Lecture 31

Homogeneous catalysis

Contribution of homogeneous catalytic process in chemical industry is significantly smaller compared to heterogeneous catalytic process, it is only about 17-20 %. But importance of homogeneous catalysis is increasing significantly. The significance of homogeneous catalysis is growing rapidly particularly in the area of pharmaceutical and polymer industry. Some of the important industrial processes include:

1. Oxidations of alkenes such as production of acetaldehyde, propylene oxide etc.
2. Polymerization such as production of polyethylene, polypropylene or polyesters.

A new major development in homogeneous catalysis is the application of organometallic complexes as catalysts. The use of organometallic catalysts has revolutionized the homogeneous processes increasing economic viability. Another new area is bio-catalysis involving enzymes catalysts. Enzyme catalysts are highly selective and active for production of fine chemicals, pharmaceuticals etc. Enzyme catalysts are discussed in a separate section.

In homogeneous catalysis, all the reactants and catalysts are present in a single fluid phase and usually in the liquid phase. Homogeneous catalysts are the simple molecules or ions such as HF, H_2SO_4, Mn^{+2} as well as complex molecules such as organometallic complexes, macrocyclic compounds and large enzyme molecules.

Advantages

Advantages of homogeneous processes can be summarized as follows:

- In many reactions, homogeneous catalysts are more active and/or selective compared to heterogeneous catalysts.
- In homogeneous catalysis, the catalysts are molecularly dispersed within the fluid. Hence, pore diffusion limitations are absent. However, bulk phase mass transfer limitation may occurs.

— Catalytic chemistry and mechanism for homogeneous catalysis are better studied and understood. Therefore, it is easier to control and manipulate the process parameters.

Disadvantages

However, homogeneous processes are also associated with some major disadvantages which result in limited use of these processes. These disadvantages are summarized below:

– Homogeneous catalysts are stable only in relatively mild conditions which limit their applicability.

– Since the catalysts are molecularly dispersed in the phase as the reactant, products and solvents, the separation at end of the process is difficult and expensive. In many cases, it is not possible to recover the catalyst.

Types of reactions

Several homogeneous catalytic systems are :

1. Acid base catalysis
2. Catalysis by metal ions
3. Catalysis by organometallic complexes
4. Catalysis by Lewis acids
5. Catalysis by porphyrin complexes
6. Catalysis by enzymes

1. Catalysis by acids or bases

Acid –base catalysts are used in the following types of reactions:

i. Condensation
ii. Dehydration
iii. Hydrolysis
iv. Halogenations

Examples

a) Acid catalyzed condensation

i. Acid catalyzed condensation of phenol and acetone to bisphenol which is an important intermediate in the manufacture of epoxy resin and polycarbonates.

$$CH_3COCH_3 + 2\phi - OH + 2H^+ \longrightarrow OH - \phi - C(CH_3)_2 - \phi - OH + H_2O$$

ϕ = benzyl group

ii. Acid catalyzed synthesis of ethyl acetate ester from ethanol and acetic acid.

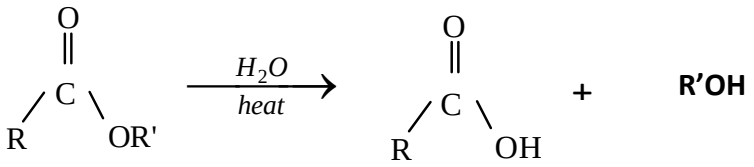
$$CH_3CH_2OH + CH_3COOH \rightleftharpoons CH_3COOCH_2CH_3 + H_2O$$

b) Acid catalyzed dehydration of ethyl alcohol to ethylene

$$CH_3CH_2OH \xrightarrow{H^+} CH_2 = CH_2 + H_2O$$

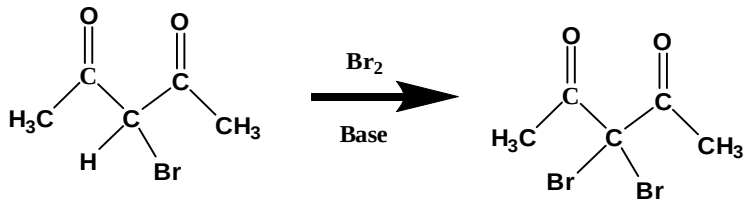
c) Hydrolysis of esters

i. Hydrolyses of carboxylic esters to form the parent carboxylic acid and an alcohol.



d) Acid or base catalyzed halogenation

Ketones can be halogenated in the presence of acid or base and X_2(X= Cl, Br).



2. Catalysis by Metal ion

Metal ions can act as catalysts. Metal ions function in different ways :

1. Metal ion can act as a "super acid". It introduces positive charge into the substrate, making it more susceptible toward nucleophilic attack.
2. Metal ions can also act as templates. Metal ions are able to coordinate to more than 2 ligands and thereby bring the molecules together.
3. Metal ions can act as redox catalysts. Many metal ions can accept or donate electrons by changing their oxidation state and thereby participate in redox reactions.

Examples

a) Catalysis by Cu^{2+} ions

Cu^{2+} ions are very effective catalysts for the hydrolysis of α-amino acid esters.

$$CHRNH_2 - COOCH_3 \xrightarrow[H_2O]{Cu^{2+}} CHRNH_2 - COOH + CH_3OH$$

b) Catalysis by Mg^{2+} ions

Hydrolysis of phosphate esters is catalyzed by metal ions, usually Mg^{2+}.

$$CH_3 - COOPO_3 \xrightarrow[H_2O]{Mg^{2+}} CH_3COOH + H_3PO_4$$

3. Catalysis by organometallic complexes

Presently, organometallic catalysts play major role in homogeneous catalysis. Organometallic complex consist of a central transition metal ion bonded to organic ligands such as $R_2C=CR_2$, RCO, R_3P, R_3N, CO etc. Catalysis occurs through dissociation

of ligands followed by co-ordination of reactant molecule to the metal ion. The transition metal ions react through exchange of d electrons. Organometallic complexes usually have octahedral or tetrahedral geometry. Reactions catalyzed by organometallic complexes include hydrogenation, hydroformylation, carbonylation and decarbonylation, hydrocarbon rearrangement, partial oxidations etc.

Effect of ligands

The nature of surrounding ligands is very important in organometallic catalysis and known as ligand effect. The product distribution depends on the ligand environment around the metal center. Using the same metal center, different products can be obtained with the same substrate when associated ligands are changed around the metal center.

Ligand types

Phosphine based ligands (PR_3 ; where R= t-Bu, n-Bu, Ph, CH_3O, CF_3CH_2O, Cl, CF_3) are most widely used. The alkyl phosphines are strong bases and are σ donor ligands while the organophosphites, $P(OR)_3$, are strong π acceptors and form stable complexes with electron rich transition metal by accepting π electrons.

Other ligands that are used are discussed below :

1. Hydrocarbyl group : Cyclopentadieneyl ligands (Cp) are associated with metals such as Ti, Zr, Hf . The Cp_2TiCl_2 catalyst is used in ethylene polymerization. Ruthenium complexes containing aromatic ligands are used for hydrogen transfer reactions such as transfer of hydrogen from alcohol to ketone producing another alcohol.
2. Alkoxide, imides and imido are used as anionic ligands in zirconium and titanium catalysts for the polymerization of alkene. These are mostly used in combination with cyclopentadienyl ligands.
3. Nitrogen ligands include pyridine and imidazole ligands. They are more stable than phosphine based ligands. Enzyme catalysts contains mostly nitrogen ligands in the form of imidazoles or porphyrins binding to metals such as copper or iron.

Some other nitrogen based ligands such as amido ligands, diimine ligand are shown in Fig 2.

4. Some other ligands such as phosphine with nitrogen substituents, carbon based ligands are also shown in Fig. 2.

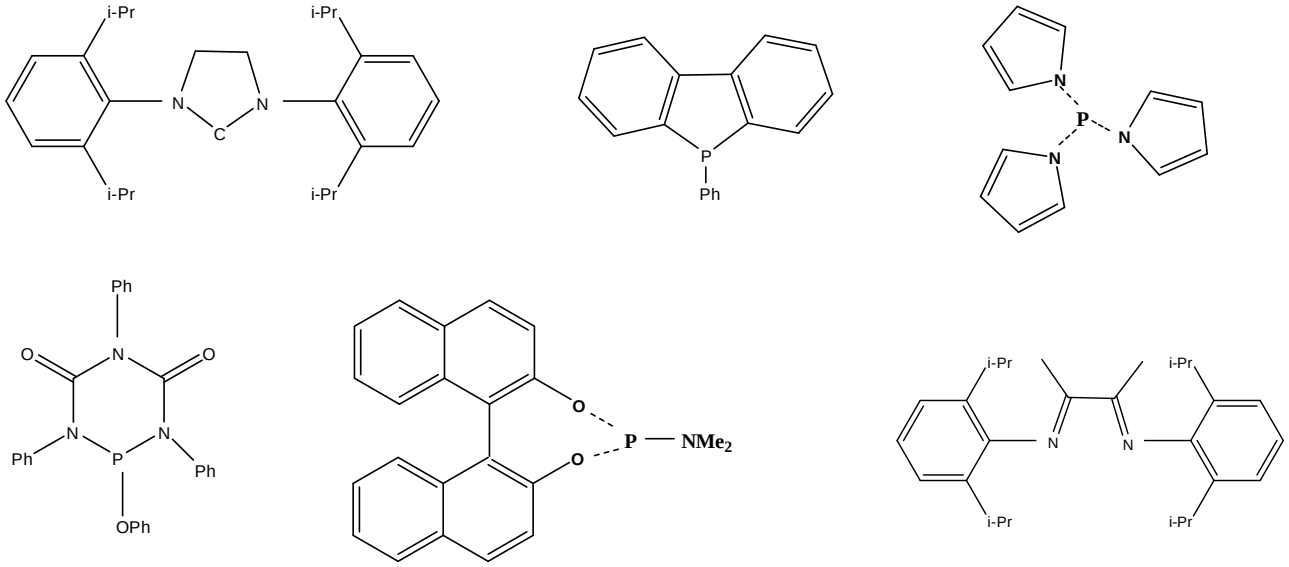
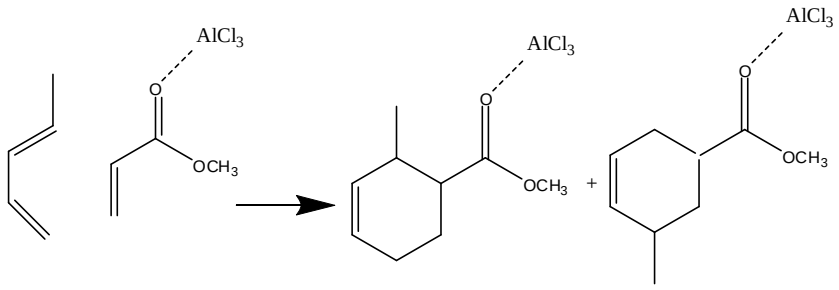


Fig. 2. Examples of phosphorous, nitrogen and carbon based ligands

4. Catalysis by Lewis acids

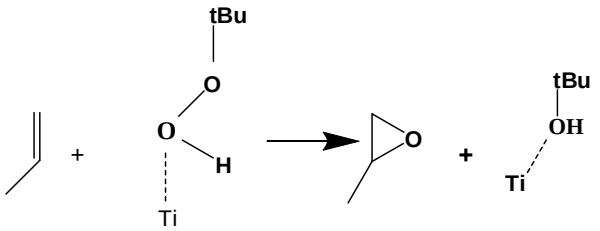
a. Diels alder reactions

Reaction of diene with a mono-ene form cyclohexene derivativeis shown below.



b. Epoxidation

Epoxidation reaction is important reaction for producing organic intermediates. Alkenes can be transformed to epoxide by hyperoxides and catalysts. Catalysts are often titanium or molybdenum complex acting as Lewis acid.



