The Kinetics and Mechanism of the Thallium(III) Ion-promoted Hydrolysis of Thiolurethanes in Aqueous Solution. A Metal Ion-promoted Elimination

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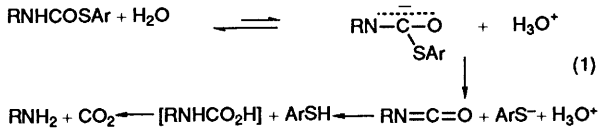
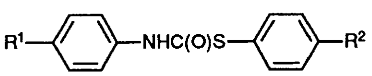
The hydrolysis of thiolurethanes $R^1C_6H_4NHCOSC_6H_4R^2$ (**1**), in dilute aqueous perchloric acid, under conditions where the spontaneous hydrolysis is negligible, is promoted by Tl^{3+} ions. The organic products are the corresponding anilinium ion and the thallium salt of the thiophenol. The effects of substituent changes (R^1,R^2) of changes in $[H_3O^+]$, temperature, ionic strength, and of replacement of the NH proton by Me, are all compatible with hydrolysis occurring by elimination–addition mechanisms *via* the isocyanate as a reactive intermediate; thallium ion-promoted E1cb and E2 routes are implicated. In effect the elimination–addition type of mechanism which is important for these esters at higher pH has been made available at low pH by complexation with Tl^{3+} ions. With the thiolurethanes $RC_6H_4NHCOSEt$, (**2**) which are less susceptible to the spontaneous and base-catalysed elimination–addition mechanisms of hydrolysis than are thiolurethanes (**1**), the presence of Tl^{3+} ions can also lead to promoted hydrolysis *via* elimination, but an $A_{AC}1$-like route (with Tl^{3+} taking the role of H^+) seems to be available to the N-Me derivatives.

Thiolurethanes (thiol carbamates)[1] [RNHC(O)SR′], like simple thiol esters[2] [RC(O)SR′] are less susceptible to Brønsted acid-catalysed hydrolysis in dilute aqueous solution than are their *O*-analogues. Indeed, when R′ = aryl an increase in $[H_3O^+]$ in dilute solution can lead to a decrease in the rate of hydrolysis of thiocarbamates owing to the inhibition of their elimination–addition mechanism of hydrolysis [eqn. (1)]. Our previous studies[3–5] have shown that soft metal ions greatly accelerate the hydrolysis of thiol- and thion-esters [RC(S)OR] and of thiocarbamates [RNHC(S)OR] in aqueous acid. We report now on the effects of Tl^{3+} ions with the thiolurethanes **1** and **2**, and with two of their *N*-methyl derivatives. Compounds of this type have some medicinal and agricultural importance.[6]



(1)



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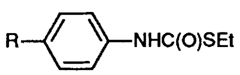


2

	R^1	R^2		R
1a	H	MeO	**2a**	MeO
1b	H	H	**2b**	H
1c	H	Cl	**2c**	Cl
1d	MeO	MeO		

Experimental

Materials.—All the thiolurethanes **1** and **2** were prepared by a method similar to that of Ulrich *et al.*[7] The corresponding isocyanate (Aldrich, 0.02 mol) was warmed (25–50 °C) with an excess (0.20 mol) of ethanethiol, or of the relevant thiophenol (Aldrich) in dry benzene in the presence of triethylamine (1 cm^3). Evaporation of the solvent led to the crude product which was recrystallised from light petroleum. All these thiolurethanes were colourless crystalline solids with m.p.: **1a**, 100; **1b**, 111; **1c**, 134; **1d**, 124; **2a**, 60; **2b**, 64; **2c**, 86 °C. Their structures were confirmed by NMR and mass spectrometry. The *N*-methyl derivatives of **1c** and **2b** were prepared using a variation of Reimschneider and Lorenz's method.[8] The thiol (1.2 mol) or thiophenol, was added over 20 min, to a stirred solution of phosgene (*ca.* 9 g) in toluene at −80 °C. Dimethylaniline (3 g) was then slowly added, and the mixture stirred overnight at room temperature. Distillation led to EtSCOCl (b.p. 136 °C/760 mmHg) or p-ClC_6H_4SCOCl (b.p. 110 °C/24 mmHg). A solution of RSCOCl in diethyl ether was added dropwise to *N*-methylaniline in ether, the solvent evaporated and the remaining material washed with aqueous hydrochloric acid and water. Drying followed by distillation or recrystallisation led to PhN(Me)COSEt as a yellow oil (b.p. 243 °C/760 mmHg) and $PhN(Me)COSC_6H_4Cl$ as colourless crystals, m.p. 135 °C. Both had appropriate NMR and mass spectra. The various thiolurethanes mostly have UV absorption maxima close to 250 nm; the *N*-methyl compounds have shoulder-like maxima at 234–247 nm.

