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Kinetics and mechanism of the aminolysis of thioesters and thiocarbonates in solution*

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Abstract: The aminolysis reactions of thioesters and thiocarbonates, in either aqueous solution or in 44 wt % aqueous ethanol at 25 °C, are subjected to a kinetic investigation. The Brønsted-type plots (lg k_N vs. amine pK_a, where k_N is the nucleophilic rate constant) obtained for these reactions can be grouped in three categories: linear plots with slopes 0.8–1, biphasic plots (two linear portions and a curve in between), and linear plots with slopes 0.4–0.6. The two former plots are attributed to stepwise reactions through a zwitterionic tetrahedral intermediate. The latter plots are associated with a concerted mechanism. The fact that some reactions are stepwise and others concerted depends on the stability of the zwitterionic tetrahedral intermediate. This work shows how the experimental data allows one to assess the mechanism of these reactions. Also discussed are the factors that affect the stability of this intermediate, which in turn determines the pathway followed by the reaction. The factors analyzed in this work are (i) the leaving group of the substrate, (ii) the nature of the amine, (iii) the non-leaving group of the substrate, (iv) the electrophilic group of the substrate (CS vs. CO), and (v) the solvent.

Keywords: kinetics; mechanism; aminolysis; thioesters; thiocarbonates.

INTRODUCTION

Although the aminolysis reactions of esters and carbonates are well documented and their mechanisms are clear [1,2], the same reactions of thioesters and thiocarbonates have received less attention [3–14]. Some of the latter reactions are driven by a stepwise mechanism, through a zwitterionic tetrahedral intermediate ($T^{\pm}$), and others are concerted, proceeding in a single step [3–14]. The mechanisms followed by these reactions have been determined usually by the shapes and slopes of their Brønsted-type plots: lg k_N vs. pK_a, where k_N is the second-order nucleophilic rate constant and pK_a refers to the conjugate acid of the amine (or sometimes the leaving or non-leaving groups of the substrate). The mechanism followed by these reactions is directly related to the relative stability of the intermediate $T^{\pm}$, and this stability depends on the groups attached to this intermediate and on the solvent. It is of interest, therefore, to investigate how these groups affect the stability of the intermediate $T^{\pm}$. This is the main objective of the present work.

The reactions that will be examined in this work are those of different thioesters and thiocarbonates with four series of amines. The structures of these compounds are shown in Scheme 1.

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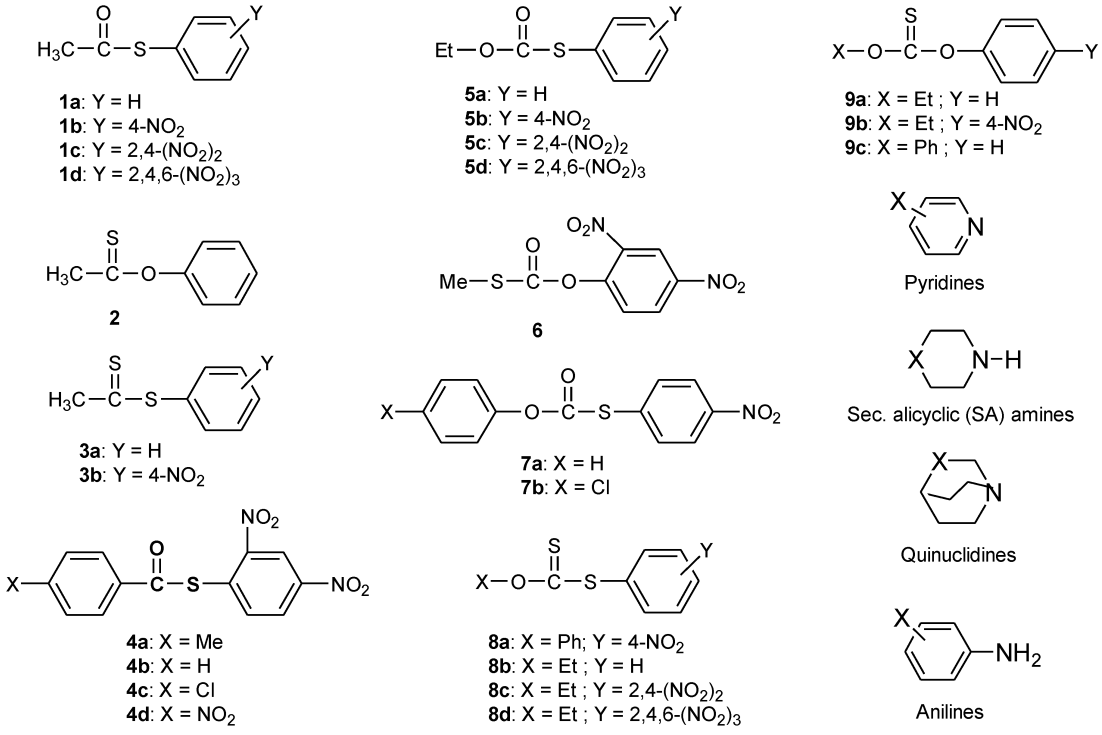


Scheme 1 Structures of the compounds studied in this work.

