Structure−Reactivity Correlations in the Aminolysis of Ethyl *S*-Aryl Thiolcarbonates

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The reactions of secondary alicyclic amines (saa) with ethyl *S*-4-X-phenyl thiolcarbonates (X = Cl, H, Me, and MeO) are subjected to a kinetic analysis in water, 25.0 °C, ionic strength 0.2 (KCl). By following the leaving groups spectrophotometrically (260−270 nm), under amine excess, pseudo-first-order rate coefficients (k_{obsd}) are obtained. Plots of k_{obsd} against free-amine concentration at constant pH are linear, with slope (k_N) independent of pH. The Brönsted-type plots (log k_N against amine pK_a) are linear for the aminolysis of the four substrates, with slopes $\beta_N = 0.7-0.8$. The magnitudes of the slopes are consistent with a stepwise mechanism through a zwitterionic tetrahedral intermediate ($T^{\pm}$) whose breakdown to products is rate-determining (k_2 step). This mechanism is simpler than that for the same aminolysis of the corresponding ethyl *S*-aryl dithiocarbonates, which includes proton transfer from $T^{\pm}$ to the amine (k_3 step), due to the fact that for the title reactions $k_2 > k_3$[amine]. With the results of the present work and those for the reactions of saa with ethyl *S*-4-nitrophenyl thiolcarbonate, a dual parametric equation is deduced for k_N as a function of amine and leaving group basicity, with both β_N and $-\beta_{lg} = 0.8$. Another dual parametric equation is deduced from literature data for the pyridinolysis of ethyl *S*-aryl thiolcarbonates. Comparison of both multiparametric expressions shows that pyridines are more reactive than isobasic saa toward thiolcarbonates when breakdown of $T^{\pm}$ to products is rate-limiting.

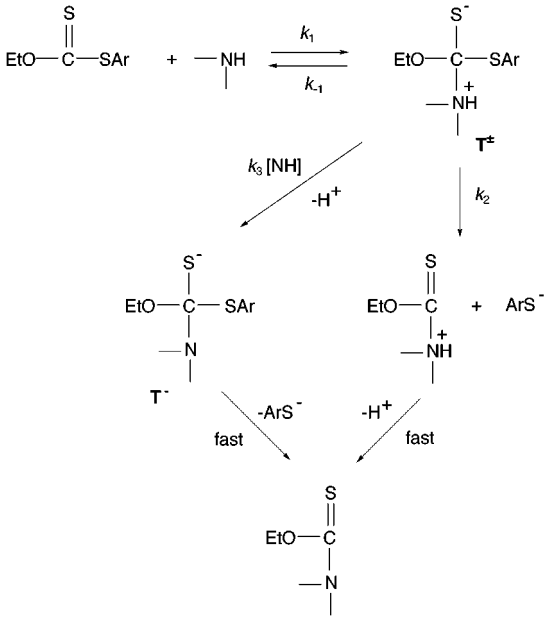
Introduction

We have been interested in the mechanisms of the aminolysis of thiolcarbonates, mainly the alkyl *S*-aryl derivatives (RO−CO−SAr). We have kinetically studied the reactions of ethyl *S*-(4-nitrophenyl) thiolcarbonate (NPTC) with secondary alicyclic amines (saa)[1] and with pyridines (py).[2] In the former reactions a biphasic Brönsted-type plot was found, which was explained by a stepwise mechanism through a zwitterionic tetrahedral intermediate ($T^{\pm}$) in the reaction pathway and a change in the rate-limiting step.[1] In the reactions of NPTC with py, a linear Brönsted plot of slope $\beta_N = 0.8$ was observed, consistent with the existence of an intermediate $T^{\pm}$ whose breakdown to products is rate-determining.[2]

The reactions of ethyl *S*-(2,4-dinitrophenyl) thiolcarbonate (DNPTC)[3] and ethyl *S*-(2,4,6-trinitrophenyl) thiolcarbonate (TNPTC)[4] with the same series of saa, and those of the latter substrate with anilines,[5] have also been subjected to kinetic scrutiny. For these reactions linear Brönsted plots of slopes β_N ca. 0.48−0.56 were obtained, which were attributed to concerted mechanisms.

