The Products, Kinetics, and Mechanisms of Metal Ion-promoted Hydrolyses of Thioimidate Esters and the Effects of Hydrogen Ions on Thioimidate Ester Hydrolyses

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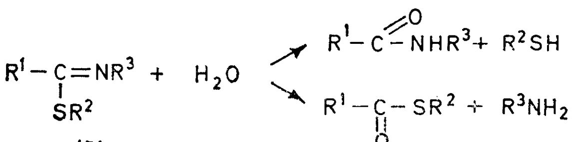
A kinetic study shows that the hydrolysis of thioimidate esters in the presence of hydrogen ions at pH $\gtrsim 2$ is promoted by mercury(II) ions. Methyl thiobenzimidate leads to benzonitrile and methyl *N*-cyclohexyl thiobenzimidate to *N*-cyclohexylbenzamide. The *N*-protonated forms of the esters, like their analogue the 1-[α-(methylthio)-benzylidene]piperidinium ion, are unreactive towards mercury(II) ions: the rate of reaction therefore falls as $[H_3O^+]$ rises. Mechanisms of the mercury-promoted reactions are given which are compatible with the observed reaction orders. The hydrolysis of the imidate esters at pH $\gtrsim 2$, in the absence of heavy metal ions, which leads predominantly to the thiol ester, is also inhibited by an increase in $[H_3O^+]$ and the explanation of this effect is discussed. Unlike mercury(II) ions, silver ions have no detectable effect on the rate of hydrolysis of thioimidate esters at pH $\gtrsim 2$, but do affect the isolable products since they rapidly convert the thiol ester to the carboxylic acid.

WE have reported recently on the effects of metal ions on the hydrolyses of a variety of thioacyl derivatives.[1] We here extend these studies to thioimidate esters (I). The hydrolysis of such esters in aqueous solution in the pH region has been thoroughly examined by Chaturvedi *et al.*[2] who also found that in acid solution the major product is the thiol ester, whereas in alkaline solution it is the *O*-amide [equation (1)]. There appears to exist no previous information about the effects of metal ions on this reaction.

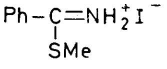


$$R^1-\underset{SR^2}{C}=NR^3 + H_2O \begin{cases} \nearrow R^1-\overset{O}{C}-NHR^3 + R^2SH \\ \searrow R^1-\underset{O}{C}-SR^2 + R^3NH_2 \end{cases} \quad (1)$$

(I)

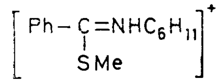
EXPERIMENTAL

Materials.—Three thioimidate esters were prepared as their corresponding hydrogen iodides[3] [(II) and (III)], or iodide (IV), in *ca.* 60% yield from the thioamides[4] and methyl iodide in acetone solution. The yellow crystalline solids all gave excellent microanalyses. The free ester, methyl *N*-cyclohexyl thiobenzimidate, was prepared[3] from (III) by dissolving (III) in water and neutralising the hydrogen iodide with base. This neutralisation was followed by immediate extraction with diethyl ether. Drying and removal of the ether led to the free ester, a pale yellow liquid, b.p. 302°. In aqueous solution at pH $\lesssim 4$ (II)—(IV) have absorption maxima at 260 (ε 12 600), 265 (13 700), and 265 nm (13 000), respectively. Under these conditions the esters from (II) and (III) are effectively fully protonated.[2] At pH *ca.* 7 the free ester prepared from (III) displayed on dissolution an absorption maximum at 265 nm (ε 7 400). On acidifying the solution this absorption immediately increased, as expected, to that characteristic of (III) at pH $\lesssim 4$. (Since the iodide ion absorbs significantly these measurements involved, where necessary, the use of an appropriate blank solution containing potassium iodide.)



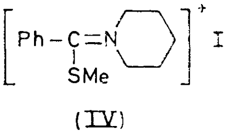
$$Ph-\underset{SMe}{C}=\overset{+}{N}H_2\,I^-$$

(II)



$$\left[Ph-\underset{SMe}{C}=NHC_6H_{11}\right]^+ I^-$$

(III)



(IV)

Acetone, diethyl ether, methyl iodide, and silver perchlorate were from B.D.H. A stock solution of mercury(II) perchlorate was prepared as before.[5] All other reagents were of AnalaR grade.

