Kinetics and Mechanism of the Aminolysis of Phenyl and Methyl 4-Nitrophenyl Thionocarbonates

Enrique A. Castro,* Claudia Saavedra, José G. Santos,* and María I. Umaña

Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Santiago 22, Chile

Received January 15, 1999

The reactions of secondary alicyclic amines with the title substrates are subjected to a kinetic study in aqueous solution, 25.0 °C, ionic strength 0.2 (KCl), by following spectrophotometrically the release of 4-nitrophenoxide ion. Under amine excess, pseudo-first-order rate coefficients (k_{obsd}) are found. For the reactions of phenyl 4-nitrophenyl thionocarbonate (**1**), linear plots of k_{obsd} vs [NH] (NH is the free amine) are obtained, except for the reaction with piperazinium ion, which shows nonlinear upward plots. The aminolysis of methyl 4-nitrophenyl thionocarbonate (**2**) exhibits nonlinear plots of k_{obsd} vs [NH], except that with piperidine, which is linear. The Brönsted-type plot for **1** is linear with slope $\beta = 0.25$, indicating that the formation (k_1 step) of a tetrahedral addition intermediate ($\mathbf{T}^{\pm}$) is rate determining. For the aminolysis of **2** (except piperidine), $k_{-1} \approx k_3[NH] > k_2$, where k_{-1}, k_3, and k_2 are the rate coefficients for amine expulsion, amine deprotonation, and leaving group expulsion from $\mathbf{T}^{\pm}$, respectively. For the reaction of **2** with piperidine, $k_{-1} < k_3[NH]$; therefore, the k_1 step is rate limiting. By comparison of the reactions under investigation among them and with similar aminolyses, the following conclusions can be drawn: (i) The change of MeO by EtO in **2** does not affect the k_1, k_{-1}, or k_2 values. (ii) Substitution of MeO by PhO in **2** results in lower k_1 values due to steric hindrance. (iii) The change of 4-nitrophenoxy (NPO) by PhO in **2** lowers the k_1 values and enlarges those of k_{-1}. (iv) Secondary alicyclic amines are less reactive toward **2** than isobasic pyridines when the breakdown of $\mathbf{T}^{\pm}$ is rate determining; this is mainly due to larger k_{-1} values for the former amines. (v) The change of PhO by NPO in **1** changes the mechanism from stepwise to concerted. (vi) Substitution of NPO by PhO in **1** does not alter the k_1 values significantly. (vii) The change of NPO by Cl in **1** increases the k_1 values. (viii) Substitution of C═S by C═O in **1** shifts the rate-limiting step from k_1 to k_2 due to a larger k_{-1}/k_2 ratio by this change.

Introduction

Although there has been much interest on the mechanism of alcoholysis,[1] solvolysis,[1] and aminolysis[2,3] of thioesters and alkyl xanthates,[4] less attention has been focused on the aminolysis mechanisms of thiol,[5] dithio,[6] and thionocarbonates.[7] The latter reactions have been the least studied.

We have lately investigated kinetically the reactions in aqueous solution of phenyl and 4-nitrophenyl ethyl thionocarbonates (EtO−CS−OAr) with secondary alicyclic amines (SAA),[7a] those of 4-nitrophenyl methyl, 4-nitrophenyl ethyl, and 2,4-dinitrophenyl ethyl thionocarbonates with pyridines,[7b] and those of bis(phenyl) and bis(4-nitrophenyl) thionocarbonates (ArO−CS−OAr) with both amine series.[7c]

We have found that all the above reactions of thionocarbonates, except those of bis(4-nitrophenyl) thionocarbonate with SAA, are governed by a stepwise mechanism whereby a zwitterionic tetrahedral addition intermediate ($T^{\pm}$) is formed. The exceptional reaction is enforced concerted[7c] due to the high instability of the "intermediate" as a consequence of the two 4-nitrophenoxy groups and the SAA moiety bound to its central carbon. These groups should destabilize the "intermediate" kinetically due to their large nucleofugality rates.[7c]

(1) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451. Guthrie, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 5892. Pohl, E. R.; Wu, D.; Hupe, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 2759. Douglas, K. T.; Yaggi, N. F.; Mervis, C. M. *J. Chem. Soc., Perkin Trans. 2* **1981**, 171. Okuyama, T.; Komoguchi, S.; Fueno, T. *J. Am. Chem. Soc.* **1982**, *104*, 2582. Allen, J. M.; Venkatasubban, K. S. *J. Org. Chem.* **1985**, *50*, 5108. Douglas, K. T. *Acc. Chem. Res.* **1986**, *19*, 186. Um, I.-H.; Chun, S.-E.; Kwon, D.-S. *Bull. Korean Chem. Soc.* **1991**, *12*, 510. Bunton, C. A.; Foroudian, H. J.; Kumar, A. *J. Chem. Soc.; Perkin Trans. 2* **1995**, 33. Richard, J. P.; Lin, S.-S.; Buccigross, J. M.; Amyes, T. L. *J. Am. Chem. Soc.* **1996**, *118*, 12603.

(2) (a) Campbell, P.; Lapinskas, B. A. *J. Am. Chem. Soc.* **1977**, *99*, 5378. (b) Um, I.-H.; Choi, K.-E.; Kwon, D.-S. *Bull. Korean Chem. Soc.* **1990**, *11*, 362. (c) Castro, E. A.; Ureta, C. *J. Chem. Soc.; Perkin Trans. 2* **1991**, 63. (d) Lee, I.; Shim, C. S.; Lee, H. W. *J. Chem. Res. (S)* **1992**, 90. (e) Castro, E. A.; Ibáñez, F.; Santos, J. G.; Ureta, C. *J. Org. Chem.* **1993**, *58*, 4908. (f) Um, I.-H.; Kwon, H.-J.; Kwon, D.-S.; Park, J.-Y. *J. Chem. Res. (S)* **1995**, 301. (g) Oh, H. K.; Shin, C. H.; Lee, I. *J. Chem. Soc.; Perkin Trans. 2* **1995**, 1169. (h) Oh, H. K.; Shin, C. H.; Lee, I. *Bull. Korean Chem. Soc.* **1995**, *16*, 657. (i) Ljevakovic, B.; Tomic, S.; Tomasic, J.; Horvat, J. *Croatica Chem. Acta* **1996**, *69*, 1329. (j) Oh, H. K.; Woo, S. Y.; Shin, C. H.; Park, Y. S.; Lee, I. *J. Org. Chem.* **1997**, *62*, 5780.

