

# Kinetics and Mechanism of the Aminolysis of Thiophenyl Acetates in Acetonitrile

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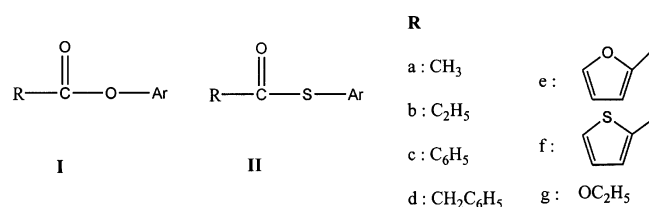
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Kinetics and mechanism of the aminolysis of Z-thiophenyl acetates with X-benzylamines are investigated in acetonitrile at 45.0 °C. The magnitudes of Brönsted coefficients  $\beta_X (=1.3\sim 1.6)$  and  $\beta_Z (= -2.1\sim -2.4)$  are all large and cross-interaction constant  $\rho_{XZ}$  is relatively large and positive (0.90). These trends are consistent with the rate-limiting breakdown of a tetrahedral intermediate,  $T^\ddagger$ . The proposed mechanism is also supported by adherence of the rate data to the reactivity-selectivity principle (RSP). The kinetic isotope effects,  $k_H/k_D$ , are greater than unity (1.3-1.4) suggesting a possibility of hydrogen-bonded four-centered transition state. The activation parameters,  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ , are consistent with this transition-state structure.

## Introduction

In contrast to extensive reports on the studies of aminolysis of oxyesters (**I**), there has been relatively little work published on the mechanism of the aminolysis of thiol esters (**II**). Our previous works on the aminolysis of thiol esters<sup>1</sup>



(for **II**b-g), with benzylamines (XC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>NH<sub>2</sub>) in acetonitrile have shown that all except **II**g proceed by rate-limiting breakdown of a tetrahedral intermediate,  $T^\ddagger$ , with large Brönsted  $\beta_X (= \beta_{nuc})$  values ranging from 1.3 to 2.1.<sup>1</sup> These large  $\beta_X$  values are considered to be a characteristic of the rate-limiting breakdown of a zwitterionic tetrahedral intermediate  $T^\ddagger$  which includes benzylammonium ion. For other aminolysis reactions with secondary and tertiary amines, the  $\beta_X$  values for the rate-limiting breakdown of  $T^\ddagger$  are smaller, in the range from 0.8 to 1.0.<sup>2</sup>

On the other hand, however, concerted processes are found only in the reactions of **II**g (O-ethyl S-aryl-thiocarbonates) with good leaving groups (Ar = PhZ with Z = 2,4-(NO<sub>2</sub>) and 2,4,6-(NO<sub>2</sub>)<sub>3</sub>) and alicyclic secondary amines ( $\beta_X = 0.4\text{--}0.6$ ). This concerted mechanism has been shown to be enforced by (i) instability incurred by the ArS group, (ii) stronger push provided by EtO which enhances the nucleofugality of both the amine and ArS<sup>-</sup> ion from the  $T^\ddagger$  intermediate relative to other R groups, (iii) much faster expulsion of a given amine and ArS<sup>-</sup> from  $T^\ddagger$  formed with **II** than those from  $T^\ddagger$  with any thionocarbonates (RC(=S)SAr), and (iv) greater push to expel ArS<sup>-</sup> from  $T^\ddagger$  provided by the primary (benzylamines) and secondary (alicyclic) amines than the tertiary amines (pyridines).