RESULTS AND DISCUSSION

All the reactions studied in this work have been carried out under excess of amine over the substrate, at 25 °C, in aqueous or aqueous ethanol solution, and an ionic strength of 0.2 M (KCl). The great majority of the reactions follow the rate law given by eqs. 1 and 2, where P and S represent one of the products and the substrate, respectively, and k_{obs} is the pseudo-first-order rate constant. The rate constants k_0 and k_N are those for hydrolysis (or solvolysis in the cases where aqueous ethanol was used) and [amine] is the molar concentration of the free amine. In these cases, the values of k_0 and k_N are obtained as the intercept and slope, respectively of plots of k_{obs} against [amine]. Only the reactions of thiono and dithio compounds with secondary alicyclic (SA) amines showed a nonlinear plot of k_{obs} vs. [amine] (see below).

$$\frac{d[P]}{dt} = k_{obs}[S] \tag{1}$$

$$k_{obs} = k_0 + k_N\,[\text{amine}] \tag{2}$$

For the reactions of a common substrate with a homogeneous series of amines, the Brønsted-type plot (lg k_N against the amine pK_a) has usually been employed to clarify the reaction mechanism. For poor or relatively poor leaving groups, usually the Brønsted plots are linear, with slopes 0.8–1, in agreement with a stepwise process, through a zwitterionic tetrahedral intermediate ($T^{\pm}$), where its breakdown to products is the rate-determining step [3]. For very good leaving groups (e.g., 2,4-dinitrophenoxide and 2,4,6-trinitrophenoxide) generally nonlinear biphasic plots (two linear portions and a curve in between) are obtained, with slopes β_1 = 0.1–0.3 (at high pK_a) and β_2 = 0.8–1 (at low pK_a) [3,15]. These plots have been explained by a stepwise mechanism and a change in the rate-limiting step, from $T^{\pm}$

breakdown to its formation, as the amine basicity increases [3,15]. In other reactions, linear Brønsted plots with slopes 0.4–0.6 have been obtained, which are consistent with a concerted mechanism (single step, without the $T^{\pm}$ intermediate) [3]. Since the relative stability of the intermediate $T^{\pm}$ is a key factor in driving the course followed by the reaction (stepwise vs. concerted), it is of interest to investigate the effect of the groups attached to this intermediate, as well as the effect of the solvent, on the stability of $T^{\pm}$ and, therefore, on the mechanism chosen by the reaction.

We will examine in this work how the groups attached to the intermediate $T^{\pm}$ and the solvent affect the stability of this intermediate and the reaction mechanism.

Effect of the leaving group

The reactions of SA amines with phenyl thiolacetate (**1a**) in water show a linear Brønsted-type plot with slope $\beta = 0.8$ [5a]. The reactions of the same amines with Y-substituted phenyl thiolacetates, where Y = 4-NO_2, 2,4-$(NO_2)_2$ and 2,4,6-$(NO_2)_3$ (**1b–d**), exhibit nonlinear biphasic Brønsted-type plots [5a,b]. These plots are shown in Fig. 1. The plots are statistically corrected with $q = 2$ for piperazine, $p = 4$ for piperazinium dication, and $p = 2$ for the conjugate acids of the other amines. The parameter q is the number of equivalent basic sites on the free amine and p is the number of equivalent protons on the conjugate acid of the amine [16].

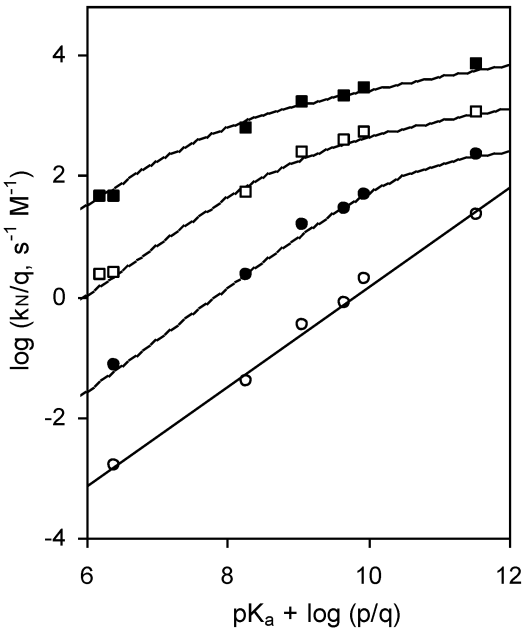
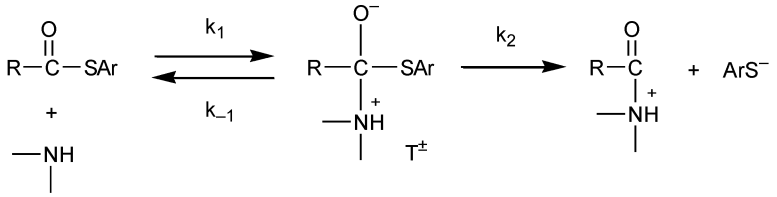


Fig. 1 Brønsted-type plots obtained for the reactions of SA amines with aryl thiolacetates **1a** (○, ref. [5a]), **1b** (●, ref. [5a]), **1c** (□, ref. [5b]), and **1d** (■, ref. [5b]), in water, at 25.0 °C, and an ionic strength of 0.2 M.

The slope value of the Brønsted-type plot for the reactions of SA amines with **1a** is consistent with a stepwise process (shown in Scheme 2), through a zwitterionic tetrahedral intermediate ($T^{\pm}$), where its breakdown to products (k_2 step) is the rate-determining step [1c,e,3,5]. The biphasic plots are in agreement with a stepwise mechanism and a change in the rate-limiting step, from breakdown of $T^{\pm}$ (k_2 step) to its formation (k_1 step), as the basicity of the amine increases [1c,e,3,5].



Scheme 2 Stepwise mechanism for the SA aminolysis of thiolesters.

The curved lines of the Brønsted plots in Fig. 1 were calculated by a semi-empirical equation, eq. 3, based on the existence of the intermediate $T^{\pm}$ and a change in the rate-limiting step [3,5,15]. In eq. 3, k_N^0 and pK_a^0 are the corresponding parameters at the curvature center of the Brønsted plots, and β_1 and β_2 are the slopes at high and low pK_a values. By nonlinear fittings, the following parameters were found for the curved Brønsted plots: $\beta_2 = 0.86$, 0.85, and 0.80; $\beta_1 = 0.1$, 0.2, and 0.2; $\lg k_N^0 = 2.0$, 2.2, and 2.7; and $pK_a^0 = 10.5$, 8.9, and 7.8, for the reactions of **1b**, **1c**, and **1d**, respectively.

$$\lg (k_N/k_N^0) = \beta_2 (pK_a - pK_a^0) - \log [(1 + \alpha)/2] \quad (3)$$

$$\log \alpha = (\beta_2 - \beta_1) (pK_a - pK_a^0)$$

The pK_a^0 value corresponds to the pK_a of an amine for which $k_{-1} = k_2$. As seen above, the pK_a^0 value shifts to lower values as the leaving ability of the nucleofuge increases. This is consistent with the stepwise mechanism depicted in Scheme 2: the better the leaving group, the larger the k_2 value and the larger must be the k_{-1} value to match k_2; a larger k_{-1} value corresponds to a less basic amine (of lower pK_a). This is why pK_a^0 decreases as the nucleofuge leaves faster from the $T^{\pm}$ intermediate.