5. Catalysis by porphyrin complexes

Porphyrin complexes are used to catalyze epoxidation and hydroxylation reactions. The porphyrins are macrocyclic compound. The porphyrin molecule contains fourpyrrole rings linked via methine bridges.The structure of porphyrin macro molecule is shown in Fig. 3. The porphyrin ring system is very stable and exhibits aromatic character. The porphyrin nucleus is a tetradentate ligand inwhich the space is available for a coordinating metal and has a maximum diameter of approximately 3.7 A^0. When coordination occurs, two protons are removed from the pyrrole nitrogen atoms, leavingtwo negative charges. Various metals such as Na, K, Li Co, Ni, Cu, Fe, Mn form complexes.

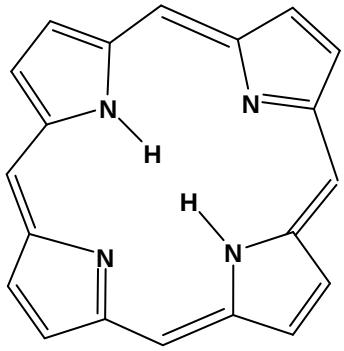


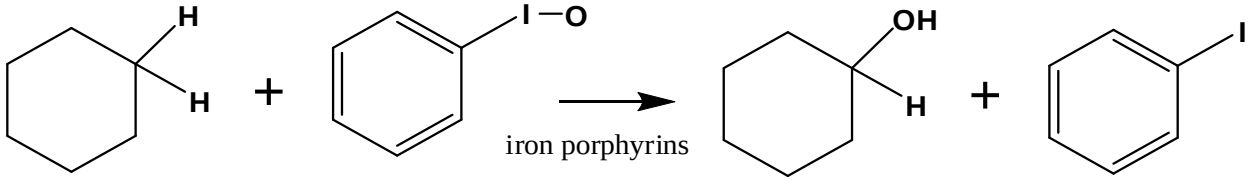
Fig 3.Structure of porphyrin macro molecule

Epoxidation

The Ru(II)porphyrin complexes is used as epoxidation catalyst of olefins.Ruthenium(II) carbonyl tetraphenylporphyrinscatalyze epoxidation of olefins in the presence ofmetachloroperbenzoic acid as oxidants.

Hydroxylation

The hydroxylation of unactivated alkanes can be done inthe presence of iodosylbenzene and iron porphyrins catalyst. The oxidation of cyclohexane in presence of iodosylbenzenewith chloro(5,10,15,20-tetra-o-tolylporphyrinato)iron(III) [Fe(TTP)CI] producescyclohexanol andcyclohexanone as shown below.



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Lecture 32

Mechanism and reaction rate

Activity

The homogeneous catalyst precursors are added in the reaction system in different forms and are transformed into the active form insitu. During one catalytic cycle, the catalyst may pass through several intermediate forms and finally produce the products. After end of each catalytic cycle, the catalyst itself should be regenerated without any change.

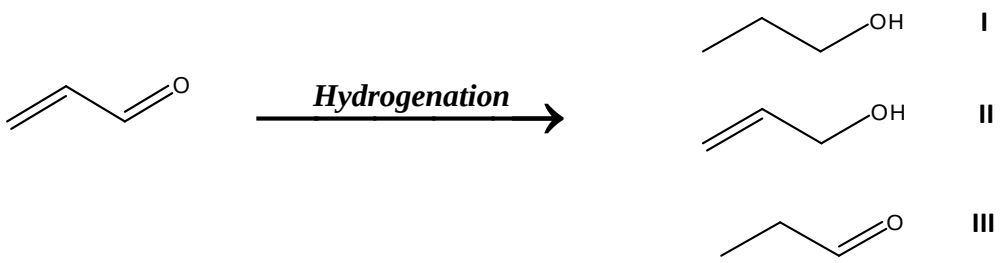
A catalyst should be able to pass through the catalytic cycle multiple times. Higher the number of times the catalyst passes through this cycle, higher is the activity of the catalyst. The number of times that a catalyst can go through this cycle converting substrate molecule to product molecules is defined as the turnover number. In other words, the turnover number, TON, is the total number of substrate molecules that a catalyst can convert into product molecules. In homogeneous systems, the turnover frequency is defined as the number of molecules of substrate converted per second which is the turnover number in a certain period of time.

Selectivity

Following type of selectivities are defined :

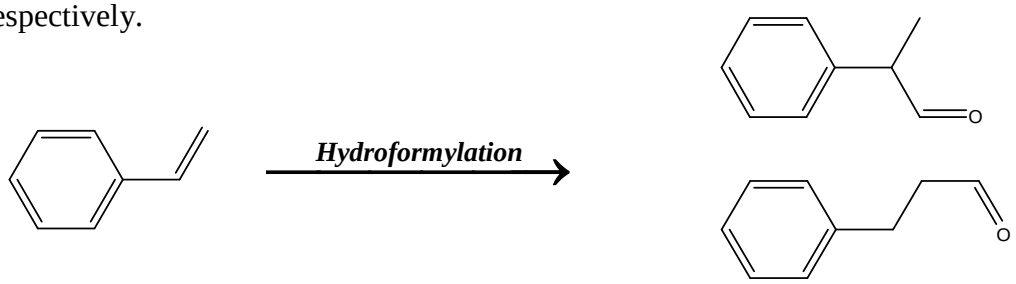
1. Chemoselectivity

When two chemically different functionalities are present in same molecule, then the selective reaction of one functional group in presence of the other is known as chemoselectivity. As shown below, the alkene and aldehyde groups present in the same molecule can undergo hydrogenation resulting in products I, II or III as a result of hydrogenation of both groups, only aldehyde or only alkene respectively. Selectively hydrogenating any one of the two functional groups and maximizing the corresponding product is known as chemoselectivity.



2. Regioselectivity

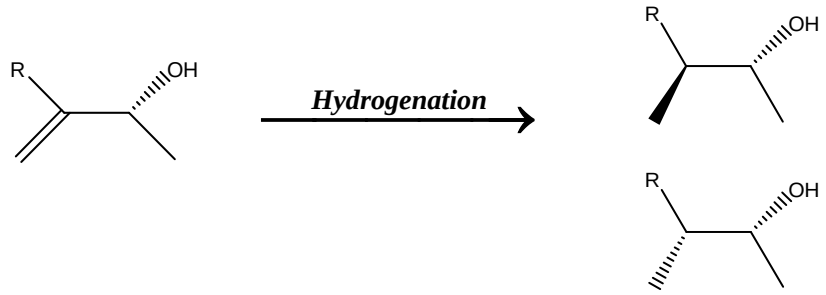
When the functional group can attach to multiple sites, then the selectivity determining the site of attachment is known as regioselectivity. As in the example shown, for the hydroformylation reaction of styrene, the formyl group can attach to either terminal carbon atom or secondary internal carbon atom resulting in linear or branched product, respectively.



3. Diastereoselectivity

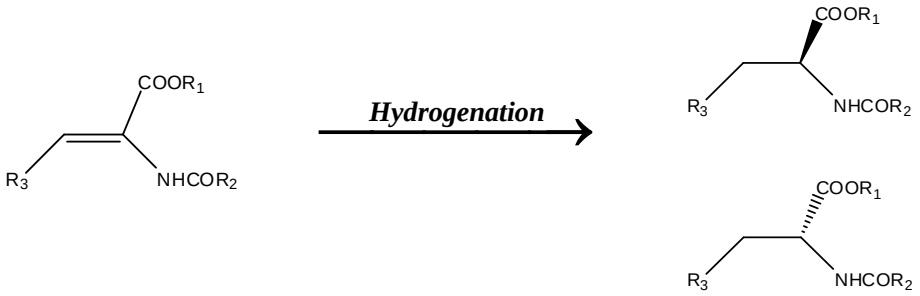
The isomeric molecules having similar molecular formula but differing in the three-dimensional orientation of atoms are known as stereoisomers. Diastereomers are two or more stereoisomers of a compound that are not mirror images of each other. When stereoisomers are mirror images of each other that are non-superimposable, they are called enantiomers.

For a substrate containing a stereogenic centre, the catalyst can direct the addition of atoms to give two diastereomers. The selectivity for either diastereomer is called diastereoselectivity. For example, the addition of dihydrogen as shown below gives two diastereomers.



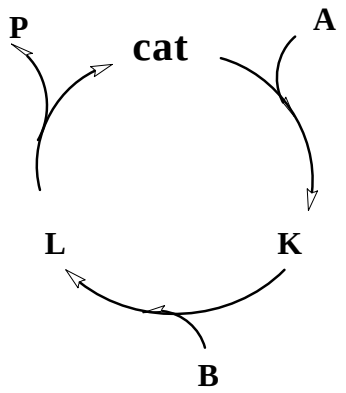
4. Enantioselectivity

When substrate is achiral, that is the molecule is superimposable on its mirror image, catalyst may give rise to the formation of specific product enantiomer as shown in the example below. This is known as enantioselectivity.



Homogeneous catalysis mechanism is often represented by catalytic cycles. In catalytic cycles, usually catalysts are shown as member of cycle and all reactants and products are placed outside the cycle and connected to it by arrows.

For example, the cycle of a catalytic reaction A+B $\rightarrow$ P, having intermediates K and L can be represented as



The stable metal complex added to the reaction at the beginning is called catalyst precursor or precatalyst. Turnover frequency in terms of catalytic cycle can be defined as number of times the cycles is completed in unit time.

The intermediates species can be studied using various spectroscopic studies such as FTIR, NMR, UV-Vis etc.

Acid -base catalysis

Mechanism

In acid-base catalysis, both acid and bases may act as catalysts in solution. The H^+ is used for protonating the intermediates and a base or solvent is used for removing the proton at a later stage. The rate of acid –base reactions depends on pH since the rate is a function of both H^+ and OH^- concentrations. The proton transfer mechanism in general can be represented as

$$B^- + H - A \rightleftharpoons \left[B \cdots H \cdots A\right]^- \rightleftharpoons B - H + A^-$$

Kinetics

In acid catalysis, the proton transfer step is slower and is the rate determining step. Subsequently, the protonated substrate rapidly reacts to give the product(s) as shown below :

$$S + HA \underset{}{\overset{slow}{\rightleftharpoons}} SH^+ + A^-$$

$$SH^+ \xrightarrow{fast} products$$

Reaction rate is dependent on all acids/bases present in solution. Rate constant for reaction is function of concentrations of H+, OH^-, HA and A^- . First order rate constant can be calculated from

$$k = k_0 + k_{H^+}C_{H^+} + k_{OH^-}C_{OH^-} + k_{HA}C_{HA} + k_{A^-}C_{A^-}$$

where k_0 = rate constant for uncatalyzed reaction (small relative to other terms)

Activity of acid-base catalyst

Activity of an acid depends on its acid strength and molecular structure. Acids of higher strength are more catalytically active. Strength is defined in terms of equilibrium constant (K_{HA}) for dissociation. $HA \rightleftharpoons H^+ + A^-$

$$K_{HA} = \frac{a_{H^+}a_{A^-}}{a_{HA}}$$ where a_i is the respective activity

For general acid catalyst, rate constant depends on its acid strength as :

$$\log k_{HA} = \alpha \log K_{HA} + \text{constant}$$

Where,

k_{HA} = rate constant of the catalytic step

K_{HA} = dissociation constant of acid HA

α = Bronsted coefficient (normally 0< α <1)

α indicates the sensitivity of catalytic step for changes in acid strength of HA.Similarly, Brønsted relation for general base catalysis is

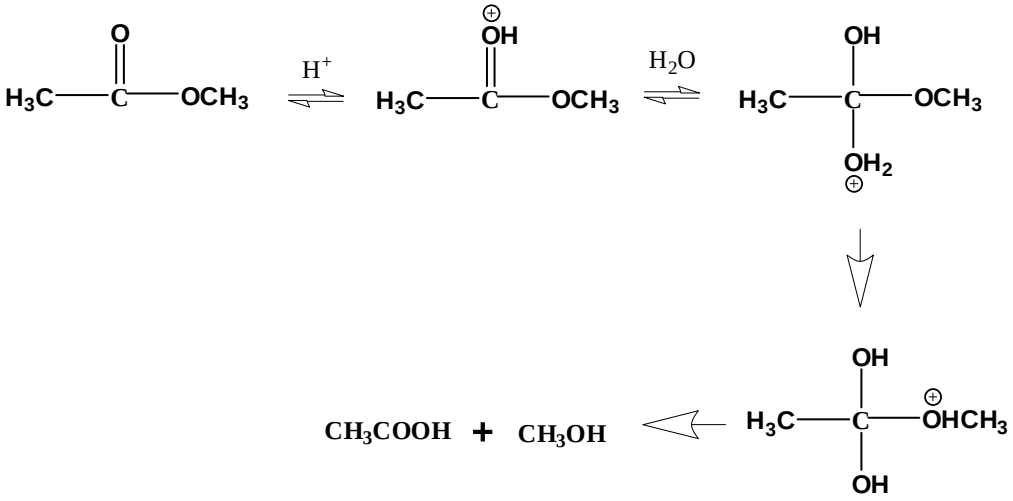
$$\log k_B = \beta \log K_{HB} + \text{constant}$$

The coefficient β has the same meaning as α for general acid catalysis.

