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Kinetics and Mechanism of Polythioamidation in Solution. 1. Reaction of Mono- and Bis(dithioester)s with Excess Amine

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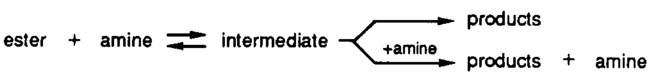
ABSTRACT: Thioamidation kinetics have been studied for reaction in solution between mono- and bifunctional amines and dithioesters near room temperature (30–50 °C) using large amine excess. We have used aliphatic reagents as well as several ether mono- and diamines and a diether bis(dithioester), which are able to maintain polythioamides in solution throughout the condensation reaction and thus give rise to significant results in polycondensation kinetics for which sufficient solubility is needed. Pseudo-first-order constants (first order relative to dithioesters) were correlated to amine concentrations and allowed to appreciate the values of second- and third-order reaction rate constants. The influences of solvent nature, structure of reagents, and temperature were examined in numerous examples. Added tertiary amines do not have significant influence on reaction rates whereas the primary amine concentration is an important factor of reaction rates. All the collected data are correlated through kinetic analysis with a reaction mechanism involving first a reversible nucleophilic addition of the amine to the dithioester thiocarbonyl group to give a zwitterionic intermediate, followed by a primary amine assisted prototropy and then decomposition of the so-formed neutral hemidithioacetal-like structure to thioamide and thiol. Such a mechanism predicts global order variations for reactions in stoichiometric ratio. Kinetically, thioamidation of dithioesters looks like amidation of esters except for tertiary amine catalysis, which is ineffective in the first case.

Ester aminolysis was intensively studied in various aprotic solvents in recent years.[1-8] A generally accepted reaction rate law is described by

$$r = k_{\mathrm{II}}[\text{ester}][\text{amine}] + k_{\mathrm{III}}[\text{ester}][\text{amine}]^2$$

According to experimental conditions, either the second-order (k_{II}) or the third-order (k_{III}) rate constants may be found equal to zero. Such results are consistent with a reaction mechanism beginning by the reversible formation of a tetrahedral intermediate followed by the rate-determining disparition of this intermediate, through either reaction of an amine molecule or spontaneous reaction.



Dithioesters react with primary and secondary aliphatic amines much faster than esters do, leading irreversibly to thioamides and thiols according to

$$R^1C(S)SR^2 + R^3NHR^4 \rightarrow R^1CSNR^3R^4 + R^2SH$$

This reaction was described to be so rapid that no kinetic measurements could be made on it.[9]

In our laboratory, numerous polythioamides have been obtained in solution from bis(dithioester)s and diamines[10] but some improvements may be expected if the reaction mechanism could be known for this step-growth polymerization process. Particularly, aromatic polythioamide synthesis remains a problem to be solved correctly.[11]

Polythioamides are quite stable polymers, very similar to polyamides although their melting points are lowered in respect to the melting points of the homologous polyamides (50–80 °C for aliphatic compounds[12]). Solubilities are low for purely aliphatic or semiaromatic polythioamides (concentrated H_2SO_4 and 5% LiCl in dimethylformamide (DMF) are the usual solvents). However, the absence of hydrogen bonding to thiocarbonyl compounds is evidently responsible for the solubilization observed in the course of thionation of poly(amide-*block*-ether) leading to a poly(thioamide-*block*-ether), which becomes soluble in more convenient solvents such as chloroform.[13]

We report here the results of a kinetic study of the thioacylation reaction of primary amines, in the course of which we have also used amine and dithioester reagents containing ether groups in order to maintain the formed thioamides in solution, even in nonpolar solvents. Thus, the use of specific UV–visible absorptions of thiocarbonyl compounds could allow accurate kinetic measurements on thioacylation reactions.

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1. Choice of Reagents

Mono- and bifunctional compounds were chosen according to their availability (diaminodi- and diaminotriethers 3 and 4 are commercial products) or their accessability through synthesis. Mono- and diamines were vacuum distilled just before use, whereas dithioesters were either distilled or crystallized and stored in the cold.

Amines and diamines: *n*-butylamine, $CH_3(CH_2)_3NH_2$ (1); 3-ethoxy-1-propylamine, $CH_3CH_2O(CH_2)_3NH_2$ (2); 4,9-dioxa-1,12-diaminododecane, $H_2N(CH_2)_3O(CH_2)_4O(CH_2)_3NH_2$ (3); 4,7,10-trioxa-1,13-diaminotridecane, $H_2N(CH_2)_3O(CH_2)_2O(CH_2)_2O(CH_2)_3NH_2$ (4).

Dithioesters and bis(dithioester)s: ethyl hexanedithioate $CH_3(CH_2)_4C(S)SC_2H_5$ (5); didodecyl 1,12-dodecanebis(dithioate) $RSCS(CH_2)_{10}C(S)SR$ ($R = n\text{-}C_{12}H_{25}$) (6); didodecyl 4,7-dioxa-1,10-decanebis(dithioate) $RSCS(CH_2)_2O(CH_2)_2O(CH_2)_2C(S)SR$ ($R = n\text{-}C_{12}H_{25}$) (7).

Solvents. Reagents and products are somehow different in behavior: bis(thioamides) are soluble in toluene only when also containing ether groups. Dithioesters, which are not polar at all, require the use of a cosolvent if highly polar solvents are used. So we have studied the thioacylation reaction both in toluene and toluene/DMF mixtures (mainly 1/1) to explore the influence of solvent polarity on the reaction kinetics.

2. Kinetic Measurements

Aliphatic dithioesters afford strong absorption in the UV–visible range: λ_{max} values are located near 310 nm ($\epsilon \approx 12\,500$–$13\,000$ L·mol^{-1}·cm^{-1}) and 450 nm ($\epsilon \approx 50$–80 L·mol^{-1}·cm^{-1}), allowing us to follow the dithioester concentration from absorbance measurements; useful concentrations are in the ranges of 10^{-4} mol·L^{-1} for the UV band and 10^{-2} mol·L^{-1} for the visible band.

Secondary aliphatic thioamides exhibit absorptions near 270 nm (intense) and 340 nm (weak). Therefore, it was not possible to follow at 310 nm the dithioester disappearance until completion as the thioamide group absorbs slightly at this wavelength; an isosbestic point was noted near 285 nm in the course of the reaction between butylamine (1) and ethyl hexanedithioate (5). The extent of the reaction was then limited to ca. 75% when kinetic measurements were made at 310 nm.

Preliminary tests have established that the reaction between aliphatic dithioester and amine follows a first-order reaction rate with respect to dithioester, and in this paper we report the results of reactions devoted to the establishment of the global reaction order and postulate a likely mechanism.

