Kinetics and Mechanism of the Aminolysis of *S*-Ethoxycarbonyl *O*-Ethyl Dithiocarbonate and Related Pyrothiocarbonates

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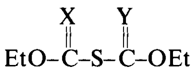
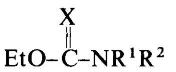
The reactions of *S*-ethoxycarbonyl *O*-ethyl dithiocarbonate (**1**), bis(ethoxythiocarbonyl) sulphide (**4**), and bis(ethoxycarbonyl) sulphide (**5**) with pyrrolidine, piperidine, and morpholine in 95% aqueous ethanol have been subjected to kinetic study. The rate equation found for all the reactions is $k_{obs} = k_o + k_N[N]$, where k_{obs} is the pseudo-first-order rate constant (amines were in excess over the substrates) and N represents the free amine. The rate law accounts for reaction schemes with zwitterionic tetrahedral intermediates, $EtOC(S^-)(NH^+)SCXOEt$ and $EtOC(O^-)(NH^+)SCXOEt$, where X is O or S, formation of which from reactants is the rate-determining step. The intermediates break down to products faster than their deprotonation by the solvent or another amine molecule. This is confirmed by estimation of the rate constants involved in the schemes and evaluation of the pK_a value of the intermediates. From the k_N values obtained it is deduced that amines attack at the CS group of the substrate faster than at the CO group, although the nature of both the substrate and the amine could change this order of reactivity. Activation parameters are reported for all the reactions, and it was found that $\Delta S^{\ddagger}$ was lower for attack for CO compared with that at CS. This is explained in terms of higher solvation of the transition state for CO attack relative to that for CS attack.

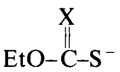
In previous studies[1,2] we have established that the reactions of *S*-(ethoxycarbonyl) *O*-ethyl dithiocarbonate (1) with primary and secondary aliphatic amines lead to the corresponding thiocarbamate (2) and carbamate (3) by nucleophilic attack of the amine at the thiocarbonyl and carbonyl groups of compound (1), respectively. In these reactions it was found that the symmetrical pyrothiocarbonates (4) and (5) are formed by transesterification of (1) with the nucleophiles *O*-ethyl xanthate (6) and *O*-ethyl thiocarbonate (7) ions, which are the leaving groups in the aminolysis of compound (1). Compounds (2) and (3) were also formed by aminolysis of pyrothiocarbonates (4) and (5).[1,2]


$EtO{-}\overset{\overset{X}{\|}}{C}{-}S{-}\overset{\overset{Y}{\|}}{C}{-}OEt$

(1) X = S, Y = O
(4) X = Y = S
(5) X = Y = O


$EtO{-}\overset{\overset{X}{\|}}{C}{-}NR^1R^2$

(2) X = S
(3) X = O


$EtO{-}\overset{\overset{X}{\|}}{C}{-}S^-$

(6) X = S
(7) X = O

The sequence of steps involved in the reaction of (1) with amines is well established[2] and although the product ratio [(2)]/[(3)] > 1 suggests a greater overall reactivity of the thiocarbonyl group than the carbonyl of compound (1), this result is only apparent because (*a*) the leaving groups in both reactions are different, (*b*) the amine was only in 10% excess over (1), so during the reactions the concentration of the amine was decreasing while those of (6) and (7) were increasing, and (*c*) the reactions were complicated by the thiolyses of (1), (4), and (5) and aminolyses of (4) and (5). On the other hand, Kato *et al.*[3] have reported that amine preferentially attacks the carbonyl group of thioacyl acyl sulphides.

Recent work[4] on the kinetic study of the reactions of (1) with (6) and (7) and the back-reactions of (4) with (7) and (5) with (6) shows that the thiocarbonyl group is more reactive than carbonyl toward (6) and that the carbonyl group is more reactive than thiocarbonyl toward (7).

In order to shed more light on the reactivities of carbonyl and thiocarbonyl groups, we report here a kinetic study of the reactions of compounds (1), (4), and (5) with pyrrolidine, piperidine, and morpholine in 95% ethanol at different temperatures.

Experimental

Materials.—The synthesis of (1)–(3),[1] (4) and (5),[5] and the potassium salts of (6)[6] and (7)[7] have been described previously. Ethanol (95%) was analytical reagent grade and all the amines were purified by standard methods prior to use.

Kinetic Measurements.—Buffered solutions (2.5 cm^3) of the appropriate amine in 95% aqueous ethanol, ionic strength 0.05 mol dm^{-3} (maintained with LiCl), were introduced into 1 cm cells and placed in the thermostatted cell holder of a Pye-Unicam SP-1800 spectrophotometer. After thermal equilibration (±0.1 °C) a stock solution (1–10 mm^3) of the substrate (1), (4), or (5) in ethanol was injected into the reaction solution. The reactions were followed by monitoring the increase of absorbance with time at 304 nm corresponding to (6) [reaction with (1)], at 246–250 nm corresponding to (2) [reaction with (4)], and at 223 nm corresponding to (7) [reaction with (5)]. The reaction of morpholine with (1) was also studied at 275 nm following the absorbance decrease of this substrate. The initial concentration of the substrate was $(1.0\text{–}7.2) \times 10^{-5}$ mol dm^{-3} in all runs.

