Types of organic reactions

Objectives

The main objectives of the topic are

- to provide a basic foundation of the general organic reactions.
- to place the different mechanisms associated with the different reaction types.
- to impart the stereochemistry associated with the different types of reactions.
- to encourage enterprising research in organic chemistry.

Summary

The study of reactions and relevant synthetic applications of organic compounds concernswith the development of powerful and useful reactions, inventionof strategies for the construction of defined target molecules.To pursue the objectives general organic reactions are grouped together into some categories based on their kinetic and dynamic characters. The general groups are substitution, addition, elimination and rearrangement reaction. Further each group may be subdivided on the basis of the reactive intermediates involved or the nature of the reaction center. Different types of the reactions are accompanied by different stereochemical outcome also.

TEXT

Introduction:

There are millions of reactions involving naturally occurring as well as synthetic organic molecules. It is very difficult to learn and understand each and every reaction if they are treated and analyzed as unique and isolated process.Using certain generalized basic principles such vast organic reactions can be woven together and fitted neatly into general patterns. Based mainly on the functional groups, electron rich sites, electron deficient sites and weak polar bonds of the molecules, organic reactions may be categorized into four general types: Substitution reaction, Addition reaction, Elimination reaction and rearrangement reaction. In substitution reactions an atom or group bonded to a carbon atom of the reactant molecule is replaced by a new atom or group. In an elimination reaction two atoms or groups are removed from the reactant molecule to form the product. Substitution and elimination take place side by side in a competitive pattern. Addition reactions two reactant molecules or reactant

molecule and reagent add together to form a single product without leaving out any other part.In rearrangement reactions there is reorganization of bonds along with atoms and groups of the reactant molecule to give a new compound.

Organic reactions:

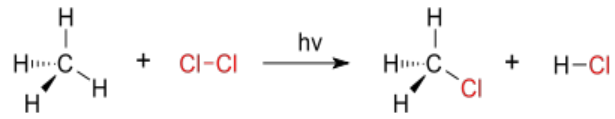
Enterprises in chemical synthesis concernwith the development of powerful and useful reactions, inventionof strategies for the construction of defined target molecules.So as to pursue the objectives general nature of the reactions encountered with organic molecules should be thoroughly understood. Here one must be familiar with two aspects:first the structure and representation of organic molecules and secondly the descriptionof the reaction mechanism. From static and dynamic aspects organic reactions may be classified into four general categories mentioned below:

1. Substitution reactions
2. Addition reactions
3. Elimination reactions and
4. Rearrangement reactions

1. Substitution reactions

Substitution reactions involve the replacement of an atom or group of the reactant molecule by a new atom or group.

For example,in the presence of diffused sunlight chlorine substitutes hydrogen from methane to form chloromethane as product



On the basis of the mechanism involved or nature of the leaving and the incomingatom / group, substitution reactions may be classified into the following types:

(i) Nucleophilic substitution reactions
(ii) Electrophilic substitution reactions
(iii) Free radical substitution reactions

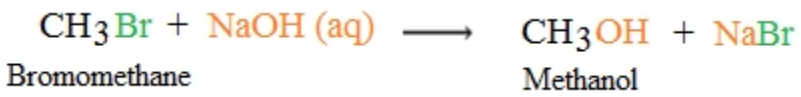
1.1 Nucleophilic substitution reactions

Innucleophilic substitution reactions both the attacking atom/group and the leaving atom/group are nucleophiles (ei. electron rich species). The attacking atom or group comes with an electron pair and uses it to form a new sigma bond while the leaving group moves away along with the bonding electron pair.

This type of reactions occurs mainly in compounds with an electronegative atom or group bonded to a sp^3-hybridized carbon atom.Haloalkanes are a good family of compounds that undergo nucleophilic substitution reactions

with many different nucleophilic reagents. The halogen atom can easily go away with the bonding electrons to be stable halide ions and are thus said to be good leaving groups.

For example,
Hydrolysis of bromomethane with aqueous sodium hydroxideto givemethanol is a nucleophilic substitution reaction. Here the leaving group bromide ion at the sp^3-hybridized carbon is substituted by the attacking nucleophile, hydroxide ion of sodium hydroxide.



Based on the timing of bond formation and bond cleavage at such sp^3 hybridized carbon atom, two main reaction types of nucleophilic substitution, are available:

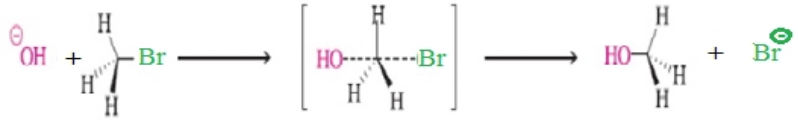
(i) 2reaction
(ii) 1 reaction

2 reaction

The abbreviation2 stands for substitution nucleophilic bimolecular. The reaction is characterized by

- a second order kinetics ei. its rate depends on the first power of the concentration of both the substrate and reagent,

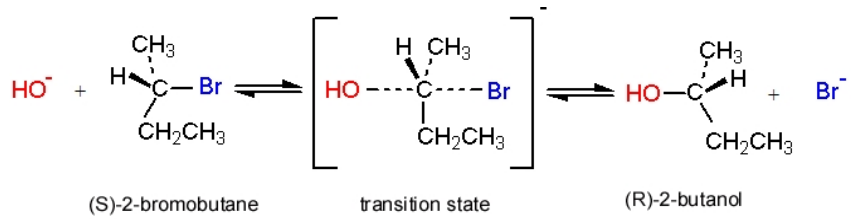
- a concerted single step mechanism passing through a transition state without intermediate species formation. Partial bond formation and partial bond cleavage take place in the transition state.



