A Thesis Entitled

Rate of Hydrolysis of Phenolic Esters

Presented by

BOSHRA MOSSAD AWAD

B. Sc., Cairo University

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A C K N O W L E D G E M E N T

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C O N T E N T S

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S U M M A R Y

The rates of hydrolyses of the p-chlorophenyl- and p-tolyl hydrogen succinate in buffer solutions at different pH's from (1.80 to 6.85) indicate that the reaction follows a first order rate. The rate of hydrolysis decreases with increase of pH value attaining a minimum at about p. = 2, and then increasing regularly till it reaches a value at which the rate tends to become independent of pH from about 4.75 to about pH 5.65. In the pH independent region the rate appears to be proportional to $C^2_{H_2O}$. The hydrolysis appears to proceed by the $A_{AC}2$ mechanism, at pH below 2, whereas at pH above 2 it proceeds by $B_{AC}2$ mechanism.

The rate of hydrolysis in 50:50 dioxan-water was found to be higher than that in 50:50 acetone-water mixture, in spite of the fact that the former solution has a lower dielectric constant than the latter. This shows that the reaction must be a pseudo first order. However, the higher rate of hydrolysis in dioxan-water mixture is attributed to the fact that the mole fraction in this solution (0.828 mole) is higher than that in acetone-water mixture (0.806 mole).

The rates of hydrolysis of p-chlorophenyl-, phenyl- and p-tolyl hydrogen succinate lie in the following order

p-chlorophenyl-> phenyl-> p-tolyl hydrogen succinate. This indicates that electron-attracting groups (e.g. Cl atom) enhance the hydrolysis and electron-releasing groups (e.g. CH_3 group) retard it.

The activation energies are determined, from which the entropies of activation are calculated.

A cyclic intermediate in the hydrolysis of these esters in the pH range between 2 and 6.65 is proposed. This is supported by the fact that the entropy of activation of p-chlorophenyl hydrogen succinate at pH 6.65 is very small (-29.25 cal $degree^{-1}$) compared with that at pH 1.60 (23.5 cal $degree^{-1}$). The low entropy of activation at pH 6.65 indicates that the rate determining step involves a more organized transition state (less degrees of freedom) than that at pH 1.60. The organized transition state can be arrived at by the formation of such a cyclic intermediate.

The positive ρ-value for this reaction at pH 6.65 supports the proposed mechanism. The low ρ-value indicates that the reaction is not highly sensitive to the polar character of substituents in the phenyl group.

INTRODUCTION

INTRODUCTION

Esters are hydrolysed to their components in acid, neutral or alkaline media. The mechanism of hydrolysis in these media may be different or identical. The hydrolysis depends upon the nature of the reagent and the position of the rupture of the carboxyl compound. According to the nature of the reagent the hydrolysis is classified into alkaline, neutral and acid hydrolysis. In both alkaline and neutral hydrolysis the carboxyl from which undergoes reaction is the neutral ester molecule; $R'.CO_2R$, while in acid hydrolysis it is the ionic conjugate acid, $R'.CO_2HR^+$. Thus, it seems that the first two groups, namely the alkaline and neutral hydrolysis are more closely related to each other.

In order to classify the nature of hydrolysis, one should determine the position of rupture of the carboxyl compound. The modes of rupture and the names given to them are as follows:[1,2]

a) The acyl-oxygen fission which is the usual but not the only one for alkaline hydrolysis

$$R'.CO.\vert.OR + H.\vert OH$$

b) The alkyl-oxygen fission which is not infrequent in case of neutral hydrolysis

$$R'.COO\vert.R + HO\vert H$$

For each of the two main groups of mechanisms, the basic

hydrolysis in which the attacked entity is the neutral molecule $R'CO_2R$ and the acid catalysed hydrolysis in which the attacked entity is the conjugate-acidic ion, $R'CO_2HR^+$ or $R'CO_2H_2^+$; either acyl-oxygen, or alkyl-oxygen fission may take place according to the structure and conditions.

A study of the kinetics of the hydrolysis of esters shows that two mechanisms exist, which are related to each other like the bimolecular and unimolecular mechanisms of nucleophilic substitution or elimination. The following table summarises the classification suggested by Ingold[3] according to the mentioned features:

Type of Mechanism	Form Attacked	Known Reaction	Fission	
			Acyl	Alkyl
Basic	$R'CO_2R$	Hydrolysis	.....	$B_{AL}1$
			$B_{AC}2$	$B_{AL}2$
Acidic	$R'CO_2^+HR$	Hydrolysis	$A_{AC}1$	$A_{AL}1$
			$A_{AC}2$	....