We have deduced an equation that quantifies of the pK_a^0 shift, eq. 4, based on the existence of the tetrahedral intermediate [3,5]. As seen in this equation, the larger the k_2 value, the lower is the pK_a^0 value.

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

From the above results, the relative leaving abilities of SA amines and benzenethiolates can be assessed. For instance, the SA aminolysis of thiolacetate **1c** shows a pK_a^0 value of 8.9. This means that a SA amine of pK_a 8.9 leaves $T^{\pm}$ as fast as 2,4-dinitrobenzenethiolate (of pK_a 3.4). Namely, SA amines are much better nucleofuges than *isobasic* benzenethiolates. Quantification through eq. 4 yields $k_{-1}/k_2 =$ 3760 for an SA amine of pK_a of 3.4, i.e., the latter amine leaves $T^{\pm}$ 3760 times faster than 2,4-dinitrobenzenethiolate.

As seen above, good leaving groups increase the k_2 value, therefore, destabilizing the intermediate $T^{\pm}$. A much more drastic leaving group effect was found for the following reactions.

The reactions of SA amines with ethyl *S*-4-nitrophenyl thiolcarbonate (**5b**) in water exhibit a biphasic Brønsted plot, with $pK_a^0 = 10.7$ (see Fig. 2), in agreement with a stepwise mechanism [6b]. In contrast, the reactions of the same amines with ethyl *S*-2,4-dinitrophenyl thiolcarbonate (**5c**) in the same solvent show a linear Brønsted plot with a slope of 0.56 (Fig. 2), compatible with a concerted mechanism [6a]. As seen above, for the stepwise SA aminolysis of thiolacetate **1c**, the pK_a^0 value is 1.6 pK_a units lower than that for thiolacetate **1b**. If a similar pK_a^0 decrease applies to thiolcarbonates, the predicted pK_a^0 for a *stepwise* SA aminolysis of thiolcarbonate **5c** would be 10.7 – 1.6 = 9.1. Since the Brønsted plot for thiolcarbonate **5c** in Fig. 2 shows no break at p*K*a 9.1, the stepwise mechanism for this reaction can be ruled out, which confirms the concerted mechanism for the SA aminolysis of **5c**. This illustrates the dramatic change in mechanism that takes place in the SA aminolysis of thiocarbonates by substitution of 4-nitrophenoxide by 2,4-dinitrophenoxide as the leaving group. The $T^{\pm}$ intermediate formed in the reactions of **5b** is so much destabilized by the above change of the leaving group

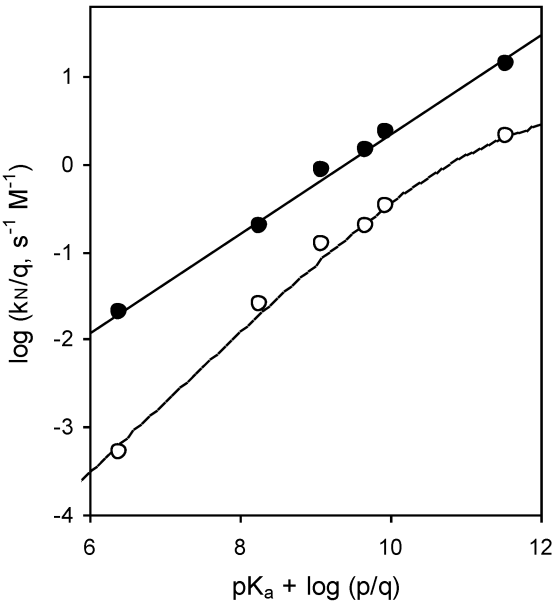


Fig. 2 Brønsted-type plots obtained for the reactions of SA amines with thiolcarbonates **5b** (○, ref. [6b]) and **5c** (●, ref. [6a]), in water, at 25.0 °C, and an ionic strength of 0.2 M.

that the intermediate either no longer exists (enforced concerted mechanism) or exists but is so unstable that the concerted process occurs through a path of lower energy [17].

Effect of the amine

It is obvious that the nucleofugality of the amine from the intermediate $T^{\pm}$ decreases (lower k_{-1}) as its basicity increases (larger pK_a). What is not obvious is how the *nature* of the amine affects k_{-1} and thus the stability of the intermediate $T^{\pm}$. In this section we examine the latter effect.

The pyridinolysis of thiolacetate **1c** shows a biphasic Brønsted plot with $pK_a^0 = 6.6$ [5b]. This value is lower than that exhibited by the reactions of SA amines with the same substrate ($pK_a^0 = 8.9$, see above). According to eq. 4 this means a lower k_{-1}/k_2 ratio for the reactions of pyridines compared with *isobasic* SA amines. Since k_2 should not be affected by the amine nature or basicity [15], this indicates a lower k_{-1} value for pyridines. Therefore, pyridines leave $T^{\pm}$ more slowly than isobasic SA amines. There are many other examples in the literature that point to the same direction [3]. The above means that SA amines destabilize the intermediate $T^{\pm}$ compared with isobasic pyridines. A drastic effect of the amine nature on the destabilization of a tetrahedral intermediate is shown by comparison of the following reactions.

The reactions of pyridines with *S*-methyl 2,4-dinitrophenyl thiolcarbonate (**6**) show a biphasic Brønsted plot with $pK_a^0 = 7.3$ [7a]. In contrast, the reactions of SA amines with the same substrate exhibit a linear plot with slope 0.36, consistent with a concerted process [7b]. These plots are shown in Fig 3.

