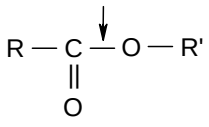
Mechanisms of Ester hydrolysis

[Ref: Jerry March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 2nd edn., McGraw-Hill, 1977, p 349-53]

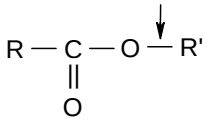
Reaction of an acid with an alcohol in presence of traces of a mineral or Lewis acid to give an ester as product is called **esterification**. The reverse reaction, i.e., the splitting of an ester into the component acid and alcohol is known as **ester hydrolysis**. *In principle, these reactions are reversible, and both reactions can be catalysed either by acids or bases*. The acid catalysed hydrolysis reactions are also **symmetric**, meaning that it is only necessary to reverse the steps to get the mechanism for esterification.But hydrolysis is usually favoured by base catalysis, because the acid formed is removed as the salt, thus driving the reaction forward to completion. They are not reversible in practice, and therefore indicated by arrows in the forward direction only.

Since **base-catalysed hydrolysis of oils and fats** [oils and fats = triglycerides = esters of long-chain (fatty) acids with glycerol] to give salts of fatty acids (= soap) is the crux of the soap industry, the base-catalysed ester hydrolysis is generally known as **saponification** (= soap-making) among the industrial community.

Ingold has classified the esterification-hydrolysis reactions from a mechanistic point of view. In all, there can be eight different mechanisms operating. These are given in a tabular form on the next page. Special terminology such as $A_{AC}1$, $B_{AL}2$ etc. have been used by Ingold to differentiate these possible mechanisms. In these terms, 'A' stands for 'acid-catalysed', and 'B' for 'base-catalysed'. 'AC' stands for breaking of the bond at the 'acyl' carbon, and 'AL' for breaking of the bond at the 'alkyl' carbon. (Acyl carbon is the carbon on the acid part while alkyl carbon is the one on the alcohol part). '1' represents a 'unimolecular' mechanism and '2' represents 'bimolecular' (look at the slow step). Thus $A_{AC}1$ is read as "acid-catalysed acyl cleavage unimolecular", and $B_{AL}2$ as "base-catalysed alkyl cleavage bimolecular" etc.



Acyl cleavage (AC)



Alkyl cleavage (AL)

The following general points are useful:

(1) Sterically hindered esters are very difficult to hydrolyse.

(2) Acyl bond-breaking is observed to be easier than alkyl bond-breaking.

(3) There is much evidence to show that of the two oxygen atoms available, protonation usually takes place only on the acyl oxygen atom.

(4) $A_{AC}1$ and $A_{AC}2$ mechanisms are simply called A1 and A2 respectively by some authors.

Proof in favour of acyl cleavage are the following:

(1) When hydrolysis is carried out using H_2O^{18} (oxygen-labelled water), the O^{18} appears in the acid part of the product and not in the alcohol.

(2) On hydrolysis, esters with chiral R' groups give alcohols with **retention** of configuration, indicating that the O-R' bond is not broken.

(3) Esters with allylic alcohol part do not undergo allylic rearrangement on hydrolysis.

(4) Neopentyl R' does not undergo rearrangement on hydrolysis.

Discussion:

$A_{AC}1$: This mechanism for acid-catalysed ester hydrolysis occurs only in rare cases, where R is very bulky and a bimolecular step is sterically hindered. This mechanism has been demonstrated for esters of 2,4,6-trimethyl benzoic acid (mesitoic acid). Mesitoic acid depresses the freezing point of sulphuric acid four times as much as that predicted from its molecular mass, indicating the following ionization scheme producing four particles from one acid molecule:

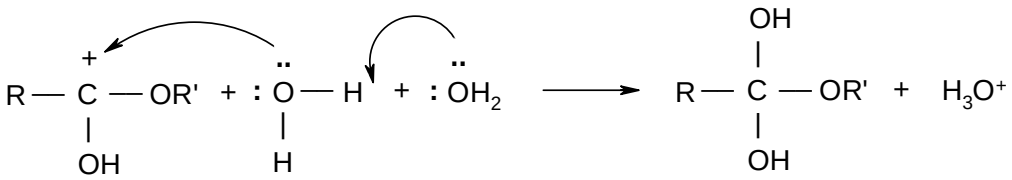
$$ArCOOH + 2\,H_2SO_4 \longleftrightarrow ArCO^+ + H_3O^+ + 2\,HSO_4^-$$

But on the other hand, benzoic acid gives only twice the predicted depression:

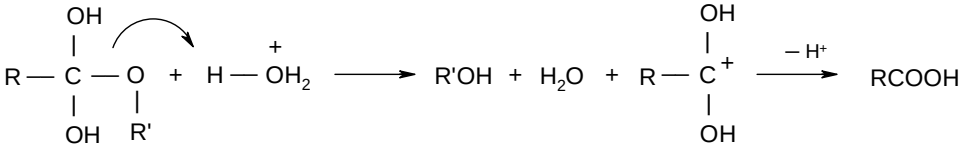
$$ArCOOH + H_2SO_4 \longleftrightarrow ArCOOH_2^+ + HSO_4^-$$

This indicates the formation of the acyl carbonium ion in the case of mesitoic acid, but not for benzoic acid. Another proof is provided by the observation that mesitoic acid is formed when a solution of methyl mesitoate in sulphuric acid is poured into water, but benzoic acid is not obtained from methyl benzoate under similar conditions.

$A_{AC}2$: This is the most common mechanism for acid-catalysed ester hydrolysis. It proceeds through a tetrahedral intermediate and acyl cleavage. It has been concluded that this mechanism will actually require two molecules of water in the intermediate step, one molecule acting as a proton donor as well as a nucleophile at the same time:



If this is the case, then the protonated derivatives (c) and (d) will not appear. ***Termolecular processes*** (processes in which three molecules collide at the same time) are rare, but in this case the water molecules are already connected by a *H*-bond. To maintain symmetry of the process, the reaction will then continue as follows:

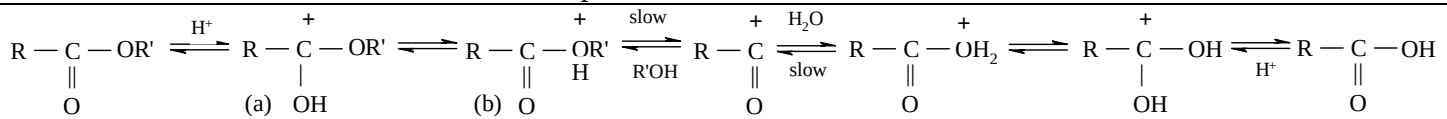
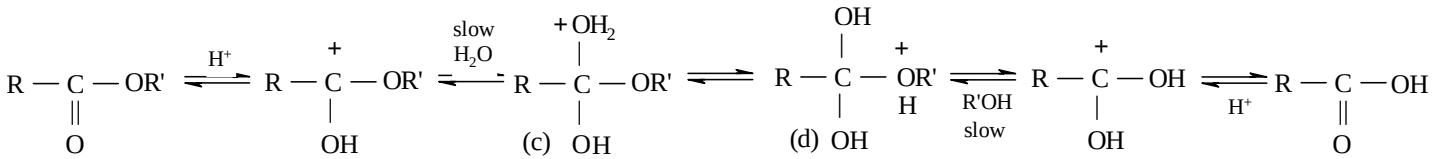
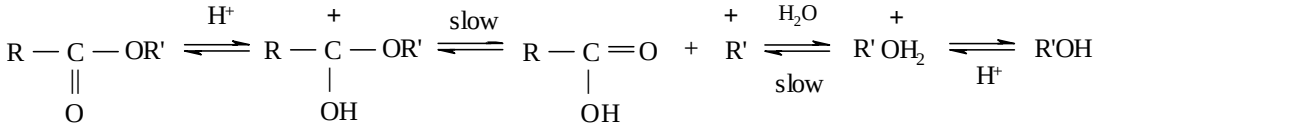
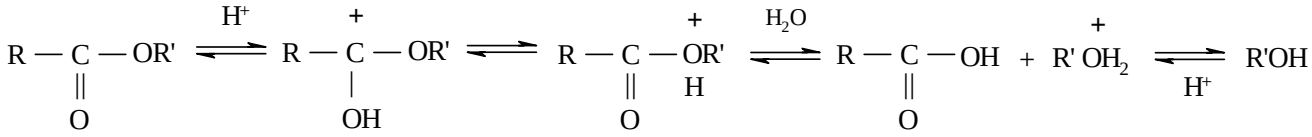
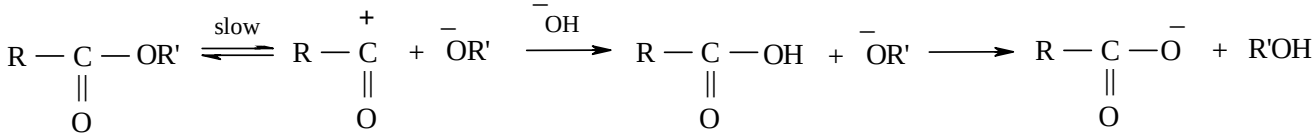
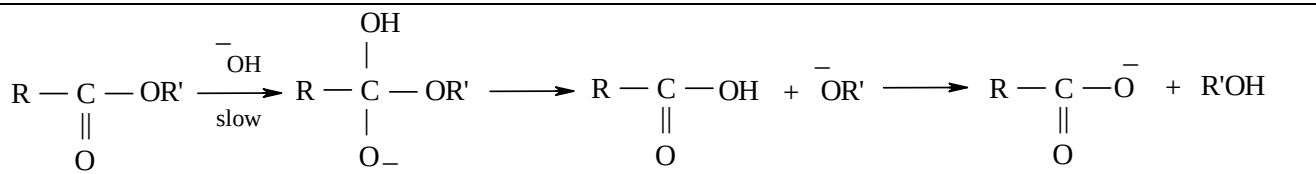
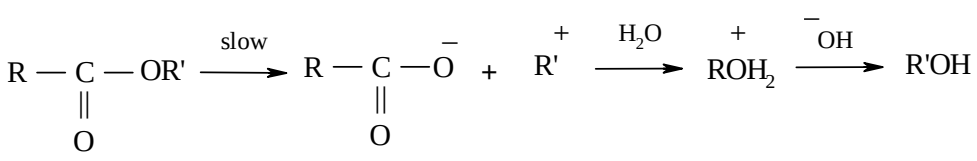
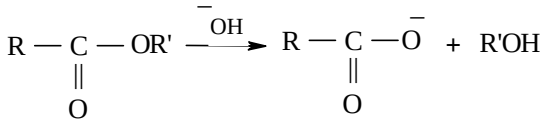


