Kinetics and Mechanism of the Aminolysis of Thiophenyl Cyclohexanecarboxylates

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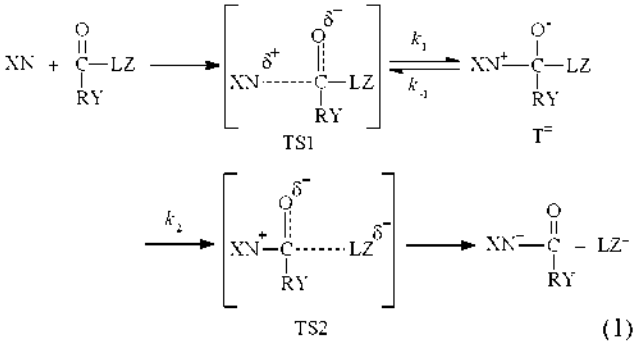
The aminolysis reaction of carbonyl compounds is one of the most extensively investigated subjects in mechanistic organic chemistry. In this type of reaction, a non-linear Brönsted-type plot showing a break from a large (β = 0.8 ~ 1.0) to a small (β = 0.1 ~ 0.3) rate dependence on basicity of the attacking amine is often obtained at pK_o as the basicity of nucleophile is increased.[1-8] The break at pK_o where $k_{-1} = k_2$ has been attributed to a change in the rate-determining step from breakdown (k_2) to formation (k_1) of a tetrahedral intermediate, $T^{\pm}$, in the reaction path.[1-8] eq. (1), where X, Y and Z are the substituents in the nucleophile, substrate and leaving group, respectively. Such rate-limiting breakdown of $T^{\pm}$ has been reported, for example, in the reactions of methyl chloroformate with pyridines,[1] substituted diphenyl carbonates with quinuclidine,[2] 2,4-dinitrophenyl acetate and methyl carbonate with pyridines,[3] aryl cyclobutanecarboxylate with benxylamines,[4]



(1)

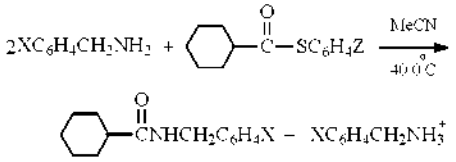
O-2,4-dinitrophenyl Thionobenzoate with pyridines,[5] S-2,4-dinitophenyl thiobenzoate with pyridines,[6] phenyl benzoate with piperidines[7] and thiophenyl cyclobutanecarboxylate with benzylamines reaction path.[8]

Based on the results of these experimental studies, we were able to determine the signs of the cross-interaction constants, ρ_{ij} in eq. (2)[9] where i, j = X, Y or Z in eq. (1), for the rate-limiting

$$\log (k_{ij}/k_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \quad (2)$$

breakdown mechanism of the zwitterionic tetrahedral intermediate, $T^{\pm}$.[10] For this type of mechanism, it was found that in the rate-limiting breakdown step, k_2, the sign of ρ_{YZ} is negative while for equilibrium $K = k_1/k_{-1}$ the sign of ρ_{XY} is positive, which are in quite contrast to those ($\rho_{YZ} > 0$ and $\rho_{XY} < 0$)[9] for a normal concerted bimolecular nucleophilic displacement, S_N2 mechanism. On the other hand, the sign of ρ_{XZ} is always positive, whereas in the concerted S_N2 reactions it can be either positive or negative.[10]

In the present work, we carried out a kinetic and mechanistic study of the reactions of thiophenyl cyclohexanecarboxylates with benzylamines (BA) in acetonitrile at 40.0 °C. We varied the two substituents X and Z on the nucleophile and leaving group, respectively.



