Kinetics and Mechanisms of the Reactions of 4-Nitro- and 3-Nitrophenyl 4-Methylphenyl Thionocarbonates with Alicyclic Amines and Pyridines

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The reactions of the title thionocarbonates (1 and 2, respectively) with a series of secondary alicyclic amines and pyridines are subjected to a kinetic investigation in 44 wt % ethanol-water, 25.0 °C, ionic strength 0.2 M (KCl). Under amine excess over the substrates pseudo-first-order rate coefficients (k_{obsd}) are obtained for all the reactions. Those of the alicyclic amines with the two substrates show nonlinear upward plots of k_{obsd} vs [amine], except the reactions of piperidine, which exhibit linear plots. For these reactions a reaction scheme is proposed with two tetrahedral intermediates, one zwitterionic (T[±]) and the other anionic (T⁻), with a kinetically significant proton transfer from T^{\pm} to an amine to give T^{-} . From an equation derived from the scheme the rate microcoefficients are obtained through fitting. The rate coefficient for formation of $T^{\pm}(k_1)$ is larger for 1 compared to 2, which can be explained by a stronger electron-withdrawal of 4-nitro in 1 than 3-nitro in 2, which leaves the thiocarbonyl carbon of 1 more positive and, therefore, more susceptible to nucleophilic attack. For the pyridinolyses of both thionocarbonates the plots of k_{obsd} vs [amine] are linear, with the slope (k_N) independent of pH. The Brönsted plots (log k_N vs pyridine pK_a) for these reactions are linear with slopes $\beta = 0.9$ and 1.2 for the pyridinolysis of 1 and **2**, respectively. These slopes are consistent with a mechanism through a T^{\pm} intermediate on the reaction path, whereby decomposition of T^{\pm} to products is the rate-determining step. The $k_{\rm N}$ values are larger for the reactions of **1** than those of **2**. This is attributed to a larger equilibrium formation of T^{\pm} and a larger expulsion rate of the nucleofuge from T^{\pm} in the reactions of **1** compared to those of 2.

Introduction

Although the mechanisms of the aminolysis of alkyl aryl and diaryl carbonates¹ and aryl acetates² are well understood, much less is known on the mechanisms of the aminolysis of thiocarbonates³ and thioacetates,⁴ particularly thionocarbonates.⁵

Recently, we have investigated kinetically the reactions of alkyl aryl thionocarbonates,^{5a,b} bis(aryl) thionocarbonates,^{5c} and phenyl 4-nitrophenyl thionocarbonate^{5d} with a series of secondary alicyclic amines and pyridines.

To evaluate the effects of the leaving and nonleaving groups and the amine nature on these mechanisms, we study in this work the kinetics of the aminolysis (secondary alicyclic amines) and pyridinolysis of 4-nitro- and 3-nitro-phenyl 4-methylphenyl thionocarbonates (1 and 2, respectively). The aim is to compare these reactions between them and with the other thionocarbonates described above.



1 (X = 4-Nitro) 2 (X = 3-Nitro)

Experimental Section

Materials. The secondary alicyclic amines and pyridines were purified as reported.⁶ 4-Nitrophenyl 4-methylphenyl thionocarbonate (1) was synthesized by a modification of a standard procedure,⁷ as follows: To a solution of 4-nitrophenol (4.17 g, 30 mmol) dissolved in THF (20 mL) in a Schlenk flask in an ethanol-liquid nitrogen bath, a solution (12.5 mL, 30 mmol) of 1.6 M butyllithium (Aldrich) dissolved in THF (20 mL) was added slowly under nitrogen atmosphere. This lithium 4-nitrophenoxide solution was added dropwise, with

⁽¹⁾ Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963, 6970.

⁽²⁾ Satterthwait, A. C.; Jencks, W. P. J. Am. Chem. Soc. 1974, 96, 7018.

⁽³⁾ Oh, H. K.; Lee, J. Y.; Yun, L. H.; Park, Y. S. *Int. J. Chem. Kinet.* **1998**, *30*, 419. Humeres, E.; Soldi, V.; Klug, M.; Nunes, M.; Oliveira, C. M. S.; Barrie, P. J. *Can. J. Chem.* **1999**, *77*, 1050. Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1999**, *64*, 6342.

<sup>C. M. S., Barle, F. J. Call. J. Chem. 1999, 67, 1030. Cd810, E. A., Cubillos, M.; Santos, J. G. J. Org. Chem. 1999, 64, 6342.
(4) Oh, H. K.; Shin, C. H.; Lee, I. J. Chem. Soc., Perkin Trans. 2
1995, 1169. Oh, H. K.; Woo, S. Y.; Shin, C. H.; Park, Y. S.; Lee, I. J. Org. Chem. 1997, 62, 5780. Oh, H. K.; Lee, J.-Y.; Lee, I. Bull. Korean Chem. Soc. 1998, 19, 1198. Koh, H. J.; Han, K. L.; Lee, I. J. Org. Chem. 1999, 64, 4783.</sup>

^{(5) (}a) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 3501. (b) Castro, E. A.; Cubillos, M.; Santos, J. G.; Tellez, J. *J. Org. Chem.* **1997**, *62*, 2512. (c) Castro, E. A.; Santos, J. G.; Tellez, J.; Umaña, M. I. *J. Org. Chem.* **1997**, *62*, 6568. (d) Castro, E. A.; Saavedra, C.; Santos, J. G.; Umaña, M. I. *J. Org. Chem.* **1999**, *64*, 5401.

