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REVIEW ARTICLE

Kinetics and mechanisms of reactions of thiol, thiono and dithio analogues of carboxylic esters with nucleophiles. An update

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The objective of this review is to update a previous one (published in 1999) on the kinetics and mechanism of the reactions of thioesters, thiocarbonates and analogous thiocarbonyl derivatives with different nucleophiles in solution. There has been abundant literature on this topic since 1999 and it is of interest to chemists and biochemists to have a comprehensive view on the recent developments on the title reactions. Most of these occur through a tetrahedral intermediate, usually in steady state condition, whose breakdown generally leads to the final products (stepwise reactions). Nevertheless, depending on the stability of the tetrahedral intermediate, some reactions take place in one step (concerted mechanism). This review also discusses the factors that affect the stability of this intermediate, which in turn determines the pathway followed by the reaction.

Keywords: Kinetics and mechanism; Thioesters; Thiocarbonates; Thiocarbonyl compounds; Aminolysis; Solvolysis

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1. Introduction

The reactions of thioesters and other thio derivatives of carboxylic esters with nucleophiles are of great interest in chemistry and also in biochemistry since some of these reactions take place in many biological processes.

This review updates a previous one on the kinetics of thio derivatives of carboxylic esters with nucleophiles [1]. This review deals with the kinetic and mechanistic studies in solution of the reactions of nucleophilic reagents with thioesters,† *i.e.*, thiol, thiono and dithio esters (R−CO−SR′, R−CS−OR′ and R−CS−SR′, respectively), thiocarbonates,† *i.e.*, thiol, thiono and dithio carbonates (RO−CO−SR′, RO−CS−OR′ and RO−CS−SR′, respectively),

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†In this Review the terms thioesters, thiocarbonates, thiocarbamates, etc, will be used to include the corresponding thiol, thiono, and dithio derivatives.

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isothiocyanates (R−N=C=S), thioamides and thioureas, thiocarbamates,† *i.e.*, thiol, thiono and dithio carbamates (RS−CO−NR^1R^2, RO−CS−NR^1R^2 and RS−CS−NR^1R^2, respectively), and halogenothioformates,† *i.e.*, the thiol, thiono and dithio derivatives (RS−CO−Hal, RO−CS−Hal and RS−CS−Hal).

The aim of this review is to discuss all the reports that have appeared in the literature since 1999, date of the last review [1], on the kinetics and mechanisms of the reactions of nucleophilic reagents with the thio compounds described above. Whenever possible, these mechanisms will be compared with those of the corresponding all oxygen derivatives in order to evaluate the effect of the replacement by sulphur on these reactions.

Most of the reactions described in this review occur by attack of the nucleophile at the C=O or C=S group of the thiocompound, which, in most cases is its most electrophilic centre. These reactions usually proceed in two steps: formation of an unstable tetrahedral intermediate followed by departure of the nucleofuge (RO^-, RS^- or Hal^-). This mechanism is usually called stepwise.

Some of the reactions reported in this work are believed to take place in a single step. This is the concerted mechanism, where the nucleophilic attack at the electrophilic centre of the substrate is concerted with the leaving group detachment. This mechanism occurs when the tetrahedral intermediate is very unstable, or when it is so unstable that it cannot exist. The latter mechanism is called enforced concerted [2].

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Whether a particular reaction proceeds by a stepwise or a concerted mechanism depends primarily on the stability of the tetrahedral intermediate. One of the aims of this review is to assess the variables that influence the stability of this intermediate, and thereby, the mechanism of the reaction.

Structure-reactivity relationships, notably Hammett and Brønsted plots have been employed in order to discriminate between the stepwise and concerted mechanisms. The former is a graphical representation of log k (where k is the nucleophilic rate constant) *vs.* σ (the substituent constant) and the latter is a plot of log k against pK_a, where K_a is the dissociation constant of the conjugate acid of either the nucleophile or the nucleofuge of the substrate. Most of these plots have been found to be linear, although some are found to be curved downwards. The slopes are usually named as β_{nuc} and β_{lg}, respectively. The magnitudes of these slopes are often very different, according to the mechanism (concerted or stepwise). For the latter mechanism the values of either the Hammett or the Brønsted slopes differ, if the rate-determining step is the formation or breakdown of the tetrahedral intermediate.

As mentioned above, some reactions show Brønsted-type plots curved downwards. Among these, there are some with linear sections at low and high pK_a values, the values of the slopes (β) being usually $\beta = 0.8 - 1.1$ (low pK_a) and $\beta = 0.1 - 0.3$ (high pK_a). These are called biphasic Brønsted plots. The break of these plots has been explained in terms of the formation of a tetrahedral intermediate on the reaction path coupled with a change in the rate-determining step from its formation to its breakdown, as the basicity of the nucleophile or the leaving group changes [1]. A significant part of this review will be devoted to a discussion of these types of reactions.

Another important issue concerns the zwitterionic tetrahedral intermediate that is formed in the nucleophilic substitution reactions of primary and secondary amines with thiocarboxylic derivatives. In these cases the pK_a of the intermediate is important, since it is possible that in some instances there is a proton transfer from the intermediate to an amine molecule or a solvent molecule to give an anionic intermediate. This issue will also be addressed in this review.

The kinetics and the mechanism of the nucleophilic substitution reactions involving isothiocyanates, thioamides, thioureas, thiocarbamates and halogenothioformates will also be dealt with in this review.

2. Thioesters

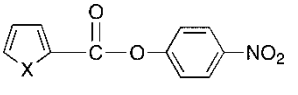
2.1 *Thioalkanoates*

The reactivity of methyl thiolacetate (MeCOSMe) towards hydroxide anion is similar to that of methyl acetate. This was confirmed by quantum mechanical calculations [3], which reproduced the experimental observations [4]. In contrast, methyl thiolacetate was indicated (by quantum mechanics) to be about 100 and 2000-fold more reactive than the corresponding oxy derivative towards ammonia and methyl cyanoacetate anion, respectively [3], again in accordance with the experimental results [5]. The quantum mechanical calculations provided evidence that electron delocalization and especially $p_X \rightarrow \sigma^*(C-Nu)$ interactions play a major role in the reactivity of these compounds in nucleophilic acyl transfer. Especially important is the large role of delocalization energy in stabilizing the transition state for the reaction of methyl acetate with hydroxide, enhancing, therefore, this reactivity up to the level of the generally higher reactivity of thioacetates, compared with acetates, towards other nucleophiles.

Ethyl thiolacetate (MeCOSEt) was found (through theoretical studies) to be more reactive than ethyl acetate towards ammonia [6], in agreement with the experimental results [4]. The theoretical calculations predict stepwise mechanisms, involving water-catalysed proton transfer, for both reactions and indicate that ethyl thiolacetate is more reactive than the oxy derivative in both the addition and elimination steps [6].

The effect of the sulphur atom (relative to oxygen) in both the electrophilic centre and leaving group was studied kinetically by Um, Buncel *et al.* [7]. They found that 4-chlorobenzenethiolate anion ($4-ClPhS^-$) reacts much faster with *S*-4-nitrophenyl thioacetate and 4-nitrophenyl thionobenzoate than with their corresponding oxy analogues. In contrast, hydroxide anion is less reactive towards the thiocompounds. Also, 4-chlorophenoxide anion ($4-ClPhO^-$) is 4 to 6-fold more reactive towards these thioesters compared with the corresponding oxyesters [7]. The α-effects shown by HOO^- and related anions are strongly dependent on the nature of the electrophilic centre of the substrates [7].

The reactions of 4-nitrophenyl 2-thiophenecarboxylate (**1a**), its oxy analogue (**1b**) and the corresponding benzoate (**1c**) with secondary alicyclic (SA) amines have been subjected to a kinetic study in water-20 mol DMSO [8]. The order of reactivities found is **1c** < **1a** < **1b**. The Brønsted-type plots obtained are linear with slopes $\beta_{nuc} = 0.92$, 0.84 and 0.85 for the aminolysis of **1a**, **1b** and **1c**, respectively. The reactions of piperidine with a series of aryl 2-thiophenecarboxylates give a linear Hammett plot (using the σ^- scale) with slope $\rho^- = 3.1$. The magnitude of the slope of these plots suggests that these reactions are stepwise, through a zwitterionic tetrahedral intermediate, which breaks down to products in the rate-limiting step [8].



1a (X = S)
1b (X = O)
1c (X = CH=CH)

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Lee *et al.* have extensively investigated the kinetics of the aminolysis of thioesters in acetonitrile. They found that the reactions of Z-substituted *S*-aryl thioacetates with X-substituted benzylamines in MeCN show linear Brønsted plots with slopes β_{nuc}1.3–1.6 and $\beta_{lg} - 2.41$ to -2.4 [9]. The Hammett cross-interaction constant [10] is large and positive ($\rho_{XZ} = 0.9$). These results are in agreement with two-step reactions, with rate-limiting breakdown of the tetrahedral intermediate [9]. Very similar results were obtained for the reactions of *S*-aryl phenylacetates [11], *S*-aryl methylacetates [12], *S*-aryl dimethylacetates and trimethylacetates [13] and *S*-aryl cyclopropanecarboxylates [14] with the same amines in the same solvent.

It has been found that the reactions of *S*-aryl acetates derivatives (R−(C=O)−S−Ar, with R=Me, Et, *i*-Pr, *t*-Bu and CH_2Ph) with benzylamines in MeCN are not well correlated with the Taft's polar (σ^*) and/or steric constant (E_S) [15]. This is due to an abnormal enhancement of the rate constant for the thioester with R = Et, which also shows the largest cross-interaction coefficient [15]. The abnormal behaviour for R = Et was explained by assuming that in the zwitterionic tetrahedral intermediate ($T^{\pm}$) the vicinal $\sigma_{C-C} - \sigma^*_{C-S}$ delocalization is the strongest with an optimum antiperiplanar position and a narrow energy gap ($\Delta\varepsilon = \varepsilon_{\sigma*} - \varepsilon_{\sigma}$). Due to these interactions, both the equilibrium constant for $T^{\pm}$ formation and the rate constant for its breakdown are enhanced, compared with those for the other substrates (R ≠ Et). These results and others indicate that for all the reactions studied the rate-determining step is the breakdown of $T^{\pm}$ towards products [15].

The reactions of *S*-aryl phenyldithioacetates ($PhCH_2$(C=S)−S−Ar) with benzylamines in MeCN at −25 °C show large Brønsted and Hammett slopes for both the nucleophile (X) and leaving group (Z) and a positive and large cross-interaction constant (ρ_{XZ} = 2.05) [16]. This, consistent with the reactivity–selectivity principle (RSP), suggests that the breakdown of $T^{\pm}$ to products is rate-limiting for these reactions [16]. Similar kinetic results and conclusions were reported for the reactions of *S*-aryl propanedithioates (Et-(C=S)−S−Ar) with the same amines and solvent, at −35 °C [17]. The faster rates observed for dithioesters relative to thioesters are also in agreement with the proposed mechanism [17].

The reactions of *S*-aryl dithioesters (R−(C=S)−S−Ph−Z, with R = Et and $PhCH_2$) with X-substituted anilines in MeCN at 45 °C exhibit large Brønsted β_X and β_Z values, as well as large Hammett ρ_X and ρ_Z values, together with ρ_{XZ} = 1.4–1.9 [18]. The dithioester with R = Et shows a faster rate, which was explained by the stronger electron donation of Et in the intermediate $T^{\pm}$ and a larger steric crowding in $T^{\pm}$. The much faster rates observed for thiocarbonyl compared with carbonyl esters was ascribed to the lower $\pi^*_{C=S}$ and π^*_{C-lg} levels for the former compounds relative to the corresponding levels in the carbonyl esters [18]. This could also be explained by the relatively softer character of anilines, which prefer to bind to a relatively softer thiocarbonyl group compared with carbonyl.

The reactions of X-substituted pyridines with Z-substituted-*S*-aryl dithioacetates (**2a**) and *S*-aryl furan-2-carbodithioates (**2b**) in MeCN at 60 °C show biphasic Brønsted plots with limiting slopes $\beta_X = 0.9$ and 0.4 for **2a** [19] and β_X = 0.7–0.8 and 0.4 for **2b** [20]. All the Brønsted plots are centred at $pK^0_a = 5.2$. These results were attributed to stepwise mechanisms, through the intermediate $T^{\pm}$, and a change in the rate-limiting step, from breakdown of $T^{\pm}$ to its formation as the pyridine becomes more basic [1, 20, 21]. A clear-cut change in the cross-interaction constants, from $\rho_{XZ} = +0.86$ (rate-limiting $T^{\pm}$ breakdown) to $\rho_{XZ} = -0.11$ (rate-limiting $T^{\pm}$ formation) for **2a** and $\rho_{XZ} = +1.34$ (rate-limiting $T^{\pm}$ breakdown) to $\rho_{XZ} = -0.15$ (rate-limiting $T^{\pm}$ formation) for **2b** supports the proposed mechanisms [19, 20]. Nevertheless, it is surprising that pK^0_a remains constant with the variation of the

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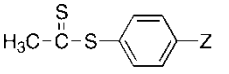
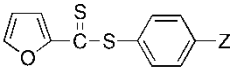
leaving group–for most aminolysis reactions pK_a^0 increases as the basicity of the leaving group increases [1].



