

CARBONYL COMPOUNDS

PART-29, PPT-29, SEM-3

Part-29: Substitution at sp^2 Carbon (C=O System) (Part I)

CONTENTS

1. *General Reactions of the Monocarboxylic Acids and their Derivatives*
2. *Mechanism of Carboxyl Esterification and Hydrolysis of Carboxylic Esters: Introduction*
3. *Bimolecular Base-Catalyzed Hydrolysis with Acyl-Oxygen Heterolysis (B_{AC2}) of Carboxylic Esters*
4. *Bimolecular Acid-Catalyzed Hydrolysis and Esterification with Acyl-Oxygen Heterolysis (A_{AC2} Mechanism)*

Dr. Kalyan Kumar Mandal

Associate Professor

St. Paul's C. M. College

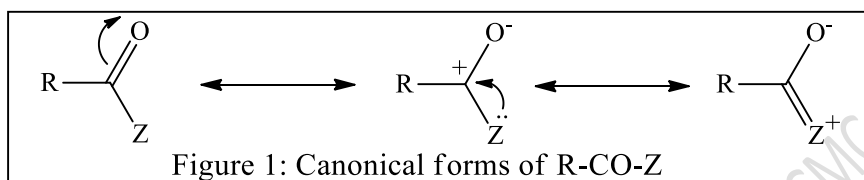
Kolkata

CARBONYL COMPOUNDS
PART-29, PPT-29
Substitution at sp^2 Carbon (C=O System)

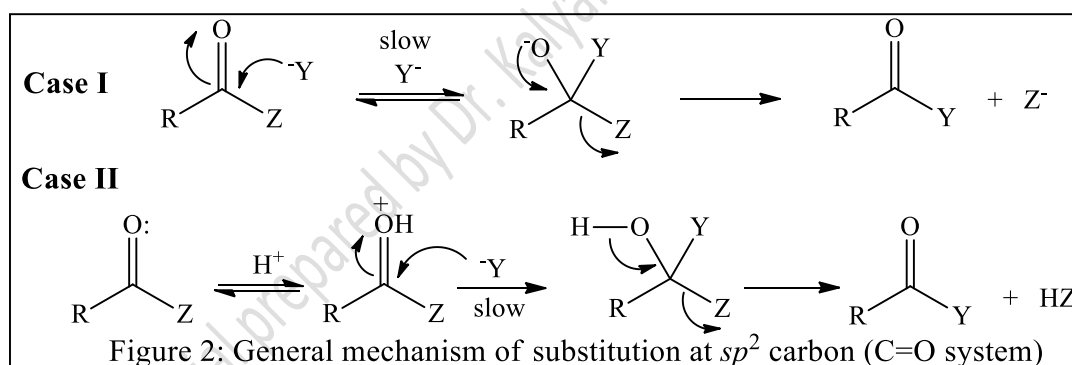
General Reactions of the Monocarboxylic Acids and their Derivatives

Substitution at sp^2 Carbon

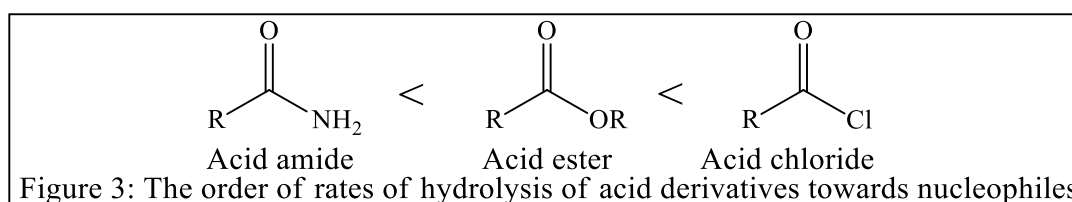
Acids and their derivatives may be represented as follows: Z = OH, OR, X, NH₂, etc.



Thus, all are resonance hybrids and the behaviour of the 'carbonyl' group depends on the nature of Z, Z may have a -I and a +R effect and consequently the actual weights of the canonical forms will depend on the relative contributions of these two electronic effects, e.g., Z = NH₂ (acid amide), +R > -I, whereas for Z = Cl (acid chloride), -I > +R. Hence, the rates of reaction of the carbonyl group in these compounds can be expected to be different. Many of the reactions of the acids and their derivatives may be generalized as in Figure 2.



