

Kinetics and Mechanism of Pyridinolysis of Aryl Dithiocyclopentanecarboxylates in Acetonitrile

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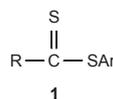
Kinetic studies on the pyridinolysis of aryl dithiocyclopentanecarboxylates **2** were carried out at 60.0 °C in acetonitrile. In the aminolysis of **2**, the β_X values were 0.5 - 0.8 with anilines, and there was no breakpoint. However, in the pyridinolysis of **2**, biphasic Brønsted plots were obtained, with a change in slope from a large value ($\beta_X \cong 0.7$) to a small value ($\beta_X \cong 0.4$) at $pK_a^0 = 5.2$. This was attributed to a change in the rate-limiting step from breakdown to the formation of a zwitterionic tetrahedral intermediate, T^\ddagger , in the reaction path, with an increase in the basicity of the pyridine nucleophile. An obvious change in the cross-interaction constant ρ_{XZ} from a large positive ($\rho_{XZ} = +1.02$) value to a small negative value ($\rho_{XZ} = -0.17$) supports the proposed mechanistic change.

Key Words: Nucleophilic substitution reaction, Pyridinolysis, Cross-interaction constant, Zwitterionic tetrahedral intermediate, Stepwise mechanism

Introduction

The transfer of a carbonyl (or thiocarbonyl) group among nucleophiles is one of the most extensively investigated subjects in mechanistic organic chemistry.¹ The rate-determining step and transition state (TS) structure of acyl transfer reactions have been found to depend on the nucleophile, leaving and non-leaving groups, and solvent.¹ In the aminolysis of aryl esters and carbonates, a biphasic dependence of the rate on amine basicity is often observed, with the slope changing from a large value ($\beta_{\text{nuc}} \geq 0.8$) to a small value ($\beta_{\text{nuc}} \cong 0.1 - 0.3$) at pK_a^0 , where the amine and leaving group have the same expulsion rates from a zwitterionic tetrahedral intermediate, T^\ddagger . This has been attributed to a change in the rate-limiting step from the breakdown to the formation of T^\ddagger with an increase in the basicity of the amine.

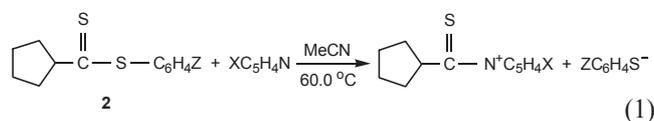
The aminolysis of dithio esters **1** has been reported in water^{1c,2} and in acetonitrile³ with various amines, e.g., benzylamines, anilines, alicyclic secondary amines, pyridines, etc. For example, the aminolysis of dithio esters with benzylamines^{3c-d} in acetonitrile exhibited rather



high pK_a^0 values (> 9.0), whereas that with pyridines^{3fg} gave low pK_a^0 values (≤ 5.0). On the other hand, our recent results on the pyridinolysis of aryl dithioacetates^{3g} ($\text{R} = \text{Me}$ in **1**) and aryl furan-2-carbodithioates^{3c} ($\text{R} = \text{C}_4\text{H}_4\text{O}$ in **1**) in acetonitrile at 60.0 °C indicated that the effect of the acyl group (R) on the pK_a^0 value is insignificant with a similar pK_a^0 value of 5.2. This means that in acyl group transfer reactions, the breakpoint pK_a^0 in a biphasic plot of rate vs. basicity of amine depends on the nucleophile and leaving group, but seems practically independent of the acyl group. This is quite plausible because

pK_a^0 depends on the pK_a values of the nucleophile (amine) and leaving group, but should be independent of the acyl group.

In this work, we report the results of kinetic studies on the pyridinolysis of aryl dithiocyclopentanecarboxylates **2** in acetonitrile at 60.0 °C (eq. 1). The aim was to complete the



X = 4-MeO, 4-Me, 3-Me, 4-C₆H₄CH₂, H, 3-Ph, 3-MeCO, 3-Cl, and 4-MeCO
Z = 4-Me, H, 4-Cl, and 4-Br

previous studies⁴ on the aminolysis of **2** and to further clarify the influence of the amine nature on the pK_a^0 value. We especially wanted to demonstrate that the breakpoint pK_a^0 in biphasic Brønsted plots has a much lower pK_a^0 value than the corresponding point for carbonyl esters. As an additional investigation to elucidate the mechanism, we determined the cross-interaction constant⁵ ρ_{XZ} in eqs. 2a and 2b, where X and Z represent the substituents in the nucleophile and leaving group, respectively.

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

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

Results and Discussion

The reactions obeyed the simple kinetic law given by eqs. 3 and 4, where ArS^- is a thiophenoxide ion and Py is pyridine. The plots of k_{obs} vs. $[\text{Py}]$ were linear, and the second-order rate constants (k_N) were obtained from the slopes of these plots. The k_N values are summarized in Table 1.

$$d[\text{ArS}^-]/dt = k_{\text{obs}} [\text{Substrate}] \quad (3)$$

Table 2. Second-order rate constants k_N Based on various temperatures and activation parameters^a for reactions of Z-phenyl dithiocyclopentanecarboxylates with X-pyridines in acetonitrile.