Pseudo-first-order rate constants (k_{obs}) were obtained in all cases (at least 12-fold excess of amine over the substrate was employed). These were determined from 'infinity' plots, and those giving correlation coefficients worse than 0.9990 were discarded.

After completion of the aminolysis of (1) the [(2)]/[(3)] ratios were evaluated from the equation $[(2)]/[(3)] = [(7)]/[(6)] = (\varepsilon[(1)]_o l/A_\infty) - 1$, where A_∞ is the final absorbance at 304 nm, ε is the molar absorptivity of compound (6) at the same wavelength [determined in the aminolysis of (4) at each

Table 1. Experimental conditions and rate constants obtained in the aminolysis of compound (**1**).[a]

Amine	pK_a[b]	T/°C	10^3[N][c]/ mol dm^{-3}	10^3k_{obs}/s^{-1}	Number of runs	[(**2**)]/[(**3**)][d]	k_N^{CO}/ dm^3 mol^{-1} s^{-1}	k_N^{CS}/ dm^3 mol^{-1} s^{-1}
Pyrrolidine		20.0	0.136–0.663	13.2–69.7	8	2.9 ± 0.2	28.1 ± 0.5	81 ± 1
	9.66	25.0	0.136–0.663	13.7–81.5	10		33 ± 1	95 ± 4
		30.0	0.119–0.663	16.1–94.6	10		36 ± 2	104 ± 5
		35.0	0.119–0.663	18.5–117.7	10		42 + 3	123 ± 10
		40.0	0.138–0.663	29.6–138.5	10		49 ± 2	143 ± 7
Piperidine		20.0	0.159–2.21	4.36–62.8	14	1.9 ± 0.2	9.4 ± 0.4	17.9 ± 0.7
	9.37	25.0	0.159–2.21	4.58–78.3	14		12.1 ± 0.3	22.9 ± 0.6
		30.0	0.161–2.21	6.20–101.0	13		15.2 ± 0.5	29 ± 1
		35.0	0.163–2.21	9.59–123.0	12		18.7 ± 0.4	35.6 ± 0.8
		40.0	0.161–2.21	11.0–133.0	11		21.8 ± 0.5	42 ± 1
Morpholine	7.52	25.0	0.47–2.33	4.22–21.0	12	4.5 ± 0.3	1.7 ± 0.1	7.5 ± 0.2
		30.0	0.47–2.33	5.35–27.7	12		2.2 ± 0.1	9.8 ± 0.1
		35.0	0.47–2.33	6.36–32.9	12		2.6 ± 0.1	11.7 ± 0.2
		40.0	0.47–2.33	7.93–42.0	12		3.2 ± 0.1	14.4 ± 0.5
		45.0	0.47–2.33	9.43–50.7	10		4.0 ± 0.1	18.0 ± 0.4

[a] In 95% aqueous ethanol, ionic strength 0.05 mol dm^{-3} (maintained with LiCl). All the errors shown in this table are standard errors. [b] Of the conjugate acids of the amines. The values were obtained potentiometrically at 25 °C, under the experimental conditions of the kinetic experiments. [c] Free amine concentration. All solutions were buffered by partial protonation of the amine. [d] The values shown are the average of those obtained at each temperature since the individual values agreed within experimental error.

temperature, by using the values of A_∞ at 304 nm and the initial concentration of (**4**)], $[(\mathbf{1})]_0$ is the initial concentration of (**1**), and l is the cell pathlength. Some ratios were checked by g.l.c.[2] The pseudo-first-order rate constants for amine attack at the thiocarbonyl and carbonyl groups of substrate (**1**) (k_{obs}^{CS} and k_{obs}^{CO}, respectively) were obtained from equations (i) and (ii).

$$k_{obs} = k_{obs}^{CS} + k_{obs}^{CO} \qquad \text{(i)}$$

$$[(\mathbf{2})]/[(\mathbf{3})] = k_{obs}^{CS}/k_{obs}^{CO} \qquad \text{(ii)}$$

The experimental conditions and the values found for [(**2**)]/[(**3**)] ratios and k_{obs} for reactions of substrate (**1**) are shown in Table 1. Table 2 shows the experimental conditions and the rate constants obtained in the aminolysis of compounds (**4**) and (**5**).

Product Studies.—The presence of compounds (**6**), (**7**), (**2**), and (**3**) in the solutions after completion of the reactions was determined by g.l.c. analysis as previously described.[2]

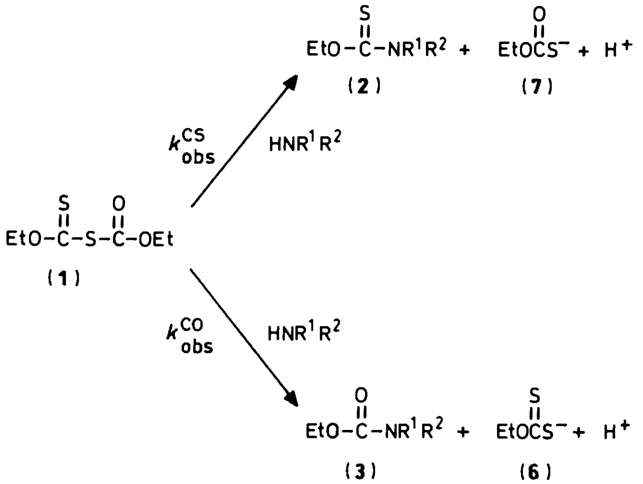
Determinations of pK_a.—The pK_a values of the conjugate acids of the amines were obtained potentiometrically at 25.0 °C in 95% ethanol, ionic strength 0.05 mol dm^{-3} (LiCl). The method and equipment used have been previously described.[8]

Results and Discussion

A spectrophotometric study of the reaction of substrate (**1**) with the amines initially shows an increase of the absorption bands at 224, 252, and 304 nm. After the kinetic measurements were complete we observed a slow decrease of the 224 nm band, which revealed a new band at 212 nm, previously masked by the 224 nm band.