Transition state

- stereospecificoutcome in the sense that different stereoisomers undergoing the reaction give different stereoisomericforms of the product. The incoming nucleophile attacks from a side opposite to the leaving group and attaches to a position opposite to that the leaving group was present. The backside attack turns the tetrahedral configuration around the carbon centre inside out and it is said to undergo inversion of configuration (often called Walden inversion). When the reaction centre is a chiral carbon inversion of configuration

around it in the product results in enantiomeric form. For example the substitution of the bromine atom by hydroxide ion at the chiral carbon with S-configuration of 2-bromobutane by 2 mechanism results in 2-butanol with R- configuration at the chiral carbon.



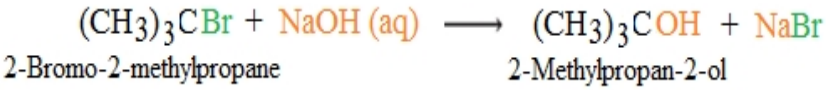
(S)-2-bromobutane transition state (R)-2-butanol

Factors which favour2 reactions are
(a) strong nucleophiles
(b) good leaving group with polarizableand electronegative nature
(c) small groups with less steric hindrance around the reaction centre
(d) Polar aprotic solvents

1reactions

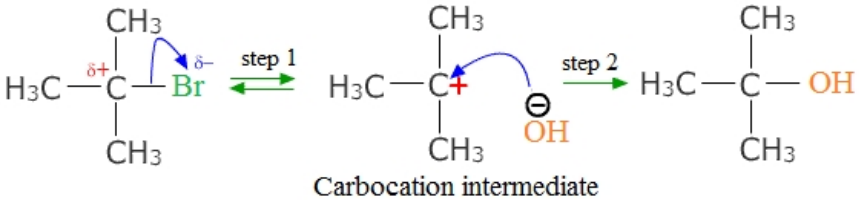
The abbreviation 1stands for substitution nucleophilicunimolecular. These reactions are characterized by:

- a first order kinetics with respect to the substrate ei. its rate depends on the first power of the concentration of only the substrate and independent of the reagent. For example for hydrolysis of 2-bromo-2-methylpropane with aqueous alkali is expressed as



2-Bromo-2-methylpropane 2-Methylpropan-2-ol

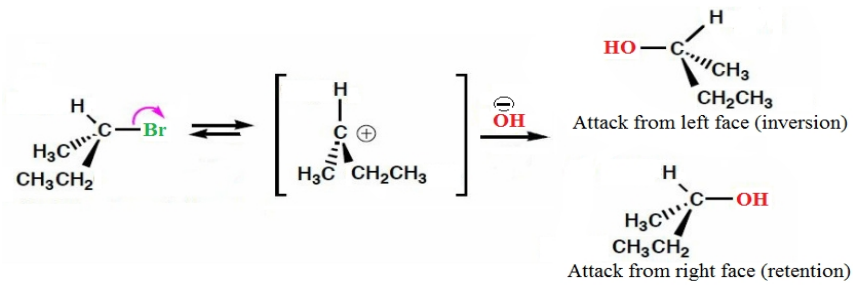
- atwo-step mechanism in which the leaving group is releasedfirst in a reversible slow process followed by a fast second step in which the attacking nucleophile attaches to the carbocation intermediate.



Carbocation intermediate

- non-stereospecific in nature in the sense that a mixture of inversion and retention in configuration around the reaction centre in the product is achieved. In the case of substrates with chiral reaction centre,

racemization (ei. formation of enantiomers in equal amounts) occurs. Here the cationic carbon in the carbocation intermediate is sp^2 hybridized and is planar in shape. The attacking nucleophile can attach to the carbon from either side with equal chances. When the attack takes place from the side in which the leaving group left the product has retention in configuration and attack from the other side results in inversion of configuration.



Here hydrolysis of 2-bromobutane with alkali by S_N1 process gives a racemic mixture of the product butan-2-ol.

Factors which favour1 reactions are

(a) good leaving group with polarizable and electronegative nature
(b) groups that stabilize carbocation like alkyl groups, conjugated multiple bonds
(c) Polar protic solvents

Nucleophilic substitution can take place at sp^2-hybridized carbon also. There are two main cases- nucleophilic substitution at aromatic carbon and nucleophilic substitution at acyl carbon. In these cases the mechanism follows different processes.

