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Kinetics and mechanisms of the reactions of *S*-methyl chlorothioformate with pyridines and secondary alicyclic amines

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Abstract—The pyridinolysis of *S*-methyl chlorothioformate shows a biphasic Brønsted-type plot, in agreement with a stepwise mechanism and a change in the rate-limiting step, from formation of a zwitterionic tetrahedral intermediate ($T^{\pm}$) at high pK_a to its breakdown at low pK_a. The reaction of the same substrate with secondary alicyclic amines shows a linear Brønsted-type plot of slope 0.23, which is in accordance with a stepwise mechanism where formation of $T^{\pm}$ is the rate-determining step for the whole pK_a range examined.

1. Introduction

There have been many reports on the kinetics and mechanisms of the solvolysis[1,2] and aminolysis[3] of chloroformates (RO–CO–Cl). Nevertheless, the solvolysis of chlorothioformates (RS–CO–Cl) and chlorothionoformates (RO–CS–Cl),[4] as well as the aminolysis of the latter compounds[5] have received little attention. Furthermore, to our knowledge, there have been no investigations concerning the kinetics of the aminolysis of *S*-alkyl chlorothioformates.

The hydrolysis of *S*-methyl chlorothioformate (**1**) and the solvolysis of the *S*-ethyl analogue in several alcohol–water mixtures were found to be driven by an S_N1 mechanism.[4a,b] Nevertheless, the solvolysis of the latter substrate in pure methanol and ethanol, and in 90% ethanol–water is governed by an addition–elimination process.[4b]

The pyridinolysis of methyl chloroformate (**2**) in water shows a curved (biphasic) Brønsted-type plot, with slopes β=0.93 at low pK_a and β=0.15 at high pK_a.[3b] This was explained by a stepwise mechanism, through a zwitterionic tetrahedral intermediate ($T^{\pm}$), and a change in the rate-limiting step, from $T^{\pm}$ breakdown to $T^{\pm}$ formation as the amine becomes more basic.[3b] The reactions of piperidine and pyrrolidine, as well as a series of aliphatic amines, with isopropyl chloroformate are driven by an addition–elimination mechanism involving a $T^{\pm}$ intermediate.[3c] The pyridinolysis of phenyl and 4-nitrophenyl chloroformates in acetonitrile exhibits linear Brønsted-type plots with slopes (β) of ca. 0.3, which was attributed to a stepwise mechanism where the formation of the intermediate $T^{\pm}$ is the rate-limiting step.[3d]

The reactions of secondary alicyclic (SA) amines[5a] and pyridines[5b] with phenyl and 4-nitrophenyl chlorothionoformates (**3** and **4**, respectively) and those of the former amines with a series of aryl chloroformates,[3f,g] in water exhibit linear Brønsted-type plots consistent with a stepwise process, where the formation of the intermediate $T^{\pm}$ is the rate-limiting step.

On the other hand, the anilinolysis of a series of aryl chlorothionoformates in acetonitrile has been claimed to proceed by a concerted mechanism through a four-membered hydrogen-bonded cyclic transition state.[5c] Similarly, the phenolysis of **3** and **4** in an aqueous solution was found to be governed by a concerted process.[6]

Due to these apparent contradictory results and in order to clarify the mechanisms of the aminolysis of chlorothioformates and their oxy analogues, in the present work we undertake a kinetic and mechanistic study of the reactions of pyridines and SA amines with chlorothioformate **1** in aqueous solution. Specific aims are the comparison of these reactions between them, and with the pyridinolysis of the corresponding chloroformate (**2**) in water,[3b] and the pyridinolysis and SA aminolysis of *S*-methyl 4-nitrophenyl and *S*-methyl 2,4-dinitrophenyl thiocarbonates (**5** and **6**, respectively) in water.[7] Through these comparisons the effects of the amine nature and the S atom in the nonleaving group, as well as the influence of the leaving group on the kinetics and mechanism will be assessed.