(3)

Results and Discussion

The pseudo-first order rate constants observed (k_{obs}) for all reactions obeyed eq. 4 with negligible k_o ($\cong$ 0) in acetonitrile. The second-order rate constants, k_2 (M^{-1} s^{-1}), were obtained as the slopes of the k_{obs} *vs.* benzylamine concentration [BA] and are summaried in Table 1. No third-order or higher order terms

$$k_{obs} = k_o + k_2\,[BA] \quad (4)$$

in benzylamine were detected and no complications were found neither in the determination of k_{obs} nor in the linear plots of eq. 4. This suggests that there is no base catalysis or noticeable side reactions. The rate is faster with a stronger nucleophile and a better nucleofuge as normally expected from a nucleophilic substitution reaction. The rates for the thiophenyl cyclohexanecarboxylates are faster, due less probably to strain effects, than those for the thiophenyl cyclopentanecarboxylates.[11]

The ρ_X (ρ_{nuc}) and β_X (β_{nuc}) values are presented in Table 1. We note that the magnitude of the two selectivity parameters is large. These β_X values can be considered to represent reliable values since although the absolute values of pK_a in MeCN differ from those in water, a constant ΔpK_a ($pK_{CH_3CN} - pK_{H_2O} \cong 7.7 \pm 0.3$) was experimentally found for 22 alkyl and alicyclic amines.[12] Recent theoretical work of the solvent effects on the basicities of pyridines has shown that the ΔpK_a ($\cong$ 7.7) value arises solely from the ion solvation energy

Table 1. The Second Order Rate Constants, $k_2 \times 10^4$ dm^3 mol^{-1} s^{-1} for the Reactions of Z-Thiophenyl Cyclohexanecarboxylates with X-Benzylamines in Acetonitrile at 40.0 °C.

X	Z				ρ_Z[a]	β_Z[b]
	p-Me	H	*p*-Cl	*p*-Br		
p-OMe	45.7 ± 1.2 31.6 ± 0.9[c] 22.1 ± 0.5[d]	81.8 ± 1.7	379 ± 9	591 ± 15 408 ± 10 277 ± 7	2.78 ± 0.03	−1.17 ± 0.03
p-Me	16.9 ± 0.3	49.1 ± 1.5	242 ± 5	258 ± 6	2.95 ± 0.04	−1.24 ± 0.05
H	5.24 ± 0.05	16.2 ± 0.2	87.3 ± 2.0	98.5 ± 1.5	3.15 ± 0.03	−1.31 ± 0.05
p-Cl	2.08 ± 0.03 1.48 ± 0.02 1.03 ± 001	4.51 ± 0.04	26.2 ± 0.6	46.8 ± 1.3 32.8 ± 0.9 23.3 ± 0.6	3.29 ± 0.06	−1.35 ± 0.04
m-Cl	0.578 ± 0.005	1.76 ± 0.02	13.2 ± 0.2	17.1 ± 0.3	3.62 ± 0.08	−1.47 ± 0.08
ρ_X[e]	−2.69 ± 0.02	−2.60 ± 0.02	−2.31 ± 0.03	−2.17 ± 0.03	ρ_{XZ}[f] = 1.18 ± 0.05	
β_X[g]	2.71 ± 0.04	2.62 ± 0.04	2.34 ± 0.03	2.19 ± 0.03		

[a]The σ values were taken from C. Hansch, A. Leo, and R. W. Taft, *Chem. Rev.* **1991**, *91*, 165. Correlation oefficients were better than 0.995 in all cases. [b]The pK_a values were taken from ed., J. Bukingham. *Dictionary of Organic Chemistry*. Chapman and Hall. New York, 1982. 5th. ed. Z = *p*-Br was excluded from the Brönsted plot for β_Z due to an unreliable pKa values. Correlation coefficients were better than 0.998 in all cases. [c]At 30 °C. [d]At 20.0 °C. [e]The source of σ is the same as for footnote a. Correlation coefficients were better than 0.999 in all cases. [f]Correlation coefficient was 0.998. [g]The pK_a values were taken from: *Introduction to Organic Chemistry*, A. Streitwiser, Jr and C. h. Heathcock. Third Edition, 1989, p 693. Macmillan Publishing Co., New York. Correlation coefficients were better than 0.999 in all cases.

