

Table 1. The Second Order Rate Constants, $k_2 \times 10^3 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for the Reactions of Z-Thiophenyl Cyclopentanecarboxylates with X-Benzylamines in Acetonitrile at 40.0°C

X	Z				ρ_Z^a	β_Z^b
	<i>p</i> -Me	H	<i>p</i> -Cl	<i>p</i> -Br		
<i>p</i> -OMe	7.98 ± 0.15	23.0 ± 0.5	113 ± 3	135 ± 4	3.01 ± 0.12	-1.24 ± 0.07
	5.58 ± 0.12^c			95.8 ± 1.5^c		
	3.84 ± 0.08^d			67.1 ± 0.8^d		
<i>p</i> -Me	4.87 ± 0.08	16.3 ± 0.2	79.2 ± 1.2	99.8 ± 1.8	3.17 ± 0.13	-1.29 ± 0.13
H	1.92 ± 0.05	7.14 ± 0.08	41.0 ± 0.3	53.7 ± 0.6	3.49 ± 0.15	-1.42 ± 0.13
<i>p</i> -Cl	0.620 ± 0.005	2.61 ± 0.05	19.6 ± 0.2	26.0 ± 0.4	3.94 ± 0.17	-1.61 ± 0.12
	0.427 ± 0.003^c			18.4 ± 0.2^c		
	0.303 ± 0.002^d			12.6 ± 0.1^d		
<i>m</i> -Cl	0.300 ± 0.002	1.34 ± 0.03	10.7 ± 0.1	14.4 ± 0.2	4.07 ± 0.17	-1.66 ± 0.13
ρ_X^a	-2.23 ± 0.02	-1.95 ± 0.03	-1.58 ± 0.03	-1.51 ± 0.03	$\rho_{XZ}^e =$	1.72 ± 0.04
β_X^f	2.25 ± 0.04	1.97 ± 0.05	1.59 ± 0.05	1.52 ± 0.05		

^a The σ values were taken from Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 166. Correlation coefficients were better than 0.998 in all cases.

^b The pKa values were taken from ed., Buckingham, J. *Dictionary of Organic Chemistry*, Chapman and Hall, New York, 1982, 5th, ed. Z = *m*-Me was excluded from the Brønsted plot for β_Z due to an unreliable pKa values. Correlation coefficients were better than 0.996 in all cases. ^c At 30°C. ^d At 20°C. ^e Correlation coefficients was 0.998. ^f The pKa values were taken from Fischer, A.; Gilloay, W. J.; Vaughan, J. J. *Chem. Soc.* **1964**, 3588. Correlation coefficients were better than 0.998 in all cases. pKa = 9.64 was used for X = *p*-CH₃O. (reference Oh, H. K.; Lee, J. Y.; Lee, I. *Bull Korean Chem. Soc.* **1998**, *19*, 1198)

shown that the ΔpK_a ($\cong 7.7$) value arises solely from the ion solvation energy difference of H⁺ ion in water and acetonitrile, $\delta\Delta G_s^0(\text{H}^+) = 10.5 \text{ kcal mol}^{-1}$, which corresponds to $\Delta pK_a = 7.7$, at the MP2/6-31G**/MP2/6-31G* level¹¹ of theory. Moreover, we are comparing the magnitude of β_X and β_Z determined for the reactions carried out under the same reaction condition (i.e., in acetonitrile). Since we used pKa values of thiophenolates in water, the comparison of β_Z values may not be entirely reliable.

We note that the magnitude of β_X in Table 1 ($\beta = 1.52 \sim 2.25$) is considerably larger than those for the corresponding reactions with anilines and other secondary and tertiary amines ($\beta_X = 0.6 \sim 1.0$)¹² proceeding by rate-limiting breakdown (k_b) of a zwitter-ionic tetrahedral intermediate, T[±], eq. (5). On this account (i.e., large β_X values), the aminolysis of thiophenyl cyclopentanecarboxylates with benzylamines in acetonitrile, eq. (1), is most likely to occur by rate-limiting expulsion, k_b , in eq. (5), of thiophenolate ion, ArS⁻, from T[±].

