# Kinetics and Mechanism of the Aminolysis of Phenyl and 4-Nitrophenyl Chlorothionoformates

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The reactions of a series of secondary alicyclic amines with the title substrates are subjected to a kinetic investigation in aqueous solution, 25 °C, ionic strength 0.2 M (maintained with KCl). Under amine excess pseudo-first-order rate coefficients ($k_{obsd}$) are found. The plots of $k_{obsd}$ against concentration of free amine at constant pH are linear, with the slopes ($k_N$) independent of pH. The Brönsted-type plots obtained (log $k_N$ vs amine p$K_a$) for the aminolysis of both substrates are linear with the same slope, $\beta = 0.26$. From this value, the kinetic law, and the analysis of products, it is deduced that these reactions proceed through a zwitterionic tetrahedral addition intermediate ($\mathbf{T}^{\pm}$) on the reaction path, and its formation is the rate-determining step. From a comparison of the present reactions with the concerted aminolysis of substituted phenyl chloroformates in acetonitrile it is inferred that the change of $S^-$ by $O^-$ in $\mathbf{T}^{\pm}$ and that of water by acetonitrile as solvent destabilizes $\mathbf{T}^{\pm}$ in such a way that the stepwise reaction becomes enforced concerted.

## Introduction

Although there has been much interest on the kinetics and mechanism of the hydrolysis and solvolysis of alkyl and aryl chloroformates[1,2] and fluoroformates,[1,3] less is known on the aminolysis of these compounds.[4,5] Moreover, to our knowledge there are no reports on the kinetics and mechanism of the aminolysis of either alkyl or aryl chlorothionoformates.

There are apparently conflicting conclusions regarding the mechanisms of some of the above reactions. Those of methyl chloroformate with aliphatic and aromatic primary amines and pyridines in water have been claimed to be stepwise, through the formation of a zwitterionic terahedral intermediate.[4b,c] On the other hand it was found that the reactions of anilines with substituted phenyl chloroformates in acetonitrile are governed by a concerted mechanism.[5]

In order to clarify the mechanisms of the above reactions and to assess the influence of the carbonyl or thiocarbonyl group of the substrate and the role of the solvent, we investigate in this work the kinetics of the reactions of a series of secondary alicyclic amines with the title substrates in water.

## Experimental Section

**Materials.** The amines were purified as reported.[6] Phenyl chlorothionoformate (PClTF) was from Sigma and used as purchased. 4-Nitrophenyl chlorothionoformate (NPClTF) was synthesized as follows: To a solution of 4-nitrophenol (4.6 g, 33 mmol) dissolved in THF (20 mL) in a Schlend round-bottomed flask, a solution (13.6 mL) of 2.5 M butyllithium (Aldrich) was added slowly under nitrogen atmosphere. The product, lithium 4-nitrophenoxide was rapidly transferred to a compensation funnel, under nitrogen. In another Schlend round-bottomed flask, thiophosgene (Aldrich, 4 mL) was dissolved in anhydrous THF (10 mL) under nitrogen and the flask placed in an ethanol−liquid nitrogen bath. The compensation funnel was attached to the flask and the lithium 4-nitrophenoxide solution added dropwise with stirring during 2 h. The mixture was left overnight with stirring under nitrogen at ambient temperature. Chloroform (50 mL) was added to this mixture and the solution washed with water. The organic layer was dried with $MgSO_4$ and filtered under vacuum and the solvent evaporated off. The crystallized NPClTF melted at 57 °C (lit.[7] mp 61−63 °C) and was identified as follows:

NPClTF: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.35 (sd, 2H, $J$ = 9.2 Hz), 8.36 (sd, 2H, $J$ = 9.2 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 122.71 (C-2/6), 125.78 (C-3/5), 146.49 (C-4), 158.15 (C-1), 184.66 (C=S); IR (KBr) 1552 (C=C), 1492 and 1345 (C−$NO_2$), 1244 (C=S) $cm^{-1}$.

**Kinetic Measurements.** These were performed spectrophotometrically by following the production of the aryl thionocarbamates at 245 and 320 nm for the aminolysis of PClTF and NPClTF, respectively. The reactions of both substrates with piperidine and piperazine were measured using an Applied Photophysics SF-17 MV stopped-flow spectrophotometer. The reactions with the other amines were followed by means of a Hewlett Packard HP 8453 diode array spectrophotometer attached to a Hi-Tech SFA-20 rapid kinetics accesory. The reactions were studied under the following conditions: aqueous solutions, 25.0 ± 0.1 °C, ionic strength 0.2 M (maintained with KCl), and at least a 10-fold excess of total amine over the substrate.