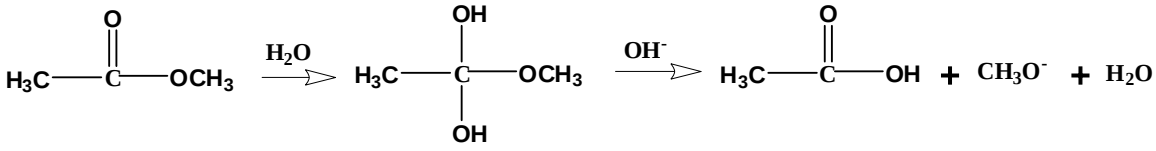
Mechanisms of few acid-base catalyzed processes are discussed below.

Ester hydrolysis : The hydrolysis of esters is catalyzed by both acids and bases. H_2O acts as the proton donor. The mechanism for acid and base catalyzed hydrolysis can be represented as :

Acid catalyzed hydrolysis :



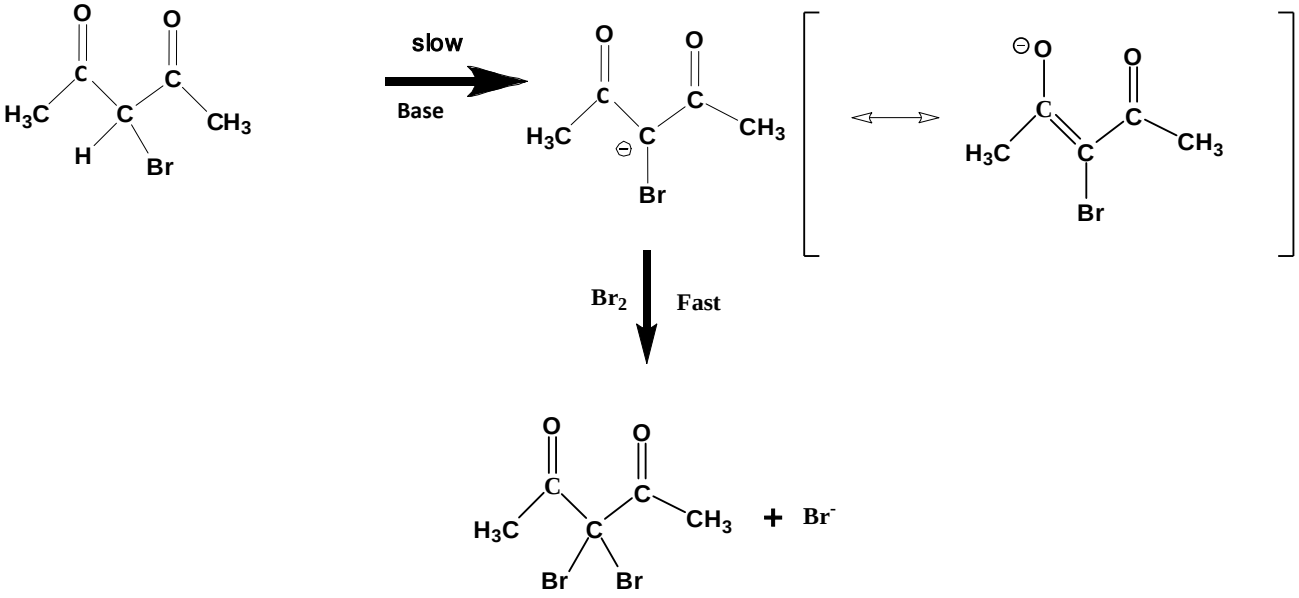
Base catalyzed hydrolysis :



Dehydration: Acid catalyzed dehydration mechanism is illustrated by dehydration of ethyl alcohol to ethene. Alcohol is initially protonated. Then, a water molecule leaves forming a carbocation. Then, ß-elimination occurs producing the alkene.

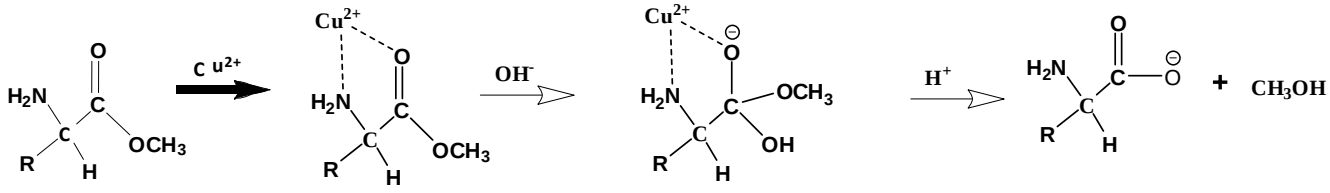
$$CH_3 - CH_2 - OH \xrightarrow{HA} CH_3 - CH_2 - \overset{+}{O}H_2 \longrightarrow CH_3 - \overset{+}{C}H_2 + H_2O \xrightarrow{A^-} CH_2 = CH_2 + HA$$

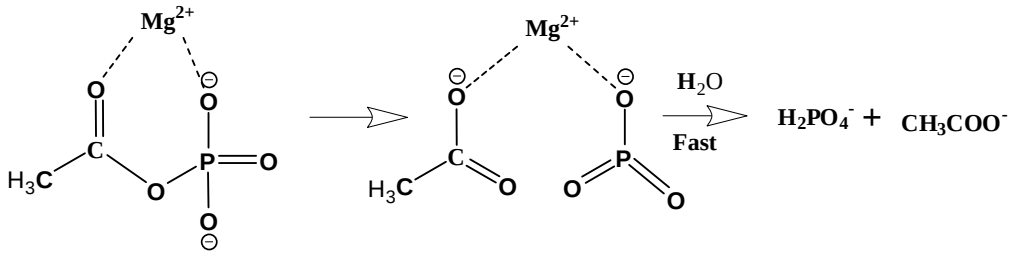
Halogenation : For base catalyzed halogenation reactions, the probable reaction mechanism is illustrated below. The ionization of the ketonic substrate in the presence of basic catalyst is the rate determining step.



Catalysis by Metal ion

The metal ions can coordinate simultaneously to electron donating atoms, such as N and/or oxygen, present in the reactant. The probable mechanisms of Cu^{2+} and $Mg^{2+:}$ ion catalyzed hydrolysis are shown below.



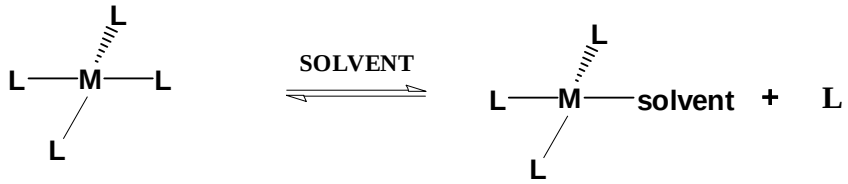


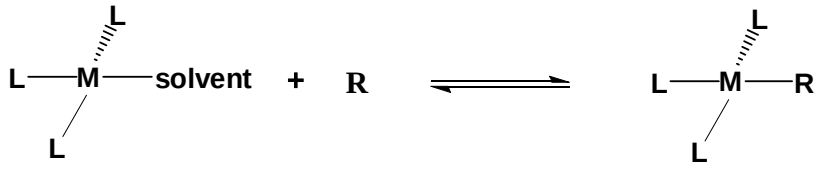
Catalysis by Organometallic complexes

As discussed, for heterogeneous catalysts the reaction starts with the adsorption of reactant on a vacant site on the catalyst surface. Similarly, for homogeneous organometallic complex catalysts, the reaction begins with the reactant molecule getting attached to a metal centre in the catalyst. Hence, the metallic centers must have vacant coordination sites. However, it is difficult to maintain vacant sites on the metallic center as the molecules are always in solvated conditions. Over all, the mechanism can be described as removal of ligand from the metallic center and addition of reactant to the vacant site. This mechanism is similar to substitution reaction. There is always competition for vacant sites between ligand, reactant or solvent molecules. The process is proposed to occur by associative or dissociative mechanism.

1. Dissociative mechanism

In dissociative ligand exchange mechanism, initially there is breaking of bond between the metal and leaving ligand. This is the slowest and rate controlling step. A solvent molecule occupies the open site. Subsequently, the solvent is replaced by reactant in a fast step.

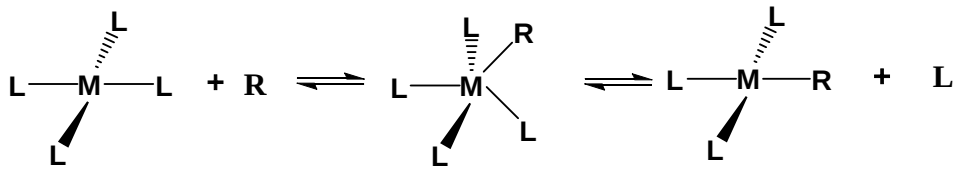




R = Reactant

2. Associative mechanism

In associative ligand exchange process, bond breaking of ligand from metal and bond formation between metal and reactant occurs simultaneously as shown below.

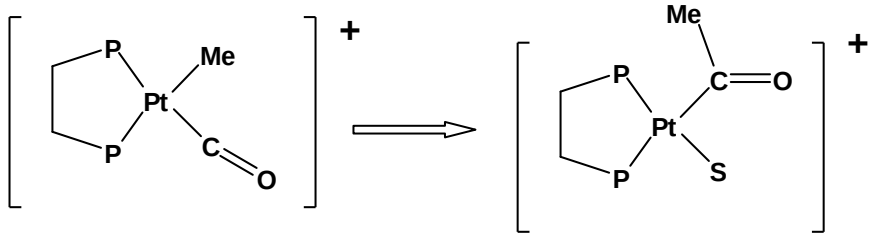


Elementary steps

The basic elementary steps that are involved in organometallic chemistry are discussed briefly.

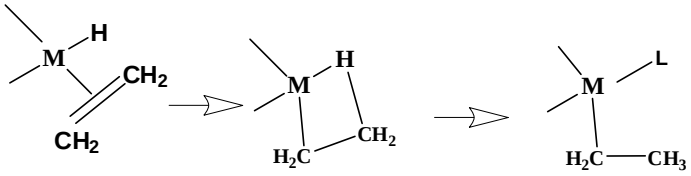
1. Insertion

In insertion mechanism an unsaturated molecule inserts into a metal- anion bond. In the shown example, the CO inserts into the metal (Pt)-methyl bond and acyl bond formed (R-CO) takes position of methyl group. The vacant position on metal is filled in solvent (S) molecule.