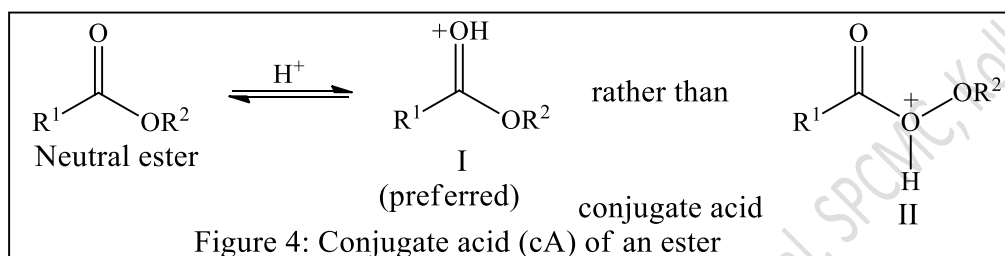
These reactions are typical of the behaviour of the carbonyl group (in aldehydes and ketones), and the greater the positive charge on the carbonyl carbon atom, the more easily is this carbon atom attacked by a nucleophile (in the rate-determining step). Since the +R effect tends to neutralize the positive charge, the greater the +R effect of Z, the slower will be the reaction. Experimental work has shown that the rates of hydrolysis are in the following order (Figure 3):



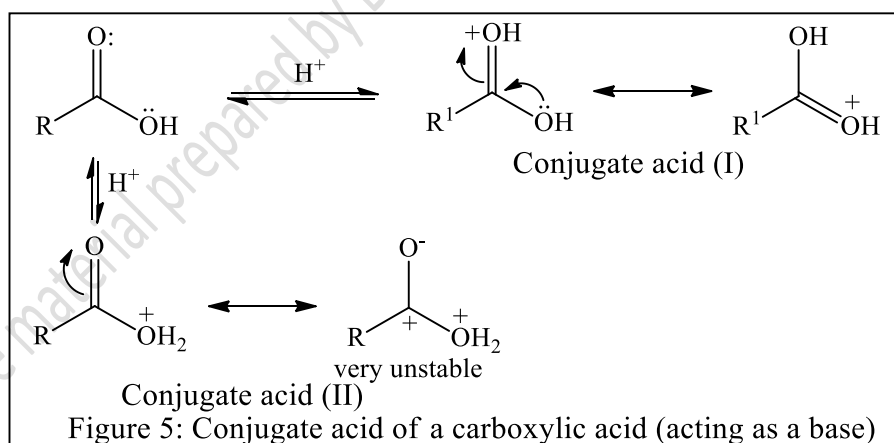
This is the reverse order of the +R effects of the groups attached to the carbonyl carbon of RCOZ, i.e., $\text{NH}_2 > \text{OR} > \text{Cl}$.

Mechanism of Carboxyl Esterification and Hydrolysis of Carboxylic Esters: Introduction

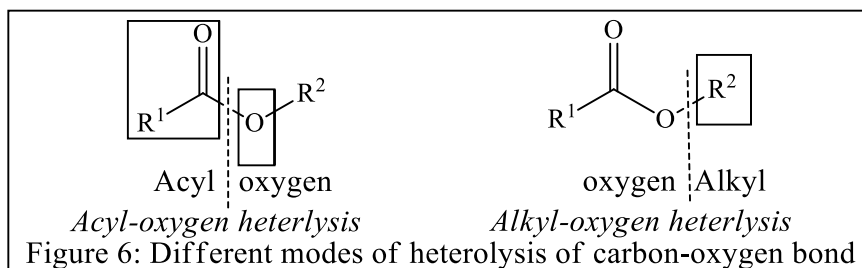
Mechanistic studies have shown that in alkaline or neutral hydrolysis, it is the neutral ester molecule which undergoes reaction, whereas in acid catalyzed hydrolysis, it is the conjugate acid of the ester which undergoes reaction.



The protonated carbonyl oxygen form (I) of the cA is preferred than that of (II), and it is observed that the ester is protonated chiefly on the carbonyl oxygen. This formulation is also used for acids and this is illustrated in Figure 5. Of the two possible conjugate acids of the carboxylic acids (acting as a base in strong acidic medium), (I) and (II) in Figure 5, (I) may be written as a resonance hybrid to which two identical canonical forms contribute, whereas for (II) the two contributing structures are different and one has fewer bonds and carries unlike charges.



The hydrolysis of carboxylic esters may be formulated in two ways as shown in Figure 6.



Both modes of fission have been demonstrated experimentally, and kinetic studies have shown that two types of mechanism may operate for each mode, *unimolecular* and *bimolecular*. Hence, eight mechanisms are possible for ester hydrolysis but so far six modes have been observed. These are summarized in Table 1.

