Kinetics and Mechanisms of Reactions of Thiol, Thiono, and Dithio Analogues of Carboxylic Esters with Nucleophiles†

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Contents

Enrique A. Castro was born in 1941 in Santiago, Chile. He received his degree of Licenciateship in Chemistry and the title of Chemist from Universidad Catolica de Chile in Santiago in 1968. He obtained his Ph.D. from the University of Exeter, England, in 1974, working under the supervision of Dr. Roy B. Moodie. He returned to Santiago as a lecturer in Physical Chemistry in the Chemistry Department of Universidad Catolica de Chile, where he is working currently. He was promoted to the position of Profesor Titular in 1991. He has spent three Sabbatical leaves, in 1982, 1990, and 1998, at the University of Exeter. His research interests concern the kinetics and mechanisms of the reactions of different nucleophiles with esters, carbonates, halogenoformates, and similar carbonyl dervatives and their thioanalogs in solution, with particular emphasis in the solvolysis, aminolysis, and phenolysis of the above compounds.

I. Introduction

The reactions of thioesters, thiocarbonates, and other thiocarbonyl derivatives with nucleophiles are of increasing interest not only in chemistry but also in biochemistry because they take place in many biological processes.

This review encompasses 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 dithiocarbonates (RO−CO−SR′, RO−CS−OR′, and RO−CS−SR′, respectively), isothiocyanates (R−N═C═S), thioaldehydes and thioketones, thioamides and thioureas, thiocarbamates, i.e., thiol-, thiono-, and dithiocarbamates (RS−CO−NR^1R^2, RO−CS−NR^1R^2, and RS−CS−NR^1R^2, respectively), and halogenothioformates, i.e., thiol, thiono, and dithio derivatives (RS−CO−Hal, RO−CS−Hal, and RS−CS−Hal).

There is abundant literature on the kinetics and mechanisms of the reactions of nucleophiles with esters, carbonates, and other carbonyl derivatives.[1] Nevertheless, the kinetics and mechanisms of their thio analogues have not received similar coverage, although literature as old as 1948 has been published regarding these matters.

The purpose of this review is to assemble and discuss all the reports on the kinetics of the reactions of nucleophilic reagents with the thio compounds described above. Whenever possible these mechanisms will be compared to those of the corresponding oxygen compounds with the aim of assessing the role of the sulfur atom on these reactions.

The majority of the reactions described in this review proceed by attack of the nucleophile to the C═O or C═S group of the substrate, which, in most cases, is its best electrophilic center. Nucleophiles interacting with those electrophilic carbons, in most cases, may attach to form transitory tetrahedral intermediates from which the leaving group (RO^- or RS^-) then detaches. This mechanism is usually called stepwise (as an example, see Scheme 1 for the thiolysis of thiolacetates). Experimental evidence has very often indicated such behavior.

Another possibility is the concerted mechanism, whereby attack of the nucleophile at the electrophilic center of the substrate occurs concertedly with leaving-group departure in a single step. This mechanism takes place when the conceivable tetrahedral intermediate is either very unstable but still exists or

† In this review, the generic terms thioesters, thiocarbonates, thiocarbamates, and halogenothioformates will be used to comprise the corresponding thiol, thiono, and dithio derivatives.

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when is so unstable that it does not exist. In the latter case, the mechanism is called enforced concerted.[1g]

According to the above antecedents, the reasons for the reactions to choose one of the above mechanisms are directly related to the stability of the tetrahedral intermediate. It is one of the purposes of this review to discuss the factors that affect the stability of this intermediate and, therefore, the mechanism of these reactions.

One of the fundamental tools that have been used to distinguish between the above mechanisms is the Brönsted-type plot, which is a graphical representation of log k vs pK_a, where k is the nucleophilic rate constant and K_a is the dissociation constant of the conjugate acid of either the nucleophile or the leaving group of the substrate. These plots are often linear, and the slopes are usually designated as β_{nuc} and β_{lg}, respectively. The magnitude of these slopes are quite different depending on the mechanism (concerted vs stepwise) and the rate-determining step, in the case of the latter mechanism. We will see in this review how the magnitude of the Brönsted slopes allow one to distinguish between both mechanisms and whether formation or breakdown of the intermediate is rate-limiting in the stepwise process.

On the other hand, some nucleophilic reactions exhibit curved Brönsted-type plots with linear portions at low and high pK_a values. These are usually called biphasic Brönsted plots. These have been interpreted in terms of a tetrahedral intermediate on the reaction path and a change in the rate-determining step from breakdown to formation of the intermediate as the basicity of the nucleophile or the leaving group varies. Examples of biphasic Brönsted plots can be seen in Figure 1 for the reactions of 2,4-dinitrophenyl acetate with pyridines and secondary alicyclic amines. These reactions will be discussed in detail under section II.A.

An important question arises from the stepwise reactions of primary or secondary amines with the above compounds. Since the zwitterionic tetrahedral intermediate formed is acidic, is it possible that it gives a proton to a base to yield an anionic intermediate? In which cases can this happen? What experimental results can show the existence of both intermediates? All these questions will be dealt with in this review.

Another interesting mechanism involves elimination of a substrate's α-hydrogen and leaving group, forming a ketene intermediate. This mechanism requires an α-hydrogen and occurs more readily with thiol esters and thiocarbamates than with their oxygen analogues, as will be seen.

Other possible mechanisms that can take place in some of the reactions involved in this review, although rarer, are desulfurization of isothiocyanates, thioamides, thioureas, and dithiocarbamates by heavy metal ions and unimolecular substitution (S_N1) in the hydrolysis of chlorothiono-, chlorodithio-, and chlorothiolformates.

Although reports as old as 1948 are included in this review, the main discussion is focused on the literature since 1980, especially that from 1990 to date.

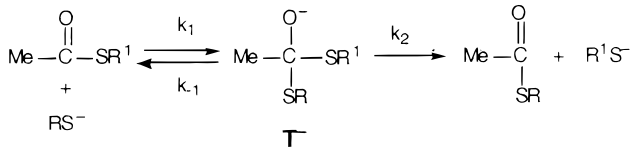
II. Thioesters

A. Thioalkanoates

The hydrolysis of thiolacetates has been the subject of numerous kinetic studies, either in water[2] or in aqueous organic solvent mixtures.[3] Also, the aminolysis and the reactions of other nucleophilic reagents with these derivatives in water[2c,d,4] and organic solvents[5] have been subjected to kinetic scrutiny.

The mechanisms of the nucleophilic reactions of thiol anions with 4-nitrophenyl thiolacetate and 2-hydroxyethylthiolate anion with aryl and alkanethiolacetates have been investigated by Hupe and Jencks.[6] A biphasic Brönsted-type plot was found in the former reactions, with slopes $\beta_{nuc} = 0.27$ and 1.0, at high and low nucleophile basicity, respectively. The plot was explained on the basis of an anionic tetrahedral intermediate (T^-) on the reaction path and a change in the rate-determining step from that for k_2 to that for k_1 as the nucleophile basicity increases (see Scheme 1).[6] An equation derived from

Scheme 1



the steady-state treatment to T^- gives excellent account for the experimental points. The curvature center on the pK_a axis of the Brönsted plot (p$K_a°$) coincides nicely with the pK_a of 4-nitrothiophenol, which confirms the existence of T^- since at this point $k_{-1} = k_{-2}$.[6]

The Brönsted plot for the reactions of 2-hydroxyethylthiolate with thiolacetates is linear with slope $\beta_{lg} = -0.32$, which was attributed to the k_1 step of Scheme 1 being rate determining. This is reasonable since the nucleophile (pK_a 9.6) is more basic than the leaving thiols (pK_a 2.7−7.9). With the values of β_{nuc} and β_{lg}, which measure the change in effective charge (compared with that upon protonation)[1c,e] in going from reactants to the rate-determining transition state, a map of effective charges on the atoms of the attacking and leaving groups can be drawn.[6] Values of 0 and −1 are assigned to the sulfur atoms of the thiol and its conjugate base. The effective charge on the sulfur atom of the thiolester is + 0.38, as indicated by the value of the Brönsted slope for the equilibrium for thiolester formation from thiol and acetic acid.[6]

The reactions of phenoxide and alkoxide anions with 4-nitrophenyl thiolacetate were also kinetically studied by Hupe and Jencks.[6] The Brönsted plots are linear with slopes $\beta_{nuc} = 0.68$ and 0.17 for phenoxide and alkoxide anions, respectively. Nucleophile attack is believed to be the rate-determining step in these cases. The former slope is abnormally large compared to that for thiolate anions; the much smaller slope for alkoxide attack was attributed to a solvation effect.[6]

Douglas has extensively studied the hydrolysis of alkyl and aryl thiolacetates and thiolesters.[7,8] For the

alkaline hydrolysis of thiolacetates, a linear Brönsted plot for the leaving thiolate group was found, with slope $\beta_{lg} = -0.33$, similar to that obtained with oxygen esters but with a lower intercept than that for the oxy analogues. The lower reactivity of thiolacetates (compared to oxyacetates with isobasic leaving groups) and the similar β_{lg} values suggest that the mechanism is the same for both classes of substrates, i.e., rate-determining formation of an anionic tetrahedral intermediate by OH^- attack to the CO group.[7] From the Brönsted plots it was also deduced that thiolacetates are as reactive toward OH^- as oxyacetates bearing the same leaving group (except for the O or S atom). For isobasic leaving groups it was found that thiolacetates are between 1 and 2 orders of magnitude less susceptible to hydroxide ion attack than are oxygen acetates.[7]

Another piece of evidence that alkaline hydrolysis of thiolacetates is not ruled by elimination−addition pathways, such as E2 or E1cB, is the nonincorporation of deuterium into the acetyl group of the acetate product in the reactions carried out in D_2O.[7] In the E1cB mechanism, incorporation of three D atoms is expected due to the fact that there is a fast equilibrium between CH_3COSR and its conjugate base CH_2^-COSR (whereby two D atoms are incorporated into the carbanion, giving CD_2^-COSR) and decomposition of the latter to $CD_2{=}CO$, which further hydrates (by D_2O) to CD_3COO^-. The E2 mechanism involves deprotonation of the substrate concerted with leaving-group departure to yield $CH_2{=}CO$. Therefore, only one D atom is expected to incorporate into the acetate product due to hydration of CH_2CO by D_2O.[7]

Douglas has also evaluated the relative nucleofugalities of RS and RO from the conjugate bases of acetoacetates and fluorene esters.[8] This was carried out through plots of $\log(k_S/k_O)$ vs ΔpK_a, where k_S and k_O are the rate constants for RS and RO leaving from the corresponding carbanions and $\Delta pK_a = pK_a$ (ROH) $- pK_a$ (RSH). From these isostructural plots it was found that at $\Delta pK_a = 0$ (isobasic point), RO is a better nucleofuge than RS by a factor of 5×10^3 for acetoacetates and 79 for fluorene esters.[8]

Storer has investigated the mechanism of alkaline hydrolysis of alkyl dithioacetates and other dithioalkanoates.[9] A rapid equilibrium of the reactants with an enethiolate anion was observed, followed by a slow reaction of OH^- with the enethiolate anion and the dithioester through a dianionic tetrahedral intermediate. The reason a similar enethiolate anion is not formed in the alkaline hydrolysis of alkane thiolacetates and acetates was attributed to the lower α-CH acidity of these esters compared to dithioesters.[9] The enethiolate anion is not observed in the reactions of methoxide ion with dithioacetates in methanol; this was attributed to a possible reversal in the relative rates of hydrolysis and formation of this species upon changing the solvent from water to methanol.[9]

The general base-catalyzed hydrolysis mechanism of ethyl trifluorothiolacetate is well established.[2i] A proton inventory was carried out for this reaction in the presence of dihydrogen phosphate monoanion at pH 4.2.[10] The proton inventory plot[11] for the water reaction indicates the presence of three protons undergoing bonding changes in the transition state, in accordance with a previous finding.[2k] For the phosphate monoanion reaction, only a one-proton transition state was found, as indicated by the linear proton inventory plot obtained.[10] The latter result is in agreement with that of the imidazole-catalyzed hydrolysis of acetylimidazole and ethyl trifluorothiolacetate.[2l]

It has been found that molybdate dianion (MoO_4^{2-}) is a remarkable nucleophile toward 4-nitrophenyl thiolacetate.[12] The nucleophilic character of the reaction is based on a solvent kinetic isotope effect of 1.0. Although molybdate dianion is over 1000 times less basic than phosphate dianion, it is 35 times more nucleophilic toward 4-nitrophenyl thiolacetate at 27 °C.[12a] It was also found that molybdate dianion (pK_a 4) is as reactive toward this substrate as a phosphonate dianion of pK_a 12.[12b]

Curved Brönsted-type plots have been found in the reactions of oxy and thiolate anions with 4-nitrophenyl thiolformate and thiolpivalate esters.[13] These plots were explained by the presence of a tetrahedral intermediate on the reaction path and a change in the rate-determining step, as in the similar reactions of thiolacetates.[6] The larger Brönsted slope exhibited by the reactions of phenoxide anions with thiolformate and thiolacetate esters, as well as with the oxy analogues, compared to thiolpivalate and pivalate esters was explained by a solvation effect. This arises from the larger solvation of alkoxide anions than phenoxide anions, which results in curved (downward) Brönsted plots for the reactions of these anions with thiolformate and thiolacetate esters and their oxy analogues. This curvature diminishes and becomes almost a straight line with a small β_{nuc} value for reactions of these anions with thiolpivalate and pivalate esters, due to sterically restricted solvation. No such effect was found for the thiolate anions since no difference in the magnitude of the above Brönsted slopes was observed for the reactions of these anions. This was attributed to a much lower solvation of thiolate anions than their oxy analogues. The greater reactivity of the formate esters relative to the acetates was attributed to the ease of formation of the tetrahedral intermediate in the former reactions.[13]

The hydrolyses of 4-nitrophenyl thiolacetate and thiolformate and phenyl thiolacetate in phosphate buffer have been subjected to kinetic analysis.[14] The pseudo-first-order rate constant (k_{obs}) is linearly dependent on the total buffer concentration, with intercept k_0 and slope k_{cat} (eq 1). The uncatalyzed

$$k_{obs} = k_0 + k_{cat}[HPO_4^{2-}] \quad (1)$$

hydrolysis rate constant (k_0) follows eq 2. A similar

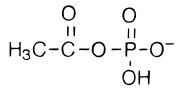
$$k_0 = k_{H_2O} + k_{OH^-}[OH^-] \quad (2)$$

equation holds for the reactions in D_2O.

