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Aminolysis and pyridinolysis of *O*-aryl *S*-(4-nitrophenyl) thiocarbonates in aqueous ethanol. Kinetics and mechanism

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The reactions of *O*-phenyl *S*-(4-nitrophenyl) thiocarbonate (PNPTC) and *O*-(4-chlorophenyl) *S*-(4-nitrophenyl) thiocarbonate (ClPNPTC) with a series of secondary alicyclic (SA) amines and pyridines are subjected to a kinetic investigation in 44 wt% ethanol–water, at 25.0°C and an ionic strength of 0.2 M. The reactions are followed spectrophotometrically at 420 nm (4-nitrobenzenethiolate anion appearance). Under amine excess, pseudo-first-order rate coefficients (k_{obs}) are found. For all these reactions, plots of k_{obs} *vs* free amine concentration at constant pH are linear, the slope (k_N) being independent of pH. The Brønsted-type plots (log k_N *vs* pK_a of the conjugate acid of the amines) for the reactions of the series of SA amines with PNPTC and ClPNPTC are linear with slopes 0.59 and 0.54, respectively. The values of these slopes are in accordance with a concerted mechanism. The Brønsted-type plots for the pyridinolysis reactions are biphasic, suggesting a stepwise mechanism with a change in the rate-determining step, from breakdown to formation of a tetrahedral intermediate, as the basicity of the pyridines increases. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: aminolysis; pyridinolysis; diaryl thiocarbonates; kinetics; mechanism

INTRODUCTION

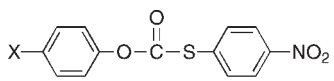
The kinetics and mechanisms of the aminolysis of *O*-alkyl *S*-aryl thiocarbonates[1–6] and *S*-alkyl *O*-aryl thiocarbonates[7–9] are well documented. Nevertheless, to our knowledge, there have been no reports on the kinetics and mechanism of the aminolysis of *O*-aryl *S*-aryl thiocarbonates.

Some of the aminolysis reactions of *O*-ethyl *S*-aryl thiocarbonates have been found to be concerted, such as those of *O*-ethyl *S*-(2,4-dinitrophenyl) and *O*-ethyl *S*-(2,4,6-trinitrophenyl) thiocarbonates (EDNPTC and ETNPTC, respectively) with secondary alicyclic (SA) amines[1] and quinuclidines[2] and those of the latter substrate with anilines, all of them in water.[3] Other reactions in water have been found to be stepwise, through a zwitterionic tetrahedral intermediate. Among these are those of *O*-ethyl *S*-(4-nitrophenyl) thiocarbonate (ENPTC) with pyridines,[1] SA amines[1] and quinuclidines,[2] those of EDNPTC with pyridines[1] and anilines,[3] those of ETNPTC with pyridines[1] and the reactions of *O*-ethyl *S*-(4-X-phenyl) thiocarbonates (X = MeO, Me, H, Cl) with SA amines.[4]

On the other hand, the reactions of benzylamines with *O*-ethyl *S*-aryl thiocarbonates in acetonitrile were claimed to be concerted.[5] In contrast, the same reactions (except for *O*-methyl instead of *O*-ethyl) in methanol were found to be stepwise, through a zwitterionic tetrahedral intermediate.[6]

Concerning the aminolysis of *S*-methyl *O*-aryl thiocarbonates, concerted as well as stepwise mechanisms have also been found. For instance, the reactions in water of *S*-methyl *O*-(2,4-dinitrophenyl) thiocarbonate (SMDNPTC) with quinuclidines[7] and SA amines[7] and those of *S*-methyl *O*-(2,3,4,5,6-pentafluorophenyl) thiocarbonate with SA amines[7] are concerted. In contrast, the reactions of *S*-methyl *O*-(4-nitrophenyl) thiocarbonate with SA amines[7] and pyridines[8] and those of SMDNPTC with pyridines[8] have been claimed to be stepwise.

With the aim to clarify the mechanism of the aminolysis of thiocarbonates, in this work we report a kinetic investigation of the reactions of *O*-phenyl *S*-(4-nitrophenyl) thiocarbonate (PNPTC) and *O*-(4-chlorophenyl) *S*-(4-nitrophenyl) thiocarbonate (ClPNPTC) with a series of SA amines and pyridines. By a comparison between the kinetic results obtained in this work and those for the aminolysis of related compounds we evaluate the effect of the amine nature, the non-leaving and the leaving (*S*-nitrophenyl *vs* *O*-nitrophenyl) groups of the substrate on the kinetics and mechanism. Also of interest is to assess the influence of the electrophilic group (carbonyl *vs* thiocarbonyl), as the site of nucleophilic attack by the amine, on the kinetics and mechanism of these reactions.



PNPTC (X = H)
ClPNPTC (X = Cl)

RESULTS AND DISCUSSION

For all the reactions, pseudo-first-order coefficients (k_{obs}) were obtained (under amine excess). These were determined by means of the kinetics software for first-order reactions of the spectrophotometer. The experimental conditions of the reactions and the values of k_{obs} are shown in Tables 1–4.