Perchloric acid, sodium perchlorate and thallium nitrate were of AnalaR grade, and dioxane was spectroscopic grade. Amines were purified before use.

Reaction Products.—Hydrolysis of the urethanes in the presence of an excess of Tl^{3+} ions in aqueous perchloric acid ($\lesssim 0.2$ mol dm^{-3}) leads ultimately to the protonated aniline and a thiol–Tl^{3+} complex [*e.g.* eqn. (2)]. Good yields of amine

$$ArNHCOSEt + 2H_2O \xrightarrow{Tl^{3+}/H^+} [ArNHCO_2H] + EtSTl^{2+} + H_3O^+ \longrightarrow ArNH_3^+ + CO_2 + EtSTl^{2+} + H_2O \quad (2)$$

could be isolated from preparative-scale hydrolyses, and the UV spectra of reaction mixtures at the end of kinetic runs corresponded closely to those of artificial product mixtures. During reaction the strong urethane absorption at 240–250 nm falls to a relatively weak absorption in the same region characteristic of the corresponding anilinium ion. When the amine is anisidine a subsequent slow increase in absorption is

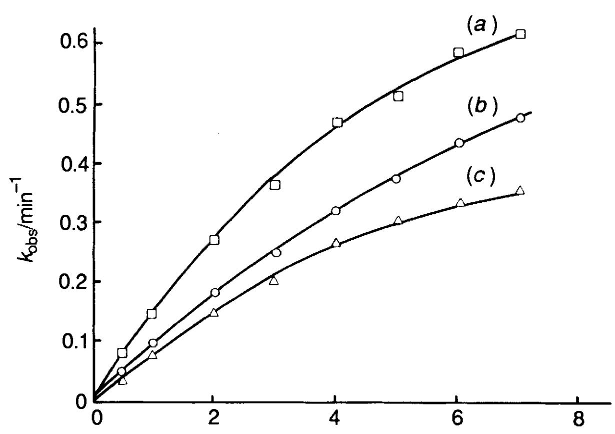


Fig. 1 Effect of $[Tl^{3+}]$ on k_{obs} for thiolurethanes **1**. [Thiolurethane] initial *ca.* 3×10^{-5} mol dm^{-3}; $T = 25$ °C; ionic strength = 1.0 mol dm^{-3}; $[H_3O^+]$ = 0.50 mol dm^{-3}. (*a*) **1a**; (*b*) **1b**; (*c*) **1c**.

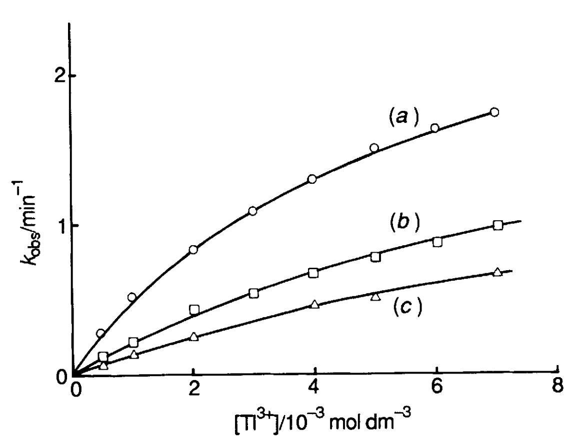


Fig. 2 Effect of $[Tl^{3+}]$ on k_{obs} for thiolurethane **2**. Conditions as in Fig. 1. (*a*) **2a**; (*b*) **2b**; (*c*) **2c**.

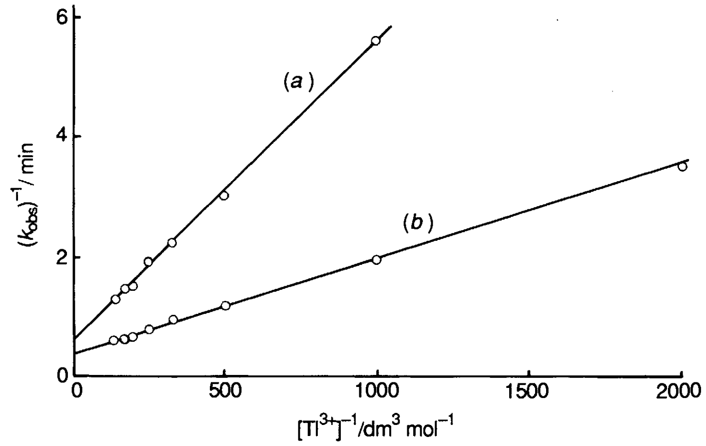


Fig. 3 Plots of eqn. (6) for (*a*) **1d**, and (*b*) **2a**

Table 1 Derived constants from eqn. (5) at 25 °C[a]

