

Kinetics and Mechanism of the Aminolysis of Thiophenyl Acetates in Acetonitrile

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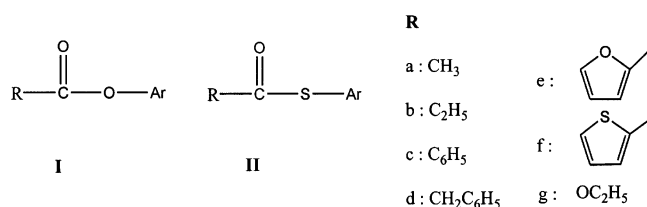
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Kinetics and mechanism of the aminolysis of Z-thiophenyl acetates with X-benzylamines are investigated in acetonitrile at 45.0 °C. The magnitudes of Brønsted coefficients β_X (-1.3~-1.6) and β_Z (-2.1~-2.4) are all large and cross-interaction constant ρ_{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, ΔH^\ddagger and ΔS^\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 esters¹



(for **IIb-g**), with benzylamines (XC₆H₄CH₂NH₂) in acetonitrile have shown that all except **IIg** proceed by rate-limiting breakdown of a tetrahedral intermediate, T^\ddagger , with large Brønsted β_X ($-\beta_{\text{mic}}$) values ranging from 1.3 to 2.1.¹ These large β_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 β_X values for the rate-limiting breakdown of T^\ddagger are smaller, in the range from 0.8 to 1.0.²

On the other hand, however, concerted processes are found only in the reactions of **IIg** (O-ethyl S-aryl-thiocarbonates) with good leaving groups (Ar = PhZ with Z = 2,4-(NO₂) and 2,4,6-(NO₂)₃) and alicyclic secondary amines (β_X = 0.4-0.6). 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⁻ ion from the T^\ddagger intermediate relative to other R groups, (iii) much faster expulsion of a given amine and ArS⁻ from T^\ddagger formed with **II** than those from T^\ddagger with any thionocarbonates (RC(-S)SAr), and (iv) greater push to expel ArS⁻ 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 β_X (β_{mic}) for the stepwise (> 0.8)² but smaller β_X for the concerted (0.4-0.6), (ii) larger negative β_Z^1 , where Z is substituents in the leaving group (Ar = Ph² · Z) for the stepwise (-1.2~-1.8) but smaller β_Z (β_g) for the concerted (β_Z = -0.2~-0.5), (iii) large positive cross-interaction constant ρ_{XZ} in Eq. (1) for the stepwise but small negative ρ_{XZ} for the concerted, and (iv) adherence to the reactivity-selectivity principle (RSP)⁵ for the stepwise but failure of the RSP for the concerted reactions.⁴ In Eq. (1),⁶ X and Z represent substituents in the nucleophile (X) and leaving group (Z), respectively.

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

In this work, we investigated the mechanism of the aminolysis of thiophenyl acetates, **II** with R = CH₃ (**IIa**), 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 ρ_{XZ} and to confirm that the aminolysis with benzylamines lead to much larger β_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 (**IIa**) 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.

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

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

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 I, where selectivity parameters, *i.e.*, the Hammett (ρ_X and ρ_Z) and Brønsted (β_X and β_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				ρ_X^a	β_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 ^c			125		
	0.877 ^d			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
ρ_X^e	-1.65 ± 0.03	-1.40 ± 0.05	-1.29 ± 0.03	-1.25 ± 0.07	ρ_{XZ}^f	0.90 ± 0.19
β_X^g	1.64 ± 0.06	1.36 ± 0.03	1.30 ± 0.06	1.28 ± 0.08		

^aThe σ 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. ^bThe $\text{p}K_a$ 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 Brönsted plot for β_Z due to an unreliable $\text{p}K_a$ values. Correlation coefficients were better than 0.995 in all cases. ^cAt 35 °C. ^dAt 25 °C. ^eThe σ 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. ^fCorrelation coefficients was 0.999. ^gThe $\text{p}K_a$ 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*-ClH₃O were excluded from the Brönsted plot for β_X (benzylamine) due to an unreliable $\text{p}K_a$ value listed.

intermediate, T¹, nor from general base catalysis by the benzylamine.

Since the reactions were conducted in acetonitrile, reliability of the magnitude β_X (β_{Nuc}) and β_Z (β_{Eq}) determined using the $\text{p}K_a$ values in water may be doubted. In this respect, we have recently shown that the β_X values determined by correlating the rate constants in acetonitrile with $\text{p}K_a$ (H₂O) are reliable in spite of the different solvent.⁴ Our theoretical work⁷ of the solvent effects on the basicities of pyridines has shown that although the absolute values of $\text{p}K_a$ (CH₃CN) differ from $\text{p}K_a$ (H₂O) a constant $\Delta\text{p}K_a [-\text{p}K_a(\text{CH}_3\text{CN}) - \text{p}K_a(\text{H}_2\text{O})] \cong 7.7$ was obtained. The theoretical $\Delta\text{p}K_a \cong 7.7$ at the MP2/6-31G*/MP2/6-31G* level of theory is in excellent agreement with the experimental $\Delta\text{p}K_a \cong 7.7 \pm 0.3$.⁸ The $\Delta\text{p}K_a (\cong 7.7)$ value was found to arise solely from the ion solvation energy difference of H⁺ ion in water and in acetonitrile, $\Delta\Delta G_s^\circ(\text{H}^+) = 10.5 \text{ kcal mol}^{-1}$, which corresponds to $\Delta\text{p}K_a \cong 7.7$.⁷ Moreover, we are comparing the magnitude of β_X and β_Z values determined for the reactions carried out