The mechanistic criteria for distinguishing between a stepwise with rate-limiting breakdown of  $T^\ddagger$  and a concerted

reaction are (i) larger  $\beta_X (\beta_{nuc})$  for the stepwise ( $> 0.8$ )<sup>2</sup> but smaller  $\beta_X$  for the concerted (0.4-0.6), (ii) larger negative  $\beta_Z^1$ , where Z is substituents in the leaving group (Ar = Ph<sup>2</sup> · Z) for the stepwise (-1.2~-1.8) but smaller  $\beta_Z (\beta_g)$  for the concerted ( $\beta_Z = -0.2\sim -0.5$ ), (iii) large positive cross-interaction constant  $\rho_{XZ}$  in Eq. (1) for the stepwise but small negative  $\rho_{XZ}$  for the concerted, and (iv) adherence to the reactivity-selectivity principle (RSP)<sup>5</sup> for the stepwise but failure of the RSP for the concerted reactions.<sup>4</sup> In Eq. (1),<sup>6</sup> X and Z represent substituents in the nucleophile (X) and leaving group (Z), respectively.

$$\log(k_{XZ}/k_{HH}) = \rho_X \sigma_X + \rho_Z \sigma_Z + \rho_{XZ} \sigma_X \sigma_Z \quad (1)$$

In this work, we investigated the mechanism of the aminolysis of thiophenyl acetates, **II** with R = CH<sub>3</sub> (**II**a), with benzylamines in acetonitrile at 45.0 °C. The objective of this work is to apply the mechanistic criteria listed above to predict the mechanism, especially to apply the criteria based on the sign and magnitude of  $\rho_{XZ}$  and to confirm that the aminolysis with benzylamines lead to much larger  $\beta_X$  values for a rate-limiting breakdown mechanism (*vide supra*) than that with other secondary amines and anilines.

## Results and Discussion

The aminolysis of thiophenyl acetates (**II**a) with a large excess of benzylamines in acetonitrile followed the simple kinetic rate law given by Eqs. (2) and (3), where P is thiophenolate anion and N represent benzylamine.

$$d[P]/dt = k_{obs}[\text{substrate}] \quad (2)$$

$$k_{obs} = k_N[N] \quad (3)$$

The  $k_N$  values were determined from the slope of the linear plot of  $k_{obs}$  against [N]. The  $k_N$  values are summarized in Table 1, where selectivity parameters, *i.e.*, the Hammett ( $\rho_X$  and  $\rho_Z$ ) and Brönsted ( $\beta_X$  and  $\beta_Z$ ), coefficients, are also shown. The reactions obeyed clean second-order kinetics, Eqs. (2) and (3), indicating that there are no complications arising from competition of the fast proton transfer from an

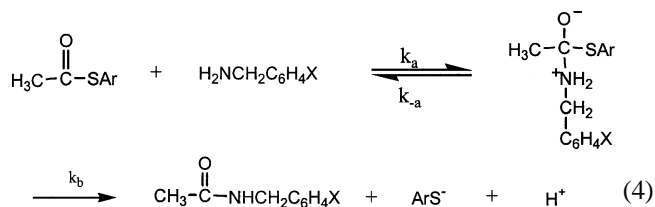
**Table 1.** The Second Order Rate Constants,  $k_N \times 10^3 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  for the Reactions of Z-Thiophenyl Acetates with X-Benzylamines in Acetonitrile at 45.0 °C

X	Z				$\rho_Z^a$	$\beta_Z^b$
	<i>p</i> -Me	H	<i>p</i> -Cl	<i>p</i> -Br		
<i>p</i> -OMe	1.65	10.2	149	169	5.00 ± 0.10	-2.10 ± 0.13
	1.21 <sup>c</sup>			125		
	0.877 <sup>d</sup>			91.4		
<i>p</i> -Me	1.07	6.82	114	131	5.20 ± 0.14	-2.18 ± 0.12
H	0.560	3.93	64.1	81.6	5.32 ± 0.15	-2.21 ± 0.16
<i>p</i> -Cl	0.249	1.88	34.5	36.6	5.42 ± 0.07	-2.30 ± 0.16
	0.175			25.6		
	0.123			17.8		
<i>m</i> -Cl	0.139	1.29	22.4	28.9	5.66 ± 0.12	-2.36 ± 0.24
$\rho_X^e$	-1.65 ± 0.03	-1.40 ± 0.05	-1.29 ± 0.03	-1.25 ± 0.07	$\rho_{XZ}^f = 0.90 \pm 0.19$	
$\beta_X^g$	1.64 ± 0.06	1.36 ± 0.03	1.30 ± 0.06	1.28 ± 0.08		