^{(6) (}a) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 68. (b) Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153.

⁽⁷⁾ Al-Kazimi H. R.; Tarbell, D. S.; Plant, D. J. Am. Chem. Soc. 1955, 77, 2479.

Table 1. Experimental Conditions and k_{obsd} ValuesObtained in the Reactions of 4-Nitrophenyl4-Methylphenyl Thionocarbonate (1) with AlicyclicAmines^a

			10 ² [N] _{tot} , ^c	$10^3 k_{\rm obsd}$,	no. of
amine	pН	$F_{\rm N}{}^b$	М	\mathbf{s}^{-1}	runs
piperidine	10.62	0.39	0.20-2.0	1.4-21.1	6
	10.82	0.50	0.20 - 2.0	2.8 - 31.3	6
	11.12	0.67	0.20 - 2.0	4.2 - 53.1	6
piperazine	9.41	0.33	0.20 - 2.0	0.98 - 15.2	8
	9.71	0.50	0.20 - 2.0	1.60 - 26.3	8
	10.01	0.67	0.20 - 2.0	3.0 - 36.7	8
1-(2-hydroxyethyl)-	8.79	0.33	0.20 - 2.0	0.30 - 4.8	8
piperazine	9.09	0.50	0.20 - 6.0	0.46 - 29.3	8
	9.39	0.67	0.20 - 2.0	0.62 - 10.3	8
morpholine	8.18	0.33	0.60 - 6.0	0.42 - 11.7	9
•	8.48	0.50	0.60 - 6.0	0.64 - 20.6	10
	8.78	0.67	0.60 - 6.0	1.4 - 35	10
1-formylpiperazine	7.33	0.33	1.0 - 10	0.32 - 5.7	6
	7.63	0.50	1.0 - 10	0.36 - 8.2	5
	7.93	0.67	1.0 - 10	0.50 - 11.0	6
piperazinium ion	5.07	0.33	3.0 - 12	0.077 - 0.44	6
	5.37	0.50	3.0 - 12	0.19 - 0.79	6
	5.67	0.67	3.0 - 12	0.24 - 1.20	6

^{*a*} In 44 wt % ethanol–water, 25.0 °C, ionic strength 0.2 M (KCl). ^{*b*} Free amine fraction. ^{*c*} Concentration of total amine (free amine + protonated forms).

stirring under nitrogen during 2 h, to a solution of 4-methyl thionochloroformate⁸ (5.6 g, 30 mmol) dissolved in THF (40 mL), placed in a Schlenk flask in an ethanol-liquid nitrogen bath. After the addition, the mixture was left at ambient temperature for 2 h with stirring under nitrogen. After evaporation of the solvent, chloroform was added to this mixture and the solution washed with cold water. The organic layer was dried with MgSO4 and filtered under vacuum and the solvent evaporated off. The crystallized (n-hexanechloroform) thionocarbonate 1 melted at 129-130 °C and was identified as follows: ¹H NMR (200 MHz, CDCl₃) δ 2.40 (s, 3H), 7.12 (d, 2H J = 8.0 Hz), 7.27 (d, 2H, J = 7.7 Hz), 7.40 (d, 2H J = 8.7 Hz), 8.35 (d, 2H, J = 8.7 Hz); ¹³C NMR (50 MHz, CDCl₃) & 21.01 (CH₃), 121.20 (C-3'/5'), 123.29 (C-2/6), 125.46 (C-3/5), 130.35 (C-2'/6'), 137.03 (C-4'),146.11 (C-4), 151.33 (C-1'), 157.56 (C-1), 193.66 (C=S). Anal. Calcd for C₁₄H₁₁O₄NS: C, 58.18; H, 3.84; N, 4.85; S, 11.09. Found: C, 58.56; H, 4.33; N, 4.55; S, 11.29.

3-Nitrophenyl 4-methylphenyl thionocarbonate (2) was synthesized in the same way but using 3-nitrophenol. This compound melted at 179–180 °C and was identified as follows: ¹H NMR (200 MHz, CDCl₃) ∂ 2.40 (s, 3H), 7.12 (d, 2H J = 8.6 Hz), 7.28 (d, 2H, J = 8.6 Hz), 7.58 (d, 1H, J = 8.1 Hz), 7.66 (t, 1H J = 8.1 Hz), 8.13 (d, 1H J = 8.1 Hz), 8.22 (d, 1H, J = 8.1 Hz); ¹³C NMR (50 MHz, CDCl₃) ∂ 21.03 (CH₃), 118.09 (C-2), 120.65 (C-4), 121.24 (C-3'/5'), 121.77 (C-6), 128.64 (C-5), 130.37 (C-2'/6'), 136.99 (C-4'), 148.94 (C-3), 151.41 (C-1'), 153.53 (C-1), 194.22 (C=S). Anal. Calcd for C₁₄H₁₁O₄NS: C, 58.18; H, 3.84; N, 4.85; S, 11.09. Found: C, 58.21; H, 3.88; N, 4.64; S, 10.90.

