyl-N-arylcarbamoyl Chlorides and X-Pyridines in Dimethyl Sulfoxide at 45.0 °C with KCl (M) Added

	X = Y	0	0.0015	0.002	0.003	0.006	0.01	0.02	0.03	0.04
$k_2/10^{-4} \text{ M}^{-1} \text{ s}^{-1}$	<i>р</i> -СН <sub>3</sub> О Н	56.2 31.6	57.4 32.9	58.0 33.8	58.6 34.8	59.2 35.7	61.3 36.6	62.0 37.3	63.4 38.0	64.2 38.5

[KC]]/M

<sup>a</sup> Averages of three to five determinations.



tion by solvent toward a predominantly S<sub>N</sub>1 solvolysis.<sup>2</sup> Kevill and co-workers<sup>1h</sup> have shown that the solvolysis of **1** and **2** involves low values of l(0.2-0.3) as well as m (0.5-0.6) in eq 7, which was interpreted to support the  $S_N1$  mechanism in which positive charge is delocalized from the developing acylium ion to the adjacent nitrogen (which provides a substantial internal assistance) leading to a relatively low sensitivity to changes in solvent ionizing power. Their product analysis,1h however, showed

$$\log(k/k_0) = mY + lN + c \tag{7}$$

clearly that products are formed primarily by reaction of the carbocation with solvent at the solvent-separated ion-pair stage. These results also support the nucleophilic attack at the resonance-stabilzed carbocations.

We have investigated salt effects on the rate by adding KCl to the solution as shown in Table 2. The plot of  $k_2$  vs [KCl] in Figure 3 shows an initial rapid nonlinear rise of  $k_2$  which is quite similar to that observed in the special salt effect on solvolyses proceeding through solventseparated ion-pairs.<sup>14</sup> Such special salt effect is only associated with long-lived carbocations, and the initial rapid increase in  $k_2$  has been ascribed to the suppression of internal return of the solvent-separated ion-pair by the added salt.<sup>14</sup> In the present reaction, however, the added anion, Cl<sup>-</sup>, is the common ion and we think that the solvent-separated ion-pairs become stabilized and the internal return is suppressed by ion-triplet formation,  $Cl^{-}||R^{+}||Cl^{-}$ , where  $R^{+}$  is the carbamoyl cation. This is reasonable since ion-pair formation becomes much more stronger in aprotic solvents than in water and cations are stabilized by the solvent, DMSO, and also by the two counterions, Cl<sup>-</sup>. This type of ion-triplet formation in the  $S_{\rm N}1$  and  $S_{\rm N}2$  processes has been discussed in detail by Ritchie.<sup>15</sup> Khan<sup>16</sup> has observed a similar sharp initial rise in  $k_{obs}$  for the alkaline hydrolysis of N-hydroxyphthalimide (NHP) with addition of salts (NaCl, KCl etc.) in aqueous acetonitrile solution. He proposed the ion-pair formation mechanism in explaining the results: ion-pair



Dekker: New York, 1990; p 132.



**Figure 3.** Plot of  $k_2$  (×10<sup>4</sup> M<sup>-1</sup> s<sup>-1</sup>) vs [KCl] for X = Y = H: (A) suppression of internal return of solvent-separated ion pairs by the ion-triplet [Cl<sup>-</sup>||R<sup>+</sup>||Cl<sup>-</sup>] formation; (B) normal salt effect with  $b \approx 2.0$ .

complexes are formed between anionic substrate (NHP<sup>-</sup>) and cations of salts which are presumed to exist in solvent-separated loose ion-pair forms. The initial rise in  $k_{obs}$  was found to become steeper with the increase in the acetonitrile content of solvent mixture due to the increase in ion-pair complex formation. The rate-determining step has been shown to be the hydroxide ion attack at the carbonyl carbon of NHP-.