The kinetic isotope effect obtained for the reactions of 4-nitrophenyl thiolacetate is $k_{H_2O}/k_{D_2O} = 2.2$ and $k_{OH^-}/k_{DO^-} = 0.6$; for 4-nitrophenyl thiolformate, $k_{H_2O}/$

$k_{D_2O} = 3.2$. These values are consistent with those found in the hydrolysis of activated oxyesters, whereby two water molecules and one OH^- are involved in the transition state of the uncatalyzed and alkaline hydrolysis, respectively.[15] It was also found that analogous *S*- and *O*-esters are of comparable reactivity toward OH^-, and water and hydroxide attack on the thiolformate ester are ca. 100-fold and 350-fold faster, respectively, than those for the corresponding thiolacetate ester.

From plots of log k_{cat} vs pH and pD, the values of the rate constants for the reactions of mono- (k^M) and dianionic (k^D) phosphate were obtained.[14] The solvent kinetic isotope effects are $k^D_{H_2O}/k^D_{D_2O} = 1.0$ and $k^M_{H_2O}/k^M_{D_2O} = 2.1$ for 4-nitrophenyl thiolacetate and $k^D_{H_2O}/k^D_{D_2O} = 0.8$ for the thiolformate. These results together with the NMR detection of acetyl and formyl phosphate intermediates (**1** and **2**, respectively) indicate that phosphate dianion acts as a nucleophile and the monoanion as a general base in these reactions. For the reaction of phenyl thiolacetate it



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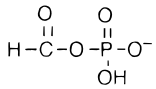


2

was found, by NMR analysis (monitoring the signals corresponding to the substrate and acetyl phosphate), that phosphate dianion behaves as both a nucleophile and a general base; the ratio of the rate constants k_{nuc}/k_{gb} is unity at 37.5 °C.[14] These observations are in agreement with well-established principles of carbonyl reactions, i.e., nucleophiles cannot displace much poorer nucleofuges from the substrates.[16]

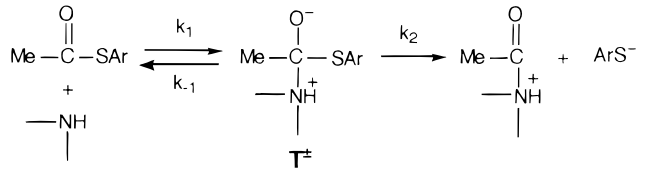
The reaction of OH^- with 4-nitrophenyl thiolacetate is 2-fold slower than that with the oxy analogue, and OH^- is 10-fold less reactive toward 4-nitrophenyl thionobenzoate than the analogous benzoate.[17] On the other hand, 4-$ClC_6H_4S^-$ is 300- and 17000-fold more reactive toward the thiolacetate and thionobenzoate, respectively, compared to the corresponding oxy analogues. These results indicate that highly polarizable nucleophiles are more reactive than nonpolarizable ones toward polarizable substrates.[17]

In the aminolysis (primary amines, including α-effect amines) of 4-nitrophenyl thiolacetate and its oxy analogue, there is no polarizability effect on the α-effect.[18] This conclusion is based on the good linear correlation between log k_s and log k_o, where the rate constants k_s and k_o refer to the aminolyses of the thio derivative and its O-analogue, respectively. The α-effect amines are considered more polarizable than normal amines.[18] Therefore, if polarizability had any influence on the α-effect, the α-effect amines would show enhanced reactivity toward the more polarizable thiolacetate than the O-analogue; this was not observed in the above correlation. This would indicate that the α-effect is not related to a polarizability effect.[18]

The kinetics of aminolysis (by imidazole) of a series of *m*- and *p*-substituted phenyl thiolacetates in aqueous solution are first order in both the substrate and the amine. The apparent second-order rate constant (k'_{im}) for the electron-releasing substituents decreases as the pH increases.[19] The second-order rate constant (k_{im}) follows a nonlinear biphasic Hammett plot with slope $\rho = -1.0$ for electron-releasing substituents and $\rho = 0.6$ for electron-withdrawing groups. A similar curve is obtained for a plot of log k_{im} vs log k_{OH^-}, where k_{OH^-} is the rate constant for the reaction of OH^-. Since OH^- reacts exclusively by a nucleophilic mechanism, the above plots were interpreted in terms of a change in mechanism with the variation of substituents: unassisted nucleophilic substitution for good nucleofuges (those with large σ) and general acid-assisted (by imidazolium ion) nucleophilic attack by free imidazole for the more basic nucleofuges (those with negative σ).[19] The problem with this interpretation is that for the latter nucleofuges the order in imidazole should have been 2 (first order in both free imidazole and imidazolium ion) and not 1 as found.

A mechanistic study of the aminolysis of aryl thiolacetates in water was undertaken.[20] In the aminolysis by secondary alicyclic amines of phenyl and 4-nitrophenyl thiolacetates in water, linear and nonlinear (biphasic) Brönsted-type plots, respectively, were observed.[20a] The slope for the linear plot is $\beta_{nuc} \approx 0.9$; the biphasic plot has limiting slopes of $\beta_{nuc} = 0.9$ and 0.1 at low and high pK_a values, respectively. These results are in accord with the formation of a zwitterionic tetrahedral intermediate ($\mathbf{T}^{\pm}$) on the reaction path (Scheme 2). Its breakdown (k_2) should

Scheme 2



be rate determining for reactions of all the amines with the phenyl compound and for most of the amines with the nitrophenyl derivative. For the latter reactions, the rate-determining step changes from breakdown of $\mathbf{T}^{\pm}$ to its formation (k_1) for reaction with the most basic amine of the series (piperidine).[20a] The pK_a values of possible tetrahedral intermediates were estimated. From the pK_a value at the curvature center (p$K_a° = 10.5$) it was deduced that an amine of pK_a 4.6 (isobasic with 4-nitrothiophenol) leaves $\mathbf{T}^{\pm}$ 3×10^4 times faster than 4-nitrothiophenolate anion.[20a] Similar results are obtained for the aminolysis of aryl acetates: amines also leave the oxy-$T^{\pm}$ much faster than isobasic aryloxide ions.[1c,e] Therefore, for the purpose of N-acylation it should not make much difference whether thiolesters or oxyesters are used.

The aminolyses by pyridines (py) and secondary alicyclic amines (saa) of 2,4-dinitrophenyl (DNPTA) and 2,4,6-trinitrophenyl (TNPTA) thiolacetates in aqueous solution exhibit nonlinear (biphasic) Brönsted plots (see Figure 1 for DNPTA) with slopes $\beta_{nuc} \approx 0.2$ and 0.85 at high and low pK_a, respectively, for DNPTA, and $\beta_{nuc} = 0.2$ and 0.8 at high and low p*K*a, respectively, for TNPTA.[20b] The p$K_a°$ values are 8.9 (saa) and 6.6 (py) for DNPTA and 7.8 (saa) and 4.9

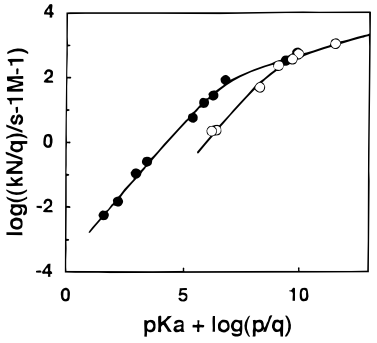


Figure 1. Brönsted-type plots (statistically corrected) for the reactions of 2,4-dinitrophenyl thiolacetate with pyridines (●) and *sec*-alicyclic amines (○) in water, 25.0 °C, ionic strength 0.2. (Reprinted with permission from ref 20b. Copyright 1991 The Royal Society of Chemistry.)

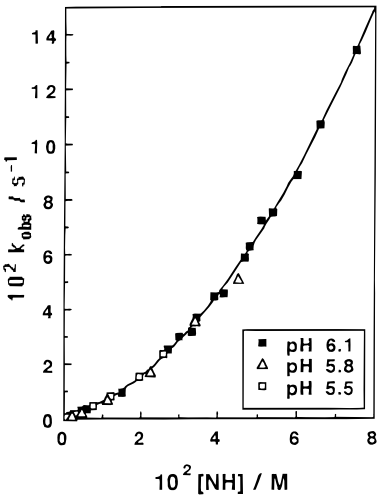
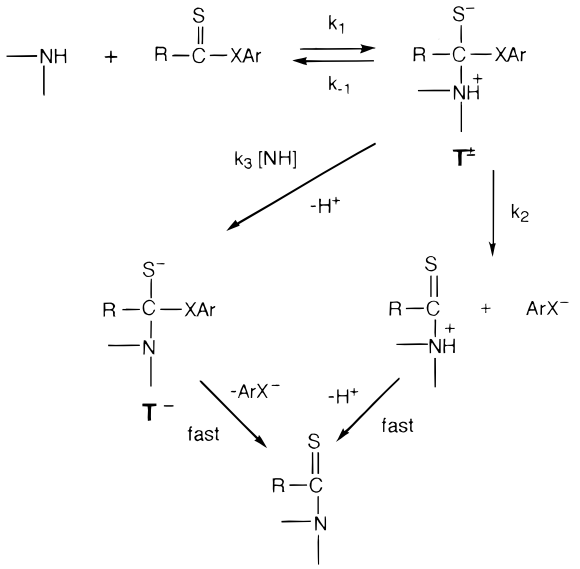


Figure 2. Plot of k_{obs} against concentration of free amine for the reaction of 4-nitrophenyl dithioacetate with piperazinium ion at three pH values, in water, 25.0 °C, ionic strength 0.2. The points are experimental, and the curve was calculated with eq 3. Adapted from ref 21b.

(py) for TNPTA. The biphasic plots can be accounted for by the presence of a $\mathbf{T}^{\pm}$ intermediate (Scheme 2) and a change in the rate-limiting step, as in the reactions of the series of saa with 4-nitrophenyl thiolacetate.[20a] On the basis of the slope values, rate equations were deduced for the nucleofugality of the two classes of amines and the leaving groups from $\mathbf{T}^{\pm}$, as functions of amine and leaving-group basicities. From these equations it was deduced that saa are better nucleofuges from $\mathbf{T}^{\pm}$ than isobasic pyridines. Comparison of these equations with others derived for the aminolysis of aryl acetates indicates that the "push" provided by ArO (to expel a given amine) from an oxy-$\mathbf{T}^{\pm}$ is stronger than that by an isobasic ArS in $\mathbf{T}^{\pm}$.[20b]

The aminolysis (saa) of phenyl and 4-nitrophenyl dithioacetates in water show nonlinear (upward) plots of the pseudo-first-order rate constants (k_{obs}) vs amine concentration (see Figure 2 as an example).[21] These were explained by a mechanistic scheme with a zwitterionic ($\mathbf{T}^{\pm}$) and an anionic ($\mathbf{T}^{-}$) tetrahedral intermediate (Scheme 3, R = Me, X = S).[21] In this scheme the k_3 step is the deprotonation of $\mathbf{T}^{\pm}$ by an

Scheme 3



amine (NH) to yield $\mathbf{T}^{-}$. By the steady-state treatment to both intermediates, eq 3 was derived. The

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

pK_a values of intermediates $\mathbf{T}^{\pm}$ were estimated and the rate micro-constants of Scheme 3 were determined by nonlinear least-squares fitting to eq 3.

