Nucleophilic Substitution Reactions of Thiophenyl Cyclobutanecarboxylates with Benzylamines in Acetonitrile

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The aminolyses of acyl compounds have been studied extensively. Brønsted plots were used in these reactions as mechanistic criteria. In many of these nucleophilic reactions curved Brønsted type plots have been found, which have been attributed to a change in the rate-determining step from breakdown (β = 0.8-1.0) to formation (β = 0.1-0.3) of a tetrahedral intermediate, $T^\ddagger$, in the reaction path as a basicity of the amine nucleophile increases. The aminolysis of thiophenol benzoates with benzylamines, however, exhibited an unusually large $\beta_1$ ($\beta_1 = 1.86$) in acetonitrile, which was considered to proceed through a rate-limiting breakdown of a tetrahedral zwitterionic intermediate, $T^\ddagger$. 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 $T^\ddagger$ may be much different from that of the secondary and tertiary amines, especially from a sulfur zwitterionic tetrahedral intermediate since it is known that $\text{ArS}^-$ is a poorer leaving group from $T^\ddagger$ than an isobasic $\text{ArO}^-$ group. In this paper, we extend our work to the aminolysis of thiophenyl cyclobutanecarboxylates (TCC) with benzylamines (BA) in acetonitrile (eqn. 1).

$$\begin{align*}
\text{C}_2\text{H}_3\text{SC}_\text{O} + 2 \text{C}_2\text{H}_4\text{CH}_2\text{NH}_2 \rightarrow & \text{MeCN} \rightarrow 35.0^\circ C \\
\text{C}_2\text{H}_3\text{NCH}_2\text{CH}_2\text{X} + \text{C}_2\text{H}_4\text{CH}_2\text{NH}_2^+ + \text{C}_2\text{H}_5\text{OS}^- \rightarrow & \\
X = & p-\text{OMe}, p-\text{Me}, \text{H}, p-\text{Cl}, m-\text{Cl} \\
Y = & p-\text{Me}, m-\text{Me}, \text{H}, p-\text{Cl}
\end{align*}$$

(1)

The purpose of the present work is to further explore the effect of the acyl group on the aminolysis mechanism by investigating the structure-reactivity behavior of thiophenyl cyclobutanecarboxylates in acetonitrile. We are interested in the effects of the small ring acyl group on the mechanism, especially on the sign and magnitude of the cross-interaction constant, $\rho_{2Z}$ in eqns. (2a) and (2b), where $X$ and $Z$ are the substituents in the nucophile, benzylamine,

$$\begin{align*}
\log (k_{\text{M}2}/k_{\text{M}1}) = & \rho_{2Z} \sigma_X + \rho_{2Z} \sigma_Z + \rho_{2Z} \sigma_X \sigma_Z \quad (2a) \\
\rho_{2Z} = & \partial \log k_{\text{M}2}/\partial \sigma_X = \rho_{2Z} \sigma_X \\
\rho_{2Z} = & \partial \log k_{\text{M}2}/\partial \sigma_Z = \rho_{2Z} \sigma_Z \quad (2b)
\end{align*}$$

and leaving group, aryl sulfoxide, respectively. Furthermore, the variation in the kinetic isotope effects, $k_{d}/k_{t}$, involving deuterated benzylamines (XCD$_2$H$_2$CD$_2$) with substituents $X$ and $Z$, and the activation parameters, $\Delta H^\ddagger$ and $\Delta S^\ddagger$, are also determined since they can provide valuable information regarding the transition state (TS) structure.

Results and Discussion

The reactions of benzylamine (BA) with thiophenyl cyclobutanecarboxylates (TCC) under the reaction conditions obey the rate law given by eqns. (3) and (4), $k_{\text{obs}}$ and $k_0$ are the rate constants for solvolysis in MeCN and aminolysis of the substrate, respectively. Plots of $k_{\text{obs}}$ against $[\text{TCC}]$

$$\begin{align*}
\text{Rate} = & k_0 [\text{TCC}] \quad (3) \\
k_{\text{obs}} = & k_0 + k_N [\text{BA}] \quad (4)
\end{align*}$$

benzylamine concentration, [BA], were linear, according to eqn. (4), with the negligible intercept ($k_0 \approx 0.0$), and the slope $k_N$ (M$^{-1}$s$^{-1}$) as summarized in Table 1. No third-order or higher-order terms were detected, and no complications were found in the determination of $k_{\text{obs}}$ nor in the linear plot of eqn. (4). This suggests that there is no base-catalysis or noticeable side reactions and the overall reaction follows the route given by eqn. (1). The Hammett coefficients, $\rho_X$ and $\rho_Z$, and the Brønsted coefficients, $\beta_X (\beta_{\text{BA}})$ and $\beta_Z (\beta_2)$, are also collected in Table 1 together with the cross-interaction constant $\rho_{2Z}$.