The concerted mechanism of the SA aminolysis of thiolcarbonate **6** can be confirmed by estimation of the Brønsted break for a hypothetical stepwise mechanism. Since the SA aminolysis of thiolacetate **1c** shows a pK_a^0 value 2.3 pK_a units larger than that of its pyridinolysis (see above), and assuming the same increase for thiolcarbonates, the predicted pK_a^0 value for the *stepwise* SA aminolysis of **6** would be 7.3 + 2.3 = 9.6. Since for this reaction no Brønsted break is observed at pK_a 9.6 (see Fig. 3) one can safely rule out a stepwise pathway, confirming, therefore, the concerted mechanism.

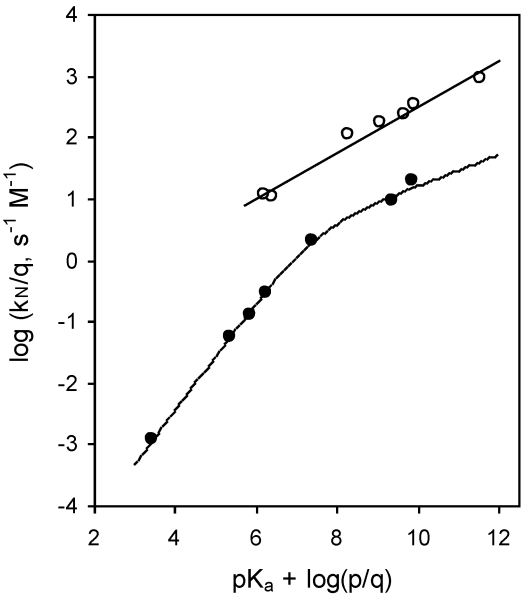


Fig. 3 Brønsted-type plots obtained for the reactions of thiolcarbonate **6** with pyridines (●, ref. [7a]) and SA amines (○, ref. [7b]), in water, at 25.0 °C, and an ionic strength of 0.2 M.

This indicates that a SA amine leaves the tetrahedral intermediate $T^{\pm}$ much faster than an isobasic pyridine, destabilizing therefore the intermediate by such an extent that this no longer exists and the concerted mechanism occurs.

Another example of a drastic destabilization of the intermediate $T^{\pm}$ caused by the change of a pyridine by an isobasic SA amine is given by the fact that the pyridinolysis of thiolcarbonates **7a** and **7b** are stepwise, whereas the SA aminolysis of these substrates are concerted [8].

The leaving abilities of pyridines and anilines from the intermediate $T^{\pm}$ can be evaluated by comparison of their reactions with thiolcarbonate **5d**. The pyridinolysis of this substrate shows a biphasic Brønsted plot (see Fig. 4) with $pK_a^0 = 7.3$ [9a], in agreement with a stepwise mechanism, whereas its anilinolysis exhibits a linear plot (see Fig. 4) of slope 0.54, consistent with a concerted process [9b]. This indicates that anilines leave the intermediate $T^{\pm}$ faster than isobasic pyridines, thus destabilizing the intermediate.

An evaluation of the nucleofugality of SA amines and anilines from $T^{\pm}$ can be made by a comparison of their reactions with thiolcarbonate **5c**. The reactions of anilines exhibit a linear Brønsted plot with slope 0.9, consistent with a stepwise mechanism where $T^{\pm}$ breakdown to products is rate-limiting [9b]. In contrast, the reactions of SA amines with **5c** show a linear plot with slope 0.56 (see Fig. 2), in agreement with a concerted process [6a]. This shows that SA amines leave $T^{\pm}$ faster than isobasic anilines, destabilizing the intermediate.

By comparison of the reactions of SA amines and quinuclidines with thiolcarbonate **5b**, the leaving abilities of quinuclidines relative to SA amines can be assessed. As seen in Fig. 2, a biphasic Brønsted plot with $pK_a^0 = 10.7$ was found for the SA aminolysis of **5b**, compatible with a stepwise mechanism [6b]. The reactions of quinuclidines with the same substrate show a linear Brønsted plot with slope 0.85 (not shown), also in agreement with a stepwise process [10]. Since the most basic quinuclidine used had a pK_a of 11.4, this means that for these reactions $pK_a^0 > 11.4$. The larger pK_a^0 value for quinuclidines, relative to SA amines, indicates that the ratio k_{-1}/k_2 is larger for quinuclidines, compared with isobasic SA amines, according to eq. 4. Since k_2 should be independent of the nature of the amine [15], this means that quinuclidines leave faster from $T^{\pm}$ compared to isobasic SA amines.

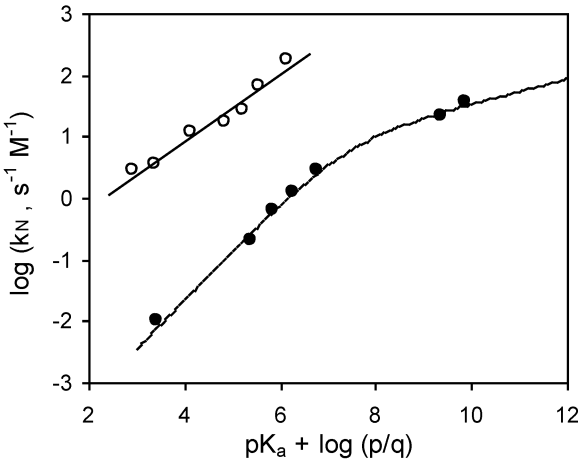


Fig. 4 Brønsted-type plots obtained for the reactions of thiolcarbonate **5d** with pyridines (●, ref. [9a]) and anilines (○, ref. [9b]), in water, at 25.0 °C, and an ionic strength of 0.2 M.

Therefore, as a conclusion for this section, the relative nucleofugalities of isobasic amines from the intermediate $T^{\pm}$, i.e., according to their k_{-1} values, are: quinuclidines > SA amines > anilines > pyridines.