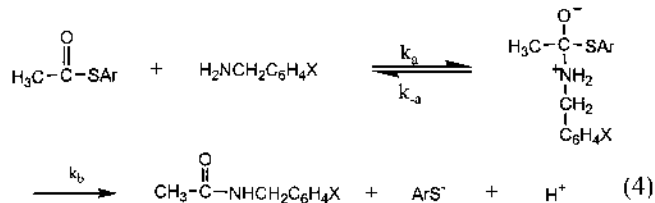
tetrahedral intermediate, T¹. On this account, *i.e.*, large β_X values obtained, the aminolysis of thiophenyl acetate (IIa) with benzylamines in acetonitrile is most likely to occur by the rate-limiting expulsion of thiophenolate ion, RS⁻, from T¹, Eq. (4), where the proton is consumed by the excess 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).

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

The magnitude of β_Z (β_{Eq}) values ($\beta_Z \cong -2.1 \sim -2.4$) is also comparable to or greater than that for the similar reaction with rate-limiting expulsion of ArS⁻ in acetonitrile ($\beta_Z \cong -1.2 \sim -1.6$).¹

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 T¹.^{4,5c,5d}

The kinetic isotope effects (Table 2) involving deuterated



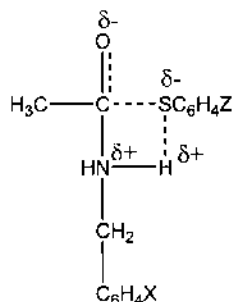
under the same reaction condition, *i.e.*, in acetonitrile. The magnitude of β_X in Table 1 ($\beta_X \cong 1.28-1.64$) is again much larger than those for the corresponding reactions with anilines and other secondary and tertiary amines ($\beta_X \cong 0.6-1.0$)³ but similar to those with benzylamines ($\beta_X \cong 1.4-2.5$).¹ All of these latter values are for the thiol ester (IIb-III) aminolysis with benzylamines in acetonitrile which are predicted to proceed by rate-limiting breakdown of a zwitterionic

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 ^a
<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

^aStandard deviation

nucleophiles, $\text{XC}_6\text{H}_4\text{CH}_2\text{ND}_2$, are normal ($k_H/k_D > 1.0$) suggesting a possibility of forming hydrogen-bonded four-center type TS^{6b} 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 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, ΔH^\ddagger , and highly negative activation entropies, ΔS^\ddagger , are also in line with the proposed TS. The expulsion of 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, T^1 . This will lower the ΔH^\ddagger value, but the TS becomes structured and rigid (low entropy process) which should lead to a large negative ΔS^\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.^{4a}

Kinetic Measurement. Rates were measured conductometrically at 45.0 ± 0.05 °C in acetonitrile. Pseudo-first-order rate constants, k_{obs} , were determined by the Guggenheim method¹¹ with large excess of benzylamine, $[\text{substrate}] \equiv 10^{-4}$ M, $[\text{benzylamine}] = 1.5 \cdot 10^{-3}$ M⁻¹. Second-order rate constants, k_N , were obtained from the slope of a plot of k_{obs} vs. $[\text{benzylamine}]$ with more than four concentrations of

Table 3. Activation Parameters^a 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 ± 0.1	55 ± 1
<i>p</i> -OMe	<i>p</i> -Br	5.2 ± 0.1	46 ± 1
<i>p</i> -Cl	<i>p</i> -Me	6.0 ± 0.1	56 ± 1
<i>p</i> -Cl	<i>p</i> -Br	6.2 ± 0.1	46 ± 1

^aCalculated 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 +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.

$\text{CH}_3\text{C(=O)NHCH}_2\text{C}_6\text{H}_4\text{-CH}_3$: mp 123-225; IR (KBr), 3300 (N-H), 2985 (C-H, CH_2), 2943 (C-H, CH_3), 1662 (C=O), 1460 (C-C, aromatic); ¹H NMR (400 MHz, CDCl_3), 2.53 (3H, s, CH_3), 3.75 (3H, s, CH_2), 4.15 (1H, br, N-H), 5.86 (2H, d, $J = 5.86$ Hz, CH_2), 6.98-7.43 (4H, m, aromatic ring); ¹³C NMR (100.4 MHz, CDCl_3), 197.8 (C=O), 137.05, 136.20, 129.45, 128.05, 55.42, 22.43, 21.05.

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