The basic mechanism, including the alkaline and related neutral mechanisms, and the acidic mechanism are symbolised by B and A, respectively. The acyl-oxygen and the alkyl-oxygen fission are represented by subscripts AC and AL, respectively,

B) UNIMOLECULAR AND BIMOLECULAR BASIC HYDROLYSIS WITH ALKYL OXYGEN FISSION (MECHANISM $B_{AL}1$ AND $B_{AL}2$)

1) Mechanism $B_{AL}1$:

The ester molecule, $R'-CO_2-R$, contains two carbon atoms which are susceptible to be attacked by nucleophilic reagents, namely, the carboxyl C-atom and the α - carbon atom of the alkyl group. However, the former one is unsaturated, and hence it should be expected to be the more powerful competitor for the reagent, with the result that the acyl-oxygen fission is the general rule in basic hydrolysis. It can be supposed that, with hydroxide ion as the reagent, two reactions which can be described as acyl attack and alkyl attack occur side by side. The former is the faster and, therefore, the only observable one. Replacing the hydroxide ion by weaker nucleophilic reagents reduces the speed for both acyl and alkyl attack, but the former one remains the faster process.

A certain finite rate of ionisation of the ester $R'.CO_2R$ to $R'CO_2^-$ and R^+ can be obtained by assuming a suitable structure of R and a suitable solvent. When the nucleophilic reagent is weakened, first the rate of alkyl attack and then that of acyl attack will fall below the ionisation rate. At this point of crossing of rates, one passes from bimolecular acyl-oxygen fission to unimolecular alkyl-oxygen fission, that is

from mechanism $B_{AC}2$ to mechanism $B_{AL}1$. As we are concerned with hydrolysis, then the chief reagents are the hydroxide ion and the water molecule.

Therefore, it can be concluded that mechanism $B_{AL}1$ overwhelms mechanism $B_{AC}2$ by weakening the nucleophilic reagent as to become a water molecule. Mechanism $B_{AL}1$ may be formulated as follows:

$$R'.COOR \underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}} R^+ + R'.CO\bar{O} \qquad B_{AL}1$$

$$R^+ + H_2O \underset{\text{slow}}{\overset{\text{fast}}{\rightleftharpoons}} R - \overset{+}{O}H_2$$

$$(R.\overset{+}{O}H_2 + R'.CO\bar{O} \xrightarrow{\text{fast}} ROH + R'.COOH)$$

The characteristics of this mechanism, as it is a basic mechanism ($B_{AL}1$), is that it will not require acid but may proceed in neutral or weakly alkaline solution.

*) Mechanism $B_{AL}2$:

It can be represented as follows:-

$$H_2\overset{+}{O} + R - O\text{-}CO.R' \underset{\text{slow}}{\overset{\text{slow}}{\rightleftharpoons}} H_2\overset{+}{O}R + \bar{O}.CO.R' \qquad (B_{AL}2)$$

$$(R\overset{+}{O}H_2 + \bar{O}.COR' \xrightarrow{\text{fast}} ROH + R'.COOH)$$

The process may be regarded as reversible in principle, although the final proton transfer from the alkyl oxonium ion to the

carboxylate ion will direct it in practice completely from left to right.

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c) UNIMOLECULAR AND BIMOLECULAR ACID HYDROLYSIS WITH ACYL-OXYGEN FISSION (MECHANISMS $A_{AC}1$ AND $A_{AC}2$)

Acid-catalysed hydrolysis proceeds by mechanism $A_{AC}1$ and $A_{AC}2$.

The mechanisms of acid-catalysed hydrolysis with acyl-oxygen fission are suggested firstly by Holmberg[4] by using a form of R which is asymmetric at its point of union in the system $R'.CO_2R$, and he assumed that if R were to separate from this system during reaction, then R would not retain its configuration, e.g. of o-acetylmalic acid $CH_3CO.OR$, where R = $(HO_2C)CH_2CO_2H$. He showed that the asymmetric group did actually retain its configuration. Hilda Ingold and Ingold[5] studied the acid hydrolysis of acetate in which R(I) if liberated as a carbonium ion would be mesomeric (e.g., R = 1-methylallyl(Ia), or R = 3-methylallyl group,(Ib).

Mesomerism of acetal:

$$CH_2 - CH = CH - {}^{+}CH_2 \longleftrightarrow CH_3 - {}^{+}CH - CH = CH_2$$

I a

$$CH_2 = CH - \overset{CH_3}{\overset{|}{\underset{+}{CH}}} \longleftrightarrow \overset{+}{CH_2} - CH = CH - CH_3$$

I b

They found that no isomerisation took place. The O^{18} method has been applied to establish acyl-oxygen fission in the acid hydrolysis of methyl-hydrogen succinate[2], and other esters such as benzhydryl formate,[6] and β-butyrolactone.[7] Both the two mechanisms involve pre-equilibrium with an added proton, but differ in what afterwards happens to the oxonium ion thus formed.