Thiolurethane	k/min^{-1}	K/mol^{-1} dm^3
1a	1.4	116
1b	1.1	96
1c	0.90	88
1d	1.7	123
2a	2.6	225
2b	1.9	145
2c	1.5	107

[a] $[H_3O^+]$ = 0.50 mol dm^{-3}; ionic strength = 1.00 mol dm^{-3}; see Figs. 1–3 and text.

observed at wavelengths >250 nm which tests showed was due to reaction of this amine with Tl^{3+} ions. This subsequent reaction did not interfere with measurements of urethane hydrolysis.

Kinetics.—Reactions were conducted in 1% (v/v) dioxane–water as solvent. Reaction mixtures were made up and reaction initiated, as in our previous work with thiocarbamates.[5] The progress of hydrolysis was followed by monitoring the fall in urethane absorption. At fixed values of $[H_3O^+]$, $[Tl^{3+}]$, and ionic strength ($NaClO_4$), and under pseudo-first-order conditions, the loss of urethane was an accurate first-order process over at least three half-lives. The observed first-order rate constant, k_{obs}, was reproducible to within ±10%. Our k_{obs} values, together with the concentration and other conditions, are in the tables and figures. Compounds **2** hydrolyse relatively slowly in dilute aqueous acid, or in neutral solution, in the absence of suitable soft metal ions. Compounds **1** hydrolyse at significant rates at pH $\gtrsim 5$, but at rates negligible compared with the thallium ion-promoted rates at pH $\lesssim 2$.

Results and Discussion

Spectroscopic and kinetic studies[5] show that in dilute aqueous acid solutions, thiocarbamates analogous to **2** form stable complexes with Hg^{2+} ions of 2 thiocarbamate: 1 Hg^{2+} stoichiometry at low metal-ion concentrations, which, in the presence of an excess of Hg^{2+} ions, are converted into complexes of lower stoichiometry which undergo rapid hydrolysis. Simpler thioamides behave similarly.[9] Thiolurethanes **1** and **2** decompose too rapidly in the presence of Hg^{2+} ions to permit convenient spectroscopic study of complex formation. With Tl^{3+} ions they decompose more slowly, but do not show any spectral evidence of complex formation. However, the way in which k_{obs} depends upon $[Tl^{3+}]$, at fixed values of $[H_3O^+]$ and ionic strength, strongly suggests that complex formation is occurring (Figs. 1 and 2). All the thiolurethanes **1** and **2** exhibit curves similar to those in Figs. 1 and 2. The curvature of the plots is compatible with 1:1 complex formation, and the outline mechanism of eqns. (3) and (4) is suggested. For this mechanism k_{obs} is given by eqns. (5) and (6). Typical plots of eqn. (6) are in Fig. 3, and the (approximate) values of k and K obtained from

$$\mathbf{1}\ (\text{or}\ \mathbf{2}) + Tl^{3+} \rightleftharpoons 1{:}1\ \text{complex} \quad K,\ \text{fast} \tag{3}$$

$$1{:}1\ \text{complex} \xrightarrow{H_2O/H_3O^+} R^1C_6H_4NH_3^+ + CO_2 + R^2C_6H_4STl^{2+}\ (\text{or}\ EtSTl^{2+}) \quad k,\ \text{slow} \tag{4}$$

$$k_{obs} = kK[Tl^{3+}]/(1 + K[Tl^{3+}]) \tag{5}$$

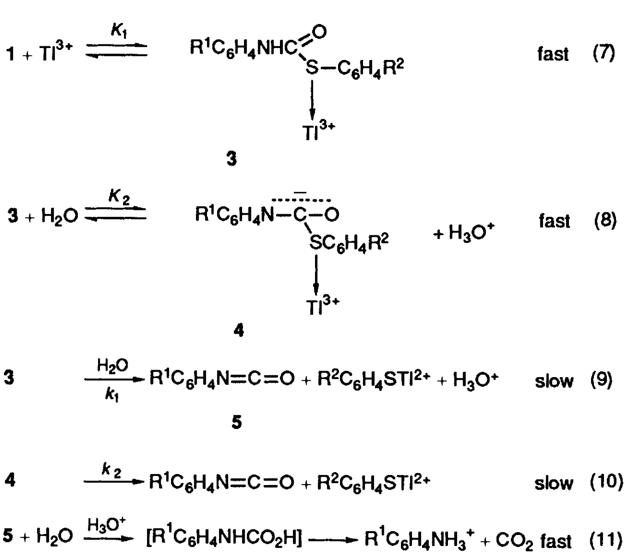
$$1/k_{obs} = 1/kK[Tl^{3+}] + 1/k \tag{6}$$