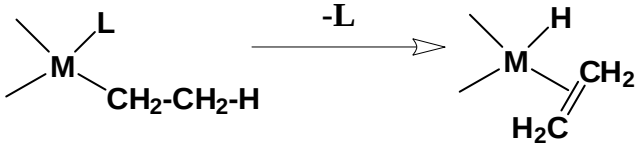
2. Migration

In migration mechanism, atom or group of atoms migrates from metal to hydrocarbon. In the shown example, hydride migrates from metal atom to ethene. The vacant position on metal is filled in by ligand (L) molecule.



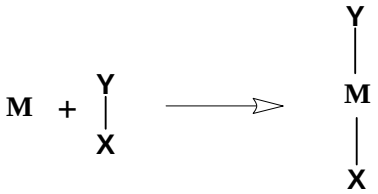
3. ß elimination

This reaction is reverse of migration. The ß-elimination requires a vacant site at the complex.



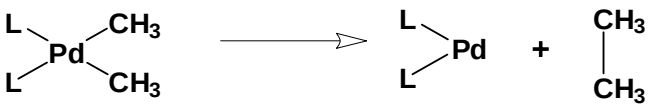
4**. Oxidative addition**

In this reaction, a compound XY adds to a metal complex during which the XY bond is broken and two new bonds MX and MY are formed



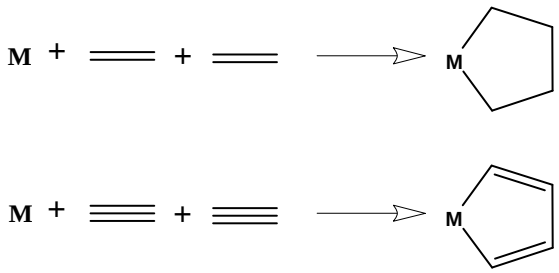
5. Reductive elimination

It is reverse of oxidative addition



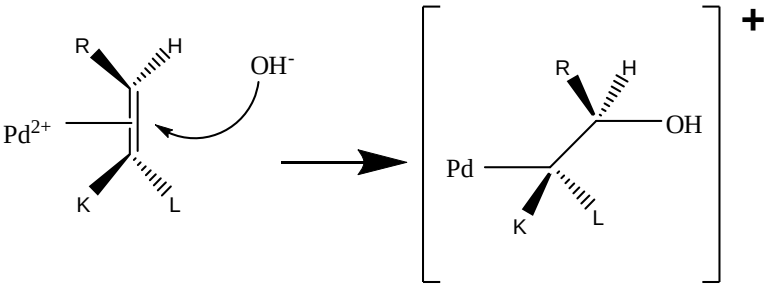
6. Cycloaddition reaction involving metal

In presence of multivalent metal, alkene/alkynes form metallacyclic compounds .



7**. Activation of substrate toward nucleophilic attack**

Co-ordination of alkene to electronegative metal (may carry a positive charge), activates the alkene toward attack of nucleophiles.



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Lecture 33

Reaction rate

An organometallic catalysis reaction is proposed to occur in two steps involving formation of an intermediate. A typical hydrogenation reaction is shown below where the first step involves the reversible formation of reactive intermediates. The second hydrogenation step is irreversible.

$$M + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} MS$$

$$MS + H_2 \xrightarrow{k_2} M + products$$

$$M = catalyst \qquad S = substrate$$

Usually, it is assumed that the concentration of reactive intermediate, MS, is small and constant compared to the total concentration of M. The rate of production of products for the given scheme can be written as follows.

$$r = k_2 C_{MS} C_{H_2} \text{ ----------(3)}$$

where C_i is the concentration of component '*i*'. A steady state approximation assumes that the amount of MS being formed and reacting are the same. Equation 4 gives the steady state approximation as :

$$\frac{dC_{MS}}{dt} = 0 = k_1 C_M C_S - k_{-1} C_{MS} - k_2 C_{MS} C_{H_2} \text{ ---------- (4)}$$

The total amount of M (C_{M_T}) can be obtained from equation 5 as summation of concentration C_M and C_{MS}.

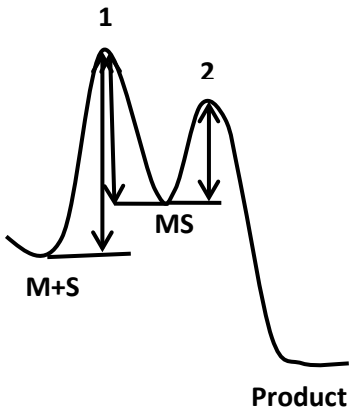
$$C_{M_T} = C_M + C_{MS} \text{ ---------- (5)}$$

By substitution the overall rate is given by equation 6.

$$r = \frac{k_1 k_2 C_{M_T} C_S C_{H_2}}{k_1 C_S + k_2 C_{H_2} + k_{-1}} \text{ ---------- (6)}$$

Consider two conditions:

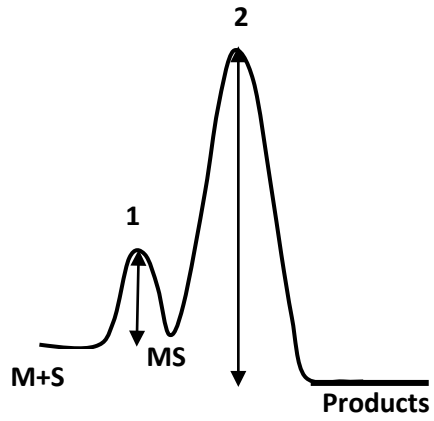
Case A : Reaction 1 is much slower than reaction 2



Case A can be represented by the above scheme which shows that the activation energy for the forward step 1 is much higher compared to the backward reaction of step 1 or step 2. Hence it implies that $k_2 > k_{-1} >> k_1$. Then, the rate equation can be simplified as $r = k_1 C_{M_T} C_S$

Here reaction 1 is slower (higher activation energy) and hence the rate determining step. As soon as the MS is formed via the slow forward reaction 1 it is converted to products. In this case, rate of reaction is independent of hydrogen concentration.

Case B : Reaction 2 much slower than 1



As shown in the above figure , energy barriers for both forward and backward reaction of step 1 are much lower than that of step 2. The rate determining step is therefore step 2. That is k, $k_{-1} >> k_2$.

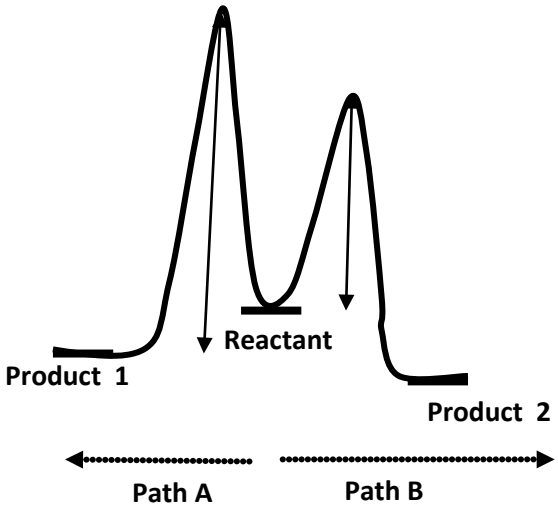
Hence ,equation 6 can be simplified and the rate equation is given as

$$r = \frac{k_1 k_2 C_{M_T} C_S C_{H_2}}{k_1 C_S + k_{-1}}$$

Selectivity

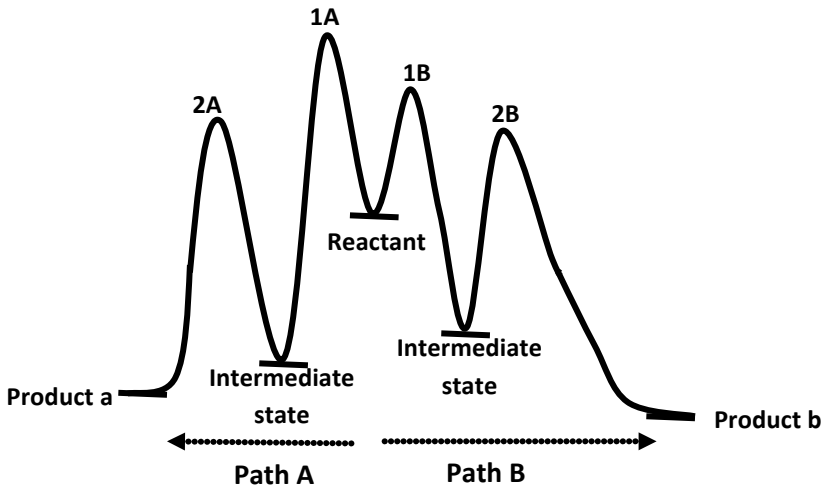
In a multistep reaction scheme, selectivity is determined as soon as an irreversible step occurs. It can be understood by the following examples.

Case 1 : Selectivity determining step coinciding with rate determining step



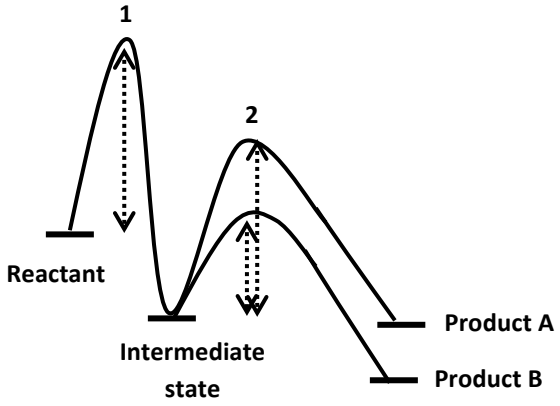
In the proposed scheme shown above, the reaction can proceed by two paths, A and B. Activation energy barrier for path **1B** is lower compared to path **1A.** Hence product 2 is formed preferentially over product 1 and rate of formation of 2 is determined by step 1B.

Case 2 : Selectivity determined by first step while second step is rate determining



In the above scheme, two products ‘a’ and ‘b’ are formed from a reactant in two steps by path A and B , respectively. Activation energy for step 2 is higher than step 1 for formation of both products. Hence, barrier 2 is the rate determining step. Again, activation energy barrier of step 1A in path A is more than step 1B in path B. Hence product ‘b’ by path B will be formed preferentially. Thus, the selectivity is determined before the rate determining step, provided that the activation energy of the backward reaction from the intermediate state is higher compared to forward reaction.

Case 3 : Selectivity determined after the rate-controlling step



In the above figure, the step 1 has the higher energy barrier and is the rate determining step. The intermediate formed by step 1 can transform to product A or B via two pathways. The ratio of products A and B is controlled by the heights of the respective energy barriers. Since activation energy barrier is lower for product B, it has higher selectivity. Thus, in this case selectivity is determined ~~in~~ by the second competing steps after the initial rate -determining step which is same for both products.

Rate equations of homogeneous catalyzed reactions often refer to the liquid phase concentrations. In most cases, the rate equations are non-linear with respect to the concentration of the reactant. The concentration of reacting species or products formed can be measured during reaction using several techniques such as chromatography, UV-visible spectroscopy , IR spectroscopy etc. Homogeneous catalyzed reactions are often carried out in multiphase systems. Gaseous reactants such as H_2, CO, O_2 have to be transferred from the gas phase to the organic liquid phase where the reaction takes place. When one of the reactants is in the gas phase, such as in hydrogenation reaction, fast dissolving of the gas into the liquid is required to avoid any external mass transfer limitations. Mass transfer limitations in a batch reactor can be checked by measuring the rate as a function of stirring rate. When mass transfer limitation is absent, there should be no change in reaction rate with stirring rate. However, in the presence of mass transfer limitations, rate increases with stirring upto an extent then become constant when mixing is sufficient. Further, to increase the solubility of the gas into liquid, high pressure has to be used. Any type of reactor such as batch, CSTR or plug flow reactor can be used. For elucidation of mechanism, rate data at low conversions are highly desirable. These can be

obtained more easily in a batch reactor. However, maintaining constant-temperature by effective removal or supply of heat is difficult in a batch reactor. To effectively control the heat and mass transfer limitations, stirring is essential in a batch reactor. If the reaction is highly exothermic or endothermic, cooling or heating coils are needed, respectively. Most homogeneous hydrogenations, halogenations, hydro-halogenations, hydro-formylation and hydro-cynation reactions are first order in olefin reactant. Intrinsic rate equations of few homogeneous catalyzed reactions are discussed below.