Pseudo-first-order rate coefficients ($k_{obsd}$) were found throughout, by means of the method described.[6] The experimental conditions of the reactions and the $k_{obsd}$ values obtained are shown in Tables 1 and 2.

**Product Studies.** Phenyl thionocarbamates of piperidine and morpholine were identified as the final products of the reactions of PClTF with these two amines. This was carried out by comparison of the UV-vis spectra after completion of these reactions with those of authentic samples under the same experimental conditions. The UV-vis spectra after the end of the reactions of both substrates with the above two amines were also compared with those after completion of the reactions of bis phenyl and bis 4-nitrophenyl thionocarbonates

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**Table 1. Experimental Conditions and $k_{obsd}$ Values for the Aminolysis of Phenyl Chlorothionoformate (PClTF)[a]**

| amine | pH | $F_N$[b] | $10^2[N]_{tot}$,[c] M | $k_{obsd}$, $s^{-1}$ | no. of runs |
|---|---|---|---|---|---|
| piperidine | 10.92 | 0.32 | 1.0−10 | 0.7−10 | 5 |
| | 11.22 | 0.49 | 0.2−10 | 0.2−13 | 6 |
| piperazine | 9.64 | 0.33 | 0.10−10 | 0.08− 8.0 | 5 |
| | 9.94 | 0.50 | 0.10−10 | 0.1−13 | 5 |
| 1-(2-hydroxyethyl)-piperazine | 9.08 | 0.33 | 0.06−1.0 | 0.12−0.52 | 6 |
| | 9.38 | 0.50 | 0.06−0.4 | 0.13−0.48 | 7 |
| | 9.68 | 0.67 | 0.06−0.6 | 0.17−0.56 | 6 |
| morpholine[d] | 6.50 | 0.0052 | 0.15−0.7 | 0.001−0.005 | 6 |
| | 6.80 | 0.010 | 0.06−0.6 | 0.001−0.008 | 7 |
| | 7.10 | 0.020 | 0.05−0.5 | 0.002−0.01 | 7 |
| 1-formylpiperazine | 7.68 | 0.33 | 0.06−0.6 | 0.05−0.3 | 7 |
| | 7.98 | 0.50 | 0.06−0.6 | 0.06−0.4 | 7 |
| | 8.28 | 0.67 | 0.06−0.5 | 0.06−0.4 | 6 |
| piperazinium ion | 5.51 | 0.33 | 0.07−0.7 | 0.006−0.05 | 6 |
| | 5.81 | 0.50 | 0.07−1.0 | 0.007−0.13 | 8 |
| | 6.11 | 0.67 | 0.07− 0.85 | 0.009−0.14 | 7 |

[a] In aqueous solution at 25.0 °C, ionic strength 0.2 M (KCl). [b] Free amine fraction. [c] Concentration of total amine (free base plus protonated forms). [d] In the presence of $5 \times 10^{-3}$ M phosphate buffer.

**Table 2. Experimental Conditions and $k_{obsd}$ Values for the Aminolysis of 4-Nitrophenyl Chlorothionoformate (NPClTF)[a]**

| amine | pH | $F_N$[b] | $10^2[N]_{tot}$,[c] M | $k_{obsd}$, $s^{-1}$ | no. of runs |
|---|---|---|---|---|---|
| piperidine | 10.92 | 0.32 | 1.0−10 | 1.0−18 | 5 |
| | 11.22 | 0.49 | 0.2−10 | 0.3−26 | 5 |
| piperazine | 9.64 | 0.33 | 0.10−10 | 0.16− 17 | 5 |
| | 9.94 | 0.50 | 0.10−10 | 0.19−24 | 5 |
| 1-(2-hydroxyethyl)-piperazine | 9.08 | 0.33 | 0.06−1.0 | 0.15−0.85 | 6 |
| | 9.38 | 0.50 | 0.06−0.4 | 0.19−0.78 | 6 |
| | 9.68 | 0.67 | 0.06−0.6 | 0.23−1.0 | 6 |
| morpholine[d] | 6.50 | 0.0052 | 0.15−0.65 | 0.002−0.008 | 6 |
| | 6.80 | 0.010 | 0.06−0.6 | 0.002−0.015 | 7 |
| | 7.10 | 0.020 | 0.05−0.5 | 0.003−0.022 | 7 |
| 1-formylpiperazine | 7.68 | 0.33 | 0.06−0.6 | 0.08−0.44 | 7 |
| | 7.98 | 0.50 | 0.06−0.6 | 0.08−0.61 | 7 |
| | 8.28 | 0.67 | 0.06−0.5 | 0.09−0.62 | 6 |
| piperazinium ion | 5.51 | 0.33 | 0.07−0.85 | 0.01−0.14 | 7 |
| | 5.81 | 0.50 | 0.07−0.85 | 0.02−0.20 | 7 |
| | 6.11 | 0.67 | 0.07−0.85 | 0.02−0.30 | 7 |