Kinetic Measurements. These were performed spectrophotometrically (Hewlett-Packard 8453) by following the production of 4-phenol and 3-nitrophenol (and/or their conjugate bases) for the reactions of **1** and **2**, respectively. The reactions of **1** were followed at 400 nm, except those at pH lower than 7, which were studied at 325-330 nm. The reactions of **2** were followed at 320-330 nm. All reactions were carried out in 44 wt % ethanol-water, 25.0 ± 0.1 °C, ionic strength 0.2 M (maintained with KCl). The initial concentration of the substrates was $(3-6) \times 10^{-5}$ M., and at least a 10fold excess of total amine over the substrates was employed.

Pseudo-first-order rate coefficients (k_{obsd}) were found throughout. The experimental conditions of the reactions and the k_{obsd} values obtained are shown in Tables 1–4.

Table 2. Experimental Conditions and k_{obsd} ValuesObtained in the Reactions of 3-Nitrophenyl4-Methylphenyl Thionocarbonate (2) with AlicyclicAmines^a

amine	pН	$F_{\rm N}{}^b$	10 ² [N] _{tot} , M ^c	$10^3 k_{\mathrm{obsd}},$ s^{-1}	no. of runs
piperidine	10.52	0.33	0.25 - 2.5	1.54 - 24.1	10
	10.82	0.50	0.25 - 2.5	2.73 - 30.1	10
	11.12	0.67	0.25 - 2.5	7.91 - 49.6	10
piperazine	9.41	0.33	0.50 - 5.0	0.96 - 21.3	10
	9.71	0.50	0.50 - 5.0	4.51 - 38.7	10
	10.01	0.67	0.50 - 5.0	4.95 - 70.3	10
1-(2-hydroxyethyl)-	8.79	0.33	0.50 - 5.0	1.12 - 13	10
piperazine	9.09	0.50	0.50 - 5.0	1.31 - 20.1	10
	9.39	0.67	0.50 - 4.5	1.69 - 23.9	10
morpholine	8.18	0.33	3.0 - 13.5	3.52 - 25.4	8
•	8.48	0.50	3.0 - 13.5	7.60 - 46.3	8
	8.78	0.67	2.0 - 10	6.12 - 45.2	9
1-formylpiperazine	7.33	0.33	2.0 - 20	0.447 - 11.9	9
	7.63	0.50	1.0 - 10	0.109 - 9.45	10
	7.93	0.67	1.0 - 8.0	0.423-10.0	8
piperazinium ion	5.07	0.33	1.0 - 8.0	0.429 - 1.27	8
• •	5.37	0.50	1.0 - 10	0.195 - 3.65	10
	5.67	0.67	1.0 - 8.0	0.464 - 4.09	8

 a In 44 wt % ethanol–water, 25.0 °C, ionic strength 0.2 M (KCl). b Free amine fraction. c Concentration of total amine (free amine + protonated forms).

Table 3. Experimental Conditions and k_{obsd} ValuesObtained in the Pyridinolysis of 4-Nitrophenyl4-Methylphenyl Thionocarbonate (1)^a

pyridine substituent	pН	$F_{\rm N}{}^b$	10 ³ [N] _{tot} , M ^c	$10^3 k_{ m obsd},$ ${ m s}^{-1}$	no. of runs
4-(dimethylamino) ^d	7.25	0.013	5.0-50	2.0-20	11
	7.55	0.025	5.0 - 50	3.8 - 40	11
	7.85	0.049	5.0 - 50	6.6 - 65.8	11
4-amino ^d	7.25	0.018	5.0 - 50	1.8 - 15.8	11
	7.55	0.036	5.0 - 50	3.0 - 32.6	11
	7.85	0.069	5.0 - 50	4.9 - 57.3	11
3.4-dimethyl	5.68	0.50	120 - 400	1.75 - 4.75	8
5	5.98	0.67	120 - 400	2.81 - 6.41	8
	6.28	0.80	120 - 400	3.56 - 8.02	8
4-methyl	5.35	0.50	120 - 400	1.21 - 3.01	8
0	5.65	0.67	120 - 400	1.87 - 4.26	8
	5.95	0.80	120 - 400	2.20 - 5.25	8
3-methyl	4.92	0.50	120 - 400	0.49 - 1.49	8
	5.22	0.67	120 - 400	0.72 - 2.21	8
	5.52	0.80	120 - 400	0.91 - 2.40	8
Н	4.63	0.50	120 - 400	0.54 - 1.30	8
	4.93	0.67	120 - 400	0.74 - 1.97	8
	5 2 3	0.80	120 - 400	0.64 - 1.84	8

 a In 44 wt % ethanol–water, 25.0 °C, ionic strength 0.2 M (KCl). b Free amine fraction. c Concentration of total amine (free amine + protonated forms). d In the presence of phosphate buffer 0.005 M.

