# Nucleophilic Substitution Reactions of Thiophenyl 4-Nitrobenzoates with Pyridines in Acetonitrile

Han Joong Koh,[†] Kwang Lae Han,[‡] and Ikchoon Lee*[,§]

*Department of Science Education, Chonju National University of Education, Chonju, 560-757, Korea, Department of Science Education, Kwangju National University of Education, Kwangju, 500-703, Korea, and Department of Chemistry, Inha University, Inchon, 402-751, Korea*

*Received January 21, 1999*

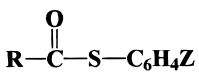
The kinetics of reactions between Z-thiophenyl 4-nitrobenzoates and X-pyridines in acetonitrile at 55.0 °C are investigated. The Brönsted plots obtained for the pyridinolysis of thiophenyl benzoates are curved, with the center of curvature at $pK_a \sim 4.2$ ($pK_a^0$). The Brönsted plots for these nucleophilic reactions show a change in slope from a large ($\beta_X \cong 0.64-0.72$) to a small ($\beta_X \cong 0.19-0.23$) value, 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 change of the cross-interaction constant $\rho_{XZ}$ from a large positive ($\rho_{XZ} = 1.41$) for the weakly basic pyridines to a small negative ($\rho_{XZ} = -0.32$) value for the strongly basic pyridines. The reactivity−selectivity principle (RSP) holds for the rate-limiting breakdown but fails for the formation of the intermediate. The aminolysis of thiophenyl benzoate with deuterated 4-chlorobenzylamine catalyzed by glymes has primary deuterium kinetic isotope effects (PKIEs), $k_{H(cat)}/k_{D(cat)} \cong 1.28-1.62$.

## Introduction

The aminolyses of acyl compounds have been the subject of numberous kinetic studies. Structure−reactivity correlations, especially Brönsted plots, have been used in these reactions as mechanistic criteria.[1−3] The Brönsted plots for these nucleophilic reactions show a change in slope from a large ($\beta_{nuc} \cong 0.8-1.0$) to a small ($\beta_{nuc} \cong 0.1-0.3$) value, 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 amine nucleophile increases.[2−5] The change in slope occurs at $pK_a^0$, where the leaving group and the nucleophile within the intermediate have the same leaving ability.

Although the mechanisms of the aminolyses of acetate[1] and benzoate esters,[6] and diaryl[7] and alkyl aryl carbonates,[2] are extensively investigated, much less is known about those concerning the thio derivatives of the above compounds.

There have been lately some reports on the aminolysis mechanisms of thiolacetates,[8] aryl *O*-ethyl thiolcarbonates,[4] and aryl thiobenzoates.[9] The results of these studies have revealed interesting trends: (i) The aminolyses of acetates (R = $CH_3$ in **I**) and *O*-ethyl carbonates



**I**

(R = $OC_2H_5$ in **I**) in aqueous solution invariably proceed

* Corresponding author. E-mail: ilee@dragon.inha.ac.kr.
[†] Chonju National University of Education.
[‡] Kwangju National University of Education.
[§] Inha University.

(1) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018.

(2) (a) Bond, P. M.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 679. (b) Castro, E. A.; Gil, F. J. *J. Am. Chem. Soc.* **1977**, *99*, 7611. (c) Castro, E. A.; Freudenberg, M. *J. Org. Chem.* **1980**, *45*, 906. (d) Castro, E. A.; Ibanez, F.; Lagos, S.; Schick, M.; Santos, J. G. *J. Org. Chem.* **1992**, *57*, 2691.

(3) (a) Bruice, T. C.; Hegarty, A. F.; Felton, S. M.; Donzel, A.; Kundu, N. G. *J. Am. Chem. Soc.* **1970**, *92*, 1370. (b) Butler, A. R.; Robertson, I. H. *J. Chem. Soc., Perkin Trans. 2* **1975**, 660. (c) Singh, T. D.; Taft, R. W. *J. Am. Chem. Soc.* **1975**, *97*, 3867. (d) Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 580. (e) Kovach, I. M.; Belz, M.; Larson, M.; Rousy, S.; Schowen, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 7360. (f) Fishbein, J. C.; Baum, H.; Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 5790. (g) Neuvonen, H. *J. Chem. Soc., Perkin Trans. 2* **1987**, 159.

(4) (a) Castro, E. A.; Ibanez, F.; Salas, M.; Santos, J. G. *J. Org. Chem.* **1991**, *56*, 4819. (b) Castro, E. A.; Salas, M.; Santos, J. G. *J. Org. Chem.* **1994**, *59*, 30. (c) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1994**, *59*, 3572.

(5) (a) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622. (b) Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5442. (c) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 68. (d) Castro, E. A.; Steinfort, G. B. *J. Chem. Soc., Perkin Trans. 2* **1983**, 453. (e) Palling, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869. (f) Castro, E. A.; Santander, C. L. *J. Org. Chem.* **1985**, *50*, 3595. (g) Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153. (h) Cabrera, M.; Castro, E. A.; Salas, M.; Santos, J. G.; Sepulveda, P. *J. Org. Chem.* **1991**, *56*, 5324. (i) Castro, E. A.; Ibanez, F.; Salas, M.; Santos, J. G.; Sepulveda, P. *J. Org. Chem.* **1993**, *58*, 459. (j) Castro, E. A.; Ibanez, F.; Santos, I. G.; Ureta, C. *J. Org. Chem.* **1993**, *58*, 4908. (k) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 3501. (l) Castro, E. A.; Pizarro, M. I.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 5982. (m) Castro, E. A.; Cubillos, M.; Santos, J. G.; Tellez, J. *J. Org. Chem.* **1997**, *62*, 2512. (n) Castro, E. A.; Araneda, C. A.; Santos, J. G. *J. Org. Chem.* **1997**, *62*, 126.

(6) (a) Koh, H. J.; Lee, H. C.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **1995**, *16*, 839. (b) Castro, E. A.; Valdivia, J. L. *J. Org. Chem.* **1986**, *51*, 1668.

(7) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963, 6970.

(8) (a) Um, I.-H.; Choi, K.-E.; Kwon, D.-S. *Bull. Korean Chem. Soc.* **1990**, *11*, 362. (b) Castro, E. A.; Ureta, C. *J. Chem. Soc., Perkin Trans. 2* **1991**, *63*.

