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Kinetics and Mechanisms of the Reactions of 3-Methoxyphenyl, 3-Chlorophenyl, and 4-Cyanophenyl 4-Nitrophenyl Thionocarbonates with Alicyclic Amines

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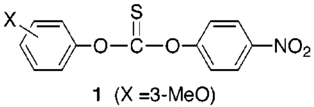
The reactions of 3-methoxyphenyl, 3-chlorophenyl, and 4-cyanophenyl 4-nitrophenyl thionocarbonates (**1**, **2**, and **3**, respectively) with a series of secondary alicyclic amines are studied kinetically in 44 wt % ethanol−water at 25.0 °C and an ionic strength of 0.2 M (KCl). Pseudo-first-order rate coefficients (k_{obsd}) are obtained for all reactions (amine excess was used). The reactions of compound **1** with piperidine, piperazine, and 1-(2-hydroxyethyl)piperazine and of compounds **2** and **3** with these amines and morpholine exhibit linear k_{obsd} versus amine concentration plots with slopes (k_1) independent of pH. In contrast, the plots are nonlinear upward for the reactions of substrate **1** with morpholine, 1-formylpiperazine, and piperazinium ion and of substrates **2** and **3** with the two latter amines. For all these reactions, a reaction scheme is proposed with a zwitterionic tetrahedral intermediate ($T^{\pm}$), which can be deprotonated by an amine to yield an anionic intermediate (T^-). When the nonlinear plots are fit through an equation derived from the scheme, rate and equilibrium microcoefficients are obtained. The Brönsted-type plots for k_1 are linear with slopes of $\beta_1 = 0.22$, 0.20, and 0.24 for the aminolysis of **1**, **2**, and **3**, respectively, indicating that the formation of $T^{\pm}$ (k_1 step) is rate-determining. The k_1 values for these reactions follow the sequence **3** > **2** > **1**, which can be explained by the sequence of the electron-withdrawing effects from the substituents on the nonleaving group of the substrates.

Introduction

We have been interested lately in the kinetics and mechanisms of the aminolysis of alkyl aryl thionocarbonates[1] and diaryl thionocarbonates.[2] In most of these reactions, the presence of one or two tetrahedral intermediates on the reaction path has been postulated. This has been inferred either from biphasic Brönsted-type plots (in the case of pyridinolysis)[1b] or from curved plots of k_{obsd} against amine concentration (in the reactions with secondary amines).[1a,c,2]

To extend our investigations on the mechanisms of the aminolysis of thionocarbonates, specially diaryl thionocarbonates, we now report the mechanism of the reactions of secondary alicyclic amines with 3-methoxyphenyl, 3-chlorophenyl, and 4-cyanophenyl 4-nitrophenyl thionocarbonates (**1**, **2**, and **3**, respectively). We compare these reactions among them and with the aminolysis of the other thionocarbonates mentioned above.[1,2]



1 (X =3-MeO)
2 (X = 3-Cl)
3 (X = 4-CN)

Experimental Section

Materials. The secondary alicyclic amines were purified as reported.[3] Thionocarbonates **1**−**3** have not been synthesized previously to our knowledge. These were prepared on the basis of a reported procedure[2b,4] from 4-nitrophenol and 3-methoxyphenyl, 3-chlorophenyl, or 4-cyanophenyl thionochloroformates. The three latter thionochloroformates were previously prepared, as reported.[4]

Thionocarbonate **1** melted at 112.3−113.2 °C and was characterized as follows: ^{1}H NMR (400 MHz, CD_3CN) ∂ 3.81 (s, 3H), 6.83−6.85 (m, 2H), 6.93 (dd, 1H, $J = 8.4$, 1.5 Hz), 7.40 (dd, 1H, $J = 8.3$ Hz), 7.49 (d, 2H, $J = 9.2$ Hz), 8.34 (d, 2H, $J = 9.2$ Hz); ^{13}C NMR (100 MHz, CD_3CN) ∂ 56.25 (CH_3O), 108.69 (C-2′), 113.49 (C-4′), 114.47 (C-6′), 124.29 (C-2/6), 126.42 (C-3/5), 131.28 (C-5′), 147.22 (C-4), 155.28 (C-1′), 158.49 (C-1), 161.71 (C-3′), 194.78 (C═S). Anal. Calcd for $C_{14}H_{11}O_5NS$: C, 55.08; H, 3.63; N, 4.59; S, 10.50. Found: C, 54.79; H, 3.65; N, 4.49; S, 10.55.

Thionocarbonate **2** melted at 97.2−98.0 °C and was characterized as follows: ^{1}H NMR (400 MHz, CD_3CN) ∂ 7.26 (dd, 1H, $J = 8.3$, 2.0 Hz), 7.37 (t, 1H, $J = 2.0$ Hz), 7.42 (dd, 1H, $J = 8.3$, 2.0 Hz), 7.48 (dd, 1H, $J = 8.3$ Hz), 7.50 (d, 2H, $J = 9.6$ Hz), 8.34 (d, 2H, $J = 9.6$ Hz); ^{13}C NMR (100 MHz, CD_3CN) ∂ 121.51 (C-6′), 123.27 (C-2′), 124.24 (C-2/6), 126.46 (C-3/5), 128.21 (C-4′), 132.04 (C-5′), 135.22 (C-3′), 147.32 (C-4), 154.71 (C-1′), 158.41 (C-1), 194.60 (C═S). Anal. Calcd for $C_{13}H_8O_4ClNS$: C, 50.41; H, 2.60; N, 4.52; S, 10.35. Found: C, 50.27; H, 2.58; N, 4.51; S, 10.60.