On the other hand, in the reactions of DNPTC and TNPTC with py, biphasic Brönsted-type plots were observed and a stepwise mechanism was proposed with a change in the rate-determining step depending on the pyridine basicity.[2] In the reactions of DNPTC with anilines, a linear Brönsted-type plot of slope $\beta_N = 0.9$ was found, which was attributed to a stepwise mechanism with rate-determining breakdown of the intermediate $T^{\pm}$.[5]

Scheme 1



In the reactions of saa with ethyl *S*-(4-X-phenyl) dithiocarbonates (X = H, Cl, Me, and MeO), a more complicated reaction mechanism was found;[6] this is shown in Scheme 1. The k_3 step is a kinetically significant proton transfer from $T^{\pm}$ to an amine to yield the anionic

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Table 1. Experimental Conditions and k_{obsd} Values for the Aminolysis of Ethyl *S*-Phenyl Thiolcarbonate (PTC)[a]

amine	pH	F_N[b]	$10^2[N]_{tot}$[c]/ M	10^3k_{obsd}/ s^{-1}	no. of runs
piperidine	10.90	0.31	4.0−28	3.75−22.5	11
	11.24	0.50	1.0−7.0	1.83−9.18	7
	11.54	0.66	1.0−7.0	2.32−12.6	7
piperazine	9.64	0.33	10−2	1.26−3.99	6
	9.94	0.50	10−34	2.27−6.59	12
	10.24	0.66	6.0−42	1.82−11.2	15
1-(2-hydroxyethyl)-	9.38	0.50	10−38	0.736−2.10	5
piperazine	9.68	0.66	8.0−36	0.612−2.40	6
	10.18	0.86	10−70	1.03−5.67	7
morpholine	9.08	0.66	20−65	0.837−2.34	7
	9.28	0.76	15−50	0.716−1.93	7
	9.58	0.86	15−40	0.726−1.87	6
1-formylpiperazine	8.54	0.80	15−90	0.119−0.824	7

[a] In aqueous solution at 25.0 °C, ionic strength 0.2 M (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 Ethyl *S*-(4-Methylphenyl) Thiolcarbonate (MPTC)[a]

amine	pH	F_N[b]	$10^2[N]_{tot}$[c]/ M	10^3k_{obsd}/ s^{-1}	no. of runs
piperidine	10.94	0.33	3.0−25	1.63−13.1	7
	11.24	0.50	1.0−8.0	0.871−6.38	7
	11.54	0.66	1.0−30	1.36−32.3	7
piperazine	9.94	0.50	7.0−40	0.913−5.05	7
	10.24	0.66	6.0−50	0.920−7.67	7
	10.60	0.83	6.0−50	1.31−10.4	5
1-(2-hydroxyethyl)-	9.38	0.50	8.0−40	0.275−1.20	6
piperazine	9.68	0.66	8.0−50	0.485−2.16	7
	10.18	0.86	6.0−60	0.347−3.06	6
morpholine	8.78	0.50	5.0−40	0.272−0.934	5
	9.08	0.66	10−60	0.259−1.16	6
	9.38	0.80	20−90	0.477−2.10	6
1-formylpiperazine	8.54	0.80	20−90	0.226−0.463	6

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

tetrahedral species T^-.[6] Therefore, the change of O^- by S^- in $T^\pm$ seems to have an important effect on the mechanism of the reactions.

These results evidence the influence of the amine nature, the leaving group basicity, and the electrophilic group (CO vs CS) on the reaction mechanism and, therefore, on the stability of the intermediate $T^\pm$.