(9) (a) Lee, I.; Shim, C. S.; Lee, H. W. *J. Chem. Res. Synop.* **1992**, 90. (b) Oh, H. K.; Shin, C. H.; Lee, I. *Bull. Korean Chem. Soc.* **1995**, *16*, 657. (c) Um, I.-H.; Kwon, H.-J.; Kwon, D.-S.; Park, J.-Y. *J. Chem. Res. Synop.* **1995**, 301. (d) Oh, H. K.; Shin, C. H.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1169.

10.1021/jo990115p CCC: $18.00 
Published on Web 06/03/1999

**Table 1. Rate Constants, $k_2$ ($\times 10^3$ $M^{-1}$ $s^{-1}$), for the Reactions of Z-Thiophenyl 4-Nitrobenzoates with X-Pyridines in Acetonitrile at 55.0 °C**

| X | p$K_a$[d] | 4-$CH_3$ 6.82 | H 6.50 | 4-Cl 5.90 | 4-Br 5.87 | $\rho_Z$[h] |
|---|---|---|---|---|---|---|
| 4-$CH_3O$ | 6.58 | 10.1 | 35.2 | 209 | 214 | 3.32 ± 0.03 |
| 4-$CH_3$ | 6.03 | 9.55 | 31.9 | 177 | 178 | 3.19 ± 0.04 |
| 3-$CH_3$ | 5.67 | 8.32 | 27.8 | 153 | 159 | 3.20 ± 0.03 |
| H | 5.21 | 5.33 | 18.0 | 99.0 | 106 | 3.22 ± 0.04 |
| 3-$CONH_2$ | 3.33[e] | 1.01 | 3.59 | 17.4 | 17.8 | 3.09 ± 0.04 |
| 3-$CH_3CO$ | (3.17)[f] | 0.741 | 2.34 | 14.8 | 15.5 | 3.32 ± 0.10 |
| 3-Cl | 2.81 | 0.398 | 1.27 | 7.41 | 7.94 | 3.24 ± 0.08 |
| 4-$CH_3CO$ | (2.38)[f] | 0.170 | 0.562 | 3.16 | 3.98 | 3.33 ± 0.14 |
| 4-CN | 1.86 | 0.0759 | 0.304 | 1.91 | 2.09 | 3.56 ± 0.03 |
| 3-CN | 1.35 | 0.0309 | 0.140 | 0.741 | 1.01 | 3.56 ± 0.03 |
| $\rho_X$[a] | | −0.43 ± 0.10 (0.973)[g] | −0.52 ± 0.05 (0.996) | −0.68 ± 0.03 (0.999) | −0.65 ± 0.09 (0.990) | $\rho_{XZ}$[i] = −0.32 |
| $\beta_X$[b] | | 0.19 ± 0.07 (0.896) | 0.21 ± 0.06 (0.928) | 0.23 ± 0.05 (0.956) | 0.23 ± 0.04 (0.974) | |
| $\rho_X$[c] | | −3.26 ± 0.54 (0.938) | −3.12 ± 0.47 (0.948) | −3.06 ± 0.51 (0.936) | −2.95 ± 0.44 (0.948) | $\rho_{XZ}$[i] = +1.41 |
| $\beta_X$[c] | | 0.72 ± 0.04 (0.933) | 0.70 ± 0.03 (0.996) | 0.69 ± 0.03 (0.996) | 0.64 ± 0.02 (0.998) | |

[a] X = 4-$CH_3O$, 4-$CH_3$, 3-$CH_3$, H. The $\sigma$ values were taken from Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. [b] X = 4-$CH_3O$, 4-$CH_3$, 3-$CH_3$, H. The $\beta_X$ values are converted to those in acetonitrile by eq 5. [c] X = 3-$CONH_2$, 3-$CH_3O$, 3-Cl, 4-$CH_3CO$, 4-CN, 3-CN. The $\beta_X$ values are converted to those in acetonitrile by eq 5. [d] p$K_a$ values of pyridines in water at 25.0 °C taken from ref 13, and thiophenols from *Dictionary of Organic Compounds*, 5th ed.; Chapman and Hall: New York, 1982. [e] Taken from Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, 1987; Table 8. [f] Calculated value using eq 4. [g] Correlation coefficients. [h] The source of $\sigma$ is the same as for footnote *a*. Correlation coefficients are better than 0.998 in all cases. [i] Correlation coefficient is better than 0.997. [j] Correlation coefficient is better than 0.951.

by a stepwise mechanism with rate-limiting expulsion of the leaving group with amines of p$K_a$ lower than p$K_a^0$, but there is only one exception of the concerted mechanism for the aminolysis of *O*-ethyl *S*-arylthiocarbonate (R = $OC_2H_5$ with Z = 2,4-$(NO_2)_2$ and 2,4,6-$(NO_2)_3$) with secondary alicyclic amines. Even for these reactions the stepwise mechanism was found to apply with pyridines. (ii) The Brönsted break points, p$K_a^0$, are lower for the reactions with pyridines than for those with secondary alicyclic amines (vide infra) under the same reaction conditions.

In the present work we carried out kinetic studies of the reactions of Z-thiophenyl 4-nitrobenzoates with X-pyridines in acetonitrile at 55.0 °C. We varied two substituents X and Z on the nucleophile and leaving group, respectively, eq 1. We have also studied the

$$XC_5H_4N + NO_2C_6H_4C(=O)\text{-}SC_6H_4Z \xrightarrow[55.0\ ^\circ C]{MeCN} XC_5H_4N^+\text{-}C(=O)H_4C_6NO_2 + {}^-SC_6H_4Z \quad (1)$$

X = 4-$CH_3O$, 4-$CH_3$, 3-$CH_3$, H, 3-$CONH_2$, 3-$CH_3CO$, 3-Cl, 4-$CH_3CO$, 4-CN or 3-CN

Z = 4-$CH_3$, H, 4-Cl or 4-Br

cat. = $CH_3O$ (O)$_{n-2}$ $OCH_3$

n = 3~8

aminolysis of thiophenyl 4-nitrobenzoate with glymes catalyst (cat.) in acetonitrile at 55.0 °C.

We have determined the cross-interaction constant, $\rho_{XZ}$ in eq 2,[10] where X and Z are substituents in the nucleophile and leaving group, respectively.

$$\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \quad (2)$$

In this work we aim to examine (i) the effects of the acyl group (R = 4-$NO_2$−$C_6H_4$) and solvent (acetonitrile) on the mechanism, and (ii) the necessary conditions regarding the sign of $\rho_{XZ}$ and adherence to the reactivity−selectivity principle (RSP)[10a,11] for the rate-limiting breakdown and formation of the tetrahedral intermediate, $T^{\pm}$. According to our proposal, the sign of $\rho_{XZ}$ should change from positive to negative[9d,10a,12] as the mechanism shifts from rate-limiting breakdown to formation of $T^{\pm}$, and the RSP should hold for rate-limiting breakdown processes.[10a,11c] In addition, we investigated the catalytic power of glymes in the aminolysis of thiophenyl 4-nitrobenzoates with a primary amine, 4-chlorobenzylamine, in acetonitrile.