(3) Castro, E. A.; Ibáñez, F.; Santos, J. G.; Ureta, C. *J. Org. Chem.* **1992**, *57*, 7024.

(4) Millican, R. J.; Sauers, C. K. *J. Org. Chem.* **1979**, *44*, 1664. Millican, R. J.; Angelopoulos, M.; Bose, A.; Riegel, B.; Robinson, D.; Wagner, C. K. *J. Am. Chem. Soc.* **1983**, *105*, 3622. Harris, P. J. *S. Afr. J. Chem.* **1984**, *37*, 91.

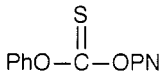
(5) (a) Castro, E. A.; Salas, M.; Santos, J. G. *J. Org. Chem.* **1994**, *59*, 30. (b) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1994**, *59*, 3572. (c) Castro, E. A.; Pizarro, M. I.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 5982.

(6) (a) Cabrera, M.; Castro, E. A.; Salas, M.; Santos, J. G.; Sepúlveda, P. *J. Org. Chem.* **1991**, *56*, 5324. (b) Castro, E. A.; Cubillos, M.; Ibáñez, F.; Moraga, I.; Santos, J. G. *J. Org. Chem.* **1993**, *58*, 5400. (c) Castro, E. A.; Araneda, C. A.; Santos, J. G. *J. Org. Chem.* **1997**, *62*, 126. (d) Oh, H. K.; Lee, J. Y.; Yun, J. H.; Park, Y. S.; Lee, I. *Int. J. Chem. Kinet.* **1998**, *30*, 419.

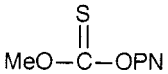
(7) (a) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 3501. (b) Castro, E. A.; Cubillos, M.; Santos, J. G.; Téllez, J. *J. Org. Chem.* **1997**, *62*, 2512. (c) Castro, E. A.; Santos, J. G.; Téllez, J.; Umaña, M. I. *J. Org. Chem.* **1997**, *62*, 6568. (d) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1997**, *62*, 4395.

10.1021/jo990084y CCC: $18.00
Published on Web 07/02/1999

In the present work, we undergo the kinetic investigation of the reactions of SAA with the tittle substrates (**1** and **2**, PN = 4-nitrophenyl) with the following aims: (i) Shed more light on the mechanism of the aminolysis of thionocarbonates. (ii) Assess the influence of the "acyl" group attached to the central carbon of $\mathbf{T}^{\pm}$ on the stability of this intermediate and, therefore, on the mechanism of these reactions. This goal will be achieved by comparing the mechanisms of the present reactions among them and with those found in the reactions of SAA with ethyl 4-nitrophenyl thionocarbonate[7a] and bis(4-nitrophenyl) thionocarbonate.[7c] (iii) Investigate the influence of the leaving group of the substrate on the mechanism by comparing the present reactions with ethyl phenyl thionocarbonate,[7a] bis(phenyl) thionocarbonate,[7c] and phenyl chlorothionoformate.[7d] (iv) Study the effect of the nucleophile by comparing the reactions under investigation with the pyridinolysis of related thionocarbonates;[7b] this will allow us to evaluate the effect of the amino moiety of $\mathbf{T}^{\pm}$ on the stability and mechanism of these reactions. (v) Examine the effect of the electrophilic center of the substrate by comparing the present reactions with the aminolyses of methyl[8] and phenyl 4-nitrophenyl carbonates.[9]



1



2

Experimental Section

Materials. The amines were purified as reported.[10] Methyl 4-nitrophenyl thionocarbonate (**2**) was prepared as described.[7b]

Phenyl 4-nitrophenyl thionocarbonate (**1**) could not be prepared in satisfactory yield by the method reported.[11] It was synthesized as follows: To a solution of 4-nitrophenol (2.02 g, 14.5 mmol) in THF (10 mL) in a Schlenk round-bottomed flask was slowly added a solution (9.1 mL, 14.5 mmol) of 1.6 M butyllithium (Aldrich) under nitrogen atmosphere. The product, lithium 4-nitrophenoxide, was rapidly transferred to a compensation funnel, under nitrogen. In another Schlenk round-bottomed flask, phenyl chlorothionoformate (Aldrich, 2.3 g) was dissolved in anhydrous THF (10 mL) under nitrogen and the flask placed in an ethanol−liquid nitrogen bath. The compensation funnel was attached to the flask and the lithium 4-nitrophenoxide solution added dropwise with stirring during 2 h. The mixture was left overnight with stirring under nitrogen at ambient temperature. Chloroform (50 mL) was added to this mixture and the solution washed with water. The organic layer was dried with $MgSO_4$ and filtered under vacuum and the solvent evaporated off. The crystallized compound **1** melted at 187−189 °C (lit.[11] mp 181−182 °C): IR (KBr) 1520, 1487, 1225, 865, 777, 759 cm^{-1}; δ_H ($CDCl_3$) 7.23, 7.3−7.5, 8.36; δ_C 121.60, 123.27, 125.48, 127.20, 129.84, 146.14, 153.40, 157.52, 193.39.

