Kinetics and Mechanism of the Aminolysis of Thiophenyl Cyclopentanecarboxylates in Acetonitrile

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The mechanisms of the aminolysis of aryl esters and carboxylates, and their thiol, thiono and dithio derivatives have been extensively studied. Curved Brønsted plots in the aminolysis reactions have been interpreted in terms of a zwitterionic tetrahedral intermediate, in the reaction path and a change in the rate-limiting step from leaving group expulsion to attack by the nucleophile as the nucleophile becomes more basic. In some of the cases, however, the aminolysis has been found to proceed concerted in a single step through a tetrahedral intermediate transition state (TS). The mechanistic change from a stepwise through an intermediate, to a concerted via a single TS has been reported to be caused by destabilization of the tetrahedral intermediate, by several factors, e.g., an enhanced leaving ability of the leaving group (LG), strong electronic push provided by the substrate (nonleaving group) and destabilization rendered by the amine and by substitution of S’ by O’ in the tetrahedral intermediate, T1.

In this work, we investigate the kinetics and mechanism of the aminolysis of Z-thiophenyl cyclopentanecarboxylates with X-benzylamines in acetonitrile at 40.0 °C, eq 1, where X = p-OMe, p-Me, H, p-Cl and m-Cl, and Z = p-Me, H, p-Cl and p-Br.

The reactions have been conducted under pseudo-first-order condition with a large excess of benzylamine. The purpose of this work is to elucidate the mechanism by determining various selectivity parameters, ρX, βX, ρZ, and βZ, including the cross-interaction constant, ρXZ in eq 2 where X and Z are substituents in the nucleophile and leaving group, respectively. The purpose of the present work is to further expose the effect of the ring acyl group on the aminolysis mechanism by investigating the structure-reactivity behavior of thiophenyl cyclopentanecarboxylates in acetonitrile.

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 much better leaving groups.

Since the reactions were conducted in acetonitrile, the magnitude of βX (βmac) and βZ (βleq) determined using the pKs values in water may not be reliable. However, as we have pointed out previously, the βX values can be considered to represent reliable values, although the absolute values of pKs in MeCN differ from those in water, a constant ΔpK (pKMCN − pKHO) ≈ 7.7 ± 0.3 was experimentally found. Our recent theoretical work of the solvent effect on the basicities of pyridines has
shown that the $\Delta pK_a (\approx 7.7)$ value arises solely from the ion salvation energy difference of $H^+$ ion in water and acetonitrile, $\Delta G^a_H = 10.5$ kcal mol$^{-1}$, which corresponds to $\Delta pK_a = 7.7$, at the MP2/6-31G$^*/$MP2/6-31G$^*$ level$^{15}$ of theory. Moreover, we are comparing the magnitude of $\beta_X$ and $\beta_Z$ determined for the reactions carried out under the same reaction condition (i.e., in acetonitrile). Since we used $pK_a$ values of thiophenolates in water, the comparison of $\beta_Z$ values may not be entirely reliable.

We note that the magnitude of $\beta_X$ 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, $T^4$, eq. (5). On this account (i.e., large $\beta_X$ values), the aminolysis of thiophenyl cyclopentanecarboxylates with benzylamines in acetonitrile, eq. (1), is most likely to occur by rate-limiting expulsion, $k_b$, of thiophenolate ion, $ArS^-$, from $T^4$.

The magnitude of $\beta_X$ in Table 1 ($\beta_X = 1.52 \sim 2.25$) is again much larger than those for the corresponding reactions with anilines and other secondary and tertiary amines ($\beta_X = 0.6\sim 1.0$)$^{12}$ but similar to those with benzylamines ($\beta_X = 1.4\sim 2.5$). 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, $T^4$. On this account, i.e. large $\beta_X$ values obtained, the aminolysis of thiophenyl cyclopentanecarboxylate with benzylamines in acetonitrile is most likely to occur by the rate-limiting expulsion of thiophenolate ion, $ArS^-$, from $T^4$, 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, $k_z$ in eq. 3, is therefore a complex quantity represented by eq. 6. The magnitude of $\beta_Z (\beta_Z)$ 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 ($\beta_Z = 1.2 \sim 1.5$).$^{13}$

$$k_z = k_{z_a} \cdot k_b = K \cdot k_b$$

(6)

The proposed mechanism is also supported by a large positive cross-interaction constant ($p_{xz}$ = 1.72) and adherence to the reactivity-selectivity principle (RSP), which are considered to constitute necessary conditions for the rate-limiting breakdown of $T^4$.$^{14}$