Products.—We have studied the hydrolysis both in the presence of hydrogen ions alone and in the additional presence of heavy metal ions. Preparative-scale experiments, and u.v. analyses of reaction mixtures from the kinetic studies left for >10 half-lives, show that in the absence of heavy metal ions and when $[H_3O^+] \gtrsim 0.01$M the product is the thiol ester, whilst at lower acidities significant amounts of amide are formed [equation (1)]. These results are in general agreement with those of Chaturvedi *et al.*[2] The mercury(II) ion-promoted reaction of (II) leads at pH $\lesssim 4$ exclusively to benzonitrile, as the organic product while that of (III) leads to the amide. No thiomethoxomercury derivatives were isolated, but the probable overall equations are (2) and (3), respectively. The yields of nitrile and amide are >90%. The hydrolysis of (II) in the presence of silver ions leads, at pH $\lesssim 4$, mainly to benzoic acid, together with some *O*-amide.

Kinetic Arrangements.—(i) *Hydrolysis in the presence of hydrogen ions.* Reaction mixtures were made up in volumetric flasks by adding to various, thermostatted aqueous perchloric acid solutions (50 ml) small aliquot portions of a freshly prepared solution of the thioimidate ester in water or ethanol. The initial ester concentration in the reaction mixtures was *ca.* 10^{-4}M. Samples (3 ml) of reaction mixture were withdrawn at known intervals and analysed for the

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[1] A. J. Hall and D. P. N. Satchell, *J.C.S. Perkin II*, 1975, 1351 and earlier papers.

[2] R. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *J. Amer. Chem. Soc.*, 1967, **89**, 6984.

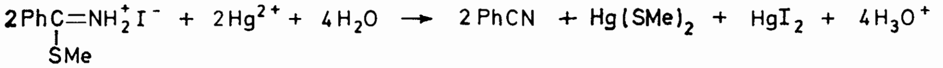
[3] P. Reynaud, R. C. Moreau, and H. T. Nguyen, *Compt. Rend.*, 1961, **253**, 1968; B. Bottcher and F. Bauer, *Annalen*, 1950, **568**, 218.

[4] A. J. Hall and D. P. N. Satchell, *J.C.S. Perkin II*, 1975, 778.

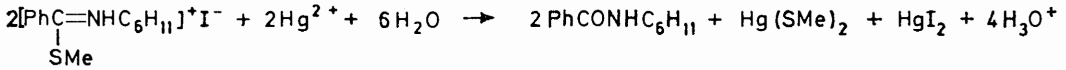
[5] D. P. N. Satchell and I. I. Secemski, *J. Chem. Soc.* (*B*), 1970, 1306.

ester remaining by spectroscopic measurements at 260—265 nm using a Unicam SP 800 instrument. The esters were added as their iodides, (II)—(IV), and the blank cell always contained the appropriate concentration of potassium iodide. An accurate first-order disappearance of ester for more than two half-lives was always observed, and the first-order rate constant, k_{obs}, was calculated from plots of $\log(D_0 - D_t)$ against time. Our results are in Table 1. Values of k_{obs} were reproducible to within ±4%.

(ii) *Mercury*(II) *ion-promoted hydrolysis*. For compounds (II) and (III) reaction mixtures were made up in the spectrophotometer cells. Solutions (2.5 ml) containing all the components save the ester were thermostatted in the cell compartment of the spectrophotometer and reaction initiated by the injection of a small volume (0.05 ml) of a freshly prepared stock solution of the ester. The hydrolysis was studied for a series of Hg^{2+} and H_3O^+ concentrations, these being always kept at least 10-fold greater than that of the ester (*ca.* 10^{-4}M). In most series of experiments the ionic strength was kept roughly constant (where necessary by addition of sodium perchlorate). Stock ester solutions were made up using either the iodide derivative or the free ester. Accurate first-order loss of ester for more than two half-lives was always observed and the first-order rate constant was calculated as in (i). Values of k_{obs} were reproducible to within ±5% and rates obtained using either the free ester or its iodide agreed within experimental error. The presence of iodide in the reaction mixtures, which will remove a small fraction of the mercury(II) ion concentration, has therefore a negligible effect on k_{obs}. All reactions remained homogeneous throughout a run. For compound (IV) the hydrolyses were similar in speed to those found in the presence of hydrogen ions alone and a sampling technique was used. Our results are in Tables 1—3.