A large amine excess was used in order to determine the apparent first-order constant $k_{1\Psi}$ relative to the dithioester concentration according to

$$r = \frac{\mathrm{d[dithioester]}}{\mathrm{d}t} = k_{\mathrm{II}}[\mathrm{dithioester}][\mathrm{amine}] + k_{\mathrm{III}}[\mathrm{dithioester}][\mathrm{amine}]^2 \quad (1)$$

If [dithioester] ≪ [amine], then relation 1 becomes

$$r = k_{1\Psi}[\mathrm{dithioester}]$$

where

$$k_{1\Psi} = k_{\mathrm{II}}[\mathrm{amine}]_0 + k_{\mathrm{III}}[\mathrm{amine}]_0^{\,2} \quad (2)$$

Table I
Kinetics of Reaction between *n*-Butylamine (1) and Ethyl Hexanedithioate (5)[a]

Toluene

[amine], mol·L^{-1}	$k_{1\Psi} \times 10^3$, s^{-1} 30 °C	40 °C	50 °C
0.0745	0.146	0.160	0.183
0.102	0.265	0.307	0.335
0.182	0.857	1.05	1.19
0.257	1.72	2.15	2.45
$k_{\mathrm{II}} \times 10^3$, L·mol^{-1}·s^{-1}	0	0	0
$k_{\mathrm{III}} \times 10^3$, L^2·mol^{-2}·s^{-1}	26.0	31.0	34.7

$E_A(k_{\mathrm{III}}) = +12$ kJ·mol^{-1}

Toluene/DMF (1/1)

[amine], ×10^2 mol·L^{-1}	$k_{1\Psi} \times 10^3$, s^{-1} 30 °C	40 °C	50 °C
1.74	2.95	2.77	2.57
2.52	5.12	5.13	4.82
4.33	11.0	11.9	11.3
5.39	15.5	16.2	15.9
$k_{\mathrm{II}} \times 10^3$, L·mol^{-1}·s^{-1}	119	106	84.5
$k_{\mathrm{III}} \times 10^3$, L^2·mol^{-2}·s^{-1}	3130	3580	3990

$E_A(k_{\mathrm{II}}) = -14$ kJ·mol^{-1} $E_A(k_{\mathrm{III}}) = +10$ kJ·mol^{-1}

[a] $[\mathrm{DTE}]_0 = 10^{-4}$ mol·L^{-1}.

Pseudo-first-order constants $k_{1\Psi}$ are determined graphically from the integrated form of relation 2:

$$\ln\,[\mathrm{dithioester}] = -k_{1\Psi}t + \ln\,[\mathrm{dithioester}]_0$$

After combination of this relation with the Beer–Lambert law, it becomes

$$\ln D_0/D = k_{1\Psi}t$$

in which D is the optical density at time t and D_0 the initial optical density. Thus $k_{1\Psi}$ was determined as the slope of the variations of $\ln D_0/D$ versus time. Every reagent pair offered linear correlations, respectively, at 30, 40, and 50 °C, thus confirming the statement the reaction is first-order relative to dithioester.

According to relation 2, it is possible to write

$$k_{1\Psi}/[\mathrm{amine}]_0 = k_{\mathrm{II}} + k_{\mathrm{III}}[\mathrm{amine}]_0 \quad (3)$$

and we have studied the variations of $k_{1\Psi}/[\mathrm{amine}]_0$ versus initial amine concentration.

Experimental values of pseudo-first-order rate constants, $k_{1\Psi}$, are reported in Tables I–VIII. Activation energies were estimated for the different reaction rate constants.

3. Experimental Section

4,9-Dioxa-1,12-dodecanediamine and 4,7,10-trioxa-1,13-tridecanediamine were gifts from BASF, France. Amines and ethyl hexanedithioate were vacuum distilled before use whereas bis(dithioester)s were crystallized from pentane–isooctane mixtures.

Bis(dithioester) 7 was obtained from 1,2-ethanediol as follows:

4,7-Dioxa-1,10-decanedinitrile: In a 100-mL round-bottomed flask are placed under nitrogen 0.167 mol of 1,2-ethanediol (10.35 g), 1 mL of 40% aqueous potassium hydroxide, and 0.095 g of 1,4-dihydroxybenzene. Acrylonitrile (0.34 mol) is added slowly and the mixture stirred at room temperature for 20 h. After acidification through 20% aqueous HCl addition, the product is extracted with chloroform, dried over $MgSO_4$, concentrated, and distilled [118 °C (0.1 mbar)]: colorless liquid; yield 65%.

Di(*n*-dodecyl) 4,7-dioxa-1,10-decanebis(dithioate): prepared from the dinitrile as previously described for bis(dithioester)s[10] through addition of dodecanethiol under an anhydrous HCl stream followed by hydrosulfuration of the obtained aminothioester; however, in the second step replacing pyridine by

Table II
Kinetics of Reaction between 3-Ethoxypropylamine (2) and Ethyl Hexanedithioate (5)[a]

Toluene

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine], mol·L^{-1}	30 °C	40 °C	50 °C
0.0812	0.418	0.502	0.568
0.104	0.687	0.807	0.908
0.175	1.87	2.28	2.63
0.255	3.83	4.83	5.28
$k_{II} \times 10^3$, L·mol^{-1}·s^{-1}	0.63	0.53	0.55
$k_{III} \times 10^3$, L^2·mol^{-2}·s^{-1}	56.7	73.8	80.2
$E_A(k_{III})$ = +15 kJ·mol^{-1}			

Toluene/DMF (1/1)

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine] × 10^2, mol·L^{-1}	30 °C	40 °C	50 °C
1.72	2.53	2.58	2.52
2.67	4.98	5.48	5.57
3.55	8.17	8.77	8.93
4.88	13.9	15.6	16.3
$k_{II} \times 10^3$, L·mol^{-1}·s^{-1}	71.7	60.0	48.3
$k_{III} \times 10^3$, L^2·mol^{-1}·s^{-1}	4390	5320	5830
$E_A(k_{II})$ = −16 kJ·mol^{-1}	$E_A(k_{III})$ = +12 kJ·mol^{-1}		

[a] $[\mathrm{DTE}]_0 = 10^{-4}$ mol·L^{-1}.

Table III
Kinetics of Reaction between 4,9-Dioxa-1,12-dodecanediamine (3) and Ethyl Hexanedithioate (5)[a]

Toluene

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine], mol·L^{-1}	30 °C	40 °C	50 °C
0.0798	0.732	0.908	1.07
0.103	1.06	1.33	1.58
0.186	2.56	3.43	3.98
0.256	4.30	5.83	7.57
$k_{II} \times 10^3$, L·mol^{-1}·s^{-1}	5.79	6.29	5.98
$k_{III} \times 10^3$, L^2·mol^{-2}·s^{-1}	43.8	64.7	89.5
$E_A(k_{III})$ = +29 kJ·mol^{-1}			

Toluene/DMF (1/1)

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine] × 10^2, mol·L^{-1}	30 °C	40 °C	50 °C
1.85	5.58	6.63	7.87
3.04	9.82	11.8	14.1
3.34	10.6	13.0	14.7
4.22	13.8	16.7	19.6
$k_{II} \times 10^3$ L·mol^{-1}·s^{-1}	286	335	401
$k_{III} \times 10^3$ L^2·mol^{-2}·s^{-1}	1030	1530	1510
$E_A(k_{II})$ = +14 kJ·mol^{-1}	$E_A(k_{III})$ = low		

[a] $[\mathrm{DTE}]_0 = 10^{-4}$ mol·L^{-1}. (DTE = dithioester.)

cross-linked poly(vinylpyridine) (Reilly Chemicals) gives improved yields of pure product: yellow solid. Mp: 28 °C. Yield: 70%. Anal. Found (calcd of $C_{32}H_{62}O_2S_4$ = 607.106): C, 63.03 (63.31); H, 10.16 (10.29); O, 5.37 (5.27); S, 20.76 (21.13). ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 6 H), 1.25 (m, 40 H), 3.22 (t, 8 H), 3.57 (m, 4 H), 3.88 (t, 4 H). ^{13}C NMR ($CDCl_3$): δ 14.09, 22.72, 27.33, 29.18, 29.38, 29.52, 29.67, 31.97, 36.72, 51.86, 71.09, 234.82. UV–visible ($CHCl_3$): 310.2 nm (ϵ = 25 400 L·mol^{-1}·cm^{-1}); 454.9 nm (ϵ = 53 L·mol^{-1}·cm^{-1}).

Kinetic Measurements. The kinetic experiments were conducted in a 1-cm-length double-walled quartz cell, thermostated by water circulation, stirred with the aid of a small magnetic bar. UV–visible absorptions were measured in a Perkin-Elmer Lambda 15 apparatus. Desired volumes of preheated reagent solutions in the solvent used are measured with micropipettes and mixed directly in the cell at time zero.