Brönsted plots were obtained for k_1, k_{-1}, and K_1 ($= k_1/k_{-1}$) that give slopes in accordance to the steps involved.[21a] It was deduced that $\mathbf{T}^{\pm}$ of Scheme 3 (X = S) is more stable kinetically than the thiol analogue since both k_{-1} and k_2 in Scheme 3 (R = Me, X = S) are smaller than the equivalent coefficients in the same aminolysis of the corresponding thiolacetates.[21] Comparison with the reactions of analogous dithiocarbonates and thiolacetates indicates that substitution of Me by MeO or EtO and S^- by O^- in $\mathbf{T}^{\pm}$ destabilizes this intermediate.[21b] The reason catalysis by the amine (step 3 in Scheme 3) was not found in the same aminolysis of aryl thiolacetates[20] is that in the latter reactions k_2 is much larger than and k_3 is similar to the coefficients in the aryl dithioacetate reactions.[21]

In contrast to the above nonlinear plots of k_{obs} vs [amine], the reactions of anilines and benzylamines with substituted phenyl dithioacetates in acetonitrile follow linear plots.[22] According to the values of the Brönsted and Hammett slopes obtained for X-substituents on the amine and Z-substituents on the leaving group, the cross-correlation coefficient[23] values of $\beta_{XZ} = 0.1-0.13$, and the secondary kinetic isotope effects on the nucleophiles ($k_H/k_D = 1.05-1.14$), it was deduced that these reactions follow a mechanism similar to Scheme 3 but with $k_3[NH] \ll k_2$. For anilines and benzylamines, the rate-determining steps are k_2 and k_1, respectively. This is because anilines are better nucleofuges from the zwitterionic intermediate than the thiolate leaving groups, but benzylamines (being much more basic than anilines) are worse leaving groups than thiolate

anions. The lack of amine catalysis was attributed to the slower proton transfer (lower k_3) in acetonitrile compared to water.[22]

The aminolysis (saa) of phenyl thionoacetate in water follows the mechanism depicted in Scheme 3 (R = Me, X = O). Base catalysis by OH^- and the amine is observed for the conversion of $\mathbf{T}^{\pm}$ to $\mathbf{T}^-$.[24] The Brönsted slopes obtained for the rate microconstants k_1, k_{-1}, and K_1 ($= k_1/k_{-1}$) are $\beta_{nuc} = 0.16$, -0.82, and 1.0, respectively, which are in line with the usual slope values for rate-determining formation of $\mathbf{T}^{\pm}$ in thio− and oxy−carbonyl derivatives.[1c,20,21,25] The values of both k_{-1} and k_2 are smaller than those for the same aminolysis of phenyl acetate. This was attributed to the higher polarizability of the C═S bond compared to C═O, which hinders the formation of the C═S bond from $\mathbf{T}^{\pm}$ relative to the C═O bond from the analogous oxy $\mathbf{T}^{\pm}$,[26] thus decreasing the rate of expulsion of both the amine and phenoxide ion from the intermediate.[24] The k_1 value for the thionoacetate is smaller than that for both the corresponding acetate and dithioacetate, due to the softer character of C═S compared to C═O (a saa is considered relatively hard) and the larger electron-donating effect of PhO relative to PhS, respectively.[24]

B. Thiobenzoates

There have been some early kinetic studies on the hydrolysis of thiolbenzoates and thionobenzoates[3b,17,27] as well as on the aminolysis of these esters.[5a,b,27a,28]

The kinetics of the hydrolysis of ethyl thiolbenzoates catalyzed by metal ions has been extensively studied.[27b−e,29] Catalysis of the hydrolysis of ethyl 4-methoxy and ethyl 4-nitro thiolbenzoates by tetrachlorogold(III), $AuCl_4^-$, is much faster than that by H_3O^+. Under the experimental conditions, the simultaneous catalyses by $AuCl_4^-$, $AuCl_3(OH)^-$, and $AuCl_3(H_2O)$ are observed. For the nitro derivative, the reaction with $AuCl_4^-$ is slower than those with the other two catalysts. No solvent kinetic isotope effects were found for either ester. Substituent effects, activation parameters, and the absence of both a solvent kinetic effect and a common ion effect at high Cl^- concentration suggest that the mechanism involves slow metal ion transfer to sulfur.[29]

The acid-catalyzed hydrolysis of ethyl thiolbenzoates and thionobenzoates has been studied kinetically.[30] For the former reactions the main mechanism is concerted A−S_E2, which involves both proton transfer (by undissociated sulfuric acid) and carbon−sulfur bond breaking. The hydrolysis of the thiono compound is governed by an A-2 mechanism consisting of a reversible protonation step, followed by water addition to form a tetrahedral intermediate. At acid concentrations lower than ca. 62 wt %, the first step can become rate limiting.[30]

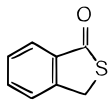
In reactions with alkali metal ethoxides in ethanol, 4-nitrophenyl thiolbenzoate and benzoate (PhCOSNP and PhCOONP, where NP is 4-nitrophenyl) had equal reactivity. Thus, it mattered little whether the nucleofuge was NPS or NPO. On the other hand, PhCOSNP with its CO moiety reacted 10 times as fast as 4-nitrophenyl dithiobenzoate (PhCSSNP) with its CS group. Reactivity also increased with the size of the metal ion.[31]

4-Nitrophenyl thiolbenzoate was found to be more reactive toward phenoxide ions than its oxy analogue, although the difference in rate becomes smaller as the phenoxide basicity increases. This fact was explained by the hard and soft acid−base principle. The softer the phenoxide ion (the more electron-withdrawing the substituent), the greater preference for a softer center such as the thiolcarbonyl carbon. When the nucleophile is OH^-, the thiol derivative is less reactive than its oxy analogue. This is because the hard OH^- anion binds preferably to the harder carbonyl carbon.[32]

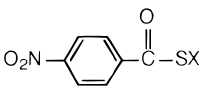
A good linear Brönsted plot has been obtained in the reactions of phenoxides with 4-nitrophenyl thiolbenzoate. However, 4-chlorobenzenethiolate shows a positive deviation whereas OH^- shows a negative deviation from the Brönsted line. These deviations were attributed to polarizability and solvation effects. Alpha-effect nucleophiles, e.g., PhCO−NH−O^- (except the very basic ones), show remarkable rate enhancements; solvation and polarizability were proposed to be important for the alpha effect.[33] This conclusion is in contrast to that drawn in the aminolysis of the corresponding thiolacetate, i.e., polarizability is not involved in the alpha effect.[18]

The reactions of 4-nitrophenyl thiolbenzoate and its thiono and oxy analogues with alkoxides, aryloxides, and thioaryloxides in ethanol have been studied kinetically.[34] For the reactions of hard nucleophiles (e.g., EtO^- and $CF_3CH_2O^-$), the substitution of O by S in the leaving group has little effect on the rate whereas the same change in the carbonyl group leads to a 10-fold rate decrease. This can be attributed to the fact that the thiocarbonyl group is softer (more polarizable) than the carbonyl. The reactivity of these esters toward delocalized phenoxide ions (of intermediate hardness) is in the order oxy < thiono < thiol. For thioaryloxides (highly polarizable, i.e., very soft), the reactivity follows the order oxy < thiol ≪ thiono. The difference in reactivity was attributed to a polarizability effect.[34]

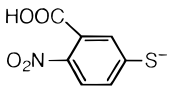
The alkaline hydrolyses of thiophthalide (**3**) and ethyl thiolbenzoate exhibit curved (upward) k_{obs} vs [OH^-] plots in highly alkaline media, yet no ^{18}O-exchange is observed in the recovered substrates.[35]



3



4 X = CH_2COOEt
5 X = CH_2COOH
6 X = $CH_2CH_2N(CH_3)_2$
7 X = $CH_2CH_2N(CH_3)_3^+$



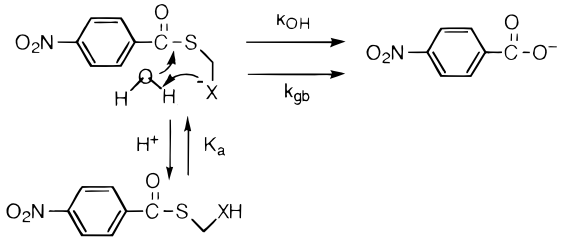
8

The solvent kinetic isotope effects for the reaction of **3** are 0.83 and 0.67 for the coefficients first and second order in OH^-, respectively. These facts argue against rate-determining OH^- intervening in the decomposition of a tetrahedral intermediate. The plot of k_{obs} vs the acidity function H^-[36] is linear, which indicates that only one OH^- is involved in the

hydrolysis and the nonlinear plots (vs [OH^-]) are due to medium and/or ion-pairing effects.[35]

The hydrolysis of 4-nitrothiolbenzoate esters of ethyl 2-mercaptoacetate, thioglycolic acid, 2-(dimethylamino)ethanethiol, and 2-(*N,N,N*-trimethylammono)ethanethiol (**4**−**7**) at different pH values has been investigated kinetically.[37] Plots of log k_{obs} vs pH are linear for **4** and **7**, which indicates exclusive OH^- nucleophilic attack. Esters **5** and **6** show a plateau in these plots, most probably due to participation of pendant carboxylate and dimethylamino groups, respectively, as intramolecular general bases. At higher pH, the nucleophilic attack of OH^- is predominant for **5** and **6**. For the latter, the solvent deuterium kinetic isotope effect at pH 10.2 (plateau region) is 2.2. This reaction was also studied in the presence of the Ellman's anion (**8**), which is one of the products of the general base reaction. The rate of appearance of this anion does not depend on its concentration, and this rate is identical to the rate of disappearance of **6**. These results support a mechanism with a preequilibrium between the substrates and their conjugate acid or base, followed by slow general base catalysis by the pendant group (Scheme 4), and rule out other types of possible mechanisms.[37]

Scheme 4



For **6**, the rate of hydrolysis at pH 8 (plateau region, where the intramolecular general base process is operative) is 50 times faster than that of **7** (where the intramolecular process is not possible) under the same conditions. The hydrolysis of **5** at pH 6.6 and 3.6 (plateau region) is 16 and 16 000 times faster, respectively, than that of **4** in the same conditions.[37]

In the aminolysis (primary amines) of 4-nitrophenyl thionobenzoate, a curved Brönsted plot (slopes of ca. 0.9 at low pK_a and 0.1 at high pK_a) was obtained, which was explained by the formation of a zwitterionic tetrahedral intermediate ($T^{\pm}$) on the reaction path and a change in the rate-determining step.[38] The center of curvature appears at pK_a 9.2. Since the pK_a of 4-nitrophenol is 7.1, it means that an amine isobasic with this leaving group would leave $T^{\pm}$ ca. 100 times faster than 4-nitrophenolate anion. The aminolysis of the oxy analogue shows a linear Brönsted plot with slope 0.9, which indicates that breakdown of $T^{\pm}$ is rate limiting over the whole basicity range.[1c,e] Amines react ca. 200-fold faster with the thiono compound than with the oxy analogue, although OH^- shows similar reactivity toward them. It is concluded that S^- in $T^{\pm}$ can provide a significantly greater driving force for the expulsion of 4-nitrophenolate ion than O^- in the analogous intermediate.[38] This is contrary to the findings for the aminolysis of dithio and thiono acetates.[21,24]

Kinetic studies have been carried out on the reactions of anilines with phenyl thiolbenzoates in methanol as a function of substituents in the amine (X) and the acyl (Y) and leaving (Z) groups of the substrate.[39] The second-order rate constants show linear Brönsted and Hammett plots. The magnitudes of both ρ_X (−5.1 for Y = Z = H) and β_X (1.84 for Y = Z = H) are relatively large, compared to similar reactions in methanol. The magnitudes of ρ_Z and β_Z are also large. This was explained in terms of a transition state (TS) where both bond formation and bond breaking are relatively advanced. The sign of both cross-interaction coefficients[23] ρ_{XZ} and β_{XZ} are positive, which would indicate an "earlier" TS for stronger nucleophiles and better nucleofuges. The magnitudes of both ρ_{XY} and ρ_{YZ} are relatively large, e.g., −1.48 and −1.38, respectively for Z = H, indicating that bond formation is more advanced than bond breaking in the TS, which in turn is consistent with an associative S_N2 mechanism. Inverse secondary kinetic isotope effects (SKIE) were observed with deuterated anilines, which would also be consistent with a concerted mechanism in which the TS has a structure similar to, but looser than, that of a typical associative S_N2 reaction.[39]

In contrast to the above results, the reactions of the same substrates with benzylamines in acetonitrile are thought to obey a stepwise mechanism, with rate-limiting breakdown of a zwitterionic tetrahedral intermediate ($T^{\pm}$).[40] This conclusion is based on the signs of the cross-interaction coefficients,[23] ρ_{XY} (>0), ρ_{YZ} (<0), and ρ_{XZ} (>0), the large magnitudes of ρ_X and ρ_Z, and the small SKIE, k_H/k_D > 1.0, involving deuterated benzylamines.[40] This is a surprising result in view of the stronger basicity of benzylamines (pK_a in water 9.1−9.5) than benzenethiolates (pK_a in water 5.9−7.0), which should lead to a mechanism in which the formation of $T^{\pm}$ is rate determining (since expulsion of benzenethiolates from $T^{\pm}$ should be faster than that of benzylamines).[1c,e] The unexpected behavior was attributed to a possible change in the relative basicities of the amines and benzenethiolates in water and acetonitrile and also to the fact that the acyl group may be acting as a relatively strong electron donor, favoring, therefore, the expulsion of the amine from $T^{\pm}$.[40] However, this result is hard to reconcile with the fact that in the reactions of phenyl dithiobenzoates with the same amines in the same solvent the formation of $T^{\pm}$ is the rate-determining step (see below).

In the reactions of 4-nitrophenyl thionobenzoate with secondary alicyclic amines in 20 mol % DMSO−water, upward curved plots of k_{obs} vs [amine] were found.[41] These are consistent with the presence of two tetrahedral intermediates, as shown in Scheme 3, in which the rate-determining step depends on both the basicity and the concentration of the amine. This step changes from k_3 to k_1 in Scheme 3 (R = Ph, X = O) as the amine concentration increases and occurs at lower concentration with a more basic amine.[41]

The reactions of phenyl dithiobenzoates with benzylamines in acetonitrile show small magnitudes of ρ_X and ρ_Z, as well as β_X and β_Z, and very small magnitudes of ρ_{XY} and ρ_{YZ}. These results, together

with an inverse SKIE for deuterated benzylamines, are in accord with a stepwise mechanism with rate-determining amine attack on the thiocarbonyl carbon to form the intermediate $T^{\pm}$.[42]

The reactions of the above substrates with anilines in the same solvent exhibit large Brönsted slopes for the nucleophile ($\beta_X = 0.80-1.07$).[43] The signs of the cross-interaction coefficients are $\rho_{XY} > 0$, $\rho_{YZ} < 0$ and $\rho_{XZ} > 0$. The SKIE for deuterated anilines are normal and close to unity ($k_H/k_D = 1.005-1.018$). All these results are in agreement with a stepwise mechanism with rate-determining breakdown of $T^{\pm}$. The magnitudes of both ρ_{XY} and ρ_{YZ} are smaller than those for the reactions of anilines with phenyl thiobenzoates,[39] indicating looser bondings in the transition state for both the amine and leaving group compared to thiobenzoates. The greater decrease in the magnitude of ρ_{XY} than that of ρ_{YZ} in going from the thiobenzoate to the dithio analogue indicates that the thiocarbonyl group favors amine expulsion from $T^{\pm}$ relative to carbonyl.[43]

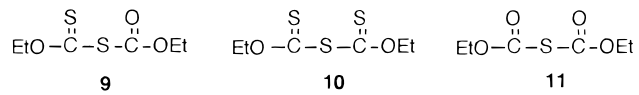
III. Thiocarbonates

The acid-catalyzed decomposition of *O*-alkyl dithiocarbonates ($ROCS_2^-$)[44] and *O*-alkyl monothiocarbonates ($ROCOS^-$)[45] in aqueous buffer solution follow the rate law given by eq 4.

$$k_{obs} = k_{H_2O} + k_{H^+}[H^+] + k_{HA}[HA] \qquad (4)$$

The Brönsted slopes for k_{H_2O} are $\beta_{lg} = -1.1$ and -1.3 for the monothio and dithio carbonates, respectively, which were interpreted as a late TS in the decomposition reaction.[45] The general acid coefficients are $\alpha = 0.57-0.58$ and $0.8-0.9$ for the monothio and dithio compounds, respectively.[45] Inverse SKIE for k_H are observed for both series of substrates. The high Brönsted α value for *O*-ethyl dithiocarbonate coupled with a large inverse isotope effect ($k_D/k_H = 2.53$) places this reaction in the borderline between specific acid-catalyzed and concerted mechanisms, although the latter is favored.[45] Brönsted β_{lg} values for the acid-catalyzed decomposition of these substrates are small, in accordance with concerted general acid catalysis.[45]

In the reactions of *S*-ethoxycarbonyl *O*-ethyl dithiocarbonate (**9**) with *O*-alkyl dithiocarbonate ($ROCS_2^-$) and *O*-alkyl thiocarbonate ($ROCOS^-$) anions in 95% ethanol−water, the symmetrical pyrothiocarbonates, bis(ethoxythiocarbonyl) sulfide (**10**) and bis(ethoxycarbonyl) sulfide (**11**), are produced, respectively. The reaction of **9** with $BuOCS_2^-$ yielded first $BuOCS_2$-CSOEt and then $BuOCS_2CO_2Et$ and $(BuOCS)_2S$.



