CARBONYL COMPOUNDS

PART-30, PPT-30, SEM-3

Part-30: Substitution at sp^2 Carbon (C=O System) (Part II)

CONTENTS

Dr. Kalyan Kumar Mandal

Associate Professor

St. Paul's C. M. College

Kolkata

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PART-30, PPT-30
Substitution at *sp*^{2} Carbon (C=O System) (Part II)

Unimolecular Acid-catalyzed Hydrolysis and Esterification with Acyl-Oxygen Heterolysis ($A_{AC}1$ Mechanism)

When the acid alkyl group, R^1 in $R^1CO_2R^2$, is sufficiently bulky, e.g., R_3C (A; Figure 1), the bimolecular hydrolysis via a *tetrahedral intermediate* is inhibited. This is because of the increasing degree of crowding that operates in the *transition state* of the reaction. In this case, a relatively rare, acid-catalyzed mechanism, $A_{AC}1$, is found to operate.

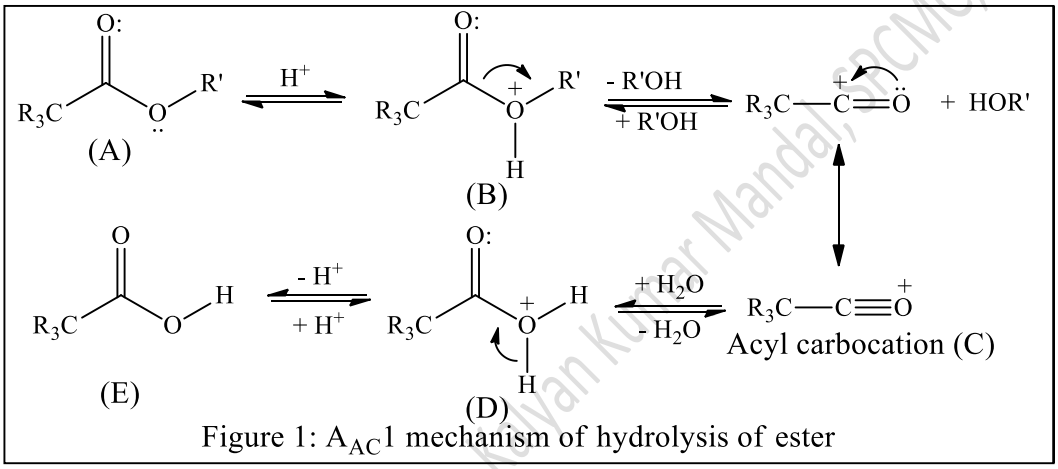


Figure 1: $A_{AC}1$ mechanism of hydrolysis of ester

This mechanism is commonly known as Acid-catalyzed, acyl-oxygen cleavage, unimolecular. It occurs only in powerful ionizing solvents. Exactly the same considerations apply to the esterification of hindered acids (C; Figure 1) in the reverse direction. It should be noticed that this mechanism requires protonation on the less favoured hydroxyl oxygen atom (D) to allow the formation of the acyl carbocationic intermediate (C).

Apart from a number of R_3C types, a very well-known example is 2,4,6-trimethylbenzoic (mesitoic) acid (A; Figure 2), which will not esterify under ordinary acid-catalysis conditions and nor will its esters (E; methyl mesitoate) hydrolysis. Let us consider the following observed results (M represents the mesityl group, 1,3,5-trimethylphenyl, in mesitoic acid, $Me_3C_6H_2CO_2H$):

(i) $PhCO_2H$ + MeOH	HCl →	$PhCO_2Me$	*occurs readily*
(ii) $PhCO_2Me + OH^-$	→	$PhCO_2^-$ + MeOH	*occurs readily*
(iii) MCO_2H + MeOH	→	*no reaction*	
(iv) $MCO_2Me + OH^-$	→	MCO_2^- + MeOH	*very slow*

It is observed (Hammett; 1937) that when methyl benzoate is dissolved in concentrated H_2SO_4 and the solution then poured into ice-cold water, almost all of the ester is recovered. On the other hand, methyl mesitoate, on the same treatment, gave a quantitative yield of

mesitoic acid. It is seen (Newman; 1941) that when a solution of mesitoic acid in concentrated H_2SO_4 is poured into cold methanol, methyl mesitoate is formed. This different behaviour of mesitoyl derivatives from benzoyl derivatives suggests that different mechanisms are operating in esterification and hydrolysis for these two sets of compounds.

Therefore, dissolving acid or ester in concentrated H_2SO_4 and pouring this solution into cold alcohol or water, respectively, is found to effect essentially quantitative esterification or hydrolysis and it can be concluded that the reaction proceeds via the acyl carbocation (C; acylium ion). The mechanism of this reaction is illustrated in Figure 2.

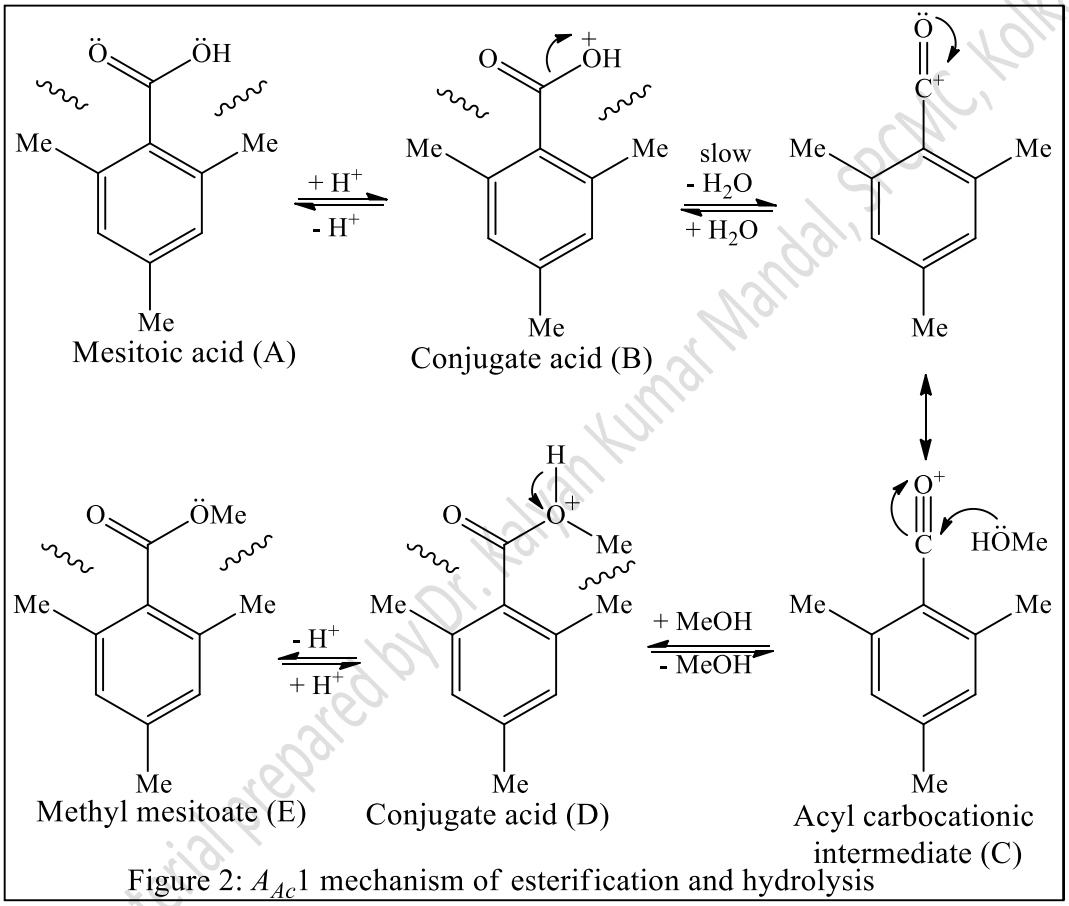


Figure 2: $A_{Ac}1$ mechanism of esterification and hydrolysis

Evidence for the formation of acylium ion is provided by the observation that while dissolution of unhindered benzoic acid (A; Figure 3), itself in concentrated H_2SO_4 results in the expected two-fold freezing point depression (the van't Hoff factor, i = 2), whereas dissolving of the hindered acid (C; mesitoic acid) results in four-fold depression (the van't Hoff factor, $i \approx 4$). The actual value of i that is observed here is 3.82. This slight shortfall from the expected value is due to incomplete protonation. The acylium ion is formed by acyl-oxygen heterolysis. Both the results are illustrated in Figure 3.