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Table 1. Experimental conditions and k_{obs} values for the reactions of SA amines with *O*-phenyl *S*-(4-nitrophenyl) thiocarbonate (PNPTC)[a]

Amine	pH	F_N[b]	10^3 [N]$_{tot}$ (M)[c]	10^3 k_{obs} (s^{-1})	No. of runs
Piperidine	10.65	0.40	1.23–10.5	3.68–21.6	6
	10.82	0.50	0.759–7.59	2.30–25.4	7
	11.05	0.63	1.12–7.84	7.56–31.6	5
Piperazine	6.80[d]	[e]	1.15–5.00	0.0142–0.0421	6
	7.00[d]	[f]	3.71–14.9	0.0143–0.102	5
	7.25[d]	[g]	1.23–12.3	0.0346–0.155	5
	7.35[d]	[h]	2.93–11.7	0.0531–0.189	6
	7.55[d]	[i]	6.92–27.7	0.0786–0.365	6
	9.41	0.33	2.60–26.0	1.88–16.9	7
	9.71	0.50	1.49–14.9	1.30–12.5	7
	10.01	0.67	1.16–11.6	1.78–19.7	7
1-(2-Hydroxyethyl)-piperazine	8.79	0.33	1.52–15.2	0.323–3.49	7
	9.09	0.50	1.15–11.5	0.302–3.99	6
	9.39	0.67	5.00–85.0	2.50–45.5	7
Morpholine	8.19	0.33	1.42–14.2	0.214–2.21	7
	8.49	0.50	1.36–13.6	0.456–3.50	7
	8.78	0.67	0.941–9.41	0.314–2.61	7
1-Formylpiperazine	7.33	0.33	10.0–85.0	0.0676–1.59	6
	7.63	0.50	9.98–99.8	0.214–2.48	7
	7.93	0.67	10.0–70.2	0.345–3.01	6

[a] In 44 wt% ethanol–water, at 25.0°C, ionic strength 0.2 M (KCl).
[b] Free amine fraction.
[c] Concentration of total amine (free base plus protonated forms).
[d] Phosphate buffer 0.01 M.
[e] Free piperazine and piperazinium ion fractions are 0.001184 and 0.96303, respectively.
[f] Free piperazine and piperazinium ion fractions are 0.0019 and 0.7524, respectively.
[g] Free piperazine and piperazinium ion fractions are 0.00341 and 0.9836, respectively.
[h] Free piperazine and piperazinium ion fractions are 0.0043 and 0.9854, respectively.
[i] Free piperazine and piperazinium ion fractions are 0.00683 and 0.98665, respectively.

For all the reactions the pseudo-first-order rate constants (k_{obs}), obtained under amine excess, obey Eqn (1), where k_0 and k_N are the rate coefficients for solvolysis and aminolysis of the substrates, respectively. The values of k_0 and k_N show no dependence on pH within the pH range employed. These values were obtained as the intercept and slope, respectively, of linear plots of k_{obs} against free amine concentration at constant pH.

$$k_{obs} = k_0 + k_N\,[\text{free amine}] \qquad (1)$$

For the reactions studied the k_0 values were much smaller than the aminolysis term, k_N [free amine] in Eqn (1). The values of k_N for the reactions of PNPTC and ClPNPTC with SA amines are shown in Table 5 and those for the reaction with pyridines are exhibited in Table 6.

For the reactions of SA amines the k_N values, as well as those of the pK_a of the conjugate acids of these amines were statistically corrected[10] with $q = 2$ for piperazine ($q = 1$ for all the other SA amines) and $p = 2$ for all the conjugate acids of the amines, except that for piperazinium ion with $p = 4$. The parameter q is the number of equivalent basic sites in the free amine and p is the number of equivalent dissociable protons in the conjugate acid of the amine.[10] Figure 1 shows the statistically corrected Brønsted-type plots.

The Brønsted plots obtained for the reactions of the series of SA amines with PNPTC and ClPNPTC (Fig. 1) are linear with slopes $\beta = 0.59 \pm 0.03$ and 0.54 ± 0.06, respectively, suggesting concerted mechanisms for these reactions (Scheme 1), since these slope values are in accordance with the β values found for the concerted aminolysis of similar compounds. Examples of these are the aminolysis of EDNPTC and ETNPTC with SA amines ($\beta = 0.56$ and 0.48, respectively)[1] and quinuclidines ($\beta = 0.54$ and 0.47, respectively),[2] and those of the latter compound with anilines ($\beta = 0.54$),[3] all of them in water. The aminolyses of some carbonates have also been proposed to be concerted, with β values in the range 0.4–0.7, some of them in water[11,12] and others in aqueous ethanol.[13,14]

The slope values of the Brønsted plots in Fig. 1 are also similar to those obtained for the concerted reactions of thiocarbonates in acetonitrile: The benzylaminolysis of *O*-ethyl *S*-aryl thiolcarbonates[5] and dithiocarbonates[15] show β values in the range 0.6–0.7.

It is known that the β value alone is not enough to conclude that a mechanism is concerted. It is also necessary to make sure that the expected pK_a value at the center of the Brønsted curvature (pK_a^0) for a hypothetical stepwise mechanism is within the pK_a range used.[16] If the reactions of SA amines with the title substrates are stepwise, a pK_a^0 value greater than 11 can be

Table 2. Experimental conditions and k_{obs} values for the reactions of SA amines with *O*-(4-chlorophenyl) *S*-(4-nitrophenyl) thiocarbonate (ClPNPTC)[a]