difference of H^- ion in water and in acetonitrile, $\delta\Delta G_s^\circ(H^-)$ = 10.5 kcal mol^{-1} which corresponds to ΔpK_a = 7.7, at the MP2/6-31G*//MP2/6-31G* level.[13] The β_X values (2.2 ~ 2.7) obtained in this work are considerably larger than those for the corresponding reactions with other secondary and tertiary amines (β_X = 0.6 ~ 1.0)[14] proceeding by rate-limiting breakdown of a zwitterionic tetrahedral intermediate, $T^\pm$, eq 4. On this account, i.e., large β_X values obtained, the aminolysis of thiophenyl cyclohexanecarboxylate with benzylamines in acetonitrile is most likely to occur by rate-limiting expulsion of thiophenolate anion, ArS^-, from $T^\pm$ (k_2 step). The large β_X values observed with benzylamine nucleophile in the present work are considered to represent a very sensitive change in the benzylamine expulsion rate (k_{-1}) with substrate (X) variation due to the loss of a strong localized charge on the nitrogen atom of the benzylinium ion in the $T^\pm$.[15] The magnitude of β_Z (β_{lg}) values (β_Z = −1.2 ~ −1.5) is also comparable to that for the similar reaction with rate-limiting expulsion of ArS^- in acetonitrile (β_Z = −1.2 ~ −1.6).[16]

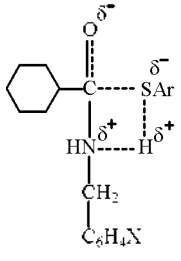
Table 2. Kinetic Isotope Effects for the Reactions of Z-Thiophenyl Cyclohexanecarboxylates with Deuterated X-Benzylamines in Acetonitrile at 40.0 °C.

X	Z	$k_{2(H)} \times 10^4$ ($M^{-1}s^{-1}$)	$k_{2(D)} \times 10^4$ ($M^{-1}s^{-1}$)	$k_{2(H)}/k_{2(D)}$
p-OMe	*p*-Me	45.7(± 1.2)	25.7(± 0.55)	1.78 ± 0.04[a]
p-OMe	H	81.8(± 1.7)	48.3(± 1.25)	1.69 ± 0.03
p-OMe	*p*-Cl	379(± 9.0)	236(± 5.25)	1.60 ± 0.03
P-OMe	*p*-Br	591(± 15)	388(± 10)	1.52 ± 0.04
p-Cl	*p*-Me	2.08(± 0.03)	1.14(± 0.02)	1.82 ± 0.03
p-Cl	H	4.51(± 0.04)	2.54(± 0.04)	1.77 ± 0.02
p-Cl	*p*-Cl	26.2(± 0.60)	15.8(± 0.26)	1.65 ± 0.03
p-Cl	*p*-Br	46.8(± 1.3)	29.8(± 0.65)	1.57 ± 0.03

[a]Standard deviations.

An important aspect we note in Tables 1 is that the magnitude of ρ_{XZ} is unusually large (ρ_{XZ} = 1.18). The size of ρ_{XZ} is considered to represent the intensity of interaction in the TS[9] between the two substituents in the nucleophile (X) and leaving group (Z), and hence the larger the ρ_{XZ}, the stronger is the interaction, i.e., the closer is the two fragments, the nucleophile and leaving group, in the TS. The relatively large magnitude observed in the present work favours the rate-limiting expulsion of ArS^- leaving group from $T^\pm$ in the stepwise mechanism relative to a concerted nucleophilic substitution.

The kinetic isotope effects (Table 2) involving deuterated nucleophile, $XC_6H_4CH_2ND_2$, are normal ($k_H/k_D > 1.0$) suggesting a possibility of forming hydrogen-bonded four-center type TS[17] as has often been proposed. Since no base catalysis was found (the rate law is first order with respect to [BA], eq. 3), the proton transfer occurs concurrently with the rate-limiting expulsion of ArS^- in the TS but not catalyzed by benzylamine. The consumption of proton by the excess benzylamine would



proposed TS

Table 3. Activation Parameters[a] for the Reactions of Z-Thiophenyl Cyclohexanecarboxylates with X-Benzylamines in Acetonitrile.