Addition of the relatively large amount of salt. [KCl] > 0.01 M, causes only a normal salt effect increase in  $k_2$ , showing that there is no appreciable trapping of a free carbocation by chloride ion. Thus the reaction seems to proceed through a solvent-separated ion-pair, not through a dissociated carbocation.<sup>14a</sup> Since the reaction is run in a poor ionizing solvent (DMSO;  $Y_{\text{OTS}} = -1.31^{17}$ ), the dissociation of ion-pairs to free carbocations become energetically unfavorable.<sup>15</sup> A relatively large increase in reaction rate due to normal salt effect is observed with  $b \approx 2$  in eq 8, since ionization is involved in less polar solvent, DMSO. For example in the ionization of 4methoxyneophyl tosylate in the presence of LiClO<sub>4</sub>, the constant *b* has been shown to increase with the decrease of solvent polarity;<sup>14b</sup> b values were 0.0 (DMSO), 1.4 (DMF), 47.0 (Me<sub>2</sub>CO), and 482 (THF).<sup>14b</sup>

$$\log k = \log k_0 + b[\text{KCl}] \tag{8}$$

Since the individual selectivities of the nucleophile and substrate,  $\rho_X$  ( $\beta_X$ ) and  $\rho_Y$ , are nonzero but there is no interaction between them,  $\rho_{XY} \approx$  0, such a mechanism, i.e., the nucleophilic attack on the resonance-stabilized

<sup>(16)</sup> Khan, M. N. J. Phys. Org. Chem. 1994, 7, 412

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carbocation, seems quite appealing for the present series of reactions, eq 9. The factors in favor of this proposed mechanism are: (i) Constant selectivities of nucleophile ( $\beta_{\rm X} = 0.42$  and  $\rho_{\rm X} = -2.25$ ) for variations of substituent Y is observed, i.e., the  $N_+$  type relation can be applied, which is known to hold primarily for the nucleophile addition to the strongly resonance-stabilized carbocations. (ii) The dipolar aprotic solvent used, DMSO, is known to stabilize cationic species specifically.<sup>18</sup> (iii) The magnitude of the  $\rho_X$  ( $\rho_{nuc}$ ) values ( $\approx$ -2.25) indicates that there is ca. one-third positive charge development on the pyridine nitrogen in the TS since the  $\rho$  value for the protonation of pyridinium ions is -5.90.<sup>19</sup> This means that there is considerable charge transfer in the TS, with substantial positive charge development on the pyridine nitrogen, as has been reported for the amine addition to the resonance-stabilized triarylmethyl carbocations.<sup>12</sup> (iv) A stronger electron donating substituent (Y) in the ring, e.g., Y = p-CH<sub>3</sub>O, reduces the addition rate (Table 1), i.e.,  $\rho_{\rm Y} > 0$ . If a limiting S<sub>N</sub>1 mechanism were to apply, bond cleavage should have progressed much ahead of bond formation in the TS, so that the converse should hold since an electron donor Y facilitates the bond cleavage ( $\rho_{\rm Y}$  < 0), as we normally find in the S<sub>N</sub>1 reactions. Similar magnitude of positive Hammett coefficients  $\rho_{\rm Y}$  ranging from  $\rho_{\rm Y} = +0.97$  (with CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-NH<sub>2</sub>) to  $\rho_{\rm Y} = +1.37$  (with CF<sub>3</sub>CH<sub>2</sub>NH<sub>2</sub>) has been observed for the primary amine additions to the substituted (Y, Y', Y''-T) triarylmethyl carbocations in aqueous acetonitrile solution at 20.0 °C.12 In this series of reactions the  $\rho_{\rm Y}$  values showed a small but definite trend of increase as the basicity of the amine decreased,  $\rho_{\rm Y} =$  $+0.97 \rightarrow +1.37$  for  $\Delta p K_X = -4.7$ ,<sup>12</sup> which is in contrast to the trend found not only in this work ( $\Delta \rho_{\rm Y} \approx 0$  for  $\Delta p K_{\rm X}$ = -5.2) but also in the original reactions from which Ritchie introduced the  $N_+$  equation. (v) If the present reaction series proceeded by an  $S_N 2$  mechanism, the positive  $\rho_{\rm Y}$  values in Table 1 indicate that negative charge development at the carbonyl carbon occurs as a result of a greater degree of bond-making than bond-breaking in the TS, which should lead to substantial interaction between the nucleophile and substrate in the  $S_N 2$  TS with  $\rho_{XY} = -0.6$  to -0.8, <sup>6a,b</sup> as we have normally observed. Thus, the near-zero value of  $\rho_{XY}$  precludes the S<sub>N</sub>2 mechanism for the present series of reactions. (vi) The Hammett plots for variation of substituent Y in the substrate showed better correlation with  $\sigma_{\rm p}^{-}$  ( $\rho_{\rm Y} > 0$ ) rather than with  $\sigma_p$  suggesting that there is through conjugation effect of the lone pair on the N toward the electron withdrawing Y substituents in the second step transition state which is absent in the cationic intermediate where the lone pair primarily delocalizes toward the carbonyl group. This type of through conjugation has been observed in the deprotonation equilibria of anilinium ions, which has led to the introduction of  $\sigma_{\rm p}^{-}$  constant with  $\rho_{\rm Y} > 0$ . (vii) The results of salt effects (Table 2) support the hypothesis that the reactions proceed via the solvent-separated ion-pairs. (viii) Finally, the activation parameters in Table 3 are in accord with the proposed mechanism. The  $\Delta H^{\ddagger}$  values are lower for both electronacceptor and donor Y with a given X. This is reasonable since an electron acceptor ( $\delta \sigma_{\rm Y} > 0$ ) facilitates the addition step ( $k_a$  in eq 9) whereas as an electron donor