Kinetic Measurements. These were performed spectrophotometrically by following the production of 4-nitrophenoxide ion (and its conjugate acid) at 400 nm. The instruments and method employed were previously described.[10] The reactions were studied under the following conditions: aqueous solutions, 25.0 ± 0.1 °C, ionic strength 0.2 (maintained with KCl), initial substrate concentration (1.7−3.4) × 10^{-5} M, and at least a 10-fold excess of total amine over the substrate.

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

amine	pH	F_N[b]	$10^2[N]_{tot}$,[c] M	10^2k_{obsd}, s^{-1}	no. of runs
piperidine	10.94	0.33	0.9−8.0	1.93−11.6	6
	11.24	0.50	2.0−8.0	5.40−17.4	7
	11.54	0.67	1.7−5.5	5.09−15.4	6
piperazine	9.64	0.33	1.0−33	3.48−24.6	7
	9.94	0.50	1.0−10	5.22−23.3	8
1-(2-hydroxyethyl)piperazine	9.08	0.33	3.0−13	1.99−7.00	6
	9.38	0.50	1.0−11	1.97−10.7	6
	9.68	0.67	1.0−11	1.72−11.6	5
morpholine	8.48	0.33	6.8−18	9.52−19.9	7
	8.78	0.50	4.0−22	5.35−17.8	10
	9.08	0.67	9.0−36	6.88−19.4	6
1-formylpiperazine	7.68	0.33	2.0−13	0.15−3.38	4
	7.98	0.50	2.0−16	1.97−5.79	6
	8.28	0.67	2.3−13	2.32−5.76	6
piperazinium ion	5.51	0.33	5.0−18	0.0040−0.0091	7
	5.81	0.50	3.0−15	0.0039−0.011	6

[a] In aqueous solution at 25.0 °C, ionic strength 0.2 (KCl). [b] Free amine fraction. [c] Concentration of total amine (free base plus protonated forms).

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

amine	pH	F_N	$10^2[N]_{tot}$, M	10^2k_{obsd}, s^{-1}	no. of runs
piperidine	10.94	0.33	0.5−5.0	1.3−14	7
	11.24	0.50	0.5−5.0	2.1−20	7
	11.54	0.67	0.5−5.0	2.9−28	7
piperazine	9.64	0.33	0.08−2.4	0.10−6.3	8
	9.94	0.50	0.05−0.9	0.09−2.6	8
	10.24	0.67	0.05−1.0	0.19−4.7	8
1-(2-hydroxyethyl)piperazine	9.08	0.33	0.15−3.0	0.07−2.8	9
	9.38	0.50	0.10−2.0	0.07−2.7	8
	9.68	0.67	0.08−1.5	0.06−2.8	8
morpholine	8.48	0.33	0.30−3.0	0.07−1.8	7
	8.78	0.50	0.20−2.0	0.06−1.7	7
	9.08	0.67	0.15−1.5	0.06−1.7	7
1-formylpiperazine	7.68	0.33	3.0−30	0.25−8.0	8
	7.98	0.50	2.0−18	0.23−5.4	6
	8.28	0.67	1.5−14	0.25−5.5	7

[a] Abbreviations and experimental conditions as in Table 1.

Pseudo-first-order rate coefficients (k_{obsd}) were found throughout, by means of the method described.[10] The experimental conditions of the reactions and the k_{obsd} values obtained are shown in Tables 1 and 2.

Product Studies. The phenyl thionocarbamates of piperidine and morpholine were identified as one of the final products of the reaction of **1** with these two amines. This was carried out by comparison of the UV−vis spectra after completion of these reactions with those of authentic samples under the same experimental conditions and also with the spectra at the end of the reactions of phenyl chlorothionoformate with the different amines. 4-Nitrophenol (and/or its conjugate base) was identified as the other product of the reactions of **1** and **2** with the amines by comparison of the UV−vis spectra after completion of these reactions with that of an authentic sample of 4-nitrophenol under the kinetic conditions.

Results

The kinetic law obtained for all the reactions studied under the experimental conditions, described in Tables 1 and 2, is that given by eq 1, where P is 4-nitrophenol (and/or its conjugate base), S represents the substrate,

(8) Bond, P. M.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 679.
(9) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963, 6970.
(10) Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153.
(11) Al-Kazimi, H. R.; Tarbell, D. S.; Plant, D. *J. Am. Chem. Soc.* **1955**, *77*, 2479.

Table 3. Values of the pK_a of Conjugate Acids of Secondary Alicyclic Amines and Rate Coefficients for the Aminolysis of Phenyl 4-Nitrophenyl Thionocarbonate (1) and Methyl 4-Nitrophenyl Thionocarbonate (2)[a]

amine	pK_a	$k_N/s^{-1}M^{-1}$ **1**	$k_1/s^{-1}M^{-1}$ **2**[b]	$10^{-8}k_{-1}/s^{-1}$ **2**[b]
piperidine	11.24	3.8 ± 0.2	8.3 ± 0.5	0.02[c]
piperazine	9.94	4.1 ± 0.1	12 ± 1	0.6 ± 0.02
1-(2-hydroxyethyl)piperazine	9.38	1.8 ± 0.1	4.8 ± 0.3	0.9 ± 0.05
morpholine	8.78	1.4 ± 0.1	3.3 ± 0.2	1.2 ± 0.1
1-formylpiperazine	7.98	0.50 ± 0.04	1.8 ± 0.1	16 ± 2
piperazinium ion	5.81	(1.5 ± 0.1) × 10^{-2} [d]		

[a] Values of pK_a and rate coefficients were determined in aqueous solution, at 25.0 °C, ionic strength 0.2 (KCl). [b] For the aminolysis of this substrate (except piperidine), the values of k_1, k_{-1}, and $k_2 = (3 \pm 2) \times 10^7$ s^{-1} (Scheme 1, R = Me) were obtained by nonlinear least-squares fitting of eq 4, using for k_3 the value 10^{10} s^{-1} M^{-1}. [c] Value obtained by extrapolation of the Brönsted-type plot for the other four amines (Figure 4). [d] Value (s^{-1} M^{-2}) obtained as the slope of a linear plot of k_{obsd} vs $[NH]^2$; the value corresponds to K_1k_3 (see text).

and k_{obsd} is the pseudo-first-order rate coefficient (excess of amine over the substrate was employed throughout).