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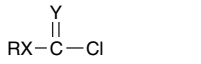
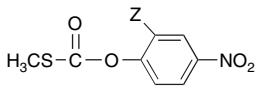


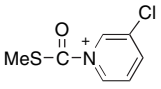
1 (R = methyl; X = S; Y = O)
2 (R = methyl; X = O; Y = O)
3 (R = phenyl, X = O; Y = S)
4 (R = 4-nitrophenyl, X = O; Y = S)



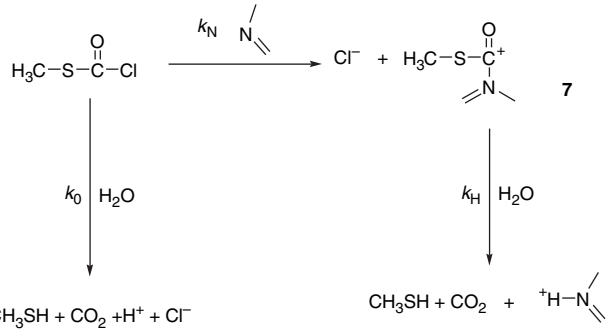
5 (Z = H)
6 ($Z = NO_2$)

2. Results and discussion

The spectrophotometric study of the reactions of **1** with pyridines in water, shows the appearance and disappearance of an intermediate at 270–320 nm. We assume this intermediate to be compound **7** (Scheme 1) because similar intermediates have been detected spectrophotometrically or isolated in the pyridinolysis of methyl chloroformate,[3b] aryl chlorothionoformates,[5b] and other compounds.[8] As an example, Figure 1 shows a plot of absorbance at 290 nm vs time obtained for the reaction of 3-chloropyridine with **1**. This intermediate is probably compound **7a**.



7a



Scheme 1.

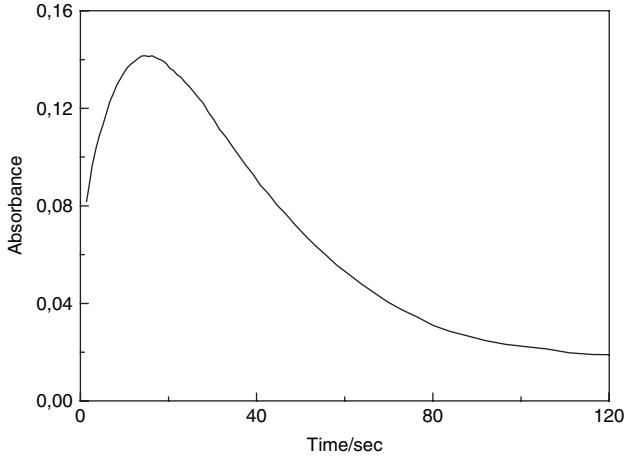
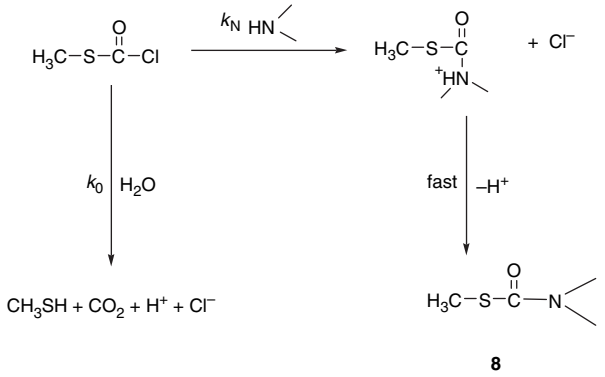


Figure 1. Plot of absorbance at 290 nm (1 cm cell) against time obtained for the reaction of **1** with 3-chloropyridine in an aqueous solution at 25.0 °C with an ionic strength of 0.2 M (KCl). Concentration of total amine 3.5×10^{-2} M, pH=2.97. The intermediate is presumably compound **7a**.