Table IV
Kinetics of Reaction between 4,7,10-Trioxa-1,13-tridecanediamine (4) and Ethyl Hexanedithioate (5)[a]

Toluene

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine], mol·L^{-1}	30 °C	40 °C	50 °C
0.075	18.6	24.5	30.3
0.103	27.2	36.5	44.8
0.182	54.3	75.7	96.0
0.250	82.2	117	150
$k_{II} \times 10^3$, L·mol^{-1}·s^{-1}	0	0	0
$k_{III} \times 10^3$, L^2·mol^{-2}·s^{-1}	26.0	31.0	34.7
$E_A(k_{II})$ = +16 kJ·mol^{-1}	$E_A(k_{III})$ = +12 kJ·mol^{-1}		

Toluene/DMF (1/1)

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine] × 10^2, mol·L^{-1}	30 °C	40 °C	50 °C
1.62	7.02	9.25	11.2
2.86	12.3	16.2	19.4
3.78	16.4	22.0	26.3
4.30	19.0	25.5	30.7
$k_{II} \times 10^3$, L·mol^{-1}·s^{-1}	426	551	673
$k_{III} \times 10^3$, L^2·mol^{-2}·s^{-1}	280	822	695
$E_A(k_{II})$ = +19 kJ·mol^{-1}		$E_A(k_{III})$ = low	

[a] $[\mathrm{DTE}]_0 = 10^{-4}$ mol·L^{-1}.

Table V
Kinetics of Reaction between *n*-Butylamine (1) and Di(*n*-dodecyl) 1,2-Dodecanebis(dithioate) (6)[a]

Toluene

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine], mol·L^{-1}	30 °C	40 °C	50 °C
0.082	0.147	0.198	0.136
0.111	0.295	0.323	0.317
0.179	0.747	0.782	0.868
0.387	3.75	4.47	5.30
$k_{II} \times 10^3$, L·mol^{-1}·s^{-1}	0	0	0
$k_{III} \times 10^3$, L^2·mol^{-2}·s^{-1}	25.7	30.5	39.5
$E_A(k_{III})$ = +17 kJ·mol^{-1}			

Toluene/DMF (1/1)

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine] × 10^2, mol·L^{-1}	30 °C	40 °C	50 °C
1.56	0.685	0.682	0.695
2.84	1.80	1.85	1.92
3.78	2.65	2.90	2.88
4.80	3.83	4.15	4.28
$k_{II} \times 10^3$, L·mol^{-1}·s^{-1}	29.2	25.2	25.7
$k_{III} \times 10^3$, L^2·mol^{-2}·s^{-1}	1080	1320	1340
$E_A(k_{III})$ = +9 kJ·mol^{-1}			

[a] $[\mathrm{DTE}]_0 = 10^{-4}$ mol·L^{-1}.

4. Results

4.1. Butylamine (1) + Ethyl Hexanedithioate (5) (Table I).

For reactions in toluene the results give linear correlation between $k_{1\Psi}/[\mathrm{amine}]_0$ and $[\mathrm{amine}]_0$; however, extrapolations to low amine concentrations would indicate negative values for k_{II}. Assuming zero value for these constants, we obtained better correlations between $k_{1\Psi}$ and $[\mathrm{amine}]_0^2$.

In the solvent mixture toluene/DMF (1/1), it appears that the reaction rate is strongly enhanced and k_{II} cannot be taken equal to zero although it remains low, whereas k_{III} is ca. 100 times greater as in pure toluene.

So it is evident that the use of a polar solvent speeds

Table VI
Kinetics of Reaction between 3-Ethoxypropylamine (2) and Di(*n*-dodecyl) 1,12-Dodecanebis(dithioate) (6)[a]

Toluene

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine], $mol \cdot L^{-1}$	30 °C	40 °C	50 °C
0.0743	0.295	0.350	0.398
0.104	0.572	0.688	0.807
0.178	1.58	1.98	2.30
0.253	3.10	3.88	4.63
$k_{II} \times 10^3$, $L \cdot mol^{-1} \cdot s^{-1}$	0.583	0.333	0.133
$k_{III} \times 10^3$, $L^2 \cdot mol^{-1} \cdot s^{-1}$	46.2	59.8	71.3
$E_A(k_{III}) = +18$ $kJ \cdot mol^{-1}$			

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine] $\times 10^2$, $mol \cdot L^{-1}$	30 °C	40 °C	50 °C
Toluene/DMF (3/1)			
1.56	0.685	0.682	0.695
2.84	1.80	1.85	1.92
3.78	2.65	2.90	2.88
4.80	3.83	4.15	4.28
$k_{II} \times 10^3$, $L \cdot mol^{-1} \cdot s^{-1}$	29.2	25.2	25.7
$k_{III} \times 10^3$, $L^2 \cdot mol^{-1} \cdot s^{-1}$	1080	1320	1340
$E_A(k_{III}) = +9$ $kJ \cdot mol^{-1}$			
Toluene/DMF (1/1)			
1.60	1.92	1.83	1.80
2.73	4.20	4.45	4.48
3.71	6.75	7.18	7.48
4.72	9.63	11.0	11.3
$k_{II} \times 10^3$, $L \cdot mol^{-1} \cdot s^{-1}$	78.7	56.6	50.5
$k_{III} \times 10^3$, $L^2 \cdot mol^{-2} \cdot s^{-1}$	2710	3740	4040
$E_A(k_{II}) = -18$ $kJ \cdot mol^{-1}$	$E_A(k_{III}) = +16$ $kJ \cdot mol^{-1}$		

[a] $[DTE]_0 = 10^{-4}$ $mol \cdot L^{-1}$.

Table VII
Kinetics of Reaction between *n*-Butylamine (1) and Di(*n*-dodecyl) 4,7-Dioxa-1,10-decanebis(dithioate) (7)[a]

Toluene

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine], $mol \cdot L^{-1}$	30 °C	40 °C	50 °C
0.0751	3.18	3.07	2.80
0.100	6.33	5.54	5.36
0.182	19.7	19.4	20.1
0.254	40.4	76.4	86.1
$k_{II} \times 10^3$, $L \cdot mol^{-1} \cdot s^{-1}$	0	0	0
$k_{III} \times 10^3$, $L^2 \cdot mol^{-2} \cdot s^{-1}$	613	577	589

Toluene/DMF (1/1)

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine] $\times 10^2$, $mol \cdot L^{-1}$	30 °C	40 °C	50 °C
0.212	0.300	0.237	0.196
0.820	3.15	2.75	2.37
1.59	8.89	8.29	7.69
2.30	15.9	15.3	13.6
$k_{II} \times 10^3$, $L \cdot mol^{-1} \cdot s^{-1}$	–	–	–
$k_{III} \times 10^3$, $L^2 \cdot mol^{-2} \cdot s^{-1}$	88300[b]	60000[b]	47500[b]

[a] $[DTE]_0 = 10^{-4}$ $mol \cdot L^{-1}$. [b] Initial slopes.