The bands at 212 nm and 252 nm correspond to products (**3**) and (**2**), respectively, as shown by comparison with those of authentic samples, and the band at 304 nm was attributed to compound (**6**) by comparison with the spectrum of its potassium salt in the same reaction medium. The 224 nm absorption band, which first increased and then decreased in intensity was attributed to compound (**7**) by comparison with the spectrum of the potassium salt of (**7**) and also because this authentic sample showed the same decomposition rate. Identification of products (**6**) and (**7**) was confirmed by comparison of the final spectra of the kinetic runs with those obtained in the aminolysis of compounds (**4**) and (**5**), respectively, before decomposition of (**7**) was significant.

In order to prevent the thiolysis of (**1**), due to the presence of compounds (**6**) and (**7**) in the reaction media,[4] the reactions were carried out in excess of amine. Under these conditions only the reactions shown in Scheme 1 are important.



Scheme 1.

Plots of k_{obs}^{CS} and k_{obs}^{CO} against free amine (N) concentration at constant pH were linear, in accord with equation (1), where k_N^{CS} and k_N^{CO}, the second-order rate constants, were obtained as

$$k_{obs}^{CS} = k_N^{CS}[\mathrm{N}];\ k_{obs}^{CO} = k_N^{CO}[\mathrm{N}] \qquad (1)$$

slopes of the above plots. Some reactions were carried out at more than one pH value and the k_N values obtained agreed within experimental error. The values of k_N^{CS} and k_N^{CO} found at various temperatures are shown in Table 1.

For the aminolysis of compounds (**4**) and (**5**) the rate law given by equation (2) was found, where k_o, the first-order rate

Table 2. Experimental conditions and rate constants obtained in the aminolysis of compounds (**4**) and (**5**).[a]

Amine	T/°C	10^3[N][b]/mol dm^{-3}	10^3k_{obs}/s^{-1}	Number of runs	k_N/dm^3 mol^{-1} s^{-1}
Bis(ethoxythiocarbonyl) sulphide (**4**)					
Pyrrolidine	20	0.136–0.663	10.4–62.1	7	100 ± 4
	25	0.136–0.828	12.1–99.7	12	124 ± 7
	30	0.119–0.663	13.1–97.9	9	145 ± 15
	35	0.119–0.663	17.6–115.8	9	174 ± 8
	40	0.138–0.544	26.2–117.9	8	213 ± 15
Piperidine	20	0.159–2.21	3.71–52.2	12	22.1 ± 0.8
	25	0.159–2.21	6.15–62.7	14	27.8 ± 0.8
	30	0.161–2.21	7.43–78.5	14	35 ± 1
	35	0.163–2.21	16.4–109	14	44 ± 2
	40	0.161–2.21	18.1–138	12	54 ± 3
Morpholine	25	0.47–2.33	4.00–18.1	12	7.9 ± 0.2
	30	0.47–2.33	4.70–23.7	10	9.5 ± 0.3
	35	0.47–2.33	5.72–26.5	12	11.6 ± 0.3
	40	0.47–1.93	6.99–27.4	7	13.7 ± 0.3
	45	0.47–2.33	8.50–43.2	11	18.0 ± 0.5
Bis(ethoxycarbonyl) sulphide (**5**)					
Pyrrolidine	20	0.059–0.819	2.39–36.1	12	44.1 ± 0.9
	25	0.083–1.095	3.85–57.6	13	55 ± 1
	30	0.061–0.521	4.40–35.4	7	68 ± 3
	35	0.060–0.521	5.76–51.6	10	96 ± 3
	40	0.058–0.527	9.15–64.7	10	113 ± 4
Piperidine	20	0.159–2.21	3.86–48.2	13	20.0 ± 0.8
	25	0.159–2.21	4.78–57.7	14	25.9 ± 0.6
	30	0.161–2.21	7.43–70.0	14	29.9 ± 0.6
	35	0.163–2.21	9.51–91.9	14	42 ± 1
	40	0.451–2.21	23.1–103	10	47.6 ± 0.9
Morpholine	25	0.47–2.33	3.28–11.5	11	4.5 ± 0.2
	30	0.47–2.33	4.26–14.7	10	5.4 ± 0.1
	35	0.47–2.33	6.70–17.4	10	6.1 ± 0.1
	40	0.47–2.33	9.63–22.5	12	7.1 ± 0.3
	45	0.47–2.33	13.5–29.4	7	8.5 ± 0.7

[a,b] As in Table 1.

$$k_{obs} = k_o + k_N[N] \qquad (2)$$

constant for solvolysis of the substrate, could be measured satisfactorily only in the reaction of compound (**5**) with morpholine (as intercept of the linear k_{obs} *vs.* [N] plot). In the other reactions k_o was negligible compared with the second term of equation (2). The k_o values found for the solvolysis of (**5**) were $10^3k_o = 1.4, 2.0, 3.6, 6.1$, and 10.0 s^{-1} at 25, 30, 35, 40, and 45 °C, respectively. An independent measurement of k_o for compound (**5**) at 45 °C was carried out in the absence of amine at pH *ca.* 8.7 (pH similar to those employed in the aminolysis). The value obtained agreed within experimental error with the one reported above.