Aromatic nucleophilic substitution reactions

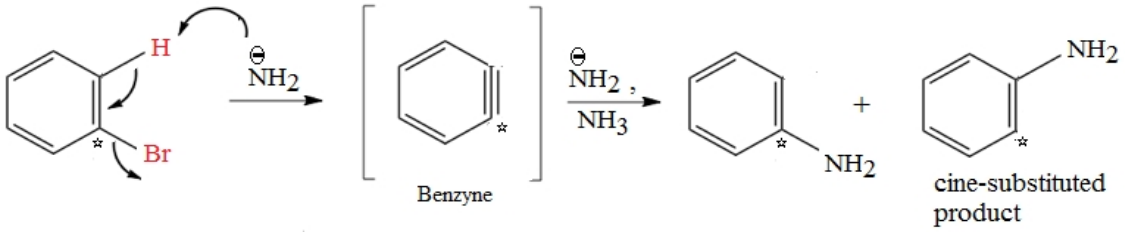
A nucleophilic leaving group from an aromatic can also be substituted by another nucleophile.Here nucleophilic substitution can take place in two different mechanisms:

(i) Elimination-Addition mechanism (also known as Benzyne mechanism) and
(ii) Addition-Elimination mechanism

Elimination-Addition mechanism

In the first step of this mechanism,with the elimination of the leaving group a strong base removes a proton from an adjacent position and generates a reactive **Benzyne** intermediatecontaining a highly strained triple bond in the ring. In the second step the nucleophilicattack at either end of the strained triple bond followed by protonation gives the product. Here the substitution at the position adjacent to that of the leaving group is called **cine-substitution**. This mechanism operates when there is no activating group in the aromatic ring. For

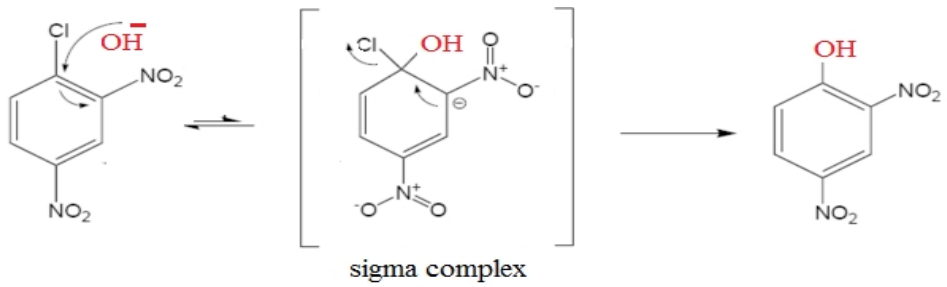
example the substitution reaction of bromobenzene with sodamide goes by this mechanism.



Addition-Elimination mechanism

When strongly electron withdrawing groups are present at o,p-positions with respect to the leaving group, the substitution mechanism goes by Addition-Elimination mechanism(also known as $S_NAr$mechanism). Here the attacking nucleophile adds to the carbon atom bearing the leaving group and generates a resonance stabilized anionic sigma complex. In a fast second step the sigma complex eliminates the leaving group to give the product.

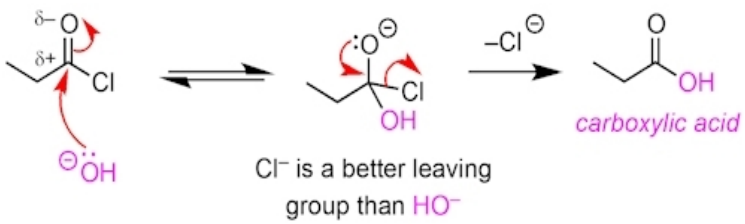
For example,2,4-dinitrochlorobenzene on heating with aqueous sodium hydroxide solution the chlorine atom is substituted by hydroxide ion by addition-elimination mechanism.



In the case of diazonium group as the leaving group, the elimination however goes by the general S_N1 mechanism.

Nucleophilic acyl substitution reactions

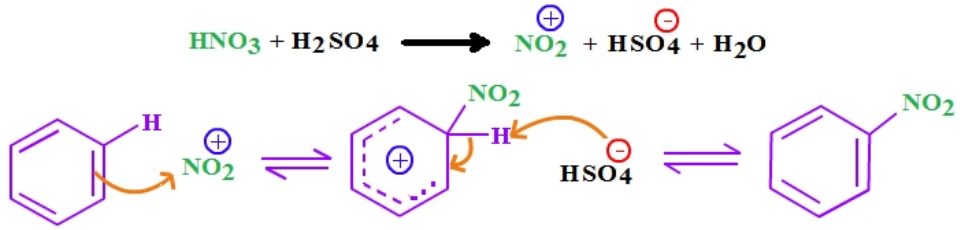
Nucleophilic substitution at acyl carbon of carboxylic acid derivatives goes in two steps. In the first step the attacking nucleophile adds to the trigonalreaction centreand forms a tetrahedral intermediate. In the second step the leaving group is eliminated to form the product. For example Propanoyl chloride on hydrolysis with alkali solution undergoes nucleophilic substitution at the acyl carbon atom.