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

In the reactions of **1** with all the amines, except those with piperazinium ion, plots of k_{obsd} against concentration of total amine, $[N]_{tot}$, at constant pH, were linear, in accordance with eq 2, where F_N is the free amine fraction. In this equation, k_0 and k_N are the rate coefficients for hydrolysis and aminolysis of the substrate, respectively. The values of k_N were obtained from the slopes of plots of eq 2 and showed no dependence on pH. Therefore, the definitive k_N values were obtained as the slopes of plots of k_{obsd} vs [NH] (eq 3), where NH is the free amine, at several pH values (ca. 16−23 points each plot). These k_N values are shown in Table 3.

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

$$k_{obsd} = k_0 + k_N [NH] \quad (3)$$

The reaction of **1** with piperazinium ion exhibited kinetics clearly second order in free amine. The slopes of the linear plots of k_{obsd} vs $[NH]^2$ showed no pH dependence. This value is reported in Table 3.

For the aminolysis of **2**, except that with piperidine, the plots of k_{obsd} vs [NH] at constant pH were nonlinear and pH independent (see Figure 1 as an example). The reactions with piperidine showed a clear first order in the free amine; i.e., they are governed by eq 3.

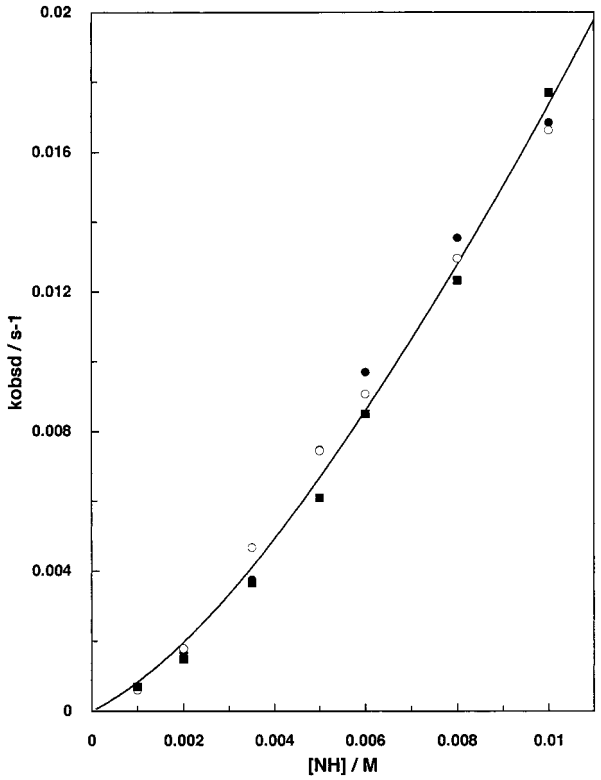


Figure 1. Plot of k_{obsd} against free-amine concentration for the reaction of morpholine with **2** at pH 8.48 (■), 8.78 (●), and 9.08 (○), in water at 25.0 °C, ionic strength 0.2.

Discussion

Reactions of 1. The Brönsted-type plot obtained with the k_N and pK_a data of Table 3 for the aminolysis of **1** is shown in Figure 2. The plot is statistically corrected[12] with $p = 2$ for all the conjugate acids of the amines, except piperazinium ion with $p = 4$ and $q = 2$ for piperazine (for the other amines $q = 1$).[10] This plot is linear with slope $\beta = 0.25 \pm 0.1$ (the point for piperazinium ion is not included since these kinetics are not first order in amine). This value of β is in agreement with those found in stepwise aminolyses, whereby the formation of a tetrahedral intermediate is the rate-determining step (β_1 ca. 0.1−0.3).[3,5b,c,6,7,9,10,13,14] According to the estimated values of the rate microcoefficients involved (see below), the concentration range of free amine employed (Table 1), and the β value obtained, the most likely mechanism for the aminolysis of **1** is that described in Scheme 1 (R = Ph). Following our estimations (see below), the k_1 step should be rate determining for the reactions with all the amines except those with piperazinium ion where deprotonation of $T^{\pm}$ by piperazinium ion to yield T^- (k_3 step) should be rate limiting. For the reactions with all the amines our estimations indicate that $k_3[NH] > k_2$ (see below).

To determine the value of k_3 in Scheme 1 (R = Ph), it is first necessary to estimate the pK_a of intermediate **3**. On the basis of the Jencks procedure,[15] which involves the use of Hammett inductive parameters for substituents attached to a tetrahedral carbon, the pK_a of inter-

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

(13) (a) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 68. (b) Castro, E. A.; Gil, F. J. *J. Am. Chem. Soc.* **1977**, *99*, 7611.

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

(15) 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.

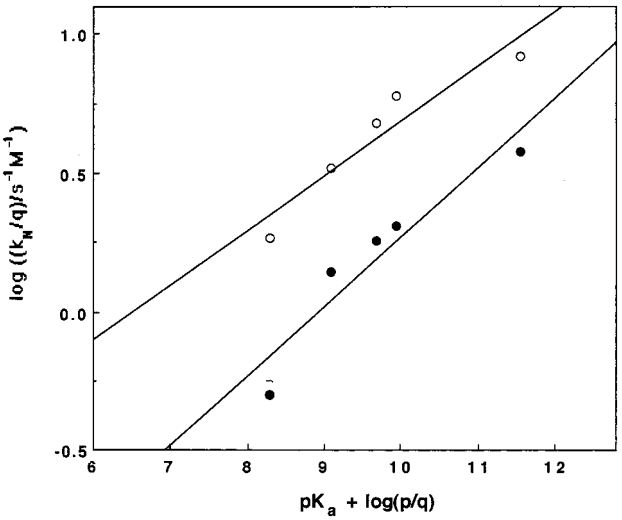
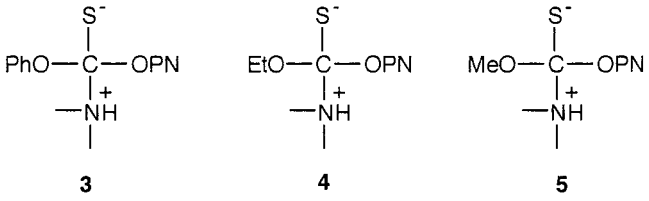