Table VIII
Kinetics of Reaction between 3-Ethoxypropylamine (2) and Di(*n*-dodecyl) 4,7-Dioxa-1,10-decanebis(dithioate) (7)[a]

Toluene

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine], $mol \cdot L^{-1}$	30 °C	40 °C	50 °C
0.0491	2.00	2.01	1.92
0.0802	4.83	5.03	5.03
0.103	8.33	8.57	8.53
0.146	16.2	17.7	17.5
$k_{II} \times 10^3$, $L \cdot mol^{-1} \cdot s^{-1}$	7.33	7.33	6.00
$k_{III} \times 10^3$, $L^2 \cdot mol^{-2} \cdot s^{-1}$	500	513	523
$E_A(k_{III}) = +2$ $kJ \cdot mol^{-1}$			

Toluene/DMF (1/1)

	$k_{1\Psi} \times 10^3$, s^{-1}		
[amine] $\times 10^2$, $mol \cdot L^{-1}$	30 °C	40 °C	50 °C
0.659	1.67	1.63	1.53
1.40	6.16	6.35	6.00
1.89	10.9	10.8	11.3
2.17	13.9	14.1	13.7
$k_{II} \times 10^3$, $L \cdot mol^{-1} \cdot s^{-1}$	86.7	73.3	60.0
$k_{III} \times 10^3$, $L^2 \cdot mol^{-2} \cdot s^{-1}$	25200	26300	25800
$E_A(k_{II}) = -15$ $kJ \cdot mol^{-1}$			

[a] $[DTE]_0 = 10^{-4}$ $mol \cdot L^{-1}$.

up the reaction between these purely aliphatic monodithioesters and monoamines. In both solvents, activation energies for k_{III} are low (10–12 kJ/mol) but become negative for k_{II}, suggesting this kind of analysis does not matter.

4.2. 3-Ethoxypropylamine (2) + Ethyl Hexanedithioate (5) (Table II). *In toluene*, these reagents behave very much like the preceding ones, with third-order rate constants approximately twice as much and second-order rate constants near zero.

In toluene/DMF (1/1), third-order rate constant enhancement is smaller than for butylamine (70–80 times the value observed in pure toluene). However, third-order rate constants are higher than those obtained for butylamine: the presence of an ether group accelerates slightly the third-order reaction in both solvents.

4.3. 4,9-Dioxa-1,12-dodecanediamine (3) and 4,7,10-Trioxa-1,13-tridecanediamine (4) + Ethyl Hexanedithioate (5) (Tables III and IV). The very large excess of amine used in these reactions allows us to study only the first thioacylation of the diamine and then the influence of the second amine group on it.

4,9-Dioxa-1,12-dodecanediamine (3). *In toluene*, second-order rate constants become appreciable although nearly constant as the temperature is varied. Third-order rate constants are quite comparable to those obtained for the monoamine.

In toluene/DMF (1/1), second-order rate constants are 4–10 times higher than for 3-ethoxypropylamine whereas third-order rate constants are divided by about 4.

In every solvent, the relative importance of the second-order reaction is increased by the presence of a second amine group in the molecule. Thus, the most important reaction acceleration is observed for the lower values of amine excess.

4,7,10-Trioxa-1,13-tridecanediamine (4). A third ether function seems to generate a new enhancement of reaction rates although third-order rate constants are decreasing in toluene/DMF mixture (1/1).

4.4. Di(*n*-dodecyl) Dodecanebis(dithioate) (6) + *n*-Butylamine (1) (Table V). Bis(dithioester)s reacting with excess monoamine allow us a priori to observe eventually reactivity differences between the unreacted bis(dithioester) and the first-formed thioamide–dithioester.

This was never observed in the conditions used; so we tried to isolate the intermediate thioamide–dithioester. However, the presence of long-chain thiol in the dithioester group—useful for obtaining crystalline bis(dithioester)s—lowers the differences between the different dithioesters, and we could not obtain thioamide–dithioester sufficiently pure for kinetic measurements.

The present kinetic results thus represent a mean of the reactivities of both dithioester functions, if any difference exists between them.

In toluene, as observed before for purely aliphatic reagents, only third-order reaction rate constants are worked out from experimental data. Calculated k_{III} values are quite similar to the previously determined third-order rate constants for reaction between the same amine and a monodithioester.

In a toluene/DMF (1/1) mixture, again second-order rate constants are appreciable although about half the values obtained for monodithioester; third-order rate constants are nearly the same for bis(dithioester) as for monodithioester.

4.5. Di(*n*-dodecyl) Dodecanebis(dithioate) (6) + 3-Ethoxypropylamine (2) (Table VI). *In toluene*, second-order reaction rate constants are very low, whereas third-order rate constants are enhanced about twice as much by the presence of an ether group as compared to *n*-butylamine reaction rates. This was previously noted for monodithioester reacting with 3-ethoxypropylamine.

In a toluene/DMF (1/1) mixture, there is no major difference with the previous results between 3-ethoxypropylamine and an aliphatic monodithioester although all rate constants are lower in the case of the bifunctional dithioester.

In a toluene/DMF (3/1) mixture, intermediate values between pure toluene and a 1/1 mixture are obtained as expected for the progressive influence of increasing solvent polarity.

4.6. Di(*n*-dodecyl) 4,7-Dioxa-1,10-decanebis(dithioate) (7) + Butylamine (1) (Table VII). *In toluene*, rapid reactions are observed as compared to the preceding ones. Moreover, a slight increase (20–30%) in pseudo-first-order correlation was noted above 50% conversion. Correlation of $k_{1\Psi}$ versus $[\text{amine}]^2$ is quite good except for higher temperatures and amine concentration. As bis(dithioester) 7 could be obtained only when using crosslinked poly(vinylpyridine) instead of pyridine (see the Experimental Section), we suppose that its very high reactivity toward nucleophiles is responsible for deviations at elevated temperatures and amine concentration. Calculated third-order rate constants are very high (ca. 10–30 times the previous values in toluene). However, an unexpected dithioester-consuming reaction is excluded as it was possible to prepare high molecular weight polythioamides from 7.

In a toluene/DMF (1/1) mixture, high reaction rates are observed, but no linear correlation was possible between $k_{1\Psi}/[\text{amine}]_0$ and the amine concentration. It seems clear that the relative amount of second- and third-order reaction rates varied as the amine concentration was increased.

4.7. Di(*n*-dodecyl) 4,7-Dioxa-1,10-decanebis(dithioate) (7) + 3-Ethoxypropylamine (2) (Table VIII). *In toluene*, as with *n*-butylamine, a slight increase in pseudo-first-order rate constant was noted above 50% conversion. Initial rates allow us to determine low values of second-order rate constant and very high third-order rate constants: ether amine 2 behaves similarly to alkylamine against diether bis(dithioester) 7.

Surprisingly, *in a toluene/DMF (1/1) mixture*, good linear correlation was found again for this reaction. Both second- and third-order rate constants are very high.

It is clear the presence of ether functions in the chain of a bis(dithioester) greatly enhances its reaction rates toward primary amines. As dithioesters are useful reagents for protein modification,[14] this result affords a way to promote rapid thioacylation reaction as needed for many of these very versatile substrates.

Table IX
Kinetics of Reaction between *n*-Butylamine (1) and Di(*n*-dodecyl) 1,12-Dodecanebis(dithioate) (6) in the Presence of Triethylamine (TEA)[a]

Toluene[b]

	$k_{1\Psi}' \times 10^3$, s^{-1}		
[TEA], $mol \cdot L^{-1}$	30 °C	40 °C	50 °C
0	1.46	2.00	2.22
0.128	1.48	1.93	2.21
0.252	1.47	1.91	2.06
0.375	1.43	1.93	2.12
$k_{III}^{cat} \times 10^3$, $L \cdot mol^{-1} \cdot s^{-1}$	0	0	0
$k_{1\Psi} \times 10^3$ (mean), s^{-1}	1.46	1.94	2.15
$k_{1\Psi} \times 10^3$ (Table V), s^{-1}	1.61	1.91	2.47

Toluene/DMF (1/1)[c]

	$k_{1\Psi}' \times 10^3$, s^{-1}		
[TEA] $\times 10^2$, $mol \cdot L^{-1}$	30 °C	40 °C	50 °C
0	4.55	4.53	4.23
0.0125	4.65	4.63	4.18
0.0252	4.50	4.50	4.18
0.0381	4.48	4.45	4.14
$k_{III}^{cat} \times 10^3$, $L \cdot mol^{-1} \cdot s^{-1}$	0	0	0
$k_{1\Psi} \times 10^3$ (mean), s^{-1}	4.54	4.52	4.18
$k_{1\Psi} \times 10^3$ (Table V), s^{-1}	4.18	4.01	3.67

[a] $[DTE]_0 = 10^{-4}$ $mol \cdot L^{-1}$. [b] $[NH_2]_0 = 0.25$ $mol \cdot L^{-1}$. [c] $[NH_2]_0 = 0.027$ $mol \cdot L^{-1}$.