The values of k_N for the reactions of compounds (**4**) and (**5**) were obtained as slopes of linear plots of k_{obs} *vs.* [N], at different pH values. The k_N values were independent of pH, as in the aminolysis of (**1**), and are reported in Table 2.

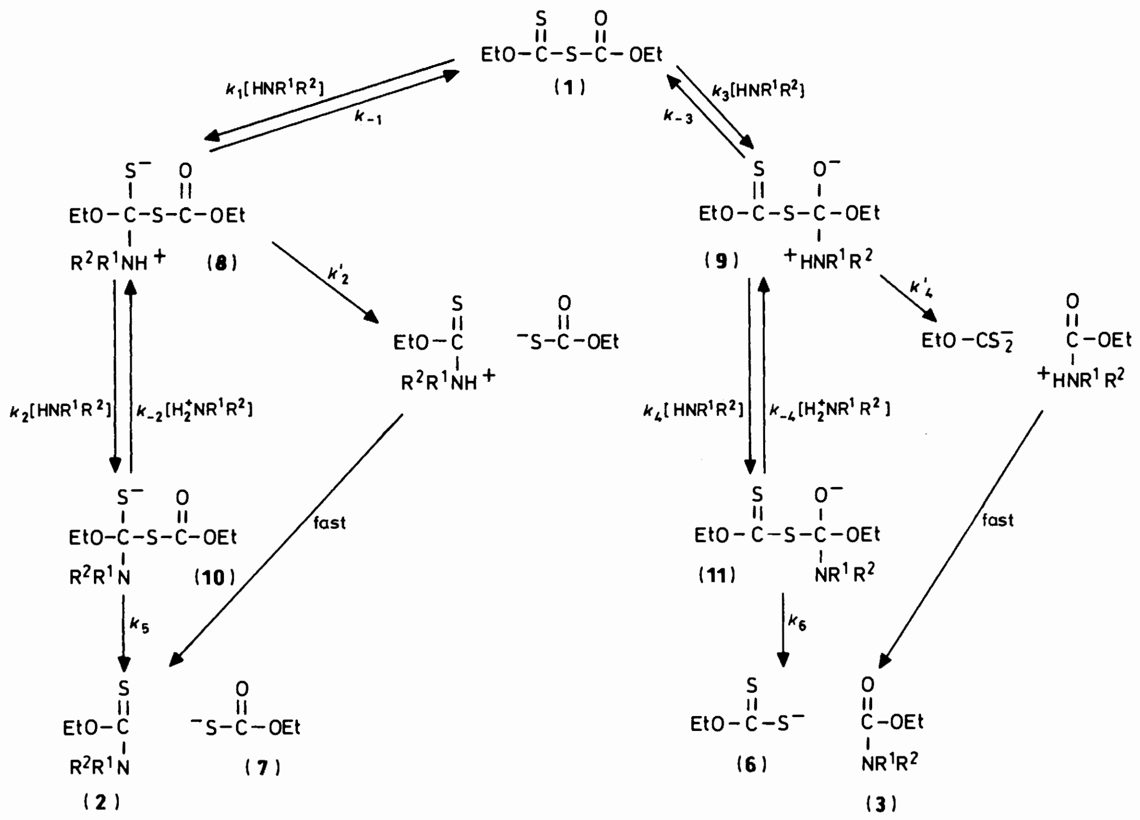
A probable mechanism for the aminolysis of compound (**1**) is depicted in Scheme 2.

It is likely that the first steps on both sides of Scheme 2 as depicted are rate determining. This is suggested by the values of the Brönsted-type slopes (β) obtained for k_N^{CO} and k_N^{CS}. With the data of Table 1 at 25 °C tentative Brönsted-type plots can be drawn for the reaction of compound (**1**) with piperidine (PI) and morpholine (MO). The slopes β are 0.26 and 0.46 for k_N^{CS} and k_N^{CO}, respectively. The low β values are an indication that amine attack is the rate-determining step, since values of β 0.1–0.4 have been reported in the aminolysis of esters,[9,10] carbonates,[11] isocyanates[12,13] and isothiocyanates[12] when the first step of these reactions is rate limiting. Small β values have also been found or estimated in the reactions of basic amines with CO_2, COS, and CS_2,[14,15] where the addition step is rate determining.

Additional proof that k_1 and k_3 of Scheme 2 are the rate-determining steps comes from estimation of the $k_{-1'}$, $k_{-3'}$, k_2, k'_2, k_4, and k'_4 values. Although the reactions studied in the present work were carried out in 95% ethanol, the estimated rate constants and pK_a values will be referred to water at 25 °C. We will start with the estimation of k_{-3} for the reaction with MO.