Figure 2. Brönsted-type plots (statistically corrected) for the reactions of secondary alicyclic amines with **1** (●) and **2** (○) in water at 25.0 °C, ionic strength 0.2. For **2** the k_N values are those of k_1 in Table 3. The slope values are 0.25 for **1** and 0.2 for **2**.

mediate **4** has been estimated as 6.4 pK_a units lower than that of the corresponding amine.[7a,16] Using $\rho_I = -9.2$ for the Hammett correlations for the pK_a of tetrahedral intermediates similar to **3**,[17] and employing $\sigma_I = 0.26$ and 0.37 for EtO and PhO,[18] respectively, one obtains: $\Delta pK_a = -9.2\ (0.37-0.26) = -1.0$. Namely, the p$K_a$ of **3** should be 6.4 + 1.0 = 7.4 pK_a units lower than that of the corresponding free amine; i.e., the proton transfer from **3** to the corresponding amine should be thermodynamically favorable, and k_3 of Scheme 1 (R = Ph) can be estimated as ca. 10^{10} s^{-1} M^{-1}.[3,6,7a,10,19]



3 **4** **5**

Reactions of 2. For the reactions of secondary alicyclic amines with **2**, we propose the mechanism depicted in Scheme 1 (R = Me) on the basis of the kinetic results and the analysis of products. Applying the steady-state treatment to both tetrahedral intermediates in Scheme 1, and taking into account that the two bottom steps are fast, the rate law described by eq 4 can be deduced.

$$k_{obsd} = \frac{k_1(k_2 + k_3[NH])[NH]}{k_{-1} + k_2 + k_3[NH]} \qquad (4)$$

For the reaction of **2** with piperidine, it is reasonable that $k_{-1} \ll k_2 + k_3[NH]$ due to the high basicity of this amine, which should result in a low nucleofugality from the intermediate **5**. In this case, eq 4 reduces to $k_{obsd} = k_1[NH]$, in accordance to the experimental kinetic equation (eq 3). The value of k_1 was found as the slope of a linear plot of k_{obsd} vs [NH]; the k_1 value is shown in Table 3.

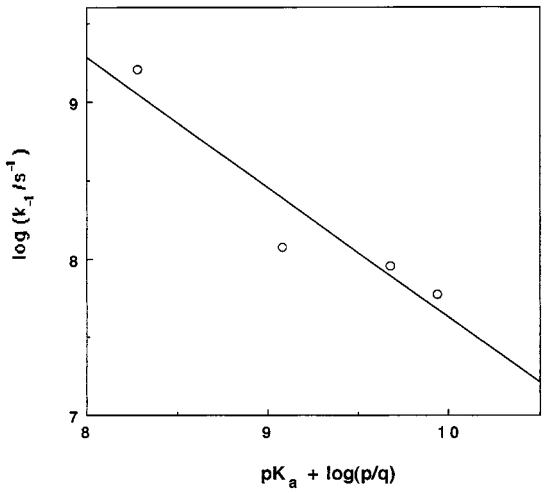


Figure 3. Brönsted-type plot for k_{-1} (statistically corrected) for the reactions of secondary alicyclic amines with **2** in water at 25.0 °C, ionic strength 0.2. The value of the slope is −0.83.

For the reactions of **2** with the other amines the value of k_{-1} should be larger than that for piperidine and, therefore, would be comparable to that of k_3[NH] (see below).

To determine the value of k_3 in Scheme 1 (R = Me) we must estimate the pK_a of intermediate **5**. Knowing that the pK_a of **4** is 6.4 pK_a units lower than that of the corresponding amine (see above) and employing $\sigma_I = 0.26$ and 0.29 for EtO and MeO,[18] respectively, by the Jencks procedure[15,17] one obtains: $\Delta pK_a = -9.2\ (0.29-0.26) = -0.28$. Therefore, the p$K_a$ of **5** should be 6.4 + 0.3 = 6.7 pK_a units less than that of the corresponding amine, the proton transfer from **5** to the corresponding free amine should be difussion controlled, and therefore, the value of k_3 of Scheme 1 (R = Me) should be ca. 10^{10} s^{-1} M^{-1} (see above).