## Results

The pseudo-first-order rate constants observed ($k_{obs}$) for all the reactions obeyed eq 3 with negligible $k_0$ ($\cong$0) in acetonitrile. The second-order rate constants, $k_2$ ($M^{-1}$ $s^{-1}$) summarized in Table 1, were determined using eq 3 with

$$k_{obs} = k_0 + k_2[Py] \quad (3)$$

at least five pyridine concentrations, [Py]. No third-order or higher-order terms were detected, and no complications were found in the determination of $k_{obs}$ and also in the linear plots of eq 3. This suggests that there is no base-catalysis or noticeable side reactions and the overall reaction follows the route given by eq 1. The rate is faster with a stronger nucleophile and a better nucleofuge as normally observed for a nucleophilic substitution reac-

(10) (a) Lee, I. *Adv. Phys. Org. Chem.* **1992**, *27*, 57. (b) Lee, I. *Chem. Soc. Rev.* **1994**, *24*, 223.

(11) (a) Pross, A. *Adv. Phys. Org. Chem.* **1977**, *14*, 69. (b) Buncel, E.; Wilson, H. *J. Chem. Educ.* **1987**, *64*, 475. (c) Lee, I.; Lee, B.-S.; Koh, H. J.; Chang, B. D. *Bull. Korean Chem. Soc.* **1995**, *16*, 277.

(12) (a) Lee, I. *Bull. Korean Chem. Soc.* **1994**, *15*, 985. (b) Lee, D.; Kim, C. K.; Lee, B.-S.; Lee, I. *Bull. Korean Chem. Soc.* **1995**, *16*, 1203. (c) Lee, I.; Koh, H. J. *New J. Chem.* **1996**, *20*, 131. (d) Koh, H. J.; Kim, T. H.; Lee, B.-S.; Lee, I. *J. Chem. Res. Synop.* **1996**, 482. (e) Oh, H. K.; Woo, S. Y.; Shin, C. H.; Park, Y. S.; Lee, I. *J. Org. Chem.* **1997**, *62*, 5780.

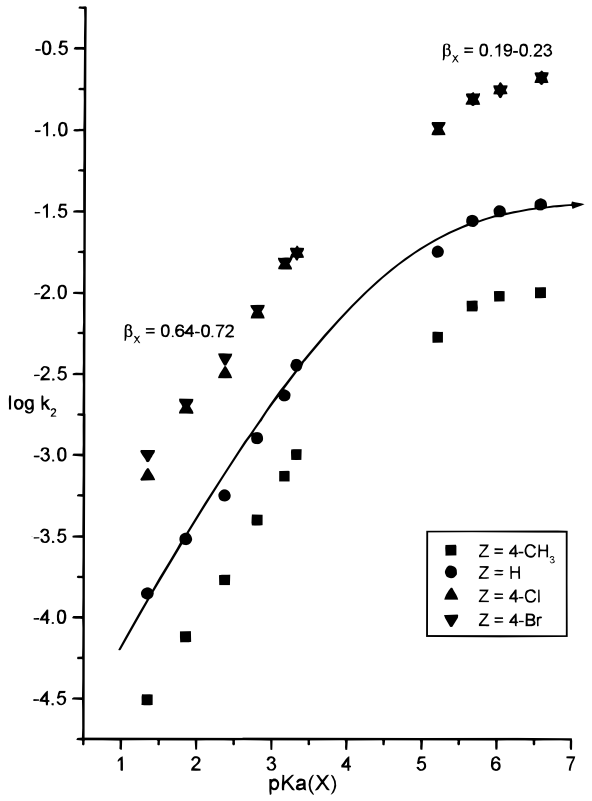



**Figure 1.** Bronsted plots ($\beta_x$) for the pyridinolysis of Z-thiophenyl 4-nitrobenzoates in MeCN at 55.0 °C.

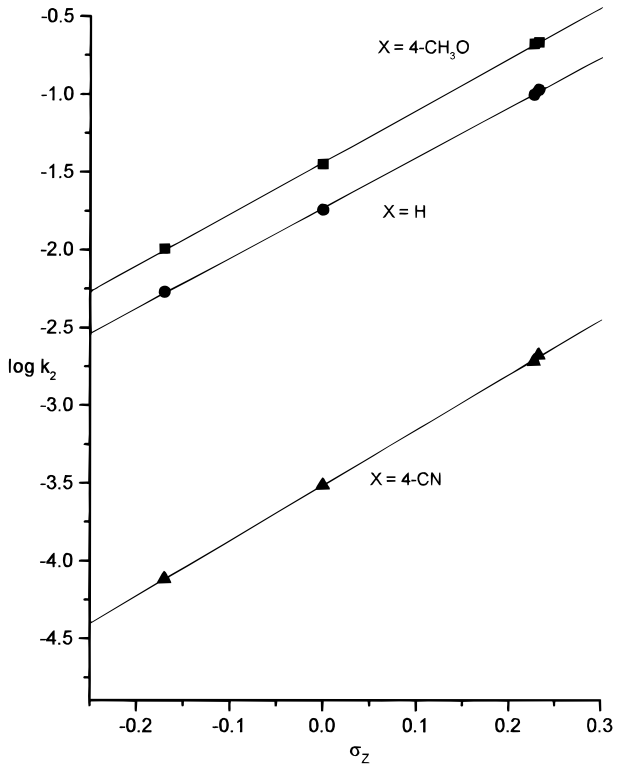



**Figure 2.** Hammett plots ($\sigma_z$) for the pyridinolysis of Z-thiophenyl 4-nitrobenzoates (for X = 4-$CH_3O$, H, and 4-CN) in MeCN at 55.0 °C.

tion. The Brönsted $\beta_X$ ($\beta_{nuc}$) (Figure 1) and Hammett $\rho_Z$($\rho_{lg}$) and $\rho_X$ ($\rho_{nuc}$) values (Figures 2 and 3) are also shown in Table 1. The p$K_a$ values of 4-$CH_3CO$ ($\sigma_{para}$ = 0.50, p$K_a$ = 2.38) and 3-$CH_3CO$ ($\sigma_{meta}$ = 0.38, p$K_a$ = 3.17)