X	Z	$\Delta H^{\neq}$/kcal mol^{-1}	$-\Delta S^{\neq}$/cal mol^{-1} K^{-1}
p-OMe	*p*-Me	6.1	50
p-OMe	*p*-Br	6.5	45
p-Cl	*p*-Me	6.1	56
p-Cl	*p*-Br	6.0	50

[a]Calculated by the Eyring equation. The maximum errors calculated (by the method of K. B. Wiberg, Physical Organic Chemistry, Wiley, New York, 1964, p 378.) are ± 0.6 kcal mol^{-1} and ± 2 e.u. for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, respectively.

therefore take place in a subsequent rapid step.

The low activation enthalpies, $\Delta H^{\neq}$, and highly negative activation entropies, $\Delta S^{\neq}$, (Table 3) are also in line with the proposed TS. The expulsion of ArS^- 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, $T^{\pm}$. This will lower the $\Delta H^{\neq}$ value, but the TS becomes structured and rigid (low entropy process) which should lead to a large negative $\Delta S^{\neq}$ value.

In summary, the reactions of thiophenyl cyclohexanecarboxylates with benzylamines in acetonitrile are proceed by a stepwise mechanism in which the rate-determining is the breakdown of the zwitterionic tetrahedral intermediate with a hydrogen-bonded four-center type TS. These mechanistic conclusions are drawn based on (i) the large magnitude of ρ_X and ρ_Z, (ii) the normal kinetic isotope effects ($k_H/k_D > 1.0$) involving deuterated benzylamine nucleophiles, (iii) a small positive enthalpy of activation, $\Delta H^{\neq}$, and a large negative entropy of activation, $\Delta S^{\neq}$, (iv) lastly the larger positive ρ_{XZ} value than that for normal S_N2 processes.

Experimental Section

Materials. Merck GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used without further purification. Thiophenols and cyclohexanecarbonyl chloride were used Tokyo Kasei GR grade. Preparations of deuterated benzylamines were as described previously.[8]

Preparartions of thiophenyl cyclohexanecarboxylates. Thiophenol derivatives and cyclohexnaecarbonyl chloride were dissolved in anhydrous ether and added pyridine carefully keeping temperature to 0 ~ 5 °C. Ice was then added to the reaction mixture and ether layer was separated, dried on $MgSO_4$ and distilled under reduced pressure to remove solvent. The product mixture was treated with column chromatography. IR (Nicolet 5BX FT-IR) and ^{1}H and ^{13}C NMR (JEOL 400 MHz) data are as follows:

***p*-Thiotolyl cyclohexanecarboxylate:** Liquid, IR (KBr), 2960 (C-H, aromatic), 2935 (C-H, CH_3), 1705 (C=O), 1609 (C=C, aromatic), 963 (C-S); ^{1}H NMR(400 MHz, $CDCl_3$), 1.20 ~ 2.39 (10H, m, CH_2), 2.35 (3H, s, CH_3), 2.42 ~ 2.48 (H, m, CH), 7.22 (2H, d, J = 8.30 MHz, meta H), 7.29 (2H, d, J = 8.30 MHz, ortho H); ^{13}C NMR(100.4 MHz, $CDCl_3$), 176.6 (C=O), 139.2, 134.4, 129.7, 124.3, 52.3, 39.4, 28.9, 25.6.; Mass, *m/z* 234 (M^+). Anal. Calcd. for $C_{14}H_{18}OS$: C, 71.8; H, 7.74. Found: C, 71.6; H, 7.76.