1.2 Electrophilic Substitution reactions

Substitution reactions in which both the attacking group and the leaving group are electrophiles (ei. electron deficient species) are called electrophilic substitution reaction.The leaving group is eliminated without the bonding electron pair and the same is used to form a new sigma bond with the attacking electrophile. This type of substitution is generally encountered at aromatic ring with a hydrogen atom as the leaving group.

All aromatic electrophilic substitution reactions proceed through two basic steps. In the rate determining first step the attacking electrophile is generated and it adds to the aromatic ring to produce a resonance stabilized cationic sigma complex (also known as arenium ion). In the second step the sigma complex regains the aromatic stability by eliminating a proton from the tetrahedral carbon atom. For example in nitration of benzene with a mixture of concentrated nitric acid and concentrated sulphuric acid the electrophile nitronium ion substitutes a proton from the aromatic ring.

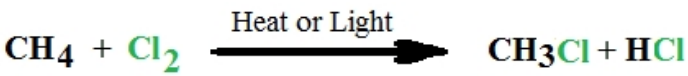


Halogenation, sulphonation, Friedel Craft's alkylation, Friedel Craft's acylation are the other important electrophilic substitution reactions at aromatic rings.

1.3 Free radical substitution

Free radicals are highly reactive species with an odd number of electrons. They can abstract an atom with one bonding electron from a molecule leaving behind another radical resulting in radical substitution reaction.This type of reaction is not so common as the cases of electrophilic and nucleophilic substitutions but is important as it shows many effects in biological systems.

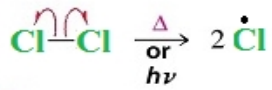
A simple free radical substitution reaction may be cited by the chlorination of methane.



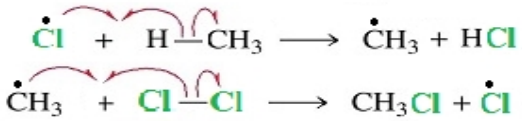
A general free radical substitution reaction occurring at saturated sp^3-hybridized carbon atom proceeds through a chain mechanism. The Basic steps in the chain

mechanism may be represented as follows:

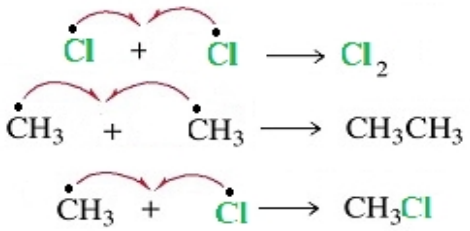
(a) Chain initiation: Chain initiation involves the absorption of energy form radiation or heat and breaking the covalent bond between the chlorine atoms homolytically to generate chlorine free radicals.



(b) Chain propagation: The chlorine free radical abstracts a hydrogen atom from the substrate molecule thereby leaving the carbon as another radical. The carbon free radical then reacts with a chlorine molecule to form product and leave behind a chlorine free radical.



(c) Chain termination: Chain termination involves combination of free radicals to form neutral molecules. As no free radical is generated the chain process stops once such a step occurs.



In aromatic systems however the mechanism simply does not operate. Here the reaction goes just like electrophilic substitution. The aryl radical formed adds to another aromatic ring thereby generating a resonance stabilized radical intermediate.

2. Addition reaction

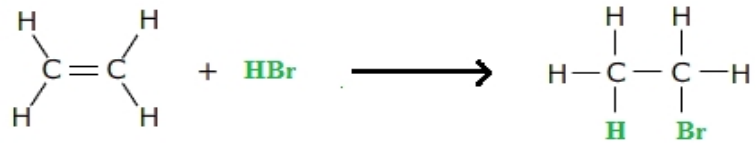
In addition reaction two molecules combine to form a product molecule. This type of reaction is encountered in substrate molecules containing multiple bonds. In principle many reagents can add to a multiple bond to form stable products usually in two steps. Based on the nature of the species added in the primary stage of the mechanism, the reaction may be classified into the following classes:

(i) Electrophilic addition reaction
(ii) Free radical addition reaction and
(iii) Anionic addition reaction

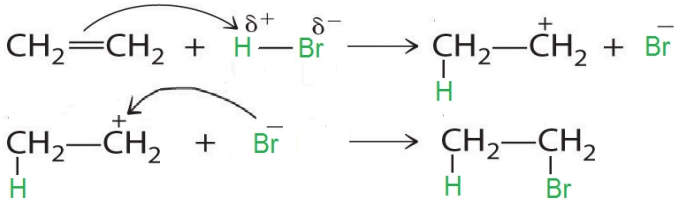
2.1 Electrophilic addition reaction

The pi- electrons of multiple bonds are loosely held by the carbon nuclei

and hence addition of electrophilic part of the reagent is highly encouraged. For example addition of hydrogen bromide to ethene takes place by electrophilic addition mechanism.

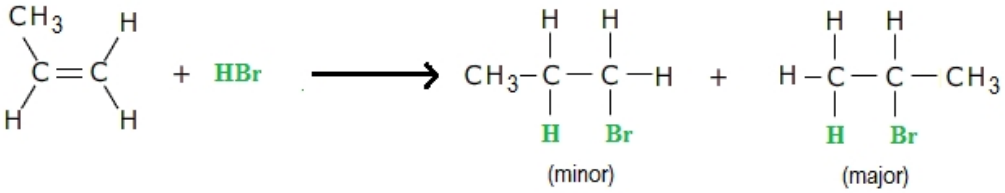


In the first step of the reaction the electrophile is added to the multiple bond and generates a carbocation intermediate. In the second stage of the reaction a nucleophile adds to the cationic intermediate.