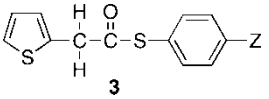
2a



2b

The reactions of Z-*S*-aryl 2-thiopheneacetates (**3**) with X-benzylamines in MeCN at 45 °C are governed by stepwise mechanisms with rate-limiting breakdown of the zwitterionic tetrahedral intermediate $T^{\pm}$ [22]. This conclusion is based on (i) the large magnitude of ρ_X and ρ_Z, (ii) the positive and large value of the cross-interaction coefficient ρ_{XZ} and (iii) agreement with the RSP [22].

On the other hand, the pyridinolyses of *S*-aryl thiophene-2-carbodithioates (**4**) in MeCN at 60 °C show curved biphasic Brønsted plots centred at $pK_a^0 = 5.2$, with slopes $\beta_X = 0.8$–0.9 (low pK_a) and $\beta_X \approx 0.3$ (high pK_a) [23]. This is in line with a change in the rate-determining step with pyridine basicity [1, 21]. This is also confirmed by the different signs of the cross-interaction coefficients: $\rho_{XZ} = +0.92$ at low pK_a and $\rho_{XZ} = -0.23$ at high pK_a. The fact that the pK_a^0 value found in this work is the same as those obtained in the pyridinolysis of similar compounds with other R groups (R = Me and 2-furyl) suggests that R has little influence on the position of the Brønsted break [23]. Very similar results were found for the pyridinolysis of aryl dithiomethylacetates (Et−CS−S−Ar) in the same solvent and temperature [24].



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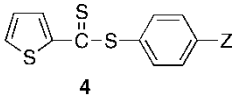

4

The ammonolysis of *S*-aryl thioacetates (Me−CO−S−Ar) in water at 18 °C shows linear Brønsted and Hammett plots for the leaving group, with $\beta_{lg} = -0.34$ and $\rho_{lg} = 0.74$, respectively [25]. The magnitude of these slopes, together with the kinetic law and product analysis suggest that these reactions are stepwise, where formation of the intermediate $T^{\pm}$ is the rate-determining step. These thiolesters are more reactive than their oxy counterparts toward ammonia and this was explained by the fact that PhO is more electron donating than PhS, rendering the carbonyl carbon of phenyl acetates less prone to nucleophilic attack than that of the corresponding phenyl thiolacetates [25].

The reactions of imidazole with these thiolacetates also proceed through the intermediate $T^{\pm}$, but a general-acid catalysed path leading to a cationic intermediate (T^+) is also important [26]. This is in contrast to the reactions of this amine with aryl acetates, where $T^{\pm}$ can be base-catalysed, to give the anionic intermediate T^- and also acid-catalysed to yield T^+ [27]. These results can be explained in terms of the stability of the intermediate $T^{\pm}$, which in turn depends on the rate constants for amine (k_{-1}) and leaving group (k_2) departure: the lower these rate constants the more stable the intermediate and there will be more room for catalysis (either basic or acid) [1].

2.2 *Thiobenzoates*

The alkaline hydrolysis of *S*-aryl 4′-hydroxythiobenzoates (**5**) has been subjected to a kinetic investigation in 40% dioxane/60% water at 25 °C [28]. The general mechanism is depicted in scheme 1. The reaction of thiobenzoate **5a** follows the E1cB pathway, through the p-oxoketene intermediate, as indicated by the much greater apparent second-order rate constant compared with that for the corresponding 4′-methoxythiobenzoate. This is also supported by the fact

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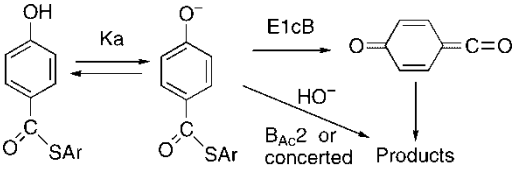
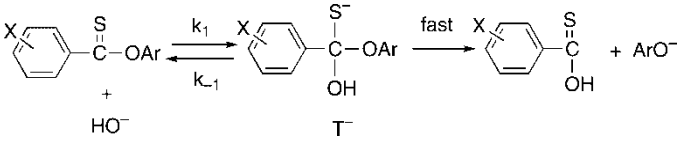
that the activation entropy for the former reaction is +18.6 eu, whereas that for the methoxy derivative is −27.4 eu, indicating a $B_{Ac}2$ mechanism for the latter. In contrast, the alkaline hydrolysis of thiobenzoates **5b–f** are driven by a concerted mechanism, as shown by (i) the good correlation obtained in the Hammett plot for σ^- (instead of σ), (ii) the large magnitude of the Brønsted slope ($\beta_{lg} = -0.8$), and (iii) the fact that ArS^- leaves the tetrahedral intermediate faster than HO^-, which rules out a $B_{Ac}2$ process with rate-limiting breakdown of the intermediate, suggesting, therefore, a concerted process [28].



5a (Ar = 2,4-dinitrophenyl)
5b (Ar = 2-nitro-4-(CF_3)phenyl)
5c (Ar = 4-nitrophenyl)
5d (Ar = 4-cyanophenyl)
5e (Ar = phenyl)
5f (Ar = pentachlorophenyl)

SCHEME 1

The alkaline hydrolysis of 4-nitrophenyl X-substituted thionobenzoates (X−Ph−CS−$OPhNO_2$) in 20 mol% DMSO-water exhibits a Hammett plot with downward curvature [29]. This was attributed to the stabilization of the ground state through resonance interaction between the electron-donating substituent X and the thiocarbonyl centre, and not to a change in the rate-limiting step. The Brønsted plot for the alkaline hydrolysis of aryl thionobenzoates (Ph−CS−OAr) is linear with slope $\beta_{lg} = -0.35$. All these data are consistent with a stepwise mechanism for all these reactions, with rate-determining formation of the anionic tetrahedral intermediate (T^-), as shown in scheme 2 [29].



SCHEME 2

The reactions of primary amines with 4-nitrophenyl thionobenzoate in 20 mol% DMSO-water show linear plots of k_{obs} *vs.* [amine], where k_{obs} is the pseudo-first-order rate constant. The Brønsted plot for k_N, where k_N is the nucleophilic second-order rate constant, is biphasic, with limiting slopes $\beta_1 = 0.2$ (high pK_a) and $\beta_2 = 0.8$ (low pK_a) and a break value of $pK_a^0 = 8.8$ [30]. These results were explained through a zwitterionic tetrahedral intermediate ($T^{\pm}$) and a change in rate-limiting step, as shown in scheme 3 [21, 30]. Step k_1 is rate-determining for very basic amines ($k_{-1} \ll k_2$), whereas the second step is rate-limiting for weakly basic amines ($k_{-1} \gg k_2$). At the centre of the Brønsted curvature (amine of $pK_a = pK_a^0$), $k_{-1} = k_2$ [21, 30].

In contrast, the reactions of the above thionobenzoate with SA amines in the same medium show plots of k_{obs} *vs.* [amine], which are nonlinear upwards, suggesting the presence of two tetrahedral intermediates, as shown in scheme 4 [30]. This type of mechanism has been previously proposed in the same aminolysis of aryl dithioacetates and phenyl thionocarbonate

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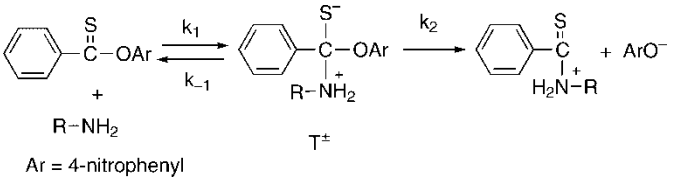
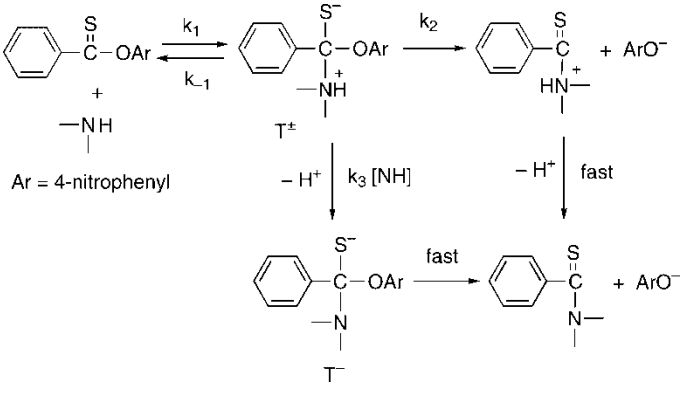


SCHEME 3

in water [31]. Through fitting of an equation derived from scheme 4 (applying the steady-state treatment to both intermediates) to the experimental points the values of k_1 and k_1 were obtained [30]. It was concluded that k_{-1} for secondary amines is greater than that for isobasic primary amines and that both k_2 and k_3 are independent of the amine. According to the authors, a smaller k_2/k_{-1} value for the former amines would make possible the observation of base catalysis [30]. This conclusion seems unreasonable since, for this type of base catalysis to occur, two conditions are required: (i) $k_{-1} \gg k_2 + k_3$ [RNH_2], *i.e.*, second step rate-determining, and (ii) k_2 smaller or equal to k_3 [RNH_2].



SCHEME 4

Scheme 4 also holds for the above reactions in acetonitrile [32]. It was found that k_1 is smaller and k_{-1} larger in MeCN compared with aqueous DMSO, whereas k_2 and k_3 would not vary significantly with the change in solvent. This means that the ratios k_2/k_{-1} and k_3/k_{-1} are smaller in MeCN, but the latter ratio diminishes more than the former in going from aqueous DMSO to MeCN [32].

The pyridinolysis of 2,4-dinitrophenyl thionobenzoate in aqueous 20 mol% DMSO shows a biphasic Brønsted plot with $\beta_1 = 0.26$, $\beta_2 = 1.1$ and $pK_a^0 = 7.5$ [33]. The change of the electrophilic centre from CS to CO results in another biphasic plot with $pK_a^0 = 9.5$ [33]. These results are in line with the stepwise mechanisms and a change in the rate-limiting steps for both reactions series. The 'earlier' Brønsted break found for the thionoester was explained by the larger k_2/k_{-1} ratio exhibited by the reaction of this ester compared with that for the oxoester. It is known that the pK_a^0 value increases as the k_{-1}/k_2 ratio increases [1]. The thionoester is more reactive towards pyridines than the oxo analogue, except for the most basic amine [33].

The reactions of *S*-(Z-aryl) 4-nitrothiobenzoates with X-pyridines in acetonitrile have been subjected to a kinetic study [34]. A curved biphasic Brønsted plot was obtained, with the break at $pK_a^0 = 4.2$, which was explained by a stepwise mechanism and a change in rate-determining step. This is supported by the change in the cross-interaction constant from $\rho_{XZ} = 1.41$, for weakly basic amines, to $\rho_{XZ} = -0.32$, for those highly basic [34].

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The pyridinolysis of aryl dithiobenzoates in acetonitrile also shows a biphasic Brønsted plot, with limiting slopes $\beta_1 = 0.2$ and $\beta_2 \approx 0.8$, with a pK_a^0 value of 5.2 [35]. These results, together with a radical change of the cross-interaction constant from $\rho_{XZ} = 1.5$ (less basic amines) to $\rho_{XZ} = -0.2$ (more basic amines) indicate that these reactions are stepwise. The pyridinolysis of these dithiobenzoates are slower than those of the corresponding dithioacetates in the same solvent and temperature [19, 35], which was explained by the hyperconjugative charge transfer effect of the Me group towards the $\pi*$ orbital of the C=S group [35]. This could also be explained by a greater steric hindrance of phenyl (in the benzoates) compared with methyl (in the acetates). The Brønsted breakpoint ($pK_a^0 = 5.2$) is similar to those found in the same aminolysis of the corresponding dithioesters with acyl substituent R = Me and 2-furyl, which suggests a negligible effect of the acyl substituent on the pK_a^0 value [35].