Table 1: Possible mechanisms of ester hydrolysis

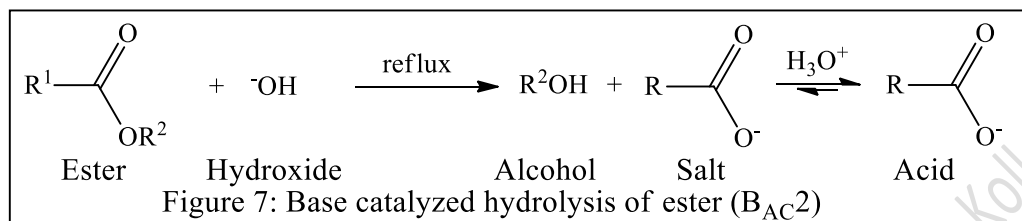
<i>Type of mechanism</i>	<i>Hydrolysis</i>	<i>Esterification</i>
$B_{AC}1$	-	-
$B_{AC}2$	Very common	-
$A_{AC}1$	Special cases	Special cases
$A_{AC}2$	Very common	Very common
$B_{AL}1$	Special cases	-
$B_{AL}2$	Rare	-
$A_{AL}1$	Very common for <i>t</i> -alcohols	Very common for <i>t</i> -alcohols
$A_{AL}2$	-	-

Since in principle, the acid-catalyzed reactions (esterification and hydrolysis) are reversible but not alkaline hydrolysis, then four mechanisms are possible for esterification. So far, three mechanisms have been observed as shown in Table 1. The eight possible mechanisms are indicated by the symbols shown in Table 1, where *A* represents the cA of the ester or acid (reaction in *acid* solution), *B* represents the unprotonated ester (reaction in *basic* or *neutral* solution), *subscripts* AC and AL, respectively, denote acyl- and alkyl-heterolysis, and numbers 1 and 2 represent the molecularity of the rate-determining step.

Most of the experimental work has been carried out on hydrolysis because this process can be studied in acidic, basic or neutral media, whereas esterification can be studied only in acidic media. It might appear at first sight that esterification could also be studied in neutral media, but since carboxylic acids are acids, reaction in the absence of added acid (as catalyst) is still effectively in an acid medium. Because of this, mechanisms of esterification are partly based on the principle of microscopic reversibility.

Bimolecular Basic Hydrolysis with Acyl-Oxygen Heterolysis (B_{AC2}) of Carboxylic Esters

A carboxylic ester is hydrolyzed to the salt of the corresponding carboxylic acid and an alcohol or phenol when heated with aqueous base. The carboxylic acid is liberated from the salt by addition of mineral acid (Figure 7).



Base promotes hydrolysis of esters by providing the strongly nucleophilic reagent OH^- . This reaction is essentially irreversible, since a resonance-stabilized carboxylate anion shows little tendency to react with an alcohol. The reaction involves attack on the ester by hydroxide ion. This is consistent with the kinetics, which is second-order, with the rate depending on both ester concentration and hydroxide ion concentration.

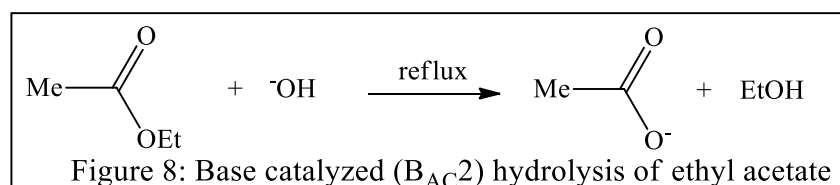
$$\text{Rate} = k [\text{ester}] [\text{OH}^-]$$

In the next step, hydroxide ion attacks at the carbonyl carbon and displaces alkoxide ion. That is to say, reaction involves cleavage of the bond between oxygen and the acyl group, $\text{RCO}-\text{OR}'$. The *rate-determining step* is certainly attack of OH^- on the original ester. This is borne out by the activation parameters for the base-induced hydrolysis of ethyl acetate (MeCO_2Et):

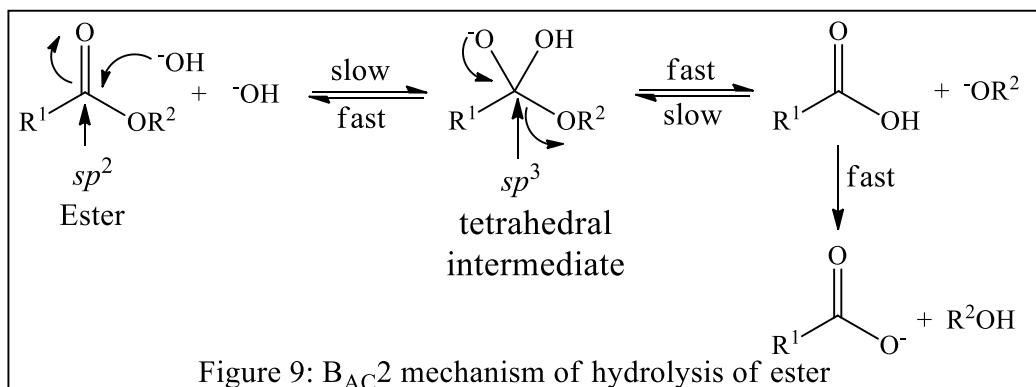
$$\Delta H^\ddagger = 112 \text{ kJ mol}^{-1}; \Delta S^\ddagger = -109 \text{ JK}^{-1} \text{ mol}^{-1}$$

The relatively large -ve value of ΔS^\ddagger indicates the decrease in *translational entropy* characteristic of two separate species ($\text{MeCO}_2\text{Et} + \text{OH}^-$) combining (an associative process) to form the *transition state* in the *rate-determining step* of the overall reaction. The overall reaction is essentially irreversible as OEt^- would remove a proton from RCO_2H (initially obtained from ester on hydrolysis) rather than attack its carbonyl carbon atom, while the carboxylate anion, RCO_2^- , will be unsusceptible to nucleophilic attack by EtOH or EtO^- . This mechanism is generally referred to as B_{AC2} (Base-catalyzed, acyloxygen cleavage, bimolecular).