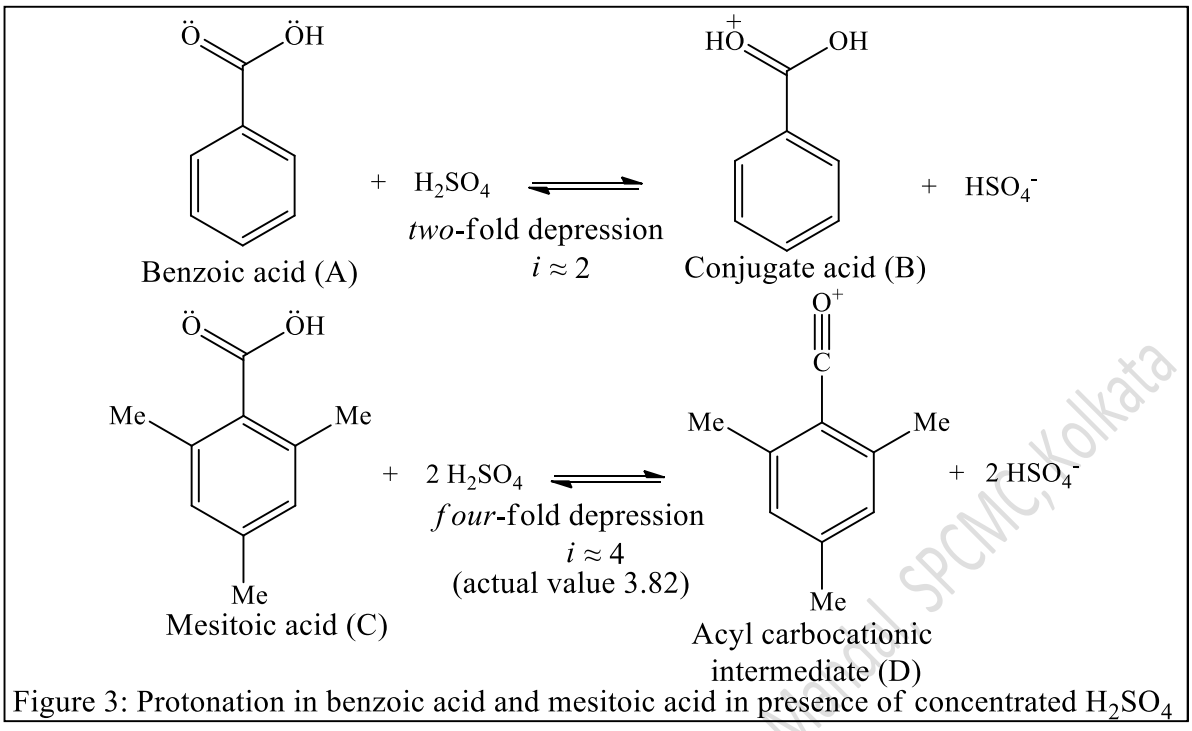


Figure 3: Protonation in benzoic acid and mesitoic acid in presence of concentrated H_2SO_4

If the trisubstituted acid, mesitoic acid, (A; Figure 4) were protonated in the normal position (on the carbonyl oxygen atom), the two bulky *o*-Me groups would force the two adjacent OH groups into a plane virtually at right angles to the plane of the ring as seen in (B) in Figure 4.

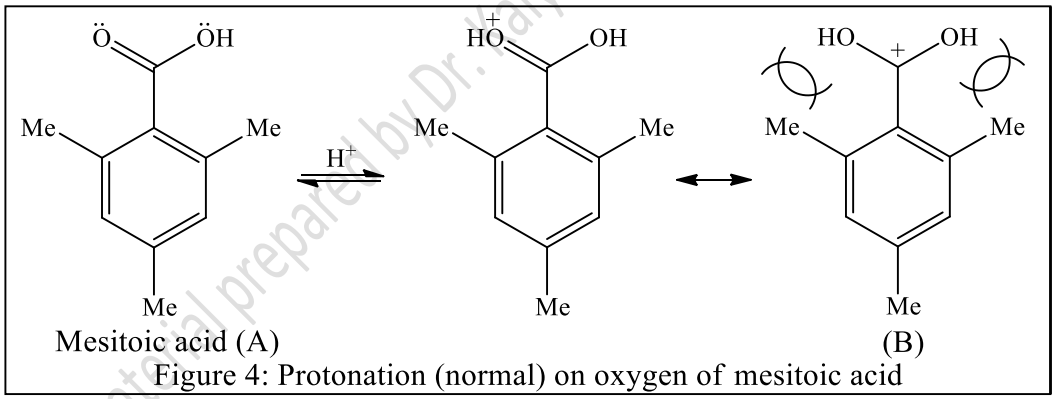
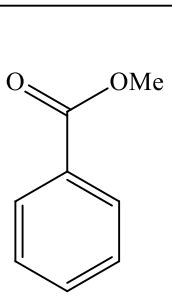
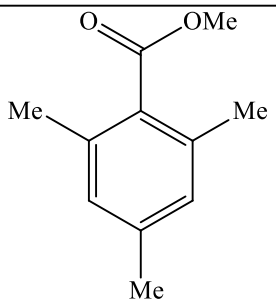


Figure 4: Protonation (normal) on oxygen of mesitoic acid

Nucleophilic attack on the cationic carbon atom by, for example, MeOH is thereby prevented from taking place from all directions. By contrast, abnormal protonation on the hydroxyl oxygen atom in mesitoic acid (A →B; Figure 2), allows formation (through loss of H_2O) of the planar acyl cation (C; acylium ion). Easy, unhindered attack on the cationic carbon atom by MeOH can now take place from either of two directions at right angles to the plane of the ring. Deprotonation from the resultant oxonium salt leads to the formation of the required ester.

Those two different pathways, $A_{AC}2$ and $A_{AC}1$ are indeed operating in acid-catalyzed hydrolysis of simple esters of (a) benzoic acid and (b) 2,4,6-trisubstituted benzoic acids, respectively, is borne out by the relevant activation parameters as shown in Figure 5.

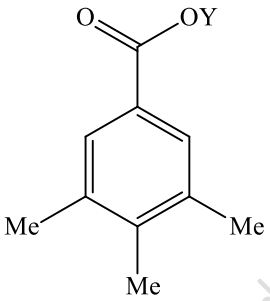




	Methyl benzoate (A)	Methyl mesitoate (B)
$\triangle H^{\ddagger}$ (kJ mol^{-1})	79	115
$\triangle S^{\ddagger}$ (kJ mol^{-1})	- 110 ($A_{AC}2$)	+ 57 ($A_{AC}1$)

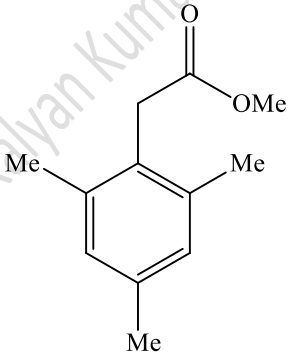
Figure 5: Activation parameters of $A_{AC}2$ (for methyl benzoate) and $A_{AC}1$ (methyl mesitoate) reaction

Therefore, the major factor responsible for this shift in reaction pathway from $A_{AC}2 \rightarrow A_{AC}1$ is indeed a steric one which can be demonstrated from the observation that the acids (A and C; Figure 6), and their simple esters (e.g., B and D), undergo ready esterification/hydrolysis by the normal $A_{AC}2$ mode.