Thionocarbonate **3** melted at 185−186 °C and was characterized as follows: ^{1}H NMR (200 MHz, $CDCl_3$) ∂ 7.36 (d, 2H, $J = 9.6$ Hz), 7.38 (d, 2H, $J = 8.3$ Hz), 7.78 (d, 2H, $J = 9.6$ Hz), 8.38 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) ∂ 111.35

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[1] (a) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 3501−3505. (b) Castro, E. A.; Cubillos, M.; Santos, J. G.; Tellez, J. *J. Org. Chem.* **1997**, *62*, 2512−2517. (c) Castro, E. A.; Saavedra, C.; Santos, J. G.; Umaña, M. I. *J. Org. Chem.* **1999**, *64*, 5401−5407.

[2] (a) Castro, E. A.; Santos, J. G.; Tellez, J.; Umaña, M. I. *J. Org. Chem.* **1997**, *62*, 6568−6574. (b) Castro, E. A.; Garcia, P.; Leandro, L.; Quesieh, N.; Rebolledo, A.; Santos, J. G. *J. Org. Chem.* **2000**, *65*, 9047−9053.

[3] Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153−2159.

[4] Al-Kazimi H. R.; Tarbell, D. S.; Plant, D. *J. Am. Chem. Soc.* **1955**, *77*, 2479−2482.

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Table 1. Experimental Conditions and k_{obsd} Values for the Aminolysis of 3-Methoxyphenyl 4-Nitrophenyl Thionocarbonate (1)[a]

amine	pH	F_N[b]	10^3[N$_{tot}$], M[c]	10^3k_{obsd}, s^{-1} [d]	n[e]
piperidine	10.52	0.33	4.2−42	5.4−40	10
	10.82	0.50	4.0−40	5.6−67	10
	11.13	0.67	4.1−41	11−99	10
piperazine	9.40	0.33	5.0−50	4.8−58	10
	9.71	0.50	5.0−45	6.8−73	8
	10.02	0.67	5.0−50	9.6−129	10
1-(2-hydroxyethyl)-piperazine	8.78	0.33	10−100	3.2−45	10
	9.09	0.50	10−100	5.5−70	10
	9.39	0.67	10−80	6.5−71	8
morpholine	8.17	0.33	10−90	1.2−23	9
	8.48	0.50	10−100	2.7−50	10
	8.79	0.67	10−100	5.6−70	10
1-formylpiperazine	7.32	0.33	10−100	0.21−6.42	10
	7.63	0.50	10−100	0.40−11	10
	7.94	0.67	10−100	0.66−19	10
piperazinium ion	5.07	0.33	10−86	0.034−0.37	9
	5.37	0.50	10−100	0.037−0.87	8
	5.67	0.67	10−100	0.078−1.4	10

[a] In 44 wt % ethanol−water at 25.0 °C and an ionic strength of 0.2 M (KCl). [b] Free-amine fraction. [c] Concentration of total amine (free-base and protonated forms). [d] Pseudo-first-order rate coefficient. [e] Number of runs.

Table 2. Experimental Conditions and k_{obsd} Values for the Aminolysis of 3-Chlorophenyl 4-Nitrophenyl Thionocarbonate (2)[a]

amine	pH	F_N[b]	10^3[N]$_{tot}$, M[c]	10^3k_{obsd}, s^{-1} [d]	n[e]
piperidine	10.52	0.33	4.2−42	8.5−71	10
	10.82	0.50	4.0−40	9.1−99	10
	11.13	0.67	4.1−41	14−153	10
piperazine	9.41	0.33	10−100	21−218	10
	9.71	0.50	10−100	28−304	10
	10.01	0.67	10−100	39−473	10
1-(2-hydroxyethyl)-piperazine	8.78	0.33	10−100	6.5−77	10
	9.09	0.50	10−100	9.8−116	10
	9.40	0.67	10−80	12−120	8
morpholine	8.18	0.33	10−100	4.1−72	10
	8.48	0.50	10−100	7.0−112	10
	8.78	0.67	7.0−70	6.6−107	10
1-formylpiperazine	7.32	0.33	10−100	0.58−13	10
	7.63	0.50	10−100	0.95−24	10
	7.94	0.67	10−100	1.5−37	10
piperazinium ion	5.06	0.33	10−80	0.083−0.67	8
	5.37	0.50	10−100	0.15−1.8	10
	5.67	0.67	10−100	0.19−2.8	10

[a] In 44 wt % ethanol−water at 25.0 °C and an ionic strength of 0.2 M (KCl). [b] Free-amine fraction. [c] Concentration of total amine (free-base and protonated forms). [d] Pseudo-first-order rate coefficient. [e] Number of runs.