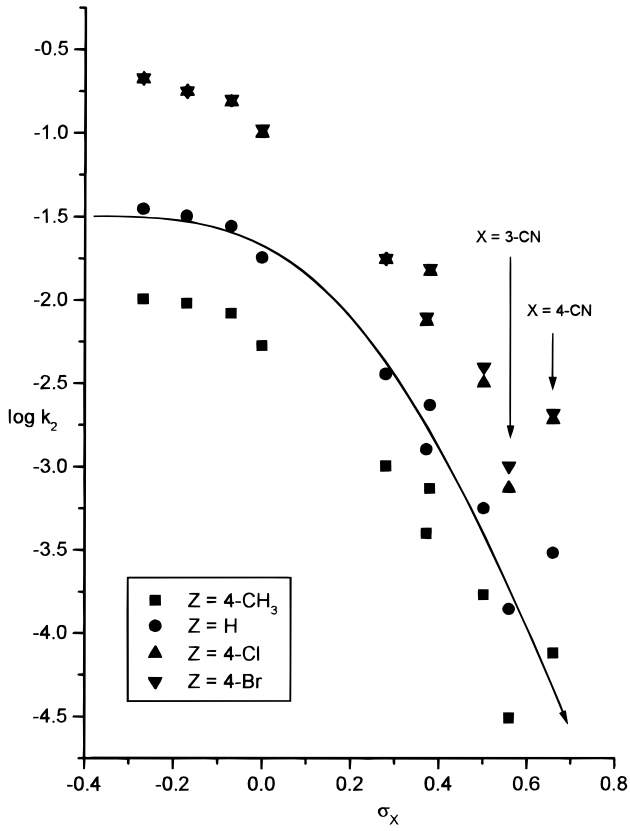



**Figure 3.** Hammett plots ($\rho_x$) for the pyridinolysis of Z-thiophenyl 4-nitrobenzoates in MeCN at 55.0 °C.

substituted pyridines were determined by extrapolation using $\sigma$ values in eq 4, which was obtained with 30 p$K_a$ values in water at 25.0 °C.[13]

$$pK_a = -5.73(\pm 0.12)\sigma + 5.16(\pm 0.05) \qquad (4)$$
$$r = 0.994, \quad n = 30$$

Structurally similar amines are known to have nearly the same $\Delta pK_a$ (=$pK_{a(MeCN)} - pK_a(H_2O)$) values.[14] The p$K_a$ values in water were used to correlate the $k_2$ values in acetonitrile, and the $\beta_X$ values were then converted to those in acetonitrile using a relationship given by eq 5.[14] The converted $\beta_X$ values are shown in Table 1.

$$pK_{a(acetonitrile)} = (1.23 \pm 0.03)pK_{a(water)} + (6.2 \pm 0.2) \qquad (5)$$

The activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (Table 2), were determined based on the $k_2$ values at three temperatures, 35.0, 45.0, and 55.0 °C. Table 3 lists rate constant ($k_{cat}$ in eq 6) for aminolysis (benzylamine) of the thiophenyl 4-nitrobenzoate catalyzed by open-chain polyethers (glymes). The pseudo-first-order catalyst rate constants observed, $k_{obs(cat)}$, for all the reactions obeyed eq 6 with negligible $k_0$ (=0) in acetonitrile. The catalyst rate constants, $k_{cat}$ ($M^{-2}$ $s^{-1}$) in eq 6, are summarized in Table 3. Deuterium kinetic isotope effects, $k_{H(cat)}/k_{D(cat)}$,

(13) Koh, H. J.; Han, K. L.; Lee, H. W.; Lee, I. *J. Org. Chem.* **1998**, *63*, 9834.

(14) (a) Foroughifar, N.; Leffek, K. T.; Lee, Y. G, *Can. J. Chem.* **1992**, *70*, 2856. (b) Spillane, W. J.; Hogan, G.; McGrath, P.; King, J.; Brack, C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2099. (c) Coetzee, J. F. *Prog. Phys. Org. Chem.* **1965**, *4*, 45.

**Table 2. Activation Parameters[a] for the Reactions of Z-Thiophenyl 4-Nitrobenzoates with X-Pyridines in Acetonitrile**

| X | Z | *T*/°C | $k_2$ ($\times 10^3$ $M^{-1}$ $s^{-1}$) | $\Delta H^{\ddagger}$ (kcal $mol^{-1}$) | $-\Delta S^{\ddagger}$ (cal $mol^{-1}$ $K^{-1}$) |
|---|---|---|---|---|---|
| 4-$CH_3O$ | 4-$CH_3$ | 55.0 | 10.1 | 7.5 ± 0.2 | 45 ± 1 |
| | | 45.0 | 6.73 | | |
| | | 35.0 | 4.49 | | |
| 4-$CH_3O$ | 4-Cl | 55.0 | 209 | 7.5 ± 0.2 | 39 ± 1 |
| | | 45.0 | 139 | | |
| | | 35.0 | 92.9 | | |
| 4-CN | 4-$CH_3$ | 55.0 | 0.0759 | 7.5 ± 0.3 | 55 ± 1 |
| | | 45.0 | 0.0506 | | |
| | | 35.0 | 0.0337 | | |
| 4-CN | 4-Cl | 55.0 | 1.91 | 7.6 ± 0.2 | 48 ± 1 |
| | | 45.0 | 1.24 | | |
| | | 35.0 | 0.843 | | |

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

**Table 3. Catalytic Power ($k_{cat}$) vs Oxygen Number Profile with Monoglyme through Hexaglyme for the Reactions of Thiophenyl 4-Nitrobenzoate with 4-Chlorobenzylamine Catalyzed by Glymes[a] in Acetonitrile at 55.0 °C**

| catalyst | oxygens | $k_{cat}$($\times 10^3$), $M^{-2}$ $s^{-1}$ | $k_{cat}$($\times 10^3$)/oxy, $M^{-2}$ $s^{-1}$ $oxy^{-1}$ |
|---|---|---|---|
| none | | $k_2 = 10.7 \times 10^{-3}$ ($M^{-1}$ $s^{-1}$) | |
| monoglyme | 2 | 2.69 | 1.35 |
| diglyme | 3 | 26.0 | 8.93 |
| triglyme | 4 | 47.4 | 11.9 |
| tetraglyme | 5 | 58.6 | 11.7 |
| pentaglyme | 6 | 70.6 | 11.7 |
| hexaglyme | 7 | 81.4 | 11.6 |

[a] Glymes = open-chain polyethers.