Y = H; 3,4,5-Trimethyl-benzoic acid (A)

Y = Me; Methyl 3,4,5-trimethyl-benzoate (B)



Y = H; 2-Mesitylacetic acid (C)

Y = Me; Methyl 2-mesitylacetate (D)

Figure 6: Simple Acids and esters undergoing $A_{AC}2$ mode of esterification and hydrolysis, respectively

Furthermore, if the 2,4,6-triphenyl ester (A; Figure 7) is dissolved in concentrated H_2SO_4, the coloured 1,3-diphenylfluorenone (D) is formed very rapidly. This is obtained via ring-closure (intramolecular Friedel-Crafts acylation) of the acyl cation (C).

Reaction of Methyl 2,4,6-triphenylbenzoate with Concentrated H_2SO_4

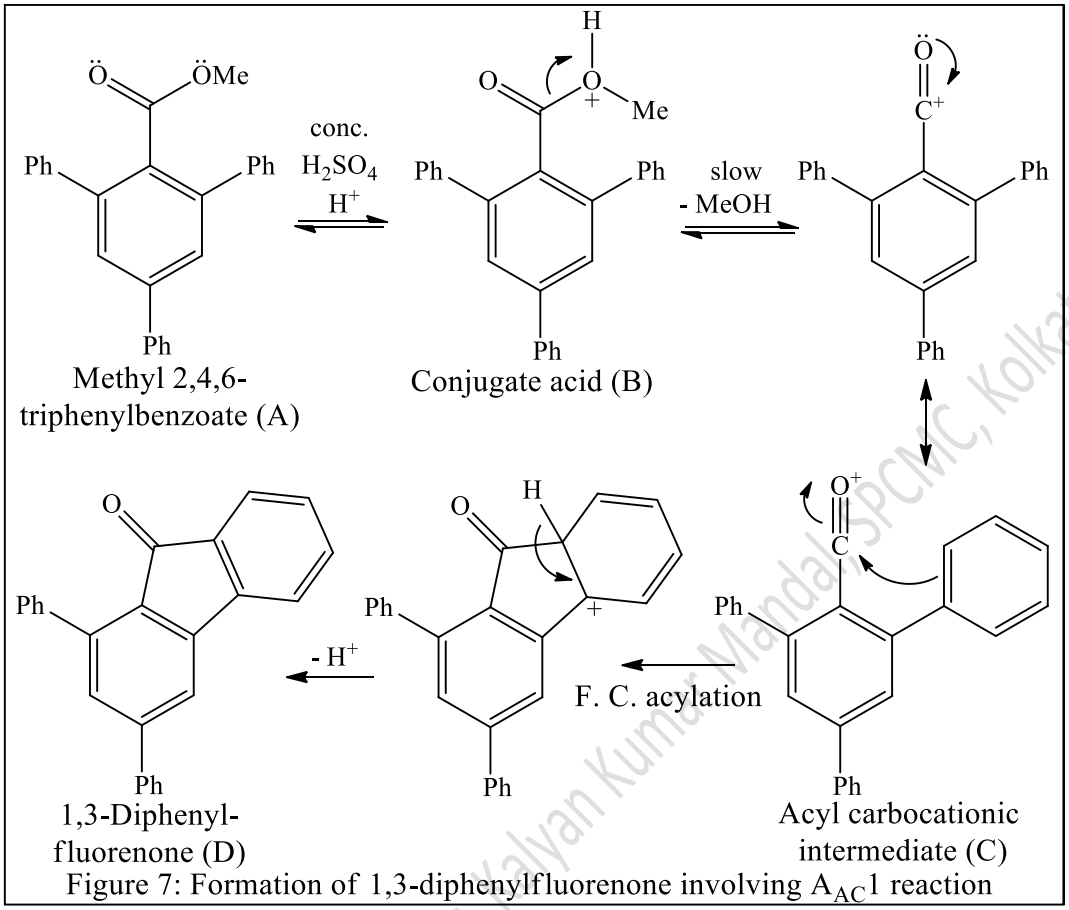


Figure 7: Formation of 1,3-diphenylfluorenone involving $A_{AC}1$ reaction

Unimolecular Acid-catalyzed Hydrolysis and Esterification with Alkyl-Oxygen Heterolysis ($A_{AL}1$ Mechanism)

Esters, $R^1CO_2R^2$, where the alkyl group R^2 can form a relatively stable carbocation, e.g., *t*-butyl carbocation (C) from *t*-butyl ester (A), have been shown to undergo alkyl-oxygen cleavage during the hydrolysis as illustrated in Figure 8.

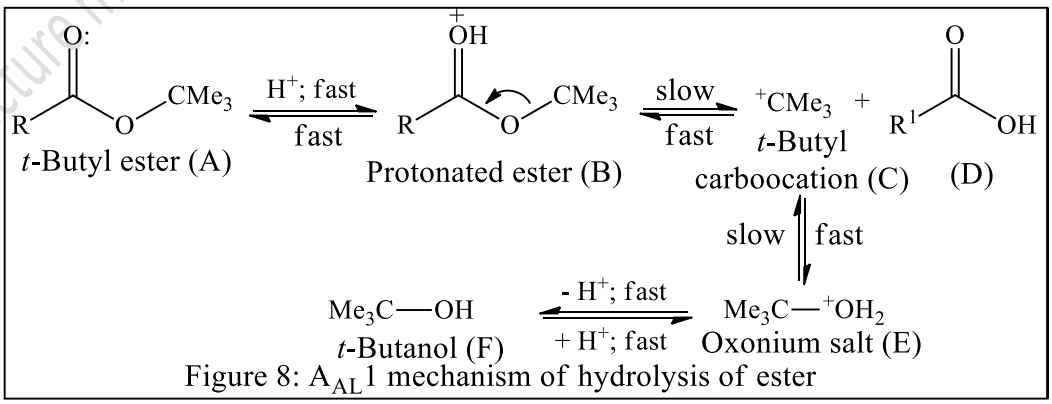


Figure 8: $A_{AL}1$ mechanism of hydrolysis of ester

The activation parameters for the acid-catalyzed hydrolysis of $MeCO_2CMe_3$ (*t*-butyl acetate) are found to be: $\Delta H^{\#}$ = 112 kJ mol^{-1}; $\Delta S^{\#}$ = + 55 JK^{-1} mol^{-1}. The now +ve value of $\Delta S^{\#}$ (indicating an increase in *translational entropy* in forming the *transition state* for the *rate-determining step*) suggests that this step is a dissociative process. This fact is illustrated in the reaction pathway shown in Figure 8 by breakdown of the protonated ester (B) into two separate species, the stable carbocation ($^{+}CMe_3$) and the carboxylic acid (D). This mechanism is generally referred to as $A_{AL}1$ (Acid-catalyzed, alkyl-oxygen cleavage, unimolecular). It also occurs with ester alkyl groups such as Ph_2CH, etc.

Evidence in Favour of $A_{AL}1$ Mechanism

Evidence for the $A_{AL}1$ mechanism was obtained for the esterification of acetic acid with optically active octan-2-ol in the presence of sulphuric acid that gave a large amount of the *racemized* product (Figure 9). Racemization is to be expected if an intermediate carbocation is formed, having enantiotopic faces, during the course of the reaction. The mechanism of this reaction is illustrated in Figure 10.