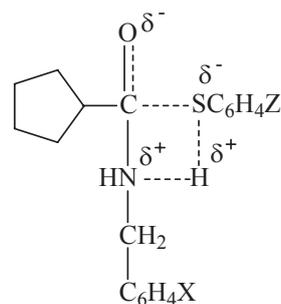
The magnitude of β_X in Table 1 ($\beta_X = 1.52\text{-}2.25$) is again much larger than those for the corresponding reactions with anilines and other secondary and tertiary amines ($\beta_X = 0.6\text{-}1.0$)¹² but similar to those with benzylamines ($\beta_X = 1.4\text{-}2.5$). All of these latter values are for the thiol ester aminolysis with benzylamines in acetonitrile which are predicted to proceed by rate-limiting breakdown of a zwitterionic tetrahedral intermediate, T[±]. On this account, i.e. large β_X values obtained, the aminolysis of thiophenyl cyclopentane- carboxylate with benzylamines in acetonitrile is most likely to occur by the rate-limiting expulsion of thiophenolate ion, ArS⁻, from T[±], eq. (5), 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_2 in eq. 3, is

therefore a complex quantity represented by eq. 6. The magnitude of β_Z (β_{lg}) values ($\beta_Z = -1.24 \sim -1.66$) is also comparable to or greater than that for the similar reaction with rate-limiting expulsion of ArS⁻ in acetonitrile ($\beta_Z = -1.2 \sim -1.5$).¹³

$$k_2 = \frac{k_a}{k_{-a}} \cdot k_b = K \cdot k_b \quad (6)$$

The proposed mechanism is also supported by a large positive cross-interaction constant ($\rho_{XZ} = 1.72$) and adherence to the reactivity-selectivity principle (RSP), which are considered to constitute necessary conditions for the rate-limiting breakdown of T[±].¹⁴

The kinetic isotope effects (k_H/k_D) in Table 2 involving deuterated benzylamine (XC₆H₄CH₂ND₂) nucleophiles in acetonitrile are greater than unity ($k_H/k_D = 1.4 \sim 1.6$), indicating that the N-H proton transfer takes place in the rate determining step¹⁵ so that a four-center type TS is involved.¹⁵ In this type of TS, hydrogen bonding of an amine hydrogen atom to the de-



Proposed TS

Table 2. Kinetic Isotope Effects for the Reactions of Z-Thiophenyl Cyclopentanecarboxylates with Deuterated X-Benzylamines in Acetonitrile at 40.0°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	7.98 ± 0.15^a	5.14 ± 0.06	1.55 ± 0.02^b
<i>p</i> -OMe	H	23.0 ± 0.5	15.4 ± 0.3	1.49 ± 0.02
<i>p</i> -OMe	<i>p</i> -Cl	113 ± 3	79.0 ± 1.8	1.43 ± 0.03
<i>p</i> -OMe	<i>p</i> -Br	135 ± 4	97.8 ± 2.2	1.38 ± 0.03
<i>p</i> -Cl	<i>p</i> -Me	0.620 ± 0.005	0.392 ± 0.003	1.58 ± 0.04
<i>p</i> -Cl	H	2.61 ± 0.05	1.71 ± 0.02	1.53 ± 0.02
<i>p</i> -Cl	<i>p</i> -Cl	19.6 ± 0.2	13.4 ± 0.2	1.46 ± 0.02
<i>p</i> -Cl	<i>p</i> -Br	26.0 ± 0.4	18.5 ± 0.2	1.40 ± 0.03

^aStandard deviations. ^bStandard errors.