**Table 4. Deuterium Kinetic Isotope Effects ($k_{H(cat)}/k_{D(cat)}$) for the Reactions of Thiophenyl 4-Nitrobenzoate with Deuterated 4-Chlorobenzylamine (4-$ClC_6H_4CH_2ND_2$) Catalyzed by Glymes in Acetonitrile at 55.0 °C**

| catalyst | oxygens | $k_{H(cat)}$($\times 10^3$), $M^{-2}$ $s^{-1}$ | $k_{D(cat)}$($\times 10^3$), $M^{-2}$ $s^{-1}$ | $k_{H(cat)}/k_{D(cat)}$ |
|---|---|---|---|---|
| monoglyme | 2 | 2.69 ± 0.02[a] | 1.65 ± 0.04 | 1.62 ± 0.04 |
| diglyme | 3 | 26.0 ± 0.5 | 18.6 ± 0.3 | 1.40 ± 0.04 |
| triglyme | 4 | 47.4 ± 0.8 | 37.6 ± 0.5 | 1.26 ± 0.03 |
| tetraglyme | 5 | 58.6 ± 0.3 | 45.8 ± 0.5 | 1.28 ± 0.03 |
| pentaglyme | 6 | 70.6 ± 0.8 | 55.7 ± 0.9 | 1.28 ± 0.02 |
| hexaglyme | 7 | 81.4 ± 1.0 | 64.1 ± 1.1 | 1.27 ± 0.03 |

[a] Standard deviation.

involving deuterated benzylamine nucleophile with glymes are shown in Table 4.

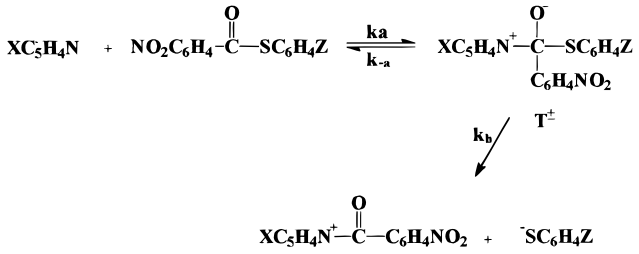
$$k_{obs(cat)} = k_0 + k_2'[BA] + k_{cat}[BA][cat] \qquad (6)$$

## Discussion

The pyridinolysis rates of carbonyl compounds with good leaving groups usually exhibit a biphasic dependence on pyridine basicity. This is also true for the pyridinolysis of thiophenyl 4-nitrobenzoates in acetonitrile.

Figure 1 shows the biphasic Brönsted plots obtained for the reactions. Application of the steady-state assumption to the tetrahedral intermediate (Scheme 1) yields $k_2 = k_a/[1 + (k_{-a}/k_b)]$, which becomes either $k_2 = k_a k_b/k_{-a}$ or $k_2 = k_a$ for the weakly basic ($k_{-a} \gg k_b$) or the strongly basic ($k_{-a} \ll k_b$) nucleophiles, respectively. Therefore, the curved Brönsted plots can be explained by a stepwise mechanism involving an intermediate in the reaction path with a change in the rate-determining step from its breakdown ($k_b$ step) to its formation ($k_a$ step) as the basicity of the nucleophile increases.[2,5c,9d]

**Scheme 1**




The curvature of the Brönsted plot is centered at p$K_a$ ~ 4.2 (p$K_a^0$), where the rate of breakdown of the tetrahedral intermediate to products equals that to reactants; that is, thiophenolate (p$K_a$ of corresponding thiophenol ~6.50) has the same leaving ability as a substituted pyridine of p$K_a$ = 4.2.

Brönsted plots are composed of two straight lines: one in the region of low basicities of the nucleophiles, with $\beta_X$ ($\beta_{nuc}$) ≅ 0.64−0.72, and the other at high basicities, with $\beta_X$ ($\beta_{nuc}$) ≅ 0.19−0.23. Nonlinear fits of the rate data ($k_2$) to a semiempirical Brönsted equation derived by Castro et al.[5n] were satisfactory with $\beta_1 = 0.2$, $\beta_2 = 0.7$, and p$K_a^0$ = 4.2 ($k_2^0 = 2.36 \times 10^{-3}$ for Z = H) in all cases (Z = p-$CH_3$, H, and p-Br). In all these reactions therefore a tetrahedral intermediate in the reaction path occurs, and the higher Brönsted slope should correspond to the rate-limiting decomposition of the intermediate to products, the $k_b$ step of Scheme 1.[2,4,5c,e]

The magnitude of these $\beta_X$ ($\beta_{nuc}$) values in acetonitrile are rather low compared to other similar reactions of stepwise acyl transfer with rate-limiting breakdown of the intermediate in aqueous solution listed in Table 5. We note that for the reactions proceeded by such a mechanism in water the $\beta_X$ values are in the range 0.8−0.9. The rather lower value of the observed $\beta_X$ (=0.6−0.7) in the present work is most probably due to the aprotic solvent, acetonitrile, used in this work. Similar lowering of the $\beta_X$ value was found for the pyridinolysis of methyl chloroformate, $\beta_X = 0.93$[5c] and 0.71[13] in aqueous solution and acetonitrile, respectively. The break point, p$K_a^0$ ≅ 4.2, also occurs at a rather low p$K_a$, being similar to the lowest value listed in Table 5 ($\beta_X = 4.9$, entry No. 6). The break points (p$K_a^0$) are in general lower for the pyridinolysis than for the aminolysis with secondary alicyclic amines. For the same amine and acyl group, the break point tends to occur successively at a lower p$K_a$ value as the leaving ability of the nucleofuge increases, from Z = H to 4-$NO_2$ and down to 2,4,6-$(NO_2)_3$. These trends seem to indicate that tertiary amines (pyridines) have a lower nucleofugality than isobasic secondary amines (alicyclic amines).[5m] Reference to Table 5 reveals that the ethoxy group in the intermediate, $T^{\pm}$, seems to act as an electron donor which destabilizes $T^{\pm}$[15] since for the same acyl (R) and leaving groups (Z) the p$K_a^0$ is higher for the ethoxy- than methyl-substituted substrate (compare the p$K_a^0$ values of entries 5 and 6 with those of entries 11 and 12), and with further destabilization by alicyclic amines (compared to pyridine) the $T^{\pm}$ becomes so unstable that it no longer exists, leading to a forced concerted process. This is reasonable since gas-phase