Thiophenyl cyclohexanecarboxylate: Liquid, IR (KBr), 2959 (C-H, aromatic), 1704 (C=O), 1474(C=C, aromatic), 962 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$), 1.35 ~ 2.05 (10H, m, CH_2), 2.33 ~ 2.42 (H, m, CH), 7.23 (2H, d, J = 7.81 MHz, meta H), 7.37 (2H, d, J = 7.81 MHz, ortho H); ^{13}C NMR (100.4 MHz, $CDCl_3$), 200.7 (C=O), 134.6, 134.5, 129.1, 129.0, 52.5, 43.2, 29.5, 25.7.; Mass, *m/z* 220(M^+). Anal. Calcd. for $C_{13}H_{16}OS$: C, 70.8; H, 7.32. Found: C, 70.6; H, 7.34.

***p*-Chlorothiophenyl hexanecarboxylate:** Liquid, IR (KBr), 2955 (C-H, aromatic), 1696 (C=O), 1450 (C=C, aromatic), 964 (C-S); ^{1}H NMR(400 MHz, $CDCl_3$), 1.16 ~ 2.04 (10H, m, CH_2), 2.23 ~ 2.32 (H, m, CH), 7.28 (2H, d, J = 8.78 MHz, meta H), 7.33 (2H, d, J = 8.78 MHz, ortho H); ^{13}C NMR (100.4 MHz, $CDCl_3$), 200.1 (C=O), 135.7, 135.4, 129.2, 126.3, 52.4, 29.4, 25.5, 25.3.; Mass, *m/z* 254(M^-). Anal. Calcd. for $C_{13}H_{15}ClOS$: C, 61.2; H, 5.93. Found: C, 61.4; H, 5.91.

***p*-Bromothiophenyl hexanecarboxylate:** Liquid, IR (KBr), 2956 (C-H, aromatic), 1695 (C=O), 1495 (C=C, aromatic), 959 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$), 1.16 ~ 1.86 (10H, m, CH_2), 2.24 ~ 2.33 (H, m, CH), 7.13 (2H, d, J = 8.78 MHz, meta H), 7.5066 (2H, d, J = 8.78 MHz, ortho H); ^{13}C NMR (100.4 MHz, $CDCl_3$), 199.9, 135.9, 132.2, 127.0, 123.6, 52.9, 29.4, 25.5, 25.4.; Mass, *m/z* 299(M^+). Anal. Calcd. for $C_{13}H_{15}BrOS$: C, 52.1; H, 5.05. Found: C, 51.3; H, 5.03.

Kinetic measurement. Rates were measured conductometrically at 10.0 ± 0.05 °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 method[18] 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 the averages of more than three runs and were reproducible to within ± 3%.

Product analysis. Substrate, thiophenyl cyclohexanecarboxylate (0.05 mole) was reacted with excess *p*-methoxybenzylamine (0.5 mole) with stirring for more than 15 half-lives at 40.0 °C in acetonitrile, and the products were isolated by evapolating the solvent under reduced pressure. The product mixture was treated with column chromatography (silica gel, 20% ethylacetate-*n*-hexane). Analysis of the product gave the following results.

Cyclohexyl-C(=O)NHCH$_2$C$_6$H$_4$-OCH$_3$: m.p. 192 ~ 194 °C, IR (KBr), 3448 (N-H), 3012 (C-H, benzyl), 2938 (C-H, CH_2), 2945 (C-H, CH_3), 1701 (C=O), 1532 (C=C, aromatic), 1261, 1032 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$), 1.15 ~ 2.05 (8H, m, CH_2), 1.53 ~ 1.61 (1H, m, CH), 3.76 (3H, s, CH_3), 4.47 (2H, d, CH_2), 7.03 (2H, d, J = 8.78 MHz, meta H), 7.13(2H, d, J = 8.30 MHz, ortho H); ^{13}C NMR (100.4 MHz, $CDCl_3$), 178.0 (C=O), 158.2, 135.4, 129.3, 116.1, 55.8, 49.1, 43.1, 28.5, 27.7, 23.2.; Mass, *m/z* 247(M^-). Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.8; H, 8.56. Found: C, 72.6; H, 8.58.

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