The reactions of *S*-4-nitrophenyl 4-X-substituted thiobenzoates (X = H, Cl) with SA amines in aqueous ethanol show biphasic Brønsted plots, with $\beta_1 = 0.27$ and 0.10, respectively, $\beta_2 = 0.86$ and 0.84 and $pK_a^0 = 10.0$ and 10.4, respectively [36]. The same aminolysis of the thiobenzoate with $X = NO_2$ exhibits a linear Brønsted plot with slope $\beta_2 = 0.81$, namely, $pK_a^0 > 10.8$ [36]. The reactions of SA amines with S-4-nitrophenyl 4-methylthiobenzoate (X = Me) also show a biphasic Brønsted plot, with $pK_a^0 = 9.7$ [37]. All these Brønsted plots are shown in figures 1 and 2. These are statistically corrected with $p = 2$ for the conjugate acids of the SA amines (except piperazinium dication with $p = 4$) and $q = 2$ for piperazine [38]. The parameter p represents the number of equivalent protons on the conjugate acid of the amine and the parameter q represents the number of equivalent basic sites on the amine [38]. The lines were calculated by a semi-empirical equation (equation (1), based on the existence of a zwitterionic tetrahedral intermediate ($T^{\pm}$) on the reaction path [21]. As seen in figures 1 and 2 the experimental results are in accordance with the stepwise mechanisms shown in scheme 5. For the substrates with X = Me, H and Cl there is a change in the rate-limiting step, from that for k_2 to that for k_1, as amine basicity increases, whereas for the thiobenzoate with

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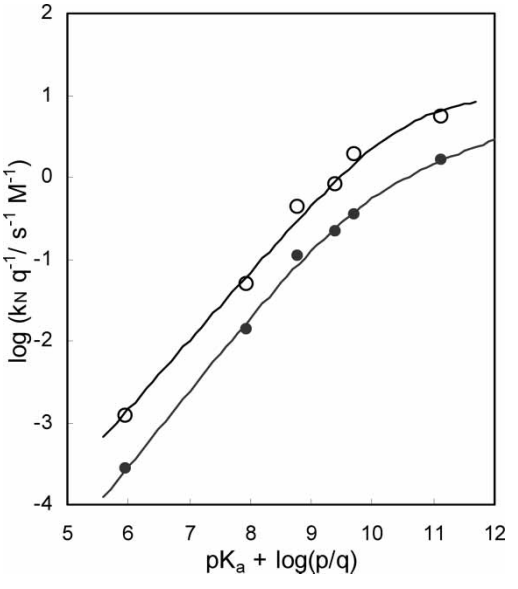

Figure 1. Brønsted plots (statistically corrected) for the reactions of SA amines with *S*-4-nitrophenyl 4-X-substituted thiobenzoates with X = Me (•) and X = Cl (○) in 44 wt% ethanol–water, at 25.0 °C, ionic strength 0.2 M. The lines were calculated using equation (1).
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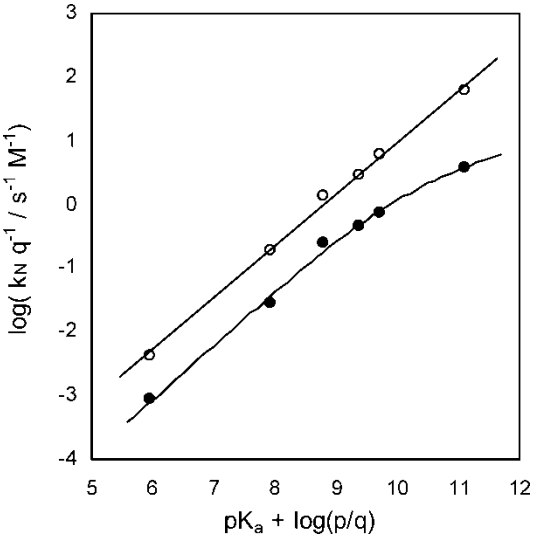

Figure 2. Brønsted plots (statistically corrected) for the reactions of SA amines with *S*-4-nitrophenyl 4-X-substituted thiobenzoates with X = H (•) and X = NO_2 (○) in 44 wt% ethanol–water, at 25.0 °C, ionic strength 0.2 M. The lines were calculated using equation (1).
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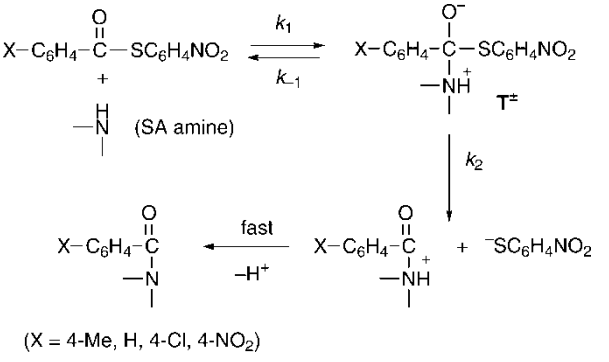
X = NO_2 expulsion of the leaving group from $T^{\pm}$ (k_2 step) is rate determining. The increase in the pK_a^0 value with the electron withdrawal from X is attributed to increasing nucleofugality of the amine from $T^{\pm}$, which means increasing k_{-1}/k_2 ratio [36, 37]. According to equation (2), a larger k_{-1}/k_2 ratio means a larger pK_a^0 value [38b].

$$\log\left(\frac{k_N}{k_N^0}\right) = \beta_2(pK_a - pK_a^0) - \log\left(\frac{1+\alpha}{2}\right)$$

$$\log\alpha = (\beta_2 - \beta_1)(pK_a - pK_a^0) \quad (1)$$

$$\log\left(\frac{k_{-1}}{k_2}\right) = (\beta_2 - \beta_1)(pK_a^0 - pK_a) \quad (2)$$

The pyridinolysis of three of the above thiobenzoates in the same solvent was subjected to a kinetic analysis [39]. The substrate with X = H shows a biphasic Brønsted plot, with $\beta_1 = 0.20$, $\beta_2 = 0.94$ and $pK_a^0 = 9.7$. The corresponding plots for X = Cl and NO_2 are linear with



(X = 4-Me, H, 4-Cl, 4-NO_2)

SCHEME 5

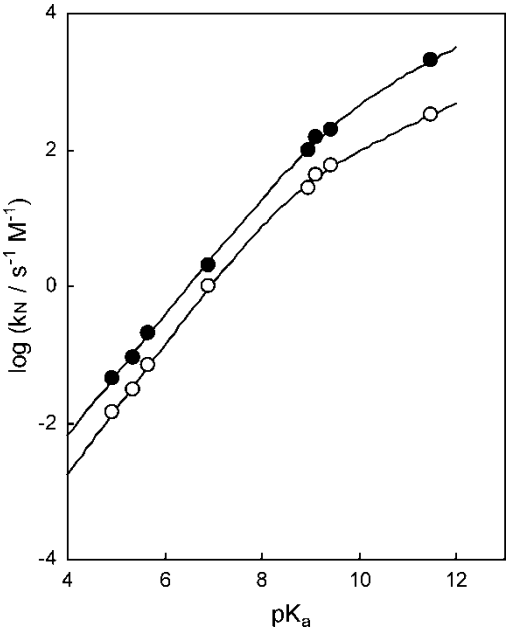


Figure 3. Brønsted plots for the pyridinolysis of *S*-2,4-dinitrophenyl 4-X-substituted thiobenzoates with X = Cl (•) and X = Me (○) in 44 wt% ethanol–water, at 25.0 °C, ionic strength 0.2 M. The lines were calculated using equation (1). Reprinted with permission from [40]. Copyright 2003 *American Chemical Society*.

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slopes $\beta_2 = 0.94$ and 1.0, respectively [39]. Nevertheless, inclusion of a very basic pyridine in a later report [37] allowed quantification of the Brønsted breaks – $pK_a^0 = 10.1$ and 10.7 for X = Cl and NO_2, respectively. The pyridinolysis of *S*-4-nitrophenyl 4-methylthiobenzoate (X = Me) shows a biphasic Brønsted plot, with $\beta_1 = 0.27$, $\beta_2 = 1.05$, and $pK_a^0 = 9.4$ [37]. All these kinetic data were explained by stepwise mechanisms, through the intermediate $T^{\pm}$, and a change in the rate-limiting step [37]. These results show a clear increase of the pK_a^0 values as the substituent X in the acyl group becomes more electron withdrawing, as observed for the SA aminolysis of these substrates [36, 37]. The lower pK_a^0 values for the reactions of 4-nitrophenyl *X*-thiobenzoates with pyridines compared with those with SA amines was attributed to the lower nucleofugality from $T^{\pm}$ (smaller k_{-1}) of pyridines relative to isobasic SA amines [37].

The pyridinolyses of *S*-(2,4-dinitrophenyl) 4-X-substituted thiobenzoates (X = Me, H, Cl and NO_2) show biphasic Brønsted plots (figures 3 and 4), with limiting slopes compatible with stepwise processes and a change in the rate-limiting step (scheme 6). The Brønsted lines were calculated through equation (1), the resulting values of pK_a^0 being 8.5, 8.9, 9.5 and 9.9 for X = Me, H, Cl and NO_2, respectively [40]. The sequence of the pK_a^0 values with the electron-withdrawing ability of X is the same as that found for the 4-nitrophenyl X-thiobenzoates [36, 37, 39]. The fact that these pK_a^0 values are smaller than those for the pyridinolysis of the corresponding *S*-4-nitrophenyl analogues is in accordance with the greater nucleofugality of 2,4-dinitrobenzenethiolate from $T^{\pm}$ (larger k_2) compared with 4-nitrobenzenethiolate. This results in a smaller k_{-1}/k_2 ratio for the former, and therefore, a lower pK_a^0, according to equation (2). The smaller pK_a^0 value for the pyridinolysis of *S*-(2,4-dinitrophenyl) thiobenzoate ($pK_a^0 = 8.9$) relative to that for the same aminolysis of the corresponding oxy derivative in the same solvent ($pK_a^0 = 9.5$) [41], was explained by the greater leaving ability of 2,4-dinitrobenzenethiolate compared with 2,4-dinitrophenoxide [40]. The larger pK_a^0 value for the pyridinolysis of the former substrate ($pK_a^0 = 8.9$) compared with that found for the same

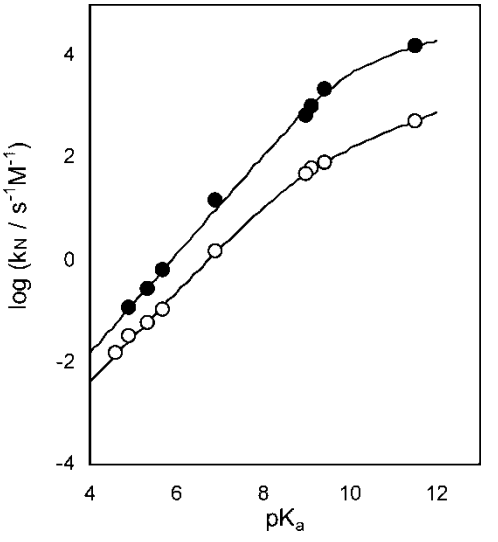

Figure 4. Brønsted plots for the pyridinolysis of *S*-2,4-dinitrophenyl 4-X-substituted thiobenzoates with X = NO_2 (•) and X = H (○) in 44 wt% ethanol–water, at 25.0 °C, ionic strength 0.2 M. The lines were calculated using equation (1). Reprinted with permission from [40]. Copyright 2003 *American Chemical Society*.

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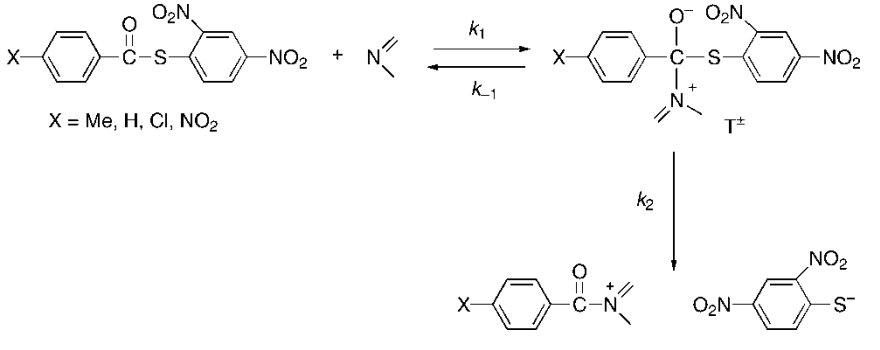
aminolysis of the corresponding thiolacetate in water ($pK_a^0 = 6.6$) [42], was attributed to the stronger electron-withdrawing ability of phenyl than methyl from the intermediate $T^{\pm}$, which means a larger k_{-1}/k_2 ratio for the thiolbenzoate and, therefore, a larger pK_a^0 value, in accordance with equation (2).