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

**Table 5. $pK_a^0$ and $\beta_X$ Values for the Aminolysis Reactions of Thiol Compounds, R−C(=O)−S−$C_6H_4Z$[a]**

| entry no. | R | Z | nucleophiles | $pK_a^0$ | $\beta_X$ | ref |
|---|---|---|---|---|---|---|
| 1 | $CH_3$ | H | alicyclic amines | >11 | 0.83 | 5g |
| 2 | $CH_3$ | 4-$NO_2$ | alicyclic amines | 10.5 | 0.86→0.10 | 5g |
| 3 | $CH_3$ | 2,4-$(NO_2)_2$ | alicyclic amines | 8.9 | 0.85→0.20 | 8b |
| 4 | $CH_3$ | 2,4,6-$(NO_2)_3$ | alicyclic amines | 7.8 | 0.80→0.20 | 8b |
| 5 | $CH_3$ | 2,4-$(NO_2)_2$ | pyridines | 6.6 | 0.82→0.2 | 8b |
| 6 | $CH_3$ | 2,4,6-$(NO_2)_3$ | pyridines | 4.9 | 0.80→0.2 | 8b |
| 7 | $OC_2H_5$ | 4-$NO_2$ | alicyclic amines | 10.7 | 0.8 | 4c |
| 8 | $OC_2H_5$ | 2,4-$(NO_2)_2$ | alicyclic amines | | 0.56 | 4b |
| 9 | $OC_2H_5$ | 2,4,6-$(NO_2)_3$ | alicyclic amines | | 0.48 | 4b |
| 10 | $OC_2H_5$ | 4-$NO_2$ | pyridines | ~10 | 0.8 | 5l |
| 11 | $OC_2H_5$ | 2,4-$(NO_2)_2$ | pyridines | 8.6 | 0.9 | 5l |
| 12 | $OC_2H_5$ | 2,4,6-$(NO_2)_3$ | pyridines | 7.3 | 0.8 | 5l |
| 13[b] | 4-$NO_2$−$C_6H_4$ | 4-$CH_3$, H, 4-Cl, 4-Br | pyridines | 5.0 | 0.6−0.7 | this work |

[a] In water. [b] In acetonitrile.

acidities of ROH have shown that[16] the EtO group ($\sigma_\alpha$ = −0.49) has a greater electron-releasing polarizability effect than MeO ($\sigma_\alpha$ = −0.35), which means a greater destabilization by the EtO group. By comparison 4-chlorophenyl and methyl groups should be much less electron donating than both EtO and MeO groups, so that they will stabilize the $T^\pm$ to an extent that can lead to an observable $pK_a^0$ for the aminolysis of thiophenyl 4-nitrobenzoate and acetate.[5l]

The Hammett plots (for the leaving group variation) are shown in Figure 2. The results in Table 1 reveal that the magnitude of $\rho_Z$ is quite large, which is again indicative of a stepwise mechanism with rate-limiting breakdown of the zwitterionic tetrahedral intermediate, $T^\pm$ (Scheme 1).[17]

Figure 3 shows the Hammett plots for variations of substituent in the nucleophile, $\sigma_X$. The $\rho_X$ values are determined for the two straight line portions: one for pyridines with electron-releasing substituents (X = 4-$CH_3O$, 4-$CH_3$, 3-$CH_3$, and H inclusive) and the other for pyridines substituted with electron-withdrawing groups (X = 3-$CONH_2$, 3-$CH_3CO$, 3-Cl, 4-$CH_3CO$, 4-CN, and 3-CN). For the former the reaction constants are $\rho_X$ = −0.43 to −0.65 and for the latter $\rho_X$ = −2.95 to −3.26, which are in agreement with lower and higher $\beta_X$ values for rate-limiting formation and breakdown of the intermediate.

We note that the strong $\pi$-acceptor para-substituent, 4-CN, exhibits strong positive deviation from the otherwise linear Hammett plots in the region of low basicities of the nucleophiles, Figure 3. This anomalous behavior of the strong para $\pi$-acceptor can be attributed to the weak $\pi$-donor effect of this para-acceptor substituent under the influence of positive charge[18] developed on N at the TS.

Since in the present work the para $\pi$-acceptor, 4-CN, behaved normally in the Brönsted plot (Figure 1) in the region of low basicities of the nucleophiles, but showed positive deviation in the Hammett plot (Figure 3), the reaction center N on pyridine must be an azonium ion type.[13,19]

Other strong support for the proposed mechanism comes from a large positive cross-interaction constant $\rho_{XZ}$ (=1.41) for the weakly basic ($k_{-a} \gg k_b$, Scheme 1) nucleophiles (X = 3-$CONH_2$, 3-$CH_3CO$, 3-Cl, 4-$CH_3CO$, 4-CN, and 3-CN); both the positive sign and the large magnitude of $\rho_{XZ}$ have been shown to be the necessary conditions for the rate-limiting breakdown of $T^\pm$. Since an electron acceptor in the nucleophile, $\delta\sigma_X > 0$ (in the nucleofuge, $\delta\sigma_Z > 0$), leads to an increase in $\rho_Z$, $\delta\rho_Z > 0$ ($\delta\rho_X > 0$), $\rho_{XZ}$ is positive, eq 2.[10,12a,d,17a−d]

However, at higher basicities ($k_{-a} \ll k_b$, Scheme 1) the $\rho_{XZ}$ has a small negative value ($\rho_{XZ}$ = −0.32). Therefore the cross-interaction constant $\rho_{XZ}$ for these acyl transfer reactions show a change from a large positive ($\rho_{XZ}$ = +1.41) to a small negative ($\rho_{XZ}$ = −0.32) value, 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.[9,12a,d,17a−d]

Another mechanistic criterion supports the proposed mechanism: For the stepwise acyl transfer with rate-limiting breakdown of the intermediate, the reactivity−selectivity principle (RSP) holds. We note that for the weakly basic pyridines (X = 3-$CONH_2$, 3-CN) the faster rate is always accompanied by the smaller selectivity ($\rho_X$, $\rho_Z$, and $\beta_X$); that is, the RSP holds, whereas for the strongly basic pyridines the RSP fails.