When the substrate and the reagent are unsymmetrical, the addition reaction shows regioselectivity. In such systems the outcome of the addition reaction follows an empirical rule called Markovnikov's rule. According to the rule the positive end of the reagent attaches to the multiple bonded carbon having more hydrogen atoms. Of all possible addition products that one formed according to the rule will be major product.

For example the addition of HBr to propene gives 2-bromopropane as the major product.



Depending on the substrate and reaction conditions the addition of the electrophile and nucleophile shows stereochemical preferences. When they are added from the same side of the multiple bond the addition is said to be syn-addition and addition from opposite sides is called anti-addition. For example addition of bromine to but-2-ene is stereospecifically anti-addition and hence the trans-but-2-ene specifically gives the meso-isomer of the product.

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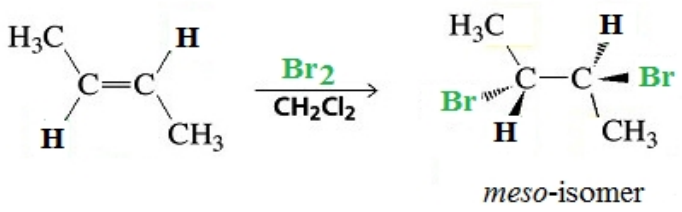
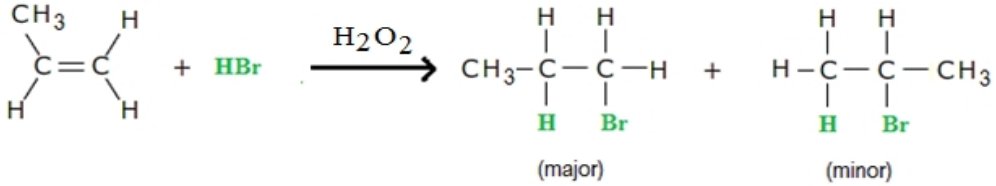


meso-isomer

2.2 Free radical addition reaction

Free radical addition reactions occur either in the gas phase or in an inert non-polar solvent in the presence of UV-light or diffused sunlight, heat or other radical sources like peroxides. The radical addition takes place through the usual chain reaction steps- initiation, propagation and termination. An interesting case of free radical addition is the addition of HBr to unsymmetrical multiple bond with a regioselectivity anti- to Markovnikov's rule. Thus addition of HBr to propene in the presence of a peroxide gives 1-bromopropane as the major product.



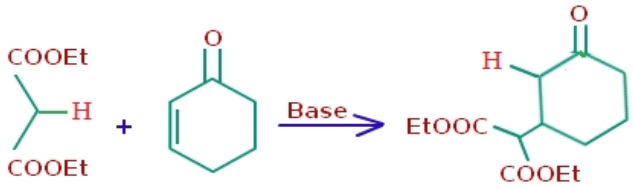
(major) (minor)

In general radical addition reactions are a little less controllable as compared to the other ionic addition reactions. However in biological systems in the presence of enzymes the reactions are more controllable.

2.3 Nucleophilicaddition reaction

Nucleophilic addition reaction operates when electron withdrawing groups and atoms are present around the multiple bonds.The electron withdrawing groups reducethe pi-electron density around the multiple bonded carbon atoms and the attack by electron rich nuleophile is facilitated.The most important reactions of this category are the Michael addition reactions.

For example, the addition of diethyl malonate to cyclohex-2-enone in the presence of a base takes place by the initial addition of the carbanion formed by removal of the acidic methylene hydrogen.



The addition reaction of all the types takes place not only at carbon-carbon

multiple bonds but also at multiple bonds involving heteroatom.Further the addition may take place not only at adjacent positions but also at 1,4-positions.

3. Elimination reaction

An elimination reaction involves the removal of two atoms or groups from the substrate molecule. Often it accompanies and competes with substitution reaction.

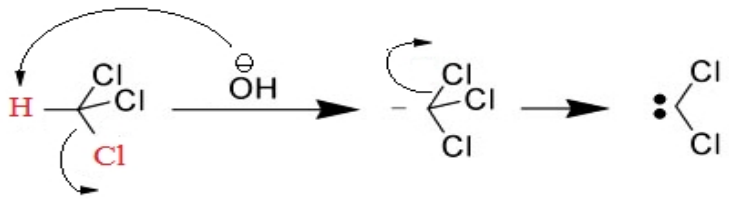
Depending on the relative positions of the atoms from which the two atoms or groups are removed, elimination reactions may be classified into two main types:

1. α- Elimination 2. β- Elimination

3.1α- Elimination

When the two atoms or groups are removed from the same centre of the substrate molecule theelimination is α-elimination or 1,1-elimination. The reaction gives an unstable carbene or nitrene as product.