1. Hydroformylation of propene

Hanna et al. [1] investigated the kinetics of propene hydroformylation over a silica-supported Rh–sulfoxantphos complex stabilized by the ionic liquid [bmim][$OctSO_4$]. The hydroformylation of propene is proposed to be initiated by the loss of a CO ligand from Rh complex (step 1) followed by coordination to propene (step 2). Migratory insertion into Rh–H bond forms a propyl-Rh complex (step 3). For alkene insertion into Rh–H bond as rate determining step following rate expression was proposed.

$$r = \frac{K_1 K_2 k_3 P_{C_3H_6} [Rh]}{P_{CO} + K_1 + K_1 K_2 P_{C_3H_6}}$$

where $\mathbf{k_3}$ is the rate coefficient of alkene insertion step 3, K_1 and K_2 are equilibrium constants for step 1 and 2 , respectively. P_{CO} and P_{C3H6} are the partial pressures of CO and propene, respectively. The [Rh] is the total moles of Rh.

2. Hydrogenation of cyclohexene

The kinetics of homogeneous hydrogenation of cyclohexene in the presence of the catalytic system consisting of $Rh_2Cl_2(C_8H_{14})_4$ and 2-aminopyridine has been investigated by Zuber et al. [2]. The proposed mechanism is described below.

$$Rh_2Cl_2(C_8H_{14})_4 + 4ampy \xrightarrow{S} 2\left[Rh(ampy)_x S_y\right]^+ + 2Cl^- + 4C_8H_{14}$$

$$\left[Rh(ampy)_x S_y\right]^+ + H_2 \xleftrightarrow{K_1} \left[RhH_2(ampy)_x S_y\right]^+$$

$$\left[Rh(ampy)_x S_y\right]^+ + C_6H_{10} \xleftrightarrow{K_2} \left[Rh\left(C_6H_{10}\right)(ampy)_x S_{y-1}\right]^+$$

$$\left[RhH_2(ampy)_x S_y\right]^+ + C_6H_{10} \xrightarrow{k} \left[RhH_2\left(C_6H_{10}\right)(ampy)_x S_{y-1}\right]^+$$

$$\left[RhH_2\left(C_6H_{10}\right)(ampy)_x S_{y-1}\right]^+ \xrightarrow{fast} C_6H_{12} + \left[Rh(ampy)_x S_y\right]^-$$

Here ampy is 2-aminopyridine and S is the solvent (EtOH). It is assumed that the catalyst forms complexes both with cyclohexene (equilibrium constant K_1) and with hydrogen (equilibrium constant K_2). The rate of reaction is expressed as:

$$r = \frac{kK_1 C_{cyclohexene} C_{H_2}}{1 + K_1 C_{H_2} + K_2 C_{cyclohexene}} C_{cat}$$

At 40 ^{0}C, the rate of hydrogenation of cyclohexene, catalyzed by $CoH_3(PPh_3)_3$ was described by Hendrikse et al. [3]. Addition of cyclohexene to the catalyst was proposed as the rate-limiting step and the following mechanism was proposed.

$$A + \frac{3}{2} H_2 \overset{1}{\rightleftharpoons} AH_3$$

$$AH_3 + P \overset{2}{\rightleftharpoons} AH_3P$$

$$A + P \overset{3}{\rightleftharpoons} AP$$

$$AH_3 + S \xrightarrow{r} AH_3S$$

A = $Co(PPh_3)_2$ or its solvated species.

$$r = \frac{k_r C_A K_1 C_S C_H^{3/2}}{1 + K_1 C_H^{3/2} + K_1 K_2 C_H^{3/2} C_P + K_3 C_P} \quad [5]$$

Where, C_A, C_S, C_H and C_P are the concentrations of catalyst, cyclohexene, hydrogen and triphenylphosphine, respectively, in solution. Equation shows that triphenylphosphine is an inhibitor for the hydrogenation reaction.

3. Carbonylation of methanol

The homogeneous rhodium complex catalyzing methanol carbonylation in the presence of methyl iodide can be described as follows [4]. First, the oxidative addition of methyl iodide to the active rhodium species occurs. Then, insertion of carbon monoxide to C-Rh bond occurs. It is followed by the elimination of methyl acetate by methanolysis, reductive dissociation of HI from the rhodium species and the regeneration of methyl iodide. The first step, the oxidative addition of methyl iodide, is believed to be the rate-determining step.

$$RhL_n + CH_3I \rightarrow CH_3 - RhIL_n$$
$$CH_3 - RhIL_n + CO \rightarrow CH_3CO - RhIL_n$$
$$CH_3CO - RhIL_n + CH_3OH \rightarrow CH_3COOCH_3 + HRhIL_n$$
$$HRhIL_n \rightarrow HI + RhL_n$$
$$HI + CH_3OH \rightarrow CH_3I + H_2O$$

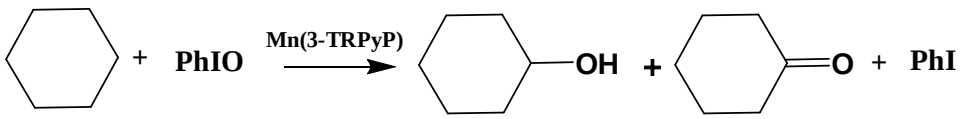
The corresponding rate expression is given as

$$r = kC_{MeI}C_{CO}^{0}C_{MeOH}^{0}$$

The formation rate has first order dependence on methyl iodide concentration and is approximately zero order with respect to concentration of both carbon monoxide and methanol.

4. Oxidation of cyclohexane

On oxidation of cyclohexane with PhIO in presence of meso-tetra(3-pyridyl) porphynatemanganese (III) [Mn(3-TRPyP)] and meso-tetra(4-pyridyl) porphynatemanganese(III) [Mn(4-TRPy-P)] species, at 25 ^{0}C, was found to yield cyclohexanol and cyclohexanone as major products.



The mechanism for cyclohexane oxidation by PhIO catalyzed by Mn(3-TRPyP) or Mn(4-TRPyP) complexes as proposed by Nunes et al. [5] is as follows :

$$< Mn > + PhIO \xrightarrow[fast]{k_1} < Mn - O - IPh >$$

$$C_6H_{12} + < Mn - O - IPh > \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} < Mn - \overset{\overset{I-Ph}{\vdots}}{O} > \quad \overset{\overset{H-C_6H_{11}}{\vdots}}{}$$

$$< Mn - \overset{\overset{I-Ph}{\vdots}}{O} > \quad \xrightarrow[k_3]{Slow} \quad < Mn - OH - C_6H_{11} > \; + PhI \quad \underset{\vdots}{H - C_6H_{11}}$$

$$< Mn - O - H - C_6H_{11} > \xrightarrow[fast]{k_4} < Mn > + C_6H_{11}OH$$

Corresponding rate of equation is given as $r = k_{cat} C_{\langle Mn \rangle} C_{C_6H_{12}}$

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Lecture 34

Industrial homogeneous processes

Hydrogenation

Homogeneous hydrogenation is one of the earliest developed industrial homogeneous processes. The most effective homogeneous hydrogenation catalyst is Wilkinson's catalyst having composition RhCl $(PPh_3)_3$,where PPh_3 is tridentate phosphine ligand. Both monomeric and dimer $[Rh_2Cl_2(PPh_3)_4]$ forms are active catalyst. Since Rh can exist in two oxidation states, it readily catalyzes oxidative addition and reductive elimination reactions. The functional groups attached to the phosphine ligands also affect the catalytic activity significantly. Activity is increased significantly by adding methoxy group to the phosphine ligands.

In hydrogenation process, the first step is dissociation of one ligand L, which is replaced by a solvent molecule. After ligand dissociation, oxidative addition reaction of H_2 takes place. This is followed by migration of hydride from metal to ethane, forming the ethyl group. Finally, reductive elimination of ethane completes the cycle. The general reaction sequence can be represented as follows :

$$RhClL_3 + S \rightleftharpoons RhClL_2S + L$$
$$RhClL_2S + H_2 \rightleftharpoons RhH_2ClL_2S$$
$$RhH_2ClL_2S + H_2C = CH_2 \rightleftharpoons RhH_2ClL_2(C_2H_4) + S$$
$$RhH_2ClL_2(C_2H_4) + S \rightleftharpoons RhH(C_2H_5)ClL_2S$$
$$RhH(C_2H_5)ClL_2S \rightarrow C_2H_6 + RhClL_2S$$

Here L=tri-arylphosphines ; S= solvent (ethanol , toluene)

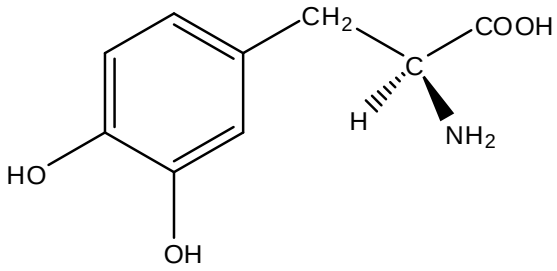
In general, homogeneous hydrogenation processes are industrially of less importance compared to heterogeneous hydrogenation processes. However, interest is growing in homogeneous hydrogenation processes particularly in the area of asymmetric hydrogenation. In pharmaceutical industry, asymmetric hydrogenation is used to produce enantiomerically pure compounds having desirable clinical properties. The main

advantage of this process is the high selectivity, which eliminates the production of non-desired enantiomer which is non active or can cause undesirable side effects.

Example of asymmetric hydrogenation

1. **Synthesis of L-dopa :**

The asymmetric hydrogenation of cinnamic acid derivatives involves synthesis of L-Dopa. L-Dopa is a drug for treating Parkinson's disease. It is one of the recently developed industrial processes. L-Dopa structure is shown below. The C atom bonded to the NH_2 group is the chiral center. The enantiomer D-Dopa is ineffective form.



The reaction is carried out in the presence of rhodium complex having asymmetric diphosphine ligand which induces enantio-selectivity. The hydrogenation reaction is carried out with a substituted cinnamic acid. The main step in L-Dopa synthesis, the hydrogenation of prochiral alkene to a specific optical isomer, is shown below.

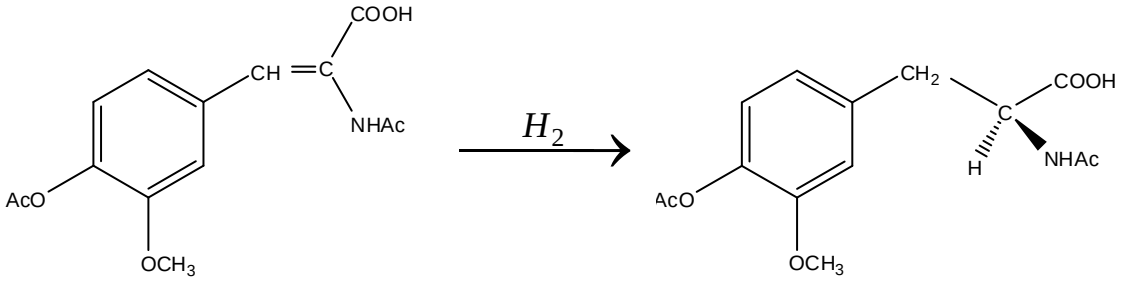


Fig. 1. Critical step in hydrogenation of prochiral alkene to specific enantiomer.

Catalyst is prepared by reacting Rh salt with an alkene chloride, such as hexadiene chloride or cyclooctadiene chloride, producing a cationic Rh species.