$$2\mathrm{PhC(SMe)}{=}\mathrm{NH_2^+I^-} + 2\mathrm{Hg^{2+}} + 4\mathrm{H_2O} \longrightarrow 2\mathrm{PhCN} + \mathrm{Hg(SMe)_2} + \mathrm{HgI_2} + 4\mathrm{H_3O^+} \quad (2)$$



$$2[\mathrm{PhC(SMe)}{=}\mathrm{NHC_6H_{11}}]^+\mathrm{I^-} + 2\mathrm{Hg^{2+}} + 6\mathrm{H_2O} \longrightarrow 2\mathrm{PhCONHC_6H_{11}} + \mathrm{Hg(SMe)_2} + \mathrm{HgI_2} + 4\mathrm{H_3O^+} \quad (3)$$

(iii) *Hydrolysis in the presence of silver ions*. These hydrolyses were also similar in speed to those involving hydrogen ions alone. In these experiments, which employed only substrate (II), the silver iodide was precipitated at the start of a run but quickly settled and did not interfere with subsequent measurements of absorbance. Values of k_{obs}, calculated as in (i), were reproducible to within ±10% (Table 4).

Tests for Complex Formation between Thioimidate Esters and Mercury(II) *Ions*.—Some sulphur-containing compounds (*e.g.* thioamides [4]) form complexes quantitatively with Hg^{2+} in aqueous solution. For thioimidates we find that any similar complexes are not formed in easily detectable amounts.

RESULTS AND DISCUSSION

(i) *Hydrolysis in the Presence of Hydrogen Ions*.—Results in Table 1 show that for compounds (II)—(IV) k_{obs} falls as $[H_3O^+]$ rises. For compound (II), for which the results are most numerous, their pattern is similar to that found for other imidate esters by Chaturvedi *et al.*[2] If we recall that the major product at low pH is the thiol ester, these authors' explanation of the deceleration produced by hydrogen ions in this region is effectively that once equilibrium (4) has been pushed far to the right (as it will be in most of our experiments) further increase in $[H_3O^+]$ will lead only to increasingly unfavourable partitioning of the intermediate (V), since step (6) is assumed by them to be unaffected by $[H_3O^+]$.[*] This latter assumption, for which no explanation is offered, seems at first sight very unlikely, for if an OH group has to be helped to leave by a proton, so surely will the much more basic NH_2 group. However, some asymmetry in the effects of H_3O^+ on the loss of OH and NH_2 from (V) is needed if the deceleration by acid is to be explained. We suggest that the thiol ester can be formed from (V) by two routes, (7) and (8). If route (7) is relatively important, then since a similar route seems much less likely for the loss of the OH group from (V), the asymmetry of the effects of H_3O^+ on the intermediate can be accounted for: loss of OH will involve the kinetic term $k_{-5}[(V)][H_3O^+]$ and loss of NH_2 the term $(k_7[(V)] + k_8[(V)][H_3O^+])$ with the k_7 component dominant. Thus

TABLE 1

Hydrolysis of thiobenzimidate esters in the presence of hydrogen ions

$[\mathrm{Ester}]_{initial} = 10^{-4}$M; for compounds (III) and (IV) reaction mixtures contained 2% (v/v) EtOH–H_2O; for k_{obs} see text, ionic strength variable

(i) Compound (II)

(*a*) Temperature = 5.5 °C

$[H_3O^+]$/M	0.001 82	0.009 02	0.018 2	0.090
10^6k_{obs}/s^{-1}	1.50	1.47	1.43	1.42
$[H_3O^+]$/M	0.450	0.902	1.82	
10^6k_{obs}/s^{-1}	0.89	0.63	0.40	

(*b*) Temperature = 41.4 °C

$[H_3O^+]$/M	0.090 8	0.362	0.908	1.816	2.72
10^5k_{obs}/s^{-1}	9.86	7.22	4.86	2.43	1.51

(ii) Compound (III)

Temperature = 60.0 °C

$[H_3O^+]$/M	0.001 82	0.018 2	0.182	1.82
10^5k_{obs}/s^{-1}	7.31	6.40	4.09	0.40

(iii) Compound (IV)

Temperature = 51.0 °C

$[H_3O^+]$/M	0.001 80	0.018 0	0.180
10^5k_{obs}/s^{-1}	1.43 (1.47) *	1.33 (1.36) *	1.05 (0.99) *

* Values in parentheses obtained under same conditions with $[Hg^{2+}] = 10^{-3}$M.