SCHEME 6

The reactions of the above four 2,4-dinitrophenyl thiolbenzoates with SA amines in the same solvent show slightly curved Brønsted plots with limiting slopes $\beta = 0.1$–0.44 (at high pK_a) and $\beta = 0.7$–0.8 (at low pK_a) [43]. These data and the fact that the difference in the limiting slopes are much smaller than those usually found in stepwise reactions, suggest that these reactions are driven by concerted mechanisms. Other proofs that these reactions are concerted are: (i) No clear dependence of the pK_a^0 value on the X substituent was found (the pK_a^0 values were constant within the experimental errors); (ii) The concerted reactions of primary amines with substituted benzoyl fluorides in water also show slight Brønsted curves and a constant pK_a position at the centre of curvature [44]; (iii) The concerted reactions of SA

amines with bis(4-nitrophenyl) thionocarbonate and 2,4-dinitrophenyl 4-methyl carbonate also exhibit small Brønsted curvatures [45]; (iv) The reactions of SA amines with 2,4-dinitrophenyl 4-cyanobenzoate in aqueous ethanol are concerted [46]. Therefore, it is more likely that the same aminolysis of the *S*-(2,4-dinitrophenyl) X-thiolbenzoates in the same solvent be concerted in view of the superior nucleofugality of 2,4-dinitrobenzenethiolate compared with 2,4-dinitrophenoxide, which should further destabilize the hypothetical tetrahedral intermediate in the reactions of thiolbenzoates. The fact that the reactions of *S*-(2,4-dinitrophenyl) X-thiolbenzoates with SA amines are concerted, in contrast to those with pyridines in the same solvent, which are stepwise, was explained by the greater leaving ability from the intermediate $T^{\pm}$ of SA amines, relative to isobasic pyridines [1, 42, 43]. This should cause a destabilization of the hypothetical $T^{\pm}$ with SA amines, forcing a change in mechanism.

Um *et al.* have claimed that the reactions of SA amines with 2,4-dinitrophenyl 4-*X*-benzoates in 20 mol% DMSO-water are stepwise [47a]. Nevertheless, for these reactions they found slightly curved Brønsted plots, with no dependence of pK_a^0 on the electronic nature of the X substituent [47a]. Therefore, it is likely that these reactions are concerted, as found for other concerted aminolyses, showing slightly curved Brønsted plots with a constant pK_a^0 value [43–45]. On the other hand, these authors found that the pyridinolyses of 4-nitrophenyl X-thionobenzoates in the above solvent mixture are stepwise, with $pK_a^0 = 9.3$, regardless of the substituent X in the non-leaving group [47b].

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3. Thiocarbonates

The hydrolysis and aminolysis of S-substituted *O*-ethyl dithiocarbonates (RS−CS−OEt) in 20% aqueous methanol have been subjected to a kinetic investigation [48]. For the neutral and hydroxide-catalysed hydrolyses the Brønsted slopes for the leaving thio groups are $\beta_{lg} = -0.1$ and -0.34, respectively, whereas for the aminolysis, β_{lg} ca. -0.12. These results were interpreted in terms of a rate-limiting formation of a tetrahedral intermediate for neutral hydrolysis and aminolysis, and a rate-determining expulsion of RS^- for alkaline hydrolysis [48].

The reactions of benzylamines with *S*-aryl *O*-ethyl thiocarbonates (ArS−CO−OEt) in acetonitrile show linear Brønsted plots with slopes $\beta_{nuc} = 0.6$–0.8 and $\beta_{lg} = -0.5$ to -0.7 [49]. These data, together with a negative cross-interaction constant, were explained by a concerted mechanism. This mechanism is enforced by the destabilization of the putative tetrahedral intermediate due to the strong electron-releasing power of EtO and benzylamines, the high nucleofugality of ArS^- and the aprotic solvent used [49].

The reactions of benzylamines with *S*-aryl *O*-ethyl dithiocarbonates (ArS−CS−OEt) in acetonitrile are also governed by concerted mechanisms [50]. This was concluded on the basis of the Brønsted slopes: $\beta_X = \beta_{nuc} = 0.67$–$0.77$ and $\beta_Z = \beta_{lg} = -0.20$ to -0.40 and the negative Hammett cross-interaction constant: $\rho_{XZ} = -0.24$. Violation of the RSP was also claimed to support the concerted process [50].

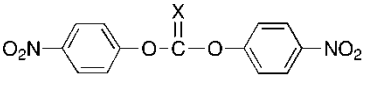
In contrast to the above results, the reactions of benzylamines with *S*-aryl *O*-methyl thiocarbonates (ArS−CO−OMe) in methanol were reported to be stepwise, with rate- determining breakdown of the zwitterionic tetrahedral intermediate [51]. This proposal is based on (i) the large values of the Hammett and Brønsted slopes for the nucleophile ($\rho_X = -1.3$ to -1.8 and $\beta_X = 1.7$–2.3) and the leaving group ($\rho_Z = 2.0$–2.6 and $\beta_Z = -0.8$ to -1.0), (ii) the normal kinetic isotope effect for deuterated amines ($k_H/k_D = 1.1$–1.3), (iii) the positive sign of the cross-interaction constant ($\rho_{XZ} = +0.5$) and (iv) adherence to the RSP [51]. The different mechanism of these reactions (stepwise) compared with the same reactions (except for OMe

instead of OEt as the non-leaving group) in acetonitrile [49] (concerted) can be explained by the destabilizing effect of the latter solvent on the intermediate $T^{\pm}$, relative to methanol.

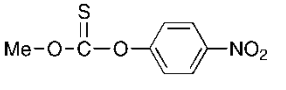
The reactions of primary amines with 4-nitrophenyl *O*-phenyl thionocarbonate (4-NO_2PhO−CS−OPh) and its carbonate analogue in 20 mol% DMSO-water show biphasic Brønsted plots with $\beta_1 = 0.11$, $\beta_2 = 0.68$ and $pK_a^0 = 8.5$ for the thiono compound and $\beta_1 = 0.27$, $\beta_2 = 0.99$ and $pK_a^0 = 9.5$ for the carbonate [52]. These results were attributed to stepwise mechanism. The microscopic rate constant for amine attack (k_1) is larger for the carbonate than its thiono analogue, which was explained by Pearsons' HSAB principle. Nevertheless, the values of the k_2/k_{-1} ratios are larger for the thionocarbonate [52]. This explains the lower pK_a^0 value found for the thiono compound, in accordance with equation (2). A decrease in the pK_a^0 value by the change of CO to CS as the electrophilic centre was also found in the aminolysis of 4-nitrophenyl thionobenzoate and its oxo analogue [53].

An empirical scale of nucleophilicity for substituted pyridines (eight pyridines) has been tested for the pyridinolysis of *S*-methyl 2,4-dinitrophenyl thiocarbonate [54]. A good relationship was found between the electrostatic potential index for the pyridines and the intermolecular force constants, obtained at the B3LYP/6 − 31 + G(d, p) level of theory. A plot of log k_N against the electrostatic potential index (taken as a nucleophilicity index), where k_N is the second-order rate constant for the pyridinolysis of this thiocarbonate, shows an excellent correlation, with $R = 0.998$ [54].

The phenolysis of bis(4-nitrophenyl) thionocarbonate (BNPTOC) and methyl 4-nitrophenyl thionocarbonate (MNPTOC) in water show curved biphasic Brønsted plots in agreement with stepwise mechanisms through an anionic tetrahedral intermediate (T^-) [55]. For both reactions the Brønsted break corresponds to $pK_a^0 = 7.1$, which is the pK_a of 4-nitrophenol. Instead, the phenolysis of bis(4-nitrophenyl) carbonate (BNPC) in water exhibits a linear Brønsted plot with slope $\beta = 0.66$, consistent with a concerted process [55]. From these results, it was concluded that substitution of S^- in the intermediate T^- by O^- destabilizes this intermediate to the point of changing the mechanism from stepwise to concerted. This destabilization was explained by the greater ability of O^- (than S^-) in the intermediate to form a double bond and expel a nucleofuge, due to the stronger π-bonding energy of the carbonyl group relative to thiocarbonyl [55, 56]. Comparison between these reactions and others allows the following conclusions: (i) the change of MeO by 4-nitrophenoxy in T^- increases the rate and equilibrium constants for the formation of T^- and also the rate constant for expulsion of 4-nitrophenoxide from T^-; (ii) substitution of an amino group in the tetrahedral intermediate by ArO destabilizes the intermediate; (iii) SA amines are more reactive towards MNPTOC than isobasic phenoxide anions [55].



BNPTOC (X = S)
BNPC (X = OI)



MNPTOC

The phenolyses of methyl 2,4-dinitrophenyl) thionocarbonate [MeO−CS−$OC_6H_3(NO_2)_2$] and phenyl 2,4-dinitrophenyl thionocarbonate [PhO−CS−$OC_6H_3(NO_2)_2$] in water show linear Brønsted plots with slopes $\beta_{nuc} = 0.27$ and 0.28, respectively, in agreement with stepwise mechanisms with rate-determining formation of the tetrahedral intermediate (T^-) [57]. The phenolysis of *O*-ethyl 2,4-dinitrophenyl dithiocarbonate [EtO−CS−$SC_6H_3(NO_2)_2$] in the same solvent yields a linear Brønsted plot with slope $\beta_{nuc} = 0.67$, consistent with a concerted mechanism [57]. The main conclusions from these data are: (i) the replacement of 2,4-dinitrophenoxy in T^- by its thio analogue destabilizes this intermediate by increasing the

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nucleofugality and (ii) substitution of MeO by PhO as the non-leaving group does not change the rate-determining step [57].

The reactions of *O*-ethyl 2,4-dinitrophenyl dithiocarbonate (EDNPDTC), *O*-ethyl 2,4,6-trinitrophenyl dithiocarbonate (ETNPDTC) and methyl 2,4-dinitrophenyl) thionocarbonate (MDNPTOC) with benzenethiolate anions in water show linear Brønsted plots with slopes $\beta_{nuc} = 0.66$ 0.66 and 0.58, respectively, in accordance with concerted mechanism [58]. This is confirmed by the fact that for the benzenethiolysis of MDNPTOC and EDNPDTC no Brønsted breaks were found at pK_a 4.1 and 3.4, respectively (the pK_a values of 2,4-dinitrophenol and 2,4-dinitrobenzenethiol, respectively). Benzenethiolates are more reactive than isobasic phenoxides towards EDNPDTC, which was explained by the softer character of the thionucleophiles [58]. The change in mechanism, from stepwise for the phenolysis of MDNPTOC, to concerted for its benzenethiolysis, was attributed to the nucleofugality of 2,4-dinitrobenzenethiolate being greater than that of 2,4-dinitrophenoxide in the putative tetrahedral intermediate. MDNPTOC and EDNPDTC are more reactive towards benzenethiolates than their corresponding carbonate and thiolcarbonate, respectively, in agreement with the softer character of the thiocarbonyl group compared with carbonyl [58].

The reactions of phenyl 4-nitrophenyl thionocarbonate with SA amines in water show a linear Brønsted plot with slope $\beta_{nuc} = 0.25$, indicating a stepwise mechanism, through a zwitterionic tetrahedral intermediate ($T^{\pm}$), with rate-limiting formation of $T^{\pm}$ [59]. The reactions of methyl 4-nitrophenyl thionocarbonate with SA amines in the same solvent exhibit curved upward plots of k_{obs} *vs*. [amine], compatible with the mechanism shown in scheme 7 (R = Me). Steady-state treatment for both tetrahedral intermediates in scheme 7 yields equation (3), where NH represents an SA amine and k_3 is the rate constant for deprotonation of $T^{\pm}$ by a SA amine to give T^- [59]. By estimation of the pK_a of the intermediate $T^{\pm}$ in scheme 7 (R = Me), it was deduced that the proton transfer from $T^{\pm}$ to the amine is thermodynamically favourable and a value for k_3 of $10^{10}\ s^{-1}\ M^{-1}$ was suggested. By fitting of equation (3) to the experimental k_{obs} *vs*. [NH] plots, the values of k_1, k_{-1} and k_2 were obtained. From this and related studies the following conclusions were drawn: (i) The change of MeO by EtO does not affect the k_1, k_{-1} or k_2 values; (ii) substitution of MeO by PhO lowers the k_1 values; (iii) SA amines are less reactive towards MDNPTOC than isobasic pyridines when the k_2 step is rate-limiting; (iv) The replacement of PhO in PDNPTOC by 4-nitrophenoxy changes the mechanism from stepwise to concerted and; (v) substitution of CS by CO in PDNPTOC changes the rate-limiting step from k_1 to k_2 due to a larger k_{-1}/k_2 ratio for this change [59].