X	Z	t (°C)	k_N ($\times 10^3 \text{ M}^{-1} \text{ s}^{-1}$)	ΔH^\ddagger (kcal mol^{-1})	$-\Delta S^\ddagger$ ($\text{cal mol}^{-1} \text{ K}^{-1}$)
4-CH ₃ O	4-CH ₃	60.0	9.49	5.5	51
		50.0	7.11		
		40.0	5.26		
4-CH ₃ O	4-Br	60.0	25.5	5.5	49
		50.0	18.8		
		40.0	14.1		
3-Cl	4-CH ₃	60.0	0.102	5.7	59
		50.0	0.0734		
		40.0	0.0535		
3-Cl	4-Br	60.0	0.373	5.7	56
		50.0	0.272		
		40.0	0.195		

^aCalculated using the Eyring equation. The maximum errors calculated (by the method of K. B. Wiberg¹⁷) are $\pm 0.6 \text{ kcal mol}^{-1}$ and $\pm 2 \text{ e.u.}$ for ΔH^\ddagger and ΔS^\ddagger , respectively.

sted curvature, $k_{-a} = k_b$, a pyridine with $\text{p}K_a = \text{p}K_a^0 (= 5.2)$ has the same leaving ability from tetrahedral intermediate T^\ddagger as the leaving group ArS^- .

In the reactions of **2**, the β_X values were 0.5 - 0.8 with anilines (at 10.0 °C)⁴ and no breakpoints were observed. This means that $\text{p}K_a^0 \geq 5.4$ (the highest $\text{p}K_a$ used; 4-methoxyaniline) for the reactions with anilines. The decreasing $\text{p}K_a^0$ value is related to a decrease in the k_{-a}/k_b ratio, with the value for aniline (≥ 5.4) greater than that for pyridine ($= 5.2$). This decreasing value is also consistent with the general sequence for the amine expulsion (k_{-a}) rates from the tetrahedral intermediate: primary amines > secondary alicyclic amines > anilines > pyridines.¹² In the aminolysis of **2**, the breakpoint $\text{p}K_a^0 (= 5.2)$, can be experimentally observed only in the reactions with pyridines because the $\text{p}K_a^0$ value is higher than the basicities of the amines used in the reactions with anilines. This is why biphasic plots with a clear-cut breakpoint $\text{p}K_a^0$ are often observed in the aminolysis with pyridine nucleophiles, as in the pyridinolysis of aryl dithioacetates¹³ and aryl dithiocyclopentanecarboxylates in this work, both of which had $\text{p}K_a^0$ values of 5.2. The other reasons for the relatively low $\text{p}K_a^0$ value ($= 5.2$) for the pyridinolysis of two compounds of the dithio series: (i) Using the thiono (S^-) series rather than the carbonyl (O^-) series leads to a lower $\text{p}K_a^0$ caused by a decrease in the k_{-a}/k_b ratio. This is because, in T^\ddagger , the lower proclivity of S^- to form a double bond and expel a leaving group, compared to O^- , leads to an amine expulsion from T^\ddagger that is slower (smaller k_{-a}) than ArS^- leaving (k_b).¹ (ii) The thiophenoxide leaving groups ($\text{ZC}_6\text{H}_4\text{S}^-$) that are used have lower basicities than the phenoxide leaving groups ($\text{ZC}_6\text{H}_4\text{O}^-$) for the same Z. Hence, k_b should be greater (with a decrease in k_{-a}/k_b), leading to a lower $\text{p}K_a^0$ than the corresponding esters with a phenoxide leaving group.

The size of ρ_Z in Table 1 also reflects the mechanistic change. The magnitudes of ρ_Z change from large values ($\rho_Z = 1.5$) for the less basic pyridines to smaller values ($\rho_Z \cong 1.0$) for the more basic pyridines; this is in agreement with the decrease in bond

cleavage because the rate-determining step switches from the breakdown to the formation of the intermediate. Such a decrease in the magnitude of the ρ_Z values from large ($\rho_Z = 2.4 - 3.2$) to small values ($\rho_Z \cong 2.3$) with the mechanistic change has also been reported in the pyridinolysis of aryl dithioacetates.¹³ Rough estimates of the $\beta_Z (= \beta_{1g})$ values indicate a decrease from $\beta_Z \cong -0.5$ to $\beta_Z \cong -0.3$ at the breakpoint, which agrees with the change in the rate-determining step.