In the first step, alkene co-ordinates to rhodium species. The next step is hydrogenation involving oxidative addition of hydrogen to the alkene complex. The oxidative addition of hydrogen is irreversible and determines the enantioselectivity. Migration of hydride locks the configuration of the enantiomeric center. In this system, the same hydrogenation step determines the rate as well as selectivity.

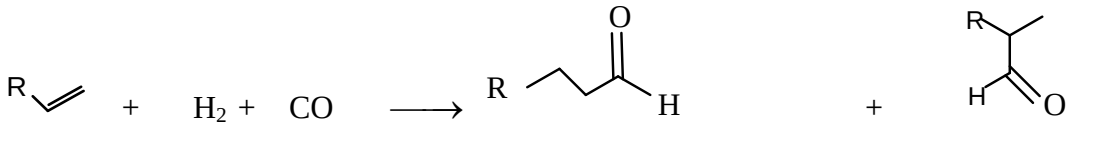
The difference between this catalytic step and step involving Wilkinson catalyst lies in the sequence of the oxidative addition and the alkene complexation. For rhodium complex catalysts , the intermediate alkene complex has been spectroscopically observed. Subsequently, oxidative addition of H_2 and insertion of the alkene occurs, followed by reductive elimination of the hydrogenation product.

Process

In a typical industrial process, the alcohol soluble catalyst along with soluble alkene prochiral compound is introduced in an autoclave under reaction conditions of 50 ^{0}C and 3 atm H_2. Since the products obtained are insoluble, separation is easier. The optical yield is 95%.

Hydroformylation

The hydroformylation reaction involves conversion of alkene to aldehyde in the presence of CO and hydrogen. The reaction is given as



Linear product **Branched product**

The process is carried out over cobalt or rhodium complex based catalysts. Both linear and branched chain products can be produced. Linear aldehydes are more valuable feed stock for plasticizers and linear alcohols. Hence, the main objective is to have high selectivity for more useful linear products.

Cobalt complex catalysts

In cobalt complex catalyzed hydroformylation reaction, the catalytically active form is $HCo(CO)_4$ complex. The sequence of hydroformylation process for linear aldehyde formation is shown below.

$$HCo(CO)_4 + CH_2 = CHR \rightleftharpoons HCo(CH_2 = CHR)(CO)_3 + CO$$
$$HCo(CH_2 = CHR)(CO)_3 + CO \rightleftharpoons Co(CH_2CH_2R)(CO)_4$$
$$Co(CH_2CH_2R)(CO)_4 + CO \rightleftharpoons Co\ (CO)(CH_2CH_2R)(CO)_4$$
$$Co\ (CO)(CH_2CH_2R)(CO)_4 + H_2 \rightarrow CHO(CH_2CH_2R) + HCo(CO)_4$$

The first step is the replacement of CO ligand by an alkene. In the next step, hydride migration to alkene occurs producing alkyl cobalt complex in which alkyl may be either linear or branched. In the subsequent step, one incoming CO occupies the vacant site. It is followed by migration of the alkyl to a co-ordinated CO to give an acyl-complex. In the final step, dihydrogen reacts with acyl complex to form aldehyde product and regenerate the starting hydrido-cobalt-carbonyl complex. In cobalt catalyzed hydroformylation, the hydrogenation step is rate determining.

Phosphine modified Co catalysts

The performance of the cobalt complex is significantly modified when associated with tertiary alkyl phosphines ligands. The selectivity to linear products is increased significantly. But the reaction becomes slower, and as a result reaction needs to be carried out at a higher temperature. The intermediate carbonyl complex formed is more stable and hence the process can be carried out at lower pressure. In case of tetra cobalt carbonyl complex $HCo(CO)_4$, high pressure is needed to prevent decomposition of carbonyls to metal and CO. The phosphine complexed catalysts can also catalyze hydrogenation and consequently cocurrent hydrogenation of aldehyde to alcohol, which is usually the desired final form.

Process

Hydroformylation of both higher and lower alkenes can be carried out using $HCo(CO)_3L$ complex. Reaction is done in two stages as shown in Fig. 1, to limit the hydrogenation of alkene. In the first reactor, low hydrogen partial pressure is used, and in the second reactor high hydrogen partial pressure is used to ensure hydrogenation of aldehyde to alcohol. The unreacted alkenes and gases are recycled back to the first reactor. Multiple distillation columns are used to separate the unreacted reactants and catalysts. Catalysts remain in the bottom phase of the distillation column and recycled back. The aldehydes and alcohols are collected as overhead products from the distillation tower.

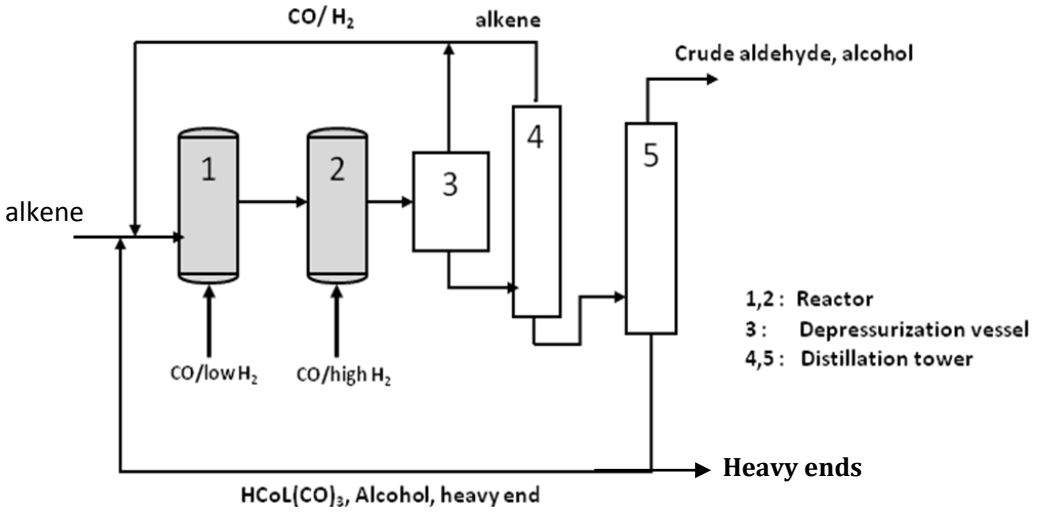


Fig 1. Process flow diagram of hydroformylation process.

Rhodium complex catalysts

The rhodium complex catalysts contain triphenylphosphine ligand [$P(C_6H_5)_3$, TPP] groups. The composition of rhodium complex catalysts is $HRh(CO)(P(C_6H_5)_3)_3$. This catalyst is highly active resulting in better utilization of feed stock. The most important example of industrial hydroformylation process is the synthesis of aldehydes, particularly conversion of propylene to butylaldehyde. Rhodium complexes are the best catalyst for low molecular weight alkene conversion however, cobalt complex catalysts are better for conversion of high molecular weight alkenes.

The overall reaction is given as :

$$CH_3CH = CH_2 + CO + H_2 \rightarrow \underset{\text{linear}}{nCH_3CH_2CH_2CHO} + \underset{\text{branched}}{(1-n)CH_3CHCHOCH_3}$$

The Rh complex catalyzed process is carried out at lower temperature and pressure of 80 -100 ^{0}C and 15-30 atm, respectively.

The catalyst is produced insitu from different starting materials such as Rh acetylacetate carbonyl , CO, H_2, TPP group. The $HRh(CO)(P(C_6H_5)_3)_3$ form gives 99 % selectivity for linear aldehyde. At higher pressure , $HRh(CO)_3P(C_6H_5)_3$ species are formed that favors the branched aldehyde which is an undesirable product. Hence, high CO partial pressure is undesirable.

Moreover, at high partial pressure of CO, the reaction rate is inhibited by CO. On the other hand, at very low partial pressures of CO, the concentration of active carbonyl as well as CO reactant concentration are low, hence reaction rate is lowered. Rate of hydroformylation is also dependent on phosphine concentration. At low TPP: Rh wt ratio, the reaction rate increases with increasing concentration. However, at higher TPP:Rh wt ratio, the rate decreases greatly with increasing TPP concentration. Hence, at high concentration, TPP acts as inhibitor similar to CO.

In hydroformylation reaction, efficient mass transfer between gas (H_2 and CO) and organic liquid phase is obtained by gas –liquid sparging and rapid stirring. Catalyst separation is usually done by distillation. Product aldehydes are separated and Rh catalyst remains in aqueous solution, which is recycled back to the reactor.

Rh complex catalysts can be deactivated by various ways. Free carboxylic acids, produced as byproduct, can coordinate with Rh deactivating it. Further, traces of chlorine or oxygen can also react with Rh decreasing its activity. When Rh catalysts are recovered at the bottom of distillation column, some of the heavy high boiling products remain with the catalyst, leading to faster deactivation. Rhodium is recovered from the deactivated catalyst and used for new catalyst preparation.

Carbonylation of methanol

Carbonylation of methanol produces acetic acid. Acetic acid is used in the production of vinyl acetate, cellulose acetate, acetic anhydride, acetyl chloride and solvent acetates. Reaction can be cobalt or rhodium complex catalyzed. The reaction is given as

$$CO + CH_3OH \rightarrow CH_3COOH$$

For cobalt carbonyl complex, catalytically active form is $HCo(CO)_4$. The cobalt complex, CH_3OH and CO are dissolved in a suitable solvent, such as butane, and reacted to obtain acetic acid at 250 ^{0}C and 475 atm pressure. High pressure is required to dissolve the CO and to stabilize the catalyst complex in the active form.

Rhodium catalysts involve milder conditions of 175 ^{0}C and 15-25 atm pressure which is advantageous. Rhodium catalyzed process is used for large scale operation. The rhodium precursors salt is RHI_3 . The two catalysts components are rhodium and iodide. Under reaction conditions, the CO and water reduce RhI_3 to monovalent rhodium complex $[Rh(CO)_2 I_2]^{-1}$ which is the active form. In the presence of a large excess of iodide , methyl iodide is formed. CH_3I is reported to participate in the mechanism and the rate is determined by the reaction of CH_3I with Rh complex. The mechanism proposed is as follows :

$$CH_3OH + HI \rightleftharpoons CH_3I + H_2O$$
$$CH_3I + RhI_2(CO)_2^- \rightarrow CH_3RhI_3(CO)_2^-$$
$$CO + CH_3RhI_3(CO)_2^- \rightarrow CH_3C(O)RhI_3(CO)_2^-$$
$$CH_3C(O)RhI_3(CO)_2^- \rightarrow RhI_2(CO)_2^- + CH_3COI$$
$$CH_3COI + H_2O \rightleftharpoons CH_3COOH + HI$$

The corresponding rate is given as $r = kC_{Rh\ complex}C_{CH_3I}$

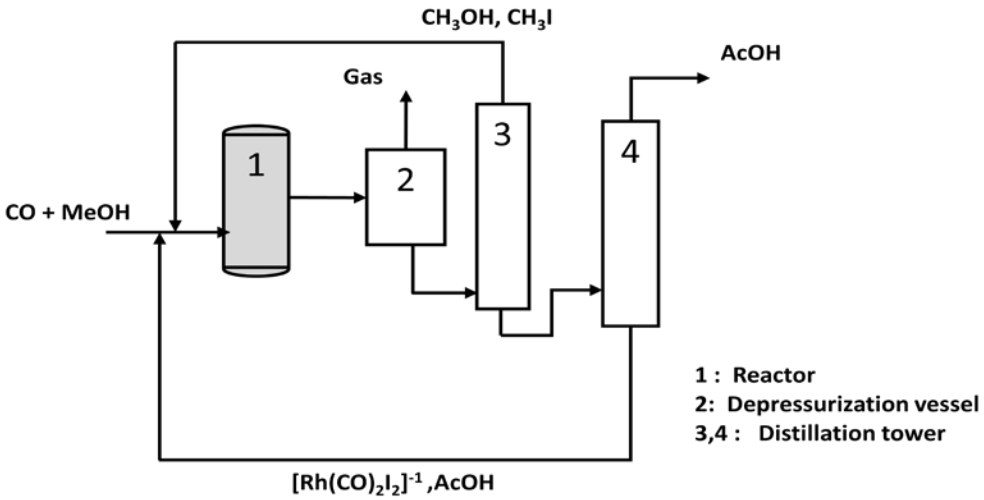


Fig 2. Process flow diagram for acetic acid production

Process

The flow diagram of the process is given in Fig 2. The liquid mixture from the reactor is first depressurized. The separation of acetic acid from catalyst components is done by distillation. In the first distillation column, the light ends are removed. In the second distillation column, the acetic acid product is removed at the top and the heavy end at the bottom, containing Rh catalysts, is recycled back to the reactor. Catalyst deactivation is associated with high solution acidity caused by increasing free HI leading to formation of an inactive complex $[Rh(CO)_2I_4]^-$.