The rate constant k for hydrazine expulsion from the tetrahedral intermediate ($T^{\pm}$) formed in the reaction of hydrazine with 1-acetoxy-4-methoxypyridinium ion has been evaluated as 6×10^7 s^{-1} in water at 25 °C.[9] 4-Methoxypyridine *N*-oxide (pK_a 2)[16] is slightly more basic than *O*-ethyl xanthate (pK_a 1.6)[17] and should also have a greater ability than the latter to expel the amine.[18] On the other hand the ethoxy group of intermediate (**9**) (Scheme 2) is more capable of expelling the amine than is the methyl group of $T^{\pm}$, compensating the above effect. Therefore, one can estimate k_{-3} for the MO reaction as *ca.* 10^7 s^{-1}, since hydrazine is as basic as MO. Obviously, k_{-3} for the reactions of the more basic pyrrolidine (PY) and PI should be smaller than 10^7 s^{-1}.

The rate constant k_{-1} for MO (Scheme 2) should be larger than 10^7 s^{-1}, as deduced by the twofold larger rate constant for butylamine expulsion (pK_a 10.6)[19] from *N*-protonated *N*-butylmonothiocarbamate compared with *N*-butylcarbamate.[15] Expulsion of less basic amines showed a greater selectivity. For



Scheme 2.

instance, 2,2,2-trifluoroethylamine and *p*-nitroaniline are expelled 20-fold and 100-fold faster, respectively, from the monothiocarbamate derivative.[15] A rough estimation of k_{-1} for MO based on the above data gives a value of *ca.* 10^8 s^{-1}. The values of k_{-1} for PY amd PI should be $< 10^8$ s^{-1}.

Let us now turn to the estimation of k_2 and k_4 of Scheme 2. Prior to this it is necessary to evaluate the pK_a values of intermediates (**8**) and (**9**). The pK_a of (**9**) for MO can be estimated as follows.

We start with the pK_a of *N*-methylmorpholinium ion (7.3).[19] Following Jencks' procedure the pK_a of $OC_4H_8NH^+$–CH_2O^- can be estimated as *ca.* 10.2.[20–22,*] The pK_a of $OC_4H_8NH^+$–CR^1R^2X has been satisfactorily correlated with σ_I, giving ρ_I 7.3,[21] and substitution of the ethoxy (σ_I 0.27)[23] and $SCOCH_3$ groups (σ_I 0.36)[24] lowers the pK_a by $(0.36 + 0.27) \times 7.3 = 4.6$ units, giving pK_a 5.6 for $OC_4H_8NH^+$–$C(OEt)(SCOMe)O^-$. Since *O*-ethyl xanthate is slightly less basic than ethyl monothioacetate ion, the pK_a of intermediate (**9**) for MO should be slightly smaller than 5.6. Similar estimations for the pK_a of intermediate (**9**) with HNR^1R^2 = PY and PI, gives values of *ca.* 8.6 and 8.4, respectively.†

An independent estimate of the pK_a of intermediate (**9**) is as follows. Guthrie and Pike have found that the pK_a values of XCH_2–ImH^+ (Im = imidazole) are correlated with σ^*, giving ρ^* −0.3.[25] Based on the pK_a of *N*-methylammonium ions (10.3, 10.1, and 7.3, for the PY, PI, and MO derivatives, respectively)[19] and assuming additivity of the substituent constants,[25] one obtains pK_a (**9**) = pK_a (Me–NH$^+$) − $0.3 \times (1.68 + 3.65 - 2.78)$, where 1.68, 3.65, and −2.78 are the σ^* values of OEt,[25] SCSEt,‡ and O^-[25] groups, respectively. The above equation gives pK_a (**9**) 9.5, 9.3, and 6.5 for the PY, PI, and MO derivatives, respectively. These values are higher than those estimated based on the works of Jencks and co-workers. Since the difference of the pK_a values obtained by the two methods is not large we will take an average of the two values. The final pK_a values of intermediate (**9**) are, therefore, 9.1, 8.9, and 6.1, for HNR^1R^2 = PY, PI, and MO, respectively, which means there is a pK_a lowering of *ca.* 2 units relative to the parent amines.[19]

It is difficult to find literature models from which to estimate the pK_a of intermediate (**8**) in Scheme 2. Jencks and co-workers have found that there is a pK_a lowering of 3.5 units when going from *N*-protonated *N*-alkylcarbamates to the corresponding thiocarbamates.[15] Obviously, the pK_a decrease of intermediate (**8**) relative to (**9**) cannot be as large as 3.5 units since delocalization of the N positive charge is much larger in the (thio)carbamate system than in the intermediates (**8**) or (**9**). Since quantification of the pK_a lowering of (**8**) is difficult we can only state that the pK_a values of (**8**) for the three amines under study should be smaller than the corresponding pK_a values of (**9**), although by much less than 3 pK_a units.

With the pK_a values of (**8**) and (**9**) for the three amines under study, we can estimate k_2 and k_4 as 10^{10} dm^3 mol^{-1} s^{-1} for the three amines since the proton transfers involved are thermodynamically favourable.[15,26]

The rate constants k_{-4} and k_{-2} can be evaluated through the relations $k_{-4} = k_4 \times K_a(NH^+)/K_a(\mathbf{9})$ and $k_{-2} = k_2 \times$

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[*] In equation (23) of ref. 21, $pK_4 - pK_1 = 4.8$, and in equation (13) of ref. 22, $pK_{a4} - pK_{a1} = 4.7$.