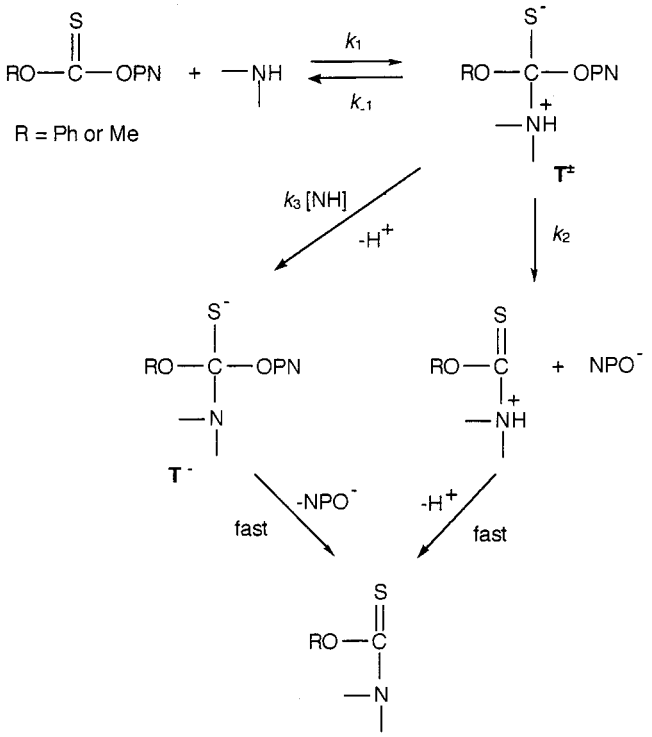
With the value of k_3 and taking as initial values those for k_2, k_1, and k_{-1} found in the reactions of piperazine, 1-(2-hydroxyethyl)piperazine, morpholine, and 1-formylpiperazine with ethyl 4-nitrophenyl thionocarbonate,[7a] the "best" values of k_2, k_1, and k_{-1} for the reactions of **2** with the same amines were obtained by nonlinear least-squares fitting of eq 4 to the experimental points. These values are shown in Table 3. As an example, Figure 1 shows such fitting for the reaction of **2** with morpholine.

With the k_1 and k_{-1} values found in the aminolysis of **2**, the Brönsted-type plots in Figures 2 (where $k_1 = k_N$) and 3 were obtained. The slopes $\beta_1 = 0.20 \pm 0.1$ and $\beta_{-1} = -0.83 \pm 0.1$, respectively, are in agreement with those expected for stepwise processes concerning the formation of a zwitterionic tetrahedral intermediate.[3,6,7,9,10,13,14] Extrapolation of the Brönsted-type plot for k_{-1} to piperidine gives $k_{-1} = 2 \times 10^6$ s^{-1}, which compared to the value of $k_2 = 3 \times 10^7$ s^{-1} (Table 3) and k_3[NH] = (2−33) × 10^7 s^{-1} (see Table 2 for the range of [NH] employed) shows that for this reaction $k_{-1} \ll k_2 + k_3$[NH], which according to eq 4 yields $k_{obsd} = k_1$[NH], justifying therefore the first-order in amine found for the reaction of **2** with piperidine.

Comparison of the Aminolyses of 1, 2, and Similar Compounds. Taking into account the probable smaller values of k_{-1} and k_2 in the aminolysis of **1**[20] compared to

(16) Castro, E. A.; Ibáñez, F.; Santos, J. G.; Ureta, C. *J. Org. Chem.* **1993**, *58*, 4908.
(17) Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1423.
(18) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
(19) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

Scheme 1



those in the same reactions of **2**, knowing that the k_3 value is approximately the same in these reactions, and considering the free amine concentration ranges in Table 1, it follows that for the reactions of **1** with all the amines, except piperazinium ion, $k_2 + k_3[NH] > k_{-1}$. Therefore, according to eq 4, $k_{obsd} = k_1[NH]$, which agrees with the kinetic equation obtained (eq 3) and the low Brönsted-type slope found for these reactions (β ca. 0.25, Figure 2). For the reaction of **1** with piperazinium ion, k_{-1} should be ca. 10^{10} s^{-1} (the value of k_{-1} for this amine from the intermediate **5**, obtained by extrapolation of the Brönsted-type plot for **2**, is 4×10^{10} s^{-1}), and therefore, $k_{-1} > k_3[NH] > k_2$. It follows from eq 4 that $k_{obsd} = K_1k_3[NH]^2$ for the reaction of piperazinium ion with **1**, in agreement with the rate law found for this reaction (see above).

The effect of the "acyl" group of the substrate on the kinetics can be assessed by comparison of the rate coefficients for aminolysis of **1** and **2** (Table 3). The k_1 values for the latter aminolysis can be directly compared with the k_N values for the reactions of the same amines (except piperazinium ion) with **1**, since in both cases the rate-determining step is the formation of $T^\pm$ in Scheme 1. The larger rate coefficients for **2** are not in line either with the larger electron donation by resonance of MeO than PhO ($\sigma_R = -0.56$ and -0.40, respectively)[18] or with the smaller inductive electron withdrawal by MeO relative to PhO ($\sigma_I = 0.29$ and 0.37, respectively).[18] These effects should leave the thiocarbonyl carbon of **1** more positively charged than that of **2** and, therefore, more susceptible to nucleophilic attack by the amine. Therefore, the smaller rate coefficient values found for the aminolysis of **1** can be attributed to steric hindrance toward amine attack by the PhO group of this substrate.

The values of k_1, k_{-1}, and k_2 obtained in the reactions of **2** (Table 3) are very similar to the corresponding values found in the same reactions of ethyl 4-nitrophenyl thionocarbonate,[7a] as expected on the basis of the similar σ_I and σ_R values for MeO and EtO, $\sigma_I = 0.29$ and 0.26, respectively, and $\sigma_R = -0.56$ and -0.50, respectively.[18] This is consistent with the single Brönsted straight line of slope unity found in the pyridinolyses of **2** and the ethyl analogue.[7b]

The reactions of secondary alicyclic amines with bis(4-nitrophenyl) thionocarbonate have been shown to be concerted on the basis of linear plots of k_{obsd} vs amine concentration and slightly curved Brönsted-type plots of limiting slopes $\beta = 0.1$ and 0.5.[7c] The reason a tetrahedral intermediate either is not formed or is very unstable in these reactions whereas it is formed in the same reactions of **1** can be attributed to the fact that there are three very good leaving groups attached to the central carbon of the "intermediate" in the aminolysis of the bis(nitrophenyl) derivative (the two NPO groups and the secondary amino moiety), whereas there are only two in intermediate **3**. Therefore, the latter intermediate is so much destabilized by the change of PhO by NPO that either it no longer exists (and the mechanism becomes enforced concerted) or it is highly unstable.[21−23]

The effect of the leaving group of the substrate can be evaluated by comparison of the aminolysis of **2** with the same reactions of ethyl phenyl thionocarbonate[7a] since the change of MeO by EtO as the "acyl" group does not affect significantly the values of the rate coefficients (see above). The values of k_1 are larger for **2** as expected from the larger electron-withdrawing effect of NPO in **2** compared to that of PhO in the phenyl derivative,[7a] resulting in a faster nucleophilic attack to the former substrate. On the other hand, the amine nucleofugality from the tetrahedral intermediate (k_{-1}) is larger for the phenyl analogue[7a] relative to **2**. This fact can be explained by the higher basicity of PhO^- relative to NPO^-, which results in a stronger "push" to expel the amine exerted by PhO than NPO from the tetrahedral intermediate.