Effect of the non-leaving group

This effect can be assessed by comparison of the pyridinolysis of 2,4-dinitrophenyl 4-X-substituted thiolbenzoates **4a–d**. All these reactions show biphasic Brønsted plots (not shown), consistent with stepwise mechanisms, with pK_a^0 values of 8.5, 8.9, 9.5, and 9.9 for X = Me, H, Cl, and NO_2, respectively [11a]. A similar trend was found for the pyridinolysis and SA aminolysis of the corresponding 4-nitrophenyl thiolbenzoates [11b,c].

The increase in pK_a^0 means an increase of the k_{-1}/k_2 ratio, according to eq. 4. The larger k_{-1}/k_2 ratio with the increasing electron-withdrawing ability of X was explained by the following argument: as X becomes more electron-withdrawing, the more positive becomes the central carbon of the intermediate $T^{\pm}$ and, therefore, the stronger the push provided by the leaving group in $T^{\pm}$ to expel the amine. The amine in $T^{\pm}$ cannot exert its push to expel the leaving group (it lacks an electron pair); therefore, electron withdrawal from X favors amine nucleofugality from $T^{\pm}$, relative to that of the leaving group [11,18]. This is why the pK_a^0 value increases as X becomes more electron-withdrawing [11].

Nevertheless, Um and coworkers have found a negligible effect of X on pK_a^0 in the SA aminolysis of aryl X-benzoates [19a,b] and aryl X-thionobenzoates [19c], all in aqueous dimethyl sulfoxide (DMSO).

We have also found a slight influence of the non-leaving group on the pK_a^0 values in the pyridinolysis of thiolcarbonates **7a** and **7b** in aqueous ethanol [8]. This small effect, relative to that found for thiolbenzoates, can be attributed to the longer distance, from X to the central carbonyl carbon, in thiolcarbonates compared with thiolbenzoates [8].

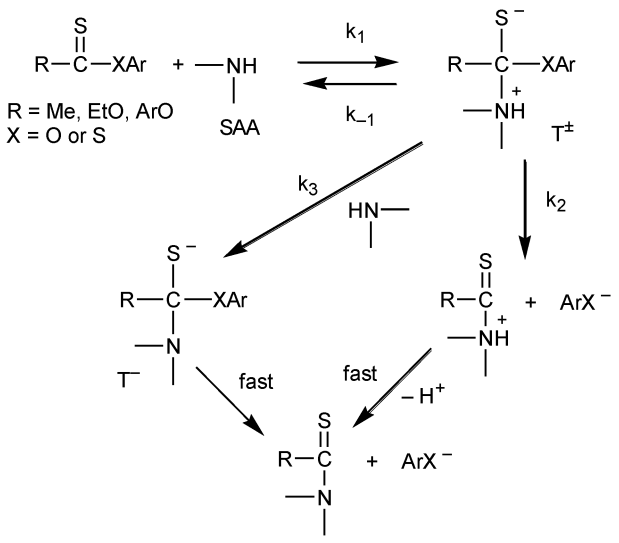
In contrast, a more pronounced effect of the non-leaving group can be observed by the comparison of the SA aminolysis of thiolcarbonates **5b** and **7a**. The former reaction is stepwise, whereas the latter is concerted [6b,8]. Namely, the change of EtO in **5b** by PhO in **7a** as the non-leaving group changes the mechanism from stepwise to concerted. This has been attributed to the great increase in k_{-1}, and therefore, great destabilization of the intermediate $T^{\pm}$, due to this change of non-leaving group [8].

Effect of the electrophilic group (CO vs. CS)

The reactions of SA amines with alkyl aryl and diaryl thiolcarbonates possessing good leaving groups show linear plots of k_{obs} vs. free amine concentration [6–8]. The same applies to the SA aminolysis of aryl thiolacetates with good leaving groups [5]. In contrast, the reactions of SA amines (except piperidine) with phenyl 4-nitrophenyl dithiocarbonate (**8a**) show nonlinear upwards k_{obs} vs. [amine] plots [12a]. Similar nonlinear plots were found for the reactions of SA amines (except piperidine) with ethyl phenyl dithiocarbonate (**8b**) [12b,c] and phenyl and 4-nitrophenyl dithioacetates (**3a** and **3b**) [12d,e]. Namely, substitution of the electrophilic CO group by CS changes the shape of these plots from a linear to a nonlinear one.

A similar trend is observed by a comparison between carbonates and thionocarbonates. All carbonates and aryl acetates with good leaving groups show linear plots of k_{obs} vs. [amine] [1c,2,15,18,20]. In contrast, the reactions of SA amines (except piperidine) with ethyl phenyl, ethyl 4-nitrophenyl and diphenyl thionocarbonates (**9a–c**) [13a,b] and phenyl thionoacetate (**2**) [13c] exhibit nonlinear upwards plots of k_{obs} vs. [amine].

The different kinetic behavior of the SA aminolysis of compounds with CS, relative to those with CO as electrophilic group, has been explained by the more complex mechanism for the former reactions. This is depicted in Scheme 3 [12,13]. In this scheme there is an additional pathway from the intermediate $T^{\pm}$ toward products. This is a general-base catalysis by the same amine to give the anionic tetrahedral intermediate T^{-}.



Scheme 3 Mechanism for the SA aminolysis of compounds with CS as electrophilic group.