Amine	pH	F_N[b]	10^3 $[N]_{tot}$ (M)[c]	10^3 k_{obs} (s^{-1})	No. of runs
Piperidine	10.65	0.40	1.23–12.3	4.21–46.9	6
	10.82	0.50	1.90–7.59	3.62–28.5	7
	11.05	0.63	1.12–7.84	6.43–32.8	5
Piperazine	7.25[d]	[e]	2.93–11.7	0.227–0.510	6
	7.60[d]	[f]	2.93–9.97	0.442–0.817	5
	7.85[d]	[g]	2.79–23.7	0.153–1.83	6
	8.00[d]	[h]	2.54–25.4	0.235–2.60	6
	9.41	0.33	2.60–26.0	2.77–33.8	7
	9.71	0.50	2.43–24.3	5.88–67.6	7
	10.01	0.67	1.16–11.6	2.63–35.0	6
1-(2-Hydroxyethyl)-piperazine	8.79	0.33	1.52–15.2	0.567–7.41	6
	9.09	0.50	1.15–11.5	0.737–8.04	7
	9.39	0.67	5.00–85.2	4.38–86.2	7
Morpholine	8.19	0.33	1.42–12.1	0.196–2.37	6
	8.49	0.50	1.36–13.6	0.756–5.64	7
	8.78	0.67	0.941–9.41	0.960–5.16	6
1-Formylpiperazine	7.33	0.33	25.0–85.0	0.333–2.52	5
	7.63	0.50	24.9–99.8	1.05–4.05	6
	7.93	0.67	10.0–70.2	0.553–3.49	6

[a] In 44 wt% ethanol–water, at 25.0°C, ionic strength 0.2 M (KCl).
[b] Free amine fraction.
[c] Concentration of total amine (free base plus protonated forms).
[d] Phosphate buffer 0.01 M.
[e] Free piperazine and piperazinium ion fractions are 0.00341 and 0.9836, respectively.
[f] Free piperazine and piperazinium ion fractions are 0.007657 and 0.9853, respectively.
[g] Free piperazine and piperazinium ion fractions are 0.01357 and 0.9832, respectively.
[h] Free piperazine and piperazinium ion fractions are 0.0191 and 0.9786, respectively.

estimated on the following grounds. (i) The reactions SA amines with ENPTC in water show a pK_a^0 value of 10.7;[1] the change of ethoxy by phenoxy as the non-leaving group shifts the pK_a^0 to a greater value, since the latter group is more electron-withdrawing than the former.[17–19] (ii) A change of solvent from water to aqueous ethanol or other less polar solvent also increases the pK_a^0 value [1,18] The simultaneous contribution of these two effects can be seen by a comparison of the pK_a^0 values found in the reactions of SA amines with methyl 4-nitrophenyl carbonate in water[11] and 4-methoxyphenyl and 4-chlorophenyl 4-nitrophenyl carbonates in ethanol–water:[20,21] the pK_a^0 values are 9.3, 10.5 and 10.6, respectively. Therefore, the two changes, MeO by ArO as non-leaving group and water by aqueous ethanol as solvent increase the pK_a^0 about 1.2 pK_a units. If this result can be extrapolated to the thiocarbonates of this study a pK_a^0 value of *ca.* 11.9 (10.7 + 1.2) could be expected for the reactions of SA amines with the title thiocarbonates, if these reactions were stepwise.

Although the expected center of curvature for a stepwise mechanism is outside the pK_a range studied (5.4–10.8), and therefore, it is not possible to confirm the concerted mechanism this way, we are more inclined to a concerted process because if the mechanism were stepwise with pK_a^0 about 12, the β value observed should correspond to that for the breakdown of the tetrahedral intermediate ($T^{\pm}$) to products, which usually is $\beta = 0.8$–1.[1,18] Nevertheless, the observed β values for the reactions of SA amines with the title substrates are 0.54 and 0.59, which are too small for rate-limiting breakdown of $T^{\pm}$ in a stepwise mechanism.

With the k_N values found (Table 5), the corrected pK_a values for the nucleophiles and the pK_a values for the non-leaving groups (11.2 and 10.5 for phenol and 4-chlorophenol in 44 wt% aqueous ethanol, respectively), Eqn (2) can be deduced by dual regression analysis ($n = 12$, $R^2 = 0.975$). In this expression N and nlg refer to the nucleophile and the non-leaving group, respectively. The pK_a(N) and pK_a(nlg) coefficients (β_N and β_{nlg}) are subject to an error of ±0.1 and ±0.2, respectively.

$$\log k_N = -1.0 + 0.6\,pK_a(N) - 0.4\,pK_a(nlg) \qquad (2)$$

A logarithmic plot (not shown) of the experimental k_N *vs* that calculated through Eqn (2) is linear with zero intercept and unity slope. The values of β_N and β_{nlg} (0.6 and −0.4, respectively) are in accordance with those expected for a concerted mechanism.[1,5,13–15,22]

For the pyridinolysis of PNPTC and ClPNPTC the Brønsted-type plots of Fig. 2 were obtained with the data in Table 6. As can be observed, the Brønsted-type plots are biphasic. These curves were calculated by means of a semi-empirical equation, Eqn (3), based on the existence of a zwitterionic tetrahedral intermediate ($T^{\pm}$) on the reaction pathway (see Scheme 2).[23] A similar equation has been reported by Gresser and Jencks.[24]

Table 3. Experimental conditions and k_{obs} values for the reactions of pyridines with *O*-phenyl *S*-(4-nitrophenyl) thiocarbonate (PNPTC)[a]