For the reactions involving SA amines, only the increase of a band in the 210–240 region is observed, probably because the corresponding cation intermediate rapidly deprotonates, leading to the stable carbamate-type product **8** (see Scheme 2).



8

Scheme 2.

Under amine excess over the substrate, pseudo-first-order rate coefficients (k_{obsd}) were obtained for all the reactions. The experimental conditions of the reactions and the values of k_{obsd} are shown in Tables 1and 2.

The rate law obtained for the reactions of **1** with the series of pyridines and SA amines is shown in Eqs. 1 and 2, where P represents either intermediate **7** (for pyridines, Scheme 1) or the corresponding thiocarbamate **8** (for SA amines, Scheme 2), S represents the substrate, and N the free amine. The rate constants k_0 and k_N are those for hydrolysis and aminolysis of the substrate, respectively.

Table 1. Experimental conditions and values of k_{obsd} for the pyridinolysis of **1**[a]

Pyridine substituent	pH	10^3 $[N]_{tot}$/M	10^2 k_{obsd}/s^{-1}	No. of runs
4-$N(CH_3)_2$	9.56	0.82–6.94	7.37–354	6
	9.87	0.82–8.17	12.0–568	7
4-NH_2	9.06	1.84–15.6	9.61–61.7	6
	9.37	0.85–7.22	16.4–59.0	6
	9.68	0.85–8.50	15.8–75.5	7
3,4-$(CH_3)_2$	6.46	1.77–7.09	6.58–17.9	6
	6.77	0.93–9.33	6.75–35.31	7
	7.08	0.54–5.35	5.54–24.4	7
H	5.06	1.01–10.1	3.63–15.9	7
	5.37	1.01–8.6	3.84–18.8	6
	5.68	1.01–10.1	7.45–23.7	7
3-$CONH_2$	3.12	14.5–58.1	10.9–23.4	6
	3.74	13.1–39.4	9.12–19.9	6
3-Cl	2.66	8.81–74.9	7.48–20.8	6
	2.97	8.81–88.1	5.55–32.6	7
4-CN	5.00[b]	8.32–83.2	1.98–6.03	7
	5.30[b]	8.32–83.2	1.89–6.57	7
	5.60[b]	8.22–82.2	1.76–5.92	7
3-CN	5.00[b]	8.28–82.8	1.29–2.72	7
	5.30[b]	8.32–83.2	1.11–2.83	7
	5.60[b]	8.32–83.2	1.08–2.78	7

[a] In aqueous solution, at 25.0 °C with an ionic strength of 0.2 M.
[b] Under the presence of an acetate buffer 0.005 M.

Table 2. Experimental conditions and values of k_{obsd} for the SA aminolysis of **1**[a]

Amine	pH	10^3 $[N]_{tot}$/M	10^3 k_{obsd}/s^{-1}	No. of runs
Piperidine[b]	8.0	0.5–5.0	8.66–15.7	6
	8.5	0.5–5.0	10.6–28.7	6
	9.0	0.5–5.0	18.3–58.6	6
Piperazine	9.64	0.05–0.50	35.6–277	6
	9.94	0.05–0.50	59.7–344	7
	10.24	0.05–0.50	67.8–365	7
1-(2-Hydroxyethyl)piperazine	9.08	0.05–0.50	50.3–104	7
	9.38	0.125–0.50	57.7–123	6
	9.68	0.05–0.50	62.0–162	7
Morpholine	8.48	0.5–5.0	123–846	7
	8.78	0.5–3.5	128–884	5
	9.08	0.10–1.25	70.2–577	8
Formylpiperazine	7.68	0.5–1.6	45.0–155	7
	7.98	0.25–2.50	38.5–340	7
	8.28	0.25–2.50	44.5–450	7
Piperazinium ion	5.51	0.5–5.0	15.9–132	7
	5.81	0.5–16.2	22.7–685	7
	6.11	0.5–5.0	24.4–225	7

[a] In aqueous solution, at 25.0 °C with an ionic strength of 0.2 M.
[b] Under the presence of borate buffer 0.01 M.

