Nucleophilic Substitution Reactions of Thiophenyl Phenylacetate with Benzylamines in Acetonitrile

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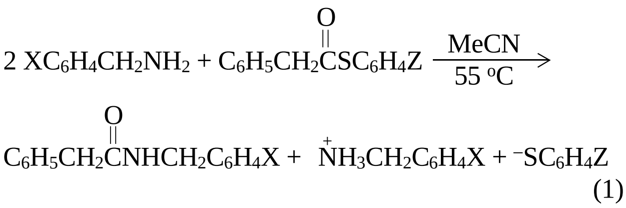
The aminolysis reactions of thiophenyl phenylacetates with benzylamines are investigated in acetonitrile at 55.0 °C. Relatively large selectivity parameters, $\beta_X \cong 1.5$, $\beta_Z = -1.5\sim-1.8$ and $\beta_{XZ} = 0.92$ together with the valid reactivity-selectivity principle are consistent with stepwise acyl transfer mechanism with rate limiting expulsion of the leaving group, thiophenolate anion, from the tetrahedral intermediate, $T^{\pm}$. The first order kinetics with respect to the benzylamine concentration and the realtively large secondary kinetic isotope effect (k_H / k_D = 1.2-1.7) involving deuterated benzylamine nucleophiles suggest a four center type transition state in which concurrent leaving group departure and proton transfer are involved.

Introduction

The aminolysis of acyl compounds has been extensively studied. The Brönsted type plots are used in these reactions as mechanistic criteria. A biphasic dependence of the aminolysis rate on amine basicity showing 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 has been 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.[1] The aminolysis of thiophenyl benzoates with benzylamines, however, exhibited an unusually large β_x (= β_{nuc} = 1.86) in acetonitrile, which was considered to proceed through a rate-limiting breakdown of a tetrahedral zwitterionic intermediate, $T^{\pm}$.[2] Benzylamines are primary amines with relatively high basicities ($pK_a \geq 9.0$) due to localized cationic charge on the benzylammonium ion and their nucleofugality from $T^{\pm}$ may be much different from that of the secondary and tertiary amines, especially from a sulfur zwitterionic tetrahedral intermediate since it is known that ArS^- is a poorer leaving group from $T^{\pm}$ than an isobasic ArO^- group.[3] In this work, we investigated the kinetics and mechanism of the aminolysis of thiophenyl phenylacetates (I) with benzylamines in acetonitrile at 55.0 °C, eq 1. The objective of the present work is to elucidate the mechanism by determining $\beta_X(\beta_{nuc})$, $\beta_Z(\beta_{lg})$ and cross-interaction constant ρ_{XZ}, eqs 2[4] where X and Z denote substituents in the nucleophile and nucleofuge, respectively.



$$2\ XC_6H_4CH_2NH_2 + C_6H_5CH_2\overset{O}{\overset{\|}{C}}SC_6H_4Z \xrightarrow[55\ ^{o}C]{MeCN} C_6H_5CH_2\overset{O}{\overset{\|}{C}}NHCH_2C_6H_4X + \overset{+}{N}H_3CH_2C_6H_4X + {}^{-}SC_6H_4Z \quad (1)$$

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

$$\rho_{XZ} = \partial\rho_Z / \partial\rho_X = \partial\rho_X / \partial\rho_Z \quad (2b)$$

It has been shown that the ρ_{XZ} is large positive and a higher reactivity is invariably accompanied by a smaller magnitude of selectivity parameters, such as ρ and β, *i.e.*, the reactivity-selectivity principle (RSP)[5] holds, for the acyl transfer reactions with rate-limiting breakdown of an intermediate, $T^{\pm}$.[5c,6]

Result and Discussion

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

$$k_{obs} = k_o + k_2\,[\,BA\,] \quad (3)$$

Table 1, were determined using eq 3 with at least five benzylamine concentrations, [BA]. No third-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 over all 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 typical nucleophilic substitution reaction.