B_{AC2} Mechanism of Hydrolysis of Carboxylic Esters

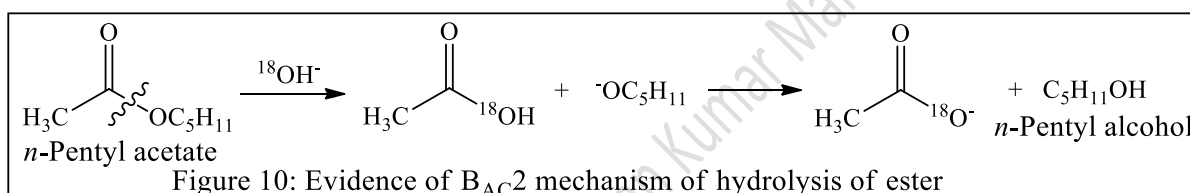


B_{AC2} mechanism consistent with the foregoing facts and also with the work of Bender (1951), who used esters labeled with ^{18}O in the carbonyl group is illustrated in Figure 9.

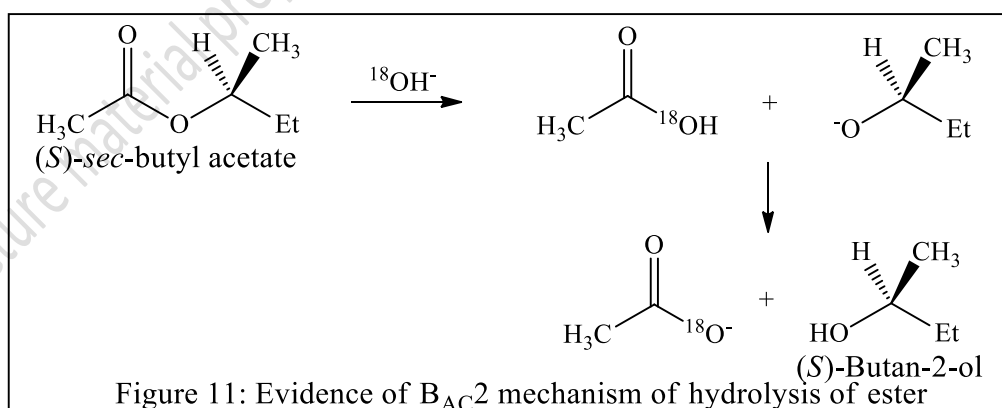


Evidence in Favour of B_{AC}2 Mechanism of Hydrolysis of Carboxylic Esters

Evidence for acyl-oxygen heterolysis has been obtained in several ways, such as, isotopic labeling study, optical activity diagnostic study, etc. The alkaline hydrolysis of *n*-pentyl acetate in water enriched with ¹⁸O gave *n*-pentyl alcohol containing no ¹⁸O. Therefore acyl-oxygen heterolysis must have occurred (Figure 10).