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

$$k_{obsd} = k_0 + k_N[N] \quad (2)$$

The values of k_N were obtained as the slopes of plots of Eq. 2 at constant pH, and were pH independent. Tables 3 and 4 summarize the values of k_N found, together with those for the pK_a of the conjugate acids of the pyridines and SA amines, respectively.

Table 3. Values of pK_a of the conjugate acid of pyridines and of k_N for the pyridinolysis of **1**[a]

Pyridine substituent	pK_a	k_N[b]/s^{-1} M^{-1}
4-$N(CH_3)_2$	9.87	128±7
4-NH_2	9.42	117±8
3,4-$(CH_3)_2$	6.77	63±2
H	5.37	34±2
3-$CONH_2$	3.43	7.0±0.7
3-Cl	2.97	6.5±0.4
4-CN	2.20	0.57±0.02
3-CN	1.55	0.22±0.06

[a] In aqueous solution, at 25.0 °C, with an ionic strength of 0.2 M.
[b] Nucleophilic rate constant for the formation of intermediate **7** in Scheme 1.

Table 4. Values of pK_a for the conjugate acid of SA amines and of k_N for the SA aminolysis of **1**[a]

SA amine	pK_a	$10^{-2}k_N$[b]/s^{-1} M^{-1}
Piperidine	11.24	17.5±0.5
Piperazine	9.94	10.9±0.6
1(2-Hydroxyethyl)piperazine	9.38	3.44±0.2
Morpholine	8.78	4.88±0.2
Formylpiperazine	7.68	2.65±0.09
Piperazinium ion	5.81	0.82±0.02

[a] In aqueous solution, at 25.0 °C, and an ionic strength of 0.2 M.
[b] Nucleophilic rate constant for the formation of product **8** in Scheme 2.

The fact that the values of k_{obsd} increase as the concentration of the amine increases rules out an S_N1 mechanism for the aminolysis of the title substrate. This is in contrast to the ionization process found for the hydrolysis of this substrate.[4a]

The Brønsted-type plots of Figure 2 were obtained with the data in Table 3 for the pyridinolysis of the substrate and with the data of Table 4, after statistical correction of k_N and pK_a, for the reactions with SA amines. The latter were corrected with $p=2$ for all the conjugate acids of the SA amines, except piperazinium ion for which $p=4$, and with $q=2$ for piperazine ($q=1$ for the other SA amines).[9,10] The statistical parameter q is the number of equivalent basic sites in the amine and p is the number of equivalent protons in the conjugate acid of the amine.[10] As can be observed, the Brønsted-type plot is linear for the SA aminolysis and biphasic for the pyridinolysis.

The curved Brønsted line in Figure 2 for the pyridinolysis of **1** was calculated by means of a semiempirical equation (Eq. 3) based on the existence of a zwitterionic tetrahedral intermediate ($T^{\pm}$) on the reaction pathway (see Scheme 3).[3b,9,11]

This equation contains four parameters: β_1 and β_2, which are the Brønsted slopes at high and low pK_a, respectively, and $\log k_N^0$ and pK_a^0, which are the corresponding values at the center of the curvature.

$$\log\left(k_N/k_N^0\right) = \beta_2\left(pK_a - pK_a^0\right) - \log(1 + a/2) \quad (3)$$

$$\log a = (\beta_2 - \beta_1)\left(pK_a - pK_a^0\right)$$

The Brønsted curve was calculated by means of the following parameters: $\log k_N^0=1.0$, $pK_a^0=3.6$, $\beta_1=0.12$, and $\beta_2=1.0$ ($n=8$, $R=0.996$). The errors of the slopes are ±0.1, and those of pK_a^0 and $\log k_N^0$ are ±0.2 and ±0.1, respectively. The curved Brønsted plot can be explained by the existence of the intermediate $T^{\pm}$ and a change in the rate-limiting step