Table 3. Experimental Conditions and k_{obsd} Values for the Aminolysis of 4-Cyanophenyl 4-Nitrophenyl Thionocarbonate (3)[a]

amine	pH	F_N[b]	10^3[N]$_{tot}$, M[c]	10^3k_{obsd}, s^{-1} [d]	n[e]
piperidine	10.52	0.33	0.60−4.2	4.7−19	7
	10.82	0.50	0.60−4.2	8.0−27	7
	11.12	0.67	0.60−4.2	11−47	7
piperazine	9.41	0.33	0.60−6.0	1.7−18	10
	9.71	0.50	0.60−6.0	2.6−29	10
	10.01	0.67	0.60−6.0	3.3−36	9
1-(2-hydroxyethyl)-piperazine	8.79	0.33	0.60−4.8	0.72−4.9	8
	9.09	0.50	0.60−4.2	0.86−6.1	7
	9.39	0.67	0.60−4.2	1.1−10.3	7
morpholine	8.18	0.33	0.60−4.2	0.62−3.4	7
	8.48	0.50	0.60−4.2	0.78−5.4	7
	8.78	0.67	0.60−4.2	0.86−7.3	7
1-formylpiperazine	7.33	0.33	6.0−60	2.1−20	8
	7.63	0.50	6.0−60	2.0−27	8
	7.93	0.67	1.0−10	0.94−4.8	7
piperazinium ion	5.07	0.33	6.0−42	0.54−7.0	7
	5.37	0.50	6.0−42	0.66−10.1	7
	5.67	0.67	6.0−42	1.0−16.1	7

[a] In 44 wt % ethanol−water at 25.0 °C and an ionic strength of 0.2 M (KCl). [b] Free-amine fraction. [c] Concentration of total amine (free-base and protonated forms). [d] Pseudo-first-order rate coefficient. [e] Number of runs.

(C-4′), 117.80 (CN′), 123.11(C-3′/5′), 123.24 (C-2/6), 125.60 (C-3/5), 134.07 (C-2′/6′), 146.32 (C-4), 155.13 (C-1′), 157.21 (C-1), 192.18 (C═S). Anal. Calcd for $C_{14}H_8O_4N_2S$: C, 56.00; H, 2.68; N, 9.33; S, 10.68. Found: C, 55.96; H, 2.55; N, 9.14; S, 10.83.

Kinetic Measurements. These were carried out spectrophotometrically using a Hewlett-Packard 8453 instrument, following the production of 4-nitrophenoxide anion and/or its conjugate acid. The aminolysis of all the substrates was studied at 400 nm, except the reactions involving piperazinium ion, carried out around pH 5, which were measured at 325−330 nm. All reactions were performed in 44 wt % ethanol−water at 25.0 ± 0.1 °C and an ionic strength of 0.2 M (maintained with KCl). The initial concentration of the substrates was $(3-6) \times 10^{-5}$ M. Excess (at least 10-fold) of total amine over the substrates was used throughout.

Pseudo-first-order rate coefficients (k_{obsd}) were obtained in all reactions. The experimental conditions of the reactions and the k_{obsd} values found are shown in Tables 1−3.

Product Studies. In the reactions of the substrates with morpholine and piperidine, the corresponding 3-methoxyphenyl, 3-chlorophenyl, and 4-cyanophenyl thionocarbamates and 4-nitrophenol (and/or its conjugate base) 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.

Results and Discussion

The rate law obtained for the title reactions is given by eq 1, where P and S represent 4-nitrophenoxide anion

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

(and/or its conjugate acid) and the substrate, respectively, and k_{obsd} is the pseudo-first-order rate coefficient (amine was in excess over the substrate).

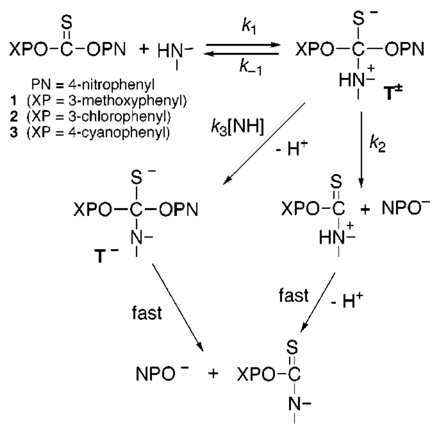
The reactions of compound **1** with the three more basic amines and compounds **2** and **3** with these amines and morpholine show linear plots of k_{obsd} versus amine concentration, the slopes being pH-independent. The above plots for the other reactions subjected to the present study are nonlinear upward. Among these reactions, those of **1** and **2** with the least basic amine, piperazinium ion, are consistent with a polynomial equation of second order in amine.

The kinetic behavior exhibited by the title reactions is in agreement with the mechanism shown in Scheme 1. In this scheme, the k_3 step is the proton transfer from the zwitterionic tetrahedral intermediate $T^{\pm}$ to an amine to yield the anionic tetrahedral intermediate T^-. By application of the steady-state treatment to the tetrahedral intermediates in Scheme 1, and taking into account the solvolysis of the substrates, eq 2 can be obtained. In

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

this equation, k_0 is the rate coefficient for solvolysis of the substrates; the rate coefficients k_1, k_{-1}, k_2, and k_3 are indicated in Scheme 1; and NH represents a free second-

Scheme 1



ary amine. In all cases, the value of k_0 was much smaller than the second (aminolysis) term of eq 2.