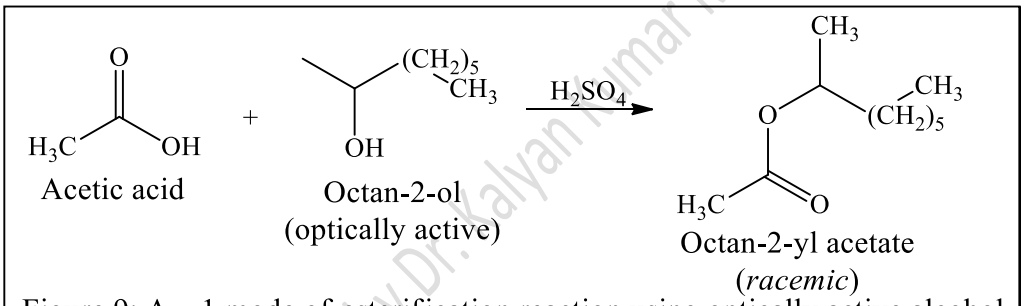


Figure 9: $A_{AL}1$ mode of esterification reaction using optically active alcohol

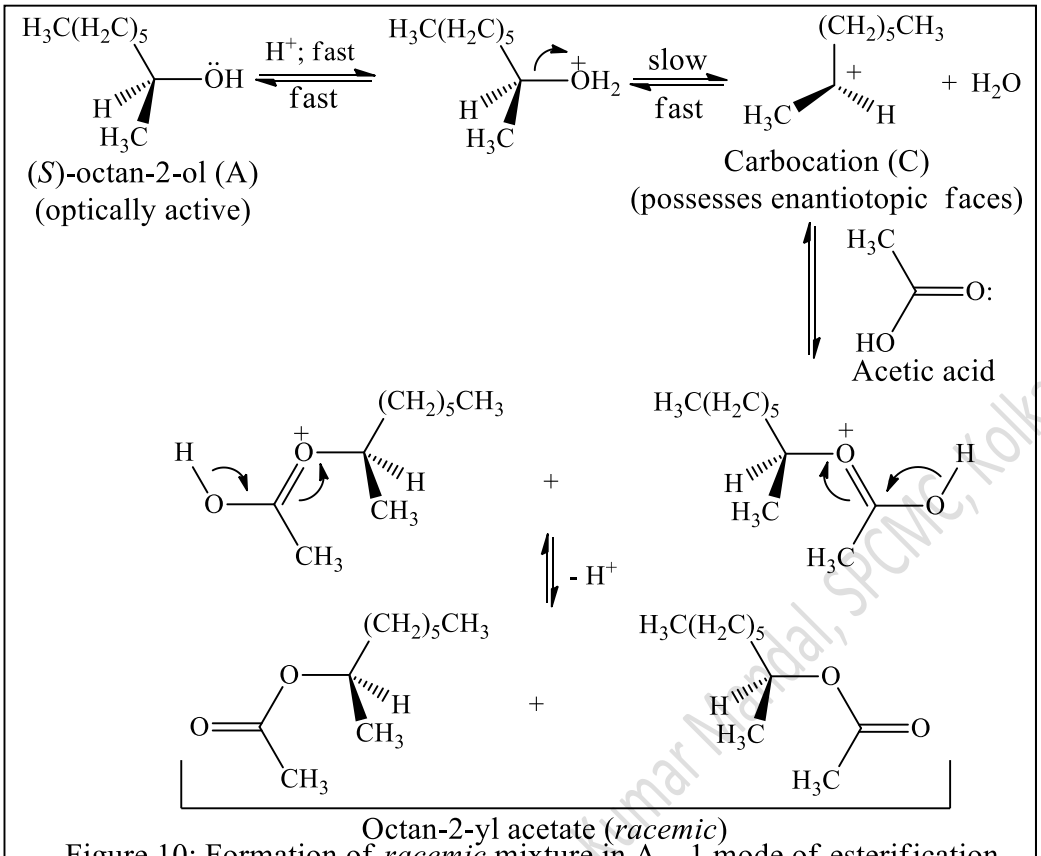


Figure 10: Formation of *racemic* mixture in $A_{AL}1$ mode of esterification reaction using optically active alcohol

Since all steps are reversible, the $A_{AL}1$ mechanism should, in principle, be possible for ester hydrolysis. Evidence for its occurrence has been obtained by the acid-catalyzed hydrolysis of *t*-butyl acetate in water enriched with ^{18}O and obtained *t*-butanol containing ^{18}O as shown in Figure 11.

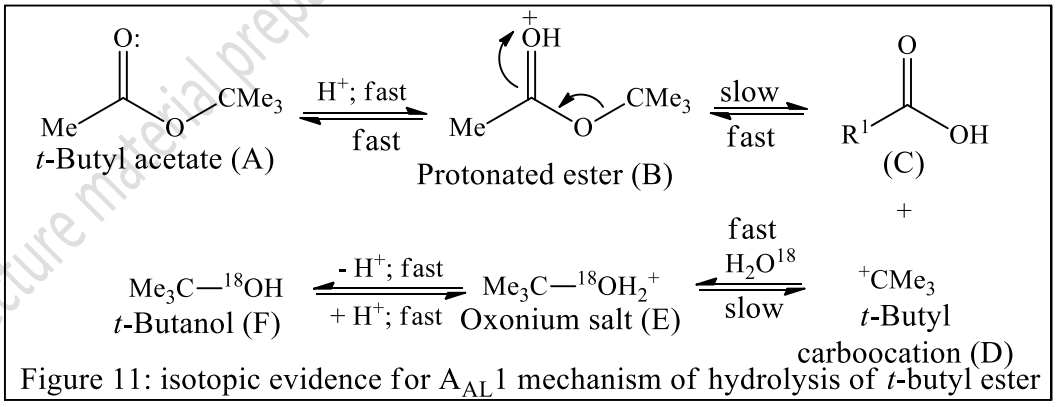


Figure 11: isotopic evidence for $A_{AL}1$ mechanism of hydrolysis of *t*-butyl ester

Hydrolysis of Carboxylic Acid Derivatives: Comparative Study

The contributing structures of an acid and its derivatives, such as, ester, anhydride, acid halide are shown in Figure 12.

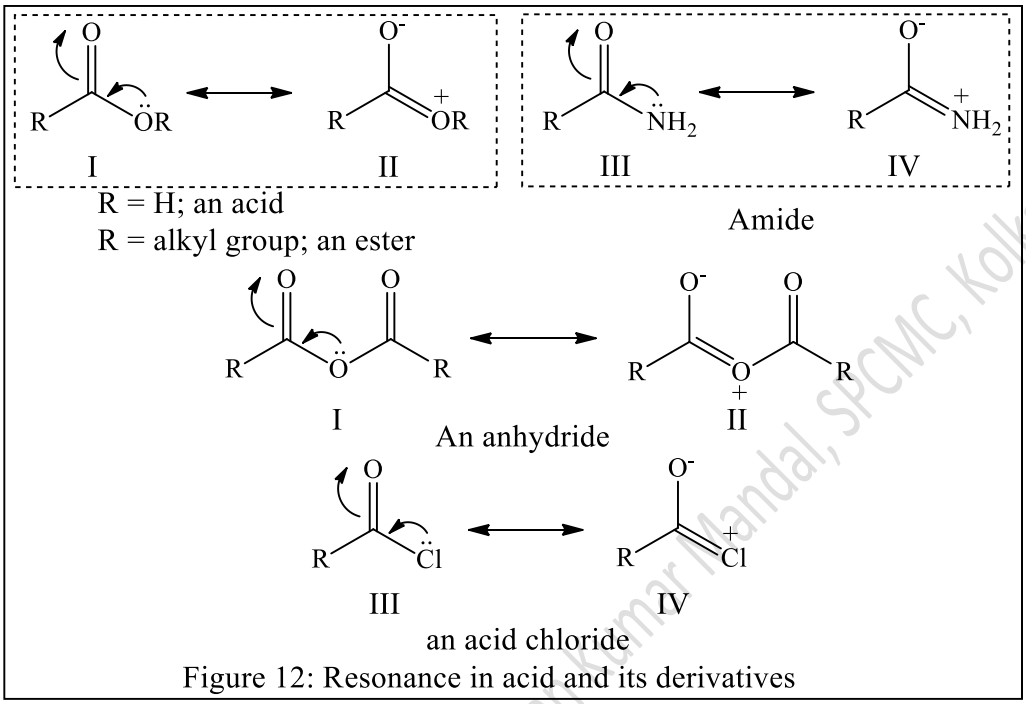
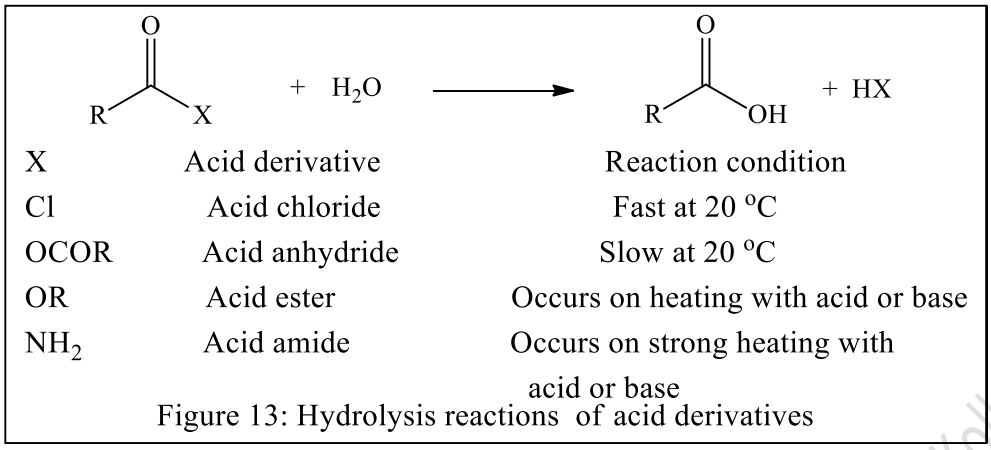