Application of the steady state condition to both intermediates in Scheme 3 yields eq. 5, where NH represents a SA amine.

$$k_{obs} = \frac{k_1 (k_2 + k_3[\mathrm{NH}])\,[\mathrm{NH}]}{k_{-1} + k_2 + k_3[\mathrm{NH}]} \tag{5}$$

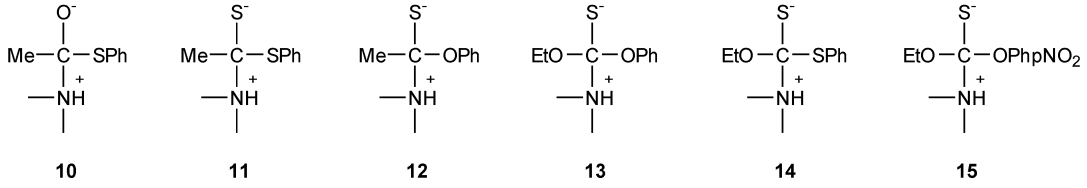
Two limiting situations can arise: for a very weakly basic SA amine, such as piperazinium cation, $k_{-1} >> k_2 + k_3$ [NH]; in this case, eq. 5 reduces to eq. 6, where $K_1 = k_1/k_{-1}$. For a very basic SA amine, such as piperidine, $k_{-1} << k_2 + k_3$[NH]; therefore, eq. 5 simplifies to eq. 7. This is why for the reactions

with this amine linear plots of k_{obs} vs. [amine] were found. Obviously, for SA amines of intermediate basicity the whole of eq. 5 applies.

$$k_{obs} = K_1 k_2 [NH] + K_1 k_3 [NH]^2 \quad (6)$$

$$k_{obs} = k_1 [NH] \quad (7)$$

Based on the method of Jencks, which assumes that the inductive effects are the most important in a tetrahedral intermediate [21], we have estimated the pK_a values of several of the zwitterionic tetrahedral intermediates ($T^{\pm}$) in Scheme 3. Their structures are shown in Scheme 4. The pK_a of intermediate **10** has been estimated equal to that of the conjugate acid of the corresponding SA amine [5a]. The pK_a of **11** was calculated by employing the Hammett inductive substituent constants $\sigma_I = 0.03$ for S^- and $\sigma_I = -0.26$ for O^- [22], and using $\rho_I = -9.2$ for the pK_a of α-substituents in $T^{\pm}$ [23]. This gives: pK_a (**11**) – pK_a (**10**) = –9.2 [0.03 – (–0.26)] = –2.7. The pK_a of **12** was estimated by employing $\sigma_I = 0.37$ for PhO and $\sigma_I = 0.30$ for PhS [22]. This gives: pK_a (**12**) – pK_a (**11**) = –9.2 (0.37 – 0.30) = –0.6. Hence, pK_a (**12**) – pK_a (**10**) = –3.3. The pK_a of **13** and **14** should be even lower than that of **12**, since σ_I for EtO is larger than that of Me [22]. Intermediate **15** should be more acidic than **13** since *p*-nitro is more electron-withdrawing than H; therefore, its pK_a should be lower than that of **13**. This means that the tetrahedral intermediates **11–15** are more acidic than the conjugate acid of the corresponding amines and, therefore, the proton transfer from any of these intermediates to the corresponding SA amine in Scheme 3 is thermodynamically favorable. Since this transfer should be diffusion controlled, an estimation of this rate constant (k_3) is 10^{10} s^{-1} M^{-1} in water [12a,b,24] and 4×10^9 s^{-1} M^{-1} in 44 wt % aqueous ethanol [12c].



Scheme 4 Structures of tetrahedral intermediates **10–15**.

With the estimated values of k_3 in Scheme 3 the other microscopic rate coefficients in this scheme were found by nonlinear least-squares fitting of eq. 5 to the experimental points [12,13]. Table 1 show examples of the results obtained for some reactions.

Table 1 Rate microcoefficients obtained for the SA aminolysis of some thiocarbonyl compounds.[a]

	Me-CS-SPh			EtO-CS-OPh			EtO-CS-$OC_6H_4NO_2$-4		
SAA	k_1/s^{-1} M^{-1}	k_{-1}/s^{-1}	k_2/s^{-1}	k_1/s^{-1} M^{-1}	k_{-1}/s^{-1}	k_2/s^{-1}	k_1/s^{-1} M^{-1}	k_{-1}/s^{-1}	k_2/s^{-1}
PA[b]	250	8×10^6	5×10^6	3.0	1.6×10^8	1×10^7	13.4	8×10^7	3×10^7
FPA[c]	30	4×10^8	5×10^6	0.6	4×10^9	1×10^7	1.3	2×10^9	3×10^7

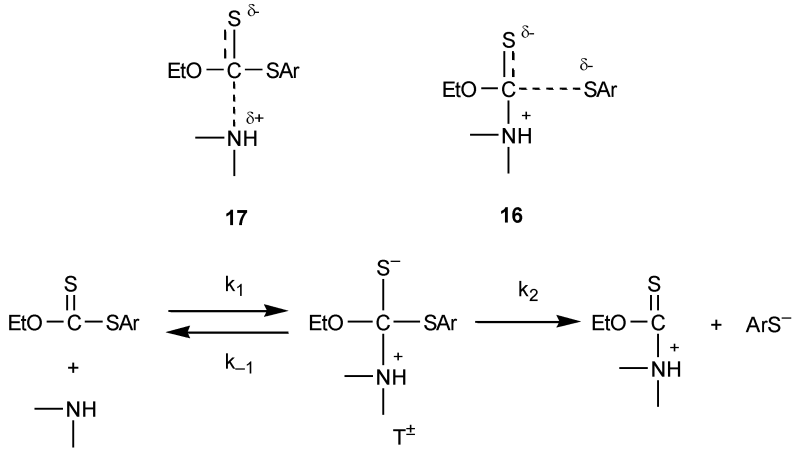
[a]In aqueous solution, at 25.0 °C, ionic strength 0.2 M.
[b]Piperazine.
[c]1-Formylpiperazine.

The reason why the SA aminolysis of thiocarbonyl compounds are more complicated kinetically than those of the carbonyl analogs (compare Schemes 2 and 3) can be attributed to the facts that (i) for the reactions of both types of compounds k_3 is diffusion-controlled, and therefore, of roughly the same value and (ii) for CO compounds the k_2 value is much larger than that for CS compounds [12,13]. This

is because the CS π-bond energy is 170 kJ/mol lower than that of CO [25]. Therefore, O^- in the intermediate $T^{\pm}$ has a more powerful driving force to form a double bond and expel the leaving group than S^- in the corresponding intermediate [12,13]. Thus, for thiocarbonyl compounds k_2 is similar to k_3 [NH] in Scheme 3, whereas for carbonyl compounds $k_2 >> k_3$ [NH], which results in linear plots of k_{obs} vs. [NH] for the latter reactions [12,13].