4.8. Reaction with Added Tertiary Amine. As it appears from the previous data, thioacylation reaction rates are correlated to amine concentration via a complex law including a second-order term with respect to this concentration. Assuming a possible occurrence of a catalytic role for amine groups, we have tested the influence of added tertiary amine in some systems.

If a tertiary amine catalyzed reaction can take place, we may assume the reaction kinetics to obey the rate law

$$r = \mathrm{d}[\mathrm{DTE}]/\mathrm{d}t = k_{II}[\mathrm{DTE}][\mathrm{NH_2}] + k_{III}[\mathrm{DTE}][\mathrm{NH_2}]^2 + k_{III}^{\mathrm{cat.}}[\mathrm{DTE}][\mathrm{NH_2}][\text{tertiary amine}]$$

in which $[NH_2]$ is the primary amine concentration.

In the case where an excess primary amine is used, a pseudo-first-order reaction rate can be observed with a pseudo-first-order rate constant, $k_{1\Psi}'$, given by

$$k_{1\Psi}' = k_{II}[\mathrm{NH_2}] + k_{III}[\mathrm{NH_2}]^2 + k_{III}^{\mathrm{cat.}}[\mathrm{NH_2}][\text{tertiary amine}]$$

or

$$k_{1\Psi}'/[\mathrm{NH_2}] = k_{II} + k_{III}[\mathrm{NH_2}] + k_{III}^{\mathrm{cat.}}[\text{tertiary amine}]$$

As $[NH_2]$ remains nearly constant, owing to the large excess of primary amine used, we have correlated the observed $k_{1\Psi}'/[\mathrm{NH_2}]$ with the tertiary amine concentration.

In Tables IX–XII are collected the observed values for $k_{1\Psi}'$ measured in the presence of various amounts of triethylamine (TEA) or 1,7-diazabicyclo[2.2.2]octane (DABCO); the later is particularly known as a powerful catalyst in ester amidation reaction.[2,6] Different reaction systems were tested including *n*-butylamine or 3-ethoxypropylamine reacting with an alkyl bis(dithioester) in toluene or a toluene/DMF mixture.

It is evident that TEA has no catalytic effect at all. Even DABCO produces only a slight increase of the reaction rates: adding more than 1 equiv of DABCO/mol of primary amine results in a 25–30% rate increase only.

Table X
Kinetics of Reaction between 3-Ethoxypropylamine (2) and Di(n-dodecyl) 1,12-Dodecanebis(dithioate) (6) in the Presence of Triethylamine (TEA)[a]

Toluene[b]

[TEA], mol·L^{-1}	$k_{1\Psi}' \times 10^3$, s^{-1}		
	30 °C	40 °C	50 °C
0	3.00	3.76	4.43
0.126	2.97	3.66	4.47
0.252	2.96	3.63	4.71
$k_{III}^{cat} \times 10^3$, L·mol^{-1}·s^{-1}	0	0	0
$k_{1\Psi} \times 10^3$ (mean), s^{-1}	2.98	3.68	4.54
$k_{1\Psi} \times 10^3$ (Table VI), s^{-1}	3.06	3.85	4.52

Toluene/DMF (1/1)[c]

[TEA] × 10^2, mol·L^{-1}	$k_{1\Psi}' \times 10^3$, s^{-1}		
	30 °C	40 °C	50 °C
0	3.67	3.84	3.84
0.0136	3.50	3.80	3.83
0.0251	3.51	3.74	3.81
0.0383	3.48	3.71	3.93
$k_{III}^{cat} \times 10^3$, L·mol^{-1}·s^{-1}	0	0	0
$k_{1\Psi} \times 10^3$ (mean), s^{-1}	3.54	3.77	3.85
$k_{1\Psi} \times 10^3$ (Table V), s^{-1}	3.66	3.75	3.79

[a] $[DTE]_0 = 10^{-4}$ mol·L^{-1}. [b] $[NH_2]_0 = 0.25$ mol·L^{-1}. [c] $[NH_2]_0 = 0.0259$ mol·L^{-1}.

Table XI
Kinetics of Reaction between n-Butylamine (1) and Di(n-dodecyl) 1,12-Dodecanebis(dithioate) (6) in the Presence of 1,4-Diazabicyclo[2.2.2]octane (DABCO)[a]

solvent[b]	[DABCO], mol·L^{-1}	$k_{1\Psi}' \times 10^3$, s^{-1}		
		30 °C	40 °C	50 °C
toluene/ DMF (1/1)	0	3.90	3.97	3.48
	0.0125	4.22	4.33	3.93
	0.0251	4.54	4.64	4.19
	0.0375	4.64	4.78	4.55
	$k_{III}^{cat} \times 10^3$, L·mol^{-1}·s^{-1}	20.3	21.8	27.7
	$k_{1\Psi} \times 10^3$ (extrapolated), s^{-1}	3.94	3.98	3.52
	$k_{1\Psi} \times 10^3$ (Table V), s^{-1}	3.73	3.56	3.23

[a] $[DTE]_0 = 10^{-4}$ mol·L^{-1}. [b] $[NH_2]_0 = 0.025$ mol·L^{-1}.

Table XII
Kinetics of Reaction between 3-Ethoxypropylamine (2) and Di(n-dodecyl) 1,12-Dodecanebis(dithioate) (6) in the Presence of 1,4-Diazabicyclo[2.2.2]octane (DABCO)[a]

solvent[b]	[DABCO], mol·L^{-1}	$k_{1\Psi}' \times 10^3$, s^{-1}		
		30 °C	40 °C	50 °C
toluene/DMF (1/1)	0	3.82	4.01	4.02
	0.0128	4.18	4.36	4.46
	0.0251	4.41	4.68	4.82
	0.0382	4.82	4.89	5.20
	$k_{III}^{cat} \times 10^3$, L·mol^{-1}·s^{-1}	977	894	1177
	$k_{1\Psi} \times 10^3$ (extrapolated), s^{-1}	3.82	3.98	3.52
	$k_{1\Psi} \times 10^3$ (Table VI), s^{-1}	3.88	3.57	4.07

[a] $[DTE]_0 = 10^{-4}$ mol·L^{-1}. [b] $[NH_2]_0 = 0.026$ mol·L^{-1}.

This acceleration is obviously lower than those observed in varying the reagent nature or adding a polar solvent. Moreover, we have previously established that tertiary amines are able to promote slow enethiolization of dithioesters, thus catalyzing self-condensation of these compounds according to a reaction pathway equivalent to the Claisen–Dieckmann condensation of esters.[10] Such a reaction seems to be sufficient, if induced by the strongly nucleophilic DABCO, to produce the observed increase in dithioester disappearance rates.

So, we think that third-order reactions are not the consequence of a nucleophilic attack of the first-formed reaction intermediate by any amine doublet.