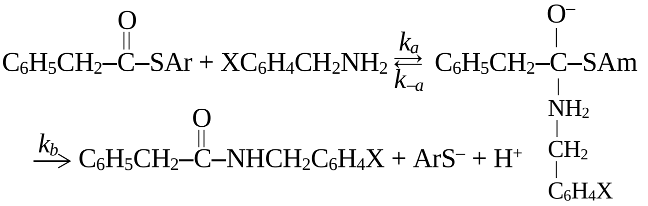
The ρ_x (ρ_{nuc}) and β_x (β_{nuc}) values are presented in Table 1. We note that the magnitude of the two selectivity parameters is large. As we have pointed out previously, these β_X values can be considered to represent reliable values since although the absolute values of pK_a in MeCN differ from those in water, a constant ΔpK_a ($pK_{a(MeCN)}$ - $pK_{a(H_2O)} \cong 7.7 \pm 0.3$) was experimentally found for 22 alkyl and alicyclic amines.[7] Our recent theoretical work of the solvent effects on the basicities of pyridines indicated that the ΔpK_a ($\cong$ 7.7) value arises solely from the ion solvation energy difference of H^+ ion in water and in acetonitrile, $\delta\Delta G_s^o$ (H^+) = 10.5 kcal mol^{-1} which corresponds to ΔpK_a = 7.7, at the MP2/6-31G*//MP2/6-31G* level.[8] The β_X values (1.5-1.6) obtained in this work is considerably larger than those for the corresponding reactions with anilines[9] and other secondary and tertiary amines

Table 1. The Second Order Rate Constants, $k_2 \times 10^3$ dm^3 mol^{-1} s^{-1} for the Reactions of Z-Thiophenyl Phenylacetates with X-Benzylamines in Acetonitrile at 55.0 ^oC

X	Z				$\rho_Z{}^a$	$\beta_Z{}^b$
	p-Me	H	*p*-Cl	*p*-Br		
p-OMe	7.98 6.68^c 5.52^d	13.9	27.5	31.7 26.2 21.5	1.42±0.08	-1.47±0.07
p-Me	4.14	7.57	15.3	17.8	1.50±0.08	-1.60±0.08
H	2.43	4.94	10.2	11.5	1.61±0.08	-1.66±0.11
p-Cl	1.77	3.53	7.89	8.58	1.66±0.09	-1.69±0.09
m-Cl	1.01 0.832 0.681	2.03	4.81	5.73 4.58 3.66	1.79±0.09	-1.72±0.08
p-CF$_3$	0.510	1.16	2.76	2.96	1.84±0.07	-1.77±0.12
$\rho_X{}^e$	-1.54 ±004	-1.50 ±0.06	-1.49 ±0.03	-1.44 ±0.05	$\rho_{XZ}{}^f$ =	0.92±0.07
$\beta_X{}^g$	1.59 ±0.06	1.55 ±0.08	1.53 ±0.04	1.48 ±0.07		

[a] The σ values were taken from Dean J. A. *Handbook of organic Chemistry*; McGraw-Hill: New York, 1987; Table 7-1. Correlation coefficients were better than 0.997 in all cases. [b] The pK$_a$ values were taken from ed., Buckingham J. *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 pK$_a$ value. Correlation coefficients were better than 0.996 in all cases. [c] At 45 ^oC. [d] At 35 ^oC. [e] The σ values were taken from McDaniel D. H.; Brown H.C., *J. Org. Chem*., **1958**, *23*, 420. Correlation coefficients were better than 0.997 in all cases. [f] Correlation coefficient was 0.996. [g] The pK$_a$ values were taken from Fischer A., Galloway W. J.; Vaughan J., *J. Chem. Soc*., **1964**, 3588. Correlation coefficients were better than 0.996 in all cases. X = p-CH$_3$O was excluded from the Brönsted plot for β_X (benzylamine) due to an unreliable pK$_a$ value listed. The pK$_a$ value for p-CF$_3$ (σ_p = 0.54, pK$_a$ = 8.76) were determined by extrapolation using σ value in the following eq.; pK$_a$ = (–1.16 ± 0.05) σ + (9.39 ± 0.02), n = 10, r = 0.992.

(β_X = 0.6-1.0) 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 phenylacetates with benzylamines in acetonitrile is most likely to occur by rate-limiting expulsion of thiophenolate ion, ArS$^-$, from T$^\pm$ (k_b step). The larger magnitude of β_X values observed with benzylamine nucleophiles in the present work is considered to represent a very sensitive benzylamine expulsion rate (k_{-a}) to the substituent (X) variation



$$C_6H_5CH_2{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}SAr + XC_6H_4CH_2NH_2 \underset{k_{-a}}{\overset{k_a}{\rightleftarrows}} C_6H_5CH_2{-}\overset{\displaystyle O^-}{\overset{|}{\underset{\underset{\underset{\displaystyle C_6H_4X}{|}}{\underset{\displaystyle CH_2}{|}}}{\underset{\displaystyle NH_2}{\underset{|}{C}}}}}{-}SAm \xrightarrow{k_b} C_6H_5CH_2{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}NHCH_2C_6H_4X + ArS^- + H^+ \quad (4)$$