Pyridine substituent	pH	F_N[b]	10^3 $[N]_{tot}$ (M)[c]	10^3 k_{obs} (s^{-1})	No. of runs
4-Oxy	8.5[d]	0.000999	1.49–14.9	0.649–3.13	7
	9.1[d]	0.003979	1.76–17.6	0.841–8.92	6
	9.5[d]	0.0099	1.45–14.5	1.71–16.5	7
3,4-Diamino	9.14	0.33	0.898–8.98	8.19–58.9	7
	9.45	0.50	1.25–12.5	12.1–116	7
	9.76	0.67	0.887–8.87	19.6–99.7	7
4-Dimethylamino	8.83	0.33	0.740–7.40	3.93–32.5	7
	9.14	0.50	1.08–10.8	11.0–87.0	7
	9.45	0.67	1.12–9.50	14.6–91.5	6
4-Amino	8.67	0.33	1.27–12.7	7.51–54.2	7
	8.98	0.50	1.21–12.1	6.59–59.8	7
	9.29	0.67	1.12–9.50	7.48–77.2	6
4-Amino-3-bromo	6.6	0.33	0.728–7.28	0.199–0.835	7
	6.9	0.50	0.751–7.51	0.143–1.17	7
	7.2	0.67	0.784–7.84	0.158–1.60	7
3,4-Dimethyl	7.5[e]	0.986	1.72–17.2	0.0523–0.240	7
	8.0[d]	0.995	1.59–15.9	0.0423–0.243	7
	9.0[d]	0.9995	1.92–19.2	0.0343–0.292	7

[a] In 44 wt% ethanol–water, at 25.0°C, ionic strength 0.2 M (KCl).
[b] Free amine fraction.
[c] Concentration of total amine (free base plus protonated forms).
[d] Borate buffer 0.01 M.
[e] Phosphate buffer 0.01 M.

Table 4. Experimental conditions and k_{obs} values for the reactions of pyridines with *O*-(4-chlorophenyl) *S*-(4-nitrophenyl) thiocarbonate (ClPNPTC)[a]

Pyridine substituent	pH	F_N[b]	10^3 $[N]_{tot}$ (M)[c]	10^3 k_{obs} (s^{-1})	No. of runs
4-Oxy	8.1[d]	0.000398	2.18–21.8	0.135–2.99	7
	8.5[d]	0.000999	0.728–7.28	0.454–3.43	7
	9.0[d]	0.00315	0.967–9.67	0.846–9.51	7
3,4-Diamino	9.14	0.33	0.656–6.56	6.01–60.7	7
	9.45	0.50	0.915–9.15	15.9–142	7
	9.76	0.67	0.629–6.29	11.6–121	7
4-Dimethylamino	8.83	0.33	1.17–11.7	17.9–114	7
	9.14	0.50	1.29–12.9	16.0–163	7
	9.45	0.67	1.06–10.6	24.0–140	7
4-Amino	8.6	0.294	0.671–6.71	4.22–41.4	7
	8.9	0.454	1.73–6.93	15.9–67.4	6
	9.2	0.624	0.516–5.16	5.86–55.1	7
4-Amino-3-bromo	8.0[d]	0.9264	0.67–6.7	0.156–1.87	6
	8.5[d]	0.9755	0.59–5.01	0.365–1.65	6
	9.0[d]	0.9921	0.67–6.70	0.209–2.15	6
3,4-Dimethyl	8.0[d]	0.9952	3.29–32.9	0.106–0.425	7
	8.5[d]	0.9985	5.68–56.8	0.157–0.65	7
	9.0[d]	0.9995	3.02–30.2	0.118–0.496	6

[a] In 44 wt% ethanol–water, at 25.0°C, ionic strength 0.2 M (KCl).
[b] Free amine fraction.
[c] Concentration of total amine (free base plus protonated forms).
[d] Borate buffer 0.01 M.

Table 5. Values of pK_a for the conjugate acids of SA amines and k_N values for the reactions of these amines with *O*-phenyl *S*-(4-nitrophenyl) thiocarbonate (PNPTC) and *O*-(4-chlorophenyl) *S*-(4-nitrophenyl) thiocarbonate (ClPNPTC)[a]

		k_N ($s^{-1}\,M^{-1}$)	
Amine	pK_a	PNPTC	ClPNPTC
Piperidine	10.82	6.2 ± 0.5	7.8 ± 0.6
Piperazine	9.71	1.96 ± 0.09[b]	5.3 ± 0.3[b]
Piperazine	9.71	1.6 ± 0.5[c]	5.1 ± 0.5[c]
1-(2-Hydroxyethyl)piperazine	9.09	0.797 ± 0.005	1.52 ± 0.02
Morpholine	8.48	0.45 ± 0.02	0.78 ± 0.05
1-Formylpiperazine	7.63	0.055 ± 0.003	0.081 ± 0.004
Piperazinium ion	5.37	0.006 ± 0.0006[d]	0.015 ± 0.002[d]

[a] Both the pK_a and k_N values were determined in 44 wt% ethanol–water, at 25.0°C, ionic strength 0.2 M (KCl).
[b] Values for the 9.41–10.01 pH range.
[c] Values for piperazine, obtained from the k_{obs} values at pH 6.8–8.0, where there is a mixture of piperazine and piperazinium ion (see 'Experimental').
[d] Values for piperazinium ion obtained from the k_{obs} values at pH 6.8–8.0, where there is a mixture of piperazine and piperazinium ion (see 'Experimental').