Product Studies. In the reactions of **1** and **2** with morpholine and piperazine, the corresponding 4-methylphenyl thionocarbamates and 4-nitrophenol or 3-nitrophenol, respectively, were found as final products. This was carried out by comparison of the UV-vis spectra at the end of these reactions with those of authentic samples under the same experimental conditions. In the reactions of 1 and 2 with 4-aminopyridine a thionocarbamate cation intermediate was detected; a similar intermediate was found in the reaction of this amine with methyl 4-nitrophenyl thionocarbonate.^{5b} For the reactions of 1 and 2 with 4-aminopyridine and 4-methylpyridine, 4-methylphenol and 4-nitrophenol or 3-nitrophenol were found as final products. All these products were identified by comparison of the UV-vis spectra at the end of the reactions with those of authentic samples under the same experimental conditions.

^{(8) 4-}Methylphenyl thionochloroformate was synthesized from 4-methylphenol and thiophosgene, as previously described.⁷

 Table 4. Experimental Conditions and k_{Obsd} Values
 Obtained in the Pyridinolysis of 3-Nitrophenyl 4-Methylphenyl Thionocarbonate (2)^a

	J	5			
pyridine substituent	pН	$F_N{}^b$	10 ² [N] _{tot} , M ^c	$10^3 k_{ m obsd}, { m s}^{-1}$	no. of runs
4-(dimethylamine)	8.84	0.33	0.25-2.50	20.0-70.3	10
Ū.	9.14	0.50	0.25 - 2.50	20.9 - 96.9	9
	9.44	0.67	0.125 - 1.25	20.3 - 68.8	10
4-amino	8.68	0.33	0.25 - 2.50	11.3 - 27.9	10
	8.98	0.50	0.25 - 2.50	12.2 - 37.3	10
	9.28	0.67	0.125 - 1.25	11.1 - 27.8	10
3,4-dimethyl	5.85	0.60	6.0 - 48.0	0.018 - 0.080	8
-	6.04	0.70	12.0 - 54.0	0.038-0.113	8
	6.28	0.80	6.0 - 60.0	0.027 - 0.137	8
4-methyl	5.53	0.60	6.0 - 48.0	0.0041 - 0.029	8
0	5.72	0.70	6.0 - 54.0	0.0061 - 0.037	9
	5.96	0.80	6.0 - 60.0	0.0057 - 0.042	10
3-methyl	5.10	0.60	6.0 - 48.0	0.0017 - 0.015	8
	5.29	0.70	6.0 - 54.0	0.0020 - 0.020	10
	5.52	0.80	6.0 - 60.0	0.0019 - 0.023	10

^a In 44 wt % ethanol-water, 25.0 °C, ionic strength 0.2 M (KCl). ^b Free amine fraction. ^c Concentration of total amine (free amine + protonated forms).



Scheme 1

Results and Discussion

Reactions of Secondary Alicyclic Amines with Thionocarbonates 1 and 2. The rate law obtained for these reactions is given by eq 1, where P represents 4-nitrophenol or 3-nitrophenol (and/or their conjugate bases), S is the substrate (1 or 2), and k_{obsd} is the pseudofirst-order rate coefficient (amine was in excess over the substrate).

$$\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = k_{\mathrm{obsd}}[\mathrm{S}] \tag{1}$$

Plots of kobsd vs [NH] are nonlinear upward (NH represents a secondary amine), except that for piperidine, which is linear. This kinetic behavior is consistent with the mechanism described in Scheme 1. In this scheme, the k_3 step is the deprotonation of the zwitterionic tetrahedral intermediate T^{\pm} by an amine to give the anionic intermediate T⁻. Applying the steady-state condition to the tetrahedral intermediates in Scheme 1, eq 2 is obtained. In this equation k_0 is the rate coefficient for solvolysis of the substrate, and the rate coefficients k_1 , k_{-1} , k_2 , and k_3 are defined in Scheme 1. In all cases the value of k_0 was much smaller than the second term of eq 2.

$$k_{\text{obsd}} = k_0 + \frac{k_1(k_2 + k_3[\text{NH}])[\text{NH}]}{k_{-1} + k_2 + k_3[\text{NH}]}$$
(2)



Figure 1. Plot of *k*_{obs} vs [piperazinium] for the reaction of **2**.

For the reactions of 1 and 2 with piperazinium ion, the plot k_{obsd} vs [NH] can be fitted by eq 3, where $K_1 (= k_1 / k_2)$ k_{-1}) is the equilibrium constant for the first step in Scheme 1.

$$k_{\text{obsd}} = k_0 + K_1 k_2 [\text{NH}] + K_1 k_3 [\text{NH}]^2$$
(3)

This amine is the least basic of the series; therefore, it is reasonable that the C–NH bond in T^{\pm} be the weakest of the series, and thus, $k_{-1} \gg k_2 + k_3$ [NH], and eq 2 reduces to eq 3. By fitting this equation to the experimental data, the values of k_0 , K_1 , and k_2 were obtained, k_3 being estimated previously (see below). The values of K_1 , k_2 , and k_3 are shown in Table 5. The plot of k_{obsd} vs [NH] for the reaction of this amine with thionocarbonate **2** is shown in Figure 1. A similar plot was obtained for the reaction of piperazinium ion with **1**.