Figure 12: Resonance in acid and its derivatives

Nitrogen is less electronegative than oxygen, therefore, resonance is more effective in amide (R-CO-NH_2) than that in acid (R-CO-OH) or in ester (R-CO-OR´). This makes carbonyl carbon of an ester more electrophilic than that of an amide. Therefore, a simple ester undergoes nucleophilic substitution at the C=O carbon at a faster rate compared to that of an amide. As a result an ester hydrolyses at a faster rate than an amide. For acid anhydride, the system is cross conjugated and the anhydride carbonyl carbon is more electrophilic than that of an acid (RCO_2H), an acid ester ($RCO_2R´$) and an acid amide ($RCONH_2$). Consequently, rate of hydrolysis occurs faster in an anhydride compared to an ester and an amide.

Chlorine is more electronegative than nitrogen and in addition to that orbital size is incomparable between chlorine and carbon. Consequently, resonance is poor in acid chloride. This makes carbonyl carbon atom of an acid chloride extremely electrophilic, hence its rate of hydrolysis in fastest amongst the acid derivatives. Let us consider the hydrolysis reactions of various carboxylic acid derivatives in the general form (Figure 13):



X	Acid derivative	Reaction condition
Cl	Acid chloride	Fast at 20 ^{o}C
OCOR	Acid anhydride	Slow at 20 ^{o}C
OR	Acid ester	Occurs on heating with acid or base
NH_2	Acid amide	Occurs on strong heating with acid or base

Figure 13: Hydrolysis reactions of acid derivatives

Hydrolysis of Acid Chlorides

The reaction occurs by nucleophilic attack of water to the sp^2 C=O carbon, and proceeds through the formation of tetrahedral intermediate as shown in Figure 14.

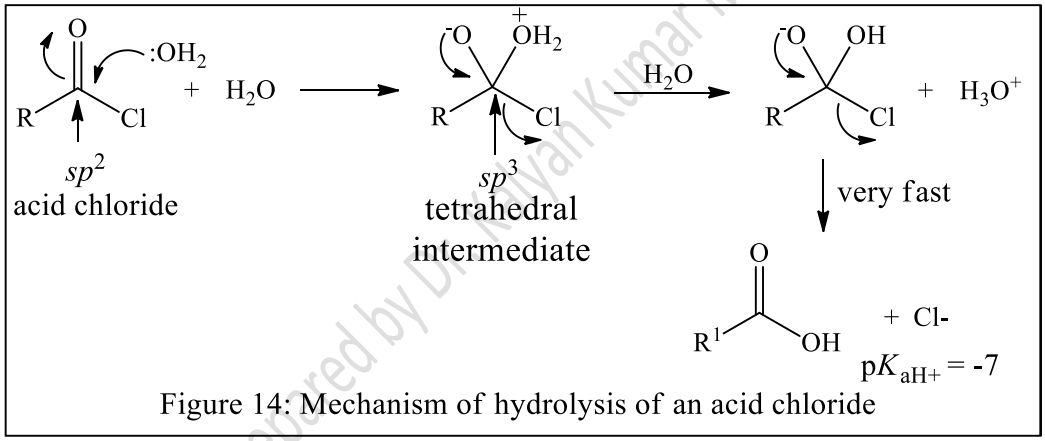


Figure 14: Mechanism of hydrolysis of an acid chloride

In the hydrolysis of an acid chloride, the leaving group (Cl^-) is the conjugate base of an extremely strong acid (HCl). Hence, collapsing of the tetrahedral intermediate occurs at a faster rate.

Hydrolysis of Acid Anhydrides

The reaction occurs by nucleophilic attack of water to the sp^2 C=O carbon, and proceeds through the formation of tetrahedral intermediate as shown in Figure 15.

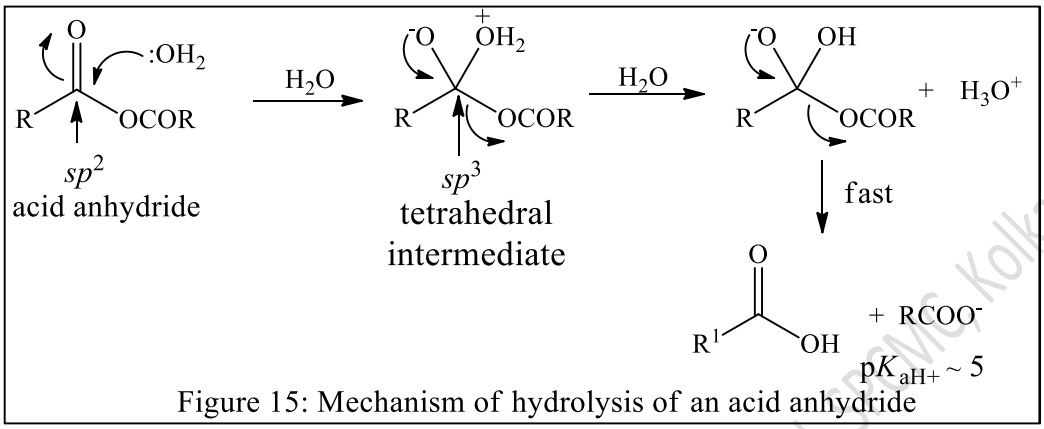


Figure 15: Mechanism of hydrolysis of an acid anhydride

The rate of hydrolysis of acid anhydride occurs at a slower rate than that of an acid chloride. This is because the leaving group RCO_2^- ($pK_{aH+} \sim 5$) is comparatively poorer than that of Cl^- ($pK_{aH+} \sim -7$).

Hydrolysis of Acid Amides

Unlike acid chlorides and acid anhydrides, hydrolysis of acid amides occurs at a slower rate and only proceeds by heating with acid or base catalyst. The mechanisms in two mediums are slightly different. In acidic medium protonation activates the carbonyl carbon towards nucleophilic (here, H_2O:) attack and the reaction proceeds through the formation of tetrahedral intermediate as shown in Figure 16.