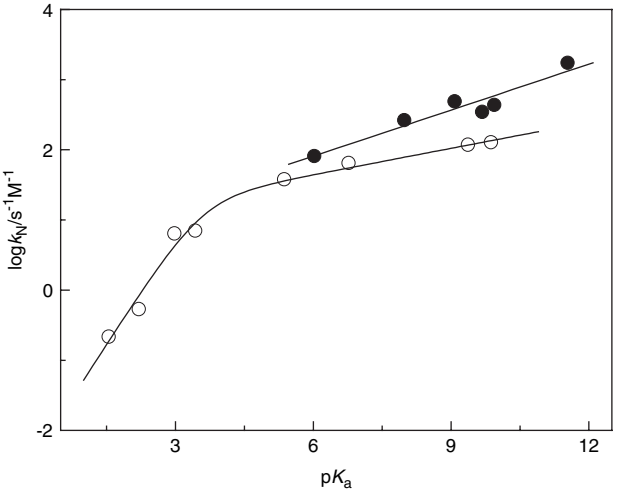
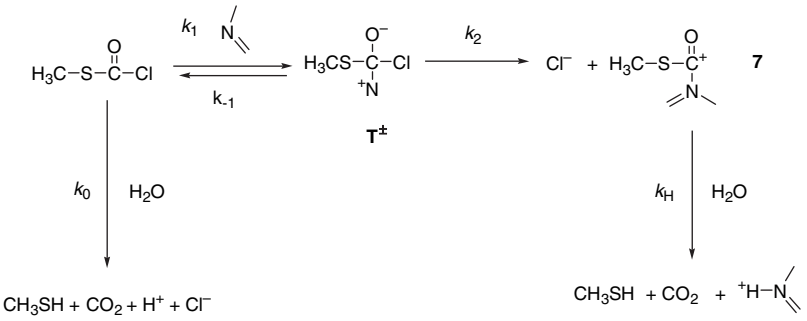


Figure 2. Brønsted plots for k_N, obtained in the reactions of **1** with pyridines (○) and SA amines (●), in an aqueous solution, 25.0 °C with an ionic strength of 0.2 M (KCl).



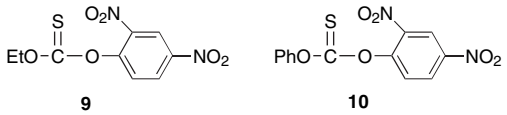
Scheme 3.

from that of k_2 in Scheme 3, to that of k_1, as the amine becomes more basic.[3b,11]

The values of β_1 and β_2 are in accordance with those reported for other aminolysis governed by the stepwise mechanisms: β_1=0.1–0.3 and β_2=0.8–1.1.[3b,9,11–14]

The slope of the linear Brønsted plot found for the SA aminolysis, β=0.23±0.05, is in agreement with the values of the Brønsted slopes found in stepwise mechanisms of similar reactions when the formation of the intermediate $T^{\pm}$ is the rate-limiting step.[3f,g,5a,11–14]

It is noteworthy that the rate constants of $T^{\pm}$ formation (k_1) for the reactions of **1** with SA amines (k_N=k_1) for the whole pK_a range are greater than those of isobasic pyridines (for amines with pK_a>3.6, where $k_2 \gg k_{-1}$), showing that SA amines are better nucleophiles than isobasic pyridines toward **1**. This result is surprising because for the reactions of these two amine series with chlorothionoformates **3** and **4** the k_1 values are similar,[5a,b] and for the reactions of these amines with ethyl and phenyl 2,4-dinitrophenyl thionocarbonates (**9** and **10**, respectively) the k_1 values for pyridines are 5–25 fold greater than those for isobasic SA amines.[12d,15] A possible explanation could be that both amine series show similar reactivities toward a thiocarbonyl carbon such as that in the chlorothionoformates, but SA amines exhibit steric hindrance toward the thiocarbonyl carbon of the dinitrophenyl derivatives when compared with the isobasic pyridines. The fact that SA amines show larger k_1 values than pyridines toward **1**, could be due to the harder character of the carbonyl carbon of this substrate, which makes it a better electrophile toward a harder base such as an SA amine relative to the softer isobasic pyridine.[16]