$$k_2 = (k_a / k_{-a})\, k_b = \mathrm{K}\, k_b \quad (5)$$

due to the loss of a strong localized positive charge on the nitrogen atom of the benzylammonium ion in the T$^\pm$. The complex k_2 value eq 5 leads to eq 6, where β_b is nearly zero

$$\begin{aligned} \beta_X\ (= \beta_{nuc}) &= \mathrm{dlog}\, k_2 / dpK_a\ (X) \\ &= \mathrm{dlog} k_a / \mathrm{dp}K_a\ (X) - \mathrm{dlog}\ k_{-a} / \mathrm{dp}K_a\ (X) \\ &\quad + \mathrm{dlog}\ k_b / \mathrm{dp}K_a\ (X) \\ &= \beta_a - \beta_{-a} + \beta_b \end{aligned} \quad (6)$$

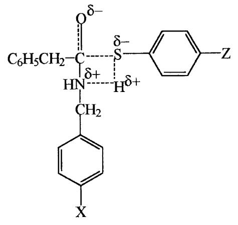
and $\beta_a \cong$ 0.2-0.3 so that the large β_X is due to the large magnitude of β_{-a} ($\cong$ –1.3).

In the conjugate acid forms of secondary and tertiary amines, and also of anilines, the cationic charge is partially delocalized and the sensitivity of the functional (positively charged) N center to the substituent (X) variation should be lower, *i.e.*, β_{-a} should be smaller in magnitude ($\beta_{-a} \cong$ –0.5~–0.7). For this reaction the ratio k_{-a} / k_b is also high so that the break point, pK$_a^o$, where the nucleofugality of benzylamine and thiophenolate is equal,[3d] lies above the pK$_a$'s of the conjugate acids of benzylamines used in this work, and a straight line Brönsted plot is obtained.

We note that the size of β_Z (–1.5~–1.8) is large, which is again an indication of the rate-limiting leaving group expulsion mechanism. For example, the reactions of thiophenyl benzoates with benzylamines in acetonitrile at 55 ^oC have been proposed to proceed by the rate-limiting expulsion of thiophenolate ion from T$^{\pm 2}$; the β_Z values for these reactions ranged from –1.4 to –1.7, which are quite similar to the values obtained in this work.

The cross-interaction constant ρ_{XZ} (=0.92 ± 0.07) is relatively large (the corresponding value for the reaction of thiophenyl benzoates is 0.3).[2] The large positive ρ_{XZ} and adherence to the RSP (Table 1) also support our proposed mechanism.[6]

The kinetic isotope effects (Table 2) involving deuterated benylamine nucleophiles,[4b] XC$_6$H$_4$CH$_2$ND$_2$, are greater than unity, $k_H / k_D \cong$ 1.2~1.7, suggesting a possibility of forming hydrogen-bonded four-center type transition state (TS) as has often been proposed.[10] The k_H / k_D value increases as



Proposed TS

Table 2. The Secondary Kinetic Isotope Effects for the Reactions of Z-Thiophenyl Phenylacetates with Deuterated X-Benzylamines in Acetonitrile at 55.0 ^oC

X	Z	$k_H \times 10^3$(M^{-1}s^{-1})	$k_D \times 10^3$(M^{-1}s^{-1})	k_H/k_D
p-OMe	*p*-Me	7.98(±0.05)	5.87(±0.02)	1.36±0.01^a
p-OMe	H	13.9 (±0.2)	10.5 (±0.1)	1.32±0.02
p-OMe	*p*-Cl	27.5 (±0.6)	22.2 (±0.4)	1.24±0.03
P-OMe	*p*-Br	32.7 (±0.8)	26.2 (±0.5)	1.21±0.04
p-Cl	*p*-Me	1.77(±0.02)	1.03(±0.01)	1.72±0.03
p-Cl	H	3.53(±0.01)	2.28(±0.02)	1.55±0.02
p-Cl	*p*-Cl	7.89(±0.05)	5.59(±0.03)	1.41±0.01
p-Cl	*p*-Br	8.58(±0.08)	6.97(±0.05)	1.23±0.02

[a] Standard deviations.

Table 3. Activation Parameters[a] for the Reactions of Z-Thiophenyl Phenylacetates 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	4.7±0.1	54±1
p-Om	*p*-Br	5.4±0.1	49±1
m-Cl	*p*-Me	4.2±0.1	60±1
m-Cl	*p*-Br	5.5±0.1	52±1

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

expected from the proposed TS structure; it is larger as the acidity of the amine proton increases with a stronger electron-withdrawing (X) substituent and as the negative charge on the thiophenolate ion becomes stronger with a stronger electron doner (Z) substituent.