To assess the influence of the above three groups and also to extend our mechanistic investigations, we describe in the present work a kinetic study of the reactions of saa with a series of ethyl *S*-aryl thiolcarbonates, with aryl = phenyl (PTC), 4-chlorophenyl (ClPTC), 4-methylphenyl (MPTC), and 4-methoxyphenyl (MOPTC). These results will be compared with those obtained in the reactions of saa and py with related thiolcarbonates[1−4] and also with the reactions of saa with the corresponding dithiocarbonates.[6]

Experimental Section

Materials. The ethyl *S*-aryl thiolcarbonates were synthesized as described[7] and identified by NMR and IR analyses. The amines were purified as reported.[8]

Kinetic Measurements. These were performed spectrophotometrically by following the production of benzenethiolate ions at 260−270 nm. The method employed was previously described.[4] The reactions were studied under the following conditions: aqueous solution, 25.0 ± 0.1 °C, ionic strength 0.2 (maintained with KCl), initial substrate concentration 5×10^{-5} M, and excess of total amine over the substrate.

Pseudo-first-order rate coefficients (k_{obsd}) were found throughout, by means of the method described.[4] The experimental conditions of the reactions and the k_{obsd} values obtained are shown in Tables 1−4.

Product Studies. The benzenethiolates, $4\text{-}XC_6H_4S^-$, with X = H, Cl, Me, and MeO, were identified as one of the products of the reactions by comparison of the UV−vis spectra after completion of these reactions with those of authentic samples under the kinetic conditions.

Table 3. Experimental Conditions and k_{obsd} Values for the Aminolysis of Ethyl *S*-(4-Methoxyphenyl) Thiolcarbonate (MOPTC)[a]

amine	pH	F_N[b]	$10^2[N]_{tot}$[c]/ M	10^3k_{obsd}/ s^{-1}	no. of runs
piperidine	10.94	0.33	1.0−7.0	0.367−3.56	7
	11.24	0.50	1.0−7.0	0.852−6.08	7
	11.54	0.66	1.0−3.0	1.20−3.70	3
piperazine	9.64	0.33	8.0−29	0.592−1.81	7
	9.94	0.50	5.0−39	0.636−4.11	6
	10.24	0.66	5.9−49	0.969−6.31	6
1-(2-hydroxyethyl)-	9.38	0.50	8.0−35	0.241−0.876	6
piperazine	9.68	0.66	5.9−57	0.189−1.91	3
	10.00	0.81	16−51	0.644−1.87	5
morpholine	8.78	0.50	24−39	0.284−0.403	3
	9.20	0.73	29−70	0.462−0.90	6
	9.50	0.84	30−80	0.485−1.18	6
1-formylpiperazine	8.54	0.80	20−80	0.437−0.894	5

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

Table 4. Experimental Conditions and k_{obsd} Values for the Aminolysis of Ethyl *S*-(4-Chlorophenyl) Thiolcarbonate (ClPTC)[a]

amine	pH	F_N[b]	$10^2[N]_{tot}$[c]/ M	10^3k_{obsd}/ s^{-1}	no. of runs
piperidine	10.94	0.33	3.0−25	4.07−38.8	7
	11.24	0.50	1.0−8.0	2.31−18.0	7
	11.54	0.66	1.0−30	3.60−92.3	7
piperazine	9.94	0.50	7.0−40	3.23−17.9	7
	10.24	0.66	6.0−50	3.69−29.4	7
	10.60	0.83	6.0−20	4.99−16.1	5
1-(2-hydroxyethyl)-	9.38	0.50	8.0−40	0.917−4.74	6
piperazine	9.68	0.66	8.0−50	1.58−8.64	7
	10.18	0.86	6.0−60	1.34−14.0	6
morpholine	8.78	0.50	5.0−30	0.385−1.63	4
	9.08	0.66	10−60	0.960−3.65	6
	9.38	0.80	20−100	1.90−8.35	7
1-formylpiperazine	8.54	0.80	20−100	0.372−1.69	7

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

Results and Discussion

The reactions subjected to the present investigation can be kinetically described by eqs 1 and 2, where ArS^-

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

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

and S represent the substituted benzenethiolate anion and the substrate, respectively, k_{obsd} is the pseudo-first-order rate coefficient, k_o and k_N are the rate coefficients for hydrolysis and aminolysis of the substrate, respectively, and N represents the amine free base.