9 **10**

Figure 3 shows the Brønsted plots obtained for the pyridinolysis of **1** (this study) and methyl chloroformate (**2**).[3b] The pK_a value at the curvature center (pK_a^0) for the latter plot is 3.6,[3b] which is same as that found in this work. Therefore, the change of SMe to OMe, as the nonleaving group, in this case does not affect the pK_a^0 value significantly. This can be explained by taking into account that: (i) the inductive effects are more important than the resonance effects in a tetrahedral intermediate,[17] and (ii) these two groups have similar Hammett inductive values (σ_I=0.23 and 0.29 for SMe and OMe, respectively).[18] The similar electron-withdrawing abilities of these two groups should result in similar k_{-1}/k_2 ratios (see Scheme 3), which means similar pK_a^0 values.[19]

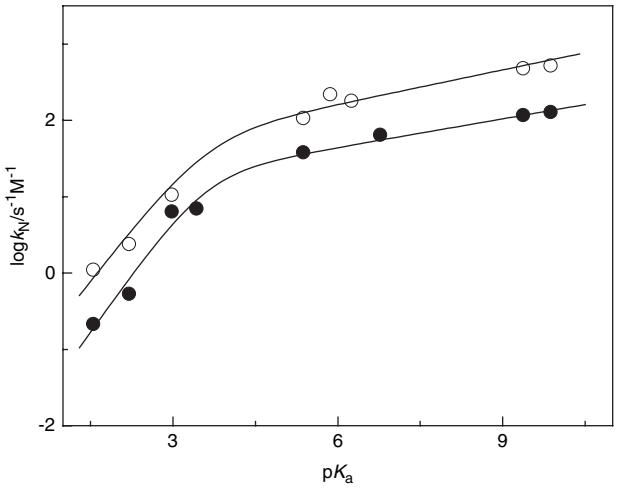


Figure 3. Brønsted plots for the pyridinolysis of **1** (this work; ●) and **2** (Ref. 3b; ○), in an aqueous solution, at 25.0 °C with an ionic strength of 0.2 M (KCl).

It can be seen in Figure 3 that the k_1 values for the pyridinolysis of **2** are greater than those for the same pyridinolysis of **1**. This result can be explained by the bulkier S atom relative to the O atom, which inhibits the attack by the pyridine. This behavior was also found for the stepwise pyridinolysis of methyl 2,4-dinitrophenyl carbonate and the corresponding *S*-methyl thiocarbonate.[7a,12a] Furthermore, the k_N values for rate-limiting expulsion of the nucleofuge from $T^{\pm}$ are also greater for methyl carbonates relative to their *S*-methyl thiol counterparts. This is the case for the pyridinolysis and SA aminolysis of methyl 4-nitrophenyl carbonate,[20,21] compared with the same aminolyses of the corresponding *S*-methyl derivative.[7a,b] Similarly, the k_N values obtained for the concerted SA aminolysis of the methyl 2,4-dinitrophenyl carbonate[21] are greater than those found for the same aminolysis of the corresponding *S*-methyl thiolcarbonate.[7b]

The fact that the shapes of the Brønsted-type plots in Figure 3 are the same indicates that both reactions are ruled by the same mechanism. An S_N1 process cannot be present

on the grounds that the k_N values increase with the basicity of the amine. This highlights the difference between the mechanism of the hydrolysis (and solvolysis in aqueous solvents) of *S*-alkyl chlorothioformates, which was found to be S_N1,[4a,b] with that of the aminolysis, which is an addition–elimination process.