[†] Both estimations are based on the pK_a value of the corresponding *N*-methylammonium ions in water at 25 °C. These are 10.3 and 10.1 for the pyrrolidine and the piperidine derivatives,[19] respectively, a pK_a lowering of 1 unit relative to the parent amines.[19]

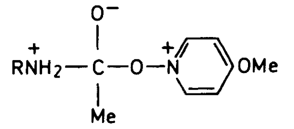
[‡] This value was calculated based on the σ^* values of *p*-nitrophenoxy and 2,4-dinitrophenoxy groups (2.91 and 3.32, respectively)[25] and assuming a linear relation between σ^* and the pK_a values of the conjugate acids.

Table 3. Estimated rate constants and pK_a values of intermediates (**8**) and (**9**) of Scheme 2.

Rate constant	Amine moiety of intermediates		
	Morpholine	Piperidine	Pyrrolidine
k_{-3}/s^{-1}	10^7	$<10^7$	$<10^7$
k_{-1}/s^{-1}	10^8	$<10^8$	$<10^8$
$k_4/dm^3\ mol^{-1}\ s^{-1}$	10^{10}	10^{10}	10^{10}
$k_2/dm^3\ mol^{-1}\ s^{-1}$	10^{10}	10^{10}	10^{10}
$k_{-4}/dm^3\ mol^{-1}\ s^{-1}$	10^8	10^8	10^8
$k_{-2}/dm^3\ mol^{-1}\ s^{-1}$	$<10^8$	$<10^8$	$<10^8$
k'_4/s^{-1}	3×10^{10}	10^{11}	10^{11}
k'_2/s^{-1}	$>3 \times 10^{10}$	$>10^{11}$	$>10^{11}$
k_5/s^{-1}	$>3 \times 10^{10}$	$>10^{11}$	$>10^{11}$
k_6/s^{-1}	$>3 \times 10^{10}$	$>10^{11}$	$>10^{11}$
pK_a			
(**8**)	5–6	7.8–8.8	8–9
(**9**)	6.1	8.9	9.1

$K_a(NH^+)/K_a(\mathbf{8})$, where NH^+ refers to the protonated amine.[26,27] Considering that p$K_a(NH^+)$ − p$K_a(\mathbf{9}) \sim 2$, and that p$K_a(NH^+)$ − p$K_a(\mathbf{8}) > 2$ one notes that k_{-4} *ca.* 10^8 dm^3 mol^{-1} s^{-1} and $k_{-2} < 10^8$ dm^3 mol^{-1} s^{-1} for all the amines.

The value of k'_4 of Scheme 2 can be estimated from the rate constants for expulsion of 4-methoxypyridine *N*-oxide from compound (**12**). With RNH_2 = methylamine and hydrazine,



(**12**)

$k = 3 \times 10^{10}$ and 8×10^9 s^{-1} (water; 25 °C), respectively.[9] Interpolation of these values for MO and extrapolation to PI and PY gives k *ca.* 9×10^9 s^{-1} for MO and *ca.* 4×10^{10} s^{-1} for the two latter amines. The stronger leaving-group expulsion by the ethoxy group of intermediate (**9**) compared with that of the methyl group of (**12**), and the fact that ethyl xanthate is slightly less basic than 4-methoxypyridine *N*-oxide, are compensated by the fact that thiol anions are worse nucleofuges than oxy anions of the same basicity.[18,28] Since quantification of these opposing effects is uncertain, we can tentatively assume that k'_4 is *ca.* 10^{10} s^{-1} and we will attempt another estimation of k'_4 based on a different system.

The rate constants for expulsion of RS^- from $CH_3C(O^-)(H)SR$ (**13**) have been evaluated for R = Et, CH_2OMe and CH_2CO_2Me.[29,30] Extrapolation of the linear Brönsted relation to the pK_a of $EtOCS_2H$ (pK_a 1.6)[17] gives $k = 2 \times 10^{10}$ s^{-1}. Addition of an amine to anion (**13**) and substitution of ethoxy for methyl should increase the rate of $EtOCS_2^-$ expulsion from the anionic hemithioacetal. Therefore, $k'_4 > 2 \times 10^{10}$ s^{-1} for MO, PI, and PY. We can assume that k'_4 is *ca.* 10^{11} s^{-1} for the two most basic amines and *ca.* 3×10^{10} s^{-1} for MO.*

It has been found that partitioning of tetrahedral intermediates similar to (**8**) and (**9**) favours aryl oxide expulsion relative to amine when the oxy anion of the intermediate is changed to a sulphur anion.[31,32] We will assume, therefore, that $k'_2 > k'_4$, since the two sulphur nucleofuges involved have similar basicities.[17]

The rate constants k_5 and k_6 of Scheme 2 are larger than k'_2 and k'_4, respectively, in view of the additional leaving-group expulsion provided by the lone electron pair of the amine nitrogen atom in anions (**10**) and (**11**).

A summary of all the estimated rate constants of Scheme 2 and the pK_a values of intermediates (**8**) and (**9**) are shown in Table 3. The evaluation of these rate constants and pK_a values are based on the corresponding values of model reactions reported in water at 25 °C; therefore the values of Table 3 are referred to the above conditions.