The linear plots of k_{obsd} vs [NH] obtained for the reactions of the substrates with the more basic amines can be explained assuming that $k_{-1} \ll k_2 + k_3[NH]$. This is reasonable in terms of the stronger C–N bond in T$^{\pm}$, compared to the same bond for the less basic amines. In these cases, eq 2 reduces to eq 3. Another possibility to

$$k_{obsd} = k_0 + k_1[NH] \qquad (3)$$

explain the linear plots is $k_2 \gg k_3[NH]$, whose substitution in eq 2 yields eq 4. Nonetheless, the magnitude of

$$k_{obsd} = k_0 + \frac{k_1k_2}{k_{-1} + k_2}[NH] \qquad (4)$$

the slopes of the Brönsted-type plots obtained indicates that eq 3, and not eq 4, is the valid one for the reactions showing linear plots of k_{obsd} vs [NH] (see below).

For the reactions of the substrates **1** and **2** with the least basic amine, piperazinium ion, it can be assumed that the bond between the amine and the central carbon of the intermediate T$^{\pm}$ in Scheme 1 is weak. Therefore, $k_{-1} \gg k_2 + k_3[NH]$. In these cases, eq 2 reduces to eq 5,

$$k_{obsd} = k_0 + K_1k_2[NH] + K_1k_3[NH]^2 \qquad (5)$$

where K_1 (which equals k_1/k_{-1}) is the equilibrium constant for the first step in Scheme 1.

Equation 5 satisfactorily describes the nonlinear k_{obsd} vs [NH] plots obtained in the reactions of **1** and **2** with piperazinium ion. Through nonlinear least-squares fitting of this equation, the values of k_0, K_1, and k_2 were obtained, the k_3 value being estimated previously (see below). The values of K_1, k_2, and k_3 found are shown in Table 4. The plot of k_{obsd} vs [NH] for the reaction of piperazinium ion with thionocarbonate **1** is shown in Figure 1. A similar plot (not shown) was obtained for the reaction of piperazinium ion with thionocarbonate **2**.

The nonlinear upward k_{obsd} vs [NH] plots found for the reactions of **1** with morpholine and 1-formylpiperazine, of **2** and **3** with the latter amine, and of **3** with piperazinium ion are not consistent with the polynomial equation (eq 5). These reactions were found to be governed by eq 2. Through nonlinear least-squares fitting of eq 2 to the experimental points, with previous estimation of the k_3 value (see below), the rate microcoefficients k_0, k_1, k_{-1}, and k_2 were obtained. In all cases, the k_0 value was much smaller than the values of the other coefficients. The values of k_1, k_{-1}, and k_2 for these reactions are shown in Table 4. Figure 2 shows the fitting of the k_{obsd} vs [NH] plot, at three pH values, for the reaction of **2** with 1-formylpiperazine. Similar fittings were obtained for the other reactions mentioned above.

Table 4. Values of the Rate and Equilibrium Microcoefficients Obtained in the Aminolysis of 3-Methoxyphenyl, 3-Chlorophenyl, and 4-Cyanophenyl 4-Nitrophenyl Thionocarbonates (1–3)[a,b]

		k_1, s^{-1} M^{-1}			$10^{-8}k_{-1}$, s^{-1}		
amine	pK_a	**1**	**2**	**3**	**1**	**2**	**3**
piperidine	10.82	3.7	5.7	13			
piperazine	9.71	4.0	7.0	10.4			
1-(2-hydroxyethyl)-piperazine	9.09	1.4	2.4	3.4			
morpholine	8.48	1.3	2.2	2.6	1.3		
1-formylpiperazine	7.63	0.74	1.3	1.5	6.5	5.6	2.0
piperazinium cation	5.37			0.74			10

[a] The values of both the pK_a and the microcoefficients were determined in 44 wt % ethanol–water at 25.0 °C and an ionic strength of 0.2 M (KCl). [b] Other rate microcoefficients: $10^{-8}k_2$ (s^{-1}) = 1.2 (**1**), 1.4 (**2**), and 2.0 (**3**); $k_3 = 2 \times 10^9$ s^{-1} M^{-1} (piperazinium ion); $k_3 = 4 \times 10^9$ s^{-1} M^{-1} (other amines). Equilibrium microcoefficients: $K_1 = 8.3 \times 10^{-11}$ M^{-1} (piperazinium + **1**); $K_1 = 1.6 \times 10^{-10}$ M^{-1} (piperazinium + **2**).

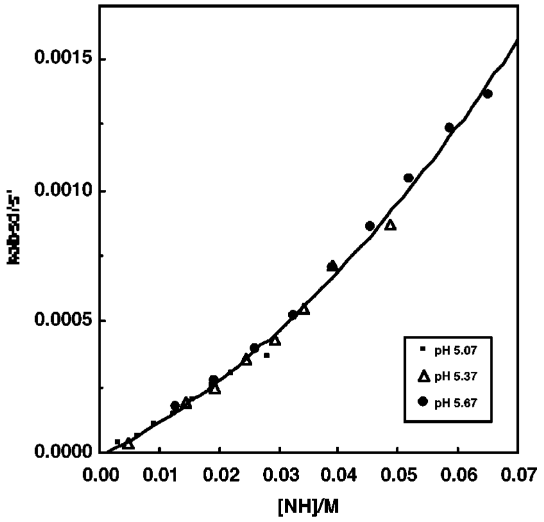


Figure 1. Plot of k_{obsd} against free amine concentration for the reaction of thionocarbonate **1** with piperazinium ion in 44 wt % ethanol–water at 25.0 °C and ionic strength of 0.2 M. The line was calculated through eq 5 with the parameters listed in Table 4.