Figure 4 shows the Brønsted-type plots for the pyridinolysis of **1** (this work) and those for the pyridinolysis of 4-nitrophenyl and 2,4-dinitrophenyl *S*-methyl carbonates (**5** and **6**, respectively).[7a] The curved plot for the reactions of **6** has been explained by a stepwise mechanism through a zwitterionic tetrahedral intermediate ($T^{\pm}$) and a change in the rate-limiting step,[7a] as for the pyridinolysis of **1**. The pK_a value at the curvature center is pK_a^0=7.3.[7a] The linear Brønsted plot found for the pyridinolysis of the mononitro derivative shows a slope of 1.1, which is consistent with a stepwise process where breakdown to products of the intermediate $T^{\pm}$ is the rate-limiting step.[7a] This means that for the latter reaction, $pK_a^0>10$.[7a] The fact that the pK_a^0 value increases as the leaving group becomes worse can be attributed to the decrease in the rate constant for expulsion of the nucleofuge from $T^{\pm}$ (k_2), which results in a greater k_{-1}/k_2 ratio for the mononitro derivative.[11,19]

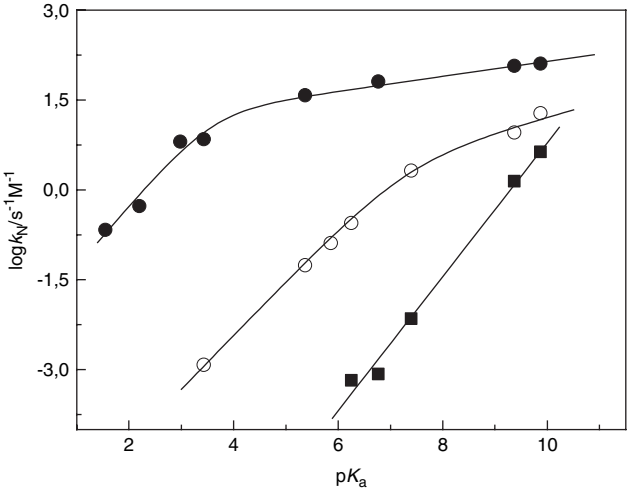


Figure 4. Brønsted-type plots for the pyridinolysis of **1** (this work; ●), **5** (Ref. 7a; ■) and **6** (Ref. 7a; ○), in an aqueous solution, 25.0 °C with an ionic strength of 0.2 M (KCl).

It can be seen in Figure 4 that the values of k_1 (for the two most basic pyridines) for the reactions of **1** are greater than those of **6**. For instance, for the reactions with 4-dimethylaminopyridine (pK_a=8.97) the k_1 values are 128 (this work) and 19 $s^{-1}\,M^{-1}$,[7a] respectively. This result can be explained by the greater steric hindrance towards the amine attack shown by 2,4-dinitrophenoxy group in **6** compared with Cl in **1**.

In the lower pK_a region of the Brønsted plots in Figure 4, where $k_N=k_1k_2/k_{-1}$, the k_N value of a given pyridine is about 10^4 times greater for its reaction with **1** relative to that with **6**. Considering that k_1 is about 10 times greater for **1**, the ratio k_2/k_{-1} must be about 10^3 times greater for **1** compared to **6**. This should be a consequence of the larger value of k_2 for the reactions of **1** relative to the dinitrophenyl derivative, since Cl should be a better nucleofuge than 2,4-dinitrophenoxy group.

The reactions of SA amines with **1** (this work) and **5**[7b] are stepwise. For the former, formation of the intermediate $T^{\pm}$ is the rate-limiting step (β=0.23), whereas for the latter the rate-limiting step is the breakdown of $T^{\pm}$ to the products (β=0.9).[7b] This is due to the much greater nucleofugality of Cl than 4-nitrophenoxy group from the corresponding $T^{\pm}$. In fact, for the aminolysis of **1** Cl is expelled faster than all the SA amines of the series from the tetrahedral intermediate, whereas for the reactions of **5** all the SA amines are expelled faster than the 4-nitrophenoxy group from the corresponding $T^{\pm}$ intermediate.