Equation (3) contains four parameters: β_1 and β_2, which are the Brønsted slopes at high and low pK_a, respectively, and k_N^0 and pK_a^0, which are the corresponding values at the center of the Brønsted curvature.

$$\log (k_N/k_N^0) = \beta_2 (pK_a - pK_a^0) - \log ((1 + a)/2)$$
$$\log a = (\beta_2 - \beta_1) (pK_a - pK_a^0) \quad (3)$$

The Brønsted curves were calculated by means of the following parameters: $\log k_N^0 = 0.52$, $pK_a^0 = 8.1$, $\beta_1 = 0.37$ and $\beta_2 = 1.1$ ($n = 6$, $R^2 = 0.9997$) for the reactions of PNPTC and $\log k_N^0 = 0.53$, $pK_a^0 = 7.9$, $\beta_1 = 0.46$ and $\beta_2 = 1.2$ ($n = 6$, $R^2 = 0.9999$) for the reactions of ClPNPTC. The errors of the slopes are ±0.1, and those of pK_a^0 and $\log k_N^0$ are ±0.2 and ±0.1, respectively. The curved Brønsted plots can be explained by the existence of the tetrahedral intermediate $T^{\pm}$ and a change in the rate-determining step, from that for k_2 in Scheme 2, to that for k_1, as the amine becomes more basic.[1,23,24]

The values of β_1 and β_2 are in accordance with those reported for other aminolyses governed by stepwise mechanisms: $\beta_1 = 0.1-0.3$ and $\beta_2 = 0.8-1.1$.[1,23–25]

Table 6. Values of pK_a for the conjugate acids of pyridines and k_N values for the reactions of pyridines with *O*-phenyl *S*-(4-nitrophenyl) thiocarbonate (PNPTC) and *O*-(4-chlorophenyl) *S*-(4-nitrophenyl) thiocarbonate (ClPNPTC)[a]

		k_N ($s^{-1}\,M^{-1}$)	
Pyridine substituent	pK_a	PNPTC	ClPNPTC
4-Oxy	11.5	121 ± 5	302 ± 9
3,4-Diamino	9.45	17.1 ± 0.4	30.1 ± 0.7
4-Dimethylamino	9.14	14.8 ± 0.5	23.0 ± 0.8
4-Amino	8.98	11.2 ± 0.5	18.8 ± 0.8
4-Amino 3-bromo	6.9	0.262 ± 0.02	0.31 ± 0.02
3,4-Dimethyl	5.68	0.0133 ± 0.0005	$0.0107 \pm .0006$

[a] Both the pK_a and k_N values were determined in 44 wt% ethanol–water, at 25.0°C, ionic strength 0.2 M (KCl).

Effect of the amine nature

The reactions of the title substrates with SA amines are driven by a concerted pathway; in contrast to the reactions of the same substrates with pyridines, which are stepwise. These results are consistent with those observed in the reactions of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl *O*-ethyl thiolcarbonates and their corresponding *O*-methyl carbonates with the same amines in aqueous solution.[1,7,8,11] The change in mechanism, from stepwise for pyridines to concerted for SA amines, was explained by the destabilization of the putative tetrahedral intermediate formed with the latter amines, due to a

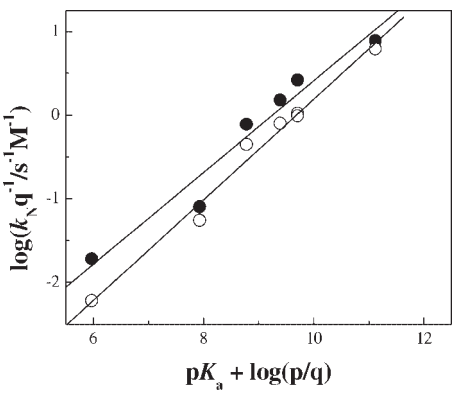
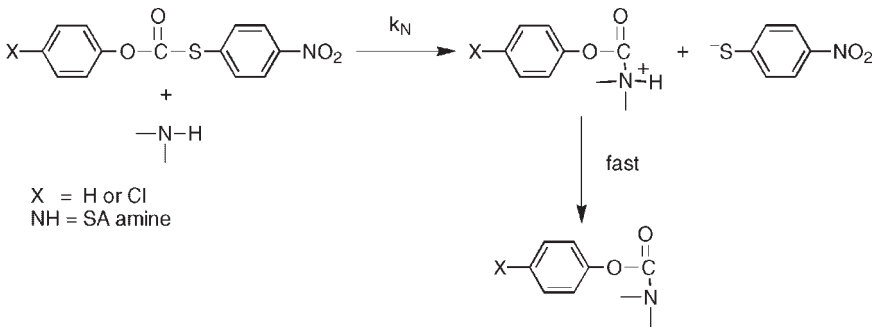


Figure 1. Brønsted-type plots (statistically corrected, see text) for the reactions of SA amines with PNPTC (O) and ClPNPTC (●) in 44 wt% ethanol–water, at 25.0°C, ionic strength 0.2 M (KCl)



Scheme 1.

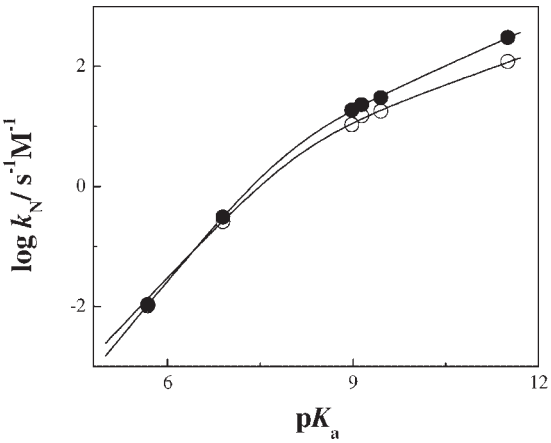


Figure 2. Brønsted-type plots for the reactions of pyridines with PNPTC (O) and ClPNPTC (●) in 44 wt% ethanol–water, at 25.0°C, ionic strength 0.2 M (KCl)

faster leaving ability of these amines from the intermediate compared with isobasic pyridines.[1,7,8,11]