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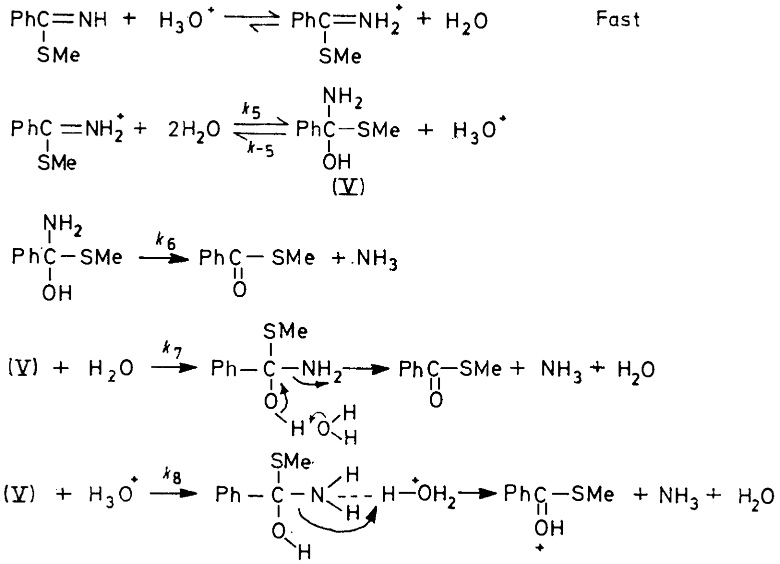
[*] If H_3O^+ were included as a reactant in step (6), then k_{obs} would be expected to become independent of $[H_3O^+]$ at low pH.



(4)
(5)
(6)
(7)
(8)

any increase in $[H_3O^+]$ will decelerate thiol ester formation relatively more than it accelerates it, as found. It follows too that $k_{obs} \simeq k_5k_7/(k_7 + k_{-5}[H_3O^+])$ and therefore a plot of $1/k_{obs}$ against $[H_3O^+]$ should be rectilinear with an intercept $1/k_5$. We find $k_5 \simeq 1.5 \times 10^{-6}$ s^{-1} for compound (II) at 5.5 °C (Figure).

TABLE 2

Mercury(II) ion-promoted reaction of *N*-cyclohexyl methylthiobenzimidate

Except as indicated, $[\text{Ester}]_{\text{initial}} = 10^{-4}$M; solvent = 2% (v/v) EtOH–H_2O; for k_{obs} see text

(i) Effect of $[Hg^{2+}]$

(*a*) Temperature = 25.0 °C; $[H_3O^+]$ = 0.456M; ionic strength 0.456 ± 0.005M

$10^3[Hg^{2+}]$/M	1.00	2.00	3.00	4.00	5.00	6.00
10^3k_{obs}/s^{-1}	3.55	7.10	10.9	14.0	18.0	22.1

(*b*) Temperature = 5.9 °C; $[H_3O^+]$ = 0.0274M; ionic strength = 0.038 ± 0.008M

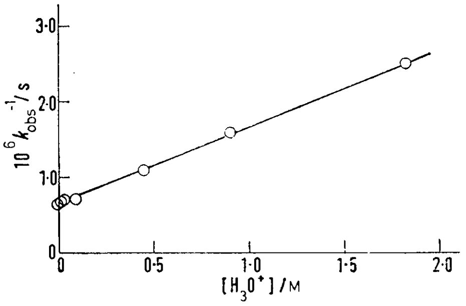
$10^3[Hg^{2+}]$/M	1.00	2.00	3.00	4.00	5.00	6.00
10^3k_{obs}/s^{-1}	0.70	1.38	2.20	2.66	3.63	4.28

(ii) Effect of $[\text{Ester}]_{\text{initial}}$ ($[H_3O^+]$ = 0.0274M; $10^3[Hg^{2+}]$ = 1.0M; ionic strength = 0.0304M; temperature = 5.9 °C)

10^5[Ester]/M	4.00	5.00	7.50	10.0
10^3k_{obs}/s^{-1}	10.1	9.7	10.1	9.3

(iii) Effect of $[H_3O^+]$ ($10^3[Hg^{2+}]$ = 1.0M; ionic strength = 2.50M; temperature = 5.9 °C)