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Table 5. Statistically Corrected Values of pK_a for Amines and k_N for the Aminolysis of Ethyl *S*-Aryl Thiolcarbonates[a]

amine	pK_a + log(p/q)	$10^2(k_N/q)/(s^{-1}\ M^{-1})$ PTC (6.4)[b]	MPTC (6.4)[b]	MOPTC (6.5)[b]	ClPTC (6.0)[b]
piperidine	11.54	24.2	16.7	16.8	46.2
piperazine	9.94	1.95	1.22	1.00	4.51
1-(2-hydroxyethyl)-piperazine	9.68	0.905	0.604	0.455	2.65
morpholine	9.08	0.516	0.253	0.157	1.07
1-formylpiperazine	8.28	0.089	0.039	0.097	0.196

[a] Both pK_a and k_N values in aqueous solution, 25.0 °C, ionic strength 0.2 (KCl). The values are statistically corrected with $p = 2$ and $q = 1$, except piperazine with $q = 2$.[8,9] [b] Values of the pK_a for the leaving groups of the substrates, under the kinetic conditions.[6b]

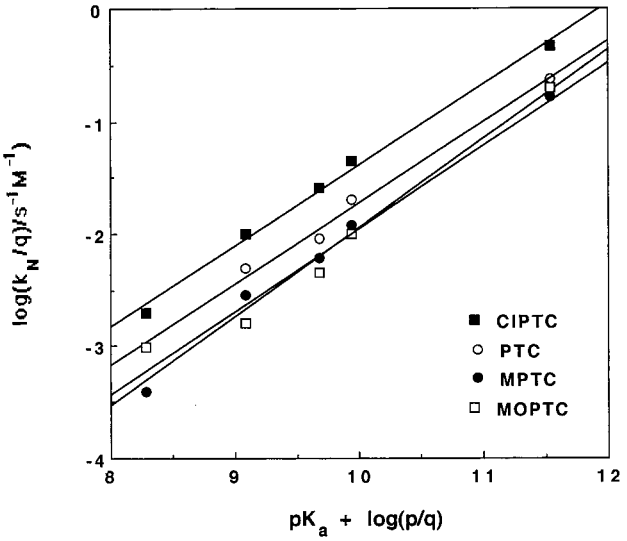


Figure 1. Brönsted-type plots (statistically corrected) obtained in the reactions of secondary alicyclic amines with ethyl *S*-4-X-phenyl thiolcarbonates, X = Cl (ClPTC), X = H (PTC), X = Me (MPTC), and X = MeO (MOPTC), in aqueous solution, 25.0 °C, ionic strength 0.2 (KCl).

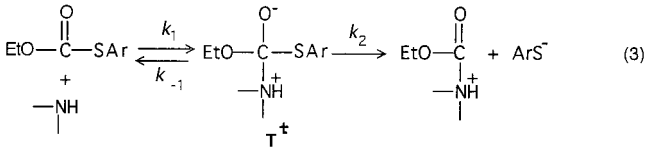
The values of k_o and k_N were obtained as the intercept and slope, respectively, of linear plots of k_{obsd} against [N] at constant pH, using at least three pH values, except in the reactions of 1-formylpiperazine where only one pH was employed. The values of k_N were found to be pH independent over the pH range studied.

The k_o values were in general negligible compared to those of k_N[N] in eq 2, except in the slow aminolysis of the substrates with the least basic amine (1-formylpiperazine).

The values of k_N together with those of the pK_a of the conjugate acids of the amines were statistically corrected with $p = 2$ and $q = 1$, except piperazine with $q = 2$.[1−4,6,8,9] These corrected values are shown in Table 5.