Table 3. Activation Parameters<sup>a</sup> for the Reactions of Y-Substituted N-Methyl-N-arylcarbamoyl Chlorides with X-Pyridines in Dimethyl Sulfoxide

	5			<b>J</b>	
		Т	$k_2 (10^{-4})$	$\Delta H^{\sharp}$	$-\Delta S^{\ddagger}$
Х	Y	(°C)	$M^{-1} s^{-1}$ )	(kcal mol <sup>-1</sup> )	$(cal mol^{-1} K^{-1})$
p-CH <sub>3</sub>	p-CH <sub>3</sub> O	55	49.8	$7.1\pm0.3$	$48\pm2$
		45	33.9		
		35	23.0		
p-CH <sub>3</sub>	Н	55	125	$9.9\pm0.3$	$37\pm1$
		45	74.1		
		35	43.8		
Н	<i>p</i> -CH <sub>3</sub> CO	55	21.5	$5.6\pm0.2$	$54\pm2$
		45	15.8		
		35	11.6		
Н	Н	55	52.2	$9.4\pm0.3$	$41 \pm 1$
		45	31.6		
		35	19.2		
Н	p-NO <sub>2</sub>	55	1150	$8.7\pm0.4$	$37\pm1$
		45	724		
		35	455		
<i>m</i> -CN	Н	55	1.55	$10.9\pm0.4$	$43\pm2$
		45	0.871		
		35	0.489		
<i>m</i> -CN	p-NO <sub>2</sub>	55	24.2	$5.5\pm0.2$	$54\pm2$
		45	17.8		
		35	13.1		

 $^{a}\,\mathrm{Calculated}$  by the Eyring equation. Errors shown are standard deviations.

 $(\delta \sigma_{\rm Y} < 0)$  stabilizes the cationic form **3**<sup>+</sup>. The large negative entropies of activation,  $\Delta S^{\rm t}$ , are consistent with the rate-limiting addition of the two reacting species in the TS.



