DIRECTORATE OF DISTANCE & CONTINUING EDUCATION

MANONMANIAM SUNDARANAR UNIVERSITY

TIRUNELVELI- 627 012

OPEN AND DISTANCE LEARNING (ODL) PROGRAMMES

(FOR THOSE WHO JOINED THE PROGRAMMES FROM THE ACADEMIC YEAR 2023–2024)

M. Sc. Chemistry

Course material

Core I - Organic Reaction Mechanism - I

Course Code SCHM11

Prepared by

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Tirunelveli - 12

Semester - I

Course: CORE - I **Course Code** SCHM11

ORGANIC REACTION MECHANISM - I

UNIT-I: Methods of Determination of Reaction Mechanism: Reaction intermediates, The transition state, Reaction coordinate diagrams, Thermodynamic and kinetic requirements of reactions: Hammond postulate. Methods of determining mechanism: non-kinetic methods - product analysis, determination of intermediates-isolation, detection, and trapping. Cross-over experiments, isotopic labelling, isotope effects and stereo chemical evidences. Kinetic methods - relation of rate and mechanism. Effect of structure on reactivity: Hammett and Taft equations. Linear free energy relationship, partial rate factor, substituent and reaction constants.

UNIT-II: Aromatic and Aliphatic Electrophilic Substitution: Aromaticity: Aromaticity in benzenoid, non-benzenoid, heterocyclic compounds and annulenes. Aromatic electrophilic substitution: Orientation and reactivity of di- and polysubstituted phenol, nitrobenzene and halobenzene. Reactions involving nitrogen electrophiles: nitration, nitrosation and diazonium coupling; Sulphur electrophiles: sulphonation; Halogen electrophiles: chlorination and bromination; Carbon electrophiles: Friedel-Crafts alkylation, acylation and arylation reactions. Aliphatic electrophilic substitution Mechanisms: SE2 and SEi, SE1- Mechanism and evidences.

UNIT-III: Aromatic and Aliphatic Nucleophilic Substitution: Aromatic nucleophilic substitution: Mechanisms - S_NAr, S_N1 and Benzyne mechanisms - Evidences - Reactivity, Effect of structure, leaving group and attacking nucleophile. Reactions: Oxygen and Sulphur-nucleophiles, Bucherer and Rosenmund reactions, von Richter, Sommelet- Hauser and Smiles rearrangements. S_N1, ion pair, S_N2 mechanisms and evidences. Aliphatic nucleophilic substitutions at an allylic carbon, aliphatic trigonal carbon and vinyl carbon.S_N1, S_N2, S_Ni, and S_E1 mechanism and evidences, Swain- Scott, Grunwald-Winstein relationship - Ambident nucleophiles.

UNIT-IV: Stereochemistry-I: Introduction to molecular symmetry and chirality – axis, plane, center, alternating axis of symmetry. Optical isomerism due to asymmetric and dissymmetric molecules with C, N, S based chiral centers. Optical purity, prochirality, enantiotopic and diastereotopic atoms, groups, faces, axial and planar chirality, chirality due to helical shape, methods of determining theconfiguration. Racemic modifications: Racemization by thermal, anion, cation, reversible formation, epimerization, mutarotation. D, L system, Cram's and Prelog's rules: R, S-notations, proR, proS, side phase and re phase Cahn-Ingold-Prelog rules, absolute and relative configurations. Configurations of allenes, spiranes, biphenyls, cyclooctene, helicene, binaphthyls, ansa and cyclophanic compounds, exo-cyclic alkylidene-cycloalkanes. Topicity and prostereoisomerism, chiral shift reagents and chiral solvating reagents. Criteria for optical purity: Resolution of racemic modifications, asymmetric transformations, asymmetric synthesis, destruction. Stereoselective and stereospecific synthesis.

UNIT-V: Stereochemistry-II: Conformation and reactivity of acyclic systems, intramolecular rearrangements, neighbouring group participation, chemical consequence of conformational equilibrium - Curtin-Hammett Principle. Stability of five and six-membered rings: mono-, di- and polysubstituted cyclohexanes, conformation and reactivity in cyclohexane systems. Fused and bridged rings: bicyclic, poly cyclic systems, decalins and Brett's rule. Optical rotation and optical rotatory dispersion, conformational asymmetry, ORD curves, octant rule, configuration and conformation, Cotton effect, axial haloketone rule and determination of configuration.

Recommended Text

1. J. March and M. Smith, Advanced Organic Chemistry, 5th edition, John-Wiley and Sons.2001.
2. E. S. Gould, Mechanism and Structure in Organic Chemistry, Holt, Rinehart and Winston Inc., 1959.
3. P.S.Kalsi, Stereochemistry of carbon compounds, 8th edition, New Age International Publishers, 2015.
4. P. Y. Bruice, Organic Chemistry, 7th edn, Prentice Hall, 2013.
5. J.Clayden, N. Greeves, S. Warren, Organic Compounds, 2nd edition, Oxford University Press, 2014.

Reference Books

1. F.A. Carey and R.J. Sundberg, Advanced Organic Chemistry Part-A and B, 5th edition, Kluwer Academic / Plenum Publishers, 2007.
2. D. G. Morris, Stereochemistry, RSC Tutorial Chemistry Text 1, 2001.
3. N.S. Isaacs, Physical Organic Chemistry, ELBS, Longman, UK, 1987.
4. E. L. Eliel, Stereochemistry of Carbon Compounds, Tata-McGraw Hill, 2000.
5. I. L. Finar, Organic chemistry, Vol-1 & 2, 6th edition, Pearson Education Asia, 2004.

UNIT-I: Methods of Determination of Reaction Mechanism

Reaction intermediates, The transition state, Reaction coordinate diagrams, Thermodynamic and kinetic requirements of reactions: Hammond postulate. Methods of determining mechanism: non-kinetic methods – product analysis, determination of intermediates-isolation, detection, and trapping. Cross-over experiments, isotopic labelling, isotope effects and stereo chemical evidences. Kinetic methods - relation of rate and mechanism. Effect of structure on reactivity: Hammett and Taft equations. Linear free energy relationship, partial rate factor, substituent and reaction constants.

Reaction mechanism

A reaction mechanism is the actual process in which a reaction occurs. It explains the order and number of bonds that are broken, the number of steps involved, the rate of each step, and so on. The reaction mechanism describes the sequence of elementary reactions that must happen in order to go from reactants to products. Reaction intermediates are formed in one step and then consumed in a later step of the reaction mechanism. There are several mechanisms for different organic reactions, but certain patterns can still be used to analyse them in a more systematic and simplified way. Before we briefly classify different types of organic reaction mechanisms, it is better to first recall the basic terminology involved.

1. Substrate and reagent: A typical organic reaction is believed to occur through the breaking or making of one or more covalent bonds, and it is convenient to refer to one reactant as the "substrate" and the other as the "reagent". Generally, the more reactive species is referred to as the reagent, while the less reactive species is considered the substrate.
2. Molecularity: The molecularity of a chemical reaction can simply be defined as the number of colliding molecular species involved in a single step. The most common types are unimolecular and bimolecular reactions, which involve one and two molecular entities, respectively.
3. Electrophiles and nucleophiles: An electrophile is a species that loves electrons or accepts electron pairs. Generally, electrophiles are positively charged or neutral entities with vacant orbitals that are attracted to an electron-rich centre. Electrophiles participate in chemical reactions by accepting an electron pair to form a bond with the nucleophilic reactant. Since electrophiles accept electrons, they are considered Lewis acids. A nucleophile is a species that loves positive centres or donates electron pairs. Normally, nucleophiles are negatively charged or neutral electron-rich entities with lone pairs of electrons that are attracted to an electron-deficient centre. Nucleophiles participate in chemical reactions by donating an electron pair to form a bond with the electrophilic reactant. Since nucleophiles donate electrons, they are considered Lewis bases.
4. Leaving Group: The part of the substrate molecule that becomes detached is typically referred to as the leaving group. Leaving groups with electron pairs are labeled as nucleofuges, while those without electron pairs are called electrofuges.
5. Reaction intermediates: Chemical species that are formed at some point during a chemical reaction are called reaction intermediates. These are actual molecules that are short-lived and unstable. They are sometimes referred to as temporary reactants or products because they are neither present in the initial reactants nor the final products.
6. Transition states: Transition states are specific configurations along the reaction coordinate of an organic reaction. They represent the highest potential energy along this reaction coordinate. Unlike a "reaction intermediate," a transition state cannot be isolated as an actual molecule. Therefore, it is commonly denoted by the double dagger ‡ symbol to distinguish it.