Effect of the solvent

This effect can be observed by comparison of the reactions of SA amines with *O*-ethyl *S*-2,4-dinitrophenyl dithiocarbonate (**8c**) in water and in 44 wt % ethanol–water. For the reactions in both solvents biphasic Brønsted plots were obtained, with the center of the breaks at $pK_a^0 = 9.2$ (in water) [14a] and $pK_a^0 = 9.5$ (in aqueous ethanol) [14b]. The reactions are in agreement with a stepwise mechanism (see Scheme 5). A larger pK_a^0 value for the reactions in the latter solvent means a larger k_{-1}/k_2 ratio for these reactions, according to eq. 4. The value of k_2 should be little affected by the change of solvent in view of the similar polarities of the intermediate $T^{\pm}$ and the transition state for breakdown to products (**16**) [18]. On the other hand, k_{-1} should be larger in aqueous ethanol than in water, since the transition state for $T^{\pm}$ formation (**17**) is less polar than $T^{\pm}$ [18]. This explains the shift to a larger pK_a^0 value for the reactions in the less polar solvent.



Scheme 5 Stepwise mechanism and transition states for breakdown (**16**) and formation (**17**) of $T^{\pm}$ in the SA aminolysis of *O*-ethyl *S*-aryl dithiocarbonates.

A drastic effect of the solvent was observed in the SA aminolysis of *O*-ethyl *S*-2,4,6-trinitrophenyl dithiocarbonate (**8d**) in water and in 44 wt % ethanol–water. For the reaction in water, a biphasic Brønsted plot was obtained, with the center of the curvature, $pK_a^0 = 8.4$ [14a]. In contrast, for this reaction in aqueous ethanol a linear Brønsted plot was found, with slope $\beta = 0.53$ [14c]. This slope is consistent with a concerted mechanism. Furthermore, assuming the same increase in pK_a^0 observed for the dinitro derivative (0.3 pK_a units in going from water to 44 wt % ethanol–water), the predicted pK_a^0 value for a hypothetical stepwise process for the reaction of **8d** in aqueous ethanol would be $pK_a^0 = 8.4 + 0.3 = 8.7$. Since the linear Brønsted plot obtained does not show any break at this pK_a value, the stepwise mechanism for the SA aminolysis of **8d** in aqueous ethanol can be discarded, confirming, therefore, the concerted mechanism.

The above results indicate that for the SA aminolysis of **8d** the change of solvent, from water to 44 wt % ethanol–water, greatly increases k_{-1}, destabilizing the $T^{\pm}$ intermediate. This destabilization oc-

curs in such an extent that either the intermediate does not exist (enforced concerted mechanism), or it does exist, but it is so unstable that the concerted pathway becomes of lower energy compared to that of the stepwise process [17].

EXPERIMENTAL SECTION

Materials

The thiocompounds involved in this work were synthesized according to the procedures reported in the corresponding papers. The series of amines were commercial products.

Kinetic measurements

The reactions described in this work were measured spectrophotometrically, usually following the leaving group. The substrate concentration was $(1–5) \times 10^{-5}$ M and the total amine (free base + its conjugate acid) was always in large excess (at least 10-fold) over the substrate. Pseudo-first-order rate coefficients (k_{obs}) were found throughout.

Product studies

These were usually carried out spectrophotometrically, although occasionally high-performance liquid chromatography (HPLC) was used to analyze the products. The spectrophotometric analyses were made by comparison of the UV–vis spectra at the end of the reactions with those of authentic samples under the same experimental conditions.

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REFERENCES

1. (a) W. P. Jencks. *Prog. Phys. Org. Chem*. **2**, 63 (1964); (b) S. L. Johnson. *Adv. Phys. Org. Chem*. **5**, 237 (1967); (c) A. C. Satterthwait, W. P. Jencks. *J. Am. Chem. Soc*. **96**, 7018 (1974); (d) C. D. Johnson. *Chem. Rev*. **75**, 755 (1975); (e) A. J. Kirby. In *Organic Reaction Mechanisms*, A. C. Knipe, W. E. Watts (Eds.), pp. 29–83, John Wiley, New York (1980); (f) J. P. Guthrie. *Acc. Chem. Res.* **16**, 122 (1983); (g) R. A. McClelland, L. J. Santry. *Acc. Chem. Res.* **16**, 394 (1983); (h) A. Williams. *Adv. Phys. Org. Chem.* **27**, 1 (1992); (i) K. Bowden. *Adv. Phys. Org. Chem.* **28**, 171 (1993); (j) A. Williams. *Chem. Soc. Rev.* **23**, 93 (1994); (k) K. Bowden. *Chem. Soc. Rev.* **24**, 431 (1995); (l) W. P. Jencks. *J. Phys. Org. Chem.* **9**, 337 (1996).
2. (a) H. J. Koh, J. W. Lee, H. W. Lee, I. Lee. *Can. J. Chem.* **76**, 710 (1998); (b) E. A. Castro, M. Aliaga, P. Campodónico, J. G. Santos. *J. Org. Chem*. **67**, 8911 (2002); (c) P. Tundo, L. Rossi, A. Loris. *J. Org. Chem*. **70**, 2219 (2005); (d) E. A. Castro, M. Gazitúa, J. G. Santos. *J. Org. Chem*. **70**, 8088 (2005); (e) I.-H. Um, E. Y. Kim, H.-R. Park, S.-E. Jeon. *J. Org. Chem*. **71**, 2302 (2006); (f) I.-H. Um, Y.-M. Park, M. Fujio, M. Mishima, Y. Tsuno. *J. Org. Chem*. **72**, 4816 (2007); (g) G.-Q. Yi, Y. Zeng, X.-F. Xia, Y. Xue, C.-K. Kim, G.-S. Yan. *Chem. Phys.* **348**, 73 (2008); (h) E. A. Castro, C. Soto, B. Vásquez, J. G. Santos. *Arkivoc* **X**, 151 (2008).
3. (a) E. A. Castro. *Chem. Rev*. **99**, 3505 (1999); (b) E. A. Castro. *J. Sulfur Chem.* **28**, 401 (2007).
4. (a) D. D. Sung, I. S. Han, I. Lee. *J. Sulfur Chem*. **28**, 483 (2007); (b) I.-H. Um, S. Yoon, H.-R. Park, H.-J. Han. *Org. Biomol. Chem*. **6**, 1618 (2008).