$$k_{obs} = \frac{k_1(k_2 + k_3[NH])[NH]}{k_{-1} + k_2 + k_3[NH]} \tag{3}$$

The reactions of 3-nitrophenyl and 4-nitrophenyl 4-methylphenyl thionocarbonates with SA amines and pyridines in 44 wt% ethanol–water have been under a kinetic investigation [60]. The reactions of SA amines with both substrates show nonlinear upward plots of k_{obs} *vs*. [amine] (see figure 5 as an example), compatible with the mechanism in scheme 7 (R = 4-methylphenyl, Ar = 3- or 4-nitrophenyl) and equation (3). Determination of the pK_a of the intermediate $T^{\pm}$ in these reactions indicates that proton transfer from $T^{\pm}$ to an amine is favourable, and an estimation of k_3 in these media was $4 \times 10^9\ s^{-1}\ M^{-1}$ [60]. With this k_3 value the other rate micro-coefficients of scheme 7 were obtained by fitting through equation (3). The values of k_1 and k_2 are larger for the 4-nitrophenyl compound relative to the 3-nitro derivative. The pyridinolyses of these substrates show linear plots of k_{obs} *vs*. [amine], with slopes $= k_N$. The Brønsted plots for k_N are linear with slopes $\beta_{nuc} = 0.9$ and 1.2 for 4-nitro and 3-nitro derivatives, respectively, indicating stepwise mechanisms with rate-limiting breakdown of $T^{\pm}$ to products. These reactions can be described by the upper part of scheme 7, since the k_3 step is impossible for pyridinolysis. The k_N values for pyridinolysis are larger for the 4-nitro

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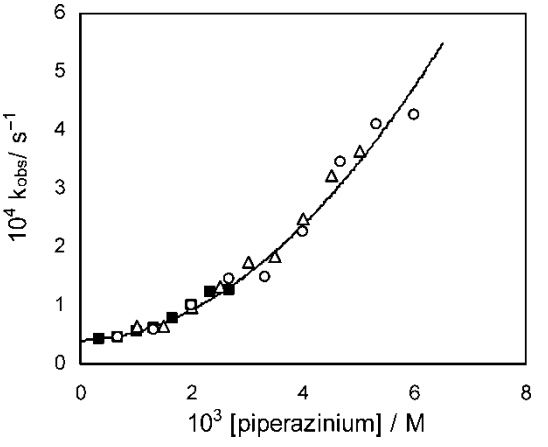

Figure 5. Plot of k_{obs} *vs.* molar concentration of piperazinium cation for the reactions of this amine with 3-nitrophenyl 4-methylphenyl thionocarbonate in 44 wt% ethanol–water, at 25.0 °C, ionic strength 0.2 M, at pH 5.07 (■), 5.37 (△) and 5.67 (○). Reprinted with permission from [60]. Copyright 2003 *American Chemical Society*.

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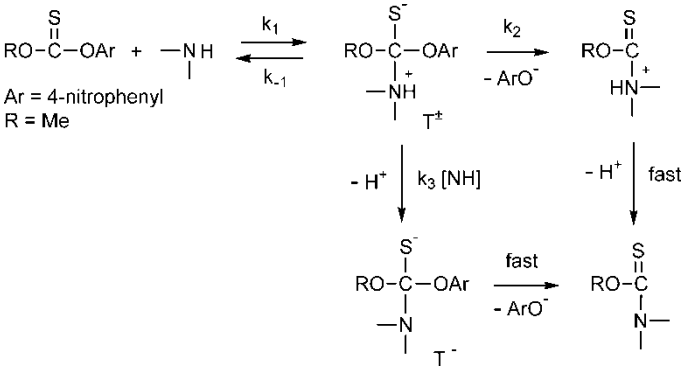


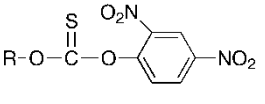
SCHEME 7

compound and this arises from larger values of both the equilibrium constant $K_1(= k_1/k_{-1})$ and the rate constant k_2 [60]. The values of K_1 for the pyridinolysis of the 4-nitro derivative are greater than those for the SA aminolysis of this substrate, which was attributed to a larger k_1 and a smaller k_{-1} for pyridines, relative to isobasic SA amines [60].

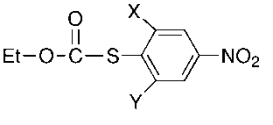
The reactions of SA amines with 3-methoxyphenyl, 3-chlorophenyl, and 4-cyanophenyl 4-nitrophenyl thionocarbonates (X−PhO−CS−OPh−NO_2, where X = 3-MeO, 3-Cl and 4-CN) in 44 wt% ethanol–water show linear plots of k_{obs} *vs.* [amine] for the more basic SA amines and nonlinear upward (such as those shown in Fig. 5) for the less basic amines [61]. These plots are consistent with the mechanism in scheme 7 (R = 3-MeOPh, 3-ClPh or 4-CNPh). Through fitting of equation (3) and assuming $k_3 = 4 \times 10^9\ s^{-1}\ M^{-1}$, the values of k_1, k_{-1} and k_2 were obtained. For the linear plots, $k_1 < k_2 + k_3$ [NH], such that equation (3) simplifies to $k_{obs} = k_1$ [NH]. For the reactions of piperazinium cation (the least basic amine used) with thionocarbonates (X = MeO and Cl), $k_{-1} \gg k_2 + k_3$ [NH], and equation (3) then reduces to $k_{obs} = K_1k_2$[NH] + K_1k_3[NH]^2. For the other reactions the full equation (3) is required. The Brønsted plots for k_1 are linear, giving slopes compatible with this step. These k_1 values show the order expected from the electron withdrawing abilities of X : CN > Cl > MeO [61].

The SA aminolysis of 3-X-phenyl 3-nitrophenyl thionocarbonates (X = MeO, Cl, and NO_2) in 44 wt% ethanol–water also show linear plots of k_{obs} *vs*. [amine] for the more basic amines and nonlinear upward for the less basic SA amines [62]. These results were explained by a mechanism analogous to that shown in scheme 7, and the rate micro-constants were obtained as described [60, 61]. The k_1 and k_2 values found are smaller than those for the corresponding aryl 4-nitrophenyl thionocarbonates [61], in agreement with the weaker electron withdrawal of 3-nitrophenyl than 4-nitrophenyl [62]. The plots of k_{obs} *vs*. [amine] are linear for the aminolysis (SA amines and quinuclidines) of similar carbonates [63], which was attributed to the fact that for these reactions $k_2 \gg k_3$ [NH], whereas for thionocarbonates $k_2 \approx k_3$ [NH]. This was explained by (i) the greater ability of O^- in $T^{\pm}$ than S^- to form a double bond and expel the leaving group (greater k_2) and (ii) the fact that the k_3 value remains relatively constant for carbonates and analogous thionocarbonates [62].

The reactions of phenyl and ethyl 2,4-dinitrophenyl thionocarbonates (PDNPTOC and EDNPTOC, respectively) with SA amines and the former with pyridines were subjected to a kinetic study in water [64]. All reactions show linear plots of k_{obs} *vs*. [amine]. The Brønsted plots are biphasic, consistent with stepwise mechanism and a change in the rate-limiting step. The pK_a^0 value is larger for the reactions of PDNPTOC with SA amines than that for the reactions with pyridines and this was attributed to the superior nucleofugality of SA amines. The linear k_{obs} *vs*. [amine] plots for the reactions of SA amines are in contrast to those nonlinear upward found for the same aminolysis of the corresponding 4-nitrophenyl thionocarbonates [59, 65]. This was explained by (i) the greater nucleofugality of 2,4-dinitrophenoxide than 4-nitrophenoxide from the corresponding $T^{\pm}$ intermediate and (ii) the fact that proton transfer from $T^{\pm}$ to an SA amine is thermodynamically favourable, *i.e.*, k_3 is similar, for both types of substrates. Namely, $k_2 \gg k_3$ [NH] for the dinitro derivatives, whereas these rates are similar for the mononitro analogues [64]. The stepwise reactions of SA amines with PDNPTOC and EDNPTOC are in marked contrast to the concerted mechanisms of the reactions of the same amines with the corresponding carbonates [66]. This was attributed to the greater ability of O^- in the putative $T^{\pm}$ to expel both the amine and leaving group [62, 66].



PDNPTOC (R = Ph)
EDNPTOC (R = Et)



ENPTC (X = Y = H)
EDNPTC (X = H ; Y = NO_2)
ETNPTC (X = Y = NO_2)

The reactions of 4-nitrophenyl, 2,4-dinitrophenyl and 2,4,6-trinitrophenyl *O*-ethyl thiolcarbonates (ENPTC, EDNPTC, and ETNPTC, respectively) with phenoxide anions in water show linear Brønsted plots with slopes $\beta = 0.92$, 0.77, and 0.61, respectively. These slope values, together with other considerations suggest that these reactions are concerted [67]. In contrast, the pyridinolysis of the same substrates are stepwise, which indicates that the tetrahedral intermediate is greatly destabilized by substitution of a pyridino moiety by phenoxy [67].

The reactions of EDNPTC and ETNPTC with benzenethiolates ($X-C_6H_4-S^-$) in water show linear Brønsted plots with slopes $\beta = 0.9$ for both [68]. The corresponding methyl carbonates, 2,4-dinitrophenyl and 2,4,6-trinitrophenyl methyl carbonates (MDNPC and MTNPC, respectively), also show linear Brønsted plots; the slopes are $\beta = 0.9$ and 1.0, respectively [68]. The values of the slopes and the fact that no Brønsted breaks at pK_a 4.1 and 3.4 were found for the reactions of MDNPC and EDNPTC, respectively, are consistent with concerted mechanisms for all four reactions. Benzenethiolate anions are better nucleophiles towards thiolcarbonates and carbonates than isobasic phenoxide anions [68].

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The reactions of EDNPTC and ETNPTC with anilines in water were studied kinetically [69]. The Brønsted plots are linear for both reactions, but the slopes β are 0.9 for the former reactions and 0.54 for the latter. The anilinolysis of EDNPTC is in agreement with a stepwise process with rate-limiting decomposition of the intermediate $T^{\pm}$ to products, whereas the reaction of ETNPTC is consistent with a concerted mechanism [69]. The change in mechanism was explained by destabilization of $T^{\pm}$ by the introduction of a third nitro group in the nucleofuge of $T^{\pm}$. Comparison of these mechanisms with the concerted SA aminolysis of EDNPTC and the stepwise pyridinolysis of ETNPTC, allows one to conclude that anilines are better nucleofuges from $T^{\pm}$ than isobasic pyridines, but are worse leaving groups than isobasic SA amines [69].

The reactions of ENPTC, EDNPTC and ETNPTC with quinuclidines (tertiary alicyclic amines) exhibit linear Brønsted plots with slopes $\beta = 0.85$, 0.54 and 0.47, respectively [70]. These results were attributed to a stepwise mechanism for the reactions of ENPTC and concerted ones for the other reactions. From these and other data the following conclusion were drawn: (i) introduction of a second nitro group in the nucleofuge of the intermediate $T^{\pm}$ formed in the ENPTC reactions, destabilizes $T^{\pm}$ and causes a change in mechanism; (ii) quinuclidines destabilize $T^{\pm}$, due to a greater nucleofugality, compared with other amines– the nucleofugalities for isobasic amines follows the sequence: pyridines < anilines < SA amines < quinuclidines and (iii) quinuclidines are more reactive towards a carbonate than the corresponding thiolcarbonate [70].

The reactions of SA amines with ethyl *S*-4-X-phenyl thiolcarbonates (X = Cl, H, Me, and MeO) in water show linear Brønsted plots with slopes $\beta = 0.7$–0.8, compatible with stepwise processes with rate-determining $T^{\pm}$ breaking [71]. This simple mechanism is in contrast to the more complex one (such as that in scheme 7) found in the same aminolysis of the analogous dithiocarbonates in the same medium. This is because, for the latter reactions, $k_2 \approx k_3$ [NH], whereas for those of thiolcarbonates, $k_2 > k_3$ [NH]. This is due to a larger k_2 value for a compound with a CO centre, compared with that with a CS centre (see above). Comparison with the pyridinolysis of similar thiolcarbonates indicates that pyridines are more reactive than SA amines towards thiolcarbonates when breakdown of $T^{\pm}$ is rate-limiting [71].

The pyridinolysis of 4-nitrophenyl and 2,4-dinitrophenyl *S*-methyl thiolcarbonates (SMNPTC, SMDNPTC, respectively) in water shows a linear Brønsted plot with slope $\beta = 1.1$ for the former and a biphasic plot with $\beta_1 = 0.25$ (high pK_a), $\beta_2 = 0.90$ (low pK_a) and $pK_a^0 = 7.3$ for the latter [72]. This is in agreement with stepwise mechanisms, where $T^{\pm}$ breakdown is the rate-determining for SMNPTC and there is a change in the rate-limiting step for SMDNPTC. From these and other results it was concluded: (i) the pK_a^0 value for the pyridinolysis of SMDNPTC is lower than that for the corresponding carbonate ($pK_a^0 = 7.8$), due to a weaker inductive electron withdrawal of MeS than MeO in $T^{\pm}$. This means a smaller k_{-1}/k_2 ratio for the thiolcarbonate and therefore, according to equation (2), a smaller pK_a^0; (ii) the rate constants for amine attack (k_1) are smaller for these thiolcarbonates than the corresponding carbonates, due to steric hindrance of MeS towards pyridine attack; (iii) these thiolcarbonates are less reactive towards pyridines than the corresponding carbonates when breakdown of $T^{\pm}$ is rate-determining [72].