such plots are in Table 1. It is found that urethanes **2** are more basic towards Tl^{3+} ions, and their complexes more reactive towards water, than are the corresponding urethanes **1**, and changes in R have a somewhat larger effect than do changes in R^2. The effects of increases in ionic strength at $[Tl^{3+}]$ = 2–4 × 10^{-3} mol dm^{-3} (Table 2) are consistent with partial complex formation between substrate and Tl^{3+} ions for it is commonly found[10] in Tl^{3+} ion-promoted reactions that when complex formation is incomplete an increase in ionic strength leads to an increase in k_{obs}.

When using Tl^{3+} ions in aqueous solution it is necessary to maintain $[H_3O^+] \gtrsim 0.2$ mol dm^{-3} to keep the ions largely in the Tl^{3+} (rather than Tl^{2+}) form.[11] Typical effects on k_{obs} of increases in $[H_3O^+]$ when $[H_3O^+] \gtrsim 0.2$ mol dm^{-3}, under otherwise fixed conditions, are shown in Fig. 4; they suggest that the ionisation of the N-bound protons in the complexes facilitates hydrolysis. That is reasonable: it should aid C–S cleavage. The effects of temperature on k_{obs} under different concentration conditions for both **1** and **2** reveal substantial positive $\Delta S^‡$ values (Table 3).This may reflect unimolecular breakdown of the 1:1 complexes.

Striking results are obtained with the *N*-methyl derivatives of **1c** and **2b**. For $PhNMeC(O)SC_6H_4Cl$ the rate of hydrolysis in the presence of Tl^{3+} ions is negligibly small compared to that of **1c**; it is clear that the *N*-bound proton is essential to the mechanism of hydrolysis employed by **1c**. On the other hand, the Tl^{3+} ion-promoted hydrolysis of PhNMeC(O)SEt is too fast to measure by our present methods, so that here the N–H proton is inessential.

The behaviour of urethanes **1** is the easier to rationalise. The various results are compatible with the mechanism of eqns. (7)–(11). Aryl isocyanates are known[12] to react relatively very rapidly with aqueous acid to yield the corresponding aniline (or its cation). For eqns. (7)–(11) k_{obs} is given by eqn. (12). For a constant value of $[H_3O^+]$, eqn. (12) reduces to the form of eqn. (5) found experimentally. At any fixed value of $[Tl^{3+}]$, and assuming that $k_2 \gg k_1$, k_{obs} will fall as $[H_3O^+]$ is raised. The roughly constant value of k_{obs} obtained at high values of $[H_3O^+]$ will, on the basis of eqns. (7)–(11) correspond to reaction *via* **3** only, with $k_{obs} = k_1K_1[Tl^{3+}]/(1 + K_1[Tl^{3+}])$.



$$k_{obs} = \frac{(k_1K_1[Tl^{3+}] + k_2K_1K_2[Tl^{3+}]/[H_3O^+])}{(1 + K_1[Tl^{3+}] + K_1K_2[Tl^{3+}]/[H_3O^+])} \qquad (12)$$

There exists an insufficient range of results to justify a full analysis but those available are qualitatively compatible with eqn. (12). In view of the effect of an *N*-methyl group (in **1c**), it seems likely that step (9) involves slow proton loss, perhaps concerted with the departure of the $ArSTl^{2+}$ group in an E2-like elimination. The mechanism as a whole represents a Tl^{3+} ion-promoted hydrolysis *via* elimination. Steps (8) and (10) correspond to an E1cB-type elimination. Both E1cB and E2 schemes are compatible with a positive value of $\Delta S^‡$. In the absence of Tl^{3+} ions, and in nearly neutral solution, compounds **1a–c** undergo a relatively slow hydrolysis (Table 4), probably by an E1cB mechanism[1,13] (which is suppressed at low pH). What is happening in the thallium-promoted reaction is that a much less nucleophilic leaving group is formed by the attachment of the Tl^{3+} ion, and the hydrolysis *via* elimination is much faster as a result.