In this process, the following side reactions occur reducing the selectivity of the process.

i. Water is essential for the reaction to occur ,but at high concentrations, it can react with CO resulting in loss of one of the reactants.

$$CO + H_2O \rightarrow H_2 + CO_2$$

ii. The other side reaction involves HI which oxidizes Rh(I) to Rh(III) iodide which may precipitate from the reaction. It has to be converted back to Rh (I) complex.

$$CH_3\ Rh\ I_3(CO)_2^- + HI \rightarrow CH_4 + Rh\ I_4(CO)_2^-$$

$$Rh\ I_2(CO)_2^- + 2HI \rightarrow H_2 + Rh\ I_4(CO)_2^-$$

Text Reference

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Lecture 35

Enzyme catalytic processes

Enzyme catalytic processes are extensively used in food industries for centuries such as in production of bread, beverages, yoghurt, cheese, vinegar etc. Enzymes have properties similar to homogeneous catalysts. New enzymes are continuously being discovered. At present, more than 3000 enzymes are reported.

Enzyme catalyst

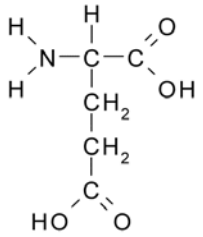
Enzymes are large macromolecular polypeptide (polymers of amino acid monomers) proteins. Molecular weight is in the range of 104-106 . Each enzyme has a unique three-dimensional structure with a binding site or active site that is chemically and geometrically compatible with a particular reactant molecule and thereby can give upto 100 % selectivity.

Enzymes are formed in living systems by condensation and/or dehydration of amino acids that have the composition of H_2N-CHR-COOH, to form peptide C-N bonds. Large structure contains hundreds of amino acids and there is enormous number of possible structures. Only few are characterized and well known. Naturally occurring metal ions in enzymes reported are Mg, Zn, Ca, Ni, Fe, Co, Mo.

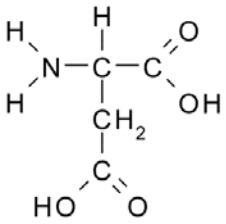
Example :

Lysozyme enzyme

- Catalyze splitting of polysaccharide chains
- 129 amino acids residues joined by peptide linkage
- Glutamic acid and aspartic acid are important functional groups at the active sites



Glutamic acid



Aspartic acid

Enzymes are synthesized by living organisms and can be extracted from their biological source, purified and used in laboratory and industrial processes. Enzymes can also be synthesized in vitro that is in an artificial environment outside the living organism. Enzymes are only active within a limited range of pH and temperature.

Enzyme catalysis

Enzyme catalyze a variety of biological reactions such as :

- Breakdown of proteins and sugars
- Photosynthesis
- Oxidation –reduction that converts food to CO_2, water and energy
- Production of hormones

Enzymes are classified into six different groups based on the type of reactions catalyzed:

i. Oxidoreductases : oxidation-reduction
ii. Transferases : functional group transfer
iii. Hydrolases : hydrolysis
iv. Lyases : addition or formation of double bonds
v. Isomerases : isomerization
vi. Ligases : bond formations

Activity

Enzymes generally function only under mild conditions of temperature and pH. Activity of a typical enzyme increases with temperature upto 50-60 ^{0}C passes through a maximum and then declines. Enzymes catalyze biochemical reactions with very high rates, 10-10000 molecules /enzyme/second compared to one or less for conventional catalysts. High activity of enzyme is illustrated in Table 1

Table 1. Comparison of activation energies and relative rates of acid catalyzed and enzyme catalyzed hydrolysis reactions

	Activation energies		**Relative rates**	
Reactions	Conventional catalysis	Enzyme catalysis	Conventional catalysis	Enzyme catalysis
Hydrolysis of urea	Acid catalyzed: 104 kJ/mol	Urease catalyzed : 29 kJ/mole	1	1012

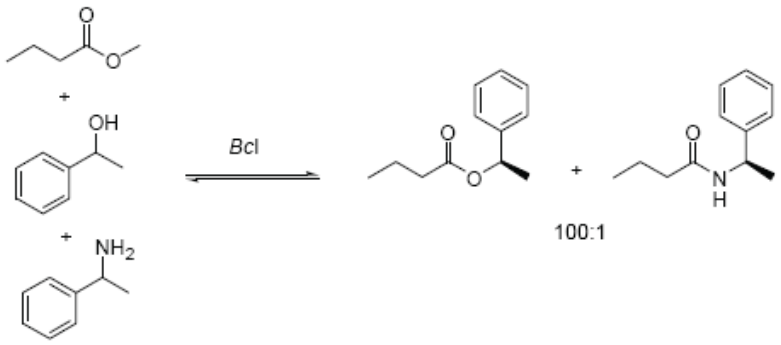
Selectivity of enzyme

Major advantage of enzymes is their selectivity. Enzymes are characterized by their ability to catalyze biochemical reactions with high selectivity (essentially 100 %). Most enzymes are only active for a single reaction i.e. stereochemical specificity of enzymes is absolute. Three types of selectivity are exerted by enzymes :

1. Chemoselectivity
2. Regioselectivity
3. Stereoselectivity

1.Chemoselectivity

Enzyme can catalyze transformation of one type of functional group in the presence of other sensitive groups in the substrate molecule . This reduces undesired reactions to a great extent. The lipase of Burkholderia cepacia catalyzes acylation of 1-phenylethanol hundred times faster than of the corresponding amine using methyl butyrate as acyl donor.



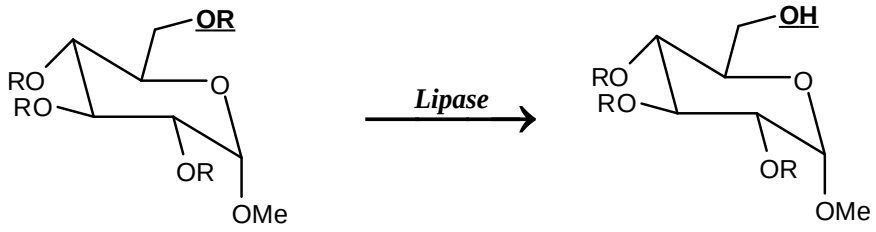
As shown in the figure, in a transacylation reaction , Burkholderia cepacia lipase (Bcl) prefer the alcohol over the amine as acyl acceptor by a factor of 100.

2. Regioselectivity

Enzymatic catalytic center has a complicated 3D structure that can distinguish between two or more identical functional groups located in different sites of the substrate molecule. As a result only one group participates in the reaction resulting in selective products.

Example :

During deacylation of polyacylated sugar, high yield (80-90 %) of the product as shown in following reaction is obtained. The other minor derivatives are products of deacylation at other positions.



2

R= COC_4H_9

3. Stereoselectivity

Stereoisomers are defined as isomers of a substrate whose chemical compositions are same but their structure differ such that their mirror images are non-superimposable. Each one of the two stereoisomers is known as optical isomer or enantiomer. Production of only one enantiomer with 100 % selectivity is important as activity depends on stereochemistry. For the same substrate, one stereoisomer may be active while the other stereoisomer may be inactive or active for an undesirable reaction. This enantioselectivity is the most important feature of enzymes. Enzymes are capable of recognizing any type of chirality of substrate and synthesizing one particular enatiomers. There are three approaches to synthesis of enantiomerically enriched compounds using enzymes.

1. Kinetic resolution
2. Desymmetrization
3. Deracemization

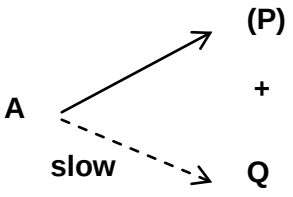
$$\begin{array}{ccc} \mathbf{R} & \xrightarrow{fast} & (\mathbf{P}) \\ + & & + \\ (\mathbf{S}) & \xrightarrow{slow} & (\mathbf{Q}) \end{array}$$

R, S = enntiomers of a racemic substrate
P, Q = enantiomers of a product
***yield* = 50%(*P*); 50%(*S*)**

Kinetic resolution of a racemic mixture rests upon chiral discrimination of enantiomers. Each enantiomer is transformed into a product at a different rate. The theoretical yield is then 50% of the product (P) and the unreacted substrate (S).

1. Desymmetrization

In desymmetrization process, a prochiral mesosubstrate is preferentially transformed into one enantiomers of the product. In the ideal case, the yield of the product may be 100 %.

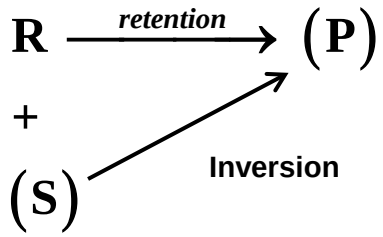


P, Q ⇒ enantiomers of a product
A ⇒ prochiralor mesosubstate
***yield* = 100%(*P*)**

2. Deracemization

Racemic mixture is defined as equal amounts of enantiomers of a chiral molecule. In this process racemic substrate is transformed into one enantiomer of the product.

R, S = enntiomers of a racemic substrate
P = enantiomeric product
yield = $\mathbf{100\%(P)}$



Kinetics

Some functional groups on enzymes such as carboxylic COO- group can act as Bronsted base. Some acidic functional groups are also proton donors. Proton bounded to one of the functional groups result in most active enzyme form. The addition or removal of proton to a critical functional group redistributes the charge on the active site and affects its binding with the substrate. Accordingly, the rate of an enzymatic reaction is a strong function of pH.

Most enzymes follow the kinetics proposed by Michaelis and Menten. Enzyme (E) and substrate (S) first form an enzyme-substrate complex [ES], called the Michaelis-Menten complex. The complex [ES] can then either dissociate back to substrate or cross the energy barrier to form enzyme and product (P).

$$E + S \underset{}{\overset{k_1}{\rightleftharpoons}} [ES]$$
$$[ES] \xrightarrow{k_2} E + P$$

E = enzyme ; S = substrate; P= product

The Michaelis-Menten equation gives the rate of formation of products as :

$$r = k_2 C_{ES} = \frac{k_2 C_{E_0} C_S}{(K_m + C_S)}$$
$$K_m = (k_{-1} + k_2)/k_1$$

Where C_S is the concentration of substrate and C_{EO} is the initial concentration of enzyme.

K_m is known as Michaelis constant. The rate law is derived from following basic assumptions:

1. The first step of binding of substrate to enzyme is faster compared to second step of dissociation of enzyme-substrate complex [ES] to products. Hence 2nd step is the rate determining step.
2. At initial stages of reaction, concentration of product is assumed to be zero.
3. At steady state, the concentration of the intermediate ES is constant.

Rate of formation of product P is given as

$$r = k_2 C_{ES} - k_{-2} C_E C_P \quad \text{----------(1)}$$

At initial stage of reaction, concentration of product, $C_P = 0$

Hence,

$$r = k_2 C_{ES} \quad \text{---------- (2)}$$

Now at steady state condition,

Rate of formation of [ES] = Rate of breakdown of [ES]

$$k_1 C_E C_S + k_{-2} C_E C_P = k_{-1} C_{ES} + k_2 C_{ES}$$

Substituting $C_P = 0$

$$k_1 C_E C_S = k_{-1} C_{ES} + k_2 C_{ES}$$

Or $C_{ES} = \frac{k_1}{k_{-1} + k_2} C_E C_S = \frac{C_E C_S}{K_m}$ ----------(3) where $K_m = \frac{k_{-1} + k_2}{k_1}$

The ratio of rate constants, K_m is known as Michaelis constant.