The reactions of SMNPTC and SMDNPTC with SA amines and quinuclidines (QUI) and those of SA amines with pentafluorophenyl *S*-methyl thiolcarbonate (SMFPTC) in water were subjected to a kinetic investigation [73]. The Brønsted plots for the reactions of SA amines and QUI with SMNPTC are linear with slopes $\beta = 0.9$ - consistent with stepwise processes. The other reactions also show linear Brønsted plots, with $\beta = 0.36$ and 0.57 (reactions of SMDNPTC with SA amines and QUI, respectively) and $\beta = 0.39$ (reactions of SMFPTC with SA amines), in accordance with concerted mechanisms [73]. The main conclusion is that changing of 4-nitrophenoxy to pentafluorophenoxy or 2,4-dinitrophenoxy as the leaving

group destabilizes the intermediate $T^{\pm}$ formed in the reactions with SA amines and changes the mechanism from stepwise to concerted [73].

The reactions of O-phenyl 4-nitrophenyl dithiocarbonate (PhO-CS-SPhNO$_2$, PNPDTC) with SA amines in 44 wt% ethanol–water show nonlinear upward plots of k_{obs} *vs.* [amine], except the reactions with piperidine in which the plot is linear [74]. The shape of these plots, together with products analysis is compatible with a stepwise mechanism through two tetrahedral intermediates, as that shown in scheme 7 (R = Ph and SAr instead of OAr). The linear plot for piperidine was explained by equation (3), with $k_{-1} \ll k_2 + k_3$ [NH], which is due to the very weak leaving ability of this very basic amine from the intermediate $T^{\pm}$. In this case, equation (3) reduces to $k_{obs} = k_1$ [NH]. Comparison of the nonlinear plots of k_{obs} *vs.* [NH] for the reactions of this substrate with the linear plots obtained in the same aminolysis of *O*-ethyl 4-nitrophenyl dithiocarbonate in the same solvent [75], allows to conclude that for the former reactions, $k_2 \approx k_3$ [NH] in Scheme 7 and equation (3), whereas for the latter, $k_2 \gg k_3$ [NH]. This was attributed to the greater push provided by EtO in $T^{\pm}$, compared with PhO, in expelling the nucleofuge, 4-nitrobenzenethiolate (larger k_2). The value of k_3 was estimated to be the same for both reactions since the proton transfer involved in this step is diffusion controlled [74]. Comparison of the reactions of PNPDTC in aqueous ethanol with the SA aminolysis of phenyl 4-nitrophenyl thionocarbonate (PhO−CS−OPhNO$_2$) in water [59] allows one to conclude the following: (i) the k_2 value is larger for the former due to the less basic and better leaving group involved; (ii) the k_3 value is smaller for the aminolysis of PNPDTC in view of the more viscous solvent; (iii) the k_{-1} value is larger and the k_1 value is smaller for the latter reactions due to the less polar solvent employed in these reactions [74].

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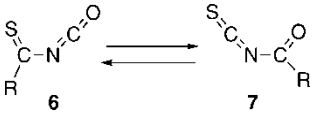
4. Isothiocyanates

The thioacyl isocyanate − acyl isothiocyanate (**6** and **7**, respectively) rearrangement has been investigated computationally [76] and the calculated free-energy barriers were found to be in agreement with the kinetic data obtained for this reaction [77]. This rearrangement, which involves a 1,3-shift of the substituent R, was studied at the *ab initio* and at the DFT levels of theory, G2(MP2,SVP) and B3LYP/6-31G*. The order of migratory abilities of R was computed as Br > Cl > NMe_2 > F, SMe, SH > OMe, NH_2 > OH ≫ H ≫ Me, with energy barriers between 75 and 285 kJ/mol, in accordance with the experimental kinetic results [77]. Acyl isothiocyanates were found to be more stable than the corresponding thioacyl isocyanates. The lone pair energies of the iso(thio)cyanates served as a satisfactory explanation of the calculated and observed reactivity order. They correlate well with the activation barriers [76].

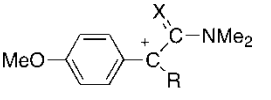


6 **7**

The reactions of aryl isothiocyanates (ArNCS) with aryl amines in non-aqueous media show overall second-order kinetics – first order in both the substrate and the amine. The effect of the substrate substituents on the rate was assessed and the activation parameters obtained. The reaction products were isolated and characterized as asymmetric thiocarbamides [78].

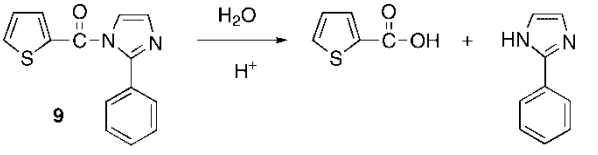
5. Thioamides and thioureas

The decomposition of α-thiocarbamoyl substituted 4-methoxybenzyl cations (**8a,b**) in 40/60 acetonitrile/water and 50/50 methanol/water in the presence of azide ion has been subjected to a kinetic investigation [79]. For comparison, the decay of α-carbamoyl **8c** was also studied. The lifetimes for **8a**, **8b** and **8c** in aqueous acetonitrile are 7 ms, 6 ms and 0.6 μs, respectively. The cation **8b** gives only an alkene product in aqueous methanol, which indicates that the solvent acts as a base by deprotonation of the α-methyl group. With azide ion, both elimination and addition occur, the limiting ratio [alkene]/[RN_3] (at high azide concentration) being 1.7. Cation **8a** lives 10^4 times longer than its oxo analogue (**8c**) and 10^6–10^7 times longer than the 4-methoxyphenethyl cation (Me instead of $CSNMe_2$). Cation **8b** is 10^5 longer lived than its α-methyl analogue (Me instead of $CSNMe_2$). The great stabilization of the α-thiocarbamoyl cations (**8a,b**) was attributed to a strong interaction between the benzylic centre and the thioamide group [79].



8a (X = S, R = H)
8b (X = S, R = Me)
8c (X = O, R = H)

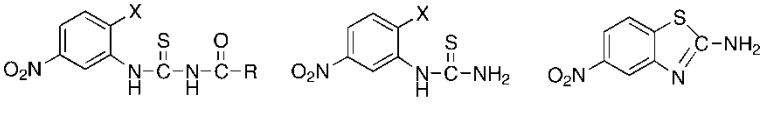
The hydrolysis of *N*-thenoyl-2-phenylimidazole (**9**, Scheme 8) was studied kinetically in water, at 40 °C, by following spectral changes at 300 nm [80]. The pH-rate profile (log k *vs.* pH) shows a constant k_{obs} value between pH 2 and 5, an increase in k_{obs} between pH 5 and 6 and a decrease in k_{obs} between pH 6 and 7. At pH > 7, k_{obs} increases sharply due to the alkaline hydrolysis. This pH profile is consistent with the formation of various tetrahedral intermediates and changes in the rate-determining step according to the different pH ranges [80].



9

SCHEME 8

The kinetics and mechanism of the methanolysis and cyclization of 1-acyl-3-(2-halo-5-nitrophenyl)thioureas (**10**) are investigated in methanol at 25 °C [81]. Nonlinear upward plots of k_{obs} *vs.* [MeO^-] were found, which were explained by a mechanism consisting of methoxide attack on the carbonyl carbon of **10** to form a tetrahedral intermediate, which by expulsion of RCOOMe gives compound **11**. Abstraction of a proton from **11** by MeO^- induces its cyclization to yield compound **12** and X^- as final products [81].



10 X = F, Cl; R = Me, Ph

11 X = F, Cl; R = Me, Ph

12 X = F, Cl; R = Me, Ph

The decomposition of thiourea dioxides (**13**) in alkaline solution has been studied kinetically [82]. A mechanism is proposed that starts with deprotonation of **13** by HO^- to form

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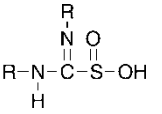
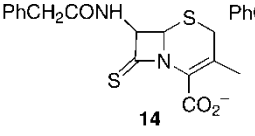
$RN(=NR)CSO_2^{2-}$, followed by attack of H_2O and the cleavage of the C−S bond to yield urea and SO_2^{2-}; this is rapidly oxidized by oxygen to give SO_2^-, which is the precursor to the formation of $S_2O_4^{2-}$. Also produced are SO_2, superoxide, peroxide and hydroxyl radical [82].



13 (R = H or Me)

The kinetics and mechanisms of hydrolysis of thioxocephalosporins (**14**) have been investigated and the influence of the S atom has been assessed by comparison with the same reactions of cephalosporin (**15**) [83]. Hydroxide attack on **14** yields compound **16**; a similar ring opening takes place by the alkaline hydrolysis of **15**. The rate constant for the reaction of **14** is only 2-fold lower than that of **15**. On the other hand, the thioxo analogue of cephalexin (**17**) undergoes intramolecular aminolysis to give **18**. This rate constant is ca. 10^3 times larger than that for the oxo analogue. Intermolecular aminolysis of **14** yields compound **19** [83]. This reaction shows only a term first order in amine, whereas the aminolysis of the oxo analogue (**15**) exhibits two dominant terms – general base- and hydroxide-catalyzed aminolysis [84]. For the aminolysis of **14**, the tetrahedral intermediate **20** is formed, the rate-determining step being its formation (k_1 step). The decomposition of **20** to product **19** (k_2 step) is a fast base-catalyzed step, *i.e.*, $k_{-1} \ll k_2$[base]. A similar mechanism was found for the aminolysis of **15**, with the important difference that the oxy tetrahedral intermediate **21** returns to reactants much faster than to products ($k_{-1} \gg k_2$ [base] – the k_2 step being rate-limiting [84]. The much lower k_{-1} value for the thio intermediate **20** was attributed to its relatively higher stability, compared with that of its oxy analogue **21** [83].



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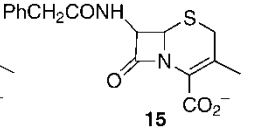

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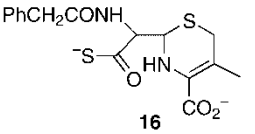

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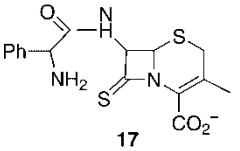

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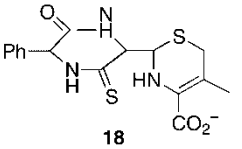

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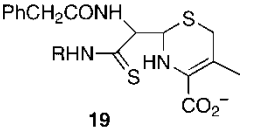

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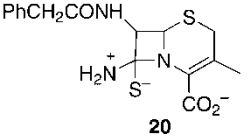

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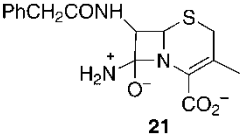

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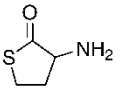

22

The hydrolysis and aminolysis of homocysteine thiolactone (**22**) and the related thiolactones have been subjected to a kinetic study [85]. The nucleophilic attack occurs at the carbonyl carbon. The aminolysis was found to be first order in amine. Anchimeric general-base catalysis by the α-amino group of **22** or general-acid catalysis by its conjugate acid was not detected. The Brønsted plot for aminolysis shows a slope $\beta = 0.66$, which was claimed to be consistent with rate-determining formation of a zwitterionic tetrahedral intermediate [85].

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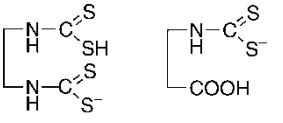
6. Thiocarbamates

The acid hydrolysis of ethylene bis(dithiocarbamate) (**23**) and glycinedithiocarboxylate (**24**) were investigate kinetically in water in the range H_0 -5 to pH 5 [86]. According to the pH-rate profiles, mechanisms are proposed for decomposition of these thiocarbamates, which take into account all possible protolytic forms of **23** and **24**. The pK_a of these forms were calculated by LFER or from the pH-rate profiles. Expulsion of CS_2 proceeds through both specific acid and intramolecular general acid catalysis. The latter is exerted by the neighbour dithiocarbamic or carboxylic acid groups and the decomposition takes place through the dithiocarbamate anion and a zwitterion intermediate [86].