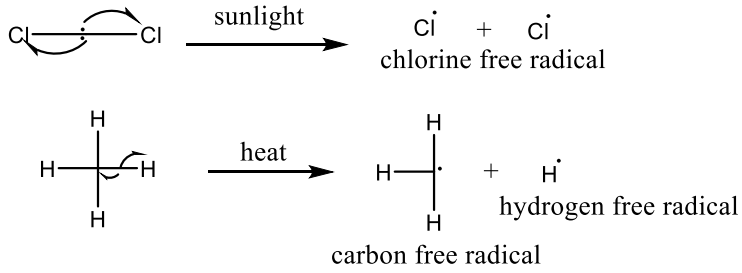
The reaction mechanism of organic compounds can be classified into three fundamental types based on the breaking of bonds.

Types of mechanism

Depending on how the bonds break, organic mechanisms can be divided into three basic types.

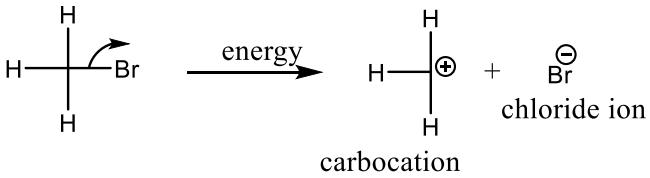
a. Homolytic or free radical mechanism:

When a bond breaks in a manner where each fragment receives one electron, it results in the formation of free radicals. These reactions are commonly referred to as occurring through a homolytic or free radical mechanism.



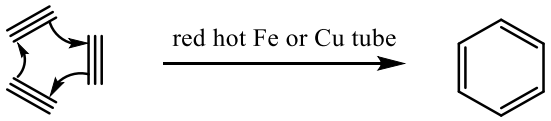
b. Heterolytic mechanism:

When a bond breaks and both bonding electrons remain with one fragment, it leads to the formation of ions. These reactions are known as occurring through a heterolytic mechanism.



c. Pericyclic mechanism:

The pericyclic mechanism refers to the cyclic movements of electrons involved in the breaking and making of bonds, without any intermediates, ions, or free radicals present.



Thermodynamic and kinetic requirements for a reaction:

Thermodynamic requirements for chemical reactions: For a reaction to occur spontaneously, the free energy of the products must be lower than the free energy of the reactants. That is, ΔG must be negative.

We know that $\Delta G = \Delta H - T\Delta S$; Where,

ΔG = change in free energy, ΔH = change in enthalpy, ΔS = change in entropy & T = temperature

For ΔG to be negative, the enthalpy of the system should decrease and the entropy should increase.

For many reactions, entropy has only a small effect; it is enthalpy that determines whether a reaction will occur spontaneously. However, in some types of reactions, entropy is important and can dominate the enthalpy. Some examples are:

• In general, gases have higher entropy than liquids and solids because gas molecules have greater randomness. Liquids have higher entropy than solids, but lower than gases. Therefore, any reaction in which the reactants are solids and the products are liquids and gases is thermodynamically favourable.

• When the number of products formed is greater than the number of reactants, the degrees of freedom and therefore the entropy increase, making the reaction thermodynamically favourable. On the other hand, entropy decreases when the number of reaction product molecules is less than

the number of reactant molecules, in which case the enthalpy must decrease significantly for ΔG to be negative.

• Open-chain molecules have more entropy than similar cyclic molecules because they have more conformations. Therefore, the ring-opening reaction is thermodynamically favourable.

Kinetic requirements for a chemical reaction:

A reaction will only occur spontaneously if the change in Gibbs free energy (ΔG) is negative, but this is not enough on its own. Take the reaction between H_2 and O_2 to form H_2O as an example; it has a strongly negative ΔG, yet the mixture of H_2 and O_2 can be stored at room temperature for many centuries without undergoing significant reaction. This is because reactions require an additional amount of energy, known as activation energy, in order for the molecules involved to convert into products. Activation energy is the minimum energy required to activate or energize molecules or atoms so that they can undergo a chemical transformation.

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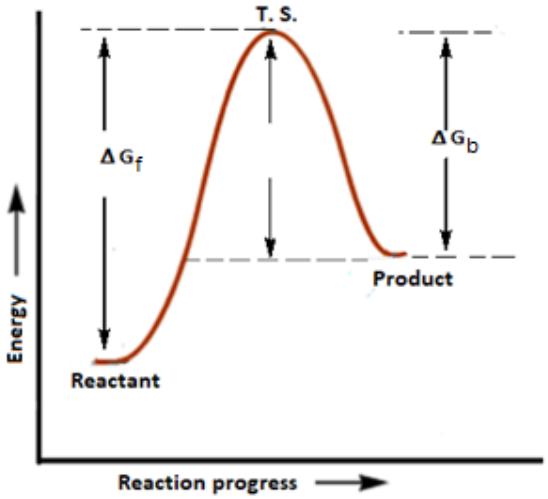


Figure : Diagram illustrating the energy profile of an endothermic reaction with free energy.

In the energy profile diagram shown above, ΔGf represents the free energy required for the activation of the forward reaction, while ΔGr represents the free energy required for the activation of the backward reaction.

Kinetically vs Thermodynamically controlled reaction:

Let's examine a chemical reaction where a reactant 'A' produces two distinct products 'B' and 'C' through different mechanisms.

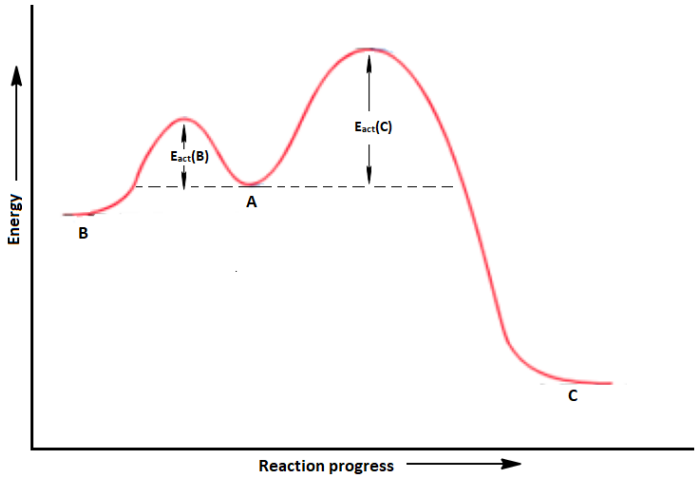
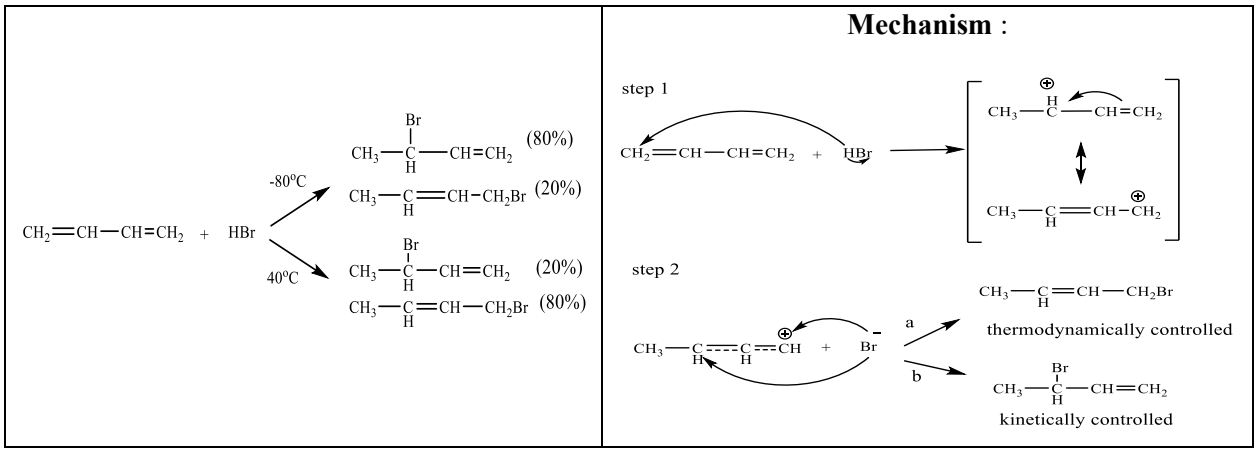