For example removal of hydrogen and chlorine from the same carbon of chloroform by the action of alkali to form dichlorocarbene is α- elimination reaction.



3.2β- Elimination

Elimination reaction in whichthe two atoms or groups are removed from adjacent centres is called β- elimination or 1,2-elimination reaction. This type of elimination is the most common elimination reaction and results in the formation of a new π-bond ei. a double bond or triple bond. Here one of the atom or group is eliminated with the bonding electron pair while the other atom or group is removed without bonding electron (often hydrogen atom).

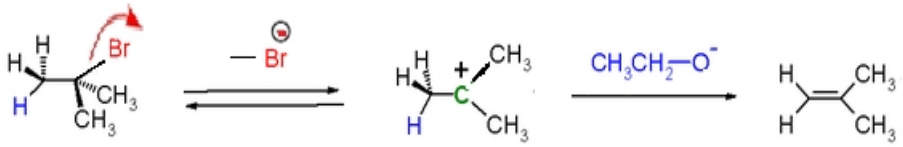
Depending on the conditions involved and timing of removal of the two atoms or groups, elimination reactions are classified into three types:

(i) El reaction
(ii) E2 reaction
(iii) E1cB reaction

3.2.1El reaction

The abbreviation E1 stands for elimination unimolecular. The reaction obeys

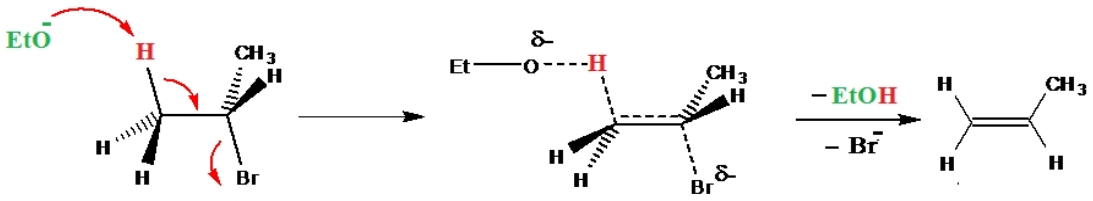
a first order kinetics with a mechanism of two basic steps. In the first slow rate determining step the leaving group is eliminated along with the bonding electron pair to generate a carbocation intermediate. In thefast second step, abase abstracts a proton from the carbon atom adjacent to the cationic carbon(referred to as β-hydrogen)anda new pi bond is formed in between the two carbon atoms.



Like other reactions involving carbocation intermediate, the E1 may be accompanied by rearrangement to give mixtures of products.In a pure E1 reaction(without ion pairs, etc.), the product should be completely non-stereospecific.

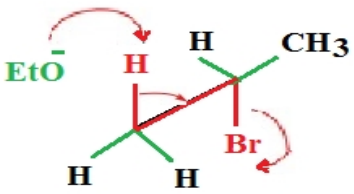
3.2.2 E2 reaction

The abbreviation E2 stands for elimination bimolecular. It obeys asecond order kinetics (firstorder in substrate and first order in base).The mechanism takes place in one step in whichthe two groups depart simultaneously,with the proton being pulled off by a base.

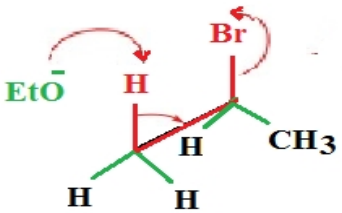


Transition state

Stereochemically, E2 reaction is stereospecific in nature.The five atomsinvolved (including the base) in the transition state must be in one plane. There aretwo ways for this to happen. The two atoms or groups may be trans to one another with a dihedral angle of 180° (called anti-periplanar) or they may be cis with a dihedral angle of 0°(called syn-periplanar). Elimination from anti-periplanar conformation is called **anti-elimination** and elimination from the syn-periplanar conformation is called **syn-elimination**.



Anti-elimination



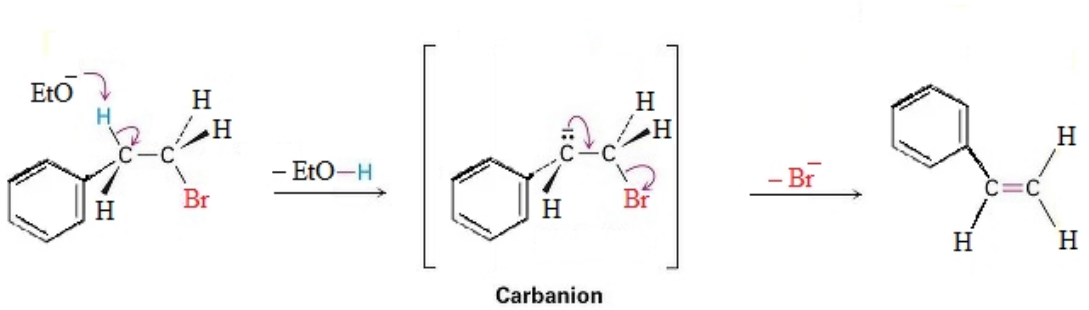
Syn- elimination

In the absence of special effects (such as ring strain) anti-elimination is usually greatlyfavored over syn-elimination, probablybecause anti-periplanar is a staggered conformation and the molecule requires lessenergy to reach this transition state than it does to reach the eclipsed transition state of syn-periplanar form.