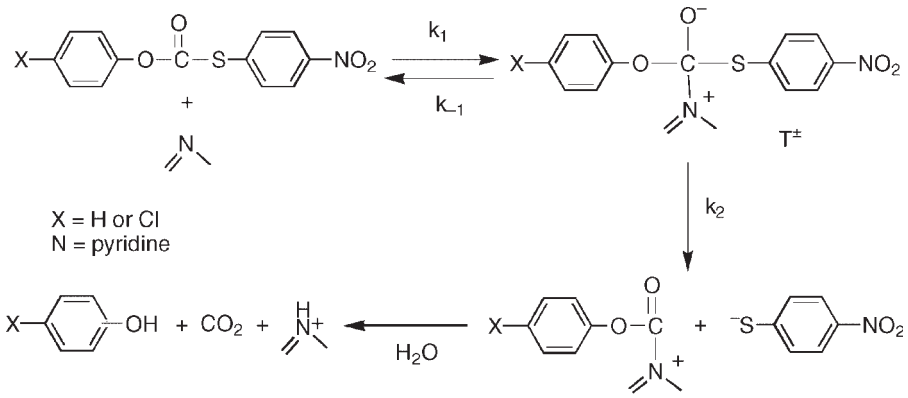
Effect of the leaving group

The reactions of SA amines with 4-chlorophenyl 4-nitrophenyl carbonate in aqueous ethanol were found to be stepwise, showing a biphasic Brønsted plot with the curvature center at $pK_a^0 = 10.6$.[21] The fact that the reactions of the same amines with the corresponding thiolcarbonate (ClPNPTC, this study) in the same solvent are concerted shows that the tetrahedral intermediate $T^{\pm}$ formed in the former reactions is greatly destabilized by changing the nitrophenoxy group by 4-nitrobenzenethio. This result is in accordance with the greater leaving ability of 4-nitrobenzenethiolate, relative to 4-nitrophenoxide, from the intermediate $T^{\pm}$.[1] Although phenoxides are better nucleofuges than isobasic benzenethiolates,[26] the above result can be explained by the rather large difference in basicity of the groups involved ($pK_a = 4.5$ and 7.5 in aqueous ethanol for 4-nitrobenzenethiol and 4-nitrophenol, respectively).

Effect of the non-leaving group

As seen in Figs. 1 and 2, ClPNPTC is more reactive than PNPTC toward the title amines. This can be explained by the greater electron-withdrawing effect of Cl than H, which leaves the carbonyl carbon of ClPNPTC more positive, and therefore, more prone to nucleophilic attack.

For the reactions with SA amines, the change of the non-leaving group from phenyl in *S*-(4-nitrophenyl) thiobenzoate[27] to phenoxy in PNPTC (this study), changes the mechanism from stepwise to concerted. This result is in agreement with the fact that the reactions of SA amines with *S*-(2,4-dinitrophenyl) acetate are stepwise, in contrast to the reactions of the same amines with *O*-ethyl *S*-(2,4-nitrophenyl) thiocarbonate, which are concerted.[1] This has been explained by the greater electron withdrawal (inductively) from ethoxy (or methoxy) than methyl in



Scheme 2.

the corresponding intermediate $T^{\pm}$.[17] This means that the change of methyl to ethoxy (or methoxy) as the non-leaving group increases the rate of expulsion of both the amine (k_{-1}) and the nucleofuge (k_2) from $T^{\pm}$, destabilizing, therefore, this intermediate.[1]

The reactions of SA amines with ethyl *S*-(4-nitrophenyl) thiocarbonate in water are stepwise,[1] whereas the reactions of the same amines with PNPTC in aqueous ethanol are concerted (this study). This means that the replacement of both ethoxy by phenoxy as non-leaving group, and water by aqueous ethanol as solvent, destabilize the intermediate $T^{\pm}$ in such a way that the mechanism changes from stepwise to concerted. The destabilization of $T^{\pm}$ caused by the change of non-leaving group can be attributed to the greater inductive electron-withdrawing ability of PhO ($\sigma_I = 0.37$) than EtO. ($\sigma_I = 0.26$).[17] The change of solvent, from water to aqueous ethanol, should also destabilize the intermediate in view of its zwitterionic nature.

The pyridinolysis of *O*-ethyl *S*-(4-nitrophenyl) thiocarbonate in water shows a linear Brønsted plot of slope 0.8, with $pK_a^0 > 10$, consistent with a stepwise mechanism where breakdown of the intermediate $T^{\pm}$ is rate limiting.[1] Instead, the stepwise pyridinolysis of PNPTC shows a biphasic Brønsted plot with $pK_a^0 = 8.1$ (this work). Although the greater electron withdrawal of OPh than OEt results in an increase in the values of both k_{-1} (rate constant for amine leaving from $T^{\pm}$) and k_2 (rate constant for nucleofuge expulsion from $T^{\pm}$), see above, the fact that the pK_a^0 value is larger for the *O*-ethyl derivative means that the k_{-1}/k_2 ratio is also larger for the latter compound. This is because, according to the hypothesis of the tetrahedral intermediate, an equation can be deduced,[8] Eqn (4), that shows that a larger pK_a^0 value means a larger k_{-1}/k_2 ratio.