By comparing the reactions of secondary alicyclic amines with **1** and bis(phenyl) thionocarbonate,[7c] the leaving group effect can also be analyzed. The latter reactions exhibit upward curved plots of k_{obsd} vs amine concentration, from which the k_1 and k_{-1} values were obtained.[7c] The k_1 values for the reactions of the bis(phenyl) derivative are very similar to those for **1** (except piperazinium ion, see above). This is surprising in view of the stronger electron withdrawal by NPO than PhO, which should leave the thiocarbonyl carbon of **1** more electrophilic. This could be explained by the fact that in the bis compound there are already two relatively powerful electron-attracting groups and its thionocarbonyl carbon should possess a relatively large positive charge. Therefore, the change of one PhO by NPO should not change this positive charge significantly.

Another example of leaving group effect can be seen by comparison of the reactions of secondary alicyclic amines with **1** and phenyl chlorothionoformate (PhO−

(20) For the aminolysis of **1** it is expected that the values of both k_{-1} and k_2 be smaller than those for **2** since the push exerted by PhO from **3** to expel both the amine and NPO^- should be weaker than that by MeO from **5**. This is due to the fact that $\sigma_R(PhO) = -0.40$ and $\sigma_R(MeO) = -0.56$,[18] which means that PhO should be less electron donating than MeO from the intermediate $T^\pm$ of Scheme 1, and therefore, the push provided by the former group should be weaker than that by the latter.

(21) Song, B. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 8479.
(22) (a) Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387. (b) Williams, A. *Chem. Soc. Rev.* **1994**, *23*, 93.
(23) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345.

CS−Cl),[7d] although in these cases the leaving groups are very different in nature. The k_1 values for the reactions of the latter substrate are larger by ca. 2 orders of magnitude than those of **1**. Since NPO is more electron withdrawing than Cl, the present result can be explained by steric reasons. A similar situation occurs in the pyridinolysis of acetates and carbonates: The rate-determining attack of 4-(dimethylamino)pyridine (DMAP) to acetyl chloride[24] to form a tetrahedral intermediate is ca. 10^3 faster than that to 4-nitrophenyl acetate.[25,26] Similarly, DMAP is ca. 10-fold more reactive toward methyl chloroformate[13a] than methyl 4-nitrophenyl carbonate,[8] when formation of the tetrahedral intermediate is rate determining.[27]

The effect of the nucleophile nature on the kinetics can be studied by comparing the reactions of **2** with pyridines[7b] and secondary alicyclic amines (this work). A linear Brönsted-type plot of slope $\beta = 1.0$ was obtained for the former reactions, indicating the presence of a tetrahedral intermediate whose breakdown to products is rate determining.[7b] This means that for these reactions $k_{-1} \gg k_2$. The difference in the mechanism of both reaction series arises from the fact that a significant proton transfer from $\mathbf{T}^{\pm}$ (Scheme 1, R = Me) to the secondary amine takes place in the reaction with these amines, whereby $k_{-1} \approx k_3$[NH] in Scheme 1 (R = Me), except in the reactions with piperidine whereby $k_{-1} \ll k_3$ [NH] (see above).

By dividing the values of k_1 by k_{-1} in Table 3 for the reactions of **2** with the secondary amines, the values of K_1 (equilibrium constant for the first step in Scheme 1, R = Me) can be obtained. On the other hand, by dividing the $k_N = K_1k_2$ values found in the pyridinolysis of the same substrate[7b] by $k_2 = 3 \times 10^7$ s^{-1},[28] the K_1 values for these reactions can be obtained. The Brönsted-type plots for K_1 for both reactions series are shown in Figure 4. It can be seen that pyridines are thermodynamically more favorable toward the formation of the intermediate than the alicyclic amines, and since k_2 has ca. the same value for both reactions series,[28] it means that the former amines are more reactive toward this substrate than the alicyclic amines when the breakdown of the intermediate to products (k_2 step) is rate determining.

The rate coefficients for amine attack to the substrate (k_1) are slightly larger for pyridines than secondary alicyclic amines in their reactions toward aryl acetates and methyl aryl carbonates.[29] Therefore, if this is also true for the reactions of **2**, the much larger K_1 values for the reactions of pyridines (Figure 4) mean that k_{-1} is smaller for these amines compared to isobasic alicyclic amines. A similar result was found by Gresser and Jencks in the aminolysis of phenyl aryl carbonates. They found that pyridines leave the zwitterionic tetrahedral intermediate slower than isobasic quinuclidines (alicyclic tertiary amines).[9] Moreover, in the aminolysis of aryl acetates and methyl aryl carbonates it was found that the k_{-1} values for pyridines are smaller than those for isobasic secondary alicyclic amines.[29] The poor leaving ability of pyridines has been attributed to "a significant contribution of resonance stabilization by electron donation from the pyridine to the carbonyl group of the product and to the oxygen leaving group in the transition state for the breakdown of the tetrahedral intermediate".[9]