$A_{AL}1$: This mechanism occurs very readily when R' easily comes off as a stable carbonium ion, ie., when R' is tertiary alkyl, allyl, benzyl etc. This is the common mechanism for acid hydrolysis of esters of tertiary alcohols. This mechanism has been confirmed by kinetic studies, ^{18}O labeling and isomerisation in R'. Secondary and benzylic acetates hydrolyse by the $A_{AC}2$ mechanism in dilute sulfuric acid, but the mechanism is $A_{AL}1$ in concentrated acid.

$A_{AL}2$: This mechanism has not actually been observed in ester hydrolysis. This is probably because it requires water to act as a nucleophile in an S_N2 process, and is quite unlikely to happen.

$B_{AC}1$: This mechanism has also not actually been observed in ester hydrolysis. This may be because it is an S_N1 mechanism in which OR' acts as a leaving group, which is extremely unlikely.

$B_{AC}2$: This is the most common mechanism for base-catalysed ester hydrolysis, and proceeds through a tetrahedral intermediate with acyl cleavage.

Class		Name	Type	Steps involved in the reaction
Acid catalysis	Acyl cleavage	$A_{AC}1$	S_N1	
		$A_{AC}2$	Tetra hedral	
	Alkyl cleavage	$A_{AL}1$	S_N1	
		$A_{AL}2$	S_N2	
Base catalysis	Acyl cleavage	$B_{AC}1$	S_N1	
		$B_{AC}2$	Tetra hedral	
	Alkyl cleavage	$B_{AL}1$	S_N1	
		$B_{AL}2$	S_N2	

$B_{AL}1$: This mechanism also occurs very readily when R' easily comes off as a stable carbonium ion as in the case of $A_{AL}1$ mechanism. This mechanism occurs only in neutral or weakly basic solutions, where the rate of attack by OH^- is so slow such that the normally unlikely unimolecular mechanism takes over. Under such conditions, this mechanism has been confirmed by kinetic studies, ^{18}O labeling and isomerisation in R'.

$B_{AL}2$: This mechanism is also very rare because it requires OH^- to attack an alkyl carbon when an acyl carbon is also available. But it has been observed in the hydrolysis of β-lactones under neutral conditions, because cleavage of the C—O bond opens the four-membered ring and relieves strain. It is also observed in the alkaline hydrolysis of methyl 2,4,6-*tri-t*-butyl benzoate (again probably due to relief of strain), and in the unusual reaction:

$$ArCOOMe + RO^- \longrightarrow ArCOO^- + \textbf{ROMe}\ (\text{an ether!})$$

When this mechanism is occurring, it is easy to detect, since this is the only mechanism which requires **inversion** of R'. It is quite evident in the last example because the ether cannot be formed in any other way.

Summary:

$A_{AC}2$ and $A_{AL}1$ are the common mechanisms for acid hydrolysis, the latter for R' which give stable carbonium ions and the former for practically all the rest. $A_{AC}1$ is rare, observed only in strong acid medium and sterically hindered R. $A_{AL}2$ has not been observed. For basic catalysis, $B_{AC}2$ is the most common. $B_{AL}1$ occurs only with R' which give stable carbonium ions, that too in weakly basic or neutral solutions. $B_{AL}2$ is very rare and $B_{AC}1$ has never been observed.