<sup>a</sup>The  $\sigma$  values were taken from J. A. Dean, *Handbook of organic Chemistry*, McGraw-Hill, New York, 1987, Table 7-1. Correlation coefficients were better than 0.999 in all cases. <sup>b</sup>The  $pK_a$  values were taken from ed., J. Buckingham, *Dictionary of Organic Chemistry*, Chapman and Hall, New York, 1982, 5th, ed. Z = *p*-Cl was excluded from the Brønsted plot for  $\beta_Z$  due to an unreliable  $pK_a$  values. Correlation coefficients were better than 0.995 in all cases. <sup>c</sup>At 35 °C. <sup>d</sup>At 25 °C. <sup>e</sup>The  $s$  values were taken from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420. Correlation coefficients were better than 0.996 in all cases. <sup>f</sup>Correlation coefficients was 0.999. <sup>g</sup>The  $pK_a$  values were taken from A. Fischer, W. J. Galloway and J. Vaughan, *J. Chem. Soc.*, 1964, 3588. Correlation coefficients were better than 0.996 in all cases. X = *p*-CH<sub>3</sub>O were excluded from the Brønsted plot for  $\beta_X$  (benzylamine) due to an unreliable  $pK_a$  value listed.

intermediate, T<sup>±</sup>, nor from general base catalysis by the benzylamine.

Since the reactions were conducted in acetonitrile, reliability of the magnitude  $\beta_X$  ( $\beta_{\text{nuc}}$ ) and  $\beta_Z$  ( $\beta_{\text{q}}$ ) determined using the  $pK_a$  values in water may be doubted. In this respect, we have recently shown that the  $\beta_X$  values determined by correlating the rate constants in acetonitrile with  $pK_a$  (H<sub>2</sub>O) are reliable in spite of the different solvent.<sup>4</sup> Our theoretical work<sup>7</sup> of the solvent effects on the basicities of pyridines has shown that although the absolute values of  $pK_a$  (CH<sub>3</sub>CN) differ from  $pK_a$  (H<sub>2</sub>O) a constant  $\Delta pK_a [= pK_a$  (CH<sub>3</sub>CN) -  $pK_a$  (H<sub>2</sub>O)]  $\cong 7.7$  was obtained. The theoretical  $\Delta pK_a = 7.7$  at the MP2/6-31G\*/MP2/6-31G\* level of theory is in excellent agreement with the experimental  $\Delta pK_a = 7.7 \pm 0.3$ .<sup>8</sup> The  $\Delta pK_a (\cong 7.7)$  value was found to arise solely from the ion solvation energy difference of H<sup>+</sup> ion in water and in acetonitrile,  $\Delta \Delta G_s^\circ(\text{H}^+) = 10.5 \text{ kcal mol}^{-1}$ , which corresponds to  $\Delta pK_a = 7.7$ .<sup>7</sup> Moreover, we are comparing the magnitude of  $\beta_X$  and  $\beta_Z$  values determined for the reactions carried out



under the same reaction condition, *i.e.*, in acetonitrile. The magnitude of  $\beta_X$  in Table 1 ( $\beta_X = 1.28$ -1.64) is again much larger than those for the corresponding reactions with anilines and other secondary and tertiary amines ( $\beta_X = 0.6$ -1.0)<sup>2</sup> but similar to those with benzylamines ( $\beta_X = 1.4$ -2.5).<sup>1</sup> All of these latter values are for the thiol ester (IIb-IIIc) aminolysis with benzylamines in acetonitrile which are predicted to proceed by rate-limiting breakdown of a zwitterionic