Activation parameters, $\Delta H^\ddagger$ and $\Delta S^\ddagger$, for the reactions of thiophenyl 4-nitrobenzoates with pyridines are shown in Table 2. The relatively low positive $\Delta H^\ddagger$ and slightly more negative $\Delta S^\ddagger$ values for X = 4-CN than for X = 4-$CH_3O$ are in line with the stepwise mechanism.[2c,12d,20]

In a recent study of aminolyses of various esters in aprotic solvents Su and Watson[21] reported that hydrogen bonding to the ammonium ion part of $T^\pm$ is more important than proton basicity for catalysis. The $k_{cat}$ vs oxygen per catalyst profile, Table 3, for the aminolysis of thiophenyl 4-nitrobenzoate in acetonitrile shows a

(16) (a) Hehre, W. J.; Pay, C.-F.; Headley, A. D.; Taft, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 1711. (b) Taft, R. W.; Koppel, I. A.; Topsom, R. D.; Anvia, F. *J. Am. Chem. Soc.* **1990**, *112*, 2047.

(17) (a) Oh, H. K.; Shin, C. H.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2411. (b) Koh, H. J.; Kim, S. I.; Lee, B. C.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1353. (c) Koh, H. J.; Lee, J.-W.; Lee, H. W.; Lee, I. *New J. Chem.* **1997**, *21*, 447. (d) Koh, H. J.; Lee, J.-W.; Lee, H. W.; Lee, I. *Can. J. Chem.* **1998**, *76*, 710. (e) Buncel, E.; Um, I. H. *J. Chem. Soc., Chem. Commun.* **1986**, 595. (f) Buncel, E.; Um, I. H.; Hoz, S. *J. Am. Chem. Soc.* **1989**, *111*, 791. (g) Um, I. H.; Yoon, H. W.; Lee, J. S.; Moon, H. J.; Kwon, D. S. *J. Org. Chem.* **1997**, *62*, 5939. (h) Menger, F. M.; Smith, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 3824.

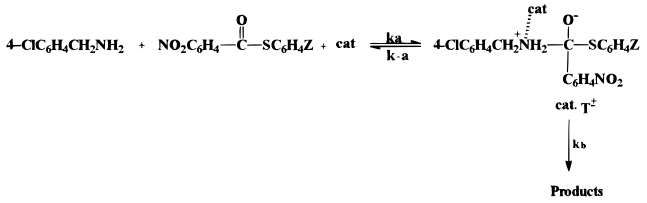
(18) (a) Dixon, D. A.; Charlier, P. A.; Gassman, P. G. *J. Am. Chem. Soc.* **1980**, *102*, 3957. (b) Paddon-Row: M. N.; Santiago, C.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6561. (c) Olah, G. A.; Arvanaghi, M.; Surya Prakash, G. K.; Surya Prakash, G. K.; Iyer, P. S.; Olah, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 1575.

(19) Hong, S. W.; Koh, H. J.; Lee, I. *J. Phys. Org. Chem.*, In press.

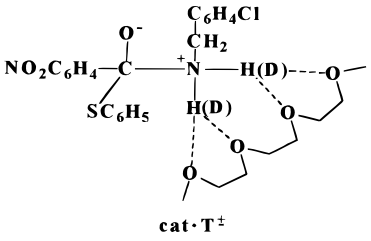
(20) (a) Neuvonen, H. *J. Chem. Soc., Perkin Trans. 2* **1995**, 951. (b) Koh, H. J.; Shin, C. H.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1329.

(21) Su, C.-W.; Watson, J. W. *J. Am. Chem. Soc.* **1974**, *96*, 1854.

**Scheme 2**




**Scheme 3**




distinct leveling effect at four oxygens. Catalysis increases as the number of oxygens increases, but glymes with four or more oxygens use only four oxygens to catalyze the aminolysis.

Glymes catalyze aminolysis of thiophenyl 4-nitrobenzoate in acetonitrile by binding to the ammonium ion part of $T^{\pm}$ formed by attack of benzylamine on the thioester, Scheme 2. The $-OCH_2CH_2OCH_2CH_2OCH_2CH_2O-$ subunit is optimal for this binding interaction, Scheme 3. The binding interaction should have an electron-donating effect to the $T^{\pm}$ and accelerates the breakdown of $T^{\pm}$ by weakening the bond to the benzoxy group, as evidenced by an increase in $\rho_Z$ reported with increasing catalysis.[22] The relationship between catalysis and subunit structure suggests that the ammonium ion part of the transition structure is recognized by the catalyst and that the rate-determining transition structure occurs after the formation of the intermediate $T^{\pm}$ since successive increase in the bulky glyme attachment to the amine will retard, not accelerate, the rate-limiting formation step.

Although the $pK_a$ value of 4-chlorobenzylamine (=9.01) is higher than the $pK_a^0$ (≅4.2) obtained for the pyridinolysis, the aminolysis proceeds by the rate-limiting breakdown of $T^{\pm}$. An obvious reason is due to the catalysis by glymes, which definitely stabilizes the tetrahedral intermediate, $T^{\pm}$. Another reason could be a higher $pK_a^0$ required for primary amines,[12c] as we noted higher $pK_a^0$ values for secondary alicyclic amines than for tertiary pyridines in Table 5. This is however in contrast to the aminolysis of aryl dithioacetates[9b,d,12e] and benzoates: These reactions were found to proceed by a stepwise mechanism with rate-limiting expulsion of thiophenoxide for weakly basic anilines ($pK_a < 5.34$) but by a concerted path for basic benzylamines ($pK_a > 9.01$). However, this could be due to a lower $pK_a^0$ for thionobenzoates than benzoates, as Castro et al.[5m] reported. For example the aminolysis of 4-nitrophenyl thionobenzoate and 4-nitrophenyl benzoate gave $pK_a^0$ values of 9.2 and >11, respectively. On the other hand, the $pK_a^0$ values are similar within experimental error for $^-$OPh and $^-$SPh leaving groups: for example, the $pK_a^0$ values for the aminolysis of EtO−C(=S)−O−$C_6H_3$-2,4-$(NO_2)_2$ and EtO−C(=S)−S−$C_6H_3$-2,4-$(NO_2)_2$ are 6.8 and 6.9 ± 0.1, respectively.[5m] These surveys show that in the present reaction series (thiolbenzoate) with carbonyl, −C(=O)−, the $pK_a^0$ can be higher than 9.01 ($pK_a$ for 4-chlorobenzylammonium acid), whereas with the thiono group, −C(=S)− (dithiobenzoates),[9b,d] the $pK_a^0$ is lower than 9.01.