There is no general agreement on why nucleophile selectivities are constant with changing electrophile reactivity for reactions of strongly resonance-stabilized carbocations that follow the Ritchie  $N_+$  equation.<sup>4,5,12,20</sup> The following analysis is an attempt to provide some insights into this problem.

Since we have obtained practically constant  $\beta_X$  values,  $\delta\beta_X = 0$  (Table 1) with changing substrate ( $\delta p K_Y$ ), the cross-interaction constant  $\beta_{XY}$  is zero since  $\beta_{XY} = \partial\beta_X / \partial\Delta p K_Y$  from eq 3b. Thus our results in Table 1 indicate that  $\beta_{XY} \approx 0$ .

It has been shown that for families of nucleophiles (X), values of log  $K_X$  ( $-\Delta G_X^{\circ}/2.3RT$ ) are linearly related to  $pK_a$ 's of the conjugate acids of nucleophiles ( $\Delta G_{HX}^{\circ}/2.3RT$ ) with slopes not far from unity.<sup>4c</sup> Similar relations,  $\delta \Delta G_Y^{\circ} = \delta \Delta G_R^{\circ}$  where  $\Delta G_R^{\circ} = -2.3RT \log K_R$  for

$$\mathbf{R}^+ + \mathbf{H}_2\mathbf{O} \rightleftharpoons \mathbf{R}\mathbf{O}\mathbf{H} + \mathbf{H}^+$$

are also observed for the electrophiles (Y) in the carbocation addition reactions.<sup>4c</sup> Thus eqs 3 can be transformed into free energy forms (e.g., eq 10), and the definitions of  $\beta_{XY}$  can be given by eq 11<sup>21</sup> with 2.3*RT* = 1.36 kcal mol<sup>-1</sup> at 298 K.

$$\Delta G^* = \beta_X' \Delta G_X^\circ + \beta_Y' \Delta G_Y^\circ + \beta_{XY}' \Delta G_X^\circ \Delta G_Y^\circ \quad (10)$$

$$\beta_{XY}' = -\frac{\beta_{XY}}{1.36} = \frac{\partial^2 \Delta G^{\ddagger}}{\partial \Delta G_X^{\circ} \partial \Delta G_Y^{\circ}}$$
(11)

<sup>(18)</sup> Reference 9, Chapter 3.

<sup>(19)</sup> Page, M.; Williams, A. Organic and Bio-organic Mechanisms, Longman: Harlow, 1997; p 200.

On the other hand, the Marcus equation<sup>22</sup> can be represented in the free energy form as eq 12, where  $\Delta G^{\circ}$ comprises two component terms,  $\delta \Delta G^{\circ} = \delta \Delta G_{X}^{\circ} + \delta \Delta G_{Y}^{\circ}$ ; i.e., the changes in the thermodynamic driving force can be disected into the contributions of the two reactants, X and Y. Arnett et al., have shown that for the addition of resonance-stabilized carbocations and organic anions the free energy of reaction,  $\Delta G^{\circ}$ , can be expressed into such an additive form.23

$$\Delta G^{\ddagger} = \Delta G_0^{\ \ddagger} + \frac{1}{2} \Delta G^{\circ} + \frac{\Delta G^{\circ 2}}{16 \Delta G_0^{\ \ddagger}}$$
(12)

$$\frac{\partial^2 \Delta G^{\dagger}}{\partial \Delta G_{\rm X} \circ \partial \Delta G_{\rm Y} \circ} = \frac{1}{8 \Delta G_0^{\dagger}}$$
(13)

Partial second derivatives of  $\Delta G^{\dagger}$  in eq 12 with respect to  $\Delta G_X^{\circ}$  and  $\Delta G_Y^{\circ}$  give eq 13.<sup>5</sup> Equations 11 and 13 link the two relationships of eq 3 and 12 as eq 14, where *c* is a constant. This equation tells us that the cross-interaction constants,  $\beta_{XY}$  ( $\rho_{XY}$ ), are dependent only on the kinetic (intrinsic) barrier,  $\Delta G_0^{\dagger}$ , and independent of the thermodynamic driving force,  $\Delta G^{\circ}$ .