The reactions of **6** with SA amines are concerted,[7b] in contrast to the reactions of the same amines with **1**, which are stepwise (this work). This means that the 2,4-dinitrophenoxy group destabilizes the corresponding $T^{\pm}$ relative to Cl. An explanation to this behavior would be that the $T^{\pm}$ intermediate possessing the latter group would be much more crowded (and, therefore, more unstable) compared to that with Cl. This is supported by the fact that the reactions of these amines with 4-methylphenyl chloroformate are stepwise,[3g] in contrast to their reactions with 4-methylphenyl 2,4-dinitrophenyl carbonate, which are concerted.[22]

On the other hand, the pyridinolysis of **6** is stepwise,[7a] whereas the SA aminolysis of this substrate is concerted.[7b] This should be due to the fact that pyridines are worse nucleofuges from a $T^{\pm}$ intermediate than isobasic SA amines,[13] stabilizing, therefore, this intermediate, and making possible the change in mechanism, from concerted for the reactions with SA amines, to stepwise for those with pyridines.

3. Concluding remarks

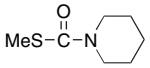
The following conclusions can be drawn from this and related works: (i) The pyridinolysis of *S*-methyl chlorothioformate (**1**) shows lower k_1 values relative to those of its oxy analog (**2**). (ii) Both reaction series show the same pK_a^0 value. (iii) The pK_a^0 values for the pyridinolysis of **1**, *S*-methyl 2,4-dinitrophenyl thiocarbonate (**6**), and *S*-methyl 4-nitrophenyl thiocarbonate (**5**) are 3.6, 7.3, and >10, respectively, showing that the value of pK_a^0 increases as the leaving group becomes worse. (iv) The value of k_1 for the pyridinolysis of **1** is 10 times greater than that for **6**. (v) The k_{-1}/k_2 ratio for the pyridinolysis of **1** is about 1000 times greater than that for **6**. (vi) The reactions of SA amines with **1** are stepwise in contrast to those of the same amines with **6**, which are concerted.

4. Experimental

4.1. Materials

The series of pyridines[3b] and secondary alicyclic (SA) amines[9] were purified either by distillation or recrystallization. *S*-Methyl chlorothioformate (**1**) was used as purchased. 1-(*S*-Methylcarbonyl)piperidine (**8a**), one of the products of the reaction of piperidine with **1**, was obtained by reaction of

the latter with piperidine in acetonitrile, and was identified by its H NMR spectrum.



8a

4.2. Kinetic measurements

These were carried out by means of a diode array spectrophotometer, in an aqueous solution, at 25.0±0.1 °C with an ionic strength of 0.2 M (KCl). The reactions were initiated by the addition (10 μL) of a stock solution of the substrate in acetonitrile into the aqueous solution of the amine (3 mL), at the appropriate pH, contained in a cell placed in the thermostated compartment of the spectrophotometer. The initial substrate concentration was $1–2\times10^{-5}$ M. Usually the pH was maintained by the corresponding amine–aminium pair, except in the reactions with 3-cyano and 4 cyano pyridines (where 0.005 M acetate buffer was used) and those with piperidine (where 0.01 M borate buffer was used). The reactions were followed at 220–500 nm and carried out under an excess (10-fold at least) of the amine over the substrate.

For the reactions with pyridines an intermediate was detected spectrophotometrically (270–320 nm), as shown by a fast absorbance increase followed by a slow decrease (see Section 2). In the case of the reactions with 3-chloropyridine we assume the intermediate to be 1-(*S*-methylcarbonyl)-3-chloropyridinium cation (**7a**). The kinetics for all the reactions were measured under conditions where decomposition of the intermediate was slower than its formation. Pseudo-first-order rate coefficients (k_{obsd}) were found for all the reactions by means of the kinetic software of the spectrophotometer.

4.3. Product studies

For the reaction with piperidine, compound **8a** was identified as one of the products. This was achieved by comparison of the UV–vis spectrum at the end of the reaction with that of an authentic sample at the same experimental conditions.

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