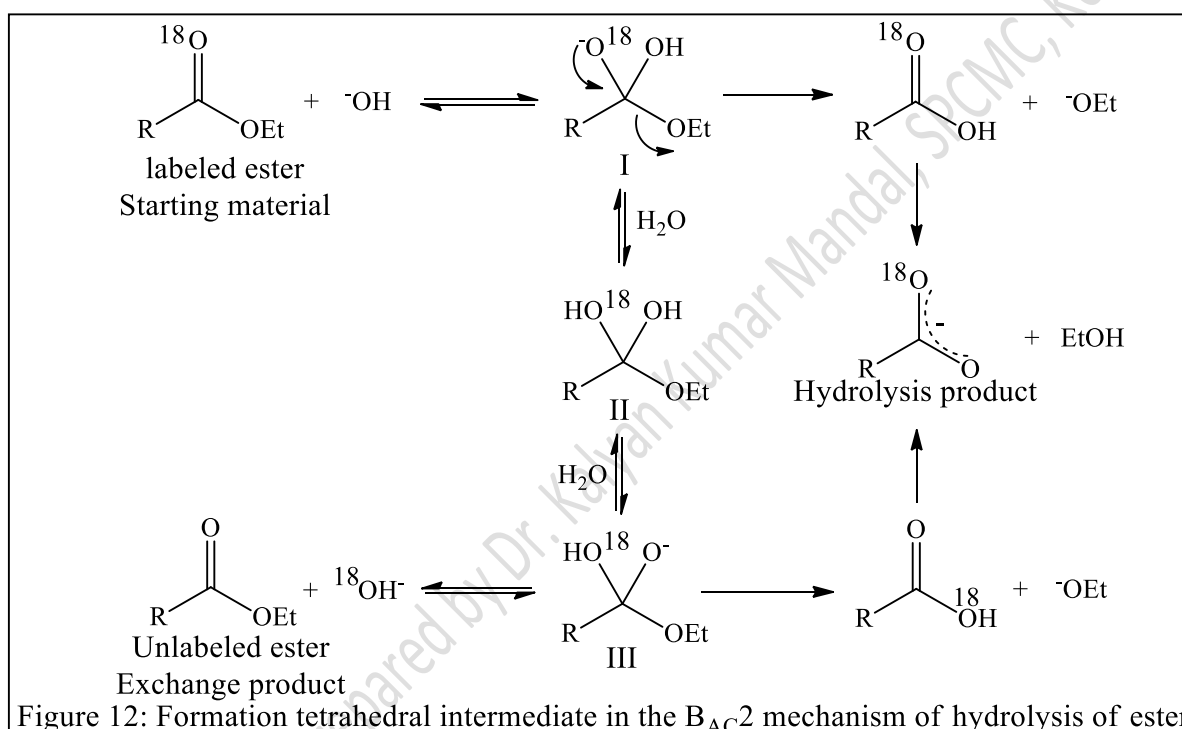


Another method uses optical activity (Figure 11) as a diagnostic test for demonstrating acyl-oxygen heterolysis. If the alcohol group is optically active and if the B_{AC}2 mechanism operates, then the ion RO⁻ will be liberated and will retain its optical activity since the bond R-O is never broken.



Evidence for Tetrahedral Intermediate in $B_{AC}2$ Hydrolysis of Carboxylic Esters

During the alkaline hydrolysis of carbonyl-labeled ethyl benzoate, $\text{PhC}^{18}\text{OOC}_2\text{H}_5$, in ordinary water, it is found that in the alkaline solution the ester was undergoing not only hydrolysis but also exchange of its ^{18}O for ordinary oxygen from the solvent as illustrated in Figure 12. Oxygen exchange is consistent with a *two-step mechanism* in which intermediate (I) is not only formed, but partly reverts into starting material and partly is converted (probably via the neutral species II) into (III) an intermediate that is equivalent to (I) except for the position of the label. If all this is so, the “reversion” of intermediate (III) into “starting material” yields ester that has lost its ^{18}O .



Electronic and Steric Effects in $B_{AC}2$ Hydrolysis of Carboxylic Esters

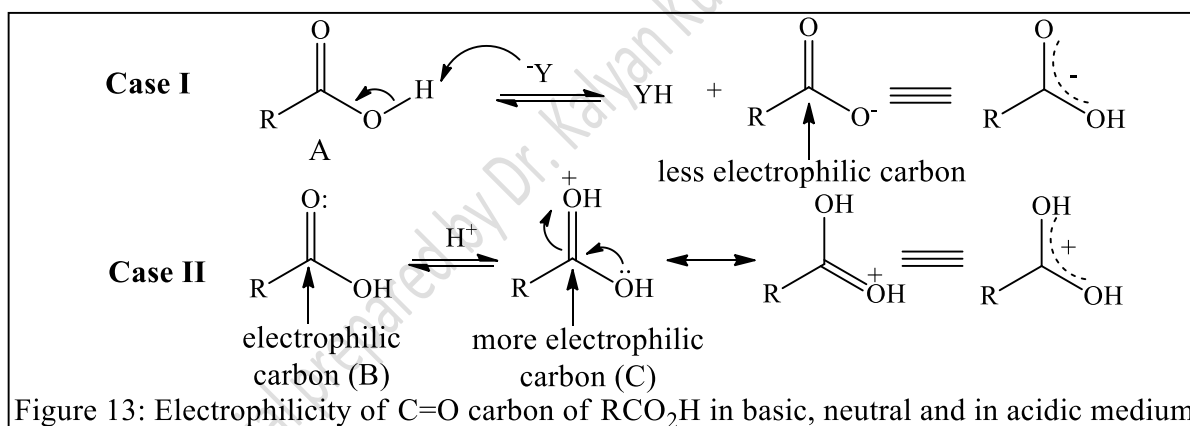
The rate of formation of the tetrahedral intermediate is affected by both electronic and steric factors: in the *transition state*, a negative charge is developing and carbon is changing from trigonal toward tetrahedral. Any R^1 group with a -I effect should accelerate hydrolysis by creating a positive charge on the attached carbon atom, thereby facilitating attack by the hydroxide ion. On the other hand, because the *rate-determining step* is bimolecular, the larger R^1 is the larger can be expected to be the steric retardation, since the hybridization of the carbon atom of the carbonyl group changes from sp^2 to sp^3 (with consequent increased crowding). These anticipated results have been observed in practice, and shown in Table 2.