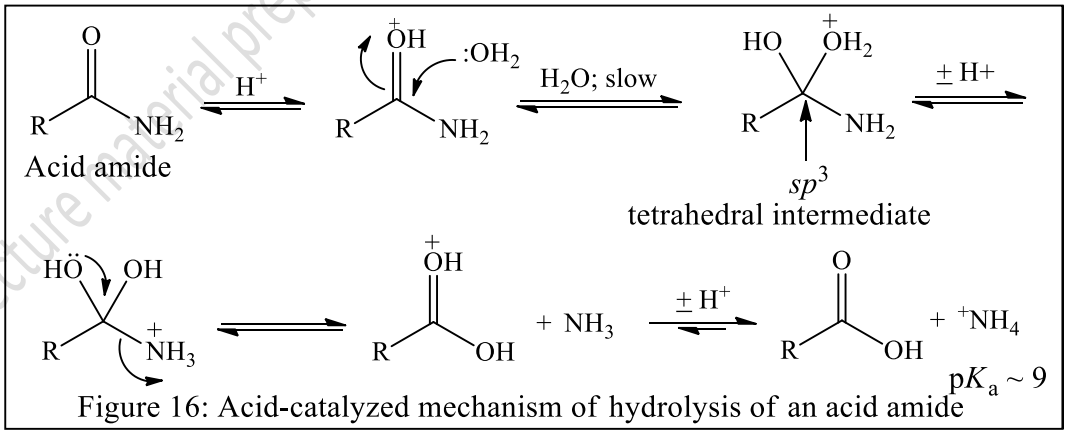


Figure 16: Acid-catalyzed mechanism of hydrolysis of an acid amide

The proton transfer at the final step converts NH_3 into NH_4^+ which is completely non-nucleophilic and hence, the reaction is driven towards completion. However, in base-catalyzed condition the reaction proceeds by nucleophilic attack of ^-OH to the sp^2 C=O carbon, and forms tetrahedral intermediate. The irreversible proton transfer in the last step drives the equilibrium towards completion (Figure 17).

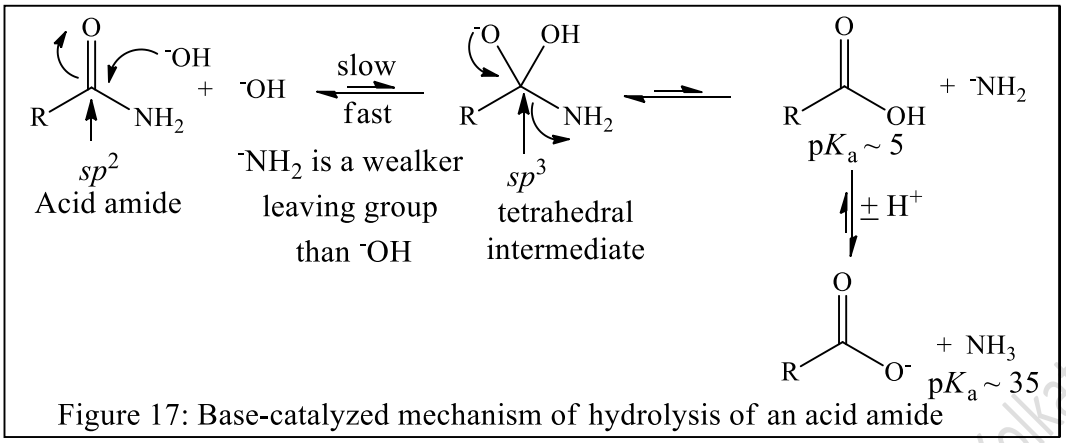


Figure 17: Base-catalyzed mechanism of hydrolysis of an acid amide

Preparation of Acid Chlorides

The general formula of the acyl groups is RCO-. Acid chlorides, which may be prepared by the replacement of the carboxyl group by chlorine, are also known as acyl chlorides because they contain the acyl group.

General methods of preparation

1. The acid chloride is heated with phosphorous trichloride or pentachloride, e.g.,

$$3RCO_2H + PCl_3 \rightarrow 3RCOCl + H_3PO_3$$

$$RCO_2H + PCl_5 \rightarrow RCOCl + HCl + H_3PO_3$$

The reaction with phosphorous trichloride is accompanied by the formation of small amounts of volatile phosphorous compounds:

$$RCO_2H + PCl_3 \rightarrow RCO_2PCl_2 + HCl$$

Preparation of Acid or Acyl Chlorides

Thionyl chloride ($SOCl_2$) may be used instead of the phosphorous chlorides:

$$RCO_2H + SOCl_2 \rightarrow RCOCl + SO_2 + HCl$$

The inorganic chloride is chosen according to the boiling point of the acyl chloride formed. Phosphorous acid (H_3PO_3) decomposes at 200 °C. The boiling point of phosphoryl chloride ($POCl_3$) is 107 °C, and that of thionyl chloride is 76 °C. Since acetyl chloride boils at 52 °C, any of the three inorganic halides may be used, but it is difficult to separate acetyl chloride from thionyl chloride (which is generally used in excess) by fragmentation. *n*-Butyryl chloride boils at 102 °C, and so phosphorus pentachloride cannot be used. Usually thionyl chloride is the most convenient.

The probable mechanism of the formation of acid chlorides from RCO_2H and PCl_3 is shown in Figure 18.

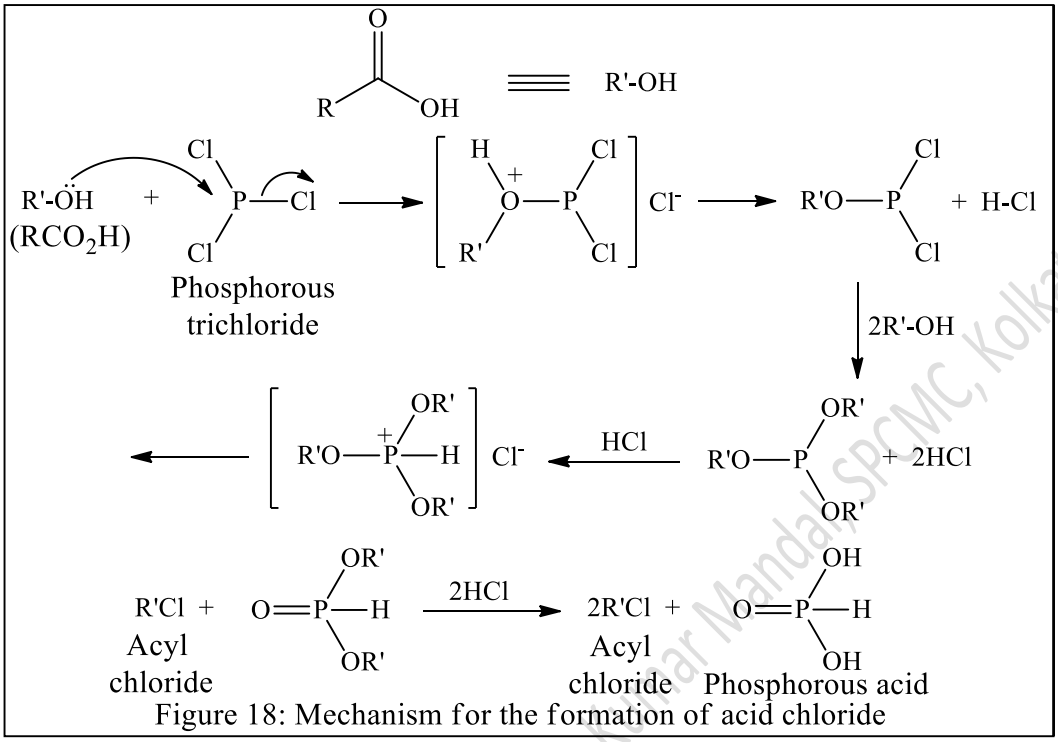


Figure 18: Mechanism for the formation of acid chloride

The mechanism of the formation of acid chlorides from RCO_2H and thionyl chloride ($SOCl_2$) is illustrated in Figure 19.