The statistically corrected Brönsted-type plots obtained for the aminolysis of all the substrates are linear (Figure 1). The slope values, $\beta_N = 0.7-0.8$, are consistent with a stepwise mechanism where a zwitterionic tetrahedral intermediate ($T^{\pm}$) is formed in the reaction pathway and its breakdown to products is rate-determining. These stepwise mechanisms are in accordance with the stepwise process for the same aminolysis of NPTC.[1] If an intermediate $T^{\pm}$ is formed in the latter reactions, where a very good leaving group (4-nitrophenoxy) is present, it is reasonable that the corresponding intermediates in the reactions of the present work be more stable in view of the worst nucleofuges involved.

Moreover, slope values similar to those of the present study have been found in the stepwise aminolysis of phenyl and 4-nitrophenyl acetates,[10] 4-nitrophenyl methyl carbonate,[11] 4-nitrophenyl benzoate,[12,13] and other reactive carbonyl compounds,[14−17] when the breakdown of $T^{\pm}$ to products is the rate-determining step. When formation of $T^{\pm}$ from reactants is rate-limiting, the Brönsted slopes are $\beta_N = 0.1-0.3$.[8,10,13−15] Therefore, the most likely mechanism for the reactions under the present investigation is that depicted in eq 3, where the first step is at equilibrium.



(3)

If the k_2 step of eq 3 is rate-determining for the reactions under scrutiny, it follows that $k_N = K_1k_2$, where K_1 is the equilibrium constant for the first step of eq 3 (after application of the steady-state treatment to the intermediate $\mathbf{T}^{\pm}$). Comparison of the k_N values for the present reactions (Table 5) with those for the same aminolysis of NPTC (except the reaction of piperidine with NPTC, whereby the first step of eq 3 is rate-limiting)[1] shows that NPTC is much more reactive than the other substrates toward saa when breakdown of $\mathbf{T}^{\pm}$ to products is rate-determining (i.e., k_N for NPTC is ca. 8−10-fold greater than that for ClPTC, and 30−70-fold greater than that for MOPTC). This is reasonable in terms of the stronger electron withdrawal from 4-nitrophenoxy, relative to the other leaving groups, in both the substrate and $\mathbf{T}^{\pm}$, resulting in greater values for both K_1 and k_2, respectively.

In the reactions of saa with ethyl *S*-(4-X-phenyl) dithiocarbonates (X = H, Cl, Me, and MeO), the plots k_{obsd} vs [N], where N is a free saa, are nonlinear upward, indicating a variable order in amine (between 1 and 2).[6] These plots were explained through the reaction mechanism described in Scheme 1, where there is proton transfer (k_3 step, partially rate-determining) from the

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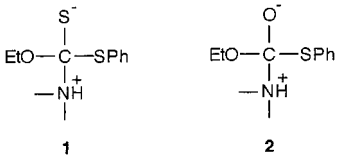
zwitterionic tetrahedral intermediate ($T^{\pm}$) to an amine (N) to yield an anionic intermediate (T^{-}).[6] For these reactions it was estimated that $k_3[N] \geq k_2$.[6] The reason the order in amine is unity in the reactions under the present study seems to be that (i) the value of k_2 is greater for the aminolysis of thiolcarbonates compared to the corresponding dithiocarbonates and (ii) the value of k_3 is similar for the reactions of both types of substrates, as explained below.

The value of k_2 for the intermediate **1** has been estimated as 7×10^7 s^{-1}.[18] Substitution of S^- by O^- in **1** should result in a larger k_2 value, in view of the stronger driving force of O^- in a tetrahedral intermediate (**2**) to



1 **2**

form a double bond and expel a nucleofuge compared to that of S^- in **1**.[19] This has been ascribed to a weaker π-bonding energy of the thiocarbonyl group relative to carbonyl.[20]

On the other hand, the pK_a value of **2** has been estimated as 2.3 pK_a units lower than that of the corresponding protonated amine, and the pK_a value of **1** was estimated as even smaller.[6a] This means that the proton transfers from the zwitterionic intermediates (**1** and **2**) to the free amine to yield the corresponding anionic intermediates are thermodynamically favorable; therefore, these processes should be diffusion controlled, and the value of k_3 for both **1** and **2** can be estimated as 10^{10} s^{-1} M^{-1}.[6,21] The k_3 value for the proton transfers from the other tetrahedral intermediates in this work (similar to **2**, but with substituted phenyl groups) should be similar to that from **2** in view of the similar basicities of the leaving groups involved.