[a] In aqueous solution at 25.0 °C, ionic strength 0.2 M (KCl). [b] Free amine fraction. [c] Concentration of total amine (free base plus protonated forms). [d] In the presence of $5 \times 10^{-3}$ M phosphate buffer.

with the same amines. It was inferred from these comparisons that the phenyl and 4-nitrophenyl thionocarbamates derivatives of these amines are one of the products of these reactions.

## Results and Discussion

The kinetic law found for the present reactions is given by eqs 1 and 2, under amine excess, where P, S, and NH represent the aryl thionocarbamate product, the substrate, and the free secondary amine, respectively, and $k_{obsd}$ is the pseudo-first-order rate coefficient; $k_o$ and $k_N$ are the rate coefficients for hydrolysis and aminolysis of the substrate, respectively. The latter values were found as the intercept and slope, respectively, of linear plots of $k_{obsd}$ against the free-amine concentration at constant pH. For all the reactions, the value of $k_o$ was negligible compared to the aminolysis term in eq 2. Throughout the reactions studied the $k_N$ values obtained were pH independent, and are shown in Table 3.

$$\frac{d[P]}{dt} = k_{obsd}[S] \quad (1)$$

$$k_{obsd} = k_o + k_N[NH] \quad (2)$$

**Table 3. Values of the p$K_a$ of the Conjugate Acids of Secondary Alicyclic Amines and $k_N$ for the Aminolysis of Phenyl Chlorothionoformate (PClTF) and 4-Nitrophenyl Chlorothionoformate (NPClTF)[a]**

| amine | p$K_a$ | $k_N$, $s^{-1}$ $M^{-1}$ PClTF | $k_N$, $s^{-1}$ $M^{-1}$ NPClTF |
|---|---|---|---|
| piperidine | 11.24 | 530 ± 23 | 1058 ± 27 |
| piperazine | 9.94 | 514 ± 18 | 962 ± 27 |
| 1-(2-hydroxyethyl)piperazine | 9.38 | 240 ± 8 | 432 ± 18 |
| morpholine | 8.78 | 130 ± 4 | 216 ± 6 |
| 1-formylpiperazine | 7.98 | 116 ± 4 | 177 ± 7 |
| piperazinium ion | 5.81 | 24 ± 1 | 48 ± 1 |

[a] Values of both p$K_a$ and $k_N$ in aqueous solution, at 25 °C, ionic strength 0.2 M (KCl).

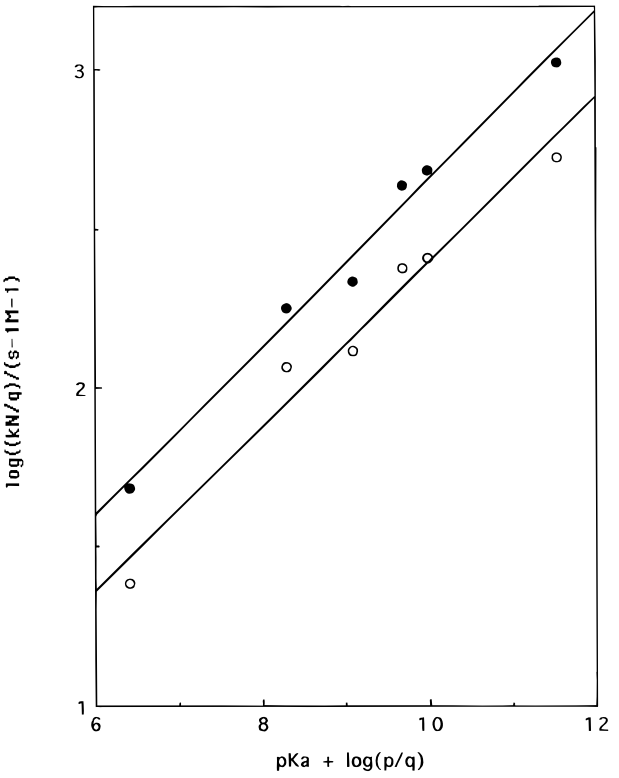


**Figure 1.** Brönsted-type plots (statistically corrected) obtained in the reactions of secondary alicyclic amines with NPClTF (●) and PClTF (○) in water, at 25 °C, ionic strength 0.2 M (KCl). The slope is $\beta = 0.26$ for the reactions of both substrates.