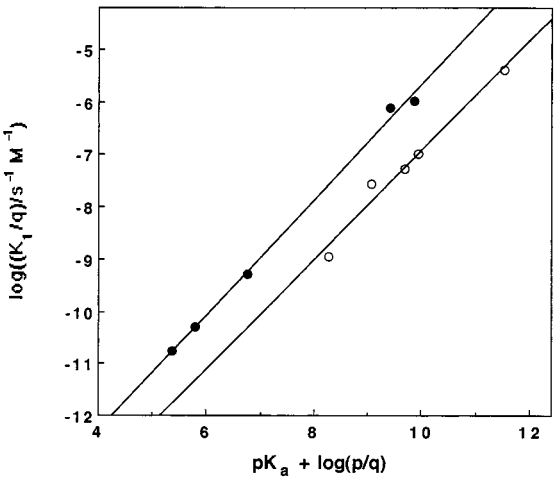


Figure 4. Brönsted-type plots for K_1 (statistically corrected) for the reactions of **2** with pyridines (●, ref 7b) and secondary alicyclic amines (○, this work) in water at 25.0 °C, ionic strength 0.2.

To examine the effect of the electrophilic center of the substrate on the kinetics and mechanism, we will compare the aminolysis of **2** and **1** (this work) with those of methyl[8] and phenyl 4-nitrophenyl carbonates,[9] respectively.

Unfortunately, the reactions of secondary alicyclic amines with methyl 4-nitrophenyl carbonate have not been subjected to a kinetic investigation, to our knowledge. Nevertheless, in the reactions of the same amines with methyl 2,4-dinitrophenyl carbonate a curved Brönsted-type plot with the center of curvature at $pK_a = 9.5$ was obtained.[29b] The curve has been interpreted through the existence of a tetrahedral intermediate on the reaction path and a change in the rate-determining step.[29b] Therefore, it is reasonable that the same aminolysis of the mononitro derivative be stepwise since the intermediate should be more stable (it has a worse nucleofuge than the dinitro derivative). On the other hand, the pyridinolysis of methyl 4-nitrophenyl carbonate shows a linear Brönsted-type plot of slope $\beta = 1.0$, which has been related to rate-determining breakdown of the tetrahedral intermediate.[8] Since this β value is only slightly dependent on the amine nature (cf. Figure 4),[9,14,29,30] it is

(24) Palling, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869.

(25) The latter rate coefficient was found by extrapolation of the Brönsted-type plot for the reactions of DMAP with 2,4-dinitrophenyl[26a] and 2,4,6-trinitrophenyl acetates.[26b] Direct comparison with the experimental rate constant for the reaction of DMAP with 4-nitrophenyl acetate is not possible since in this case the rate-determining step is breakdown of the tetrahedral intermediate.[13a]

(26) (a) Castro, E. A.; Freudenberg, M. *J. Org. Chem.* **1980**, *45*, 906. (b) Castro, E. A.; Ibáñez, F.; Lagos, S.; Schick, M.; Santos, J. G. *J. Org. Chem.* **1992**, *57*, 2691.

(27) The pyridinolysis (including DMAP) of methyl 4-nitrophenyl carbonate exhibits a linear Brönsted-type plot of slope $\beta = 1$, in agreement with rate-determining breakdown of the tetrahedral intermediate.[8] The rate constant for rate-limiting DMAP attack to this substrate was obtained, therefore, by extrapolation of the Brönsted-type plot for the reactions of DMAP with 2,4-dinitrophenyl[13b] and 2,4,6-trinitrophenyl methyl carbonates,[26b] whereby DMAP attack is the rate-determining step.

(28) The value of k_2 should not be significantly affected by either the basicity or the nature of the amine since the amino moiety of the zwitterionic tetrahedral intermediate cannot exert a push to expel the leaving group from the intermediate.[9]

(29) (a) Castro, E. A.; Ureta, C. *J. Org. Chem.* **1990**, *55*, 1676. (b) Castro, E. A.; Ibáñez, F.; Saitúa, A. M.; Santos, J. G. *J. Chem. Res., Synop.* **1993**, 56.

(30) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622.

expected that the reactions of this substrate with secondary alicyclic amines also exhibit a linear Brönsted plot of unity slope. Therefore, the change of carbonyl by thiocarbonyl as the electrophilic center of the substrate does not affect the mechanism or the change in the amine effective charge in going from reactants to the transition state for breakdown of the intermediate.[9] The only change observed is in the rate law, due to a significant proton transfer from $\mathbf{T}^{\pm}$ to the secondary amine (Scheme 1, R = Me), which is impossible for pyridines.

A linear Brönsted-type plot of slope $\beta = 1.0$ was found by Gresser and Jencks in the reactions of phenyl 4-nitrophenyl carbonate with quinuclidines.[9] These tertiary alicyclic amines cover a pK_a range very similar to that for the reactions of secondary alicyclic amines (except piperazinium ion) with **1** (Table 3). Since both the structure and basicity range of these two amine series are similar, it is expected that the Brönsted-type plots for their reactions with phenyl 4-nitrophenyl carbonate have similar slopes.[9,14,29,30] The fact that the Brönsted-type plot for the reactions of secondary amines with **1** is linear with slope $\beta = 0.25$ (Figure 2) means that the hypothetical Brönsted break (p$K_a°$) has greatly shifted to the right (larger p$K_a°$) by the change of S^- in intermediate **3** by O^-. This is in agreement with the fact that the substitution of S^- by O^- in other similar tetrahedral intermediates results in larger k_{-1}/k_2 ratios, which are related with larger p$K_a°$ values.[6c,7b] Examples of this are the pyridinolysis of 2,4-dinitrophenyl and 2.4,6-trinitrophenyl *O*-ethyl dithiocarbonates compared to the same reactions of the corresponding thiolcarbonates[6c] and the pyridinolysis of alkyl aryl thionocarbonates compared to those of the corresponding carbonates.[7b]

Acknowledgment. We thank FONDECYT ("Fondo Nacional de Desarrollo Científico y Tecnológico") of Chile for financial assistance.

JO990084Y