From data of Table 3 it follows that $k_{-1} \ll k'_2$ and $k_{-3} \ll k'_4$. These inequalities are reasonable. In the aminolysis of esters with good nucleofuges such as acetic anhydride, 2,4-dinitrophenyl acetate, and similar carbonates, curved Brönsted-type plots were obtained with the centre of curvature at pK_a 6.1–7.8.[11,33] For amines with pK_a > 7.8 expulsion of the oxy anion from $T^\pm$ is faster than that of the amine. Since $EtOCS_2^-$ is less basic than the acetate of 2,4-dinitrophenoxide ions, its removal from (**9**) must be faster than expulsion of the latter ions from $T^\pm$, so it is reasonable that $k_{-3} \ll k'_4$ and $k_{-1} \ll k'_2$.

From the data of Table 3 and the fact that both the free and protonated amine concentrations in all the reactions of compound (**1**) were *ca.* 10^{-3} mol dm^{-3} (Table 1), it follows that $k'_2 \gg k_2[HNR^1R^2]$ and $k'_4 \gg k_4[HN^1R^2]$. Since also $k'_2 \gg k_{-1}$ and $k'_4 \gg k_{-3}$, it means that almost all of the aminolysis of compound (**1**) goes to products *via* k'_2 and k'_4, and that the rate determining steps are k_1 and k_3.

According to the values shown in Table 3, it seems that some of the tetrahedral intermediates formed in the aminolysis of compound (**1**) are near to 'borderline' existence, but we think they do exist in view of their similar nature to those described elsewhere.[31,32,34]

It is likely that the pK_a values of intermediates (**8**) and (**9**) and the protonated amine vary in the same direction with a change of solvent. Since the latter pK_a value is lower in 95% ethanol compared with water (see Table 1), the pK_a values of intermediates (**8**) and (**9**) should also be lower in 95% ethanol; hence proton transfer from (**8**) and (**9**) to the amine remains thermodynamically favourable and the values of k_2 and k_4 will not be affected by the change of solvent.

The values of k'_2 and k'_4 (Scheme 2) are not expected to change significantly with the nature of the solvent, since the transition states involved, as well as (**8**) and (**9**), are highly polar.[11a,b] On the other hand, k_{-1} and k_{-3} should increase on changing from water to 95% ethanol in view of the lower polarity of the transition states concerned relative to the initial states (**8**) and (**9**).[11] Nevertheless, these increases should be small as indicated by comparison of the pK_a^0 values of the curved Brönsted-type plots found in the aminolyses of acetyl derivatives in water and 44% aqueous ethanol.[10b,35]

The reaction schemes for the aminolyses of compounds (**4**) and (**5**) should be simpler than that for (**1**), in view of the symmetrical nature of the former substrates. Most of what has been discussed for the aminolysis of (**1**) should be applicable to the reactions of (**4**) and (**5**) since the three compounds are very similar. A simplified mechanism for the aminolyses of (**4**) and (**5**), taking into account the main conclusions drawn for the analogous reaction of (**1**), is shown in Scheme 3, where X is S (**4**) or O (**5**).

Tables 1 and 2 show that for a given temperature and substrate the order of amine reactivities is PY > PI > MO, which is the order of their basicities.[19] This is in accord with the sequence found in the reactions with COS[36] and CS_2.[37]

Since amine attack on the carbonyl or thiocarbonyl functions is rate limiting for the reactions studied here, we can compare amine reactivities of carbonyl *vs.* thiocarbonyl groups, by

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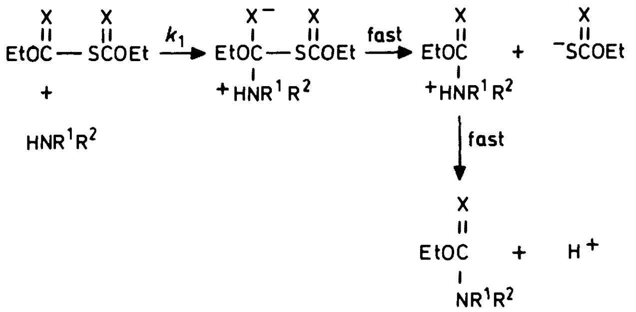
* The value of k'_4 for MO was obtained assuming that k'_4 for PY and PI is *ca.* 10^{11} s^{-1}, and that the effect of the RNH_2 basicity on expulsion of the oxy anion from (**12**) is the same as that on k'_4.

Table 4. Activation parameters found in the aminolysis of compounds (**1**), (**4**), and (**5**) in 95% aqueous ethanol, ionic strength 0.05 mol dm^{-3} (maintained with LiCl).[a]

	Pyrrolidine		Piperidine		Morpholine	
	$\Delta H^‡$/ kJ mol^{-1}	$\Delta S^‡$/ J mol^{-1} K^{-1}	$\Delta H^‡$/ kJ mol^{-1}	$\Delta S^‡$/ J mol^{-1} K^{-1}	$\Delta H^‡$/ kJ mol^{-1}	$\Delta S^‡$/ J mol^{-1} K^{-1}
Reaction of (**1**) (CS)[b]	19 ± 1	−144 ± 4	30 ± 1	−118 ± 4	31 ± 1	−124 ± 3
Reaction of (**1**) (CO)[c]	19 ± 1	−154 + 3	30 ± 1	−124 ± 4	31 ± 1	−136 ± 3
Reaction of (**4**)[d]	26 ± 1	−124 ± 2	32 ± 1	−116 ± 2	29 ± 2	−136 ± 6
Reaction of (**5**)[d]	35 ± 2	−101 ± 7	31 ± 2	−119 ± 8	22 ± 1	−156 ± 4

[a] Errors shown are standard errors. [b] Amine attack at the thiocarbonyl group of (**1**). [c] Amine attack at the carbonyl group of (**1**). [d] The experimental k_N values found in these reactions were divided by two (statistical correction) prior to determination of the activation parameters.