tetrahedral intermediate, T<sup>±</sup>. On this account, *i.e.*, large  $\beta_X$  values obtained, the aminolysis of thiophenyl acetate (IIa) with benzylamines in acetonitrile is most likely to occur by the rate-limiting expulsion of thiophenolate ion, RS<sup>-</sup>, from T<sup>±</sup>, Eq. (4), where the proton is consumed by the excess benzylamine present in the solution in a subsequent rapid step to form benzylammonium ion. The rate constant,  $k_N$  in Eq. (3), is therefore a complex quantity represented by Eq. (5).

$$k_N = \frac{k_a}{k_{-a}} \cdot k_b = K \cdot k_b \quad (5)$$

The magnitude of  $\beta_Z$  ( $\beta_{\text{q}}$ ) values ( $\beta_Z = -2.1$ ~-2.4) is also comparable to or greater than that for the similar reaction with rate-limiting expulsion of ArS<sup>-</sup> in acetonitrile ( $\beta_Z = -1.2$ ~-1.6).<sup>1</sup>

The proposed mechanism is also supported by a large positive cross-interaction constant ( $\rho_{XZ} = 0.90$ ) and adherence to the reactivity-selectivity principle (RSP), which are considered to constitute necessary conditions for the rate-limiting breakdown of T<sup>±</sup>.<sup>4,5c,5d</sup>

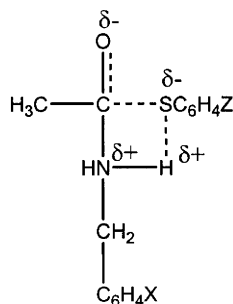
The kinetic isotope effects (Table 2) involving deuterated

**Table 2.** The Secondary Kinetic Isotope Effects for the Reactions of Z-Thiophenyl Acetates with Deuterated X-Benzylamines in Acetonitrile at 45.0 °C

X	Z	$k_H \times 10^3 (\text{M}^{-1} \text{s}^{-1})$	$k_D \times 10^3 (\text{M}^{-1} \text{s}^{-1})$	$k_H/k_D$
<i>p</i> -OMe	<i>p</i> -Me	1.65 (± 0.03)	1.24 (± 0.02)	1.33 ± 0.03 <sup>a</sup>
<i>p</i> -OMe	H	10.2 (± 0.1)	7.54 (± 0.05)	1.35 ± 0.02
<i>p</i> -OMe	<i>p</i> -Cl	149 (± 1)	108 (± 1)	1.38 ± 0.02
<i>p</i> -OMe	<i>p</i> -Br	169 (± 2)	122 (± 1)	1.39 ± 0.02
<i>p</i> -Cl	<i>p</i> -Me	0.249 (± 0.004)	0.200 (± 0.003)	1.25 ± 0.03
<i>p</i> -Cl	H	1.88 (± 0.03)	1.46 (± 0.02)	1.29 ± 0.03
<i>p</i> -Cl	<i>p</i> -Cl	34.5 (± 0.4)	26.4 (± 0.2)	1.31 ± 0.02
<i>p</i> -Cl	<i>p</i> -Br	36.6 (± 0.4)	27.3 (± 0.3)	1.34 ± 0.02

<sup>a</sup>Standard deviation

nucleophiles,  $\text{XC}_6\text{H}_4\text{CH}_2\text{ND}_2$ , are normal ( $k_{\text{H}}/k_{\text{D}} > 1.0$ ) suggesting a possibility of forming hydrogen-bonded four-center type TS<sup>6b</sup> as has often been proposed. Since no base catalysis was found (the rate law is first order with respect to [N], Eq. 3), the proton transfer occurs concurrently with the