With the k_1 values found through either eq 2 or eq 3, the Brönsted-type plots shown in Figure 3 were obtained. These Brönsted plots are statistically corrected[3,5] with $p = 2$ for the conjugate acids of the amines, except piperazinium ion with $p = 4$, and $q = 1$ for the amines, except piperazine with $q = 2$.[3,5] These statistical corrections arise from the fact that most of the conjugate acids of the amines possess two equivalent protons ($p = 2$), whereas the conjugate acid of piperazinium ion has four ($p = 4$). On the other hand, most amines possess one equivalent basic site ($q = 1$), whereas piperazine has two ($q = 2$). To correct these statistical differences, the k_N values are divided by q and the K_a values are multiplied by q/p.

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

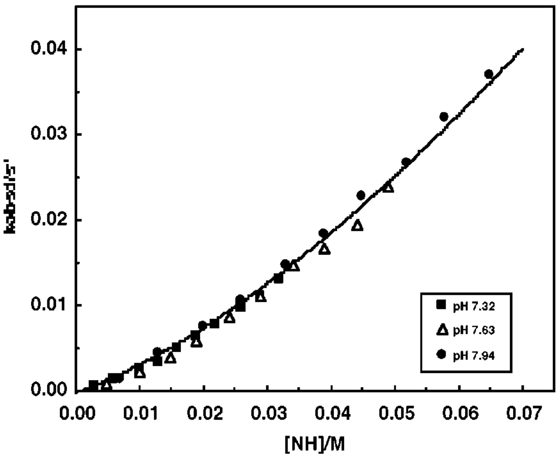

Figure 2. Plot of k_{obsd} against free amine concentration for the reaction of thionocarbonate **2** with 1-formylpiperazine in 44 wt % ethanol−water at 25.0 °C and ionic strength of 0.2 M. The line was calculated through eq 2 with the parameters listed in Table 4.

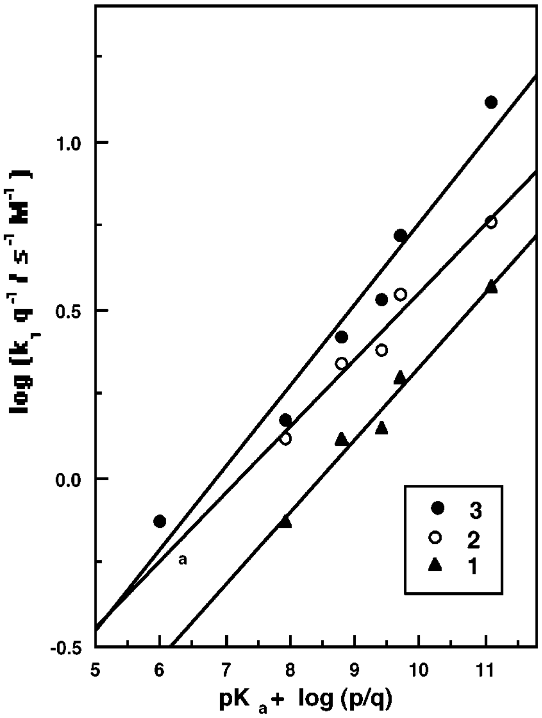

Figure 3. Brönsted-type plots (statistically corrected) for k_1 for the aminolysis of thionocarbonates **1**, **2**, and **3** in 44 wt % ethanol−water at 25.0 °C and an ionic strength of 0.2 M. The slopes (β) are 0.22, 0.20, and 0.24, respectively.

As seen in Figure 3, the Brönsted plots are linear with slopes of $\beta = 0.22 \pm 0.05$, $\beta = 0.20 \pm 0.05$, and $\beta = 0.24 \pm 0.05$ for the reactions of thionocarbonates **1**, **2**, and **3**, respectively. These slope values are in agreement with those found in similar stepwise reactions in which the formation of a zwitterionic tetrahedral intermediate ($T^{\pm}$) is the rate-determining step.[1−3,6−8] This shows that the values obtained as the slopes of the linear k_{obsd} vs [NH] plots are those of k_1, validating, therefore, eq 3 and ruling out eq 4.

According to the Brönsted plots shown in Figure 3, the sequence of reactivities of a given amine toward the thionocarbonates to yield the intermediate $T^{\pm}$ is **3** > **2** > **1**. This order of reactivities can be explained by the sequence of electron-withdrawing effects of the substituents attached to the nonleaving group of the substrates, $\sigma = 0.67$, 0.37, and 0.08 for 4-cyano, 3-chloro, and 3-methoxy, respectively.[9] This leaves the thiocarbonyl carbon of **3** the most electrophilic and therefore the most susceptible to nucleophilic attack by the amine.

As expected, the k_{-1} values (which measure amine expulsion rate from $T^{\pm}$), shown in Table 4 for the reactions of a given substrate increase as the basicity of the amine decreases because the carbon−amine bond in $T^{\pm}$ becomes weaker. In contrast, the values of k_{-1} for 1-formylpiperazine are not much influenced by the meta or para substituent in the nonleaving group (see Table 4). This could be due to the relatively long distance from these substituents in the intermediate $T^{\pm}$ to the central carbon and leaving amine. As seen in Table 4, the k_2 values (expulsion rate of the leaving groups of the substrates from $T^{\pm}$) are also little affected by the substituent on the nonleaving group. It is noteworthy that the k_2 values are not affected by the amine basicity because the amino moiety in $T^{\pm}$ cannot exert a push to expel the nucleofuge because of the lack of an electron pair.[7]

Table 4 also shows the equilibrium constants for $T^{\pm}$ formation (K_1) for the reactions of piperazinium ion with substrates **1** and **2**. As expected, the K_1 value for the reaction with **2** is larger than that for the reaction with **1**, in view of the greater electron withdrawal of 3-Cl compared to that of 3-MeO, which should favor the formation of $T^{\pm}$ by stabilizing this structure relative to reactants.