Figure: An energy profile diagram that demonstrates the distinction between kinetic and thermodynamic control of products.

In this diagram, 'C' is more stable in terms of thermodynamics (because it has lower energy), but 'B' is formed more quickly (due to lower activation energy). If the reaction cannot be reversed, the formation of 'B' requires less activation energy, resulting in faster formation. Therefore, 'B' is considered to be kinetically controlled. However, if the reaction can approach equilibrium (meaning it is reversible), the more stable product 'C' becomes more prevalent. In these circumstances, the initial product 'B' reverts back to A. Therefore, 'C' is considered to be thermodynamically controlled.

An example of the control of the reaction through both kinetic and thermodynamic factors is demonstrated. The control of the reaction can be comprehended by examining the addition of HBr to 1,3-butadiene, considering both kinetic and thermodynamic aspects. This reaction yields two distinct products, namely the 1,2-addition product and the 1,4-addition product.



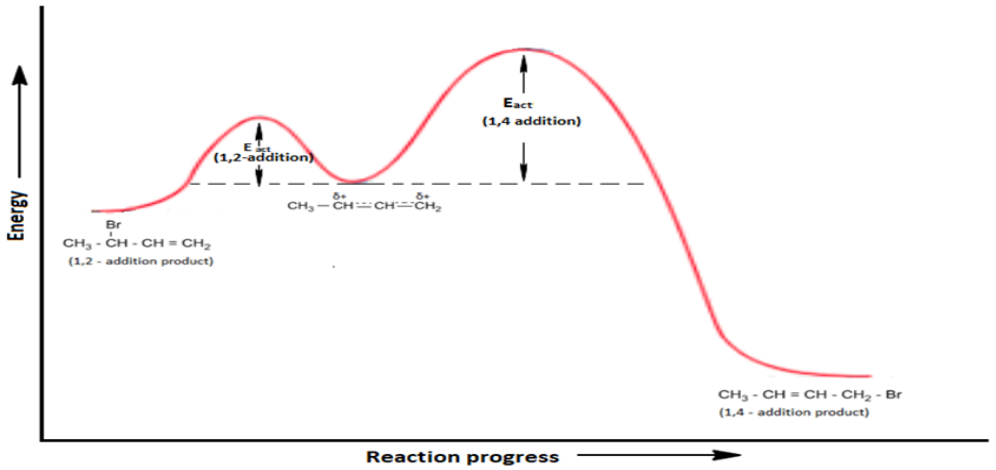
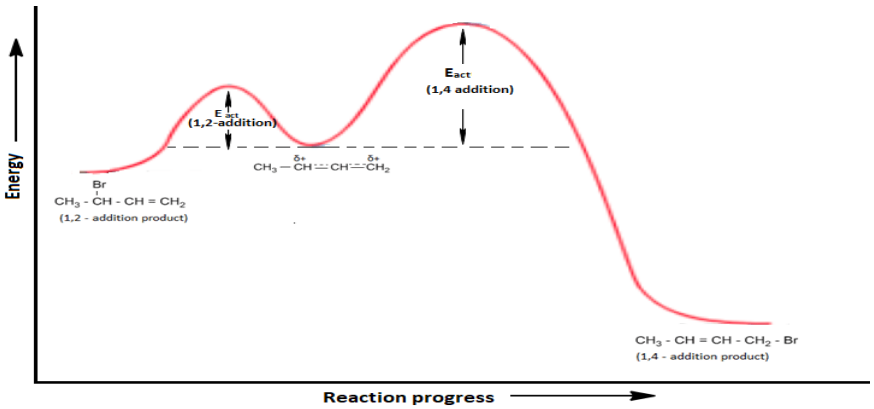


Figure : An energy profile diagram that illustrates the control of kinetic versus thermodynamic products.

Based on the data provided, it can be concluded that at -800C, the formation of the 1,2-product occurs more rapidly than the 1,4-product due to a lower energy of activation for the 1,2-product. The 1,2-addition product is the main product formed, making it the kinetically controlled product. However, when the temperature is increased, the reaction becomes reversible and reaches an equilibrium state. In this condition, the 1,4-addition product becomes the major product due to its greater stability (lower energy) compared to the 1,2-addition product. Although the 1,2-product forms more quickly, it undergoes ionization and transforms into the more stable 1,4-addition product. Therefore, the 1,4-addition product is considered the thermodynamically controlled product.

Hammond postulate:

Transition states have a lifespan of zero, making it impossible to isolate and directly study them. As a result, information about their shape and geometries must be inferred. According to the Hammond postulate, the geometry of a transition state for a particular reaction step is similar to that of the compound (either reactants or products) which it is closer in free energy to. This means that in an endothermic reaction, the transition state will resemble the products more than the reactants because it is closer to the product in the energy profile diagram ($\Delta G2 < \Delta G1$). Conversely, in an exothermic reaction, the transition state will resemble the reactants more than the products because it is closer to the reactant in the energy profile diagram ($\Delta G1 < \Delta G2$).



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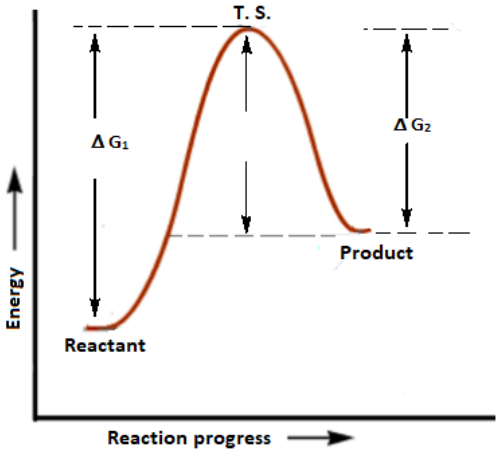


Figure : Diagram depicting the energy changes in an endothermic reaction.