$$\beta_{\rm XY}(=c\rho_{\rm XY}) \simeq \frac{-1}{6\Delta G_0^{+}} \tag{14}$$

Our experimental results of  $\beta_{XY} \approx \rho_{XY} \approx 0$  lead us then to eq 15, which shows that the cross-interaction constant,  $\beta_{XY}$  (and  $\rho_{XY}$ ), is zero when the intrinsic barrier is high

$$\beta_{\rm XY} \simeq \frac{-1}{6\Delta G_0^{\,\pm}} \approx 0 \tag{15}$$

 $(\Delta G_0^* \approx \infty)^5$  for the intrinsic-barrier controlled reaction series. This is reasonable since for the reaction series with extremely high kinetic barrier, discrimination of reactivities between different reactants becomes almost impossible, i.e., the selectivity becomes insignificantly small,  $\rho_{XY} = 0$ . Thus a necessary condition for the valid N<sub>+</sub> relationship with negligibly small cross-interaction constant,  $\rho_{XY} \approx 0$ , is high intrinsic barriers,  $\Delta G_0^{\dagger} =$ large, in the intrinsic-barrier controlled reaction series. It is natural that if the  $N_{+}$  relationship holds the crossinteraction constant is zero and vice versa, since the nucleophile selectivities are constant,  $\delta \beta_{\rm X} = 0$  or  $\delta \rho_{\rm X} = 0$ with changing electrophiles reactivity  $\delta p K_Y$  or  $\delta \sigma_Y$ , when the  $N_+$  relationship holds so that  $\delta\beta_X/\delta pK_Y = \beta_{XY} = 0$  or  $\delta \rho_X / \delta \sigma_Y = \rho_{XY} = 0$ . It is, however, rather unexpected that the negligible cross-interaction is obtained when the intrinsic barrier is high,  $\Delta G_0^* =$ large.

There are therefore two cases where the cross-interaction becomes negligible,  $\rho_{XY} \approx$  0. (i) No interaction due to large distance  $(r_{XY} = \infty)$  involved between the two reactants.<sup>6a,b</sup> (ii) Indiscrimination due to large intrinsic barriers,  $\Delta G_0^{\ddagger} \approx \infty$ . However, these seemingly different cases may be simplified into a unified condition of (i) if we assume that the nucleophile additions to the resonancestabilized cation, or the reactions that follow strictly the  $N_{+}$  relationship, proceed by an electron-transfer (ET) mechanism.<sup>24</sup> In the electron-transfer reaction, the transfer of a single electron from D to A leads to D<sup>+</sup> and A<sup>-</sup>,  $(D^+ + A^-)$  but the two moieties are not linked by a covalent bond in contrast to the nucleophilic addition pathway in which there is a covalent bond  $(D^+-A^-)$ . Since in the ET process there is no covalent link in the TS, the cross-interaction between  $D^+$  and  $A^-$  should be negligible,  $ho_{XY} \approx$  0. It has been shown that any factor (in this case electronic due to high intrinsic barrier,  $\Delta E_0^{\dagger} =$  large) that inhibits or hinders the bond coupling process tends to favor the ET process.<sup>20a</sup> The proclivity of the substrate to undergo ET reactions should increase with availability of a high lying  $\pi^*$  LUMO. This requirement is certainly met with all the strongly resonance-stabilized carbocations including the N-methyl-N-arylcarbamoyl cations.<sup>24</sup> The higher the  $\pi^*$  LUMO, the larger is the interfrontier energy gap,  $\Delta \epsilon = \epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}} (= \epsilon_{\pi}^* - \epsilon_n)$  and hence the smaller is the charge transfer stabilization in the incipient bond formation in the TS, i.e., the higher is the kinetic (intrinsic) barrier. In such kinetically hindered charge-transfer stage, the ET process should be favored with an outer-sphere complex formation in which there is no bonding interaction ( $ho_{XY} \approx 0$ ).<sup>24a</sup>