3.2.3E1cB reaction

E1cB stands for elimination unimolecular from conjugate base. The reaction mechanism goes in two steps. In the reversible first step the β-hydrogen is removed by the base to generate a carbanion intermediate (conjugate base of the substrate). The second step involves the elimination of the leaving group as a new pi-bond is formed using the electron pair of the anionic carbon.

For example, the elimination of hydrogen bromide from 1-bromo-2-phenylethane to form styrene goes by this mechanism.



This type of reaction is most likely to take place with substrate having acidic β-hydrogen and poor leaving groups.

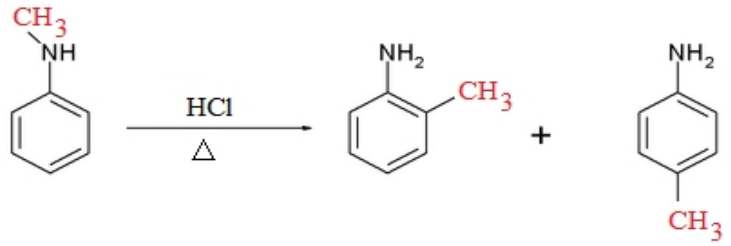
Irrespective of the types of reaction mechanism involved, in elimination reactions with substrates having two or more different β-hydrogen atoms, the multiple bond is formed regioselectively. The regioselectivity of the new multiple bond and predominant product formation is governed by certain rules.

(a) The multiple bond is not formed at bridgehead carbon.
(b) In the absence of specific conditions the multiple bond is formed according to **Zaitsev's rule**. According to the rule the elimination takes place in such a way that most substituted multiple bond(ei. having least number of hydrogen atoms) is formed.
(c) If multiple bond or aromatic ring is already present in the substrate, the new multiple bond is formed conjugated to them.
(d) In E2 reaction with charged leaving group like , etc. the elimination forms the least substituted multiple bond as predominant product (**Hofmann's rule**) if the substrate is acyclic.

4. Rearrangement reaction

In rearrangement reactions an atom or group migrates from a center to another center in the same molecule. The original center is called migration origin and the final center is called migration terminus.

For example in the Hofmann-Martiusrearrangement of N-alkylanilines the alkyl group migrates from nitrogen atom to the o- and p-carbon atom of the aromatic ring.



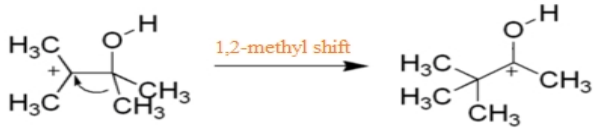
Rearrangement reactions are classified into three main categories on the basis of the nature of the group transferred.

(a) Nucleophilic or anionic rearrangement
(b) Electrophilic or cationic rearrangement and
(c) Free radical rearrangement

4.1Nucleophilic rearrangement

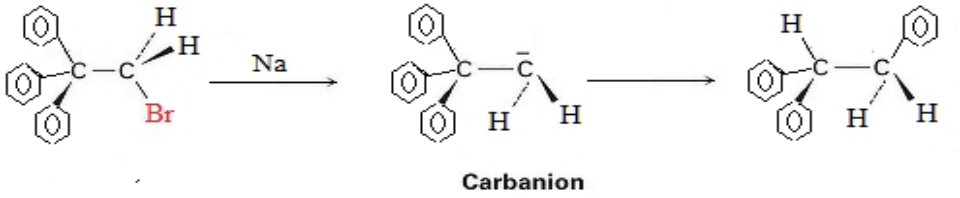
In nucleophilic rearrangement an atom or group is transferred along with the bonding electron pair. Here the migration terminus should be a center of electron deficient nature so as to accept the incoming group along with the electron pair.

For example in Pinacol-Pinacolone rearrangement the 1,2-methyl shift of carbocation intermediate is anucleophilic rearrangement.



4.2Cationic rearrangement

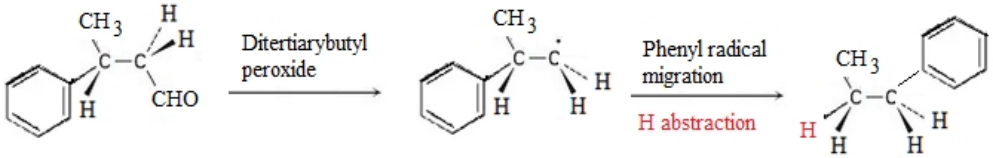
In electrophilic rearrangement the migrating group is transferred without bonding electron to an electron rich migration terminus.For example Ph_3CCH_2Br on treatment with sodium undergoes rearrangement by the cationic migration of the phenyl group towards the anionic carbon.



This type of rearrangement is very rare.

4.3Free radical rearrangement

In free radical rearrangement the migrating group is transferred with a single bonding electron to the migration terminus which must be already a radical center. The new radical then stabilizes by further reactions.For example the rearrangement of 3-phenylbutanal on treatment with ditertiarybutyl peroxide to 2,5-diphenylhexane involves the phenyl radical migration.