Proposed TS

rate-limiting expulsion of  $\text{RS}^-$  in the TS but not catalyzed by benzylamine. The consumption of proton by the excess benzylamine should therefore take place in a subsequent rapid step. The low activation enthalpies,  $\Delta H^\ddagger$ , and highly negative activation entropies,  $\Delta S^\ddagger$ , are also in line with the proposed TS. The expulsion of  $\text{RS}^-$  anion in the rate determining step (an endoergic process) is assisted by the hydrogen-bonding with an amino hydrogen of the benzylammonium ion within the intermediate,  $\text{T}^\ddagger$ . This will lower the  $\Delta H^\ddagger$  value, but the TS becomes structured and rigid (low entropy process) which should lead to a large negative  $\Delta S^\ddagger$  value.

### Experimental Section

**Materials.** Merk GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used without further purification. Thiophenols and propionyl chloride were Tokyo Kasei GR grade. The thiophenylacetates were prepared by well-known method of the reactions of thiophenols with propionyl chloride.<sup>4a</sup>

**Kinetic Measurement.** Rates were measured conductometrically at  $45.0 \pm 0.05$  °C in acetonitrile. Pseudo-first-order rate constants,  $k_{\text{obs}}$ , were determined by the Guggenheim method<sup>11</sup> with large excess of benzylamine,  $[\text{substrate}] \cong 10^{-4}$  M,  $[\text{benzylamine}] = 1.5\text{--}10 \times 10^{-3}$  M<sup>-1</sup>. Second-order rate constants,  $k_{\text{N}}$ , were obtained from the slope of a plot of  $k_{\text{obs}}$  vs.  $[\text{benzylamine}]$  with more than four concentrations of

**Table 3.** Activation Parameters<sup>a</sup> for the Reactions of Z-Thiophenyl Acetates with X-benzylamines in Acetonitrile

X	Z	$\Delta H^\ddagger/\text{kcal mol}^{-1}$	$-\Delta S^\ddagger/\text{cal mol}^{-1}\text{K}^{-1}$
<i>p</i> -OMe	<i>p</i> -Me	$5.3 \pm 0.1$	$55 \pm 1$
<i>p</i> -OMe	<i>p</i> -Br	$5.2 \pm 0.1$	$46 \pm 1$
<i>p</i> -Cl	<i>p</i> -Me	$6.0 \pm 0.1$	$56 \pm 1$
<i>p</i> -Cl	<i>p</i> -Br	$6.2 \pm 0.1$	$46 \pm 1$

<sup>a</sup>Calculated by the Eyring equation. Errors shown are standard deviations.

benzylamine, Eq. (3). The  $k_2$  values in Table 1 are the averages of more than triplicate runs and were reproducible to within  $\pm 3\%$ .

**Product Analysis.** Substrate (0.05 mole) and *p*-methylbenzylamine (0.5 mole) were added to acetonitrile and reacted at 45.0 °C under the same condition as the kinetic measurements. After more than 15 half lives, solvent was removed under reduced pressure and product was separated by column chromatography (silica gel, 20% ethylacetate-n-hexane). Analysis of the product gave the following results.

$\text{CH}_3\text{C}(=\text{O})\text{NHCH}_2\text{C}_6\text{H}_4\text{-CH}_3$ ; mp 123-225; IR (KBr), 3300 (N-H), 2985 (C-H,  $\text{CH}_2$ ), 2943 (C-H,  $\text{CH}_3$ ), 1662 (C=O), 1460 (C=C, aromatic); <sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ ), 2.53 (3H, s,  $\text{CH}_3$ ), 3.75 (3H, s,  $\text{CH}_2$ ), 4.15 (1H, br, N-H), 5.86 (2H, d,  $J = 5.86$  Hz,  $\text{CH}_2$ ), 6.98-7.43 (4H, m, aromatic ring); <sup>13</sup>C NMR (100.4 MHz,  $\text{CDCl}_3$ ), 197.8 (C=O), 137.05, 136.20, 129.45, 128.05, 55.42, 22.43, 21.05.

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