Table 3. Activation Parameters^a for the Reactions of Z-Thiophenyl Cyclopentanecarboxylates 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	6.0	48
<i>p</i> -OMe	<i>p</i> -Br	5.8	44
<i>p</i> -Cl	<i>p</i> -Me	5.8	55
<i>p</i> -Cl	<i>p</i> -Br	5.8	47

^aCalculated by the Eyring equation. The maximum errors calculated (by the method of Wiberg, K. B. *Physical Organic Chemistry*; Wiley: New York, 1964; p 378) are $\pm 1.0 \text{ kcal mol}^{-1}$ and $\pm 4 \text{ e.u.}$ for ΔH^\ddagger and ΔS^\ddagger , respectively.

parting thiophenoxide facilitates the rate-limiting bond cleavage step, forming a rather constrained four membered ring.

The low activation enthalpies, ΔH^\ddagger , and highly negative activation entropies, ΔS^\ddagger , (Table 3) are also in line with the proposed TS. Especially, the ΔH^\ddagger values are somewhat lower and the ΔS^\ddagger values are higher negative values than other aminolysis systems.¹⁴ 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[±]. 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.

In summary the aminolysis of thiophenyl cyclopentanecarboxylates with benzylamines in acetonitrile proceeds by rate-limiting breakdown of a tetrahedral intermediate, T[±]. The unusually large β_X (β_{nuc}) values can be accounted for by a strong localized cationic charge on the nitrogen atom of benzylamines in T[±], which is lost in the benzylamine expulsion from T[±] (k_{-a}). The breakdown rate ratio of k_{-a}/k_b is large due to large k_{-a} and relatively small k_b . The proposed mechanism is also supported by a large positive cross-interaction constant, ρ_{XZ} ($=1.72$), adherence to the RSP, and low activation parameters. The greater than unity k_H/k_D values involving deuterated benzylamines suggests a four-center type hydrogen-bonded TS.

Experimental Section

Materials. Acetonitrile (Merk G R) was used after three-time distillations. The benzylamine nucleophiles (Aldrich GR) were used without further purification.

Substrates. Preparations and analytical data are reported elsewhere.¹⁶

Kinetic Measurement. Rates were measured conductometrically at $40.0 \pm 0.05^\circ\text{C}$. The conductivity bridge used in this work was a self-made computer automatic A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obs} , were determined by the Guggenheim method¹⁷ with large excess of benzylamine. Second-order rate constants, k_2 , were obtained from the slope of a plot of k_{obs} vs. [benzylamine] with more than five concentrations of benzylamine eq. 4. The k_2 values in Table 1 are averages of more than three runs and were reproducible to within $\pm 3\%$.

Product Analysis. Substrate (0.05 mole) and benzylamine (0.5 mole) were added to acetonitrile and reacted 40.0°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, 10% ethylacetate-*n*-hexane). Analysis of the product gave the following results.

Cyclopentyl-C(=O)NHCH₂C₆H₄-OCH₃ : m.p, 192 ~ 194°C, IR(KBr), 3251(N-H), 3010(C-H, benzyl), 2936(C-H, CH₂), 2943(C-H, CH₃), 1634(C=O), 1534(C=C, aromatic), 1262, 1035(C-O); ¹H NMR(400 MHz, CDCl₃), 1.12 ~ 1.17(8H, m, CH₂), 1.55 ~ 1.66(1H, m, CH), 3.69(3H, s, CH₃), 4.25(2H, d, CH₂), 7.08(2H, d, $J = 8.78 \text{ MHz}$, meta H), 7.29(2H, d, $J = 8.30 \text{ MHz}$, ortho H); ¹³C NMR(100.4 MHz, CDCl₃), 176.3(C=O), 158.7, 129.1, 128.9, 113.8, 63.7, 45.6, 42.8, 30.9, 25.7; Mass, m/z 233(M⁺). Anal. Calcd. for C₁₄H₁₉NO₂ : C, 72.1; H, 8.21. Found: C, 72.3; H, 8.19.

Acknowledgments. This paper was supported by research fund of Chonbuk National University.

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