For the reactions of thionocarbonates 1 and 2 with the other secondary alicyclic amines (except piperidine) the plots k_{obsd} vs [NH] are in accord with eq 2. By dividing numerator and denominator of this equation by k_3 , eq 4 results, where $A = k_1 k_2 / k_3$, $B = k_1$, and $C = (k_{-1} + k_2) / k_3$. By fitting this equation to the experimental points, the values of k_0 , k_1 , k_{-1} , and k_2 were found, with k_3 previously estimated (see below). As an example, Figure 2 shows the plot of k_{obsd} vs [NH] for the reaction of **1** with morpholine. The values of the rate microcoefficients found for the reactions of 1 and 2 with these amines are shown in Table 5.

$$k_{\text{obsd}} = k_{\text{o}} + \frac{(A + B[\text{NH}])[\text{NH}]}{C + [\text{NH}]}$$
(4)

For the reactions of thionocarbonates 1 and 2 with piperidine, linear plots of k_{obsd} vs [NH] were obtained (plots not shown). For this very basic amine, $k_{-1} \ll k_2 + k_2$ k_3 [NH]; thus, eq 2 reduces to eq 5. From this plot the values of k_0 and k_1 were obtained. The k_0 values were

 Table 5. Values for the Rate Microcoefficients Found in the Reactions of Thionocarbonates 1 and 2 with Secondary Alicyclic Amines^a

		k_1/s^-	$k_1/{ m s}^{-1}~{ m M}^{-1}$		$10^{-7} k_{-1}/s^{-1}$	
amine	pKa	1	2	1	2	
piperidine	10.82	3.4	3.0			
piperazine	9.71	3.8	2.2	1.9	2.9	
1-(2-hydroxyethyl)piperazine	9.09	1.5	1.0	4.7	4.0	
morpholine	8.48	1.3	0.87	10	8.1	
1-formylpiperazine	7.63	0.51	0.45	44	30	
piperazinium ion	5.37	$9 imes 10^{-11}$ b	$5 imes 10^{-11}$ b			
other rate microcoefficients:	$k_2 = (0.9 - 1.5)$	$) \times 10^{7} { m s}^{-1}$ (1) and (4–6)	$10^{6}~{ m s}^{-1}$ (2)			
	$k_3 = 2 \times 10^9 \text{ s}^{-1} \text{ M}^{-1}$ (piperazinium ion)					
	$k_3 = 4 \times 10^9 \text{s}$	$s^{-1} M^{-1}$ (other sec. alicy	lic amines)			

^{*a*} Both the rate microcoefficients and p K_a values were determined in 44 wt % ethanol–water, 25.0 °C, ionic strength 0.2 M (KCl). ^{*b*} Values of K_1 (= k_1/k_{-1}) in M⁻¹.



Figure 2. Plot of k_{obs} vs [morpholine] for the reaction of **1**.

negligible compared to those of k_1 [NH]. The k_1 values are shown in Table 5.

$$k_{\rm obsd} = k_{\rm o} + k_{\rm I}[\rm NH] \tag{5}$$

With the values of k_1 obtained either through fitting of eq 2 or as the slopes of the linear plots of eq 5, the Brönsted plots for the reactions of **1** and **2** with secondary alicyclic amines (except piperazinium ion) were obtained. These plots are statistically corrected⁹ with p = 2 for all the conjugate acids of the amines and q = 1 for all amines, except piperazine with q = 2.5.6b The Brönsted plots are linear with slopes $\beta_1 = 0.25$ for the reactions of both substrates (Figure 3); the magnitudes of the slopes are in accord with those of Brönsted slopes for similar reactions when T[±] formation is rate determining.^{1,2} This indicates that the k_1 values obtained are reasonable.

According to the Brönsted plots in Figure 3, thionocarbonate **1** is more reactive than thionocarbonate **2**. The



Figure 3. Brönsted plots for k_1 for the aminolyses of thionocarbonates **1** and **2**.

larger reactivity of compound **1** than **2** can be explained by the stronger electron-withdrawing effect of the 4-nitro group in **1** than 3-nitro in **2**, which leaves the thiocarbonyl carbon of **1** more positively charged and therefore more susceptible to nucleophilic attack.

The Brönsted plots for k_{-1} (p K_a values statistically corrected)^{5,9} for the reactions of thionocarbonates 1 and **2** are linear with slopes $\beta_{-1} = -0.72$ and -0.57, respectively (Figure 4). For the first step of Scheme 1, the Brönsted slope for the equilibrium constant K_1 is $\beta_{eq} =$ $\beta_1 - \beta_{-1}$, which gives $\beta_{eq} = 0.25 - (-0.72) = ca.$ 1.0 for the reactions of **1**. A similar calculation gives β_{eq} ca. **0.8** for the reactions of **2**. Since the Brönsted slope for the k_2 step of Scheme 1 is zero or near zero, namely the k_2 value is independent of amine basicity,^{1,2} it follows that the Brönsted slopes for the equilibrium formation of T^{\pm} (β_{eq}) should be the same as those when the k_1 step of Scheme 1 is at equilibrium and the k_2 step is rate determining (with $k_3 = 0$). In fact the values of β_{eq} obtained above for the aminolyses of **1** and **2** are similar to those of the Brönsted slopes found in analogous aminolyses when decomposition of a zwitterionic tetrahedral intermediate to products is the rate-limiting step.^{1,2,5,6} This indicates

⁽⁹⁾ Bell, R. P. *The Proton in Chemistry*; Methuen: London, 1959; p 159.