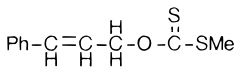
9 **10** **11**

These results seem to indicate that the thiocarbonyl group of **9** is more reactive than its carbonyl group.[46a] Nonetheless, studying the same reactions under an excess of anions, it was found that substrate **9** reacts faster than **10** toward $ROCOS^-$, which means that the CO group is more reactive than CS toward $ROCOS^-$.[46b] On the other hand, the reaction of $ROCS_2^-$ with the unsymmetrical substrate **9** is faster than that with **11**, indicating that $ROCS_2^-$ reacts faster with the CS group compared to CO.[46b]

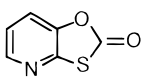
The catalytic rearrangements of *O*-alkyl *S*-alkyl dithiocarbonates (RO−CS−SR, xanthates) to *S*-alkyl *S*-alkyl dithiocarbonates (RS−CO−SR) have been subjected to kinetic analyses.[47] The solvolysis of *O*-cinnamyl *S*-methyl dithiocarbonate (**12**) in various solvents at 60 °C afforded a mixture of *S*-(1-phenylallyl) and *S*-cinnamyl *S*-methyl dithiocarbonates,[48] the former product arising from a [3,3]-sigmatropic rearrangement.[47b] The proportion of the latter was 35.8% in phenol, 10.3% in 80% aqueous ethanol, and 4% in ethanol.[48] Plots of log of the first-order rate constants vs Reichardt[49] E_T and Grunwald−Winstein[50] *Y* values are linear. The slopes are 0.143 and 0.0792 for the former plots in aprotic and protic solvents, respectively. For the Grunwald−Winstein plots, the slopes are 0.31, 0.32, and 0.58 for alcohols, aqueous ethanol, and phenol−benzene mixtures, respectively.[48] These results together with MINDO/3 calculations indicate that allylic xanthates undergo [3,3]-sigmatropic rearrangement via a polarizable transition state.[48] The thiono−thiol rearrangement of *O*-alkyl *S*-methyl dithiocarbonates (xanthates) to *S*-alkyl *S*-methyl dithiocarbonates catalyzed by substituted pyridine *N*-oxides and phenols has also been studied kinetically.[51] The best among the former catalysts is 4-piperidinopyridine *N*-oxide. MINDO/3 calculations indicate that the dithiocarbonates are more stable by ca. 9 kcal/mol than the corresponding xanthates.[51]

The kinetics of decomposition of ethyl xanthate ($EtOCS_2^-$) in aqueous solution was studied as a function of pH and temperature.[52] At pH < 7, the rate increases rapidly with decreasing pH, due to the formation of $EtOCS_2H$, which decomposes to EtOH and CS_2. At pH 7−8, the decomposition rate is small; the rate increases again at pH 9−10, due to the formation of $(EtOCS_2)_2$. At pH > 10, the decomposition becomes slower due to the appearance of an additional degradation product, $EtOCS_2O^-$.[52] No reason is given for the variation of the rate constant at pH > 9.

The aminolysis of 2(*S*),3-pyridinediyl thiocarbonate (**13**) in THF, ethyl acetate, or benzene (under excess of primary amines) leads to the corresponding symmetrically disubstituted ureas (RNH−CO−NHR).



12



13

Equivalent amounts of reactants give the carbamate intermediate. It was found that under these conditions secondary amines do not react with the carbamate.[53a] The reactivity and selectivity of **13** was attributed to electron withdrawal by the pyridine nitrogen and to the emergent tautomeric thiolactim/thiolactam array in the carbamate intermediate and the thiopyridinic product. The reactions are characterized by relatively high rates in nonpolar solvents.[53a] Similarly, the aminolysis of *S*,*S*-dimethyl dithiocar-

bonate in methanol or ethanol (using excess of primary amine) affords symmetrical ureas.[53b] α-Substituted amines react at much lower rates, and *tert*-butylamine does not react under these conditions, due to steric hindrance. Piperidine reacts at a moderate rate, affording the corresponding thiocarbamate as product. The reaction of the substrate with benzylamine in excess of the former yields the thiocarbamate and the symmetrical urea in a 1:30 ratio, indicating that the second step of the reaction is faster than the first.[53b]

The aminolyses of compounds **9**, **10**, and **11**, have been studied kinetically in 95% aqueous ethanol.[54] For the reactions with pyrrolidine, piperidine, and morpholine, under amine excess, pseudo-first-order rate constants are obtained, which are linearly related to free-amine concentration.[54b] The small slopes of the Brönsted plots are consistent with the presence of the tetrahedral intermediates $EtO-C(S^-)(NH^+)-SCXOEt$ and $EtO-C(O^-)(NH^+)-SCXOEt$, where X is O or S, whose formations are rate determining. Estimations of the rate microcoefficients involved in the reaction scheme indicates that these intermediates decompose to reactants slower than to products ($EtO-CX-NH^+$ and $EtO-CX-S^-$), confirming that formation of the tetrahedral intermediates is rate limiting. The above estimations also show that these intermediates decompose to products faster than their deprotonation by the solvent or an amine.[54b] It was found that amine attack on the CS group of the substrates is faster than that on CO, although the nature of both the substrate and the amine could change this order of reactivity.[54b]

The aminolysis of *S*-substituted phenyl *O*-ethyl dithiocarbonates ($EtO-CS-SAr$) in water has been subjected to kinetic studies.[55] Those of *S*-phenyl and *S*-(4-nitrophenyl) *O*-ethyl dithiocarbonates (PDTC and NPDTC, respectively) with a series of secondary alicyclic amines in water show pseudo-first-order rate constants under amine excess.[55a] Plots of k_{obs} vs [amine] are linear only for NPDTC; from the nonlinear plot for PDTC, rate microconstants were found for the reaction mechanism. This involves two tetrahedral intermediates, as in the aminolysis of dithioacetates[21] (see Scheme 3, R = EtO, X = S). For the aminolysis of PDTC, the Brönsted-type plot for k_1 has a slope $\beta_{nuc} = 0.22$ (Figure 3). The Brönsted plot for NPDTC is biphasic (Figure 3) with slopes $\beta_{nuc} = 0.2$ and 0.8 at high and low pK_a, respectively, and $pK_a^\circ = 9.6$ (curvature center). This was explained by a change in the rate-determining step from k_2 at low pK_a to k_1 at high pK_a (see Scheme 3, R = EtO, X = S). In the reactions of PDTC, the k_3 step competes with k_2 since the expulsion of PhS^- from $T^\pm$ is slower than the expulsion of 4-nitrobenzenethiolate from the corresponding intermediate and k_3 (diffusion controlled) is not affected.[55a]

The same aminolyses of *S*-(2,4-dinitrophenyl) and *S*-(2,4,6-trinitrophenyl) *O*-ethyl dithiocarbonates show linear plots of k_{obs} vs [amine]. The Brönsted plots for the second-order rate constants are biphasic with slopes of $\beta_{nuc} = 0.2$ and 0.8 at high and low pK_a, respectively. The Brönsted breaks at the pK_a axis for the dinitro and trinitro derivatives are $pK_a^\circ = 9.2$ and 8.4, respectively.[55b] These results are consistent with one tetrahedral intermediate ($T^\pm$) and a change in the rate-limiting step (see Scheme 2), as with the mononitro derivative.[55a] An equation was derived for $\log(k_{-1}/k_2)$ as a function of both nucleophile and leaving group basicity for *S*-aryl *O*-ethyl dithiocarbonates.[55b]

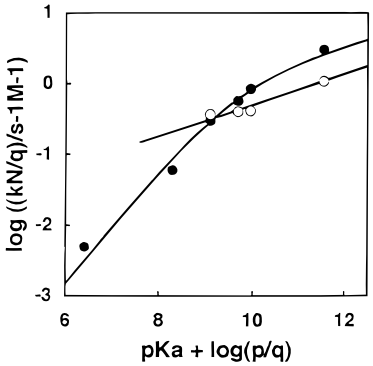


Figure 3. Brönsted-type plots (statistically corrected) for the reactions of *sec*-alicyclic amines with *S*-phenyl *O*-ethyl dithiocarbonate (○) and *S*-(4-nitrophenyl) *O*-ethyl dithiocarbonate (●) in water, 25.0 °C, ionic strength 0.2. Adapted from ref 55a.

The reactions of pyrrolidine and piperidine with a series of *S*-substituted phenyl *O*-ethyl dithiocarbonates show linear plots of k_{obs} against [amine].[55c] The plots for the reactions of piperazine and other secondary amines with 4-Cl, 4-Me, and 4-MeO phenyl *O*-ethyl dithiocarbonates are nonlinear upward, indicating the presence of two tetrahedral intermediates, as in Scheme 3. By estimation of the pK_a of $T^\pm$ it was deduced that the proton transfer from $T^\pm$ to the amine is thermodynamically favorable; therefore, k_3 is ca. 10^{10} s^{-1} M^{-1}.[55c] Estimation of the k_2 value, based on similar reactions, indicates that k_3[amine] is larger than k_2. The rate microconstants k_1 and k_{-1} were obtained by nonlinear least-squares fitting of the equation derived from the scheme to the experimental k_{obs} against [amine] points. Correlations of log k_1 and log k_{-1} with the basicity of amine and leaving groups were obtained. The k_{-1} and k_2 values in these reactions are larger than those in the same aminolysis of aryl dithioacetates, which indicates that substitution of Me by EtO as the acyl group destabilizes $T^\pm$.[55c]

The pyridinolyses of *S*-(2,4-dinitrophenyl) and *S*-(2,4,6-trinitrophenyl) *O*-ethyl dithiocarbonates in water follow kinetics first order in amine.[55d] The Brönsted plots for both substrates are biphasic with slopes $\beta_{nuc} \approx 0.2$ and 0.9 at high and low pK_a, and $pK_a^\circ = 6.9$ and 5.6 for the dinitro and trinitro derivatives, respectively; these results are in line with the mechanism in Scheme 2. Comparison of these Brönsted plots with those obtained in the reactions of the same substrates with secondary alicyclic amines[55b] shows that the latter amines are better nucleofuges from $T^\pm$ than isobasic pyridines. This is in line with the finding that quinuclidines (tertiary alicyclic amines) leave $T^\pm$ faster than isobasic pyridines.[1e] The pK_a° values for the Brönsted plots for pyridines are lower than those for the same aminolysis of *S*-(2,4-dinitrophenyl) and *S*-(2,4,6-trinitrophenyl) *O*-ethyl thiocarbonates. Since pK_a° is

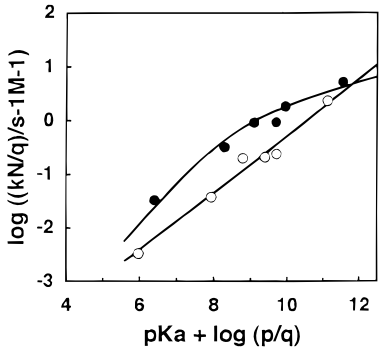


Figure 4. Brönsted-type plots (statistically corrected) for the reactions of *sec*-alicyclic amines with *S*-(2,4,6-trinitrophenyl) *O*-ethyl dithiocarbonate in water (●) and in 44 wt % aqueous ethanol (○), at 25.0 °C, ionic strength 0.2. Adapted from refs 55b and 56a. Reprinted with permission from ref 56a. Copyright 1994 John Wiley & Sons, Inc.)

linearly related to $\log(k_{-1}/k_2)$,[55d] the above result indicates that substitution of S^- by O^- in $T^\pm$ increases the amine/ArS^- nucleofugality ratio from $T^\pm$.[55d]