Table XIII
Summary of k_{II} and k_{III} Values

Solvent: Toluene

	T, °C	amine 1	amine 2	diamine 3	diamine 4
Second-Order Rate Constant $k_{II} \times 10^3$, L·mol^{-1}·s^{-1}					
dithioester **5**	30	0	0	5.79	21.6
	40	0	0	6.29	26.8
	50	0	0	5.98	32.0
bis(dithioester) **6**	30	0	0		
	40	0	0		
	50	0	0		
bis(dithioester) **7**	30	0	7.33		
	40	0	7.33		
	50	0	6.00		
Third-Order Rate Constant $k_{III} \times 10^3$, L^2·mol^{-2}·s^{-1}					
dithioester **5**	30	26.0	56.7	43.8	45.1
	40	31.0	73.8	64.7	81.2
	50	34.7	80.2	89.5	113
bis(dithioester) **6**	30	25.7	46.2		
	40	30.5	59.8		
	50	39.5	71.3		
bis(dithioester) **7**	30	613	500		
	40	577	513		
	50	589	523		

Solvent: Toluene/DMF (1/1)

	T, °C	amine 1	amine 2	diamine 3	diamine 4
Second-Order Rate Constant $k_{II} \times 10^3$, L·mol^{-1}·s^{-1}					
dithioester **5**	30	119	71.7	286	426
	40	106	60.0	335	551
	50	84.5	48.3	401	673
bis(dithioester) **6**	30	77.0	78.7		
	40	57.7	56.5		
	50	38.2	50.5		
bis(dithioester) **7**	30	1050[a]	86.7		
	40	1210[a]	73.3		
	50	1280[a]	60.0		
Third-Order Rate Constant $k_{III} \times 10^3$, L^2·mol^{-2}·s^{-1}					
dithioester **5**	30	3130	4390	1030	280
	40	3580	5320	1530	822
	50	3990	5830	1510	695
bis(dithioester) **6**	30	2910	2710		
	40	3400	3740		
	50	3660	4040		
bis(dithioester) **7**	30	88300[b]	25200		
	40	60000[b]	26300		
	50	47500[b]	25800		

[a] k_{II} was supposed to be identical with k_1. [b] Initial slopes.

5. Discussion

Considering the results of the kinetic study (Table XIII), it appears that variations of reagent structures induce similar effects, whatever the solvent is. *In toluene*, a strong increase is observed for the second-order rate constant, k_{II}, when the amine is a diamine or when ether functions are introduced in both reagents. Temperature variations have little influence, if any. The third-order rate constant, k_{III}, is mostly affected when ether functions are present or—although at a lower extent—by increasing temperature.

In a toluene/DMF (1/1) mixture, all reactions are largely accelerated and k_{II} is enhanced only in the reaction of diamines, whereas bis(dithioester) **7** remains the most reactive reagent of its kind.

From a mechanistic point of view, it seems very unlikely that kinetically different reactions could take place at the same time for all the different reagents and solvents we have studied. In one case, the analysis of kinetic data through simultaneous second- and third-order reactions has failed, with no linear correlation existing between $k_{1\Psi}$/

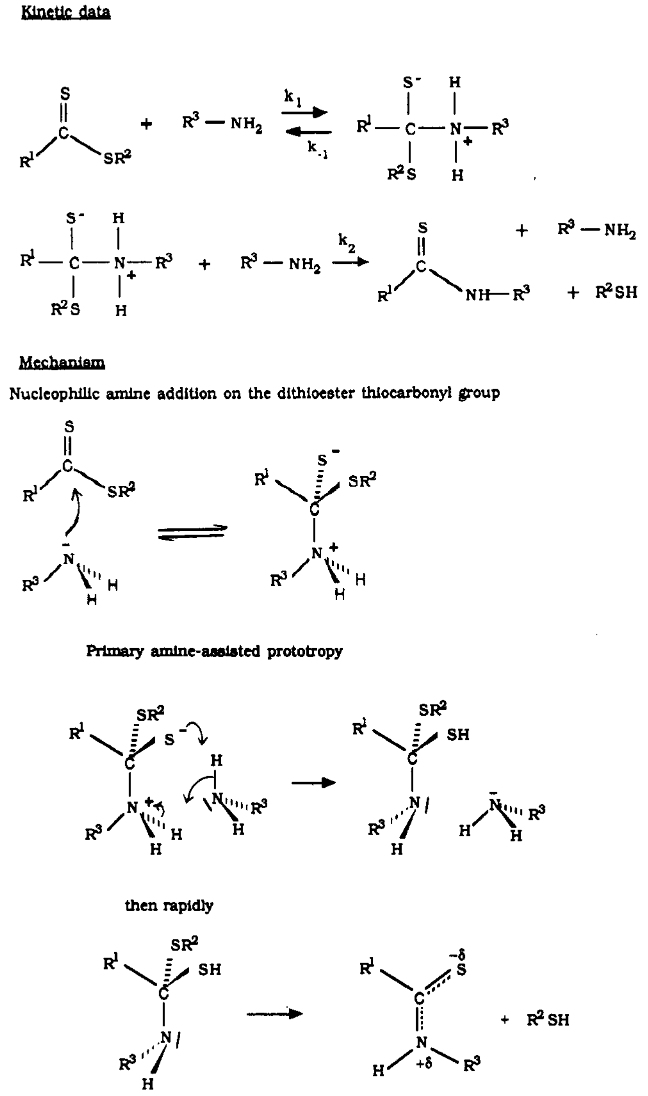


Figure 1. Primary amine thioacylation mechanism.

[amine]$_0$ and [amine]$_0$. Moreover, the occurrence of apparently negative activation energies for many of the second-order rate constants is not readily understandable. So we have looked for a mechanism able to explain all these observations in a unique but versatile pathway.

A simple mechanism may comprise first an equilibrium between the reagents and an intermediate, followed by an irreversible unimolecular decomposition of the later. Such a mechanism associated with the usual quasi-stationary state hypothesis for the intermediate gives a kinetic relation in which the dithioester disappearance rate is always first-order in both amine and dithioester and is then inadequate for our purpose.

This simplest mechanism compatible with our results consists of an equilibrium between reagents (A, B) and a reaction intermediate (I) followed by a bimolecular reaction in the later with amine (B) (Figure 1):

The dithioester disappearance rate is then

$$-\mathrm{d}[\mathrm{A}]/\mathrm{d}t = k_1[\mathrm{A}][\mathrm{B}] - k_{-1}[\mathrm{I}]$$

The variation of intermediate concentration is expressed by

$$\mathrm{d}[\mathrm{I}]/\mathrm{d}t = k_1[\mathrm{A}][\mathrm{B}] - k_{-1}[\mathrm{I}] - k_2[\mathrm{B}]$$

Assuming a steady state for the intermediate, we can evaluate its stationary concentration, $[\mathrm{I}]_{\mathrm{st}}$

$$[\mathrm{I}]_{\mathrm{st}} = k_1[\mathrm{A}][\mathrm{B}]/(k_2[\mathrm{B}] + k_{-1})$$

Then

$$-\mathrm{d}[\mathrm{A}]/\mathrm{d}t = k_1k_2[\mathrm{A}][\mathrm{B}]^2/(k_2[\mathrm{B}] + k_{-1}) \qquad (4)$$

It might be possible to have simultaneously such a second-order reaction between the amine and the reaction intermediate and a monomolecular decomposition of the later (absolute rate constant, k_2'). The steady-state hypothesis leads in that case to relation 4′:

$$-\mathrm{d}[\mathrm{A}]/\mathrm{d}t = k_1k_2[\mathrm{A}][\mathrm{B}]^2/(k_2[\mathrm{B}] + k_{-1} + k_2') \qquad (4')$$

Relations 4 and 4′ are mathematically identical, the sum $k_{-1} + k_2'$ or the constant k_{-1} playing the same role. So we have used the relation 4, but we cannot be sure that 4′ is not the correct one.