Therefore, the simple reaction mechanism found in the aminolysis of the title thiolcarbonates (eq 3) relative to the less simple one for the corresponding dithiocarbonates (Scheme 1) should be due to the fact that for the latter reactions k_3[amine] $\geq k_2$, whereas k_3[amine] $< k_2$ for the reactions of thiolcarbonates.

With the k_N values found in the present reactions and those of NPTC (except that for the reaction of NPTC with piperidine where the first step of eq 3 is rate-limiting),[1] together with the pK_a values for both the amines and leaving groups (Table 5), eq 4 can be deduced by dual

$$\log k_N = -4.3 + 0.8\mathrm{p}K_a(\mathrm{N}) - 0.8\mathrm{p}K_a(\mathrm{lg}) \qquad (4)$$

regression analysis ($n = 25$, $R^2 = 0.97$). In this expression N and lg refer to amine and leaving group, respectively; both k_N and pK_a(N) have been statistically corrected,[8,9] and the pK_a coefficients (β_N and β_{lg}) are subjected to an error of ± 0.1.

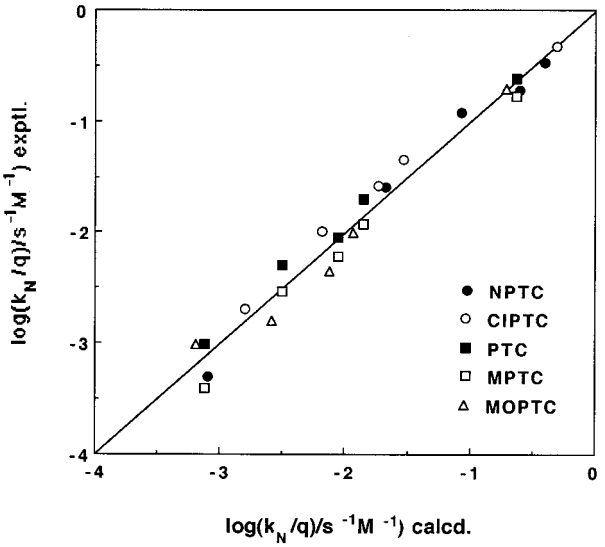


Figure 2. Logarithmic plot of experimental k_N vs calculated k_N (through eq 4) for the reactions of secondary alicyclic amines with ethyl *S*-4-X-phenyl thiolcarbonates, X = NO_2 (NPTC), X = Cl (ClPTC), X = H (PTC), X = Me (MPTC), and X = MeO (MOPTC), in aqueous solution, 25.0 °C, ionic strength 0.2 (KCl).

A logarithmic plot of the experimental k_N vs the calculated one through eq 4 is shown in Figure 2; the slope is unity.

The sensitivity of k_N to the amine and leaving group basicities ($\beta_N = -\beta_{lg} = 0.8$) is in agreement with those exhibited in the aminolysis of aryl esters and diaryl carbonates when breakdown to products of the tetrahedral intermediate ($T^{\pm}$) is the rate-determining step.[10,14] For rate-determining formation of $T^{\pm}$ the β_N and $-\beta_{lg}$ values are 0.1−0.3 and 0−0.5, respectively, for the aminolysis of the above compounds[10,14] and ethyl *S*-aryl dithiocarbonates.[6b,22] On the other hand, for the concerted aminolysis of very reactive ethyl *S*-aryl thiolcarbonates and similar compounds, in both water and aqueous ethanol, the value of β_N is 0.5−0.6,[3,4,23] and that for β_{lg} is −0.19.[4]