$[H_3O^+]$/M	0.004 56	0.006 38	0.009 12	0.018 2	0.027 4
10^3k_{obs}/s^{-1}	59.0	40.6	28.6	14.8	10.3
$[H_3O^+]$/M	0.045 6	0.063 8	0.091 2	0.182	0.456
10^3k_{obs}/s^{-1}	6.01	4.20	2.98	1.40	0.636
$[H_3O^+]$/M	0.912	1.37	1.82	2.28	
10^3k_{obs}/s^{-1}	0.312	0.219	0.136	0.106	



Hydrolysis of compound (II) in the presence of hydrogen ions at 5.5 °C

TABLE 3

Mercury(II) ion-promoted reaction of methylthiobenzimidate

Except as indicated $[\text{Ester}]_{\text{initial}} = 10^{-4}$M; for k_{obs} see text

(i) Effect of $[\text{Ester}]_{\text{initial}}$ ($[H_3O^+]$ = 0.090 8M; $10^3[Hg^{2+}]$ = 5.0M; ionic strength = 0.101M; temperature = 25.2 °C)

10^4[Ester]/M	0.50	1.00	1.25
10^3k_{obs}/s^{-1}	19.7	19.7	19.0

(ii) Effect of $[H_3O^+]$

(*a*) $10^3[Hg^{2+}]$ = 5.0M; temperature = 25.2; ionic strength variable; values in parentheses calculated from equation (22)

$[H_3O^+]$/M	0.027 2	0.045 4	0.090 8	0.182	0.272
10^3k_{obs}/s^{-1}	129	49.7	19.7	7.17	4.03
	(135)	(54)	(18)	(6.8)	(3.2)
$[H_3O^+]$/M	0.590	0.908	1.82	2.72	
10^3k_{obs}/s^{-1}	1.43	0.95	0.55	0.38	
	(1.2)	(0.68)	(0.30)	(0.21)	

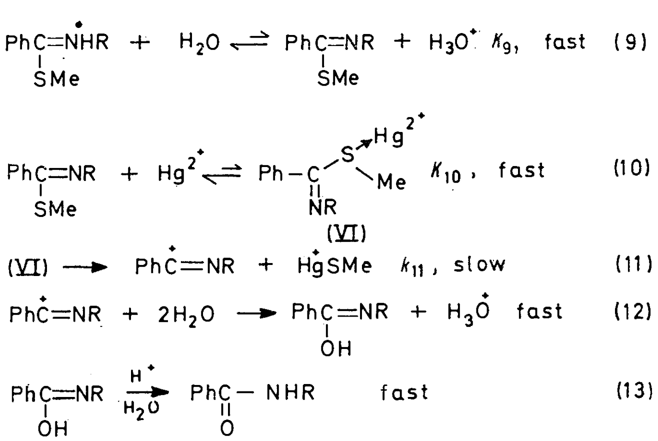
(*b*) $10^3[Hg^{2+}]$ = 1.0; ionic strength = 2.50M; temperature = 6.0 °C; values in parentheses calculated from equation (22)

$[H_3O^+]$/M	0.005 46	0.018 2	0.045 4	0.063 6	0.090 8
10^3k_{obs}/s^{-1}	61.2	7.32	0.963	0.587	0.302
	(53)	(5.7)	(1.2)	(0.70)	(0.39)
$[H_3O^+]$/M	0.182	0.454	0.908	1.82	
10^3k_{obs}/s^{-1}	0.108	0.037 5	0.018 6	0.009 33	
	(0.15)	(0.047)	(0.023)	(0.011)	

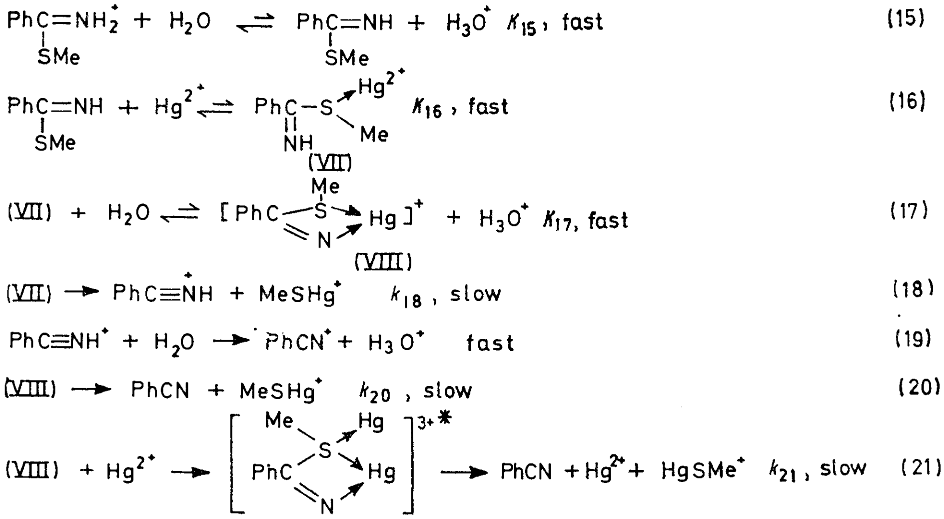
(iii) Effect of $[Hg^{2+}]$ [temperature = 25.2 °C; values in parentheses calculated from equation (22)]