(a) <u>The unimolecular mechanism</u> ($A_{AC}1$): Treffers and Hammett[8] suggest the occurrence of carboxyl reactions by this mechanism. This unimolecular mechanism[5] ($A_{AC}1$) is characterised by the formation of an oxonium ion which undergoes the rate-controlling heterolytic fission. This produces a carbonium ion, more specifically, an acylium ion $R'.CO^+$, which is then rapidly attacked by water molecule. Lastly a proton, equivalent to that originally taken up, is split off. All proton transfers are regarded as effectively instantaneous. The mechanism is distinguished by the middle two steps, and it could be formulated as follows:

$$R'.CO.OR + H^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} R'.CO.\overset{+}{O}HR$$

$$R'.CO.\overset{+}{O}HR \underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}} R'.\overset{+}{C}O + HOR$$

$$R'.\overset{+}{C}O + H_2O \underset{\text{slow}}{\overset{\text{fast}}{\rightleftharpoons}} R'.CO.\overset{+}{O}H_2$$

$$R'.CO.\overset{+}{O}H_2 \overset{\text{fast}}{\rightleftharpoons} R'.COOH + H^+$$

The formation of an acylium ion must not be rapid or reversible, and its production must be slow. So the stationary concentration of the acylium ion might be very small, because it is rate-determining. On hydrolysis of methyl benzoate[9] by water in sulphuric acid as a solvent, the reaction is slow and is first order with respect to ester, but zeroth order with respect to water in concentration up to 1M.

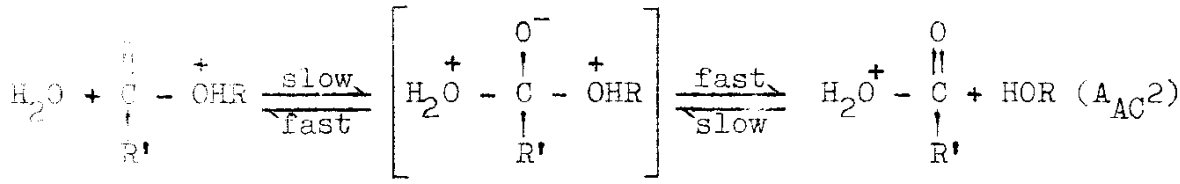
b, The bimolecular mechanism, ($A_{AC}2$): Such a mechanism can be derived from the $A_{AC}1$ mechanism, when the life of the acylium ion is reduced to the order of collision period, so that the two stages which represent the formation and destruction of this ion become fused into a single bimolecular process.[2] The initial proton uptake, and the final proton loss, are fast reversible processes as before. The characteristic stage of this mechanism is the middle one, and the mechanism is described as bimolecular, and labelled $A_{AC}2$.

$$R'.CO.OR + \overset{+}{H} \underset{\text{fast}}{\rightleftharpoons} R'.CO.\overset{+}{O}HR$$

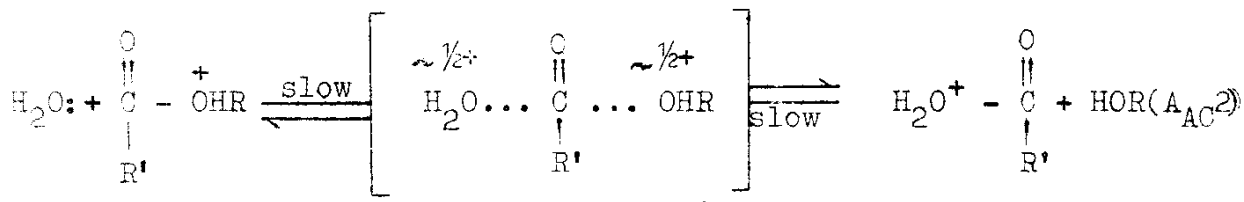
$$R'.CO.\overset{+}{O}HR + H_2O \underset{\text{slow}}{\rightleftharpoons} R'.CO.\overset{+}{O}H_2 + HOR \quad (A_{AC}2)$$

$$R'.CO.\overset{+}{O}H_2 \underset{\text{fast}}{\rightleftharpoons} R'.CO.OH + H^+$$

The rate controlling stage can be represented with stereochemical detail as a carbonyl addition.



or as a nucleophilic substitution



Mechanism $A_{AC}2$, is dependent on H_3O^+ concentration because of the covalent involvement of a water molecule in the transition state.

However, mechanism $A_{AC}1$ differs from mechanism $A_{AC}2$ in the following respects:

1) The rate of hydrolysis by $A_{AC}1$ should be independent of the concentration of water, while by $A_{AC}2$ depends on it.

2) The rates by either mechanism should be dependent on the acidity, yet there exists a fine distinction in the type of dependence required by the two mechanisms. $A_{AC}1$ is proportional to Hammett function h_o while $A_{AC}2$ mechanism is proportional to H_3O^+ concentration. The acid hydrolysis of B-propiolactone and β-butyrolactone in aqueous media were studied by Long and Purchase,[10] the acid catalysed rate was found to be proportional to h_o. Thus it appears that the hydrolysis of