Estimation of the Values of k_3 in Scheme 1. To determine these values, it is necessary to evaluate the pK_a of the intermediates $T^{\pm}$ in Scheme 1. This can be accomplished by the use of Hammett inductive (σ_I) parameters, following the method of Jencks and coworkers.[10] This method assumes that the pK_a of a tetrahedral intermediate is much more sensitive to the inductive effect than to the resonance effect from a given substituent attached to the central carbon of the intermediate.[10]

On this basis, it was estimated that the pK_a of the zwitterionic tetrahedral intermediate formed in the reactions of 4-methylphenyl 4-nitrophenyl thionocarbonate (**4**) with secondary alicyclic amines (intermediate **5**) is 7.4 pK_a units lower than that of the corresponding aminium ion.[2b] To evaluate the pK_a of **6** (one of the zwitterionic intermediates in Scheme 1), knowledge of the σ_I value of 3-methoxyphenoxy is necessary. This value has not been reported in the literature, according to our records. Nonetheless, it is known that the change of a para to a meta substituent does not alter significantly the value of σ_I. For instance, the difference in σ_I values between 4-X-phenyl and 3-X-phenyl (X = F, Cl, I, NO_2)

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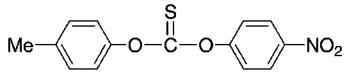
(6) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018−7031.

(7) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963−6970, 6970−6980.

(8) Castro, E. A. *Chem. Rev.* **1999**, *99*, 3505−3524.

(9) Wells, P. R. *Linear Free Energy Relationships*; Academic Press: London, 1968; pp 11, 14.

(10) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 5637−5649. Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436−1449.



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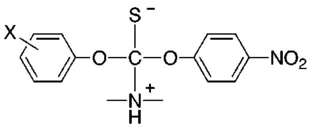

5 (X = 4-Me)
6 (X = 3-MeO)
7 (X = 3-Cl)
8 (X = 4-CN)

is 0−0.03 unit.[11] Assuming this difference would not be changed by introduction of an oxygen atom, it can be estimated that the value of σ_I is 0.39 for 3-methoxyphenoxy (the same as that for 4-methoxyphenoxy).[11] The Hammett inductive reaction constant for the pK_a of intermediates similar to $T^{\pm}$ of Scheme 1 is $\rho_I = -9.2$.[12] The pK_a of intermediate **6** can be calculated with this value and those of σ_I for 4-methylphenoxy ($\sigma_I = 0.37$)[13] and 3-methoxyphenoxy: pK_a(**6**) − pK_a(**5**) = −9.2(0.39 − 0.37) = −0.2. Therefore, the pK_a of **6** is 7.6 pK_a units lower than that of the corresponding aminium ion.

To evaluate the pK_a of **7**, the σ_I value of 3-chlorophenoxy is needed. This is unknown to us, but it can be estimated with the σ_I value of 3-chlorophenyl ($\sigma_I = 0.19$)[11] and knowing that introduction of an oxygen atom to a phenyl group increases the value of σ_I by ca. 0.25 unit. For example, the increase of σ_I from Ph to PhO and from Pr to PrO is 0.25 unit, and that from Et to EtO and 4-MeO−C_6H_4 to 4-MeO−C_6H_4O is 0.26 unit.[11] Therefore, the σ_I value of 3-chlorophenoxy can be estimated as 0.44. Knowing the value of ρ_I (−9.2)[12] and those of σ_I (0.39 and 0.44 for 3-methoxyphenoxy and 3-chlorophenoxy, respectively), it can be calculated that pK_a(**7**) − pK_a(**6**) = −9.2(0.44 − 0.39) = −0.5. Therefore, the pK_a of **7** can be estimated as 7.6 + 0.5 = 8.1 pK_a units smaller than that of the corresponding aminium ion.

Because quantification of the pK_a of **8** is not possible (σ_I for 4-cyanophenoxy has not been reported to our knowledge), we can only assume that the pK_a of intermediate **8** should be lower than that of **7**, in view of the greater electron-withdrawing effect of 4-cyano compared to that of 3-chloro. Because the pK_a values of intermediates **5**−**8** are smaller than those of the corresponding aminium ions, it follows that the proton transfers from these intermediates to the corresponding amines are thermodynamically favorable and, therefore, should be diffusion-controlled.[14] Therefore, the k_3 value of Scheme 1 should be ca. 10^{10} s^{-1} M^{-1} in water[1,14,15] and 4 × 10^9 s^{-1} M^{-1} in 44 wt % ethanol−water.[2b,16] For the proton transfer from a zwitterionic tetrahedral intermediate to a cation such as piperazinium ion in 44 wt % ethanol−water, the value of k_3 has been estimated as 2 × 10^9 s^{-1} M^{-1} because of charge repulsion.[2b,16b]