5. (a) E. A. Castro, C. Ureta. *J. Org. Chem*. **54**, 2153 (1989); (b) E. A. Castro, C. Ureta. *J. Chem. Soc., Perkin Trans. 2*, 63 (1991).
6. (a) E. A. Castro, F. Ibáñez, M. Salas, J. G. Santos. *J. Org. Chem*. **56**, 4819 (1991); (b) E. A. Castro, M. Cubillos, J. G. Santos. *J. Org. Chem*. **59**, 3572 (1994).
7. (a) E. A. Castro, M. Aliaga, J. G. Santos. *J. Org. Chem*. **69**, 6711 (2004); (b) E. A. Castro, M. Aliaga, J. G. Santos. *J. Org. Chem*. **70**, 2679 (2005).
8. E. A. Castro, M. Aliaga, J. G. Santos. *J. Phys. Org. Chem*. **21**, 271 (2008).
9. (a) E. A. Castro, M. I. Pizarro, J. G. Santos. *J. Org. Chem.* **61**, 5982 (1996); (b) E. A. Castro, L. Leandro, P. Millán, J. G. Santos. *J. Org. Chem*. **64**, 1953 (1999).
10. E. A. Castro, P. Muñoz, J. G. Santos. *J. Org. Chem*. **64**, 8298 (1999).
11. (a) E. A. Castro, R. Aguayo, J. Bessolo, J. G. Santos. *J. Org. Chem*. **70**, 3530 (2005); (b) E. A. Castro, M. Vivanco, R. Aguayo, J. G. Santos. *J. Org. Chem.* **69**, 5399 (2004); (c) E. A. Castro, R. Aguayo, J. Bessolo, J. G. Santos. *J. Phys. Org. Chem*. **19**, 555 (2006).
12. (a) E. A. Castro, L. Leandro, J. G. Santos. *Int. J. Chem. Kinet*. **31**, 839 (1999); (b) M. Cabrera, E. A. Castro, M. Salas, J. G. Santos, P. Sepúlveda. *J. Org. Chem*. **56**, 5324 (1991); (c) E. A. Castro, M. Cabrera, J. G. Santos. *Int. J. Chem. Kinet.* **27**, 49 (1995); (d) E. A. Castro, F. Ibáñez, J. G. Santos, C. Ureta. *J. Chem. Soc., Perkin Trans. 2* 1919 (1991); (e) E. A. Castro, F. Ibañez, J. G. Santos, C. Ureta. *J. Org. Chem*. **57**, 7024 (1992).
13. (a) E. A. Castro, M. Cubillos, J. G. Santos. *J. Org. Chem.* **61**, 3501 (1996); (b) E. A. Castro, J. G. Santos, J. Téllez, M. I. Umaña. *J. Org. Chem*. **62**, 6568 (1997); (c) E. A. Castro, F. Ibañez, J. G. Santos, C. Ureta. *J. Org. Chem.* **58**, 4908 (1993).
14. (a) E. A. Castro, F. Ibañez, M. Salas, J. G. Santos, P. Sepúlveda. *J. Org. Chem.* **58**, 459 (1993); (b) E. A. Castro, G. Muñoz, M. Salas, J. G. Santos. *Int. J. Chem. Kinet*. **27**, 987 (1995); (c) E. A. Castro, M. Cubillos, G. Muñoz, J. G. Santos. *Int. J. Chem. Kinet*. **26**, 571 (1994).
15. M. J. Gresser, W. P. Jencks. *J. Am. Chem. Soc.* **99**, 6963 (1977).
16. R. P. Bell. *The Proton in Chemistry*, p. 159, Methuen, London (1959).
17. (a) W. P. Jencks. *Acc. Chem. Res*. **13**, 161 (1980); (b) W. P. Jencks. *Chem. Soc. Rev.* **10**, 345 (1981); (c) A. Williams. *Acc. Chem. Res.* **22**, 387 (1989).
18. M. J. Gresser, W. P. Jencks. *J. Am. Chem. Soc.* **99**, 6970 (1977).
19. (a) I.-H. Um, J.-S. Min, H.-W. Lee. *Can. J. Chem*. **77**, 659 (1999); (b) I.-H. Um, J.-S. Min, J.-A. Ahn, H.-J. Han. *J. Org. Chem.* **65**, 5659 (2000); (c) I.-H. Um, S.-J. Hwang, M.-H. Baek, E.-J. Park. *J. Org. Chem.* **71**, 9191 (2006).
20. W. P. Jencks, M. Gilchrist. *J. Am. Chem. Soc.* **90**, 2622 (1968).
21. (a) J. M. Sayer, W. P. Jencks. *J. Am. Chem. Soc*. **95**, 5637 (1973); (b) J. P. Fox, W. P. Jencks. *J. Am. Chem. Soc.* **96**, 1436 (1974).
22. C. Hansch, A. Leo, R. W. Taft. *Chem. Rev*. **91**, 165 (1991).
23. P. J. Taylor. *J. Chem. Soc., Perkin Trans*. *2* 1423 (1993).
24. M. Eigen. *Angew. Chem., Int. Ed. Engl*. **3**, 1 (1964).
25. S. V. Hill, S. Thea, A. Williams. *J. Chem. Soc., Perkin Trans*. *2* 437 (1983).