$$\log (k_{-1}/k_2) = (\beta_2 - \beta_1)(pK_a^0 - pK_a) \quad (4)$$

Effect of the electrophilic group

The reactions of SA amines with *O*-phenyl *S*-(4-nitrophenyl) dithiocarbonate in aqueous ethanol are stepwise.[28] In contrast, the reactions of the same amines with PNPTC in the same solvent are concerted (this work). These results indicate that the change of thiocarbonyl as the electrophilic group by carbonyl destabilizes the tetrahedral intermediate ($T^{\pm}$), changing the mechanism from stepwise to concerted. This destabilization can be attributed to the greater ability of O^- than S^- in $T^{\pm}$ to form the double bond with carbon due to the stronger π-bonding energy of the C=O group relative to C=S.[29] This should increase the expulsion rate of both the amine (k_{-1}) and the nucleofuge (k_2) from the putative tetrahedral intermediate.[1] The same effect of the electrophilic group was found for the SA aminolyses of *O*-ethyl *S*-(2,4-dinitrophenyl) dithiocarbonate and *O*-ethyl *S*-(2,4-dinitrophenyl) thiolcarbonate in water: the former reactions are stepwise whereas the latter are concerted.[1]

CONCLUDING REMARKS

From the results obtained in this work, several conclusions can be drawn: (i) The mechanism of the aminolysis (SA amines) of PNPTC and ClPNPTC is concerted, in contrast to the pyridinolysis of the same substrates, which is stepwise. (ii) ClPNPTC is more reactive than PNPTC toward SA amines. (iii) For the SA aminolysis, the change of the non-leaving group of the substrate, from phenyl in *S*-(4-nitrophenyl) thiobenzoate to phenoxy (to give the corresponding thiocarbonate) destabilizes the tetrahedral intermediate and changes the mechanism from stepwise to concerted. (iv) For the pyridinolysis, the change of the non-leaving group of the substrate, from phenoxy to ethoxy, increases the pK_a^0 value. (v) For the reactions with SA amines, the simultaneous change of ethoxy in ethyl *S*-(4-nitrophenyl) thiocarbonate by phenoxy (to yield phenyl *S*-(4-nitrophenyl) thiocarbonate) and water to aqueous ethanol as solvent, destabilizes the tetrahedral intermediate, changing the mechanism from stepwise to concerted. (vi) For the SA aminolysis, the change of the electrophilic group, from thiocarbonyl in *O*-phenyl *S*-(4-nitrophenyl) dithiocarbonate to carbonyl (to yield PNPTC), destabilizes the tetrahedral intermediate and forces a mechanistic change, from stepwise to concerted.

EXPERIMENTAL

Materials

The substrates, PNPTC and ClPNPTC, were synthesized by the reaction of the corresponding aryl chloroformate with 4-nitrobenzenethiolate in acetonitrile. The solid products showed the following characteristics.

PNPTC: ^{1}HNMR (400 MHz, $CDCl_3$) 7.17–7.40 (m, 5H); 7.77 (d, 2H, J = 8.9Hz); 8.25(d 2H J = 8.9Hz). ^{13}CNMR (200 MHz,) δppm 126.78, 122.09, 143.28, 139.67, 119.45, 126.11, 142.2, 155.21, 156.9. MS anal. Calc. for $C_{13}H_9NO_4S$ 275.02521; found 275.02537.

ClPNPTC: ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm 7.04 (d, 2H, J = 8.9Hz); 7.30(d, 2H, J = 8.9Hz); 7.70(d, 2H, J = 8.9Hz); 8.12 (d, 2H, J = 8.9Hz);^{13}CNMR (200 MHz, $CDCl_3$) δ ppm 125.6, 130.1, 133.4, 150.3, 131.4, 120.8, 148.3, 140.4, 159.9. MS anal. Calc. for $C_{13}H_8ClNO_4S$ 308.98627; found 308.98768.

Kinetic measurements

The kinetics of the reactions were analyzed through a diode array spectrophotometer in 44 wt% ethanol–water, at 25.0 ± 0.1 °C and an ionic strength of 0.2 M (maintained with KCl). The reactions were followed at 420 nm (appearance of 4-nitrobenzenethiolate anion).

The reactions were studied under at least 10-fold amine excess over the substrate, the initial concentration of the latter being 2.5×10^{-5} M. Under these conditions pseudo-first-order rate coefficients (k_{obs}) were found throughout, the reactions being followed for at least five half-lives. In order to prevent the dimerization of 4-nitrobenzenethiolate,[30] the slower reactions were studied by the initial rate method.[25,31]

For all the reactions the pH was maintained constant (three pH values for each amine) either by the buffer formed by partial protonation of the amine or by the addition of an external buffer.

The reactions of PNPTC and ClPNPTC with piperazine and piperazinium ion were studied at pH 6.80–7.55 and 7.25–8.00, respectively, where a mixture of both amines are present. In these cases the k_N values were obtained through Eqns (5) and (6). In these equations k_{Nobs} is a global nucleophilic rate constant (corresponding to the mixture of nucleophiles), $[N]_{tot}$ is the total piperazine (piperazine + piperazinium ion) concentration, F_N and F_{NH} are the molar fractions of piperazine and piperazinium ion, respectively, and k_N and k_{NH} are their corresponding

nucleophilic rate constants. The values of k_{Nobs} were obtained as the slopes of linear plots of k_{obs} *vs* $[N]_{tot}$ at constant pH. The nucleophilic rate constants for the reactions of the title thiocarbonates with piperazine (k_N) and piperazinium ion (k_{NH}) were determined through Eqn (6), as described.[32]

$$k_{obs} = k_0 + k_{Nobs}[N]_{tot} \quad (5)$$

$$k_{Nobs} = F_N k_N + F_{NH} k_{NH} \quad (6)$$

The experimental conditions of the reactions are shown in Tables 1–4.