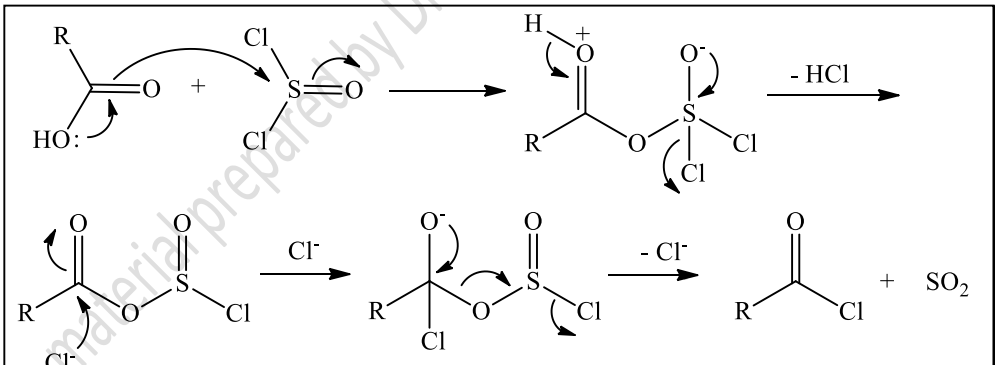


Figure 19: Formation of acid chloride using thionyl chloride

Preparation of acyl chloride is readily achieved by using oxalyl chloride (ClCO-COCl) (or bromide) as the acyl halide. The reaction is carried out with a catalytic amount of N,N-dimethylformamide (DMF). The reaction mechanism is illustrated in Figure 20.

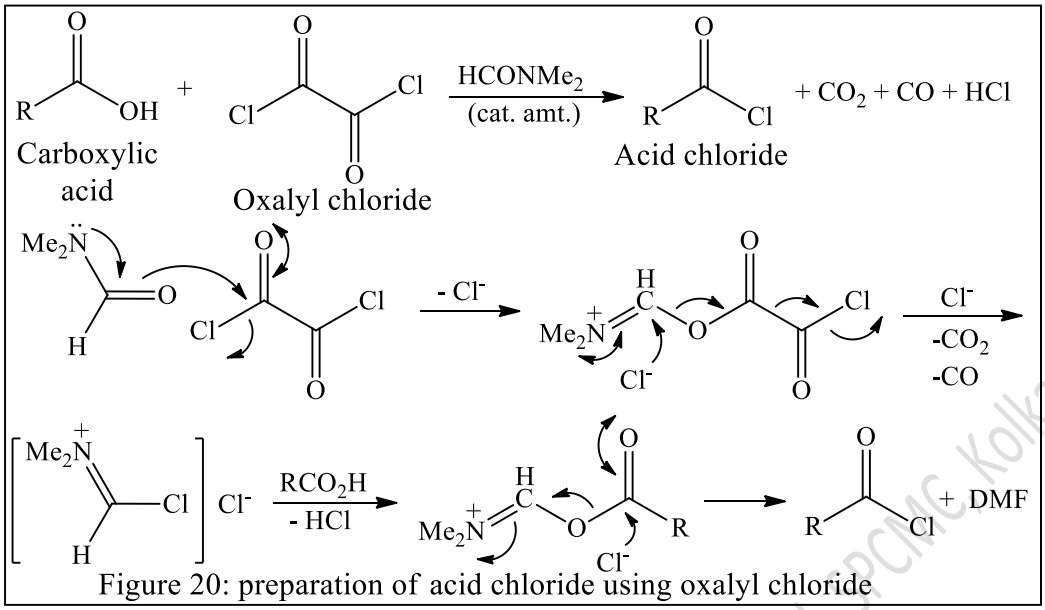


Figure 20: preparation of acid chloride using oxalyl chloride

The reaction of carboxylic acid with oxalyl chloride in presence of DMF involves conversion of DMF to the imidoyl chloride derivative ($Me_2N{=}CHCl^+$). The imidoyl chloride is the active chlorinating agent in this reaction. Use of thionyl chloride and oxalyl chloride has superseded that of PCl_5 as the by-product of using these reagents are gaseous and thus the reaction is easier to work-up. Oxalyl chloride (boiling point 64 ^oC) is prepared by treating oxalic acid with PCl_5.

Acyl halides undergo the halogen exchange reaction with acids. This occurs through the intermediate formation of the corresponding acid anhydride (Figure 21). This, therefore, offers a means of preparing acyl halides, however, the success of this reaction depends on displacement of the equilibrium to the right.

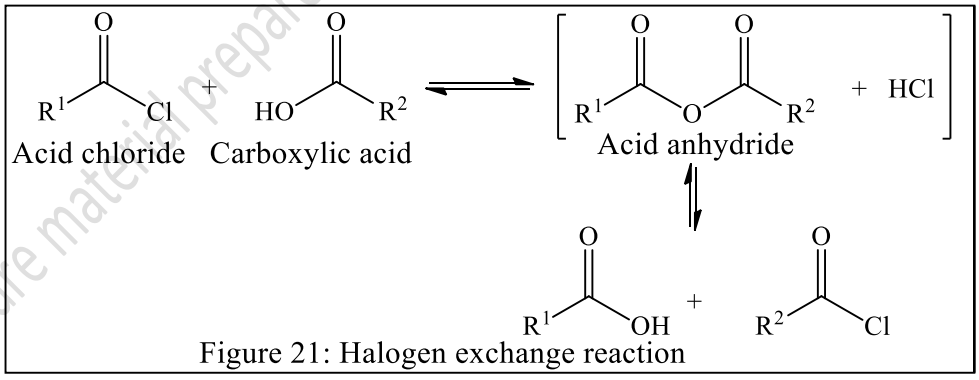


Figure 21: Halogen exchange reaction

Preparation of Acid Anhydrides

Acetic anhydride may be conveniently prepared by distilling a mixture of anhydrous sodium acetate and acetyl chloride.

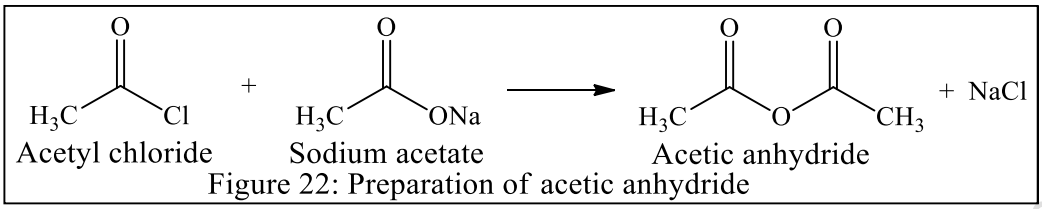


Figure 22: Preparation of acetic anhydride

Sodium salt of a carboxylic acid is used as the source of the nucleophilic carboxylic fragment to form a mixed anhydride, like acetic formic anhydride (Figure 23).

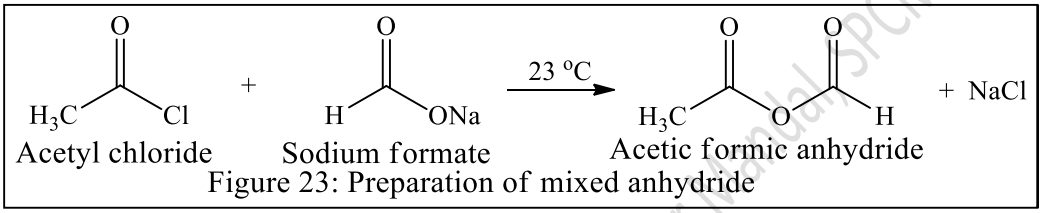


Figure 23: Preparation of mixed anhydride

Preparation of Acid Amide

Since acid amide is the least reactive member amongst the acid derivatives, it can be synthesized from either acid chlorides, acid anhydrides or from acid esters using ammonia or a properly substituted ammonia derivative as per requirement.

Method 1: By heating: Acid amide may be prepared by heating the ammonium salt of the acid:

$$RCO_2NH_4 \rightarrow RCONH_2 + H_2O$$

Since the ammonium salts tend to dissociate on heating, the reaction is best carried out in the presence of some free acid, which represses the hydrolysis and the dissociation of the ammonium salt.