Table 2: Rate of $B_{AC}2$ hydrolysis of Esters

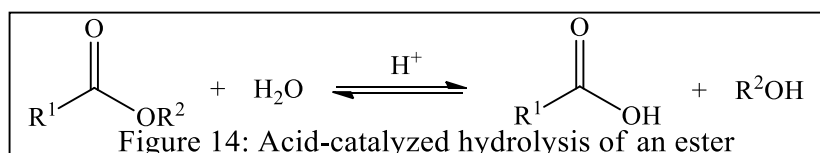
Electronic Effect			
<i>Ester</i>	MeCO ₂ Me	ClCH ₂ CO ₂ Me	Cl ₂ CHCO ₂ ME
<i>Relative rates</i>	1	761	16000
Steric Effect			
<i>Ester</i>	MeCO ₂ Et	EtCO ₂ Et	Me ₂ CHCO ₂ Et
<i>Relative rates</i>	1.00	0.47	0.10

Bimolecular Acid-Catalyzed Hydrolysis and Esterification with Acyl-Oxygen Heterolysis ($A_{AC}2$ Mechanism)

It is difficult to effect attack on the carbonyl carbon atom of RCO₂H (A; Figure 13), with nucleophiles of the general type Y⁻, as they commonly removed proton instead, and the resultant RCO₂⁻ is then insusceptible to nucleophilic attack. Weaker nucleophiles of the form YH, e.g., ROH, do not suffer this inability, but their reactions with the relatively unreactive carbonyl carbon atom of RCO₂H are slow. The carbonyl character may be enhanced by protonation.



Therefore, the acidic hydrolysis of esters is promoted by acid. Acidic hydrolysis is reversible, and the general reaction is shown in Figure 14.

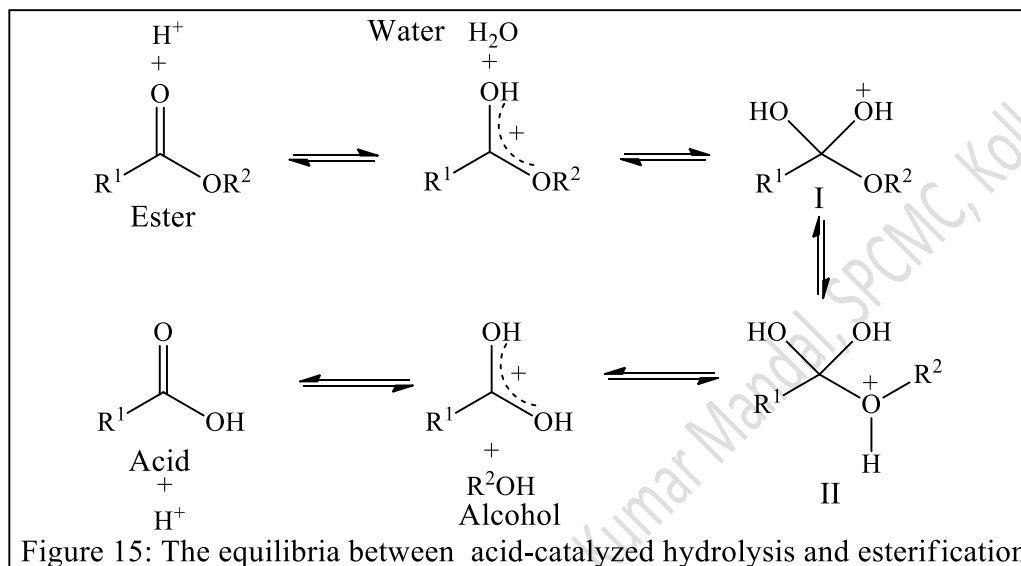


Acid-catalyzed hydrolysis and acid-catalyzed esterification are the reverse of each other, and so, according to the principle of microscopic reversibility the mechanism of acid catalyzed hydrolysis will be that of acid-catalyzed esterification, but in reverse. The rate law for acid-

catalyzed hydrolysis has been shown to be *second-order*, first-order in both ester and hydrogen ion concentration, i.e.,