Product studies

4-Nitrobenzenethiolate ion was identified as one of the products of the reactions of PNPTC and ClPNPTC. This was carried out by comparison of the UV–Vis spectra after completion of these reactions with that of an authentic sample of 4-nitrobenzenethiol, under the same reactions conditions.

A referee has pointed out that it is also possible that some C—O cleavage concomitant with C—S breakage can take place in the two substrates. This would result in a mixture of 4-nitrobenzenethiol (NPSH) and phenol (from PNPTC) or 4-chlorophenol (from ClPNPTC). Although 4-nitrobenzenethiolate (NPS^-) is a much better leaving group than phenoxide or 4-chlorophenoxide, we looked for the presence of any phenol arising from the reactions of SA amines. For this purpose we chose the reaction of piperidine with PNPTC. For the reaction of this very basic amine, the aminolysis (k_N [amine]) is fast compared with the hydrolysis of the substrate (k_0) and, therefore, little or no phenol arising from the latter reaction is expected (the hydrolysis produces both NPSH and phenol). The presence of phenol was determined by both spectrophotometric as well as HPLC techniques. No significant amounts of phenol were found.

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REFERENCES

[1] E. A. Castro, *Chem. Rev.* **1999**, *99*, 3505–3524.
[2] E. A. Castro, P. Muñoz, J. G. Santos, *J. Org. Chem.* **1999**, *64*, 8298–8301.
[3] E. A. Castro, L. Leandro, P. Millan, J. G. Santos, *J. Org. Chem.* **1999**, *64*, 1953–1957.
[4] E. A. Castro, M. Cubillos, J. G. Santos, *J. Org. Chem.* **1999**, *64*, 6342–6346.
[5] H. K. Oh, Y. H. Lee, I. Lee, *Int. J. Chem. Kinet.* **2000**, *32*, 131–135.
[6] H. B. Song, M. H. Choi, I. S. Koo, H. K. Oh, I. Lee, *Bull. Korean Chem. Soc.* **2003**, *24*, 91–94.
[7] E. A. Castro, M. Aliaga, J. G. Santos, *J. Org. Chem.* **2005**, *70*, 2679–2685.
[8] E. A. Castro, M. Aliaga, J. G. Santos, *J. Org. Chem.* **2004**, *68*, 6711–6714.
[9] P. R. Campodonico, A. Aizman, R. Contreras, *Chem. Phys Lett.* **2006**, *422*, 204–209.
[10] R. P. Bell, in *The Proton in Chemistry*, Methuen, London, **1959**. 159.
[11] E. A. Castro, M. Aliaga, P. Campodonico, J. G. Santos, *J. Org. Chem.* **2002**, *67*, 8911–8916.
[12] E. A. Castro, P. R. Campodonico, R. Contreras, P. Fuentealba, J. G. Santos, J. R. Leis, L. García-Río, J. A. Saez, L. R. Domingo, *Tetrahedron* **2006**, *62*, 2555–2562.
[13] E. A. Castro, P. Campodonico, A. Toro, J. G. Santos, *J. Org. Chem.* **2003**, *68*, 5930–5935.
[14] E. A. Castro, M. Gazitúa, J. G. Santos, *J. Org. Chem.* **2005**, *70*, 8088–8092.
[15] H. K. Oh, J. Y. Oh, D. D. Sung, I. Lee, *Coll. Czech. Chem. Commun.* **2004**, *69*, 2174–2182.
[16] A. Williams, *Acc. Chem. Res.* **1989**, *22*, 387–392.
[17] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.
[18] M. J. Gresser, W. P. Jencks, *J. Am. Chem. Soc.* **1977**, *99*, 6970–6980.
[19] D. Lee, C. K. Kim, B. S. Lee, I. Lee, *Bull. Korean Chem. Soc.* **1995**, *16*, 1203–1208.
[20] E. A. Castro, M. Andújar, P. Campodónico, J. G. Santos, *Int. J. Chem. Kinet.* **2002**, *34*, 309–315.
[21] E. A. Castro, M. Andújar, A. Toro, J. G. Santos, *J. Org. Chem.* **2003**, *68*, 3608–3613.
[22] I. H. Um, S. E. Jeon, J. A. Seok, *Eur. J. Chem.* **2006**, *12*, 1237–1243.
[23] P. M. Bond, E. A. Castro, R. B. Moodie, *J. Chem. Soc., Perkin Trans. 2* **1976**, 68–72.
[24] M. J. Gresser, W. P. Jencks, *J. Am. Chem. Soc.* **1977**, *99*, 6963–6970.
[25] A. C. Satterthwait, W. P. Jencks, *J. Am. Chem. Soc.* **1974**, *96*, 7018–7031.
[26] K. T. Douglas, *Acc. Chem. Res.* **1986**, *19*, 186–192.
[27] E. A. Castro, J. Bessolo, R. Aguayo, J. G. Santos, *J. Org. Chem.* **2003**, *68*, 8157–8161.
[28] E. A. Castro, L. Leandro, J. G. Santos, *Int. J. Chem. Kinet.* **1999**, *31*, 839–845.
[29] S. V. Hill, S. Thea, A. Williams, *J. Chem. Soc., Perkin Trans. 2* **1983**, 437–446.
[30] D. J. Hupe, W. P. Jencks, *J. Am. Chem. Soc.* **1977**, *99*, 451–464.
[31] S. Ba-Saif, A. K. Luthra, A. Williams, *J. Am. Chem. Soc.* **1987**, *109*, 6362–6368.
[32] E. A. Castro, C. Ureta, *J. Chem. Soc., Perkin Trans. 2* **1991**, 63–68.