The kinetic isotope effects ($k_h/k_0$) in Table 2 involving deuterated benzylamine $(XCH_2CH_2ND_2)$ nucleophiles in acetonitrile are greater than unity ($k_h/k_0 = 1.4 \sim 1.6$), indicating that the $N$-$H$ proton transfer takes place in the rate determining step$^{15}$ 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-
Table 2. Kinetic Isotope Effects for the Reactions of Z-2-Thiophenyl Cyclopentanecarboxylates with Deuterated X-Benzylamines in Acetonitrile at 40.0°C

<table>
<thead>
<tr>
<th>X</th>
<th>Z</th>
<th>$k_H \times 10^3$ (M$^{-1}$s$^{-1}$)</th>
<th>$k_D \times 10^3$ (M$^{-1}$s$^{-1}$)</th>
<th>$k_H/k_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-OMe</td>
<td>p-Me</td>
<td>7.98 ± 0.15</td>
<td>5.14 ± 0.06</td>
<td>1.55 ± 0.02</td>
</tr>
<tr>
<td>p-OMe</td>
<td>H</td>
<td>23.0 ± 0.5</td>
<td>15.4 ± 0.3</td>
<td>1.49 ± 0.02</td>
</tr>
<tr>
<td>p-OMe</td>
<td>p-Cl</td>
<td>113 ± 3</td>
<td>79.0 ± 1.8</td>
<td>1.43 ± 0.03</td>
</tr>
<tr>
<td>P-OMe</td>
<td>p-Br</td>
<td>135 ± 4</td>
<td>97.8 ± 2.2</td>
<td>1.38 ± 0.03</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-Me</td>
<td>0.620 ± 0.005</td>
<td>0.392 ± 0.003</td>
<td>1.58 ± 0.04</td>
</tr>
<tr>
<td>p-Cl</td>
<td>H</td>
<td>2.61 ± 0.05</td>
<td>1.71 ± 0.02</td>
<td>1.53 ± 0.02</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-Cl</td>
<td>19.6 ± 0.2</td>
<td>13.4 ± 0.2</td>
<td>1.46 ± 0.02</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-Br</td>
<td>26.0 ± 0.4</td>
<td>18.5 ± 0.2</td>
<td>1.40 ± 0.03</td>
</tr>
</tbody>
</table>

$^a$Standard deviations. $^b$Standard errors.

Table 3. Activation Parameters for the Reactions of Z-2-Thiophenyl Cyclopentanecarboxylates with X-Benzylamines in Acetonitrile

<table>
<thead>
<tr>
<th>X</th>
<th>Z</th>
<th>$\Delta H^\circ$/kcal mol$^{-1}$</th>
<th>$\Delta S^\circ$/cal mol$^{-1}$ K$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-OMe</td>
<td>p-Me</td>
<td>6.0</td>
<td>48</td>
</tr>
<tr>
<td>p-OMe</td>
<td>p-Br</td>
<td>5.8</td>
<td>44</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-Me</td>
<td>5.8</td>
<td>55</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-Br</td>
<td>5.8</td>
<td>47</td>
</tr>
</tbody>
</table>

$^c$Calculated by the Eyring equation. The maximum errors calculated (by the method of Wilberg, K. B. Physical Organic Chemistry; Wiley: New York, 1964; p 378) are ±1.0 kcal mol$^{-1}$ and ±4 e.u. for $\Delta H^\circ$ and $\Delta S^\circ$, respectively.

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.$^a$

Kinetic Measurement. Rates were measured conductometrically at 40.0 ± 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$^b$ 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 ± 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)NHCH$_2$CH$_2$OH)$\cdot$H$_2$O: m.p. 192 – 194°C, IR(KBr), 3251(N-H), 3010(C-H, bending), 2936(C-H, CH$_3$), 2843(C-H, CH$_2$), 1634(O-C), 1534(C=C, aromatic), 1262, 1035(C-O); $^1$H NMR(400 MHz, CDCl$_3$), 1.12 – 1.17(8H, m, CH$_2$), 1.55 – 1.66(1H, m, CH), 3.69(3H, s, CH$_3$), 4.25(2H, d, CH$_2$), 7.08(2H, d, J = 8.78 MHz, meta H), 7.29(2H, d, J = 8.30 MHz, ortho H), $^{13}$C NMR(100.4 MHz, CDCl$_3$), 176.3(C=O), 158.7, 129.1, 128.9, 113.8, 63.7, 45.6, 42.8, 30, 25.7; Mass, m/z 233(M$^+$$)$. Anal. Calcd. for C$_7$H$_{12}$O$_3$: 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.

References

9. The average ΔpKₐ of 7.7 ± 0.3 was obtained from 22 pKₐ values for alkyl and alicyclic amines reported in Coetzee, J. F. Prog. Phys. Org. Chem. 1966, 4, 454.
11. Huhre, W. J.; Radom, L.; Schleyer, P. V. R.; Pope, J. A. In ab initio Molecular Orbital Theory; Wiley: New York, 1986; Chapter 4.