A clear-cut change in the cross-interaction constant is another important result supporting the mechanistic change at $\text{p}K_a^0 = 5.2$ from the breakdown to the formation of T^\ddagger as the basicity of pyridine is increased. The cross-interaction constant changes from a relatively large positive value ($\rho_{XZ} = +1.02$) to a small negative value ($\rho_{XZ} = -0.17$) at the breakpoint. Similar changes in ρ_{XZ} values have been reported for the pyridinolysis of S-phenyl 4-nitrobenzoates¹⁰ ($4\text{-NO}_2\text{C}_6\text{H}_4\text{C(=O)SC}_6\text{H}_4\text{Z}$) and aryl dithioacetates¹³ ($\text{CH}_3\text{C(=S)SC}_6\text{H}_4\text{Z}$). In the former, the ρ_{XZ} value changed from +1.41 to -0.32 at $\text{p}K_a^0 \cong 4.2$, and in the latter, it changed from +1.34 to -0.15 at $\text{p}K_a^0 = 5.2$, as the basicity of pyridine was increased. These are interpreted to indicate mechanistic changes from the breakdown to the formation of T^\ddagger . These changes in the ρ_{XZ} values with changes in the reaction mechanism give further credence to the use of the cross-interaction constant as a useful mechanistic criterion.

Table 2 lists the activation parameters ΔH^\ddagger and $-\Delta S^\ddagger$ for the pyridinolysis of **2**. The values of ΔH^\ddagger and $-\Delta S^\ddagger$ are smaller for a more basic pyridine ($X = 4\text{-OCH}_3$) than for a less basic pyridine ($X = 3\text{-Cl}$). Although the differences are small, they are significant enough to be over the error limits. These trends are in accordance with the breakdown step (for $X = 3\text{-Cl}$) requiring higher energy and lower (more negative) entropy in the TS due to bond cleavage to two ionic products (eq. 2).

In summary, kinetic studies on the pyridinolysis of aryl dithiocyclopentanecarboxylates **2** were carried out at 60.0 °C in acetonitrile. In the aminolysis of **2**, the β_X values were 0.5 - 0.8 with anilines, and there was no breakpoint. However, in the pyridinolysis of **2**, biphasic Brønsted plots were obtained, with a slope change from a large value ($\beta_X \cong 0.7$) to a small value ($\beta_X \cong 0.4$) at $\text{p}K_a^0 = 5.2$. This slope change was attributed to a change in the rate-limiting step from the breakdown to the formation of a zwitterionic tetrahedral intermediate T^\ddagger in the reaction path with an increase in the basicity of the pyridine nucleophile. A clear-cut change in the cross-interaction constant ρ_{XZ} from a large positive value ($\rho_{XZ} = +1.02$) to a small negative value ($\rho_{XZ} = -0.17$) supports the proposed mechanistic change. Other selectivity parameters (ρ_X and ρ_Z) and activation parameters (ΔH^\ddagger and ΔS^\ddagger) are also consistent with the proposed mechanism, as is the adherence to the reactivity selectivity principle (RSP).

Experimental Section

Materials. Acetonitrile (Merk, GR grade) was used after three distillations. The pyridine nucleophiles (Aldrich, GR grade) were used without further purification. The preparation and analytical data are reported elsewhere.¹²

Kinetic measurement. The rates were measured conductometrically in acetonitrile. The conductivity bridge used in this

work was a homemade computer-automated A/D converter conductivity bridge. Pseudo first-order rate constants k_{obs} were determined by the Guggenheim method¹⁴ with a large excess of pyridine (Py). Second-order rate constants k_2 were obtained from the slope of a plot of k_{obs} vs. [Py] with more than five concentrations of pyridine. The k_2 values in Table 1 are the averages of more than three runs, and were reproducible to within $\pm 3\%$.

Product analysis. The substrate, *p*-bromophenyl dithiocyclopentanecarboxylate (0.05 mole), was reacted with excess 4-picoline (0.5 mole) with stirring for more than 15 half-lives at 60.0 °C in acetonitrile. The salt was filtered, and the solvent was removed from the precipitate. An analysis of the product gave the following results.

c-C₅H₉C(=S)N⁺C₅H₄-*p*-CH₃⁻SC₆H₄-4-Br: mp 65 - 67 °C, ¹H NMR (400 MHz, CDCl₃), 1.38 (8H, m, CH₂), 1.48 (3H, s, CH₃), 2.37 (1H, m, CH), 7.26-7.30 (2H, dd, pyridine), 7.32-7.36 (9H, m, phenyl), 7.36-7.39 (2H, d, pyridine); ¹³C NMR (100.4 MHz, CDCl₃), 230.1(C=S), 135.8, 135.3, 132.3, 132.1, 132.0, 129.8, 129.5, 52.7, 30.5, 27.2, 25.1 (CH₃); ν_{max} (KBr), 1567, 1456 (C=C, phenyl), 1230 (C=S), 857 (C-H, pyridine), 802 (C-H, phenyl); mass, m/z 394 (M⁺). Anal. Calcd for C₁₈H₂₀BrNS₂; C, 54.8; H, 5.11. Found C, 54.6; H, 5.13.

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