Rates for the aminolysis of thiophenyl (-SAr) cyclobutanecarboxylates are faster than those corresponding values for the aminolysis of phenolate (-OAr) analogues. Note that the former has a lower rate despite its electron acceptor substituent with a higher reaction temperature (by 20 degrees). Since the nucleophile is the same, benzylamine in both cases, the faster rates of thiophenolates indicate the importance of bond cleavage in the TS, since the thiophenolates used in the present work are weakly basic relative to the phenolates used in the studies and hence are better leaving groups.

The magnitude of $\beta_2$ in Table 1 ($\beta_2 = 1.48-1.99$) is again much larger than those for the corresponding reactions with anilines and other secondary and tertiary amines ($\beta_2 = 0.6-1.0$) but similar to those with benzylamines ($\beta_2 = 1.4-2.5$).
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 zwiterionic tetrahedral intermediate, **T**. On this account, i.e. large \( \beta \) values obtained, the aminolysis of thiophenyl cyclobutanecarboxylates with benzylamines in acetonitrile is most likely to occur by the rate-limiting expulsion of thiophenolate ion, **ArS**\(^-\), from **T**, eqn. (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, \( k_X \) in eqn. (3), is therefore a complex quantity represented by eqn. (5). The magnitude of \( \beta \) values

\[
\beta_X = \frac{k_X}{k_2} = \frac{k^*}{k^*} \quad \text{(5)}
\]

\( \beta_X = -1.3 - 1.6 \) is also comparable to or greater than that for the similar reaction with rate-limiting expulsion of **ArS**\(^-\) in acetonitrile (\( \beta_X = -1.2 - 1.5 \)).

The proposed mechanism is also supported by a large positive cross-interaction constant (\( \rho_X \times \rho_S = 1.31 \)) and adherence to the reactivity-selectivity principle (RSP), which are considered to constitute necessary conditions for the rate-limiting breakdown of **T**.\(^{10,11}\)

The kinetic isotope effects (\( k_{H}/k_{D} \)) in Table 2 involving deuterated benzylamine (\( \text{XCD}_{3} \text{H}_{4} \text{CHND}_{2} \)) nucleophiles in acetonitrile are greater than unity (\( k_{H}/k_{D} = 1.3-1.4 \)), indicating that the N-H proton transfer takes place in the rate determining step\(^{12}\) so that a four-center type **TS** is involved.\(^{13}\) In this type of **TS**, hydrogen bonding of an amine hydrogen atom to the departing thiophenoxide facilitates the rate-limiting bond cleavage step, forming a rather constrained four-membered ring.

The low activation enthalpies, \( \Delta H^\ddagger \), and highly negative activation entropies, \( \Delta S^\ddagger \) (Table 3) are also in line with the proposed **TS**. Especially, the \( \Delta H^\ddagger \) values are somewhat lower and the \( \Delta S^\ddagger \) values are higher negative values than other aminolysis systems.\(^{10}\) 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**.\(^{4}\) 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.

In summary the aminolysis of thiophenyl cyclobutanecarboxylates with benzylamines in acetonitrile proceeds by

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### Table 1. The Second Order Rate Constants, \( k_X \times 10^3 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \) for the Reactions of Z-Thiophenyl Cyclobutanecarboxylates with X-Benzylamines in Acetonitrile at 35.0°C

<table>
<thead>
<tr>
<th>X</th>
<th>( p)-Me</th>
<th>( m)-Me</th>
<th>H</th>
<th>( p)-Cl</th>
<th>( p)k( ^+ )</th>
<th>( p)k( ^- )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( p)-OMe</td>
<td>7.58</td>
<td>15.4</td>
<td>24.7</td>
<td>115</td>
<td>2.97 ± 0.02</td>
<td>-1.25 ± 0.13</td>
</tr>
<tr>
<td>( p)-Me</td>
<td>5.46</td>
<td>1.31</td>
<td>0.02</td>
<td>0.53</td>
<td>0.535</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>3.94</td>
<td>1.31</td>
<td>0.02</td>
<td>0.53</td>
<td>0.535</td>
<td></td>
</tr>
<tr>
<td>( m)-Cl</td>
<td>0.318</td>
<td>0.921</td>
<td>1.55</td>
<td>12.0</td>
<td>3.77 ± 0.07</td>
<td>-1.61 ± 0.11</td>
</tr>
</tbody>
</table>

\( \rho_X = 0.999 \) in all cases. \( \rho_X = 0.999 \) in all cases.  
\( \rho_X = 0.999 \) in all cases.  
\( \rho_X = 0.999 \) in all cases.  
\( \rho_X = 0.999 \) in all cases.  
\( \rho_X = 0.999 \) in all cases.  
\( \rho_X = 0.999 \) in all cases.  