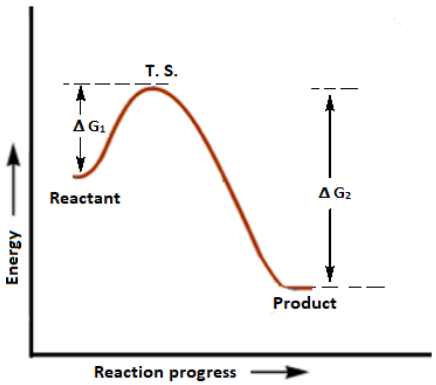
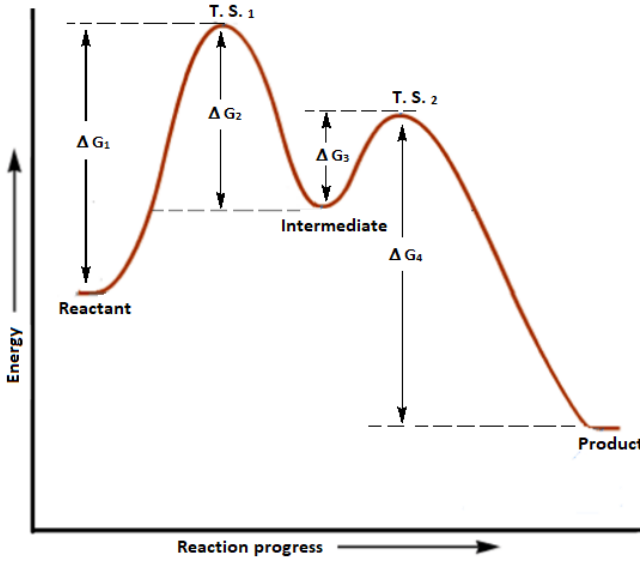


Figure : Diagram depicting the energy changes in an exothermic reaction.

The Hammond postulate is particularly valuable in situations where intermediates are involved in reactions. This is shown in the energy profile diagram of the reaction, where the reactant transforms into an intermediate through a transition state (T.S.1), and subsequently proceeds through another transition state (T.S.2) to ultimately yield the product.



The figure shows a diagram that illustrates the free energy profile of a two-step exothermic reaction.

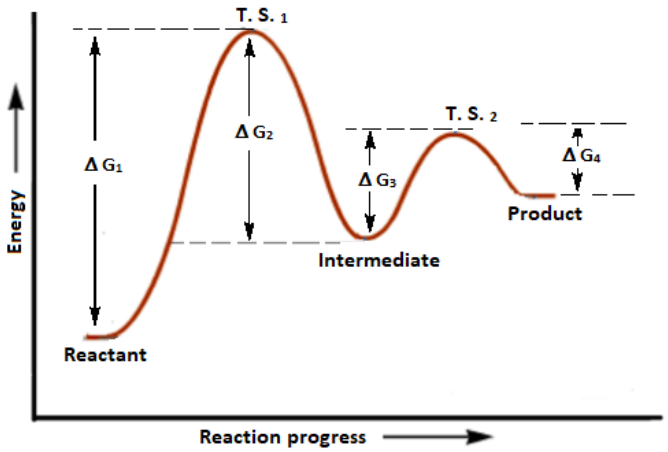
The T.S.1 is much closer in free energy to the intermediate than to the reactants, indicating that the geometry of T.S.1 is more similar to that of the intermediate rather than the reactants. Similarly, T.S.2 also has a free energy that is much closer to that of the intermediate compared to the products. Therefore, both transition states resemble the intermediate more than the reactants and products.

Difference between transition state and intermediate state:

The transition state is an imaginary molecule with no lifespan and cannot be separated. It is the state where the system has the highest energy and is the most unstable. Direct observation of transition states is impossible, so information about their shapes must be inferred.

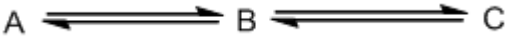
On the other hand, the intermediate is a relatively stable product formed from the reactants during the reaction, which then undergoes further reactions to produce the final product. The energy of the intermediate is lower than that of the transition state and can be isolated and studied.

Techniques such as IR and NMR spectroscopy can be used to determine the geometry of intermediates. We often use knowledge of intermediates to understand the shape and geometry of transition states.

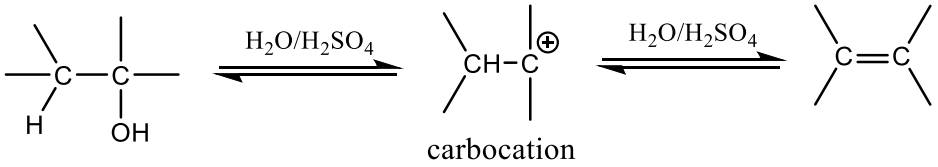


Microscopic reversibility refers to the concept of describing a reaction or process in a way that can be reversed and still maintain the same overall outcome.

If the reaction is reversible under the same conditions, both the forward and reverse reactions must occur using the same mechanism. This concept is known as the principle of microscopic reversibility. For instance, if a reaction A → B includes an intermediate 'C', then 'C' must also be an intermediate in the reaction B → A.

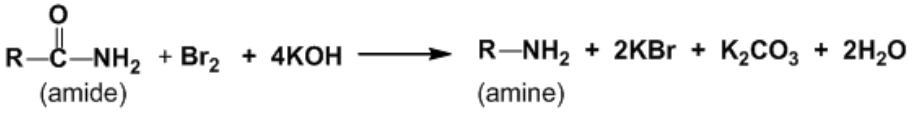


This principle is extremely valuable for predicting the mechanism of reversible reactions. For instance, when alcohol is reacted with H_2O and H_2SO_4, an alkene is formed through the use of a carbocation intermediate. Similarly, when the same alkene is reacted with H_2O and H_2SO_4, an alcohol is produced using the same carbocation intermediate.

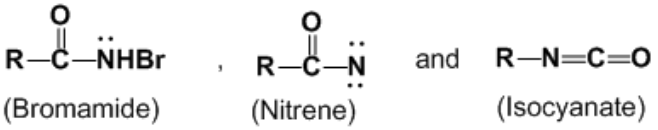


Determining the reaction mechanism can be achieved through various methods.

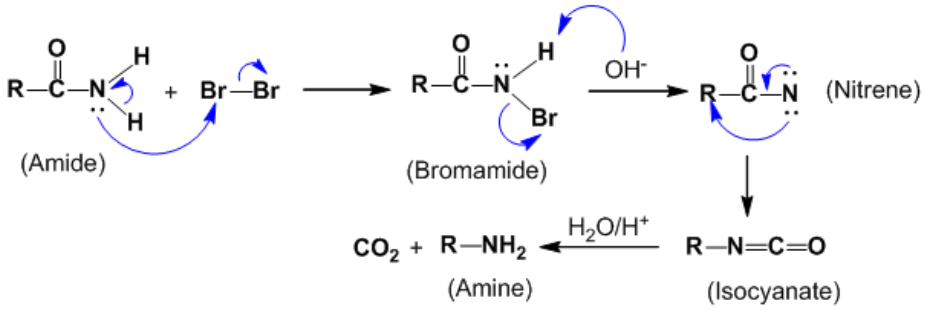
The isolation of intermediates provides valuable information for identifying the precise mechanism. Occasionally, it is possible to isolate an intermediate from a reaction mixture by either stopping the reaction quickly or using gentle conditions. For instance, the bromamide reaction by Hoffmann is an example of this. There are several commonly used methods for determining reaction mechanisms, but typically one method alone is not enough. Reaction intermediates, which are a significant type of chemical species, are helpful in understanding the mechanism of a chemical reaction.



During this reaction, the following intermediates were formed and isolated.