The low activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (Table 3) are also in line with the mechanism proposed. The expulsion of thiophenolate anion is aided by hydrogen-bonding by the benzylamine reguiring not much energy in the activation but highly structured TS leads to large negative entropies of activation.

In summary, the aminolysis of thiophenyl phenylacetates with benzylamines in acetonitrile proceeds by rate-limiting breakdown of a tetrahedral intermediate, $T^{\pm}$. The unusually large β_X (β_{nuc}) values can be accounted for by a strong localized cationic charge on the nitrogen atom of benzylamine expulsion from $T^{\pm}$ (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} (=0.92), 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. Merk GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used without further purification. Thiophenols and phenylacetyl chloride were Tokyo Kasei GR grade.

Preparartions of thiophenyl phenylacetates. Thiophenol derivatives and phenylacetyl chloride were dissolved in anhydrous ether and added KOH 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 melting point, IR (Nicolet 5BX FT-IR), ^{1}H and ^{13}C NMR (JEOL 400 MHz), data are as follows:

p-Methylthiophenyl phenylacetate: m.p. 62-64 °C, IR (KBr), 1703 (C=O), 1501 (C-C, aromatic), 1495 (C=C, aromatic), 1434 (C-H, CH_2), 1329 (C-H, CH_3), 675 (C-H, aromatic); ^{1}H NMR (400 MHz, $CDCl_3$), 2.35 (3H, d, J = 2.66 Hz, CH_3), 3.90 (2H, s, CH_2), 7.18-7.37 (9H, m, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 195.8 (C=O), 139.7, 134.4, 133.4, 130.0, 129.5, 129.2, 128.5, 127.5, 127.0, 124.0, 123.7, 50.0, 21.3.

Thiophenyl phenylacetate: liquid, IR (KBr), 1717 (C=O), 1515 (C-C, aromatic), 1475 (C=C, aromatic), 1468 (C-H, CH_2), 702 (C-H, aromatic); ^{1}H NMR (400 MHz, $CDCl_3$), 4.15 (2H, s, CH_2), 7.24-7.35 (10H, m, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 202.5 (C=O), 139.5, 134.3, 132.1, 131.4, 130.4, 130.2, 129.0, 128.2, 127.9, 127.0, 125.9, 123.1, 51.2.

p-Chlorothiophenyl phenylacetates: m.p. 58-61 °C, IR (KBr), 1710 (C=O), 1524 (C-C, aromatic), 1475 (C=C, aromatic), 1459 (C-H, CH_2), 702 (C-H, aromatic); ^{1}H NMR (400 MHz, $CDCl_3$), 4.16 (2H, s, CH_2), 7.26-7.37 (9H, m, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 200.3 (C=O), 139.3, 133.9, 133.1, 129.7, 129.3, 128.9, 128.5, 128.2, 127.1, 126.9, 124.2, 50.5.

p-Bromothiophenyl phenylacetate: m.p. 57-59 °C, IR (KBr), 1703 (C=O), 1501 (C-C, aromatic), 1468 (C=C, aromatic), 1454 (C-H, CH_2), 674 (C-H, aromatic); ^{1}H NMR (400 MHz, $CDCl_3$), 4.12 (2H, s, CH_2), 7.26-7.37 (9H, m, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 197.6 (C=O), 139.4, 134.2, 132.9, 130.3, 129.8, 129.5, 129.1, 128.5, 128.1, 126.9, 126.6, 123.8, 50.4.

Kinetic measurement. Rates were measured conductometrically in acetonitrile. The conductivity bridge used in this work was a homemade computer-automatic A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obs}, were determined by the Guggenheim method with large excess of benzylamine.[11] The k_2 values were reproducible to within ±5%.

Product analysis. Thiophenyl phenylacetate was reacted with excess benzylamine with stiring for more than 15 half-lives at 55.0 °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.

$C_6H_5CH_2C(=O)NHCH_2C_6H_4$: m.p. 60-62 °C, IR (KBr), 1703 (C=O), 1594 (N-H), 1501 (C-C, aromatic), 1495 (C=C, aromatic), 1464 (C-H, CH_2), 675 (C-H, aromatic); ^{1}H NMR (400 MHz, $CDCl_3$), 3.81 (1H, s, NH), 4.35 (2H, s, CH_2), 7.32-7.41 (9H, m, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 200.8 (C=O), 139.3, 134.4, 133.0, 130.2, 129.9, 129.3, 128.9, 128.7, 128.2, 126.9, 126.4, 123.6, 50.1.

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