23 **24**

The kinetics of the acid decomposition of *p*-substituted aryldithiocarbamates (p−X−C_6H_4 $NHCS_2^-$) was studied in 20% aqueous ethanol in the acidity range from H_0 − 5 to pH 4 [87]. The pH-rate profiles are dumb-bell shaped with a plateau region representing the rate constant for the spontaneous hydrolysis of the dithiocarbamic acid species (k_0). The value of k_0 is more than 10^4 fold larger than that for alkyldithiocarbamates with similar amine basicity. Proton inventory indicates a proton transfer from SH to N through a water molecule to form a zwitterion followed by fast C−N bond cleavage. Also compatible with the kinetic data is a concerted mechanism where *N*-protonation is more advanced than C−N bond rupture. The main driving force to reach the transition state is the torsional effect on the C−N bond that inhibits the resonance with both the thiocarbonyl group and the aromatic moiety [87].

The above water-catalyzed hydrolysis was studied theoretically using *N*-methyl and *N*-phenyldithiocarbamic acids [88]. The calculations were carried out by DFT (BL3YP), both in gas phase and in solution (by dielectric continuum methods). For the *N*-methyl derivative the decomposition is stepwise, through a zwitterion intermediate formed by slow proton transfer through a water molecule, followed by fast C−N bond cleavage. For the *N*-phenyl analogue the proton transfer is concerted with bond rupture. Most of the activation energy difference for decomposition of these dithiocarbamic acids comes from the difference in the rotational barrier of the N−CS_2 moiety [88].

The hydrolysis of ethyl *N*-p-substituted phenylthioncarbamates (EtO−CS−NH−Ar) was investigated kinetically at 100 °C at pH 6.5–12.5 [89]. From pH-rate profiles it was deduced that the alkaline hydrolysis proceeds by an E1cB process, with the formation of an isothiocyanate (Ar−N=C=S) intermediate. Also studied was the alkaline hydrolysis of these intermediates at 25 °C in both water and aqueous ethanol [89]. Leffler plots for the elimination of EtO^- from the thioncarbamates and for the addition of EtO^- to the isothiocyanates were linear. From Leffler's equation, a modified Marcus equation was obtained [89].

The kinetics of the hydrolysis of ethyl *N*-ethylthioncarbamate (EtO−CS−NH−Et) was studied at 100 °C in the range 7 M HCl to 4 M NaOH [90]. From the pH-rate profile and other data an A1 mechanism was proposed for the acid hydrolysis (pH < 2). Protonation occurs preferentially on the N atom of the thioncarbamate, following by C−N bond breaking to yield ethylamine and S=C−OEt^+, which rapidly hydrolyses to give ethanol and COS. At pH 2–6.5, where the main species is the neutral substrate, the hydrolysis is pH-independent and consists of a slow general-base catalysis by water to yield an isothiocyanate intermediate, which hydrolyses to $EtNH_2$ and COS (E1cB mechanism). At pH > 6.5, specific base catalysis

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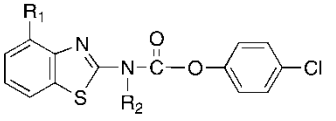
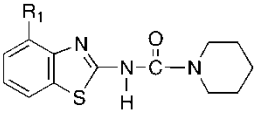
occurs, also by an E1cB mechanism, forming ethylisocyanate in the rate-limiting step, which rapidly decomposes to products [90].

The basic hydrolysis of phenyl *N*-methyl-*N*-thiobenzoylcarbamate (PhO−CO−N(Me)−CS−Ph) was investigated kinetically [91]. In the absence of buffers the reaction is first order in HO^-; in the presence of buffers the reaction is first order in the buffer base. A $B_{Ac}2$ mechanism involving general base catalysis was proposed on the basis of the Brønsted plot obtained with the bases ($\beta = 0.7$), the fact that the rate constants for piperidine and tetramethylpiperidine are similar and the normal solvent isotope effect obtained ($k_{H2O}/k_{D2O} = 1.3$) [91]. This mechanism involves general base hydrolysis to form an anionic tetrahedral intermediate, which breaks down to *N*-methylthiobenzamide, CO_2 and phenoxide [91].

The kinetics of the basic hydrolysis of 4-chlorophenyl *N*-(2-benzothiazolyl)carbamates (**25**) has been subjected to a study [92]. The secondary compounds (**25a,b**) hydrolyse by an E1cB mechanism, as indicated by the shape of the k_{obs} *vs*. [HO^-] and [DO^-] plots (with a levelling off), the absence of general-base catalysis by piperidine and piperazine and the formation of a urea (**26**) by the attack of piperidine to the isocyanate intermediate (**27**). The corresponding tertiary carbamate (**25c**) hydrolyses by a general base $B_{Ac}2$ mechanism, as suggested by the linear plot of k_{obs} *vs*. [HO^-], significant base catalysis by piperidine and pyrrolidine and the normal solvent isotope effect [(k_B (H_2O/k_B (D_2O)=2.2)] [92]. This mechanism is similar to that found for phenyl *N*-methyl-*N*-thiobenzoylcarbamate [91].



25a (R_1 = H, R_2 = H)
25b (R_1 =Me, R_2 = H)
25c (R_1 = H, R_2 = Me)



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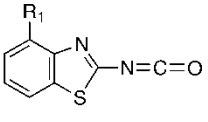

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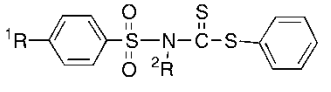
The kinetics of the alkaline hydrolysis of phenyl arylsulphonyl-alkyl-dithiocarbamates (**28**) was studied at 25 °C in aqueous dioxane [93]. On the basis of the linear k_{obs} *vs*. [HO^-] plots, the linear Hammett plot (σ^0) for the ^{1}R substituent (with $\rho = 1.2$), the solvent isotope effects ($k_{OH}/k_{OD} = 0.9$–1.0) and the large k_{HOO}/k_{OH} ratios, a $B_{Ac}2$ mechanism was proposed. This involves rate-determining formation of an anionic tetrahedral intermediate (**29**) by direct attack of HO^- to the thiocarbonyl group. This intermediate then decomposes with the expulsion of benzenethiolate anion and COS to yield the arylsulphonamide (**30**). The change of ^{2}R from Me to Et to Pr decreases the k_{OH} value due to steric hindrance towards HO^- attack [93]. This mechanism is in contrast to that shown by the corresponding carbamates, which undergo a general base-catalysed process and are ca.100-fold more reactive [94].



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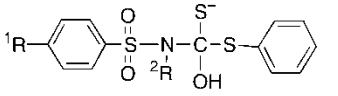

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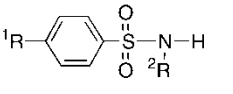

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The reactions of X-substituted benzylamines with Z-substituted aryl *N*-phenylthiolcarbamates (PhNH−CO−SAr) in acetonitrile are governed by a concerted mechanism [95]. This was deduced on the basis of (i) the much greater increase in reactivity relative to that expected for a change of OAr to SAr in the stepwise reactions of the corresponding carbamates; (ii) the negative cross-interaction constant ($\rho_{XZ} = -0.63$); (iii) the failure of the RSP and (iv) the values of the activation parameters [94]. This change in mechanism is in agreement with that found in the aminolysis of ethyl aryl carbonates (stepwise) and *O*-ethyl *S*-aryl thiolcarbonates (concerted) [49].

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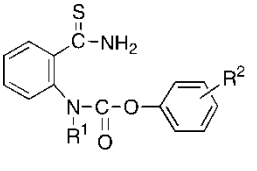
The reactions of Z-substituted aryl *N*-ethylthiolcarbamates (EtNH−CO−SAr) with X-benzylamines in acetonitrile are faster than those of the corresponding *N*-phenylthiolcarbamates [96]. This was attributed to the stronger push exerted by N−Et, compared with N−Ph, to expel the leaving ArS^- group. The reactions of the *N*-ethyl compounds are also concerted [96] (as those of the *N*-phenyl analogues [95]), as indicated by the negative cross-interaction constant ($\rho_{XZ} = -0.86$), the failure of the RSP and the values of the kinetic isotope effects involving deuterated nucleophiles ($k_H/k_D = 1.5$–1.7) [96].

The benzylaminolysis of aryl thiolcarbamates (H_2N−CO−SAr) in acetonitrile is also concerted, as deduced from the values of the cross-interaction constant ($\rho_{XZ} = -0.38$) and the Brønsted slope for the leaving group ($\beta_Z = -0.54$) and the failure of the RSP [97]. The order of reactivities according to the non-leaving group is: NH_2 < PhNH < EtNH, indicating that the polar and steric effects are not significant and the push exerted by the RNH group is of paramount importance [97].

The benzylaminolysis of aryl *N*-ethylthionocarbamates (EtNH−CS−OAr) in acetonitrile was found to be concerted on the basis of the values $\rho_{XZ} = -0.87$ and $\beta_Z = -0.36$ to -0.50 and the failure of the RSP [98]. These compounds are ca. 3-fold less reactive than the corresponding thiolcarbamates (EtNH−CO−SAr). From a comparison with the aminolysis of similar compounds in acetonitrile the following sequence of reactivities is deduced: −CS−S < −CS−O < −CO−S < −CO−O [98].

The benzylaminolysis of phenyl *N*-Y-arylthionocarbamates (ArNH−CS−OPh) in acetonitrile is ruled by a stepwise mechanism where breakdown of the zwitterionic tetrahedral intermediate ($T^{\pm}$) is rate limiting [99]. This was deduced by the following arguments: (i) The large magnitude of the Hammett ($\rho_{nuc} = \rho_X = -0.94$ to -1.4, $\rho_{nlg} = \rho_Y = 0.96$ to 1.6) and Brønsted slopes ($\beta_{nuc} = \beta_X = 0.95$ to 1.4); (ii) the normal kinetic isotope effects for the nucleophile ($k_H/k_D = 1.33$–1.52); (iii) the small positive enthalpy of activation (4.6 to 5.5 kcal mol^{-1}) and the large negative entropy of activation (-36 to -39 cal mol^{-1} K^{-1}); (iv) the positive sign and large magnitude of the cross-interaction constant ($\rho_{XY} = 0.98$) and (v) adherence to the RSP in all cases [99].

The kinetics of the reactions of substituted phenyl *N*-(2-thiocarbamoylphenyl)carbamates (**31**, R^1 = H) catalysed by methoxide anion has been subjected to an investigation in aqueous solution [100]. The final products obtained were species **32** and the substituted phenoxide anion. Linear Hammett (for R^2) and Brønsted (for the leaving group) plots were found, with slopes $\rho = 3.14$ and $\beta = -1.15$, respectively. These reactions were found to proceed by a $B_{Ac}2$ mechanism: methoxide anion deprotonates the ortho-thiocarbamoyl moiety followed by intramolecular attack of the CS-NH^- group to the carbonyl carbon to produce the anionic tetrahedral intermediate **33**, which breaks down rapidly to the final products. The reactions under identical conditions of the *N*-(4-thiocarbamoylphenyl) derivatives were found to be driven by an E1cB process. This was concluded on the basis of the large magnitude of the Hammett ($\rho = 4.6$) and Brønsted ($\beta = -1.55$) slopes and the fact that the rate constants are two orders of magnitude smaller than those for the ortho-thiocarbamoyl derivatives (**31**), which are ruled by the $B_{Ac}2$ mechanism [100].



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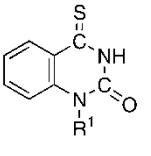

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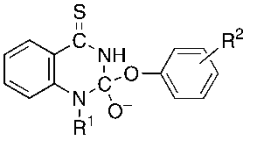

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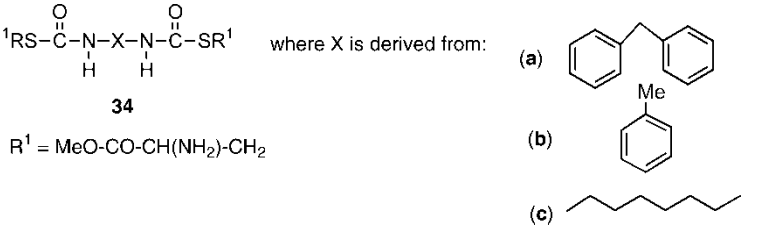
The kinetics and mechanistic study of the hydrolysis of diisocyanate-derived bis-thiocarbamates of cysteine methyl ester (**34**) has been reported [101]. Reactions of these three bis-thiocarbamates with methylamine or human serum albumin produced urea, monourea and diamine, $R(NH_2)_2$, consistent with a base-catalysed elimination mechanism (E1cB) being the main process. The basic hydrolysis of compounds **34a-c** was first order in both HO^- and the substrates. Most of this hydrolysis proceeds by an E1cB mechanism, leading to diisocyanates as intermediates, and a minor part obeys a $B_{Ac}2$ process. The activation energies were in agreement with the following sequence of stability: **34c** > **34b** > **34a** [101].