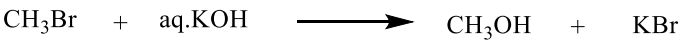


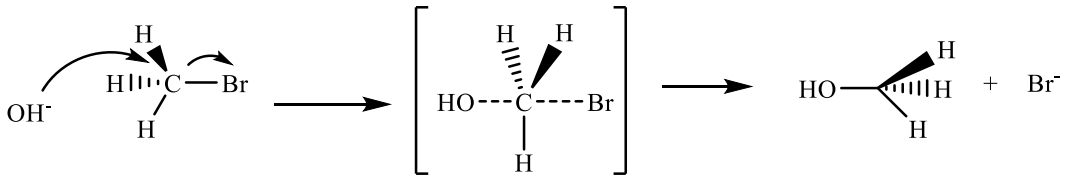
The proposed mechanism explains how these intermediates are formed.:



Stereochemical evidence:

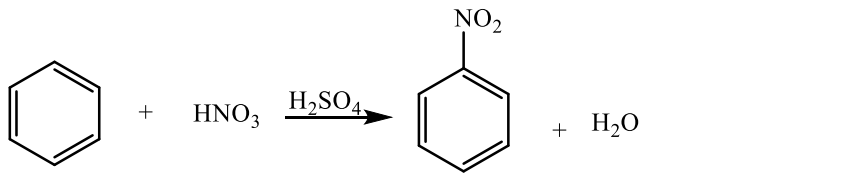
If the reaction's products have the ability to exist in multiple stereoisomeric forms, the form that is obtained can provide insight into the mechanism. For instance, in an SN2 reaction, the resulting product is consistently inverted. This inversion is only feasible if the nucleophile attack and leaving group removal occur simultaneously. In these instances, the nucleophile approaches from the opposite side of the leaving group to yield the inverted product.



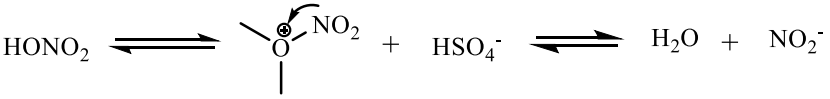


Detection of intermediate:

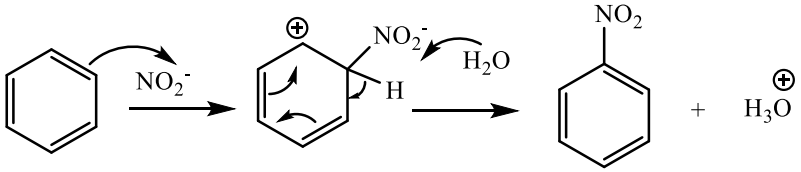
In numerous instances, intermediates may not be able to be isolated but can certainly be detected. Their detection can be achieved through the use of IR, NMR, or other spectroscopic techniques. The identification of the Raman spectra of NO^{2+} (nitronium ion) indicates that it serves as an intermediate in the nitration process of benzene. As a result, the nitration of benzene can be classified as an electrophilic substitution reaction, and the proposed mechanism for this reaction is as follows.



step I

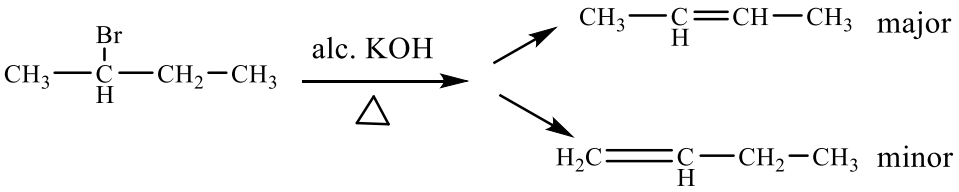


step II

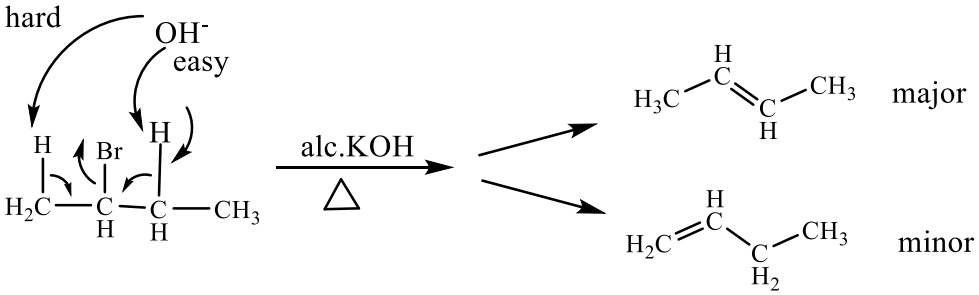


Identification of products:

Determining the reaction mechanism is also advantageous in identifying the products of a reaction. An illustration of this is the elimination reaction of 2-bromobutane.



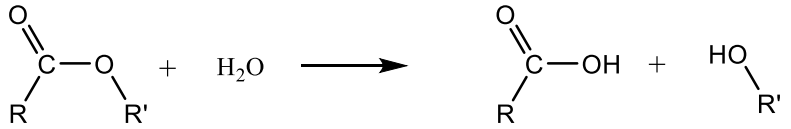
The identification of but-2-ene as the main product and but-1-ene as the minor product indicates the following mechanism.



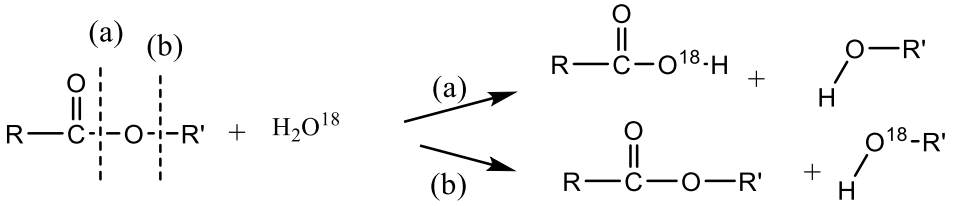
Isotope labelling (Tracer technique) :

When a heavier isotope replaces one of the isotopes in a bonded atom, the bond breaking occurs at a slower rate. By comparing the rate of bond breaking between the original bond and the substituted bond with the heavier isotope, we can determine if a specific bond breaks during the rate determining step. The influence of the heavier isotope on the bond breaking rate is known as the isotope effect. Valuable insights can be gained by using isotopically labeled molecules and following the reaction pathway in this way.

As an example, when ester reacts with water, it breaks down into a combination of carboxylic acid and alcohol.



The products can be formed by cleavage of an acyl-oxygen bond (a) or by cleavage of an alkyl-oxygen bond (b). If ester hydrolysis is carried out using H2O18 (i.e. oxygen of mass 18), the following products would be expected:

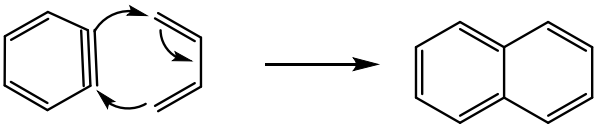


In this reaction, the appearance of O18 in carboxylic acid has been confirmed by mass spectroscopy. So the fission must have occurred at acyl-oxygen bond in the hydrolysis of ester.

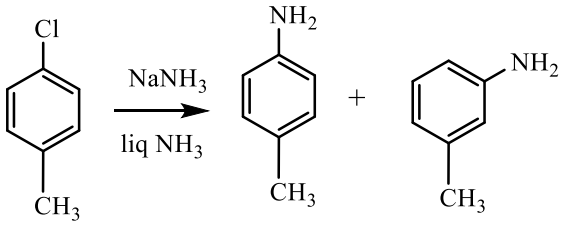
Trapping of intermediate :

In certain instances, the intermediate that is suspected is recognized as one that will react with a specific compound in a particular manner. The way to capture the intermediate is by conducting the reaction while the compound is present.

For example, benzyne reacts with dienes in Diels- Alder reaction. In any reaction where a benzyne is suspected intermediate, the addition of a diene and the detection of Diels-Alder addition product indicates that the benzyne was present.