The Brönsted-type plots (statiscally corrected)[6,8] obtained with de $k_N$ data are linear with slopes $\beta = 0.26 \pm 0.1$ for the reactions of both substrates (see Figure 1). The value of the slopes is in agreement with those found in the aminolysis of aryl acetates,[9] diaryl carbonates,[10] methyl chloroformate,[4c] acetyl chloride,[11] aryl thiolacetates,[6,12] and *O*-alkyl aryl dithiocarbonates,[13] thiolcarbonates,[14] and thionocarbonates[15] in aqueous solution,

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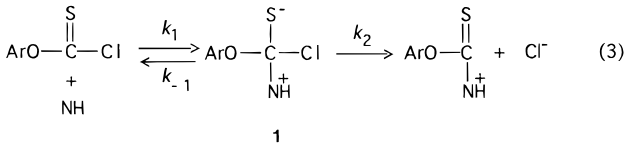
when the formation of a zwitterionic tetrahedral addition intermediate ($\mathbf{T}^{\pm}$) is the rate-determining step ($\beta = 0.1-0.3$). A larger value of the Bronsted slope ($\beta = 0.8-1.0$) has been found in the above aminolyses when the expulsion of the leaving group from $\mathbf{T}^{\pm}$ is rate determining.[6,9−14]

According to the rate law obtained, the analysis of products, and the Bronsted-type plots found for the reactions under investigation, the mechanism of these reactions can be described by eq 3, where Ar is either phenyl or 4-nitrophenyl and NH represents a secondary alicyclic amine. In eq 3 the $k_1$ step is rate limiting.



1 (3)

The higher reactivity of NPClTF compared to PClTF toward these amines (Figure 1) for the formation of intermediate **1** (eq 3) is reasonable in terms of the larger electron-withdrawing ability of the *p*-$NO_2$ substituent (relative to H), both by resonance and inductive effects.[16] This fact renders the thiocarbonyl carbon of NPClTF more positive than that of PClTF and therefore more susceptible to amine attack.

It has been reported that the reactions of substituted phenyl chloroformates with anilines in acetonitrile are concerted (although the possibility of a two-step mechanism was not entirely precluded).[5] The apparent discrepancy with our work can be clarified as follows:

(i) It is known that the change of $O^-$ by $S^-$ in the zwitterionic tetrahedral addition intermediate ($\mathbf{T}^{\pm}$) makes it less unstable. This has been explained by the superior ability of $O^-$ (relative to $S^-$) in $\mathbf{T}^{\pm}$ to form a double bond and expel faster both its leaving and amino groups.[17]

(ii) The intermediate $\mathbf{T}^{\pm}$ should be less stable in acetonitrile than in water due to its zwitterionic nature and the high polarity of water. In fact we have found that the reactions of secondary alicyclic amines with *O*-ethyl 2,4,6-trinitrophenyl dithiocarbonate are concerted in aqueous ethanol,[18] whereas the same reactions are stepwise in water.[13] It was concluded that expulsion of the amine from $\mathbf{T}^{\pm}$ should be faster in the less polar solvent, and the nucleofugality of the leaving group of the substrate should not change significantly with the solvent polarity.[18] This fact should render the intermediate more unstable kinetically in the less polar solvent.[18]

The above two arguments can explain the reason for the different mechanisms followed by the aminolysis of phenyl chloroformates in acetonitrile[5] and the reactions under the present study.

The aminolyses of methyl chloroformate[4b,c] and acetyl chloride[11] in water have been shown to be stepwise processes. It could be possible that the aminolysis of aryl chloroformates in *water* were concerted due to the kinetic destabilization of the intermediate $\mathbf{T}^{\pm}$ involved in the latter reactions. Taking into account that the inductive effects are more important in $\mathbf{T}^{\pm}$ than the resonance effects,[19] this destabilization should arise from the larger electron-withdrawing inductive ability of the phenoxy group ($\sigma_I = 0.37$)[20] relative to that of methyl ($\sigma_I = 0.01$)[20] and methoxy ($\sigma_I = 0.29$).[20] This fact should render the central carbon of the intermediate $\mathbf{T}^{\pm}$ with phenoxy more positively charged than those with methyl and methoxy, facilitating therefore the formation of the C=O double bond and the amine expulsion from the intermediate. At present we are beginning a kinetic study on the aminolysis of substituted phenyl chloroformates in water in order to investigate whether there is a change in mechanism from stepwise for the reactions of acetyl chloride and methyl chloroformate in water to concerted for those of aryl chloroformates in the same solvent.

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