Finally we have determined kinetic isotope effects involving deuterated 4-chlorobenzylamine. In our previous work of the aminolysis of thiophenyl benzoates in acetonitrile, which is believed to proceed by a stepwise mechanism with rate-limiting breakdown of $T^{\pm}$, the $k_H/k_D$ values with deuterated benzylamines were all near unity values[12c] (secondary deuterium kinetic isotope effects). However, the aminolysis of thiophenyl 4-nitrobenzoate in acetonitrile with glymes with deuterated 4-chlorobenzylamine has $k_{H(cat)}/k_{D(cat)}$ (= 1.28−1.62, Table 4) values much greater than the uncatalyzed reaction ($k_H/k_D$ = 1.01−1.03). As the number of oxygens per glyme increases from two to four, primary deuterium kinetic isotope effects (PKIEs) decrease from 1.62 to 1.26 (Table 4) and the RSP is adhered to as required for the stepwise mechanism proposed. The PKIEs observed are in line with the catalysis of glymes in acetonitrile by hydrogen bonding to the ammonium ion part of $T^{\pm}$, Scheme 3,[22] which is consistent with the stepwise mechanism with a rate-limiting breakdown of the tetrahedral intermediate, $T^{\pm}$.

In summary, the rates of the pyridinolysis of thiophenyl 4-nitrobenzoates in acetonitrile show a biphasic dependence on the basicity of the pyridine nucleophiles. The slope of the Brönsted plot changes from a large ($\beta_X = \beta_{nuc} \cong 0.64-0.72$) to a small ($\beta_X = 0.19-0.23$) value at $pK_a^0 \cong 4.2$ as the basicity of pyridine increases. This change is accompanied not only by a decrease in the magnitude of the Hammett coefficient from $\rho_X = \rho_{nuc} = -3.0$ to $-3.3$ to $\rho_X = -0.4$ to $-0.7$ but also by a change of the cross-interaction constant $\rho_{XZ}$ from a large *positive* (=1.41) to a small *negative* (=−0.32) value. These results are consistent with a change in the rate-determining step from breakdown to formation of a tetrahedral intermediate. This mechanistic change is also supported by a change from adherence to failure of the RSP as the basicity of the pyridine nucleophile increases. The aminolysis with 4-chlorobenzylamine catalyzed by glymes also proceeds by the same mechanism.

## Experimental Section

**Materials.** Merck GR acetonitrile was used after three distillations. The pyridine and benzylamine nucleophiles, Aldrich GR, were used without further purification. Preparation of deuterated 4-chlorobenzylamine was as described previously.[6a,7,12d] The analysis (NMR and GC−mass spectrometry) of the deuterated 4-chlorobenzylamine showed more than 99% deuterium content, so that no correction to deuterium kinetic isotope effects for incomplete deuteration was made. The thiophenyl 4-nitrobenzoates were prepared by a well-known method, reaction of Tokyo Kasei GR thiophenols with benzoyl chlorides.[23]

Monoglyme, diglyme, triglyme, and tetraglyme (Aldrich) were purified by simple distillation from metallic sodium. Hexaglyme (Parish) was purified in the same fashion. These purified polyethers all showed single spots by silica gel TLC (10% 2-propanol/*n*-hexane). The pentaglyme was prepared by a known method.[22]

**Kinetics.** Rates were measured conductometrically at 55.0 ± 0.05 °C. The conductivity bridge used in this work was a

(22) Hogan, J. C.; Gandour, R. D. *J. Org. Chem.* **1991**, *56*, 2821.

(23) Kirsch, J. F.; Clewell, W.; Simon, A. *J. Org. Chem.* **1968**, *33*, 127.

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 Origin program, which fits conductance vs time data to the equation $A = A_8 + (A_0 - A_8)\exp(-k_{obs}t)$, where $A_\infty$, $A_0 - A_8$, and $k_{obs}$ are iteratively optimized to achieve the best possible least-squares fit with a large excess of pyridine; [thiophenyl 4-nitrobenzoate] $\cong 1 \times 10^{-3}$ M and [Py] = 0.03−0.24 M. The reactions were followed to ≥90% completion. 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 3. The $k_2$ values in Table 1 are the averages of more than three runs and were reproducible to within ±3%.

**Catalysis Kinetics.** Reactions were carried out by weighing the polyether catalysts in conductance cell, pipetting 5 mL of 4-chlorobenzylamine/acetonitrile stock solution ([4-chlorobenzylamine] = 0.03−0.24 M) into the cell, injecting 50 μL of thiophenyl 4-nitrobenzoate/acetonitrile solution into the cell at 55.0 °C, stoppering the cell, shaking, and collecting conductance vs time data at fixed temperature. The resulting time−conductance data were stored on floppy diskette by computer. Pseudo-first-order catalyst rate constants were determined by the same method (pyridinolysis). Catalysis kinetics were run with eight different catalyst concentrations in eight sample cells of reacting solution. The runs were triplicated for each catalyst/ester combination studied. All samples in a simultaneous run were made from the same 4-chlorobenzylamine stock solution. Catalytic rate constants, $k_{cat}$, were determined by fitting $k_{obs(cat)}$ to eq 6. Values of $k_2$ were obtained from the slopes of plots of $k_{obs}$ vs [4-chlorobenzylamine] from noncatalytic experiments in which eight different 4-chlorobenzylamine concentrations were studied. Values of $k_{cat}$ for different polyether catalysts with a given substrate were obtained from the slopes of plots of $k_{obs(cat)}$/[4-chlorobenzylamine] vs [catalyst].

**Product Analysis.** 4-Bromothoiphenyl 4-nitrobenzoate ($NO_2C_6H_4C(=O)SC_6H_4Br$) was reacted with an excess of 4-acetylpyridine (4-$CH_3COC_5H_4N$) with stirring for more than 15 half-lives at 55.0 °C in acetonitrile, and the products were isolate by evaporating the solvent under reduced pressure. The product mixture was treated with column chromatography (silica gel, 20% ethyl acetate/*n*-hexane). Analysis of the product gave the following results.

$CH_3COC_5H_4N^+-C(=O)C_6H_4NO_2$: mp 164−166 °C; $\delta_H$, NMR (250 MHz, $CDCl_3$), 2.15(3H, s, $CH_3$), 7.16−7.50(8H, m, $C_5H_4N$, $C_6H_4$); $\nu_{max}$(KBr), 2900(CH, aromatic), 1760($CH_3CO$), 1700(C=O); mass, *m*/*z* 283($M^+$). Anal. Calcd for $C_{15}H_{11}N_2O_4$; C, 63.6; H, 3.89. Found: C, 63.5; H, 3.88.

**Acknowledgment.** We thank the Korea Science and Engineering Foundation and Inha University.

JO990115P