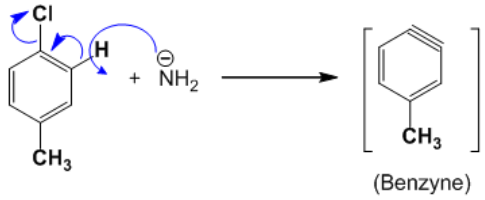


The action of p-chlorotoluene with sodamide in the presence of liquid ammonia results in the formation of a mixture of para and meta toluidene.

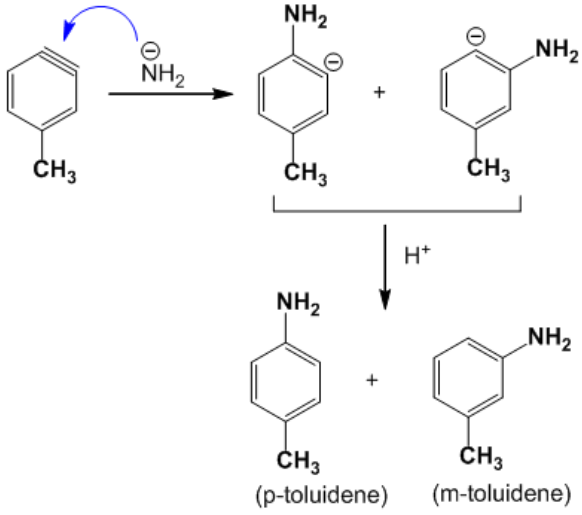


The mechanism of this reaction is believed to proceed as follows by trapping benzyne intermediate.

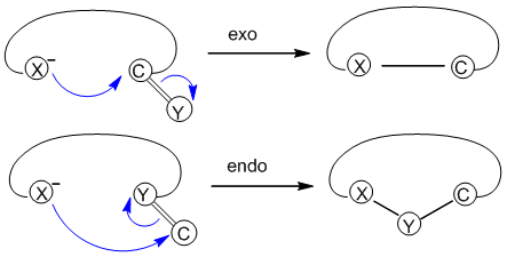
Step – I : The first step involves the loss of H+ and Cl- from p-chlorotoluene to form a benzyne intermediate.



Step – II : The second step involves the attack of the benzyne intermediate by NH_2– followed by protonation.



Baldwin's rule of ring closure, proposed by J.E. Baldwin, includes a set of guidelines for the reactions that result in the formation of 3 to 7 membered rings. These reactions can be categorized as either 'endo' or 'exo'. In the 'exo' case, the bond that is broken during the ring closure is located outside the ring, whereas in the 'endo' case, the bond broken during the ring closure is located inside the ring.



The hybridization of carbon atom (C) undergoing the ring closure reaction is of three types :

Tetrahedra (Tet) – sp^3 (i.e. a single bond centre)

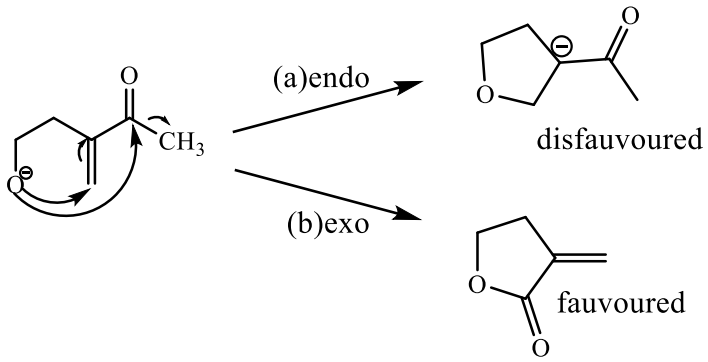
Trigonal (Trig) – sp^2 (i.e. a double bond centre)

The following are Baldwin's rule for closing rings of 3 to 7 members:

Rule 1: Tetrahedral system	Rule 2: Trigonal system	Rule 3: Diagonal system
1.3 to 7 – Exo – Tet are all favoured	1.3 to 7 – Exo – Trig are favoured	1.3 to 4 – Dig are disfavoured
2.5 to 6 – Endo – Tet are disfavoured	2.3 to 5 – Endo – Trig are disfavoured	2.5 to 7 – Dig are favoured
	3.6 to 7 – Endo – Trig are favoured	3.3 to 7 – Dig are favoured

Disfavoured does not mean it cannot occur but only it is more difficult than the favoured cases. A reaction that is disfavoured (slow) does not have a rate that is able to compete effectively with an alternative reaction that is favoured (fast).

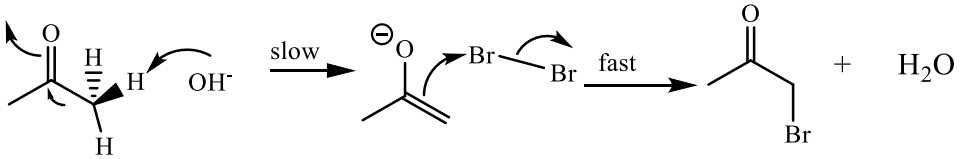
Example: 5 – Exo – Trig



Kinetic Isotope Effects:

Deuterium kinetic isotope effect = k_H/K_D ; = $\frac{\text{Rate constant of H-reactant}}{\text{Rate constant of D-reactant}}$

C-D bond is 1.2 kcal/mol more stronger than C-H bond. K_H/k_D values are greater than 1.5 –Primary kinetic isotope effect, C-H(D) bond breaks in the rate determining step. K_H/k_D is 1-1.5, Secondary kinetic isotope effect- C-H(D) bond cleavage is not involved in the rate determining step.



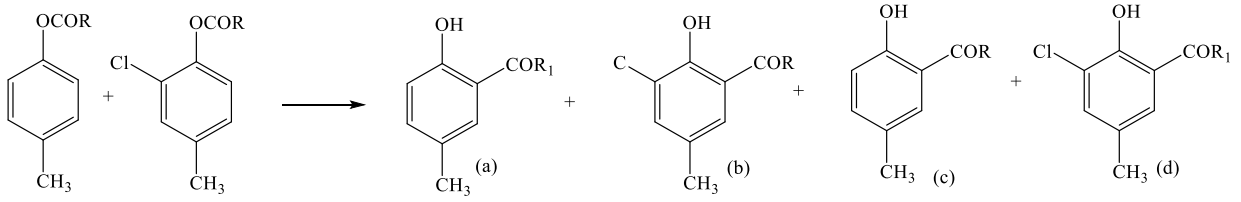
k_H/k_D = 7 primary kinetic isotope effect indicates that the proton removal is involved in the rate determining step.

Kinetic Evidence

Rate is dependent on the concentration of both reactants in the rate determining step and hence it is bimolecular in nature.

$CH_3\text{-}Br + I^- \rightarrow CH_3I + Br^-$ Rate= $k[CH_3Br][I^-]$

Crossover Experiments: Crossover experiments involve conducting an experiment with a mixture that has similar compositions but is not identical. After the reaction takes place, the resulting products are analysed. In the case of intermolecular reactions (two steps), the bonds are initially broken to form different reactive species. These reactive species can then combine to form products that contain fragments from both substrates in the mixture.



B) The Hoffmann Reaction involves an intra-molecular rearrangement in which the migrating group remains attached to the substrate. When a mixture of 3-deuteriobenzamide and 15N benzamide is used, the reaction produces deuterobenzene and benzamine. It should be noted that no mixed anilines are produced.

$$C_6H_4DCONH_2 + C_6H_5CO^{15}NH_2 \rightarrow C_6H_4DNH_2 + C_6H_5CO^{15}NH_2$$

The Hammett Equation and Linear Free Energy Relationship

Quantitative studies on how structure affects reactivity, specifically examining how the resonance effect, field-effect, and steric effect influence reaction rates in measurable quantities.