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### Table 2. The Secondary Kinetic Isotope Effects for the Reactions of Z-Thiophenyl Cyclobutanecarboxylates with Deuterated X-Benzylamines in Acetonitrile at 35.0°C

<table>
<thead>
<tr>
<th>X</th>
<th>( Z )</th>
<th>( k_H \times 10^3 )</th>
<th>( k_D \times 10^3 )</th>
<th>( k_H/k_D )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( p)-OMe</td>
<td>( p)-Me</td>
<td>7.58 ± 0.05</td>
<td>1.36 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>( p)-OMe</td>
<td>( m)-Me</td>
<td>15.4 ± 0.35</td>
<td>1.30 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>( p)-OMe</td>
<td>H</td>
<td>24.7 ± 0.30</td>
<td>1.26 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>( p)-OMe</td>
<td>( p)-Cl</td>
<td>115 ± 2.5</td>
<td>1.21 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>( p)-Cl</td>
<td>( p)-Me</td>
<td>0.76 ± 0.01</td>
<td>1.42 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>( p)-Cl</td>
<td>( m)-Me</td>
<td>1.78 ± 0.02</td>
<td>1.37 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>( p)-Cl</td>
<td>H</td>
<td>3.17 ± 0.03</td>
<td>1.31 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>( p)-Cl</td>
<td>( p)-Cl</td>
<td>19.9 ± 0.25</td>
<td>1.25 ± 0.02</td>
<td></td>
</tr>
</tbody>
</table>

\( \rho_X = 0.999 \) in all cases. \( \rho_X = 0.999 \) in all cases.  
\( \rho_X = 0.999 \) in all cases.  
\( \rho_X = 0.999 \) in all cases.  
\( \rho_X = 0.999 \) in all cases.
Table 3. Activation Parameters for the Reactions of Z-Thiophenyl Cyclobutanecarbonyl with X-Benzylamines in Acetonitrile

<table>
<thead>
<tr>
<th>X</th>
<th>Z</th>
<th>δH°/kcal mol⁻¹</th>
<th>δS°/kcal mol⁻¹ K⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-OCH₃</td>
<td>p-CH₃</td>
<td>5.2</td>
<td>51</td>
</tr>
<tr>
<td>p-OCH₃</td>
<td>p-CH₂Cl</td>
<td>5.8</td>
<td>44</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-CH₂Cl</td>
<td>5.2</td>
<td>56</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-CH₂Cl</td>
<td>5.7</td>
<td>48</td>
</tr>
</tbody>
</table>

*Calculated 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 ± 0.5 kcal mol⁻¹ and ± 2 e.u. for δH° and δS°, respectively.

Experimental Section

Materials. Merck GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used without further purification. Thiophenols and cyclobutanecarbonyl chloride were Tokyo Kasei GR grade. Preparation of deuterated benzylamine, benzylamine was dissolved in excess D₂O under nitrogen atmosphere and left over 5 hours. The deuterated benzylamine was extracted with dry ether and dried again over MgSO₄ and then the solvent was removed. This procedure was repeated three times. The analysis (NMR) of dried deuterated benzylamine has more than 99% deuterium content and thus the k/d values were not corrected for the deuterium content.

Preparations of thiophenyl cyclobutanecarboxylates. Thiophenol derivatives and cyclobutanecarbonyl 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 MgSO₄ and distilled under reduced pressure to remove solvent. IR (Nicolet 580 FTIR) and ¹H and ²³C NMR (JEOL 460 MHz) data are as follows:

* p-Thiotioly cyclobutanecarboxylate. Liquid, IR (KBr), 3001 (C=H, aromatic), 2932 (C-H, CH₃), 1709 (C=O), 1609 (C=O, aromatic), ¹H NMR (400 MHz, CDCl₃), 1.94-2.29 (6H, m, CH₃), 2.39 (3H, s, CH₃), 2.40-2.46 (H, m, CH), 2.74 (2H, d, J = 8.30 MHz, meta H), 3.74 (2H, d, J = 8.30 MHz, ortho H); ²³C NMR (100 MHz, CDCl₃), 199.1 (C=O), 146.3, 134.3, 129.6, 124.1, 25.9, 21.2, 17.9; Mass, m/z 206 (M⁺). Anal. Caled. for C₁₅H₁₀O₂: C, 71.7; H, 7.81. Found: C, 71.0; H, 6.83.

n-Thiophenyl cyclobutanecarboxylate. Liquid, IR (KBr), 3013 (C-H, aromatic), 2932 (C-H, CH₃), 1705 (C=O), 1584 (C=C, aromatic); ¹H NMR (400 MHz, CDCl₃), 1.99-2.07 (6H, m, CH₂), 2.25 (3H, s, CH₃), 2.33-2.45 (H, m, CH), 7.21-7.23 (4H, m, aromatic ring); ¹C NMR (100.4 MHz, CDCl₃), 199.3 (C=O), 138.9, 135.2, 129.9, 128.8, 127.3, 38.8, 26.1, 24.9, 21.3, 18.1; Mass, m/z 206 (M⁺). Anal. Caled. for C₁₅H₁₀O₂: C, 69.9; H, 6.81. Found: C, 70.0; H, 6.83.

Thiophenyl cyclobutanecarboxylate. Liquid, IR (KBr), 3010 (C=H, aromatic), 1701 (C=O), 1473 (C=C, aromatic); ¹H NMR (400 MHz, CDCl₃), 1.88-2.23 (6H, m, CH₂), 2.35-2.45 (H, m, CH), 7.38 (2H, d, J = 7.81 MHz, meta H), 7.42 (2H, d, J = 7.81 MHz, ortho H); ¹C NMR (100.4 MHz, CDCl₃), 198.9 (C=O), 134.3, 130.0, 129.7, 46.5, 26.1, 18.0; Mass, m/z 192 (M⁺). Anal. Caled. for C₁₅H₁₀O₂: C, 68.7; H, 6.31. Found: C, 68.9; H, 6.33.

p-Chlorothiophenyl cyclobutanecarboxylate. Liquid, IR (KBr), 3988 (C=H, aromatic), 1707 (C=O), 1498 (C=C, aromatic); ¹H NMR (400 MHz, CDCl₃), 1.80-2.20 (6H, m, CH₂), 2.23-2.34 (H, m, CH), 7.22 (2H, d, J = 8.78 MHz, meta H), 7.28 (2H, d, J = 8.78 MHz, ortho H); ¹C NMR (100.4 MHz, CDCl₃), 198.3 (C=O), 135.5, 129.1, 126.2, 46.6, 26.1, 25.3, 22.7; Mass, m/z 226 (M⁺). Anal. Caled. for C₁₅H₁₀O₂: C, 58.3; H, 4.91. Found: C, 58.5; H, 4.89.

Kinetic measurement. Rates were measured conductometrically at 35.0 ± 0.5 °C. The conductivity bridge used in this work was a self-made computer automatic A/D converter conductivity bridge. Pseudo-first-order rate constants, kₐ, were determined by the Guggenheim method with large excess of benzylamine. Second-order rate constants, k averages, were obtained from the slope of a plot of kₐ vs. benzylamine with more than one concentrations of more than three runs and were reproducible to within ±3%.

Product analysis. Substrate (0.5 mole) and benzylamine (0.5 mole) were added to acetonitrile and reacted 35.0 °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.

Cyclobutyl-(C=O)NHCH₂C₆H₅p-OCH₃, m.p. 192-194 °C, IR (KBr), 3313 (N=H), 3010 (C=H, benzyl), 2965 (C=H), 2941 (C=H, CH₃), 1700 (C=O), 1532 (C=C, aromatic), 1521 (N-H), 1262, 1035 (C=O); ¹H NMR (400 MHz, CDCl₃), 0.9, 0.0, 1.4 (6H, m, CH₃), 1.40-1.46 (H, m, CH), 7.24 (2H, d, J = 8.30 MHz, meta H), 7.34 (2H, d, J = 8.30 MHz, ortho H); ¹C NMR (100 MHz, CDCl₃), 128.8, 127.3, 125.3, 112.9, 111.6, 110.5, 46.6, 24.9, 24.9, 212.7; Mass, m/z 219 (M⁺). Anal. Caled. for C₁₅H₁₀O₂: C, 71.7; H, 7.81. Found: C, 71.0; H, 7.83.

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References


Notes