Scheme 3.

comparing the k_N values of Tables 1 and 2. The k_N values for the reactions of (**4**) and (**5**) should be divided by two (both have two equivalent electrophilic sites) before comparison with the k_N values for the aminolysis of (**1**). All three amines are more reactive, at all the temperatures studied, toward C=S than toward C=O, as measured by $k_N/2$ for (**4**) compared with k_N^{CO} for (**1**), where the nucleofuge is *O*-ethyl xanthate in both cases. When the leaving group is *O*-ethyl monothiocarbonate, we also see that the C=S group is more reactive toward amines than is the C=O group [k_N^{CS} for the reaction of (**1**) is larger than $k_N/2$ for that of (**5**)] at all temperatures. The C=S reactivity is only (1.1–1.9) times larger than that of C=O for PI, (1.8–3.6) times larger for PY, and (2.1–4.2) times larger for MO.

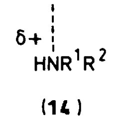
It was found that *O*-(*p*-nitrophenyl) thiobenzoate reacted with some primary amines *ca.* 100 times faster than did *p*-nitrophenyl benzoate, when the rate-determining step is breakdown of the zwitterionic tetrahedral intermediate ($T^{\pm}$).[32] This has been explained mainly through the superior ability of S^- in $T^{\pm}$ to expel *p*-nitrophenoxide ion compared with that of O^-.[32] In contrast to this, when the formation of $T^{\pm}$ is rate limiting the benzoate derivative is more reactive than the thiobenzoate analogue toward hydroxide ion, although only eightfold.[32] On the other hand, it has been found that amines react with CO_2, COS, and CS_2 in the rate proportions $10^5:10^3:1$, respectively,[36] although comparison with the reactions studied in this work is inappropriate in view of the high resonance involved in the above electrophiles. A better comparison with our work comes from the aminolysis of thioacyl acyl sulphides (although the solvent used was hexane), where amines seem to react faster with carbonyl functions relative to thiocarbonyl ones.[3] Unfortunately, quantification of these reactivities cannot be made since the kinetics of these reactions were not studied.[3]

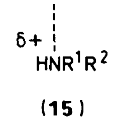
According to the results above, it seems that amines should be slightly more reactive toward CO than CS groups, when amine attack is rate determining. The fact that, in the reactions studied in this work, amines react slightly faster with C=S compared with C=O groups means that the nature of both the substrate and the amine (and perhaps the solvent), is very important in dictating the order of reactivities.

The reactivities of amines toward carbonyl and thiocarbonyl groups are governed by the principle of 'hard and soft acids and bases,' by which CO groups are considered harder acids than are CS groups.[38] Amines are classified as 'hard' and borderline 'hard' and 'soft' bases, and depending on their nature the harder ones should react more easily with CO and the softer ones more readily with CS groups.[38] So it is not unreasonable that our results differ from other data obtained for similar reactions.

Table 4 shows the activation parameters found in the reactions studied in this work. In all cases negative $\Delta S^‡$ values were found, which can be explained in terms of (i) the loss of translational degrees of freedom in these bimolecular reactions when going from reactants to the corresponding transition states, and (ii) the greater solvation of the latter relative to reactants in view of their higher polarity. The transition states for these reactions are more polar than the reactants since the products in the rate-determining steps of the reactions are zwitterions [compounds (**8**) and (**9**) in the reaction of (**1**) and very similar intermediates in the reactions of (**4**) and (**5**)].

Table 4 shows that amine attack at CO gives lower $\Delta S^‡$ values than does attack at CS, the only exception being the reaction of PY with (**5**), where higher $\Delta S^‡$ values are obtained relative to its reaction with both (**4**) and (**1**). The lower $\Delta S^‡$ values for CO attack can be explained through the structures of the transition states involved in the reactions. Structure (**14**) (X = O or S) should be less polar than (**15**) (X = O or S) and, therefore less strongly solvated, since it is known that in solution sulphur can delocalize a negative charge better than can oxygen.[15] The fact that $S^{\delta-}$ from (**14**) has a greater driving force to expel $^-$SCXOEt than does $O^{\delta-}$ from (**15**)[32] confirms that the negative charge on the carbonyl oxygen of intermediate (**15**) is more localized, rendering (**15**) more polar (and more strongly solvated) than (**14**). This results in smaller $\Delta S^‡$ values for amine attack at the carbonyl group of the substrates compared with attack at thiocarbonyl.


(**14**)


(**15**)

Acknowledgements

We are grateful to Dirección Investigación Universidad Católica de Chile for financial assistance. We thank Dr. J. C. Vega and Dr. M. Palominos for the synthesis of some compounds and chromatographic assistance.

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Received 16*th May* 1988; *Paper* 8/01943F