The Hammett Equation

Consider a situation where an organic reaction is performed on a substrate denoted as XRY, where X represents a variable substituent, Y is the reaction spot, and R represents the basic substrate structure. In this scenario, if X is replaced with CH_3 instead of H, the reaction rate increases by up to ten times. However, it is still unknown which factor, whether it be resonance effect, field-effect, or steric effect, contributes to this rate enhancement. To investigate this, it is reasonable to use compounds where the effects of one or two of these factors are negligible and can be ignored. Although this simplification may not fully capture the complexity of the problem, it is still possible to obtain quantitative results. The Hammett equation was developed as an initial attempt to assign numerical values to the quantitative analysis of structure on reactivity.

Hammett proposed the equation for the cases of *m*- and *p*-XC_6H_4Y as given below.

$$\log \frac{k}{ko} = \sigma\rho$$

The constants for the group X ≠ H and X = H are represented by k and k0, respectively. Similarly, the constants for reaction conditions and substituent X are denoted by ρ and σ, respectively.

Derivation of Hammett Equation

In order to obtain the Hammett equation, it is necessary to first remember the quantitative connection between structure and reactivity. To achieve this, it is necessary to identify a mathematical parameter that can effectively represent the combined impact of inductive and resonance effects from various substituents. This can be accomplished by examining the hydrolysis of a range of distinct benzoic acids, as shown below.

$$XC_6H_4COOH + H_2O \underset{}{\overset{Ka}{\rightleftharpoons}} XC_6H_4COO^- + H_3O^+$$

Where X is the substituent at the meta or para position, and Ka is the dissociation constant. As expected, the dissociation constants were found to differ for the different substituted substrates.
The presence of an electron withdrawing group will stabilize the conjugate base (XC6H4COO−), resulting in a higher Ka value (lower pKa). On the other hand, electron-donating groups will destabilize the conjugate base, leading to a lower Ka value (higher pKa). Therefore, we can determine the electronic effect of a substituent by comparing the pKa value of its benzoic acid derivative to that of benzoic acid itself.
Mathematically, this can be expressed as σX = log(Ka) - log(Ka)0 = -p(Ka) + p(Ka)0. The parameter σX, known as the substituent constant, is determined by subtracting the pKa value of the substituent's benzoic acid derivative from the pKa value of benzoic acid.

Table 1. pK_a values and substituent constants for XC_6H_6COOH using benzoic acids $p(K_a)_0 = 4.21$.

Substituent	$p_m(K_a)$	$p_p(K_a)$	$\sigma_m = p(K_a)_0 - p_m(K_a)$	$\sigma_p = p(K_a)_0 - p_p(K_a)$
NO_2	3.50	3.43	0.71	0.78
CH_3	4.28	4.38	−0.07	−0.17
OCH_3	4.09	4.48	0.12	−0.27
$CH(CH_3)_2$	4.28	4.36	−0.07	−0.15
F	3.87	4.15	0.34	0.06
Br	3.82	3.98	0.39	0.23
Cl	3.84	3.98	0.37	0.23
I	3.86	3.93	0.35	0.28
$COCH_3$	3.83	3.71	0.38	0.50

Using log m-log n = log m/n, equation can also written as log $(Ka)/(Ka)_o = \sigma$
Now if we plot a curve between log $(Ka)/(Ka)_o$ vs σ, we will definitely get a straight line with a slope = 1.

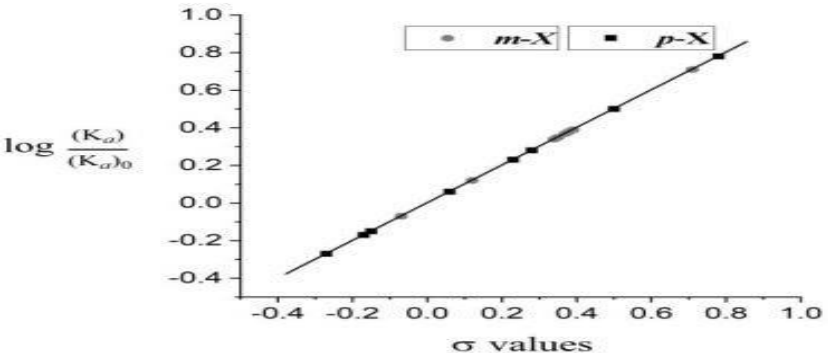
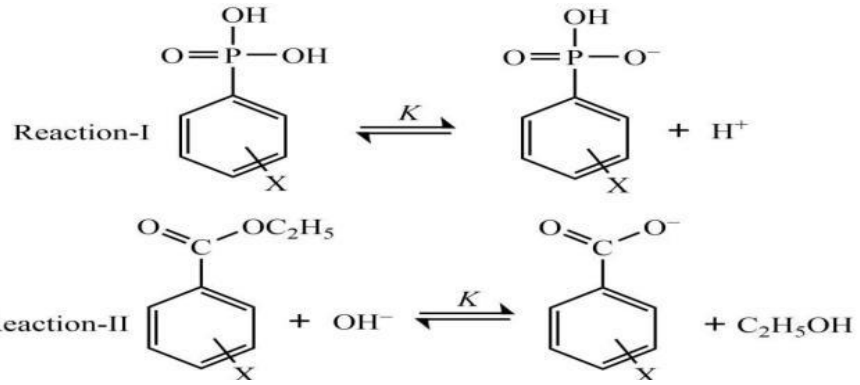


Figure 17. Variation of $\log(K_a)/(K_a)_0$ vs σ for substituted benzoic acids.

Now we need to check if these σ values (i.e., of substituted benzoic acids) can also be used for other meta- or para-substituted benzene derivatives. To do so, consider two series of reactions; the first one is the acid dissociation of phenyl phosphonic acid, and the second one is the base hydrolysis of substituted ethyl benzoate. Here we will find if different substituents affect their dissociation constants or rates in the same manner as affected in the case of substituted benzoic

acid. Also, we did not use ortho-substituents or substituents in the aliphatic system because they also contain steric factors and don't not linear variation.



The experimental $\log(K_a)/(K_a)_0$ for the reaction-I and experimental log k/k$_0$ for reaction-II are given below.

Table 2. Experimental values of $\log(K_a)/(K_a)_0$ and log k/k$_0$ for the acid dissociation of phenyl phosphonic acid and base hydrolysis of substituted ethyl benzoates respectively.

Substituent	*meta*-$\log(K_a)/(K_a)_0$	*para*-$\log(K_a)/(K_a)_0$	*meta*-log k/k_0	*para*-log k/k_0
NO_2	0.53	0.59	1.83935	2.06423
Br	0.29	0.23	–	–
Cl	0.28	0.17	0.88536	0.63347
CH_3	–	−0.15	−0.16115	−0.34679

When plotted the experimental $\log(K_a)/(K_a)_0$ for the reaction-I and experimental log k/k_0 for reaction-II vs the substituent constants obtained for the substituted benzoic acids, we get the following curves.