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R^1 = MeO-CO-CH(NH_2)-CH_2

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7. Halogenothioformates and related compounds

The solvolysis of phenyl chorothionoformate (PhO−CS−Cl) has been investigated kinetically in aqueous binary mixtures of methanol, ethanol and acetone [102]. The rate constants showed dispersion when plotted according to both the original and the extended Grunwald–Winstein equation, equations (4) and (5), respectively. Nevertheless, much better correlations were found through the corrected equations [equations (6) and (7)], which incorporate the aromatic ring parameter (I) [103].

$$\log(k/k_0) = mY + c \tag{4}$$

$$\log(k/k_0) = lN + mY + c \tag{5}$$

$$\log(k/k_0) = mY + hI + c \tag{6}$$

$$\log(k/k_0) = lN + mY + hI + c \tag{7}$$

In these equations k_0 is the rate constant in 80% ethanol, c is a residual (constant), Y is the solvent ionizing power, N is the solvent nucleophilicity, I is the aromatic ring parameter and m, l and h are the corresponding sensitivities. The best correlation was obtained through equation (7), with $l = 0.37$, $m = 0.44$, $h = 2.64$ (corr. coeff. 0.999). The values of l and m are consistent with a S_N2 mechanism. The kinetic solvent isotope effects ($\log k_{SOH}/k_{SOD}$) were also determined; the values found being 2.02, 1.91 and 1.45 in methanol, 50% aqueous methanol, and water, respectively. These values are in agreement with those for general base catalysis, and indicate that the solvolyses of phenyl chlorothionoformate proceed predominantly by a general base catalysed (by two solvent molecules) S_N2 mechanism with a relatively tight transition state, where bond formation is more advanced in methanol than in water [102].

The solvolyses of phenyl chorothionoformate (PhO−CS−Cl) in aqueous mixtures of ethanol, methanol and acetone and mixtures of trifluoroethanol (TFE)-ethanol were claimed to be ruled by an addition–elimination route [104a]. This was deduced from the values of $l = 1.53$ and $m = 0.36$, obtained through the extended Grunwald–Winstein equation [equation (5)]. In contrast, for the solvolyses of this compound in aqueous mixtures of TFE and hexafluoro-2-propanol (HFIP), the values of l and m were 0.43 and 1.19, respectively, which are

consistent with an ionization channel (S_N1 mechanism). The kinetic behaviour of this compound is very similar to that found for the same solvolyses of phenyl chlorothiolformate (PhS−CO−Cl) [105].

The solvolyses of phenyl chorodithioformate (PhS−CS−Cl) showed a good correlation through equation (5) in all the above solvent mixtures [104a]. The values of l and m obtained were 0.55 and 0.84, respectively, consistent with an S_N1 mechanism. Since the solvolysis of phenyl chloroformate (PhO−CO−Cl) follows an addition-elimination pathway [106], it was concluded that the gradual substitution of O by S increases the ionization character of the mechanism [104a]. The same was concluded from a study comparing EtO−CO−Cl and EtS−CO−Cl [104b].

The rate constants of the solvolyses of *N*,*N*-dimethylthiocarbamoyl chloride ($(Me)_2N-CS-$-Cl) were found to be two to three orders of magnitude greater than those for the oxo analogue ($(Me)_2N-CO-Cl$) [107]. The values of l and m and the l/m ratio, obtained through equation (5), for the thiono compound are lower than those for the oxo derivative. It was concluded that the thiono compound forms a more stable carbocation (than that for the oxo analogue), leading to an earlier transition state and reduced nucleophilic solvation [107].

The reactions of aryl chlorothionoformates ($Y-C_6H_4O-CS-Cl$, **35**) with X-substituted anilines have been studied kinetically in acetonitrile [108]. The rate constants (k_N) were found to be ca. 10-fold lower than those for the same aminolysis of the oxo analogue (**36**) in the same solvent [109]. A concerted mechanism was proposed for the reactions of **35** on the following basis (i) The rate constant for **36** is larger than that for **35**, both being in acetonitrile, which is the reverse of what was found in the alkoxy series in water, reflecting a different mechanism for the two series. For the aminolysis of the alkoxy series in water a stepwise process was found, with rate-determining formation of the zwitterionic tetrahedral intermediate ($T^{\pm}$). (ii) The negative sign for the cross-interaction coefficient ($\rho_{XY} = -0.77$). (iii) The RSP does not hold. (iv) The kinetic isotope effects (k_H/k_D) involving deuterated anilines are normal (1.5–1.7), which is not consistent with a stepwise process with rate-limiting bond formation. A four-membered cyclic TS structure was proposed, where one H of the aniline helps the expulsion of Cl. (v) The low enthalpy of activation and large negative entropy of activation are in agreement with the proposed TS. The same aminolysis of **35** in water is stepwise. The change in mechanism to concerted in acetonitrile was attributed to destabilization of $T^{\pm}$ by the latter solvent [108].

The kinetics and mechanism of the pyridinolysis of phenyl and 4-nitrophenyl chlorothionoformates (**37** and **38**, respectively) have been investigated in water [110]. Two consecutive reactions are observed – formation of 1-(aryloxythiocarbonyl)pyridinium cation (**39**) and its decomposition to substituted phenol, COS and pyridine (scheme 9). Under amine excess, both processes are first order in amine (N), according to equations (8) and (9). The Brønsted plots for k_N are linear with slopes $\beta_{nuc} = 0.07$ and 0.11 for **37** and **38**, respectively, in agreement with a stepwise mechanism through a zwitterionic tetrahedral intermediate ($T^{\pm}$), where its formation is rate-limiting. This is in contrast to the concerted phenolysis of the same substrates in the same solvent, which means that substitution of the pyridino moiety in $T^{\pm}$ by phenoxy destabilizes this intermediate and forces a change in mechanism.

$$k_{obs1} = k_0 + k_N[N] \tag{8}$$

$$k_{obs2} = k_{02} + k_H[N] \tag{9}$$

In equation (9) the pyridine (N) acts as a general base catalyst for the hydrolysis of **39** [110]. The Brønsted plots for k_H are linear with slopes $\beta = 0.19$ and 0.26 for the cationic intermediates (**39**) derived from **37** and **38**, respectively. These low values are due to the fact

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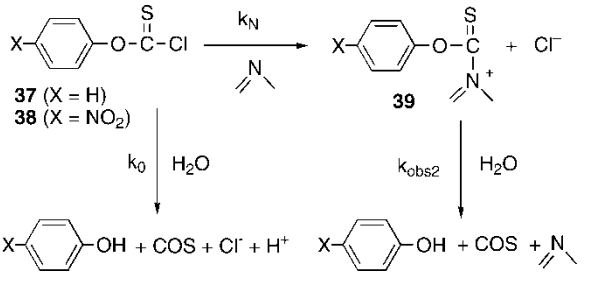
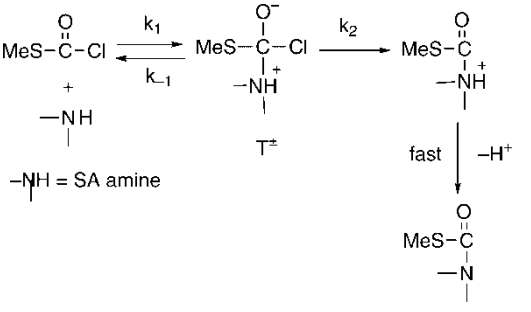


SCHEME 9

that there is a simultaneous change in the pyridine as general base and as leaving group and, therefore, a more basic pyridine catalyst is counterbalanced by an inferior leaving group [110].

The reactions of *S*-methyl chlorothioformate (MeS−CO−Cl) with pyridines and SA amines have been investigated kinetically in aqueous solution [111]. For the reactions with pyridines, a similar mechanism to that shown in scheme 9 was found. The Brønsted plot for k_N is biphasic, with slopes $\beta_1 = 0.12$ (high pK_a region) and $\beta_2 = 1.0$ (low pK_a region) and a centre of curvature, $pK_a^0 = 3.6$. These results are consistent with a stepwise mechanism, through $T^{\pm}$, and a change in the rate-determining step, from breakdown of $T^{\pm}$ to its formation, as the basicity of the pyridine increases [1, 63, 111]. The value of pK_a^0 is the same as that found in the pyridinolysis of methyl chloroformate (MeO−CO−Cl) in water [21]. This means that the change of O by S in the non-leaving group does not affect the pK_a^0 value, and according to equation (2), this change does not alter the k_{-1}/k_2 ratio (where k_{-1} and k_2 measure the leaving abilities from $T^{\pm}$ of the pyridine and Cl^-, respectively). Comparison with the stepwise pyridinolyses of *S*-methyl 4-nitrophenyl thiocarbonate (**40**) and *S*-methyl 2,4-dinitrophenyl thiocarbonate (**41**) ($pK_a^0 > 10$ and 7.3, respectively [72]) shows that pK_a^0 increases with the basicity of the leaving group; this is in accordance with the hypothesis of the tetrahedral intermediate on the reaction path [1, 21, 63].

The reactions of *S*-methyl chlorothioformate with SA amines show a linear Brønsted plot with slope $\beta = 0.23$ [111], which is in agreement with a stepwise process (scheme 10) where formation of $T^{\pm}$ is rate-limiting [1, 21, 63, 111]. Comparison with the stepwise reactions of the SA amines with thiocarbonate **40** (where the k_2 step is rate limiting [73]) confirms that Cl^- is a much better leaving group from $T^{\pm}$ than 4-nitrophenoxide. Comparison with the concerted reactions of the same amines with thiocarbonate **41** [73] shows that 2,4-dinitrophenoxy destabilizes the intermediate $T^{\pm}$ relative to Cl. This was attributed to steric crowding in the former intermediate [111].



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8. Conclusions

From this review the following conclusions can be drawn:

(1) Most of the reactions analysed in this review occur through a tetrahedral intermediate (stepwise mechanism). When this intermediate is highly unstable or non-existent the mechanism is concerted (single step).
(2) For the aminolysis of these thiocompounds a zwitterionic tetrahedral intermediate ($T^{\pm}$) is usually formed. For substrates with relatively poor or moderate leaving groups the rate-determining step is the breakdown of $T^{\pm}$ to products, whereas for good nucleofuges, formation of $T^{\pm}$ is rate limiting. For exceptionally very good leaving groups and amines of high nucleofugality (SA amines and quinuclidines), the mechanism is concerted due to the great destabilization caused to $T^{\pm}$.
(3) For the reactions of the title substrates with alkoxide or hydroxide anions, usually an anionic tetrahedral intermediate (T^{-}) is formed. In contrast, the reactions of phenoxide anions are usually ruled by a concerted mechanism.
(4) The stability of the tetrahedral intermediate, and, therefore, the mechanism followed by the reaction, depends on the groups attached to its central carbon and on the solvent:
   (i) Amines stabilize the intermediate relative to aryloxide or benzenethiolate. For aminolysis, destabilization increases as the nucleofugality of the amine from $T^{\pm}$ increases. The sequence of nucleofugalities for isobasic amines is: pyridines < anilines < SA amines < quinuclidines.
   (ii) The leaving group of the substrate destabilizes the intermediate according to their nucleofugality. For a given family of leaving groups in the same solvent, the lower their basicity the greater the nucleofugality and, therefore, the greater the instability of the intermediate. Aryloxides are worse nucleofuges from T^{-} than benzenethiolates with the same Ar group. The exception is Ar = 2,4,6-trinitrophenyl. Nevertheless, aryloxides are *better* nucleofuges from T^{-} than *isobasic* benzenethiolates.
   (iii) The non-leaving group affects the tetrahedral intermediate as follows: MeO or EtO destabilize it, relative to Me or Et. The more electron withdrawing is ArO the greater the instability of the intermediate. The change of MeO to MeS does not affect the stability of the intermediate.
   (iv) The replacement of S^{-} by O^{-} in the tetrahedral intermediate destabilizes it, due to the stronger driving force of O^{-} to form a CO double bond and expel a leaving group.
   (v) The more polar the solvent the greater the stability of its nucleofugality.
(5) For the reactions of primary and secondary amines that form a relatively stable $T^{\pm}$ intermediate (with a comparatively poor leaving group and S^{-} rather than O^{-}) at neutral or basic pH, a second amine or HO^{-} can deprotonate $T^{\pm}$ to give an anionic intermediate T^{-}. At relatively low pH, $T^{\pm}$ can be protonated to yield a cationic intermediate T^{+}.
(6) For some reactions (especially thiocarbamates) the $B_{Ac}2$ and E1cB mechanisms have been found to operate, depending on the substrate structure. The S_N1 mechanism takes place in some reactions of halogenothioformates, carried out in solvents of high ionization power.

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