Substituting concentration C_{ES} from equation (3) in equation (2), rate expression is obtained as

$$r = k_2 C_{ES} = k_2 \frac{C_E C_S}{K_m} \quad \text{----------(4)}$$

The total concentration of enzyme is summation of concentration of free enzyme C_E and concentration of enzyme bound to substrate C_{ES}. Hence total concentration of enzyme C_{E0} is given as

$$C_{E0} = C_E + C_{ES}$$

Substituting value of C_{ES} from equation (3) we obtain

$$C_{E0} = C_E + \frac{C_E C_S}{K_m} = C_E\left(1 + \frac{C_S}{K_m}\right) \qquad \because C_{ES} = \frac{C_E C_S}{K_m}$$

Or $C_E = \dfrac{C_{E0}}{\left(1 + \dfrac{C_S}{K_m}\right)}$

Substituting C_E in equation (4)

$$r = k_2 C_{ES} = \frac{k_2 C_S}{K_m} C_E = \frac{k_2 C_S}{K_m} \frac{C_{E0}}{\left(1 + \dfrac{C_S}{K_m}\right)} = \frac{k_2 C_S}{K_m}\left[\frac{K_m C_{E0}}{\left(K_m + C_S\right)}\right]$$

Or $r = \dfrac{k_2 C_{E0} C_S}{\left(K_m + C_S\right)}$

The rate expression is often referred as Michaelis-Menten rate law. This is valid for many enzyme reactions at constant pH.

Stability & deactivation

If exposed to severe conditions of temperature and pH, enzyme catalysts can undergo

- Loss or modification of functional groups or amino acid residues
- Change in conformations which alter and deactivate the site

The deactivation rate is extremely high with slight increases in temperature for e.g 50% loss of activity in 5 min at 65-70 ^{0} C. Because of their high deactivation, enzymes are shipped and stored under refrigeration (0 - 4 ^{0}C). Some enzymes are active and stable at higher temperature. The α-amylase catalyzes starch liquefaction at 105-115 deg ^{0}C. Catalysts stability can be improved by the following methods:

- Immobilizing enzymes on inert support
    - Covalent binding to a support
    - Adsorption on solid surface
    - Entrapment in gel

Immobilization of enzymes also facilitates recovery of the catalysts.

Enzyme catalysts : limitations

Major limitations for industrial applications are :

1. Expense of isolating and purifying the catalysts
2. Lack of stability when removed from cell or living extra-cellular environment
3. Difficulty and expense of separation in batch operations

Second and third difficulties can be reduced by immobilized enzyme technology mentioned above. Separation of enzymes from the product is difficult, expensive and can cause deactivation.

Industrial bio-catalytic process

Over 300 enzymes are available commercially. About 20 of these enzymes are used in large and moderately large scale production of chemicals, food products and pharmaceuticals. Enzymes used in largest quantities include amylase, glucoamylase, glucose isomerase, lipase, prolease and rennet. Applications of these include starch processing, production of detergents, beverage, milk products and medicine.

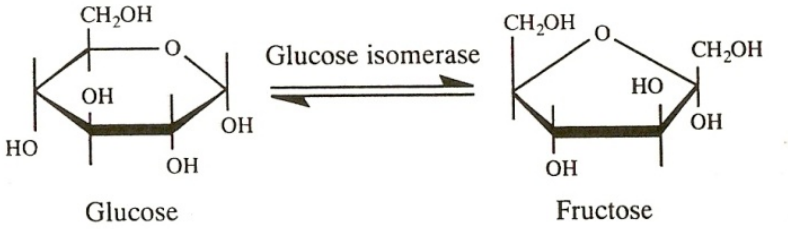
Table 2 : Examples of different types of enzymes used in industry

Enzyme type	Enzyme	applications
Oxidoreductase	catalase	sterilization of milk
	glucose oxidase	removal of glucose from food
	lipoxidase	bleach in white bread
	peroxidase	paper manufacturing
Hydrolase	α and β amylase	brewing
	cellulase	wine making
	glucoamylase	starch processing
	penicillin amidase	antibiotics
	keratinase	leather manufacturing
Lyase	fumerate hydratase	malic acid
Isomerase	glucose isomerase	fructose syrup production

Example of industrial processes

1. Glucose isomerization

Glucose is produced from starch using glucoamylase catalyst. The conversion of glucose to its sweeter form , fructose, is an important enzymatic process. For this reaction, conventional acid –base catalysis is ineffective. This can be done using glucose isomerase catalysts. It is the largest commercial application of immobilized enzymes.



Commercial glucose isomerase catalysts are produced from : *Actinoplanes missouriensis, Bacillus coagulans, Flavobacterium aborescens*

Commercial immobilized form of the catalyst is relatively insensitive to temperature and is effective at high substrate concentration. They require Co^{2+}, Mn^{2+} or Mg^{2+} cofactors and are inhibited by Ca^{2+}, Cu^{2+}, Zn^{2+}, and Hg^{2+} as well as sugar alcohols such as sorbitol and xylitor.

Reported immobilization methods include :

1. Occlusion in gelatin followed by crosslinking with glutaraldehyde
2. Adsorption of purified enzyme on silica followed by crosslinking with glutaraldehyde
3. Binding with polystyrene or resin

However, the third method has been less successful as the catalyst is distorted during processing. Immobilized catalyst forms are granulated to particle size of 0.1 -1.5 mm.

Process

The process is carried out in continuous flow fixed bed reactors at 55-60 ^{0}C temperature. The pH is maintained at 7.5 to 8 by adding Na_2CO_3. $MgSO_4$ is added as catalyst activator and also helps to adjust the pH. Multiple reactors are used to control the product quality. The catalyst has a half-life of 50-175 years at 55 ^{0}C. The schematics in Fig. 1 shows the major steps involved in glucose isomerise process. Filter removes the materials that can plug the catalysts pores. Carbon adsorbent bed is used to remove the impurities that can poison the catalysts. The feed evaporator concentrate the feed to 35-45 % .

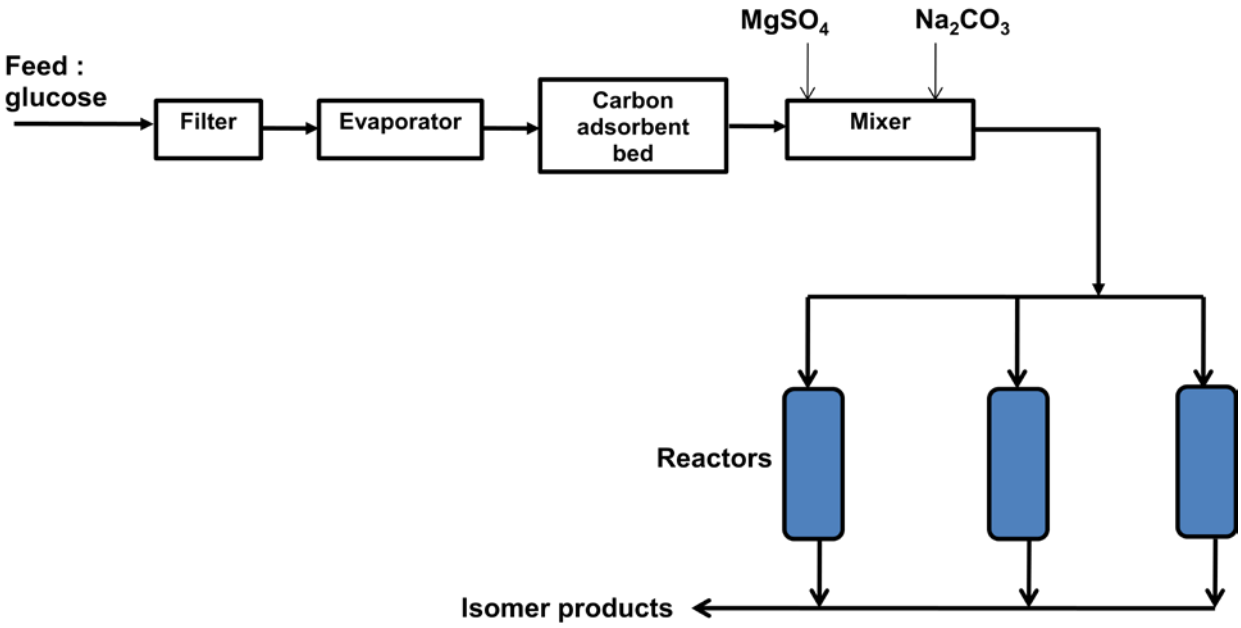


Fig.1. Schematics showing major steps in glucose isomerise process

2. Chiral synthesis of L-aspartic acid

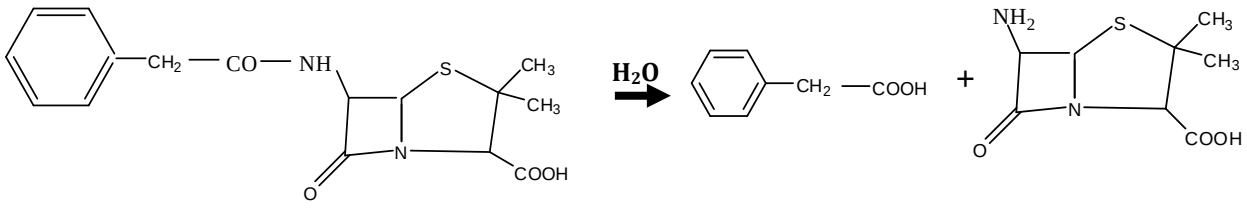
L-aspartic acid is widely used in food and pharmaceutical industries, for example in production of low calorific sweetener aspartame and in treatment of leukemia. It is produced by the reaction of fumaric acid with ammonia over L-aspartase

$$HOOC-CH=CH-COOH+NH_3 \rightarrow HOOC-CH_2-CH(NH_2)-COOH$$

Isolated enzymes are highly unstable. It is prepared by trapping E.colli cell in matrix of polyacryl amide or poly urethane. The immobilized cells are very active at 35-40 ^{0}C achieving 95% conversion. The half-life of these immobilized cells is 120-680 days. Reaction is conducted in a column reactor at 37 ^{0}C at pH 8.5 using a feed of ammonium fumarate. $MgCl_2$ is added for catalyst stability.

3. Enzymatic hydrolysis : production of 6 aminopenicillanic acid (6-APA)

The 6 aminopenicillanic acid is produced by penicillin-acylase catalyzed acetal hydrolysis of penicillins G and U. It is used to produce a large family of highly effective antibiotics such as ampicillin and amoxicillin. Acylase catalyzed hydrolysis of penicillin G involves the removal of the phenyacetyl side chain to produce phenylacetic acid and 6-APA as shown below.



Penicillin G **Phenylacetic acid** **6-APA**

Reaction occurs at 35 ^{0}C at pH 7-8. The pencillin acylase can be obtained from bacterial and fungal organisms. Bacterial acylase are best for penicillin G and fungal acylase most active for penicillin U.

Production of 6-APA is conducted in a stirred batch reactor or continuous stirred tank reactor (CSTR) at 35-40 ^{0}C and 7-8 pH using a feed of 4-15 wt% penicillin G. The pH of the reactor is controlled at 7-8 by continuous addition of alkali to compensate for production of phenylacetic acid.

Text reference

- Piet W.N.M. van Leeuwen, Homogeneous catalysis: Understanding the Art, Springer, 2004
- Piet W.N.M. van Leeuwen, and John C. Chadwick, Homogeneous catalysis: Activity-stability –deactivation, Wiley, VCH, 2011
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