In relation 4, the global reaction order depends on the relative values of terms included in the denominator:

If $k_2[\mathrm{B}] \ll k_{-1}$ or $k_{-1} + k_2'$, we may observe a third order according to

$$-\mathrm{d}[\mathrm{A}]/\mathrm{d}t \,\#\, k_1k_2[\mathrm{A}][\mathrm{B}]^2/k_{-1}$$

or

$$-\mathrm{d}[\mathrm{A}]/\mathrm{d}t = k_{\mathrm{III}}[\mathrm{A}][\mathrm{B}]^2 \qquad (5)$$

in which $k_{\mathrm{III}} = k_1k_2/k_{-1}$ or $k_{\mathrm{III}} = k_1k_2/(k_{-1} + k_2')$. If $k_2[\mathrm{B}] \gg k_{-1}$ or $k_{-1} + k_2'$, the global order is only 2 as

$$-\mathrm{d}[\mathrm{A}]/\mathrm{d}t \,\#\, k_1k_2[\mathrm{A}][\mathrm{B}]/k_2[\mathrm{B}]$$

or

$$-\mathrm{d}[\mathrm{A}]/\mathrm{d}t = k_{\mathrm{II}}[\mathrm{A}][\mathrm{B}] \qquad (6)$$

in which $k_{\mathrm{II}} = k_1$. If $k_2[\mathrm{B}] \,\#\, k_{-1}$, then the global order would vary throughout the reaction and no linear correlation could be obtained in the usual treatment for second- or third-order reactions.

Relation 4 is thus able to explain how a reaction obeying a unique mechanism may fit either a second-order or a third-order kinetic equation, or sometimes neither.

When large amine excess (concentration noted as [amine]$_0$) is used, eq 4 can be rearrange to

$$-\mathrm{d}[\mathrm{A}]/\mathrm{d}t = k_1k_2[\mathrm{dithioester}][\mathrm{amine}]_0^{\,2}/(k_2[\mathrm{amine}]_0 + k_{-1}) = k_{1\Psi}[\mathrm{A}]$$

where

$$k_{1\Psi} = k_1k_2[\mathrm{amine}]_0^{\,2}/(k_2[\mathrm{amine}]_0 + k_{-1})$$

or

$$\frac{1}{k_{1\Psi}} = \frac{k_{-1} + k_2[\mathrm{amine}]_0}{k_1k_2[\mathrm{amine}]_0^{\,2}}$$

or

$$\frac{[\mathrm{amine}]_0}{k_{1\Psi}} = \frac{k_{-1}}{k_1k_2}\frac{1}{[\mathrm{amine}]_0} + \frac{1}{k_1} \qquad (7)$$

This new relation was first tested on results that gave no linear correlation according to relation 3. A linear plot was obtained between [amine]$_0/k_{1\Psi}$ and 1/[amine]$_0$ using the results reported in Table VII for the reaction of *n*-butylamine (1) and diether bis(dithioester) 7 (Figure 2).

Such linear correlations are fitted by all the reported kinetic results when using relation 7, thus verifying the validity of the postulated hypothesis. This result allows us to estimate more interesting rate constants; namely (1) the second-order rate constant, k_1, of the direct reaction between aliphatic dithioesters and primary amines leading to the formation of intermediate I, as the reverse of

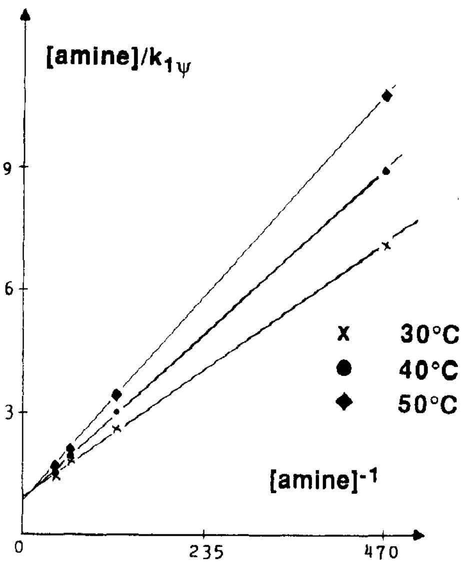


Figure 2. Correlation between [amine]/$k_{1\psi}$ and [amine]$^{-1}$ for reaction between didodecyl 4,7-dioxa-1,10-decanebis(dithioate) (**7**) and *n*-butylamine (**1**) according to relation 7.

Table XIV
Application of Relation 7, $[NH_2]/k_{1\psi} = f(1/[NH_2])$, to Kinetic Results

dithioester	amine	solvent[a]	T, °C	k_1, L·mol^{-1}·s^{-1}	k_{-1}/k_2, mol·L^{-1}
5	**1**	T	30	~1	~40
			50		~30
5	**1**	T/DMF (1/1)	30	0.4	0.025
			50	0.6	0.050
5	**2**	T	30 50	~0.2	~10
5	**2**	T/DMF (1/1)	30	0.8	0.08
			50	1.1	0.11
5	**3**	T	30	0.25	1 × 10^{-3}
			50	0.60	3 × 10^{-3}
5	**3**	T/DMF (1/1)	30	2.8	3 × 10^{-3}
			50	2.0	3 × 10^{-3}
5	**4**	T	30	0.4	30 × 10^{-3}
			50	0.7	80 × 10^{-3}
5	**4**	T/DMF (1/1)	30	0.5	2 × 10^{-3}
			50	0.7	2 × 10^{-3}
6	**1**	T	30 50	>0.2	>8
6	**1**	T/DMF (1/1)	30	0.3	0.03
			50	0.5	0.07
6	**2**	T	30 50	>0.1	~5
6	**2**	T/DMF (1/1)	30	0.04	0.04
			50	0.06	0.06
6	**2**	T/DMF (3/1)	30	0.14	0.03
			50	0.18	0.05
7	**1**	T	30	0.4	0.6
			50	0.4	0.7
7	**1**	T/DMF (1/1)	30	1.0	0.01
			50	1.6	0.03
7	**2**	T	30 50	~1	~1.2
7	**2**	T/DMF (1/1)	30 50	~2.3	~0.06
7	**3**	$CHCl_3$/DMF (1/1)	30	0.7	0.4

[a] T = toluene.

intercept ordinate in relation 7 ($1/k_1$), and (2) the ratio k_{-1}/k_2 between the intermediate decomposition first-order rate constant and the second-order products formation rate constant, as the ratio of the slope to the intercept ordinate of relation 7.

The results obtained from these correlations are reported in Tables XIV and XV at 30 and 50 °C.

Table XV
Calculated Apparent Reaction Order at Various Conversion Rates[a]

	conv degree		
	0	0.90	0.99
$k_{II}[A][B]$	5.04 × 10^{-4}	5.04 × 10^{-6}	5.04 × 10^{-8}
$k_{III}[A][B]^2$	1.38 × 10^{-3}	1.38 × 10^{-6}	1.38 × 10^{-9}
second-order contribution	≈0.3/1	≈3/1	≈30/1
third-order contribution			

[a] Reaction at 30 °C between bis(dithioester) **6** and 3-ethoxypropylamine (**2**) in toluene/DMF (1/1). [Dithioester]$_0$ = [amine]$_0$ = 0.08 mol·L^{-1}; k_{II} = 0.0787 L·mol^{-1}·s^{-1}; k_{III} = 2.71 L^2·mol^{-2}·s^{-1} (Table VI).

Reagents. In some cases, the absolute values of $1/k_1$ are very small in comparison with the variable term in eq 7, so an important error is made on the value of k_1 and then on the value of k_{-1}/k_2; the estimations done for these examples (monoamine and alkylmono- or alkylbis(dithioester)) afford the highest values found for k_{-1}/k_2, indicating in that case the reverse reaction of the intermediate toward the reagents presents higher rate constants than the formation of products (but in different units). As the reaction rate to products is equal to k_2[amine][I] whereas the reverse reaction to reagents depends on k_{-1}[I] only, it is evident that the amine concentration influences the relative importance of these reaction paths.