The kinetics of the aminolysis of *S*-aryl *O*-ethyl dithiocarbonates have also been examined in 44 wt % aqueous ethanol.[56] In the reactions of secondary alicyclic amines with the *S*-(2,4,6-trinitrophenyl) derivative, linear plots of k_{obs} vs [amine] are found.[56a] The Brönsted plot is also linear with slope $\beta_{nuc} = 0.53$ (Figure 4). The predicted curvature center for a stepwise mechanism was estimated as $pK_a° = 8.7$, which was not observed within the p*K*a range of the amine series (pK_a range ca. 6−11). These results indicate that the mechanism is concerted. Comparison with the stepwise mechanism found for the same reactions in water[55b] (see the nonlinear Brönsted-type plot in Figure 4) shows that the intermediate $T^\pm$ formed in water (as in Scheme 2) is destabilized in aqueous ethanol. This was claimed to be due to an increase in k_{-1} in the latter solvent mixture.[56a]

The reactions of *S*-phenyl *O*-ethyl dithiocarbonate with secondary alicyclic amines in 44% aqueous ethanol show nonlinear upward plots of k_{obs} vs [amine] (as in Figure 2), which is in accord with a stepwise mechanism with two tetrahedral intermediates (as in Scheme 3).[56b] The rate microcoefficients were determined or estimated from these plots. Comparison with those obtained in water reveals that k_1 is smaller and k_{-1} is larger in aqueous ethanol, in accord with the expected transition states. The Brönsted slopes for k_1, k_{-1}, and K_1 ($= k_1/k_{-1}$) are $\beta_{nuc} =$ 0.4, −0.6, and 1.0, respectively, which are consistent with those obtained in stepwise mechanisms with rate-determining formation of $T^\pm$. Comparison with the concerted aminolysis of the trinitrophenyl derivative in the same solvent mixture[56a] shows that the change of PhS by TNPS (where TNP is 2,4,6-trinitrophenyl) in $T^\pm$ greatly destabilizes this intermediate.[56b]

The reactions of *S*-(4-nitrophenyl) and *S*-(2,4-dinitrophenyl) *O*-ethyl dithiocarbonates with the same amines and solvent mixture as that used above show rate constants first order in amine.[56c] The Brönsted plots are biphasic for the reactions of both substrates, with slopes of $\beta_{nuc} = 0.3$ at high pK_a (both substrates) and 0.95 and 0.8 for the nitro and dinitro compounds at low pK_a; the $pK_a°$ values are 9.8 and 9.5, respectively. These $pK_a°$ values correlate well with that estimated for the same aminolysis of the unsubstituted substrate ($pK_a° = 11.4$); the correlation of the $pK_a°$ values with the pK_a of the leaving groups is that expected for stepwise processes. These facts confirm that in these reactions $T^\pm$ is stable enough to exist, and the mechanism for the nitro and dinitro derivatives is the same as that shown in Scheme 2.[56c]

In the reactions of *S*-(X-phenyl) *O*-ethyl dithiocarbonates (X = 4-Me, 4-MeO, H, 4-Cl, 4-NO_2, 2,4-$(NO_2)_2$, and 2,4,6-$(NO_2)_3$ with pyrrolidine in 44% aqueous ethanol, linear plots of k_{obs} vs [amine] were obtained.[56d] The Brönsted plot for the leaving group is linear with slope $\beta_{lg} = -0.2$. These results are consistent with the mechanism in Scheme 2, with the first step (k_1) rate limiting in these reactions. The reaction of *S*-phenyl *O*-ethyl dithiocarbonate with pyrrolidine is kinetically different from that with piperidine in the above solvent (despite similar basicities); the k_{obs} vs [amine] plot is linear for the former[56d] and nonlinear upward for the latter.[56b] This difference was attributed to a greater leaving ability from $T^\pm$ of piperidine than pyrrolidine.[56d] The same result was obtained for the aminolysis of aryl phenyl ethers, in which it was claimed that pyrrolidine has a superior ability, relative to piperidine, to expel a leaving group from the intermediate.[57] This fact should make the pyrrolidino N−C bond in the intermediate stronger than that for piperidine, resulting in a slower leaving rate of pyrrolidine than piperidine.

The kinetics for reactions of some of the above substrates (4-Me, 4-Cl, and 4-NO_2 derivatives) with anilines and *N*,*N*-dimethylanilines in acetonitrile have also been studied.[58] Small Brönsted slopes for the nucleophile ($\beta_{nuc} = \beta_x$ in the range from 0.4 to 0.7) and the leaving group (β_z in the range from −0.1 to −0.4) were obtained. The kinetic isotope effects for deuterated anilines are $k_H/k_D = 1.1-1.9$, and the cross-interaction coefficient is $\rho_{xz} = -0.56$. All these results were attributed to concerted mechanisms for both amine series.[58] The change in mechanism from stepwise in water and aqueous ethanol to concerted in acetonitrile can be attributed to destabilization of $T^\pm$ by the aprotic solvent.

The reactions of *S*-substituted phenyl *O*-ethyl thiocarbonates (EtO−CO−SAr, thiolcarbonates) with secondary alicyclic amines in water have been subjected to kinetic analysis.[59] The Brönsted plots for the dinitro[59a] and trinitro[59b] compounds are linear with slopes of $\beta_{nuc} = 0.56$ and 0.48, respectively (Figure 5). The Brönsted breaks for stepwise mechanism were estimated as $pK_a° = 9.3$ and 7.9, respectively.[59a,b] The absence of breaks (amine pK_a range 6.4−11.5) and the magnitude of the Brönsted slopes were attributed to a concerted mechanism. Comparison with the same aminolysis of the corresponding dithiocarbonates (which follow stepwise mechanisms)[56b] indicates that the intermediate $T^\pm$ formed in the reactions of dithiocarbonates is greatly destabilized by the change of S^- by O^-. This was attributed to a much easier formation of a C=O bond in the thiol intermediate, relative to the C=S bond in the dithio intermediate, due to the weaker π-bonding energy of

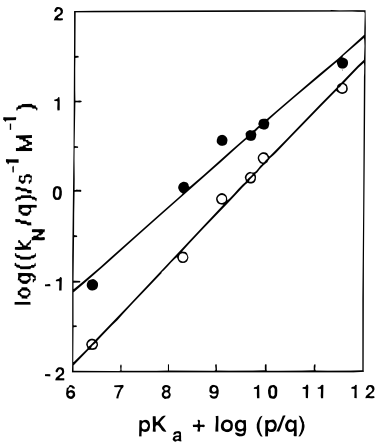


Figure 5. Brönsted-type plots (statistically corrected) for the reactions of *sec*-alicyclic amines with *S*-(2,4-dinitrophenyl) *O*-ethyl thiolcarbonate (○) and *S*-(2,4,6-trinitrophenyl) *O*-ethyl thiolcarbonate (●) in water, 25.0 °C, ionic strength 0.2. Adapted from refs 59a and 59b.

the C═S group relative to C═O.[60] This should increase the nucleofugality rate of both the amine and the leaving group from the thiol intermediate, resulting in kinetic instability.[59b] Comparison with the same aminolysis of the corresponding thiolacetates (stepwise mechanisms[20b]) indicates that $T^{\pm}$ is also very destabilized by the change from Me to EtO.[59b]

The aminolysis (secondary alicyclic) of *S*-(4-nitrophenyl) *O*-ethyl thiocarbonate in water follows a biphasic Brönsted plot with limiting slopes $\beta_{nuc} = 0.2$ and 0.8 and $pK_a°$ 10.7, consistent with the stepwise mechanism of Scheme 2.[59c] The larger $pK_a°$ value of the Brönsted break relative to those for the same aminolysis of the corresponding dithiocarbonate and thiolacetate indicates that amine expulsion is favored (relative to 4-nitrobenzenethiolate expulsion) from the thiolcarbonate intermediate $T^{\pm}$.[59c]

The pyridinolysis of *S*-(4-nitrophenyl), *S*-(2,4-dinitrophenyl), and *S*-(2,4,6-trinitrophenyl) *O*-ethyl thiocarbonates (NPTC, DNPTC, and TNPTC, respectively) in water follows a linear Brönsted plot for the former and biphasic plots for the two latter substrates. The slope β_{nuc} is 0.8 for NPTC. For DNPTC and TNPTC, the slopes β_{nuc} are 0.9 and 0.8, respectively, at low pK_a, and $\beta_{nuc} = 0.2$ for both at high pK_a. The Brönsted breaks at the pK_a axis are $pK_a° = 8.6$ and 7.3, respectively.[61] These data are consistent with the mechanism shown in Scheme 2, with k_2 rate limiting for NPTC and a change in rate-determining step from k_2 to k_1 as the amine is more basic, for DNPTC and TNPTC. Comparison of the pyridinolysis of DNPTC and TNPTC with the concerted reactions of the same substrates with secondary alicyclic amines[59a,b] indicates that these amines destabilize $T^{\pm}$ relative to pyridines. This should be a kinetic destabilization due to the greater nucleofugality from $T^{\pm}$ of the secondary alicyclic amines than that of isobasic pyridines.[25,55d] Comparison of the pyridinolysis of DNPTC and TNPTC with the same aminolysis of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl thiolacetates, stepwise mechanisms with $pK_a° = 6.6$ and 4.9, respectively,[20b] shows that the change from Me to EtO in $T^{\pm}$ enlarges the ratio k_{-1}/k_2 and destabilizes this intermediate.[55d,61]

The reactions of alkyl aryl thionocarbonates (RO−CS−OAr) with secondary alicyclic amines and pyridines have been investigated kinetically in water.[62] The reactions of the former amines with phenyl and 4-nitrophenyl ethyl thionocarbonates follow kinetics first order in piperidine but variable order, from 1 to 2, for the other amines.[62a] These results are consistent with the formation of two tetrahedral intermediates, as in Scheme 3. Step k_1 is limiting for piperidine; for the other amines there is a partial change in the rate-determining step as [amine] increases. The rate microcoefficients involved in the mechanism were determined, and equations for k_1 and k_{-1} as a function of the basicity of both the amine and the leaving group were deduced.[62a] The catalysis by the amine found in these reactions contrasts with the lack of such catalysis in the aminolysis of 4-nitrophenyl methyl carbonate.[63] This was explained by a smaller k_2 for the 4-nitrophenyl ethyl thionocarbonate relative to that for the carbonyl analogue, which competes with the k_3 step in the reactions of the thiono derivative.[62a]

The pyridinolyses of 4-nitrophenyl methyl, 4-nitrophenyl ethyl, and 2,4-dinitrophenyl ethyl thionocarbonates show Brönsted plots which are linear for the first two, with a single slope of $\beta_{nuc} = 1.0$ for both, and are biphasic for the dinitro derivative (limiting slopes $\beta_{nuc} = 0.1$ and 1.0; $pK_a° = 6.8$).[62b] These data are consistent with a mechanism such as that shown in Scheme 2, with k_2 rate limiting for the mononitro compounds and a change in the rate-limiting step for the dinitro analogue. Comparison of these Brönsted plots with each other and with similar ones allows the following conclusions: (I) The values of the rate constants k_1, k_{-1}, and k_2 are the same for methoxy or ethoxy as the "nonleaving" group of the substrate or $T^{\pm}$. (ii) The $pK_a°$ value is smaller for the less basic aryloxide nucleofuge due to a larger k_2 value. (iii) The change of C═O for C═S in the substrate results in larger values of k_{-1}, k_2, and also the k_{-1}/k_2 ratio. (iv) The values of both k_1 and K_1k_2 are larger for the pyridinolysis of carbonates than for the corresponding thionocarbonates. (v) Pyridines react faster with 4-nitrophenyl ethyl thionocarbonate than isobasic secondary alicyclic amines, irrespective of which step is rate limiting. This was attributed to the softer nature of pyridines than isobasic alicyclic amines (k_1 step) and the greater nucleofugality (k_{-1}) of the latter amines than isobasic pyridines, leading to a larger k_2/k_{-1} ratio for pyridines.[62b]

The reactions of bis(phenyl) and bis(4-nitrophenyl) thionocarbonates with secondary alicyclic amines and the reaction of the latter substrate with pyridines in water have been examined kinetically.[63] The reaction of the bis(phenyl) compound with piperidine is first order in amine, but the other amines show a complex reaction order in amine that is compatible with the mechanism in Scheme 3 (R = PhO, XAr = OPh). The reactions of secondary amines with the nitro derivative are first order in amine, and the rate constants follow a nonlinear Brönsted plot, with limiting slopes of $\beta_{nuc} = 0.1$ and 0.5 (Figure 6), consistent with a concerted process. The intermediate $T^{\pm}$ would not be formed due to the presence of three very good leaving

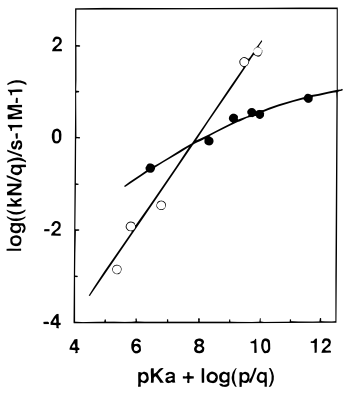


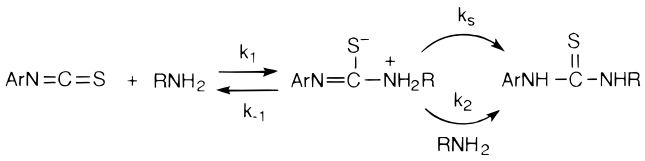
Figure 6. Brönsted-type plots (statistically corrected) for the reactions of bis(4-nitrophenyl) thionocarbonate with *sec*-alicyclic amines (●) and pyridines (○) in water, 25.0 °C, ionic strength 0.2. Adapted from ref 63.

groups. The pyridinolysis of this substrate exhibits a linear Brönsted plot of slope $\beta_{nuc} = 1.0$ (Figure 6, open circles), consistent with the stepwise mechanism in Scheme 2, with k_2 rate determining. The intermediate $T^{\pm}$ formed in the pyridinolysis should be less unstable than that in the reactions with secondary amines due to the fact that k_{-1} is smaller for pyridines compared to isobasic secondary alicyclic amines.[63]

IV. Isothiocyanates

There have been some early reports on the kinetics of the reactions of isothiocyanates (RNCS) with nucleophilic reagents such as alcoholates, thiolates, and amines.[64] The reactions of 4-nitrophenyl isothiocyanate with alkyl and aromatic primary amines in diethyl ether and isooctane are of complex order in amine (between 1 and 2) except for the strongest bases, *n*-butylamine and benzylamine.[65] The kinetics are compatible with Scheme 5, where the k_S step is negligible in isooctane.