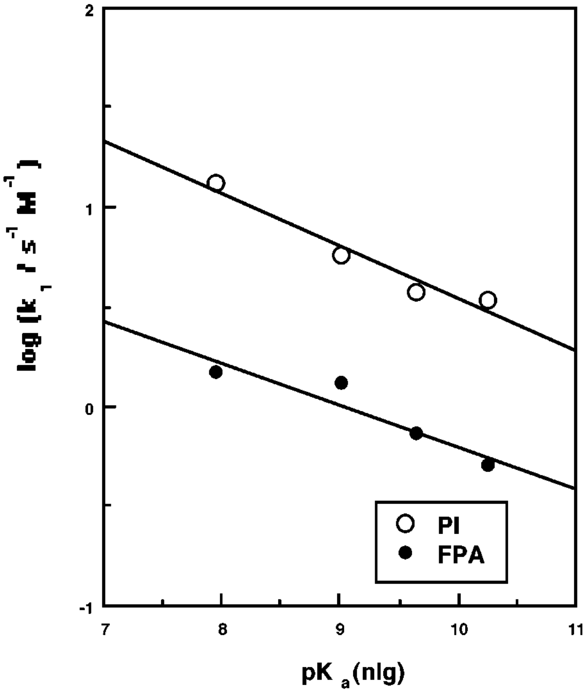

Figure 4. Brönsted-type plots (log k_1 vs pK_a of the nonleaving group) for the reactions of piperidine (PI) and 1-formylpiperazine (FPA) with thionocarbonates **1**−**4** in 44 wt % ethanol−water at 25.0 °C and ionic strength of 0.2 M. The slopes (β_{nlg}) are −0.26 and −0.21 for the reactions of PI and FPA, respectively.

Comparison of the Aminolysis of 1−3 with Other Reactions. In the reactions of 4-methylphenyl 4-nitrophenyl thionocarbonate (**4**) with secondary alicyclic amines in 44% ethanol−water, the k_1 values found by fitting through eq 2 are slightly smaller than those obtained in this work for the same reactions of substrate **1**.[2b] This can be accounted for by the greater electron-donating effect exerted by 4-methyl in **4** than that exerted by 3-methoxy in **1**. This should leave the thiocarbonyl carbon of **4** less positive than that of **1** and therefore less prone to nucleophilic attack by the amine to form the zwitterionic tetrahedral intermediate.

Figure 4 shows the Brönsted plots obtained with the k_1 values for the reactions of piperidine and 1-formylpiperazine with substrates **1**−**3** (this work) and **4**[2b] and the pK_a values[17] of the nonleaving groups (nlg) of the substrates. The slopes are $\beta_{nlg} = -0.26$ for piperidine and $\beta_{nlg} = -0.21$ for 1-formylpiperazine. The Hammett plots for the same reactions (not shown), obtained with the σ values[9] for the meta and para substituents on the nonleaving groups, exhibit slopes of $\rho_{nlg} = 0.73$ and 0.61 for the reactions of piperidine and 1-formylpiperazine, respectively.

With the values of k_1 found in this work (Table 4) and in the aminolysis of thionocarbonate **4**,[2b] a dual parametric equation can be obtained (eq 6). In this equation,

$$\log(k_1/q) = (0.23 \pm 0.01)\mathrm{p}K_a(\mathrm{NH}) - (0.20 \pm 0.02)\mathrm{p}K_a(\mathrm{nlg}) \quad (6)$$

pK_a(NH) and pK_a(nlg) are the pK_a of the amine and

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[11] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

[12] Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1423−1427.

[13] It is assumed that the value of σ_I for 4-methylphenoxy is the same as that for phenoxy because the σ_I values for phenyl and 4-methylphenyl are the same.[2b,11]

[14] Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1−19.

[15] Castro, E. A.; Ureta, C. *J. Org. Chem.* **1990**, *55*, 1676−1679.

[16] (a) Castro, E. A.; Cabrera, M.; Santos, J. G. *Int. J. Chem. Kinet.* **1995**, *27*, 49−57. (b) Castro, E. A.; Leandro, L.; Santos, J. G. *Int. J. Chem. Kinet.* **1999**, *31*, 839−845.

[17] Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hall: London, 1971; p 87.