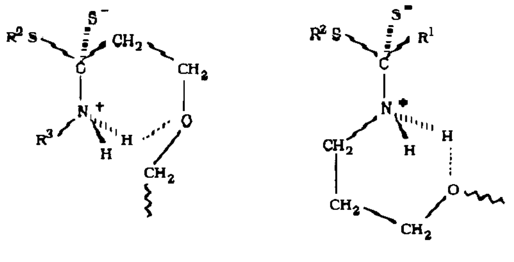
The main influence from the nature of reagents is observed in the ratio k_{-1}/k_2, which varies in large proportions (from 10^{-3} to 30–40 mol·L^{-1}). The lowest values of k_{-1}/k_2 are always noted when diamines are used, particularly in a toluene/DMF (1/1) mixture. The presence of a second primary amine function in these cases seems to greatly increase k_2, i.e., the product formation reaction rate constant, at least in the very diluted conditions used for this study.

Temperature. The influence of temperature on the values of k_1 and k_{-1}/k_2 is rather small, so we have reported only their values for 30 and 50 °C. Reaction rate constant k_1 of the first step is quite high for a bimolecular reaction (between 0.1 and 3 mol·L^{-1}·s^{-1}) and the temperature variations have little influence on them: activation energies are very low, only 1 or 2 kJ·mol^{-1}.

The ratio k_{-1}/k_2 presents somewhat more intense variations as the temperature is raised and is generally increasing. At higher temperatures it seems then the reverse reaction to reagents is slightly more accelerated than the product formation.

Reaction Order in Stoichiometric Ratio. As a consequence of complex rate variations versus reagent concentrations, we have estimated what would be observable when amine thioacylation will be conducted with stoichiometric amounts of amine and dithioester. Another important feature is the forecast of what would happen in a polycondensation reaction in which the reaction needs to be conducted at very high conversion rates. As the UV absorption band of thioamide is nearly as intense as a dithioester band, it was only possible to study a polycondensation reaction through the less intense visible band and then in the range of concentrations near 0.1 mol·L^{-1}.

Preliminary results have shown order variations during the course of polythioamidation together with the occurrence of second order as the conversion degree becomes higher than 85–90%.[15] Simulation of a polycondensation reaction can be illustrated in calculating the values of dithioester disappearance rates according to apparent second- and third-order reaction according to relation 1: the results are collected in Table XV, and it



Ether-dithioester Ether-amine

Figure 3. Internal solvation probably occurring in the zwitterionic reaction intermediate.

is evident that the global reaction order will change throughout the reaction. Initial reaction rate would be only ca. 20% second order, but this proportion increases to 80% at a conversion degree of 0.90 and 98% at 0.99. Thus the postulated kinetics is able to fit the order variations observed in polythioamidation reactions.

6. Thioamidation Mechanism

The most important feature of this kinetic study is the tendency of primary amine to promote the second step in thioamidation reaction whereas an added tertiary amine does not.

Some structural influences may be understood in terms of internal solvation of the ammonium part in the intermediate, mainly when ether functions are present in the vicinity. Such interactions are illustrated in Figure 3 and might be responsible for stabilization of the zwitterionic intermediate: we have observed important rate accelerations when using bis(dithioester) **7** in which two ether functions may play such a role. In Table XIV, it seems the main difference between the two bis(dithioester)s **6** and **7** is the ratio k_{-1}/k_2 value, which is clearly lower for dithioester **7** than for **6**, particularly in toluene as a solvent.

Some authors have postulated in ester amidation the intervention of an amine hydrogen-bonded dimer,[4] but this could explain only third-order reaction in an apolar solvent; in a toluene/DMF mixture the presence of such a dimer is quite unprobable as DMF is a strong hydrogen-bonding solvent.

It seems more general to explain the primary amine intervention in the product formation step through an amine-assisted prototropy taking place before thiol liberation (Figure 1). A concerted proton transfer is likely because a tertiary amine is able to react in a nonconcerted one. This primary amine catalyzed prototropy does not need a particular conformation in the transition state as it would be the case in a second-order nucleophile-catalyzed elimination.

The thiol and thioamide formation must be very rapid from the hemidithioacetal-like neutral structure formed by prototropy.

7. Conclusion

The kinetic study of a thioamidation reaction conducted in dilute solution on mono- and bifunctional amines and dithioesters has shown this reaction is best described by eq 4, thus fitting all the results and allowing us to explain the global order variations observed in the course of polythioamidation. A mechanism is proposed on this basis, involving first the nucleophile addition of the amine to the highly polarizable thiocarbonyl group, followed by a primary amine catalyzed prototropy in the zwitterionic intermediate, and finally thiol elimination from the neutral hemidithioacetal-like structure thus formed.

As our results are similar to the published kinetic study of polyamidation of esters (variable contributions of apparently simultaneous second- and third-order reactions), it seems likely that similar mechanisms may operate in the two reactions. However, the prototropy involved in the thioamidation mechanism does not need to be concerted in the ester amine reaction, as in that case, tertiary amines are effective catalysts for the amidation reaction.

References and Notes

(1) Detar, D. F.; Delahunty, C. *J. Am. Chem. Soc.* **1983**, *105*, 2743.
(2) Satchell, D. P. N.; Secemski, J. J. *J. Chem. Soc. B* **1969**, 130; **1970**, 1013.
(3) Böhmer, V.; Wörsdorfer, K.; Becher, U. *Tetrahedron* **1978**, *34*, 2737.
(4) Rony, D. R. *J. Am. Chem. Soc.* **1966**, *88*, 3081.
(5) Menger, F. M.; Vitale, A. C. *J. Am. Chem. Soc.* **1973**, *95*, 4931.
(6) Anderson, H.; Su, C.; Watson, J. W. *J. Am. Chem. Soc.* **1969**, *91*, 482. Su, C.; Watson, J. W. *J. Am. Chem. Soc.* **1974**, *96*, 1854.
(7) Menger, F. M.; Smith, J. H. *J. Am. Chem. Soc.* **1971**, *94*, 3824.
(8) Chase, H. H. *J. Chem. Soc.* **1963**, 1334.
(9) Scheithauer, S.; Mayer, R. Thio and Dithiocarboxylic Acids and Their Derivatives. *Topics in Sulfur Chemistry*; Thieme, G., Ed.; Verlag: Stuttgart, FRG, 1979; Vol. 4. Tao, N. S.; Scheithauer, S.; Mayer, R. *Z. Chem.* **1970**, *12*, 133.
(10) Levesque, G., Thuillier, A. *Makromol. Chem.* **1977**, *178*, 3175. Gressier, J. C., Levesque, G. *Eur. Polym. J.* **1980**, *16*, 1093, 1101.
(11) Gressier, J. C.; Levesque, G. *Eur. Polym. J.* **1981**, *17*, 697. Delfanne, I.; Levesque, G. *Macromolecules* **1989**, *22*, 2020.
(12) Gressier, J. C.; Levesque, G. *Eur. Polym. J.* **1980**, *16*, 1167.
(13) Delêtre, M.; Levesque, G. *Macromolecules*, in press.
(14) Souppe, J.; Urrutigoïty, M.; Levesque, G. *Biochim. Biophys. Acta* 1988, 957, 254. Souppe, J.; Urrutigoïty, M.; Levesque, G. *New J. Chem.* **1989**, *13*, 503.
(15) Delêtre, M. Thèse de doctorat, Caen University, 1989.

Registry No. **1**, 109-73-9; **2**, 6291-85-6; **3**, 7300-34-7; **4**, 4246-51-9; **5**, 13831-10-2; **6**, 65222-84-6; **7**, 129285-50-3; 4,7-dioxa-1,10-decanedinitrile, 3386-87-6; 1,2-ethanediol, 107-21-1; 1,4-dihydroxybenzene, 123-31-9; acrylonitrile, 107-13-1.