$10^3[Hg^{2+}]$/M	0.50	1.00	2.00	4.00	5.00	6.00
10^3k_{obs}/s^{-1}						
$[H_3O^+]$ = 0.090 8M and ionic strength = 0.101 ± 0.008M	0.55 (0.75)	1.30 (1.7)	4.15 (4.5)	14.9 (12)	19.7 (17)	30.9 (23)
$[H_3O^+]$ = 0.908M and ionic strength = 0.918 ± 0.008M	0.061 (0.058)	0.13 (0.13)	0.27 (0.23)	0.60 (0.52)	0.95 (0.68)	1.0 (0.80)

(ii) *Reaction in the Presence of Mercury*(II) *Ions*.—Our results are in Tables 2 and 3. There are three important preliminary points. (a) No Hg^{2+}–imidate ester complexes were detectable spectroscopically (*i.e.* their concentrations must be low). (b) The rate of hydrolysis of compound (IV) is not affected by the presence of Hg^{2+} ions: the observed rate constants are very similar to those expected in the presence of H_3O^+ ions alone (Table 1). This however, is not the case for compounds (II) and (III) for which the contribution to k_{obs} from the rate in the presence of hydrogen ions alone is mostly negligible. (c) Compounds (II) and (III) are largely protonated at the hydrogen ion concentrations used in the reaction mixtures containing Hg^{2+}.



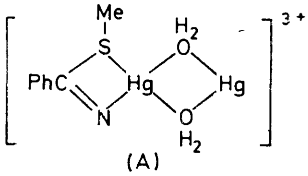
$$-\mathrm{d[Ester]}/\mathrm{d}t = k_{11}[(\mathrm{VI})] = k_{11}K_9K_{10}[\mathrm{Hg^{2+}}][\mathrm{Ester}]/[\mathrm{H_3O^+}] = k_{\mathrm{obs}}[\mathrm{Ester}] \quad (14)$$



The results for (III) can be explained readily and we therefore deal first with these. The product here is the amide. Examination of Table 2 shows that the reaction is of the first order in thioimidate ester and in mercury(II) ions, but that k_{obs} is inversely related to $[H_3O^+]$. A plot of k_{obs} against $1/[H_3O^+]$ is an excellent straight line and passes through the origin. In view of the complete inactivity towards mercury ion-promotion of compound (IV), which cannot lose the charge on its nitrogen atom by dissociating a proton, and in the light of mechanisms revealed by our earlier studies of the mercury(II) ion-promotion of other reactions,[4] we suggest reactions (9)—(13) for amide formation. (The solvation of Hg^{2+} is omitted for simplicity; equilibria such as $Hg(H_2O)_n^{2+} + H_2O \rightleftharpoons Hg(H_2O)_{n-1}OH^+ + H_3O^+$ will be unimportant at the pH values used.[6]) The corresponding rate equation (14) is in agreement with the observed reaction orders.

Our results for compound (II) (Table 3) are similar in pattern to those for (III), except that the dependence on the hydrogen ion concentration varies from $1/[H_3O^+]$ at the highest acidities used to nearly $1/[H_3O^+]^2$ at the very lowest, whilst the order in mercury ion varies from close to unity at high hydrogen ion concentrations to significantly greater than unity at low hydrogen ion concentrations. Changes in ionic strength have little effect on the trends in the data. The probably significant feature of (II) is that it has two NH protons available for ionisation and, remembering that the product in this case is the nitrile, we suggest modifying reactions (9)—(13) to (15)—(21). Recalling our earlier work with thiobenzamides,[4,7] steps (15)—(20) seem likely; step (21) is at

* A referee has suggested that a transition state structure such as (A) might be more likely.