Figure 4. Brönsted plots for k_1 for the aminolyses of thionocarbonates **1** and **2**. The ordinate values for 1 are increased by 0.5 units.

that the k_1 and k_{-1} values obtained as stated above for the reactions of **1** and **2** with alicyclic amines are reasonable.

Estimation of the pK_a Value of T^{\pm} of Scheme 1. To determine the value of k_3 in Scheme 1, we must first estimate the pK_a value of the intermediate T^{\pm} in this scheme. On the basis of Jencks' procedure, which involves the use of Hammett inductive parameters,10 it was estimated that the pK_a of the tetrahedral intermediate **3** is 6.4 units lower than that of the corresponding aminium ion.^{5a} That is, the proton transfer from **3** to the corresponding amine is thermodynamically favorable and should be diffusion controlled.^{5,10} Employing the Hammett inductive reaction constant $\rho_{I} = -9.2$ for the pK_a of intermediates similar to 3,¹¹ and the values of Hammett inductive substituent constants $\sigma_{I} = 0.26$ and 0.37 for EtO and PhO, respectively,¹² it can be determined that pK_a (4) - pK_a (3) = -9.2(0.37-0.26) = -1.0. Therefore, the pK_a of **4** should be 6.4 + 1.0 = 7.4 pK_a units lower than that of the corresponding aminium ion. Since σ_1 for phenyl is the same as that for 4-methylphenyl,¹² the pK_a of 5 should be the same as that of **4**. Taking into account that $\sigma_{\rm I} = 0.47$ for 4-nitrophenoxy¹² and $\sigma_{I} = 0.44$ for 3-nitrophenoxy,¹³ replacement of the 4-nitro group by 3-nitro should change the pK_a by -9.3(0.44 - 0.47) = 0.3 unit. Therefore, the pK_a of **6** should be 7.1 units lower than that of the aminium ion. Namely, the proton transfers from either 5 or 6, which are the intermediates T^{\pm} in Scheme 1, to the corresponding amines are thermodynamically favorable and diffu-

(11) Taylor, P. J. J. Chem. Soc., Perkin Trans. 2 1993, 1423.
 (12) Hansch, C.; Leo, A.; Taft, R. W. Chem. Rev. 1991, 91, 165.

(13) The $\sigma_{\rm I}$ value for 3-nitrophenoxy is unknown but it can be deduced from that for 4-nitrophenoxy (=0.47)¹² and assuming there is the same $\sigma_{\rm I}$ difference than that between 3-nitrophenyl and 4-nitrophenyl ($\sigma_{\rm I} = 0.23$ and 0.26, respectively).¹²



Figure 5. Brönsted plots for k_1 for the pyridinolyses of thionocarbonates **1** and **2**.

sion controlled.¹⁰ Therefore, the k_3 value should be ca. $10^{10} \text{ s}^{-1} \text{ M}^{-1}$ in water, ^{5,14} and $4 \times 10^9 \text{ s}^{-1} \text{ M}^{-1}$ in 44 wt % ethanol—water.^{15,16} In the particular case of the proton transfer from T[±] of Scheme 1 to piperazinium cation, the value of k_3 in 44 wt % ethanol—water has been estimated as $2 \times 10^9 \text{ s}^{-1} \text{ M}^{-1}$, due to repulsion of the positive charges involved.¹⁶



Reactions of Pyridines with Thionocarbonates 1 and 2. The rate law found for these reactions is described by eqs 1 and 6, where N represents a pyridine, and k_0 and k_N are the rate constants for solvolysis and pyridinolysis, respectively.

$$k_{\rm obsd} = k_{\rm o} + k_{\rm N}[{\rm N}] \tag{6}$$

For these reactions, the plots of k_{obsd} vs [N] at different pH values are linear (plots not shown), with the slopes (k_N) independent of pH. In all cases the k_o values were much smaller than those of the second term of eq 6. The k_N values obtained for the pyridinolysis of thionocarbonates **1** and **2** are summarized in Table 6.

With the $k_{\rm N}$ data determined for these reactions the Brönsted plots shown in Figure 5 were obtained. The Brönsted slopes for the pyridinolysis of **1** and **2** are $\beta = 0.9$ and 1.2, respectively. According to their slope values the reactions of pyridines with both substrates follow the mechanism depicted in Scheme 2, where the

⁽¹⁰⁾ Sayer, J. M.; Jencks, W. P. J. Am. Chem. Soc. **1973**, *95*, 5637. Fox, J. P.; Jencks, W. P. J. Am. Chem. Soc. **1974**, *96*, 1436.

⁽¹⁴⁾ Eigen, M. Angew. Chem., Int. Ed. Engl. 1964, 3, 1.

⁽¹⁵⁾ Value estimated knowing that the viscosity coefficient of 44 wt % ethanol-water is 2.5-fold higher than that of water at 25 °C.

⁽¹⁶⁾ Castro, E. A.; Leandro, L.; Santos, J. G. Int. J. Chem. Kinet. 1999, 31, 839.