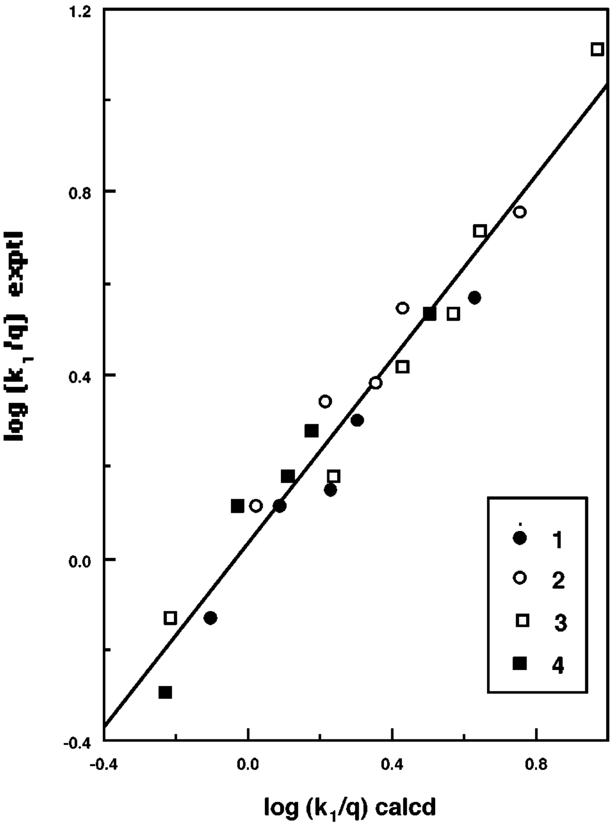


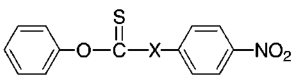
Figure 5. Plot of log(k_1/q) experimental against log(k_1/q) calculated (through eq 6) for the reactions of thionocarbonates **1**−**4** with secondary alicyclic amines in 44 wt % ethanol−water at 25.0 °C and ionic strength of 0.2 M. The slope is unity.

nonleaving group, respectively. The low absolute values of the coefficients β_N and β_{nlg} are in agreement with a stepwise mechanism with rate-determining formation of a zwitterionic tetrahedral intermediate.[1−3,6−8,18]

Figure 5 shows a plot of the experimental vs calculated (through eq 6) k_1 values. The slope is 1.0, and R^2 is 0.951 (21 points). The good correlation and the value of the slope mean that the cross correlation coefficient[18] is not significant in this case. We think that this is because the reactions examined do not show a large range of reactivities to allow for the determination of the cross correlation coefficient.[18]

The linear k_{obsd} vs [NH] plots found in the reactions of compound **1** with piperazine and 1-(2-hydroxyethyl)-piperazine and of substrates **2** and **3** with these amines and morpholine (this work) are in marked contrast with the nonlinear upward plots obtained in the reactions of these three amines with compound **4**.[2b] This different behavior arises from the fact that the values of k_{-1} and k_3[NH] are similar for the reactions of a given amine with these substrates but the k_2 values for the reactions of compounds **1**−**3** are ca. 10−20-fold larger than that for **4**. This means that $k_2 \gg k_{-1} + k_3$[NH] holds for the reactions of the above amines with substrates **1**−**3**, reducing eq 2 to eq 3. For the reactions of 1-formylpiperazine and piperazinium ion with substrates **1**−**3**, the k_{-1} values are much larger, because of the lower basicity of these amines, and either eq 2 or eq 5 takes place.

The k_1 values for the reactions of secondary alicyclic amines with phenyl 4-nitrophenyl thionocarbonate (**9**) in water are larger[1c] than those for **1** (this work) and **4**[2b]. This can be attributed to a solvent effect, because the transition state for T$^{\pm}$ formation should be more stabilized in water, relative to reactants, than in the less polar ethanol−water solvent.[7] It is expected that the above aminolysis of **9** in 44 wt % ethanol−water would exhibit k_1 values intermediate between those of **1** and **4**. These values can be obtained either by interpolation of the Brönsted plots in Figure 4 or by the use of eq 6, using the pK_a value of 10.0 for phenol.[17]



9 (X = O)
10 (X = S)

On the other hand, the k_1 values found in the reactions of secondary alicyclic amines with *O*-phenyl 4-nitrophenyl dithiocarbonate (**10**) in 44 wt % ethanol−water[16b] are much smaller than those obtained for the thionocarbonate **9** (see above) under the same experimental conditions. This is contrary to what is expected on the basis of the electronic effects exerted by 4-nitrophenoxy (NPO) and 4-nitrobenzenethio (NPS) from the corresponding substrates. NPS$^-$ is less basic than NPO$^-$ (pK_a's of NPSH and NPOH are 4.6 and 7.2 in water,[3,17] respectively), and therefore, NPS should leave the thiocarbonyl carbon of **10** more positively charged, enhancing the value of k_1 for **10** compared to that for **9**.[19] The larger k_1 value for the reaction of **9** with a given secondary alicyclic amine, relative to that for the reaction of the same amine with **10**, can be explained by taking into account Pearson's "hard and soft acids and bases" (HSAB) principle.[20] Alicyclic amines are relatively hard bases[20a] that would prefer to bind to the thiocarbonyl group of a thionocarbonate rather than to the softer thiocarbonyl of a dithiocarbonate. This is because it is known that sulfur is much softer than oxygen.[20a,21]

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(18) Lee, I. *Adv. Phys. Org. Chem.* **1992**, *27*, 57−116.

(19) The electronic effects of NPO and NPS could be better assessed if the inductive and resonance effects (as measured by the Hammett constants σ_I and σ_R) of these groups were known. To our knowledge, the latter constant for NPO has not been reported. Nevertheless, as a guide, the normal Hammett σ_p constants for these substituents could be used. These values are $\sigma_p = -0.03$ and 0.07 for NPO and NPS, respectively,[11] which means that NPS is more electron-withdrawing than NPO. Alternatively, the values of σ_I and σ_R of similar groups, such as PhO and PhS, can be used. Inductively, PhO is slightly more electron-attracting than PhS ($\sigma_I = 0.37$ and 0.30, respectively),[11] but regarding resonance, PhO is much more electron-releasing than PhS ($\sigma_R = -0.40$ and -0.23, respectively).[11]

(20) (a) Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 581−587. (b) Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 643−648.

(21) Pearson, R. G. *J. Org. Chem.* **1989**, *54*, 1423−1430.