Scheme 5

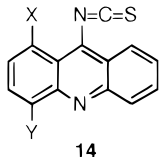


For the very basic amines, the first step should be rate limiting since $k_{-1} < k_s + k_2[RNH_2]$; for the others, at low [amine] the k_2 step (deprotonation of the intermediate either by the amine or diethyl ether) is rate determining, which partially changes to the first step as [amine] increases. It was found that the second step of Scheme 5 is also catalyzed by propionic, benzoic, and chloroacetic acids. Nevertheless, the reaction with benzylamine is inhibited by added propionic acid. This would be due to free-base removal by the acid to form an inactive base−acid (1:2) complex; less basic amines would not be capable of forming this complex.[65]

The hydrolysis of the above isothiocyanate in water−DMSO mixtures generates the thiocarbamic acid, which decomposes very rapidly to yield the amine and COS.[66] In aqueous acid media and in the presence of Hg^{2+} ions, the k_{obs} vs $[Hg^{2+}]$ plots are linear and k_{obs} decreases with the increase of $[H_3O^+]$.[67] In the presence of Ag^+ there are two pathways: the main one is first order in Ag^+ and the minor path second-order in this metal ion. According to the isotope effects ($k_{H_2O}/k_{D_2O} = 1.12$ and 1.07 for the reactions first order in Hg^{2+} and Ag^+, respectively) and the activation parameters, a mechanism was proposed involving a preequilibrium association of the substrate with the metal ion, followed by a slow water attack to give a metal derivative of the thiocarbamic acid, which rapidly undergoes acid decomposition to yield *p*-nitroaniline, metal sulfide, and carbon dioxide.[67] The acid hydrolyses of X-phenyl isothiocyanates (X = *p*-MeO, H, *o*-Me, and *p*-NO_2) catalyzed by Hg^{2+} and Tl^{3+} in *water* show kinetics first order in these catalysts.[68] The small increase in k_{obs} with ionic strength, the independence of k_{obs} on $[H_3O^+]$, and the small increase in the second-order rate constant (k) upon increase of electron release from X are in agreement with the previous[67] mechanism. The most striking feature of these reactions is the $5 \times 10^2-10^3$ fold smaller k for Tl^{3+} compared to Hg^{2+}. This suggests that Tl^{3+} has great difficulty in coordinating with isocyanates (smaller preequilibrium constant than Hg^{2+}).[68]

The acid ($HClO_4$) hydrolysis of 4-X-phenyl isothiocyanates (X = H, F, and NO_2) in DMSO−water shows nonlinear k_{obs} vs $[HClO_4]$ plots, reaching a limiting value at high $[HClO_4]$. This is consistent with water attack to form a dipolar intermediate, which by two routes (H_2O and H^+ catalyzed) can yield a thiocarbamic acid intermediate, which rapidly decomposes to substituted aniline and COS.[69] The above acid hydrolysis (including other substituents and also alkyl derivatives) in *water* shows linear plots of log $k_{obs} - \log[H_3O^+]$ vs excess acidity and large negative $\Delta S^{\ddagger}$ values, which together with small kinetic effects produced by substituent changes suggests a mechanism where the formation of a thiocarbamic acid is rate determining, through a cyclic transition state involving one H_3O^+ ion and one or two H_2O molecules, followed by fast decomposition to products.[70]

The kinetics of the addition of glycine to 2- and 4-substituted 9-isothiocyanatoacridines (**14**) in DMF−H_2O has been studied. The products, *N*-(9-acridinylthiocarbamoyl)glycines, were characterized by IR, UV, NMR, mass, and fluorescence spectra. The highest fluorescence was found for the unsubstituted derivative.[71] The reaction of **14** (X = Y = H) with aliphatic and aromatic amines in organic solvents was found to be ca. 2 orders of magnitude faster than that of phenyl isothiocyanate.[72] The reaction rates of aliphatic amines were very much affected by steric effects, and the products exhibited less fluorescence than the substrate.[72]



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The rate law for hydrolysis of allyl isothiocyanate (CH_2=$CHCH_2N$=C=S) is consistent with nucleo-

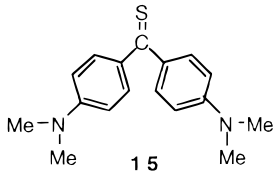
philic attack of water and OH^-. Temperature has a large effect on the rate.[73]

V. Thioaldehydes and Thioketones

The reactions of these compounds with nucleophiles prior to 1992 have been reviewed.[74]

A systematic comparison of structural effects on the intrinsic reactivities of thiocarbonyl and carbonyl compounds, based on gas-phase basicities, has been carried out for thioaldehydes and thioketones.[75] Correlation analysis of the experimental data shows that substituent effects on the basicity of these thiocompounds are linearly correlated to those of their carbonyl homologues with a slope of 0.8. Comparison of the gas-phase basicity of the above compounds with solution basicity and nucleophilicity sheds light on differential structural and solvation effects. The results confirm that all these thiocarbonyl compounds are sulfur bases in the gas phase.[75]

4,4′-Bis(dimethylamino) thiobenzophenone (**15**) and *N*-(thiobenzoyl)morpholine undergo desulfurization in their reactions with malononitrile ($NC-CH_2-CN$) in the presence of Ag^+, yielding the corresponding olefinic compounds and silver sulfide. The reactions



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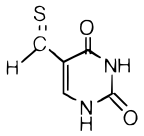

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of the thiocompounds with aniline derivatives afford the corresponding imines.[76]

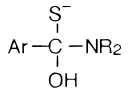
The reactions of the 5-thioformyl uracyl **16** with phenyl hydrazine ($PhNHNH_2$) and other amines afford the corresponding hydrazone ($R_2C{=}NNH_2$) and Schiff bases, respectively. The 5-formyl uracyl derivative shows lower rates toward these nucleophiles than **16**.[77]

The cycloaddition reaction of thioketene ($CH_2{=}C{=}S$) with formaldimine ($CH_2{=}NH$) was studied theoretically. The most favorable mechanisms, both in the gas phase and in solution, are two- and three-step processes which have in common the product 2-thioazetidinone (**17**). Gauche and trans zwitterionic intermediates play a fundamental role in these stepwise mechanisms. The calculated free-energy barrier in the gas phase is 33.0 kcal/mol, while in solution the corresponding values are 28.9 and 26.8 kcal/mol in anisole ($\epsilon = 4.3$) and *N*,*N*-dimethylformamide ($\epsilon = 37.0$) as solvents, respectively. The calculations show that the rate of this reaction is not very sensitive to solvent polarity.[78]

VI. Thioamides and Thioureas

The mechanisms of the alkaline solvolyses of thioamides have been studied for some time, and there is agreement that the neutral thioamide molecule is involved in the mechanism.[79] In water the reaction is first order in $[OH^-]$,[79a−e] whereas in water−ethanol higher orders have been found in some cases.[79f,g]

In the alkaline solvolysis of *N*,*N*-diphenylthiobenzamide and 4-chloro *N*,*N*-dimethylthiobenzamide in water−ethanol mixtures, the order of OH^- was found to vary from 1 to 2 with varying solvent composition. This was attributed to the formation of three tetrahedral intermediates in the reaction path: two arising from OH^- attack (one monoanionic, **18**, and the other dianionic, **19**) and one formed by EtO^- attack (**20**).[80]



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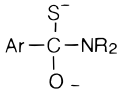

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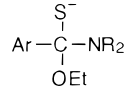

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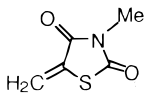
The kinetics and mechanism of the hydrolysis of *S*-benzamides in aqueous solution promoted by $AuCl_4^-$ and various amino-chlorogold(III) ions[81] and $AuBr_4^-$ and $Au(CN)_2Br_2^-$ [82] have been subjected to scrutiny. All these reactions proceed by desulfurization leading to the *O*-amide.

In the reaction of *N*-cyclohexylthiobenzamide with $Au(CN)_2Br_2^-$, a 1:1 adduct is quantitatively formed with the *S*-amide, whereas with $AuBr_4^-$ the adduct stoichiometry depends on $[Br^-]$.[82] In the former reaction it was found that k_{obs} is independent of the excess of $Au(CN)_2Br_2^-$ and H_3O^+, depends little upon ionic strength, and increases markedly by increases in $[Br^-]$. These results were found to be compatible with a mechanism consisting of equilibrium formation of various adducts, followed by slow decomposition to yield *N*-cyclohexylbenzamide.[82] In the reaction with $AuBr_4^-$ it was found that (i) k_{obs} increases sharply in the region $[Br^-] = 0.005-0.1$ M but becomes independent of $[Br^-]$ at higher concentration, (ii) k_{obs} is independent of $[H_3O^+]$, and (iii) k_{obs} decreases slightly to a constant value when $[AuBr_4^-]_{stoich} \gg [S\text{-amide}]_o$. These features were explained by a mechanism analogous to that proposed for $Au(CN)_2Br_2^-$ at high $[Br^-]$.[82]

The alkaline hydrolyses of 3-methyl-5-methylidene- and 3,5-dimethylthiazolidine-2,4-diones (**21** and **22**, respectively) have been investigated in water at 25 °C.[83] Both reactions are first order in both the



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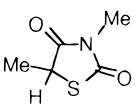

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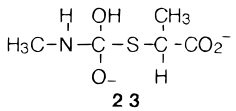

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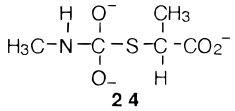

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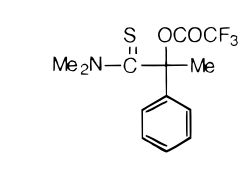
substrate and OH^-. For the reaction of **21**, the solvent kinetic isotope effect is $k_{H_2O}/k_{D_2O} = 0.80$, which together with the products obtained and the rate law led the authors to propose a mechanism with rate-determining OH^- attack on the 4-carbonyl group to form a tetrahedral intermediate. This is followed by rupture of the 4-C−3-N bond. The reaction of **22** is complicated by the formation of two tetrahedral intermediates (**23** and **24**) on the reaction path. The

reaction of **21** with thiols is first order in both substrate and thiol; the suggested mechanism involves RS^- attack on the CH_2 group followed by protonation, without ring rupture.[83] The Brönsted-type plot obtained, slope ca. 0.3, indicates an "early" transition state with the carbanion only partially developed.[83]

The kinetics of the reaction of 1-(*N*,*N*-dimethylthiocarbamoyl)-1-phenylethyl trifluoroacetate (**25**) was studied and found to proceed by a stepwise mechanism through a carbocation intermediate.[84] In the



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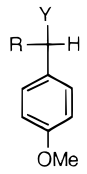

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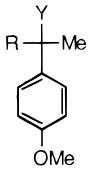

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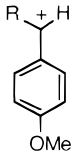

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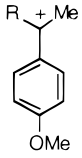

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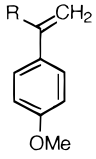

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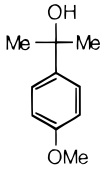


31

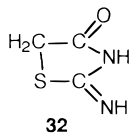
kinetic investigation of the reactions of **26** and **27** (Y = 4-nitro-, 4-methoxy-, and 3,5-dinitrobenzoxy, R = Me_2NCS) in 50:50 (v:v) $MeOH/H_2O$ in the presence of N_3^-, the yield of the product of nucleophilic substitution by azide ion was at least 40% and the reactions are zero order in azide.[85] These observations show that these substrates react by a stepwise $D_N + A_N$ (S_N1) mechanism through the liberated carbocation intermediates **28** and **29**, which can be trapped by N_3^-.[85] It was also found that the rate constants for solvent attack on **28** and **29** are much smaller compared to those with other R substituents (Me, EtOCO, and Me_2NCO); this was attributed to a large stabilization of the carbocation by resonance delocalization of the positive charge onto the strongly polarizable sulfur atom.[85]

It was found that the solvolysis of the 1-(*N*,*N*-dimethylthiocarbamoyl)-1-(4-methoxyphenyl)ethyl carbocation (**29**, R = Me_2NCS) yields exclusively product **30** (R = Me_2NCS), in contrast to the Me derivative (**29**, R = Me) which exclusively shows nucleophilic addition of the solvent to give **31**. This was explained on the basis of a large stabilization of **30** by the change of R from Me to Me_2NCS and a great destabilization of **31** by the same change, concurrent with the same effects on the corresponding transition states.[85]

It was found that *N*-methyl *N*-arylthiobenzamides are less reactive in methanol than their oxygen analogues. Linear Hammett plots were found, with ρ values similar to those obtained for related oxyamides. A higher activation energy and less negative activation entropy for thioamides was found, consistent with rate-determining breakdown of a tetrahedral intermediate.[86]

In dilute sulfuric acid, the hydrolysis of thioacetanilide proceeds by C−S cleavage of the tetrahedral intermediate to give H_2S and acetanilide. The latter is further hydrolyzed to acetic acid and aniline. As the sulfuric acid concentration increases, hydrolysis via C−N fission to yield aniline and thioacetic acid becomes more important. The C−S and C−N bond cleavages were explained through neutral and protonated (on the amino moiety) tetrahedral intermediates, respectively.[87] In concentrated sulfuric acid it was found that thioacetamide and thiobenzamide undergo a rapid equilibrium addition of a proton followed by rate-determining addition of a water molecule to yield amide + H_2S + H^+.[88]