Table 6. Values for the Nucleophilic Rate Coefficients (k_N) and the Equilibrium Constants K_1 of Scheme 2 for the Pyridinolysis of Thionocarbonates 1 and 2^a

pyridine		$k_{ m N}$,	$s^{-1} M^{-1}$	$10^9 K_1$, M ⁻¹	
substituent	pKa	1	2	1	2
4-(dimethylamino)	9.14	30	6.7	3000	1340
4-amino	8.98	18	2.3	1800	460
3,4-dimethyl	5.68	0.019	$2.8 imes10^{-4}$	1.9	0.056
4-methyl	5.35	0.013	$9.2 imes10^{-5}$	1.3	0.018
3-methyl	4.92	0.0070	$4.9 imes10^{-5}$	0.7	0.010
н	4.63	0.0060		0.6	

^{*a*} Both the rate coefficients and pK_a values were determined in 44 wt % ethanol–water, 25.0 °C, ionic strength 0.2 M (KCl).



first step is at equilibrium (K_1) and the k_2 step is rate limiting.^{1,2,5,6}

Since for these reactions $k_N = K_1 k_2$, and assuming the k_2 values are independent of the amine basicity and nature,^{1,2} the K_1 values can be determined from the k_2 values found in the reactions of **1** and **2** with secondary alicyclic amines (k_2 values in Table 5 and K_1 values in Table 6). The larger K_1 values for the pyridinolysis of thionocarbonate **1** than thionocarbonate **2**, are reasonable, in view of the stronger electron-withdrawing effect of 4-nitro in **1** compared to 3-nitro in **2**, which should favor the nucleophilic attack by a pyridine and also the equilibrium formation of the zwitterionic tetrahedral intermediate (T^{\pm} in Scheme 2).

The larger k_N values for the pyridinolysis of **1** relative to those for **2** (Figure 5 and Table 6) should be due to larger K_1 values for the reactions of **1** than **2**, and also to a larger k_2 value for the former reactions. The latter is reasonable on the grounds of the better nucleofugality of 4-nitrophenoxide anion than 3-nitrophenoxide from the intermediate T^{\pm} .^{1,2,5}

Comparison between the Aminolysis and Pyridinolysis of 1 and 2. This comparison is not straightforward since the mechanisms are different. Nevertheless, we can compare the K_1 values for these reactions. Those for the pyridinolysis of thionocarbonates 1 and 2 can be calculated as $K_1 = k_N/k_2$. The K_1 values for the reactions of thionocarbonates 1 and 2 with secondary alicyclic amines can be determined as k_1/k_{-1} (Table 5). Figure 6 shows the Brönsted plots (statistically corrected) obtained for the reactions of thionocarbonate 1 with the two amine series. As seen in this figure, the K_1 values are larger for the reactions of pyridines compared to isobasic alicyclic amines. The same situation occurs for the reactions of thionocarbonate 2. This indicates that pyridines favor the equilibrium formation of T^{\pm} more than isobasic secondary alicyclic amines. This could be due in part to larger k_1 values for pyridines toward these types of substrates, as found in the reactions of ethyl 4-nitrophenyl thionocarbonate with these two amine series.^{5b} This could also be due to smaller k_{-1} values for pyridines relative to isobasic alicyclic. amine, since it is



Figure 6. Brönsted plots for K_1 for the reactions of thionocarbonate **1** with pyridines and alicyclic amines.

well-known that pyridines can leave a zwitterionic tetrahedral intermediate slower than isobasic quinuclidines (tertiary alicyclic amines)^{1,17} and isobasic alicyclic amines.^{5b,c,18}

Comparison of the Title Reactions wth the Aminolysis of Other Substrates. The reactions of secondary alicyclic amines with ethyl 4-nitrophenyl thionocarbonate (7) in water^{5a} are governed by the same mechanism (Scheme 1) as that for the reactions of the same amines with substrate 1 in ethanol-water (this work). In both cases, the order in amine is one for piperidine and between one and two for the other amines. Nevertheless, the k_1 values for the reactions of thionocarbonate 7 are larger than those of 1.5a This fact cannot be explained by electronic effects since EtO is probably as electron donating as 4-MePhO by resonance and the former group should possess a smaller inductive electron-withdrawing ability than the latter.¹⁹ These effects should leave the thiocarbonyl carbon of 1 more positively charged than that of 7, which would result in a faster amine attack to **1**. The larger k_1 values for the aminolysis of thionocarbonate 7 in water than those of 1 in aqueous ethanol could be explained by the more polar solvent used in the former reactions. It can also be explained by a larger steric hindrance caused by the 4-methylphenyl group of 1, compared with the Et group of 7. A similar situation was found in the same aminolyses of methyl and phenyl 4-nitrophenyl thionocarbonates in water,^{5d} whereby the values of k_1 for the reactions of the former substrate are

⁽¹⁷⁾ Castro, E. A.; Muñoz, P.; Santos, J. G. J. Org. Chem. **1999**, 64, 8298.

⁽¹⁸⁾ Castro, E. A.; Ureta, C. *J. Org. Chem.* **1990**, *55*, 1676. Castro, E. A.; Ureta, C. *J. Chem. Soc., Perkin Trans.* **2 1991**, 63. Castro, E. A.; Araneda, C. A.; Santos, J. G. *J. Org. Chem.* **1997**, *62*, 126. Castro, E. A.; Pizarro, M. I.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 5982.