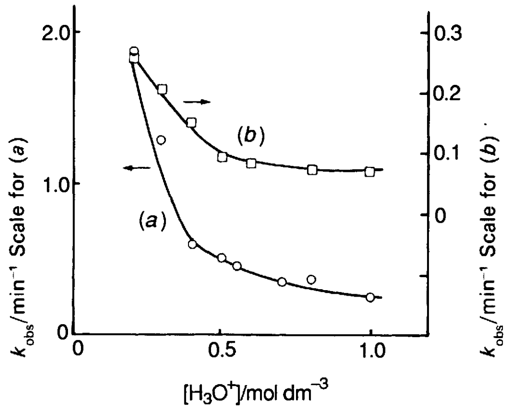


Fig. 4 Effect of $[H_3O^+]$ on k_{obs}. $[Tl^{3+}] = 1 \times 10^{-3}$ mol dm^{-3}; T = 25 °C; ionic strength = 1.0 mol dm^{-3}. (*a*) **2a**; (*b*) **1b**.

Table 2 Effect of ionic strength on k_{obs}[a]

Thiolurethane	$[Tl^{3+}]/10^{-3}$ mol dm^{-3}	Ionic strength/ mol dm^{-3}	k_{obs}/min^{-1}
2a	2.00	0.51	0.49
		0.70	0.64
		1.00	0.84
2c	4.00	0.51	0.30
		0.70	0.37
		0.90	0.44
		1.00	0.47

[a] $[H_3O^+] = 0.50$ mol dm^{-3}; T = 25 °C.

Table 3 Effects of temperature on k_{obs}[a]

Thiolurethane	$[H_3O^+]$/ mol dm^{-3}	$[Tl^{3+}]/10^{-3}$ mol dm^{-3}	T/°C	k_{obs}/min^{-1}	$\Delta H^‡$/ kJ mol^{-1}	$\Delta S^‡$/ J K^{-1} mol^{-1}
1b	0.20	1.00	18.3	0.11		
			25.0	0.27	78 ± 4	28 ± 3
			36.1	0.72		
	0.50	2.00	25.0	0.17		
			35.5	0.63	84 ± 4	40 ± 4
			44.0	1.4		
2a	0.20	1.00	17.3	0.47		
			25.0	1.8	81 ± 4	53 ± 4
			36.1	4.1		
	0.80	1.00	18.2	0.12		
			25.0	0.36	85 ± 4	55 ± 6
			36.0	0.94		

[a] $[Thiolurethane]_{initial}$ *ca.* 3×10^{-5} mol dm^{-3}; solvent = 1% (v/v) dioxane–water, ionic strength 1.0 mol dm^{-3}.

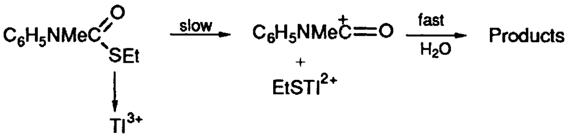
Table 4 Spontaneous hydrolyses of thiolurethanes **1** at 25 °C[a]

Thiolurethane	$k_{obs}/10^{-2}$ min^{-1}
1a	1.4
1b	3.7
1c	4.8

[a] [Thiolurethane]$_{initial}$ *ca.* 3×10^{-5} mol dm^{-3}; solvent = 1% (v/v) dioxane–water, pH = 6.6.

An analogue of the present reaction is known in a preparative context using rather special *S,S*-urethanes and zinc acids, when the (unreactive) isothiocyanate can be isolated.[14]

A mechanism analogous to eqns. (7)–(11) cannot be wholly adequate for urethanes **2** since the effect of an *N*-methyl substituent is so different. Perhaps the *N*-methyl derivatives of **2b** can hydrolyse *via* a unimolecular mechanism [eqn. (13)]. If



$$\underset{\underset{Tl^{3+}}{\downarrow}}{C_6H_5NMeC(=O)SEt} \xrightarrow{\text{slow}} C_6H_5NMe\overset{+}{C}{=}O + EtSTl^{2+} \xrightarrow[H_2O]{\text{fast}} \text{Products} \quad (13)$$

so, this route may be open to the N–H compounds also. It would correspond to an $A_{AC}1$ mechanism (with Tl^{3+} replacing H^+), and $\Delta S^\ddagger$ would be likely to be positive, as found. The product-forming steps for the deprotonated forms of **2a–c** are suggested to remain similar to eqn. (10).

The reason that the effects of changes in R^2 in **1**, and in R in **2**, on the overall rate constant k_{obs} and on both k and K [eqn. (5)] are rather small may be that various opposed effects are involved: an increase in electron release by R^2 should decrease k_1, k_2 and K_2 but increase K_1, whereas more electron release by R should increase K_1 and k_2, but decrease K_2, and perhaps also k_1 if N–H cleavage is involved.

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