

THE KINETICS AND MECHANISM OF METAL ION PROMOTED THIOL ESTER HYDROLYSIS

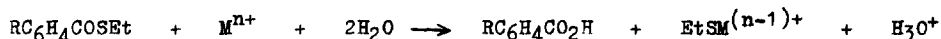
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(Received in UK 14 April 1969; accepted for publication 25 April 1969)

The mechanisms of hydrolysis of thiol esters are currently receiving much attention and are of particular interest to bioorganic chemists (1). Such hydrolyses are known to be accelerated by metal ions, especially mercuric and silver ions, but little quantitative information about this effect is yet available (2). The underlying reaction mechanisms have not been studied. We have now examined the hydrolyses of ethyl thiol benzoate, and of its p-nitro and p-methoxy derivatives, in aqueous solutions of silver and mercuric ions. We find that the overall hydrolyses can be represented by Scheme A and that they proceed in high (> 90%) yield.

Scheme A



The kinetics of the hydrolyses were studied spectrophotometrically, using low (ca. 10^{-4} M.) ester concentrations and various amounts (10^{-3} - 6×10^{-2} M.) of either mercuric or silver perchlorate. The reaction mixtures always contained sufficient (10^{-2} M.) perchloric acid to keep the hydrogen ion concentration effectively constant throughout the hydrolysis and were made up to a constant ionic strength of 0.1 M. with sodium perchlorate.

In the absence of the silver or mercuric ions the hydrolyses were very slow, and the contributions from the spontaneous and the hydrogen ion catalysed hydrolyses were normally negligible compared with those from the metal ion promoted hydrolyses. Some of our results for the latter reactions are in the Table.

TABLE

Rate constants and activation parameters

R=p-substituent in RC_6H_4COSEt ; rate constants ($\pm 3\%$) defined by
 $-d[\text{Ester}]/dt = \{k_1[M^{n+}] + k_2[M^{n+}]^2\} [\text{Ester}]$; significant term in
 k_2 found in one system only (3).

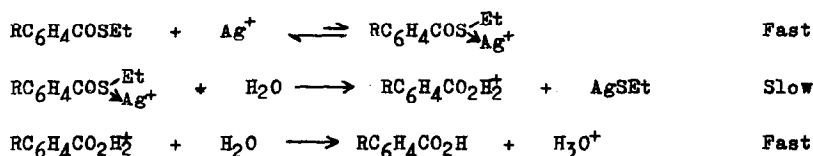
R	M^{n+}	$T_p(^{\circ}C)$	k_1 ($l \cdot \text{mole}^{-1} \text{ sec}^{-1}$)	k_2 ($l^2 \cdot \text{mole}^{-2} \text{ sec}^{-1}$)	ΔH^{\ddagger} ($\pm 1 \text{ Kcal. mole}^{-1}$)	ΔS^{\ddagger} (e.u.)
NO ₂	Hg ²⁺	25.0	0.70 x 10 ⁻² (in D ₂ O)		} 14	-22(± 1)
		25.0	1.10 x 10 ⁻²			
		49.0	6.70 x 10 ⁻²			
H	Hg ²⁺	25.0	8.60 x 10 ⁻²		} 20	+5(± 1)
		48.4	1.16			
MeO	Hg ²⁺	9.4	1.37		} 19	+10(± 1)
		25.0	8.61			
		25.0	10.3 (in D ₂ O)	1.52 x 10 ⁻⁴		
NO ₂	Ag ⁺	24.9	6.33 x 10 ⁻⁵		} 10	-43(± 2)
		49.8	2.59 x 10 ⁻⁴			
H	Ag ⁺	24.9	1.38 x 10 ⁻⁵		} 10	-48(± 3)
		49.9	5.33 x 10 ⁻⁵			
MeO	Ag ⁺	24.9	3.72 x 10 ⁻⁶	9.89 x 10 ⁻⁴	} 13	-38(± 2) (for k_1)
		49.9	2.34 x 10 ⁻⁵			

In every case, save that of the silver ion assisted hydrolysis of the p-methoxy derivative, the reactions were of the first-order in both ester and metal ion. The Table shows that:

- (i) With Ag^+ the sequence of ester reactivity (k_1) is $\text{p-NO}_2 > \text{p-H} > \text{p-MeO}$.
- (ii) With Hg^{2+} the sequence is $\text{p-MeO} \gg \text{p-H} > \text{p-NO}_2$; i.e., it is the reverse of that found with Ag^+ and involves a much larger change in overall reactivity.
- (iii) With Ag^+ , ΔS^\ddagger is always very negative, but with Hg^{2+} ΔS^\ddagger varies from a negative to a positive value along the series p-NO₂, p-H, p-MeO.
- (iv) ΔH^\ddagger is larger for the Hg^{2+} assisted reactions of the p-H and p-MeO esters than for the other reactions.
- (v) With Hg^{2+} the solvent isotope effect, $(k_1)_{\text{H}_2\text{O}} / (k_1)_{\text{D}_2\text{O}}$, is significantly different for the p-NO₂(1.6) and the p-MeO(0.8) esters.

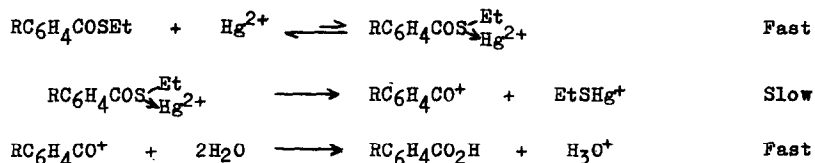
We have also found that changes in ionic strength affect the Hg^{2+} promoted hydrolysis of the p-MeO ester more than they affect the other hydrolyses.

The various facts are consistent with a bimolecular rate determining step for all the silver ion promoted hydrolyses, e.g. Scheme B. With mercuric ion, however, the pattern Scheme B



of effects is very similar to that normally interpreted, when found for other related hydrolyses, as indicating a transition from a bimolecular to a unimolecular slow step (4). Our results strongly suggest therefore that the mercuric ion assisted hydrolysis of the p-methoxy ester (if not of the unsubstituted ester also) proceeds via an acylium ion ($\text{A}_{\text{AC}}1$) mechanism, e.g. Scheme C. It is difficult to devise a satisfactory alternative explanation of the facts.

Scheme C



Acylium ion routes are uncommon in ester hydrolysis, generally only appearing for esters of favourable structure and under the influence of powerful Brønsted acid catalysis. Thiol esters are less susceptible than are their O-analogues to Brønsted acid catalysis (1). The results given here, apart from constituting the first kinetic analysis of metal ion assisted thiol ester hydrolysis and the first examination of substituent effects in these reactions, show (i) that Ag^+ and Hg^{2+} ions bring about such hydrolysis much more readily than does H_3O^+ , (ii) that Hg^{2+} is more effective than is Ag^+ , and (iii) that with favourably substituted esters Hg^{2+} can probably induce an acylium ion mechanism. This unusual type of route must therefore be considered seriously for other metal ion assisted reactions of esters and similar compounds (1).

A final point of interest is that whereas qualitative experiments show (1,2) that Cu^{2+} and Pb^{2+} , as well as Ag^+ and Hg^{2+} , assist the aminolysis of thiol esters, we have found Cu^{2+} and Pb^{2+} entirely without effect in our hydrolyses.

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