Amides may also be prepared by heating an acid with urea:

$$RCO_2H + CO(NH_2)_2 \rightarrow RCONH_2 + CO_2 + NH_3$$

Method 2: By ammonolysis: Acid amides are conveniently prepared by the action of concentrated ammonia on acid chlorides, acid anhydrides or acid esters:

$$RCOCl + 2NH_3 \rightarrow RCONH_2 + NH_4Cl$$

$$(RCO)_2O + 2NH_3 \rightarrow RCONH_2 + RCO_2NH_4$$

$$R^1CO_2R^2 + NH_3 \rightarrow R^1CONH_2 + R^2OH$$

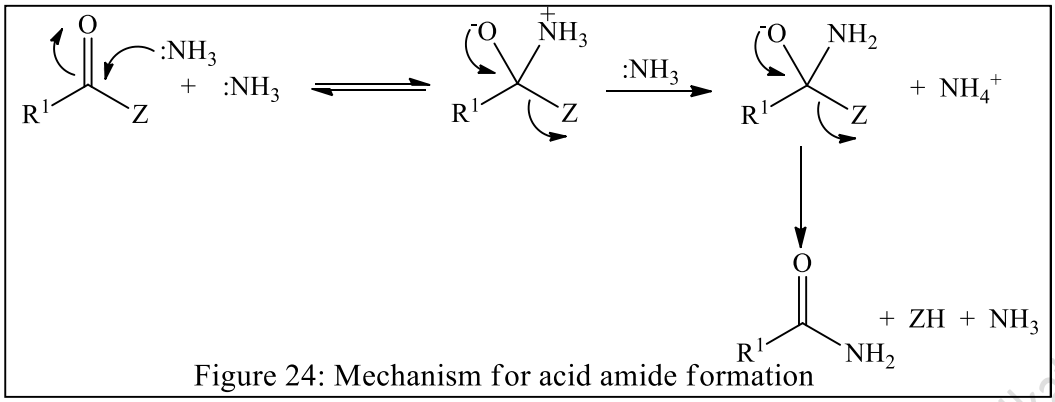


Figure 24: Mechanism for acid amide formation

Method 3: By hydrolysis: Acid amides may be prepared by the graded hydrolysis of alkyl cyanide. This may be carried out satisfactorily by dissolving the alkyl cyanide in concentrated H_2SO_4 and then pouring the solution into cold water, or by shaking the alkyl cyanide with cold concentrated HCl. The hydrolysis with polyphosphoric acid gives very good yields of acid amide.

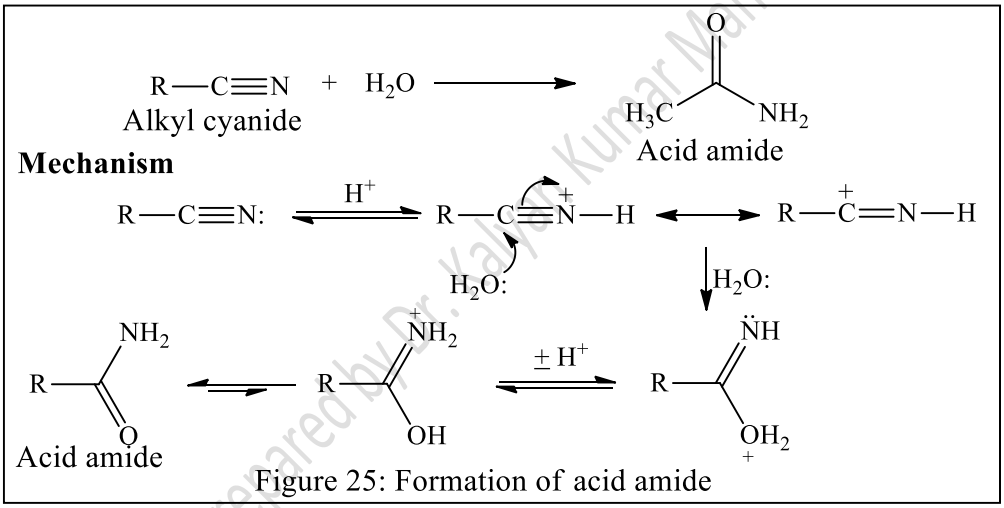


Figure 25: Formation of acid amide

Method 4: By hydrolysis: The conversion of alkyl cyanide into acid amide may also be effected by means of alkaline hydrogen peroxide. The possible mechanism of this reaction is shown in Figure 26.

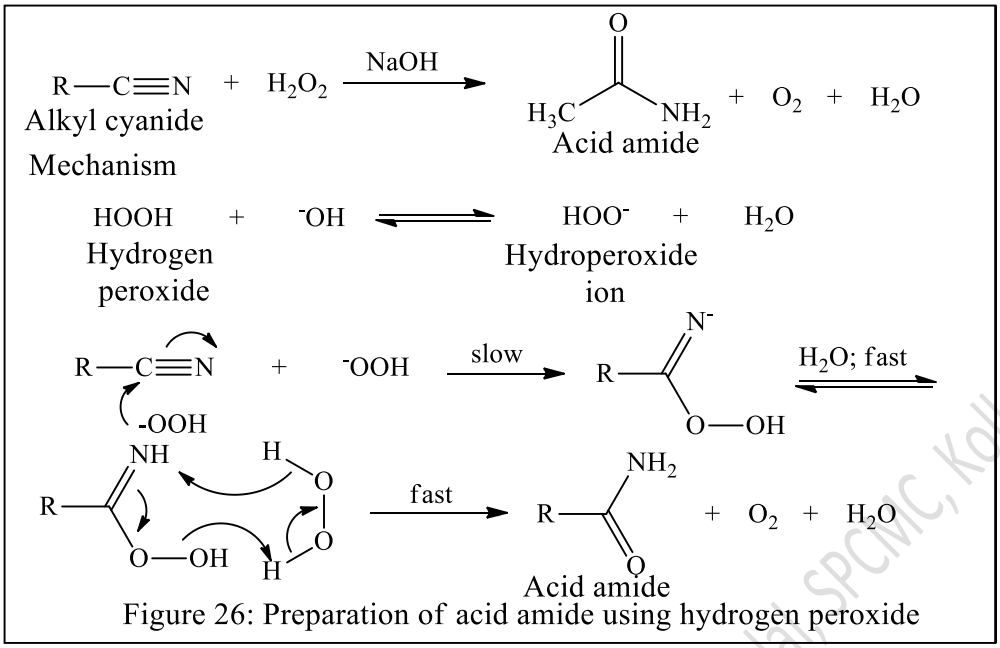


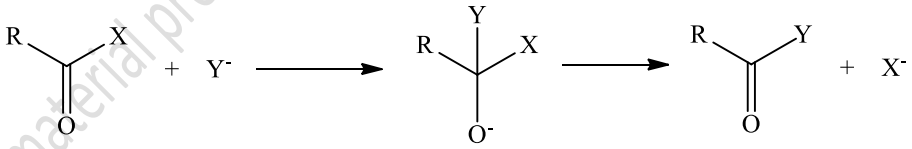
Figure 26: Preparation of acid amide using hydrogen peroxide

Solve the Problems

Problem 1: It is observed that electron-withdrawing substituents in the *m*- or *p*-positions enhance the rates of $B_{AC}2$ hydrolysis of substituted methyl benzoates while the effect is negligible for $A_{AC}2$ reactions.

Problem 2: Give the mechanism of alkaline hydrolysis of the following esters in ordinary water (H_2O^{16}) and indicate the distribution of ^{18}O in the products (i) PhCO-^{18}OEt; (ii) MeCO-^{18}OBu^t.

Problem 3: Consider the following reaction and explain the following questions:



a) The reaction rate is accelerated by acid.

b) The reaction rate though bimolecular at the first step is not essentially an S_N2 reaction.

c) What would be the mechanistic detail for the reaction when X is OR^- and Y is OH^-?

d) When R = Me, X = Et and Y = OH^-, what would be the fate of the reaction?