In the kinetic study of the reactions of chloro- and bromoacetic acids with thiourea, it was found that the former acid reacts ca. 100-fold slower than the latter. This was explained by the lower nucleofugality of Cl relative to Br in an S_N2 mechanism whereby the sulfur atom of the thiourea attacks the acid to give a cationic intermediate that slowly undergoes cyclization to product **32**.[89]



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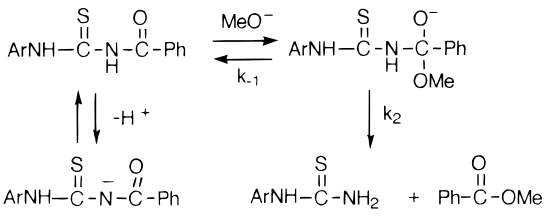
The methanolysis of benzoyl aryl thioureas proceeds according to Scheme 6, where the k_2 step is rate

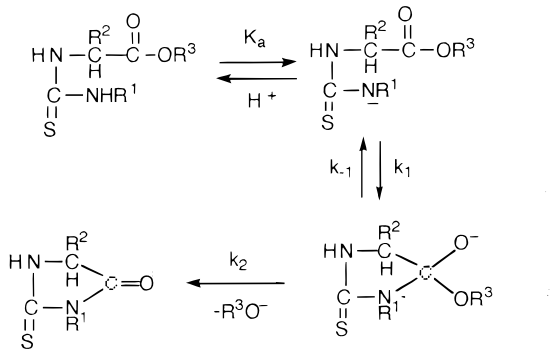
Scheme 6



limiting. It was found that these thioureas are 1 order of magnitude more acidic than their oxygen derivatives and that they react faster with methoxide anion by 2 orders of magnitude. The higher reactivity of thioureas compared to ureas was attributed to the superior leaving ability of arylthiourea from the tetrahedral intermediate (k_2) relative to the oxy analogue.[90]

The rearrangement of 1-acyl-1-phenylthioureas ($RCON(Ph)-CS-NHR^1$, where R is Me or Ph) to 1-acyl-3-phenylthioureas ($PhNH-CS-N(R^1)COR$) in methanol is catalyzed by methoxide anion.[91] There is a concurrent nucleophilic attack by this anion at the carbonyl carbon of the substrate (as shown in Scheme 6). Also, the product of the rearrangement reaction can be subject to attack by methoxide anion.[91] The ethyl and methyl esters of thiohydantoic acid ($R^1NH-CS-NHCHR^2COOR^3$, where R^1 = Ph, Me; R^2 = H, Me; and R^3 = Et, Me) undergo cyclization in water and methanol.[92] The reactions proceed by the mechanism of Scheme 7, where deprotonation of the substrate is carried out by hydroxide or methoxide anions. There is a parallel hydrolysis or methanolysis of the substrates. When R^1 = Ph, the cyclization proceeds with rate-determining expulsion of R^3O^- from the tetrahedral intermediate (k_2 step in

Scheme 7



Scheme 7). This step was found to be catalyzed by general acids; therefore, the whole process is general-base-catalyzed (due to the equilibrium K_a).[92] For R^1 = Me and for the oxy analogues of the substrates (CO instead of CS), $k_2 > k_{-1}$; therefore, the rate-limiting step is k_1. In these cases only specific base catalysis was found, due to the equilibrium step K_a.[92]

The methanolysis of acyl and 1,3-diacylthioureas is first order in the substrate. The order in methoxide varies with its concentration. The mechanism for the monoacyl (benzoyl and acetyl) derivatives is that in Scheme 6. For the diacyl compounds, the monoacylthiourea is formed in the first step, which is further solvolyzed according to Scheme 6. At high [MeO^-] there is a steep increase of k_{obs} with [MeO^-] which was attributed to reaction of the anion of the diacylthiourea with MeO^- to form a tetrahedral intermediate, which finally gives the monoacylthiourea and ester.[93] The reaction of diacetyl thiourea with butanamine was also studied kinetically. This reaction proceeds by amine attack to form a zwitterionic tetrahedral intermediate, which is deprotonated by another amine molecule to form an anionic tetrahedral intermediate, which further decomposes to acetylthiourea and butylacetamide.[93]

The reaction of thiourea with $Ag(OH)_4^-$ in alkaline media is first order in $Ag(OH)_4^-$. The pseudo-first-order rate constant (k_{obs}) obeys eq 5, where T represents thiourea. In the reactions involving T and

$$k_{obs} = k + k'[T] + k''[T][OH^-] \qquad (5)$$

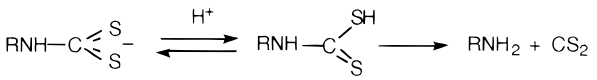
Ag(III), with rate constants k' and k'', this metal is reduced to Ag(I) and T is primarily oxidized to formamidine disulfide, $H_2NC(=NH)SSC(=NH)NH_2$. Finally, Ag_2S was found as one of the products.[94]

VII. Thiocarbamates

The acid decomposition of alkyl dithiocarbamates in water was subjected to a kinetic analysis; a mechanism was proposed (Scheme 8), where the first step is at equilibrium. It was claimed that protonation occurs on the S atom and not on the N atom.[95]

This mechanism was confirmed in mixed aqueous solvents, although with a minor variant, whereby the

Scheme 8

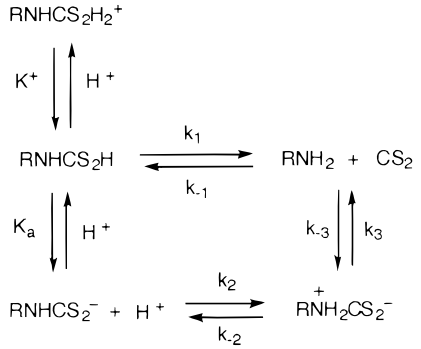


acid intermediate in Scheme 8 rapidly rearranges to a species with an intramolecular hydrogen bond between the N and S atoms.[96] The latter was confirmed by studying the effects of the ionic strength, dielectric constant, pH, and temperature on the rate constants.[97] A zwitterionic intermediate (protonated on N) on the reaction path was also proposed.[98] The log of the rate of decomposition of diisobutyldithiocarbamate in aqueous solution is linearly proportional to the pH values.[99]

Thiocarbamates derived from basic aliphatic amines undergo rate-determining C−N cleavage after protonation on the N atom in a preequilibrium step, as shown by $k_{D_2O}/k_{H_2O} = 3.6-4.8$.[100] General acid catalysis is exhibited by thiocarbamates of anilines, which becomes progressively more difficult to detect as the amine moiety is more basic (because of competition with specific acid catalysis). For dithiocarbamates, no general acid catalysis was found. The Brönsted slopes for the leaving group are smaller for mono- and dithiocarbamates compared to their oxygen analogues, suggesting transition states that are late for amine expulsion and early for amine attack.[100]

The acid decomposition of *N*-alkyldithiocarbamic acids (RNHCSSH) in water was studied kinetically in the range $H_o = -5$ to pH = 5.[101] According to the pH−rate profile, the rate equation, the Brönsted-type plot for specific acid catalysis, and the inverse deuterium solvent isotope effects, the mechanism depicted in Scheme 9 was proposed. For dithiocar-

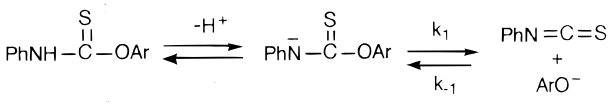
Scheme 9



bamates whose parent amine pK_N are 7−10, the path through the zwitterion (steps 2 and 3) is predominant. At pK_N > 10, step 1 becomes dominant; this path is a direct intramolecular proton transfer (probably catalyzed by water) concerted with C−N bond cleavage. It was found that for pK_N < 9.2, the k_2 step is slower than k_3, and for pK_N > 9.2, the k_2 step is faster than k_3. The pK_a of the zwitterion was calculated to be 14 pK units lower than the parent amine, being lower than that of the hydronium ion; therefore the proton transfer from the zwitterion to water (k_{-2}) is thermodynamically favorable, and k_{-2} was estimated as 10^{10} s^{-1} M^{-1}. The inverse kinetic solvent isotope effect found for pK_N 9−10 was explained on the basis of a late transition state in step 3.[101]

The hydrolysis of *O*-aryl *N*-phenylthionocarbamates (PhNH−CS−OAr) proceeds through phenyl isothiocyanate, which together with the high value of the Hammett parameter ($\rho = 3.0$) and the positive $\Delta S^{\ddagger}$ (10.8 cal mol^{-1} K^{-1}) was explained by a E1cB

Scheme 10



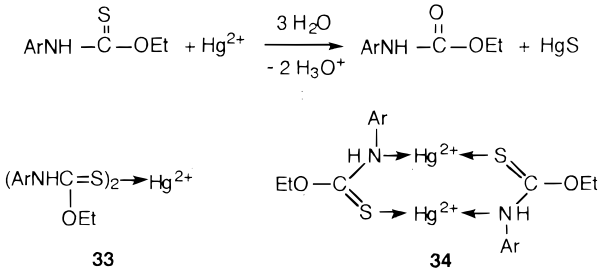
mechanism (Scheme 10).[102] This was confirmed in 20% aqueous dioxane media.[102] The same behavior was exhibited by *S*-aryl *N*-arylthiolcarbamates in the same media. On the other hand, the *N*-methyl, *N*-aryl derivatives were found to obey the $B_{AC}2$ mechanism.[103] The hydrolysis of diaryldithiocarbamates in the same media at pH 2−12 is also governed by a E1cB mechanism.[103] In acid media (pH < 2), a $A_{AC}2$ mechanism is followed.[104]

Rate constants for decomposition of *O*-aryl *N*-arylthionocarbamates in aqueous solution to give aryloxide ion and isothiocyanate have been measured in both forward and back directions.[105] The Brönsted slopes for both rate constants and for the equilibrium between the thionocarbamate and its anion (Scheme 10) were also determined. Identical Leffler−Grunwald indices (β_f/β_{eq}) for the addition step were observed for variation of the substituents in the leaving and amine groups. The relatively large positive effective charges (relative to carbamates) on the phenolic O in the thionocarbamate (+1.44) and its conjugate base (+0.72) indicate high polarization of the C=S bond in the thionocarbamates.[105] The effective charge on the phenolic O of the thionocarbamate anion was determined from the Brönsted slopes for its decomposition (step k_1 in Scheme 10, $\beta_{lg} = -0.91$) and formation (step k_{-1}, $\beta_{nuc} = 0.81$). This gives a total charge development of +1.72 from the aryloxide anion (charge −1) to the thionocarbamate anion. The effective charge on the phenolic O of the thionocarbamate was determined from the Brönsted slope ($\beta_{lg} = -0.72$) for the dissociation constant of the first step in Scheme 10; this gives a charge development of +2.44 from the aryloxide anion to the thionocarbamate.[105]

The alkaline hydrolysis of *S*-aryl thiocarbamates and *S*-aryl *N*-phenylthiocarbamates (RNHCOSAr, R = H and Ph, respectively) have been found to obey a E1cB mechanism (as in Scheme 10).[106] Equilibrium constants for the addition of thiols to isocyanic acid (the products of the reaction of $H_2NCOSAr$) were obtained both kinetically and analytically. From Hammett and Brönsted plots it was found that the effective charge on the S atom in the thiocarbamate is less than that on the O atom in the carbamate. This was explained by a poor overlap between the 3p orbital of S and the 2p orbital of C relative to the overlap in the O case.[106]

The hydrolysis of thiocarbamates in the presence of soft-metal ions has been studied kinetically.[107] In 1% dioxane−water *O*-ethyl 4-substituted-*N*-phenylthionocarbamates (4-X-C_6H_4NHCSOEt) undergo desulfurization in the presence of Hg^{2+} ions (Scheme 11).[107a] The reaction proceeds with the formation of a complex of 2:1 thiocarbamate:Hg^{2+} stoichiometry (**33**), which in the presence of an excess of Hg^{2+} ions partial conversion to a 2:2 complex (**34**) occurs. This complex decomposes to the corresponding carbamate and HgS. With X = 4-NO_2, the 2:2 complex is

Scheme 11



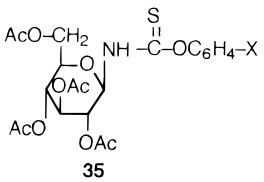
dominant even at low Hg^{2+} concentration. The effect of H^+ concentration suggests that ionization of the NH proton in complex **34** favors the reaction, because the deprotonated form of **34** is more reactive than **34** itself.[107a]

The hydrolyses of *S*-aryl *N*-arylthiolcarbamates (ArNHCOSAr) in dilute aqueous acid in the presence of Tl^{3+} ions yield anilinium ions and $ArSTl^{2+}$. The effects of substituents, [H^+], ionic strength, and the change of NH by NMe are consistent with a mechanism where both E1cB and E2 paths are followed via *N*-arylisocyanate as reactive intermediate. The reactions involve the equilibrium formation of 1:1 complexes which can be deprotonated by water.[107b] The hydrolysis of the *S*-ethyl derivatives seems to take place by an $A_{AC}1$ mechanism through a $ArNHCO^+$ intermediate derived from the 1:1 complex.[107b]

The hydrolysis of *S*-ethyl *N*-arylthiolcarbamates (ArNHCOSEt) in dilute aqueous acid and in the presence of Ag^+ ions proceeds by the slow decomposition of 2:1Ag^+:thiolcarbamate complexes derived from 1:1 complexes. A cationic 1:1 complex is deprotonated to give a neutral species, and the 2:1 complexes are formed from both species. It is suggested that the 2:1 complexes undergo nucleophilic attack by water in a A2-like mechanism. In the presence of Ag^+, these thiolcarbamates are 10^5-fold more reactive than the corresponding ethyl thiolbenzoates.[107c]