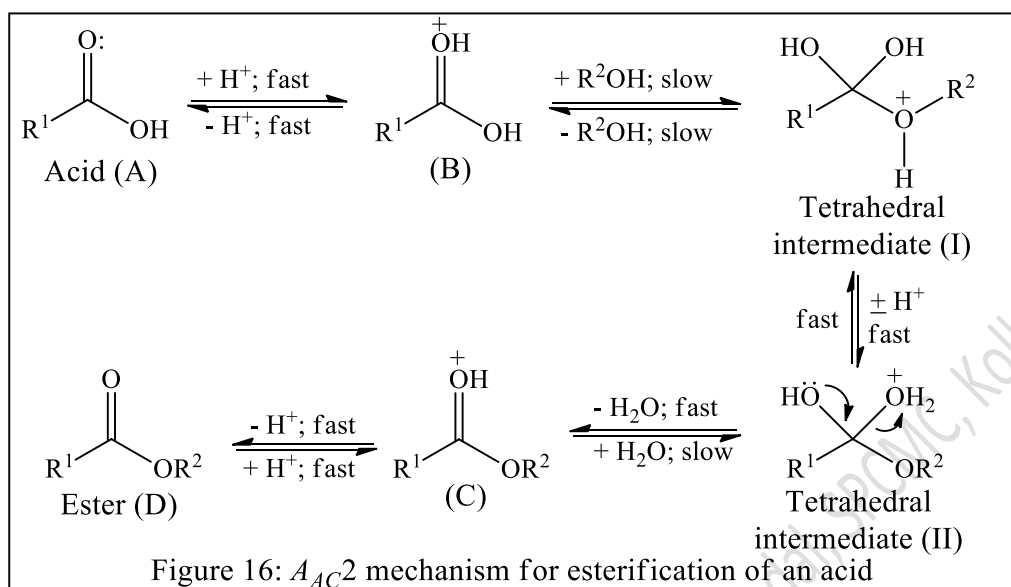
$$\text{Rate} = k [\text{ester}] [\text{H}_3\text{O}^+]$$

Any evidence about one reaction must apply to both hydrolysis and esterification. The mechanism for acid-catalyzed hydrolysis and esterification is contained in the following equilibria (Figure 15):



Mineral acid speeds up both processes by protonating carbonyl oxygen and thus rendering carbonyl carbon more susceptible to nucleophilic attack. In hydrolysis, the nucleophile is a water molecule and the leaving group is an alcohol and in esterification, the roles are exactly reversed. As in alkaline hydrolysis, a *tetrahedral intermediate* or, several of them is formed. The existence of more than one intermediate is required by the reversible nature of the reaction. Looking only at hydrolysis, intermediate (II) is likely, since it permits separation of the weakly basic alcohol molecule instead of the strongly basic alkoxide ion; but consideration of esterification shows that intermediate (II) must be involved, since it is the product of attack by alcohol on the protonated acid.

$A_{AC}2$ Mechanism of Esterification of a Carboxylic Acid



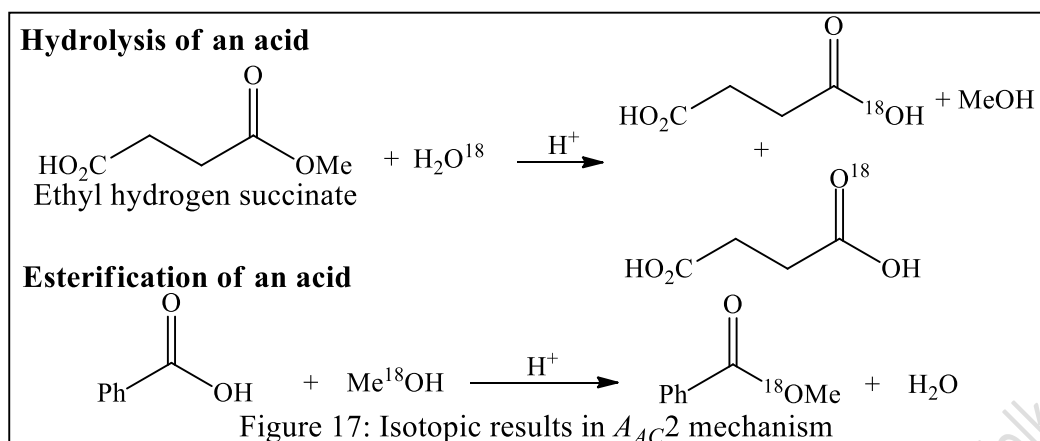
The evidence for the mechanism is much the same as in alkaline hydrolysis. The position of cleavage, R^1CO-OR^2 and R^1CO-OH , has been shown by ^{18}O studies of both hydrolysis and esterification. The existence of the *tetrahedral intermediates* was demonstrated, as in the alkaline reaction, by ^{18}O exchange between the carbonyl oxygen of the ester and the solvent.

The equilibrium is normally displaced in the desired direction by using an excess of alcohol, R^2OH (or of H_2O for hydrolysis). This mechanism is generally referred to as $A_{AC}2$ (Acid-catalyzed, acyloxy-oxygen cleavage, bimolecular). Acid catalysis also has the effect of promoting the loss of the leaving group, i.e., it is easier to lose H_2O from tetrahedral intermediate (II) in esterification reaction – or alcohol (R^2OH) from the tetrahedral intermediate (I) for hydrolysis–than it is to lose from the tetrahedral intermediate formed in $B_{AC}2$ mechanism of hydrolysis.