A direct comparison of the reactivities of saa and pyridines toward the title thiolcarbonates is not possible because kinetic studies of the reactions of these substrates with the latter amines have not been reported, to our knowledge. Nevertheless, on the basis of the data for the reactions of pyridines of pK_a 3.43−6.77 with

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(22) A reviewer has suggested that the rate-determining step for the title reactions could be the proton transfer from $T^{\pm}$ to a water molecule. Nevertheless, this proton transfer is much slower than k_2, as will be shown now. As an example, let us calculate the rate constant for the proton transfer from the intermediate **2** formed with 1-formylpiperazine (the least basic amine of the series and therefore the most acidic $T^{\pm}$) to water. It has been estimated that the pK_a of **2** is 2.3 pK_a units lower than that of the corresponding protonated amine (see the text). Since the pK_a of 1-formylpiperazine is 8.28 (Table 5), it follows that the pK_a of **2** formed with this amine is ca. 6. Therefore, the proton transfer from this $T^{\pm}$ to water (pK_a = −1.75) is not favorable thermodynamically, but the back-reaction (proton transfer from H_3O^+ to T^-) is favorable, and its rate constant should be ca. 10^{10} s^{-1} M^{-1}.[21] Therefore, the pseudo-first-order rate constant for proton transfer from this $T^{\pm}$ to water should be $10^{10} \times K_a(T^{\pm}) = 10^{10} \times 10^{-6} = 10^4$ s^{-1}. This value should not change significantly for the $T^{\pm}$ intermediates possessing other leaving groups, in view of the similar basicities of these leaving groups (see Table 5). This rate constant is much smaller than k_2, which is $> 7 \times 10^7$ s^{-1} (see the text).

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4-nitrophenyl, 2,4-dinitrophenyl, and 2,4,6-trinitrophenyl *O*-ethyl thiolcarbonates, for which the breakdown to products of $T^{\pm}$ is rate-limiting,[2] a dual parametric expression can be deduced (eq 5). In this equation the standard errors are 0.34 for the constant term and 0.05 for the β_N and β_{lg} coefficients, $R = 0.990$, standard error 0.234.

$$\log k_N = -3.93 + 0.83pK_a(N) - 0.73pK_a(lg) \quad (5)$$

With the aid of eq 5 the k_N values for the reactions of pyridines, isobasic to the saa of the present work, with the title substrates can be obtained. The resulting k_N values are larger than the experimental ones shown in Table 5.

The greater reactivity of pyridines than isobasic saa found in this work, when expulsion of the leaving group of the substrate from $T^{\pm}$ is rate-determining, is in line with the results in the aminolysis of 2,4-dinitrophenyl acetate,[24a] 2,4-dinitrophenyl methyl carbonate,[24b] 2,4-dinitrophenyl and 2,4,6-trinitrophenyl thiolacetates,[15e] 2,4-dinitrophenyl and 2,4,6-trinitrophenyl *O*-ethyl dithiocarbonates,[18,25] and *S*-4-nitrophenyl ethyl thiolcarbonate.[2]

In conclusion, (i) the kinetic results of the reactions of this study are consistent with a stepwise mechanism where the breakdown to products of the intermediate $T^{\pm}$ is rate-determining, because (a) the β_N and $-\beta_{lg}$ values of 0.8 found are in agreement with the proposed mechanism and (b) the reactions of saa with *S*-4-nitrophenyl ethyl thiolcarbonate are stepwise; therefore, the intermediate $T^{\pm}$ in the present reactions should be more stable (worse leaving groups than 4-nitrobenzenethio) than that in the reactions with the 4-nitrophenyl derivative; (ii) the mechanism for the title reactions is simpler than that for the corresponding dithiocarbonates because $k_2 > k_3$[amine]; and (iii) the k_N values calculated for the reactions of the title substrates with pyridines isobasic with the saa of this work are greater than the experimental k_N values obtained in the present investigation.

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