The acid hydrolysis of *S*-aryl *N*-aryldithiocarbamates (ArNHCSSAr) in the presence of Tl^{3+} ions occurs through a 1:1 dithiocarbamate:Tl^{3+} complex which undergoes elimination to isothiocyanate. This process is accelerated by an excess of Tl^{3+} ions. The Ar = 4-methoxyphenyl derivative is ca. 3-fold more reactive than the unsubstituted compound.[107d]

Rate constants and activation parameters for the alkaline hydrolysis of **35** (*X* = 4-MeO, 4-Et, 4-Pr, H, 4-Cl, 2-F) were determined in aqueous dioxane. The rate constants correlate satisfactorily with Hammett σ-values.[108]



VIII. Halogenothioformates and Related Compounds

The kinetics of the hydrolysis of chlorothionoformates (ROCSCl) in water were investigated. The rate increases by enhanced electron donation from the

alkyl group. These results, the positive entropy of activation for the hydrolysis of methyl chlorothionoformate, and the solvent deuterium isotope effects are consistent with a S_N1 mechanism.[109]

The effect of $NaClO_4$ and NaCl on the kinetics of solvolysis of methyl chlorodithioformate (MeSCSCl) in 70% aqueous acetone, together with a common ion rate depression, was explained by a S_N1 process.[110a] On the other hand, the reactions of chlorodithioformates with azide ion (N_3^-) in 70% aqueous acetone are governed by a bimolecular mechanism, as shown by the decrease of the rates with increasing electron donation to the reaction site. Furthermore, the highly negative $\Delta S^{\ddagger}$ values and the kinetic order of 1 in azide ion are against a S_N1 process.[110b] It was concluded that in the studied solvolyses of these compounds the S_N1 mechanism prevails while in the presence of azide ion the fast bimolecular process is more important.[110b]

The solvolyses of phenyl and ethyl chlorothiolformates (RSCOCl, R = Ph and Et) have been studied kinetically in aqueous mixtures of ethanol, methanol, acetone, trifluoroethanol (TFE), and hexafluoro-2-propanol (HFP).[111] The reactions of the former compound proceed by an addition−elimination mechanism in all solvents, except in the TFE−water and HFP−water mixtures, where a predominant S_N1 pathway takes place.[111a] This conclusion was arrived at on the basis of the *l* and *m* parameters of the extended Grunwald−Winstein equation (eq 6). In this

$$\log(k/k_o) = lN_T + mY_{Cl} + c \qquad (6)$$

equation k and k_o are the specific rates of solvolysis in a given solvent and in the standard solvent (80% ethanol−water), respectively, N_T is the solvent nucleophilicity, Y_{Cl} is the solvent ionizing power, and c is a constant (residual) quantity. The values of *l* and *m* for the addition−elimination process are 1.74 and 0.48, respectively, in good agreement with the values found for the solvolysis of phenyl chloroformate (I = 1.68, m = 0.57) where the addition−elimination mechanism is well established.[111a] The *l* and *m* values obtained in the solvolysis of phenyl chlorothiolformate in the fluoro alcohol solvents (high ionizing power and low nucleophilicity) are 0.62 and 0.92, respectively, values which are in line with the S_N1 process.[111a]

In the solvolysis of ethyl chlorothiolformate in the above solvents, except ethanol, methanol, and 90% ethanol−water, the values of *l* and *m* obtained through the extended Grunwald−Winstein equation are 0.66 and 0.93, respectively, which is indicative of a S_N1 mechanism.[111b] These values are similar to those found in the S_N1 solvolysis of ethyl chloroformate in TFE, 97% TFE−water, formic acid, and HFP−water mixtures.[111b] The *l* and *m* values obtained in the addition−elimination solvolysis of the latter compound in the other solvents are very different (1.56 and 0.55, respectively), in line with those found in the solvolysis of phenyl chloroformate in the nonfluoro alcohol solvents.[111a]

The reactions of nucleophilic reagents with phenyl and 4-nitrophenyl chlorothionoformates (ArOCSCl) in water have been subjected to kinetic analysis.[112]

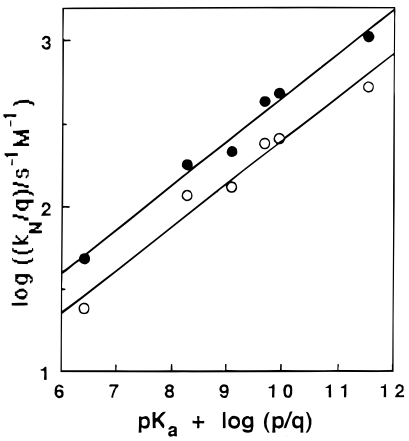


Figure 7. Brönsted-type plots (statistically corrected) for the reactions of *sec*-alicyclic amines with 4-nitrophenyl chlorothionoformate (●) and phenyl chlorothionoformate (○) in water, at 25.0 °C, ionic strength 0.2. (Reprinted with permission from ref 112a. Copyright 1997 American Chemical Society.)

The reactions of these substrates with a series of secondary alicyclic amines under amine excess show linear plots of the pseudo-first-order rate constant (k_{obs}) against free amine concentration, with slope k_N.[112a] The Brönsted-type plots for k_N are linear (Figure 7), with both slopes β_{nuc} = 0.26. The magnitude of the slopes together with the linear k_{obs} vs [amine] plots and the product studies indicate the presence of one kinetically important tetrahedral intermediate ($T^{\pm}$), whose formation from reactants is the rate-determining step (as in Scheme 2, with k_1 step rate limiting).[112a] From a comparison of these reactions in water with the concerted aminolysis of the oxy analogues, phenyl and 4-nitrophenyl chloroformates, in acetonitrile[113] it is deduced that the changes of S^- by O^- in $T^{\pm}$ and water by acetonitrile as solvent destabilizes $T^{\pm}$, changing the mechanism from stepwise to enforced concerted.[112a]

The reactions of the above compounds with a series of phenoxide ions (ArO^-) in water under ArO^- excess show linear plots of k_{obs} against [ArO^-], with slopes k_N.[112b] The Brönsted-type plots (log k_N vs amine pK_a) are linear, with slopes β_{nuc} = 0.55 and 0.47 for the phenyl and 4-nitrophenyl derivatives, respectively.[112b] The magnitude of the slopes, the kinetic law, and the product analysis suggest that these reactions are concerted, in line with the reactions of the same nucleophiles with aryl esters and acetic anhydride in water. Comparison of these reactions with the stepwise aminolysis of the same substrates[112a] indicates that substitution of a secondary amino moiety by aryloxy in a $T^{\pm}$ intermediate which already possesses an aryloxy group greatly destabilizes this intermediate.[112b]

Rate constants for hydrolysis of thiocarbamoyl chlorides (RR^1NCSCl, R = R^1 = Me, Et, Pr, isoBu; RR^1 = piperidino, morpholino; R = Ph, R^1 = Me, Et) in aqueous acetone were determined potentiometrically and conductometrically. The main reaction is first order, yielding RR^1NH and COS. The hydrolysis of COS to CO_2 and H_2S is a process with second-order kinetics.[114]

The kinetics of thiophosgene (Cl−CS−Cl) solvolysis in aliphatic alcohols (ROH with R = Me, Et, Pr, *iso*-

Pr, *iso*-Bu, *sec*-Bu, and cyclohexyl) was investigated at 4−62 °C. It was found that thiophosgene reacts 10^3−10^4-fold slower than its oxygen analogue. The effect of substituents in R on the rate is described by Taft's E_s parameter.[115]

IX. Conclusions

For the reactions of nucleophiles with thioesters and thiocarbonates the following conclusions can be drawn.

(1) The reactions of thionucleophiles occur through an anionic tetrahedral intermediate; there is a change in the rate-limiting step when the pK_a of the nucleophile is the same or similar to that for the leaving group of the substrate. The Brönsted-type slopes when formation or breakdown of the intermediate are rate limiting are similar to those found for aminolysis. For a thionucleophile with a pK_a that is larger than that for the leaving group, the formation of the tetrahedral intermediate is rate determining, whereas when the opposite is true, decomposition to products of the intermediate is rate limiting.

(2) For aminolysis, the above change in the rate-determining step occurs when amine basicity is much greater than that of the thio or oxy leaving group, i.e., amines are much better nucleofuges from the zwitterionic intermediate ($T^{\pm}$) than isobasic thio or oxy leaving groups.

(3) Hard oxynucleophiles (e.g., RO^- and OH^-) are more reactive toward hard electrophilic centers (e.g., CO) than soft centers (e.g., CS), whereas soft thionucleophiles (ArS^-) are more reactive toward CS or thiol (CO−S) groups than toward CO−O centers. PhO^-, which is of intermediate softness, reacts faster with CS or CO−S centers than with CO−O groups.

(4) Nitrogen nucleophiles that are relatively hard (e.g., secondary alicyclic amines), show higher reactivity toward CO than CS, and also react faster with CS−SAr than CS−OAr, the latter due to the more basic ArO leaving group than ArS, which leaves the thiocarbonyl carbon of the CS−O center less positive than that of CS−S. Relatively softer nucleophiles such as pyridines still react faster with CO than CS groups. Pyridines show higher reactivity toward CS than isobasic secondary amines.

(5) The reactions of primary, secondary, and tertiary aliphatic amines, as well as anilines and pyridines, that show linear plots of k_{obs} vs [NH] are usually ruled by the mechanism shown in Scheme 2. For the reactions of primary and secondary amines, usually $k_2 \gg k_3$[NH] in Scheme 3, this being the reason for the lack of base catalysis and the simple mechanism (Scheme 2) observed for these reactions.

(6) The reactions of primary and secondary amines that show nonlinear upward plots of k_{obs} vs [NH] are usually governed by the mechanism of Scheme 3, in which $k_{-1} \approx k_2 \approx k_3$[NH]. Nevertheless, for poor leaving groups of the substrates the k_2 path can become negligible compared to that for k_3.

(7) For the aminolysis in less polar solvents than water, the k_{-1} value for a given amine is larger than that in water, since the TS for the formation of $T^{\pm}$ is less polar than $T^{\pm}$. The k_3 value (usually a diffusion-controlled proton transfer) is smaller in aqueous ethanol or acetonitrile than water. The k_2 value is not very sensitive to solvent change in view of the similar polarity of the TS for $T^{\pm}$ breakdown and that of $T^{\pm}$.

(8) Substitution of Me by RO (where R is alkyl) and S^- by O^- in $T^{\pm}$ destabilizes this intermediate kinetically by increasing both k_{-1} and k_2; also, the ratio k_{-1}/k_2 is enlarged. This results in an increase of the Brönsted break at the pK_a axis (pK_a°). The intermediate $T^{\pm}$ is also destabilized by the following changes: (i) from water to less polar solvents, (ii) from poor leaving groups to good nucleofuges, and (iii) from a pyridino moiety in $T^{\pm}$ to an isobasic anilino, which is further destabilized by the change to an isobasic alicyclic amino group.

(9) Some of the above destabilizations are so great that they change the mechanism from stepwise to concerted. The latter mechanism usually exhibits a linear Brönsted plot of slope $\beta_{nuc} = 0.4-0.6$. Occasionally a slight and continuous Brönsted curvature is obtained.

For the reactions of the other thiocompounds involved in this review, the following conclusions can be drawn.

(10) The aminolysis of isothiocyanates proceeds through the formation of a trigonal intermediate which can decompose to thiourea. The rate-determining step depends on both the basicity and concentration of the amine. The hydrolysis of isothiocyanates involves rate-determining formation of the corresponding thiocarbamic acid followed by its fast decomposition to amine and COS. In the presence of metal ions such as Ag^+, Hg^{2+}, and Tl^{3+}, the hydrolysis of isothiocyanates yields amine, CO_2, and the metal sulfide.

(11) The alkaline hydrolysis of thioamides can occur through two tetrahedral intermediates, a monoanionic and a dianionic intermediate. In aqueous ethanol, a monoanionic tetrahedral intermediate can also be formed by EtO^- attack on the thioamide. Hard nucleophiles such as OH^-, EtO^-, and MeO^- react slower toward thioamides than oxyamides. The hydrolysis of thioamides in the presence of AuX_4^- (X = halogen) occurs by desulfurization, yielding amide and Au_2S_3.

(12) The hydrolysis of thioamides in dilute acid proceeds through tetrahedral intermediates which can decompose by C−S and C−N cleavage depending on the acid concentration. In concentrated acid there is an equilibrium protonation followed by rate-determining addition of water.

(13) Thioureas undergo desulfurization in the presence of metal complexes, such as $Ag(OH)_4^-$, yielding urea and Ag_2S. Thioureas are better leaving groups than ureas from a tetrahedral intermediate.

(14) Thiocarbamates and dithiocarbamate anions undergo decomposition in acid, through the corresponding thio or dithio carbamic acid, yielding amine and COS or CS_2 as final products. The hydrolyses of aryl *N*-phenylthionocarbamates and their thiol analogues, as well as those of diaryldithiocarbamates, are governed by E1cB mechanisms. Those of *N*-methyl *N*-aryl derivatives are ruled by $B_{AC}2$ mechanisms. The effective positive charge on the phenolic

O of *O*-aryl *N*-aryl thionocarbamates and their conjugate base is larger than that in the corresponding carbamates. The effective charge on the phenolic S of *S*-aryl *N*-arylthiolcarbamates is less than that in the carbamates. Thiol-, thiono-, and dithiocarbamates in the presence of metal ions such as Hg^{2+}, Ag^{+}, and Tl^{3+} undergo desulfurization.

(15) The hydrolyses of alkyl chlorothiono- and chlorodithioformates are governed by S_N1 mechanisms. The solvolyses of aryl and ethyl chlorothiolformates follow addition−elimination routes (through tetrahedral intermediates), except in high-ionizing power solvents, where they proceed by S_N1 mechanisms. The phenolysis of these compounds is concerted, while the aminolysis occurs through a tetrahedral intermediate. In less polar solvents than water and with anilines as nucleophiles, these reactions are concerted.

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XI. References

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