Conclusion

To carry out enterprising research and development, a basic foundation for organic reactions is framed by classifying them into some different categories. The general groups are substitution, addition, elimination and rearrangement reaction. Further each group are subdivided on the basis of the reactive intermediates involved, mechanism and the nature of the reaction center. A particular type of reaction may involve different mechanisms with aliphatic and aromatic reaction centres. The stereochemical nature of the different types of reaction is also different.

Glossary

1. **Walden Inversion**- Inversion in configuration around a chiral center.
2. **Syn-addition**- Addition of the reagent from the same side of the double bond.
3. **Anti-additIon-** Addition of the reagent from opposite sides of the double bond.
4. **α-Elimination**- Elimination of the two groups from the same atom

of the molecule.

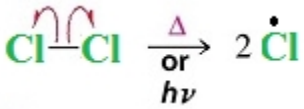
5. **β-Elimination** -Elimination of the two groups from adjacent atoms of the molecule.
6. **Stereospecific reaction**- Reaction in which a particular stereoisomer of the reactant gives a particular stereoisomer of the product.
7. **Racemic modification**- A mixture of equimolar amounts of the enantiomers.
8. **Rate equation-** An equation that shows the relationship between rate of reaction and concentration of the reactants.
9. **Reactive intermediate**- A high energy unstable species formed in the course of a reaction.
10. **Polar protic solvent-** A solvent containing polar hydrogen atom that can be involved in hydrogen bonding.

FAQ

1. **What are nucleophiles? Give example.**
   Ans: Nucleophiles are chemical reagents that come with an electron pair for bond formation during the reaction. They may be anionic nucleophile like , etc. or neutral neucleophile like, H_2O, NH_3 etc.
2. **What is a nucleofuge?**
   Ans: An atom or group which is eliminated along with the bonding electron pair during the reaction is called nucleofuge.
3. **What is an electrofuge?**
   Ans: An atom or group which is eliminated without the bonding electron pair during the reaction is called electrofuge.
4. **What are electrophiles? Give example.**
   Ans: Electron deficient chemical reagents that accept electron pair from other to form chemical bond during the reaction are called electrophile. They may be cationic electrophile like , etc. or they may be neutral electrophile like , etc.
5. **Explain heterolytic and homolytic bond cleavages.**
   Ans: Covalent bond cleavages in organic raections take place in two ways. When a covalent bond is broken in such a way that both the bonding electrons are taken away by one of the departed atom/group leaving behind the other part without electron it is called heterolytic bond cleavage. This type of cleavage results in formation of ions. For example

the ionization of HCl involves heterolytic bond cleavage.

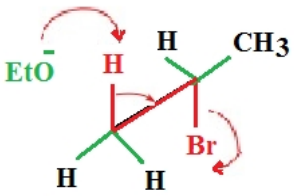
When a covalent bond is broken in such a way that the departed atoms/groups depart with one of the bonding electrons it is called hemolytic cleavage. Here free radicals are formed. For example under thermal or radiation initiation chlorine molecule undergoes hemolytic bond cleavage.



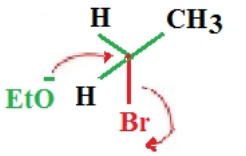
6. **Explain the difference between a base and a nucleophile.**

Ans: Both base and nucleophile are electron donors in chemical reactions. When an electron rich species uses its electron pair to form a covalent bond with a proton it is referred to as base. When the species uses its electron pair to form covalent bond with other atoms (specially carbon atom) it is referred to as nucleophile.

For example ethoxideion canfuction as base as well as nucleophile under suitable conditions.



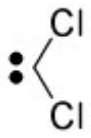
Ethoxide ion acts as base



Ethoxide ion acting as nucleophile

7. **What are carbenes?**

Ans: Reactive intermediates containing a divalent carbon with a nonbonding electron pair are called carbenes. When the two electrons occupy the orbital the species is said to be singlet carbine and when the two nonbonding electrons occupy different orbitals the species is called triplet carbine.

Example: Dichlorocarbene 

8. **Explain active methylene group.**

Ans: Methylene group (-CH_2-) linked to electron withdrawing atoms or groups can release the hydrogen atom as proton and the carbanion is

stabilized by the electron withdrawing atoms/groups. Such methylene groups are said to be active methylene group.

For example the methylene group in diethylmalonate is active because of the two ester groups.

9. **Arrange the following species in increasing order of nucleophilicity and give reason:**

, ,

Ans: The increasing order of nucleophilicity of the species is <<. Here the presence of the lone pair electrons on the adjacent oxygen linked to the nitrogen increases the nucleophilicity of hydroxylamine. The presence of the negative charge makes the amide ion highly nucleophilic.

10. **Identify the attacking electrophile in Reimer-Tiemann reaction.**

Ans: Reimer-Tiemann reaction is the formylation reaction of phenols at o,p-positions by reaction with chloroform in the presence of an alkali. Here the attacking electrophile is dichlorocarbene generated by the reaction of chloroform and alkali.