The formation of a tetrahedral intermediate (an associative process) in the rate-determining step ($C \rightarrow$ intermediate II, for hydrolysis) is borne out by the activation parameters observed for acid-catalyzed hydrolysis of a simple ethanoate ester: $\Delta H^\ddagger = 75 \text{ kJ mol}^{-1}$; $\Delta S^\ddagger = -105 \text{ JK}^{-1} \text{ mol}^{-1}$.

Evidence in Favour of $A_{AC}2$ Mechanism of Esterification of an Acid and Hydrolysis of an Ester

It is observed (Ingold, 1939) that the acid-catalyzed hydrolysis of methyl hydrogen succinate in water enriched with ^{18}O gave methanol with no extra ^{18}O . Again, esterification (Roberts, 1938) of benzoic acid with methanol enriched with ^{18}O gave water not enriched with ^{18}O . Thus, in the reactions, hydrolysis and esterification, respectively, acyl-oxygen heterolysis must have occurred (Figure 17).



Effect of Substituents on the Rate of Esterification and Hydrolysis

It should be noted that the *rate-determining step* for esterification is the addition of alcohol, whereas that for hydrolysis is the addition of water. In both cases, the *rate-determining step* involves change of hybridization of the carbon atom of the carbonyl group from sp^3 to sp^2 , and consequently steric retardation can be expected to increase as R^1 increases in size. Table 3 shows the relative rates for the esterification with methanol.

Steric Effect				
Acid	MeCO_2H	$n\text{-PrCO}_2\text{H}$	$\text{Me}_3\text{CCCO}_2\text{H}$	$\text{Et}_3\text{CCO}_2\text{H}$
Relative rates	1.0	0.51	0.037	0.00016

Solve the Problems

Problem 1: The relative rates of alkaline hydrolysis of ethyl p -substituted benzoates, $p\text{-GC}_6\text{H}_4\text{CO}_2\text{Et}$, are:

	$\text{G} = \text{NO}_2$	$>$	Cl	$>$	H	$>$	Me	$>$	OCH_3
Relative rates	110		4		1		0.5		0.2

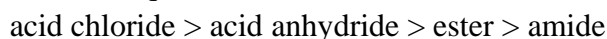
- How do you account for this order of reactivity? (b) What kind of effect, activating or deactivating, would you expect from $p\text{-Br}$? From $p\text{-NH}_2$? From $p\text{-CMe}_3$?
- Predict the order of reactivity toward alkaline hydrolysis of: p -aminophenyl acetate, p -methylphenyl acetate, p -nitrophenyl acetate, phenyl acetate.

Problem 2: The relative rates of alkaline hydrolysis of alkyl acetates, $\text{CH}_3\text{CO}_2\text{R}$, are:

	$\text{R} = \text{Me}$	$>$	Et	$>$	Me_2CH	$>$	Me_3C
Relative rates	1		0.6		0.15		0.08

- a) What two factors might be at work here?
- b) Predict the order of reactivity toward alkaline hydrolysis of: methyl acetate, methyl formate, methyl isobutyrate, methyl propionate, and methyl trimethylacetate.

Problem 3: Exchange experiments show that the fraction of the tetrahedral intermediate that goes on to products follows the sequence:



What is one factor that is probably at work here?

Problem 4: Write the steps to account for exchange between $\text{R}^1\text{C}^{18}\text{O}_2\text{R}^2$ and H_2O in acidic solution. There is reason to believe that a key intermediate here is identical with one in alkaline hydrolysis. What might this intermediate be?

Problem 5: Account for the fact that the presence of bulky substituents in either the alcohol group or the acid group slows down both acid-catalyzed esterification and hydrolysis.

Problem 6: The electronic effect of G on the rate of acid-catalyzed hydrolysis of ethyl *p*-substituted benzoates, $p\text{-GC}_6\text{H}_4\text{CO}_2\text{Et}\cdot\text{R}^1\text{CO}_2\text{R}^2$, is nil or absent. Justify the statement.

Problem 7: The electronic effect of G on the rate of acid-catalyzed esterification of *p*-substituted benzoic acid, $p\text{-GC}_6\text{H}_4\text{CO}_2\text{H}$, is nil or absent. Justify the statement.

Problem 8: Acidic hydrolysis of *tert*-butyl acetate in water enriched in ^{18}O has been found to yield *tert*-butyl alcohol enriched in ^{18}O and acetic acid containing ordinary oxygen. Acidic hydrolysis of the acetate of optically active 3,7-dimethyl-3-octanol has been found to yield alcohol of much lower optical purity than the starting alcohol, and having the opposite sign of rotation, (a) How do you interpret these two sets of results? (b) Is it surprising that these particular esters should show this kind of behavior?