A, Pizarro, M. I.; Santos, J. G. J. Org. Chem. **1996**, 61, 5982. (19) The $\sigma_{\rm R}$ and $\sigma_{\rm I}$ values for the 4-methylphenoxy group are unknown, but we can compare the groups Et with 4-methylphenyl. The value of $\sigma_{\rm R}$ is -0.15 for both and those for $\sigma_{\rm I}$ are 0.0 and 0.12, respectively.¹²

larger than those for the latter, despite the electronic effects, which should favor amine attack on the phenyl derivative. $^{\rm 5d}$



The mechanism found in the pyridinolysis of thionocarbonate 1 in aqueous ethanol (Scheme 2) is the same as that for the same reactions of thionocarbonate 7,5b and bis(4-nitrophenyl) thionocarbonate (8) in water.^{5c} In all these reactions linear Brönsted plots were obtained, with slopes ($\beta = 1.0$ for the two latter reactions) compatible with a stepwise mechanism whereby expulsion of the leaving group is rate limiting. The k_N (= K_1k_2) values for the pyridinolysis of **8** are larger^{5c} than those for the same reactions of 1 (Table 6). This can be explained by the larger *K*₁ values for the former reactions, and probably, by similar k_2 values for these reactions. The larger K_1 values for the pyridinolysis of 8 are reasonable on the basis of the stronger electron-withdrawing effect of the 4-nitro group in 8 compared to 4-methyl in 1, which should favor amine attack and also equilibrium formation of the zwitterionic tetrahedral intermediate (T^{\pm}) in the former reactions. Moreover, the solvent should also play a role here: the K_1 values in water (reactions of **8**) should be greater than those in aqueous ethanol (reactions of **1**), due to the zwitterionic nature of T^{\pm} .¹ The value of k_2 should be larger for the pyridinolysis of 1, in view of the stronger push by 4-methoxy than 4-nitrophenoxy in T^{\pm} to expel the leaving 4-nitrophenoxide group from this intermediate. Nevertheless, this can be compensated by the fact that 8 possesses two identical leaving groups, which should favor statistically the nucleofugality of 4-nitrophenoxide from the intermediate T^{\pm} formed in this reaction. On the other hand, there should be little influence of the solvent on the k_2 value since both the transition state for T^{\pm} breakdown and T^{\pm} are highly polar.1

The reactions of **8** with secondary alicyclic amines in water are concerted, as evidenced by a the slightly curved Brönsted plot found in these reactions.^{5c} This is in great contrast to the stepwise process exhibited by the reactions of the same amines with **1** in aqueous ethanol (Scheme 1). The difference in mechanism must be due to the different stability of the putative tetrahedral intermediates (T[±]) in these reactions. The hypothetical T[±] in the reactions of **8** would possess three very good nucleofuges (two 4-nitrophenoxy groups and the amino moiety), which should render this intermediate highly

unstable, and perhaps nonexistent (if the mechanism is enforced concerted).²⁰ The change of 4-nitrophenoxy to 4-methylphenoxy should stabilize this intermediate since 4-methylphenoxy is a much worse leaving group. This could be the reason for the shift in mechanism from concerted to stepwise by the above change. On the other hand, the intermediate T^{\pm} should be more stable in water than aqueous ethanol. Therefore, the stabilization of T^{\pm} brought about by the change of 4-nitro to 4-methyl should be more important than the destabilization caused by the solvent change.

The reactions of secondary alicyclic amines with phenyl 4-nitrophenyl thionocarbonate (9) in water are ruled by the stepwise mechanism of Scheme 1, whereby the k_1 step is rate determining for the reactions of most amines (except piperazinium ion).^{5d} The plots of k_{obsd} vs [NH] are linear for these reactions, in contrast to the nonlinear upward plots found in the same aminolysis (except piperidine) of **1** in aqueous ethanol (Figure 2). The reason for the k_1 step being rate limiting in the aminolysis of **9** is that $k_3[NH] + k_2 \gg k_{-1}$,^{5d} therefore, eq 2 reduces to eq 5. It was also found that in this reaction $k_3[NH] > k_2$. For the reactions of 1 there is no clear rate-determining step, i.e., the three terms in the denominator of eq 2 are of the same order of magnitude. The reasons for the different behavior between these reactions can be found in both the addition of 4-methyl in the nonleaving group and the change of solvent. Addition of 4-methyl to the T^{\pm} intermediate formed in the aminolysis of **9** should increase both k_{-1} and k_2 and also the ratio k_2/k_{-1} , since it is known that electron donation from the nonleaving group favors aryloxide expulsion (relative to amine expulsion) from $T^{\pm,1}$ The value of k_3 should be the approximately the same for both reactions due to the fact that the proton transfers from both T^{\pm} to the corresponding amine are diffusion controlled.^{5d} Also the range of amine concentration is about the same for the reactions of 1 and 9. On the other hand, the change of solvent from water to aqueous ethanol should increase the value of k_{-1} and hardly affect the value of k_2 .¹ Therefore, the different kinetic behavior between these reactions should be due to the larger values of both k_2 and k_{-1} (but much larger k_{-1} due to solvent effect) for the reactions of **1** in aqueous ethanol than those for the same reactions of 9 in water.

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⁽²⁰⁾ Jencks, W. P. Chem. Soc. Rev. 1981, 10, 345. Williams, A. Chem. Soc. Rev. 1994, 23, 93.