### Conclusions

The nucleophilic substitution reactions of Y-substituted N-methyl-N-arylcarbamoyl chlorides (YC<sub>6</sub>H<sub>4</sub>N(CH<sub>3</sub>)COCl) with pyridines (XC<sub>5</sub>H<sub>4</sub>N) in DMSO show constant  $\rho_X$  (and  $\beta_{\rm X}$ ) with changing substrates ( $\delta \sigma_{\rm Y}$ ), and constant  $\rho_{\rm Y}$  with changing nucleophiles ( $\delta \sigma_X$ ). As a result, the crossinteraction constant  $\rho_{XY}$  (and  $\beta_{XY}$ ) is vanishingly small and the Ritchie  $N_+$  type equation holds. These and other results lead us to the nucleophile addition mechanism on the resonance-stabilized carbocations, 5. From the definition of cross-interaction constant,  $\rho_{XY}$  ( $\beta_{XY}$ ), and the Marcus equation, it can be shown that for such reactions with vanishing cross-interaction and valid  $N_{+}$  type relationship the high intrinsic barrier,  $\Delta G_0^{\dagger}$ , is a necessary condition,  $\beta_{XY} \simeq 1/(6\Delta G_0^{\dagger}) \approx 0$ . The electron-transfer (ET) reactions provide a possible type of process in which cross-interaction between the nucleophile and electrophile is insignificant despite the substantial charge transfer from the nucleophile to the electrophile.

## **Experimental Section**

Materials. International Specialty Chemical ACS grade dimethyl sulfoxide (DMSO) was used after two distillations. The pyridine nucleophiles, Aldrich GR, were used without further purification. The substrate, N-methyl-N-arylcarbamoyl chloride, was Aldrich GR purchased and was recrystallized before use. Y-Substituted N-methyl-N-arylcarbamoyl chlorides were prepared by reacting Y-substituted N-methyl-N-arylanilines with triphosgene followed by small amount of triethylamine in ethyl acetate. The product, *p*-methyl-*N*-methyl-*N*-arylcarbamoyl chloride, was obtained by column chromatography (silica gel, 30% ethyl acetate/n-hexane). The other products, para-substituted (Y) N-methyl-N-arylcarbamoyl chlorides, were purified by recrystallization from *n*-hexane. The substrates synthesized were confirmed by spectral and elemental analysis as follows.

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**p**-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>N(CH<sub>3</sub>)COCl: liquid;  $\delta_{\rm H}$  (CDCl<sub>3</sub>) 6.7−7.0 (C<sub>6</sub>H<sub>4</sub>, 4H, m), 3.8 (CH<sub>3</sub>O, 3H, s), 3.2 (CH<sub>3</sub>, 3H, s);  $\nu_{\rm max}$  (neat) 3040 (CH), 2850 (CH, aromatic), 1740 (C=O); *m*/*z* 199 (M<sup>+</sup>). Anal. Calcd for C<sub>9</sub>H<sub>10</sub>ClNO: C, 54.3; H, 5.0. Found: C, 54.3; H, 5.1. **p**-ClC<sub>6</sub>H<sub>4</sub>N(CH<sub>3</sub>)COCl: mp 68−70 °C;  $\delta_{\rm H}$  (CDCl<sub>3</sub>) 6.7−7.3

*p***-ClC<sub>6</sub>H<sub>4</sub>N(CH<sub>3</sub>)COCl:** mp 68–70 °C;  $\delta_{\rm H}$  (CDCl<sub>3</sub>) 6.7–7.3 (C<sub>6</sub>H<sub>4</sub>, 4H, m), 3.2 (CH<sub>3</sub>, 3H, s);  $\nu_{\rm max}$  (KBr) 3050 (CH), 2920 (CH, aromatic), 1740 (C=O); *m/z* 203 (M<sup>+</sup>). Anal. Calcd for C<sub>8</sub>H<sub>7</sub>Cl<sub>2</sub>NO: C, 47.3; H, 3.4. Found: C, 47.2; H, 3.5.