(A)

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[6] L. E. Sillen and A. E. Martel, Chem. Soc. Special Publ. No. 17, 1961.

[7] A. J. Hall and D. P. N. Satchell, *J.C.S. Perkin II*, 1975, 953.

first unattractive but it may well be that the decomposition of (VIII), which only carries one net positive charge, benefits from assistance from another Hg^{2+} ion. Reactions (15)—(21) leads to the rate equation (22), which is compatible with the results. In equation (22) $k' = k_{18}K_{15}K_{16}$, $k'' = k_{20}K_{15}K_{16}K_{17}$, and $k''' = k_{21}K_{25}K_{16}K_{17}$. Table 3 illustrates, for a range of conditions, the fair agreement between the predicted and the observed values of k_{obs} at 25 °C with $k' = 0.1\ s^{-1}$, $k'' = 4 \times 10^{-3}$ mol $l^{-1}\ s^{-1}$, and $k''' = 3.0\ s^{-1}$. Since $k'''/k'' = k_{21}/k_{20} = 750$ l mol^{-1}, the results are consistent with the idea that the involvement of a second mercury(II) ion facilitates the decomposition of (VIII). This idea is also supported by our results for silver ions (see below). A somewhat better fit is obtained between equation (22) with $k' = 0.02\ s^{-1}$, $k'' = 0.8 \times 10^{-3}$ mol $l^{-1}\ s^{-1}$, and $k''' = 0.7\ s^{-1}$ and the results found at 6 °C using a constant ionic strength (Table 3). However, we do not wish to put forward equation (22) as necessarily representing a complete explanation. It seems likely nevertheless to be along the right lines. The significant feature of equation (22) is that at low pH the predicted kinetic form approaches that characteristic of compound (III), as found experimentally.

$$-\mathrm{d[Ester]}/\mathrm{d}t = \left\{k' + \frac{k''}{[\mathrm{H_3O^+}]} + \frac{k'''[\mathrm{Hg^{2+}}]}{[\mathrm{H_3O^+}]}\right\} \frac{[\mathrm{Hg^{2+}}]}{[\mathrm{H_3O^+}]}\cdot[\mathrm{Ester}] = k_{obs}[\mathrm{Ester}] \quad (22)$$

(iii) *Hydrolysis in the Presence of Silver Ions.*—Comparison of results in Tables 1 and 4 shows that silver ions have no detectable effect on the rate of hydrolysis. This suggests perhaps that, for silver, equilibrium (10) lies so far to the left that a negligible reaction ensues. Also, as we saw above, when the charge on the complex is reduced to unity the participation of further Hg^{2+} ions seems beneficial. Hence, as found in other similar contexts,[5,8] Hg^{2+} appears here markedly superior to Ag^+ in inducing C–S bond cleavage.

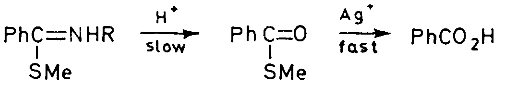
TABLE 4

Hydrolysis of methylthiobenzimidate in the presence of silver ions

$[\mathrm{Ester}]_{\mathrm{initial}} = 10^{-4}$M; $10^3[\mathrm{Ag^+}] = 2.00$M; temperature = 41.4 °C; for k_{obs} see text

$[\mathrm{H_3O^+}]$/M	0.090 8	0.182	1.82	2.72
$10^5k_{obs}/s^{-1}$	10.5	8.50	2.00	1.43

Although the presence of Ag^+ does not influence the rate of hydrolysis of (III) by aqueous acid, it does nevertheless alter the products isolated: instead of mainly the thiol ester we find mainly the carboxylic acid. This change arises because the hydrolysis of thiol esters is promoted relatively rapidly by silver ions[5] compared with the velocity of the imidate ester hydrolysis in aqueous acid. Thus as soon as thiol ester is formed it is transformed to acid [reaction (23)].



$$\underset{\mathrm{SMe}}{\mathrm{PhC{=}NHR}} \xrightarrow[\text{slow}]{\mathrm{H^+}} \underset{\mathrm{SMe}}{\mathrm{PhC{=}O}} \xrightarrow[\text{fast}]{\mathrm{Ag^+}} \mathrm{PhCO_2H} \quad (23)$$

[5/2063 *Received, 22nd October, 1975*]

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[8] A. J. Hall and D. P. N. Satchell, *J.C.S. Perkin II*, 1975, 1273.