*p***-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>N(CH<sub>3</sub>)COCI:** mp 102–104 °C;  $\delta_{\rm H}$  (CDCl<sub>3</sub>) 6.8–7.6 (C<sub>6</sub>H<sub>4</sub>, 4H, m), 3.2 (CH<sub>3</sub>, 3H, s);  $\nu_{\rm max}$  (KBr) 3100 (CH), 2950 (CH, aromatic), 1740 (C=O); *m*/*z* 214 (M<sup>+</sup>). Anal. Calcd for C<sub>8</sub>H<sub>7</sub>ClN<sub>2</sub>O<sub>3</sub>: C, 44.9; H, 3.3. Found: C, 44.8; H, 3.2.

**Rate Constants.** Rates were measured conductometrically in dimethyl sulfoxide. 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 recorded data with a modified Origin program, which fits conductance vs time data to the equation  $\lambda = \lambda_{\infty} + (\lambda_0 - \lambda_{\infty})$ exp $(-k_{obs}t)$ , where  $\lambda_{\infty}$ ,  $\lambda_0 - \lambda_{\infty}$ , and  $k_{obs}$  are iteratively optimized to achieve the best possible least-squares fit with a large excess of pyridine (Py); [*N*-methyl-*N*-arylcarbamoyl chloride]  $\approx 1 \times 10^{-3}$  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  $\pm 3\%$ . **Product Analysis.** *N*-Methyl-*N*-arylcarbamoyl chloride (C<sub>6</sub>H<sub>5</sub>N(CH<sub>3</sub>)COCl) was reacted with an excess of *p*-methylpyridine (*p*-CH<sub>3</sub>C<sub>5</sub>H<sub>4</sub>N) with stirring for more than 15 half-lives at 45.0 °C in dimethyl sulfoxide, and the products were isolated by evaporating the solvent under reduced pressure. The product mixture was separated by column chromatography (silica gel, 15% ethyl acetate/*n*-hexane). The same method was used for the other product. Analysis of the products gave the following results.

**C**<sub>6</sub>**H**<sub>5</sub>**N**(**CH**<sub>3</sub>)**CONC**<sub>5</sub>**H**<sub>4</sub>**CH**<sub>3</sub>:  $\delta_{\rm H}$ , NMR (250 MHz, CDCl<sub>3</sub>), 8.0–8.8 (C<sub>5</sub>H<sub>4</sub>, 4H, m), 7.0–7.3 (C<sub>6</sub>H<sub>5</sub>, 5H, m), 3.2 (NCH<sub>3</sub>, 3H, s), 2.2 (CH<sub>3</sub>, 3H, s,); m/z 213 (M<sup>+</sup>). Anal. Calcd for C<sub>14</sub>H<sub>15</sub>NO: C, 91.8; H, 8.20. Found: C, 91.9; H, 8.19.

**NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>N(CH<sub>3</sub>)CONC<sub>5</sub>H<sub>4</sub>CH<sub>3</sub>:**  $\delta_{\rm H}$ , NMR (250 MHz, CDCl<sub>3</sub>), 8.0–8.8 (C<sub>5</sub>H<sub>4</sub>(pyridine), 4H, m), 7.0–7.3 (C<sub>6</sub>H<sub>4</sub>, 4H, m), 3.2 (NCH<sub>3</sub>, 3H, s), 2.2 (CH<sub>3</sub>, 3H, s); *m/z* 285 (M<sup>+</sup>); Anal. Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C, 80.4; H, 6.70. Found: C, 80.3, H, 6.71.

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