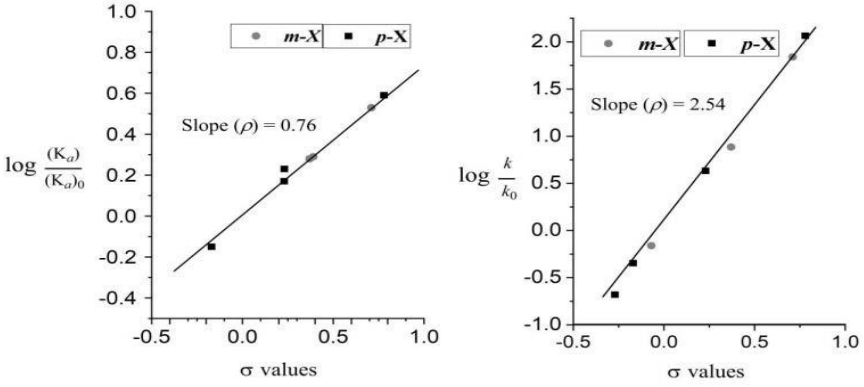


Figure: $\log(K_a)/(K_a)_0$ and log k/k$_0$ vs σ for the reaction-I and for reaction-II

Substituent and Reaction Constants

In order to discuss the substituent and reaction constants, we must first review the quantitative relationship between structure and reactivity. To accomplish this, we must identify a mathematical parameter that can represent the combined magnitude of inductive and resonance effects from various substituents. This can be done by examining the hydrolysis of a range of different benzoic acids, as shown below.

$$XC_6H_4COOH + H_2O \overset{K_a}{\rightleftharpoons} XC_6H_4COO^- + H_3O^+ \quad \rightarrow (1)$$

It is observed that an electron-withdrawing group will effectively stabilize the conjugate base ($XC_6H_4COO^-$), resulting in a larger Ka value (lower pKa). Conversely, an electron-donating group will destabilize the conjugate base ($XC_6H_4COO^-$), leading to a smaller Ka value (higher pKa). Therefore, we can conclude that the overall electronic effect (inductive plus mesomeric effect) of a substituent can be determined by comparing the pKa value of its benzoic acid derivative to that of benzoic acid itself. Mathematically, this can be expressed as the difference between the pKa values.

$$\sigma_X = \log(K_a) - \log(K_a)_0 = -p(K_a) + p(K_a)_0 \rightarrow (2)$$

The parameter σX, also known as the substituent constant, is calculated by subtracting the pKa value of a benzoic acid derivative from the pKa value of benzoic acid.

Using the equation,

$\log m - \log n = \log m/n$,

we can rewrite it as ; $\log(Ka)/(Ka)0 = \sigma$.

When we plot $\log(Ka)/(Ka)0$ against σ, we will obtain a straight line with a slope of unity.

We need to determine if these σ values can also be applied to other meta- or para-substituted benzene derivatives.

To investigate this, we consider two series of reactions: the acid dissociation of phenyl phosphonic acid and the base hydrolysis of substituted ethyl benzoate. We exclude ortho-substituents and substituents in the aliphatic system due to steric factors and non-linear variation. Plotting the experimental $\log(Ka)/(Ka)0$ for reaction-I and log k/k0 for reaction-II against the substituent constants obtained for the substituted benzoic acids, we observe linear curves with varying slopes. This indicates that the order and relative effects of different substituents on both reactions remain the same, although the magnitude has changed due to the different nature of the reactions.

Therefore, we need to determine the slope (ρ) by comparing the vertical side $[\log(Ka)/(Ka)0]$spa for reaction-I and the horizontal side (σ) or $[\log(Ka)/(Ka)_0]_{sba}$ for the base hydrolysis of substituted benzoic acid.

From equation $[\log(K_a)/(K_a)_0] = \sigma$, we know that $[\log(K_a)/(K_a)0]_{sba} = \sigma$ and therefore, we get

$$[\log(K_a)/(K_a)_0]_{sba} = \rho\sigma \rightarrow (3)$$

For any reaction,

$$\log K_a = \rho\sigma - \log(K_a)_0 \rightarrow (4)$$

Similarly, on the vertical side we have $\log k/k_o$ for reaction-II (base hydrolysis of ethyl benzoate) and horizontal side we have (σ) or $[\log(K_a)/(K_a)_0]$sba for base hydrolysis of substituted benzoic acid.

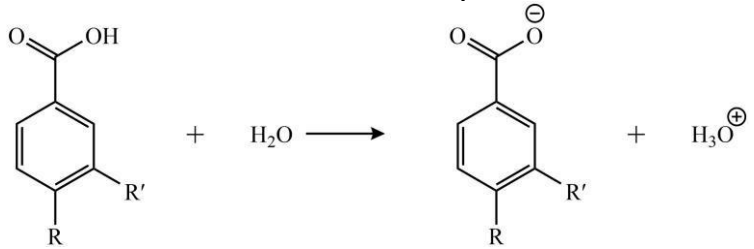
From equation $[\log(K_a)/(K_a)_0] = \sigma$, we know that $[\log(K_a)/(K_a)_0]$sba = σ and therefore, we get

$[\log k/k_0]_{sppa} = \rho\sigma \rightarrow (5)$

Equation (3) and (5) are hammatt equation where ρ and σ are the substituted and reaction constants.

Substituent Constants (σ)

Based on the derivation of Hammet's equation, we understand that the substituent constants can be obtained by determining the change in pKa value of substituted benzoic acid in water at 25 °C. The reaction constant for this "base reaction" will be equal to one.

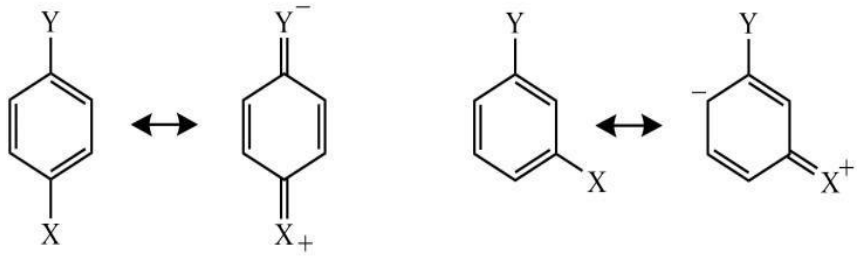


The presence of an electron-withdrawing group will provide better stability to the conjugate base ($XC_6H_4COO^-$), leading to a higher magnitude of Ka (lower pKa). Conversely, an electron-donating group will cause instability in the conjugate base ($XC_6H_4COO^-$), resulting in a lower magnitude of Ka (higher pKa). Therefore, we can conclude that the electronic effect (inductive plus mesomeric effect) of a substituent can be represented by the difference between the pKa value of its benzoic acid derivative and the pKa value of benzoic acid itself.

By examining the σ values presented in Table 1, one can determine various substituent effects. When ρ = 1, the substituent group consisting of substances with progressively higher positive values, such as nitro, causes the equilibrium constant to increase compared to hydrogen as the substituent. Consequently, the acidity of benzoic acid is increased. This occurs because substituents like NO2 stabilize the negative charge on the carboxylate ion through both an inductive effect (−I) and a negative resonance effect (−R).

The halo- groups are the second type of substituents, and they have a modestly positive substituent effect. This is because, although the inductive effect is still negative, the resonance effect (+R) partially cancels it out. Experimental data also showed that the m-effect is greater than the p-effect for these substituents, as the resonance effect is greatly reduced in the m-substituent. In the case of m-substituted substrates, the carbon atom with the negative charge is located farther from the COOH group.

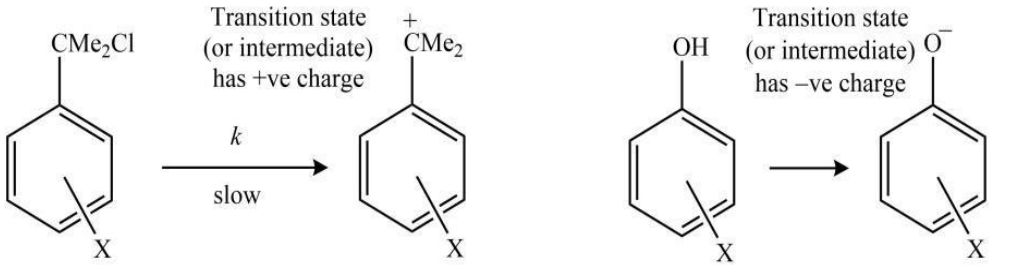
The resonance effect's behaviour in relation to substituent constants can be comprehended by considering the following scenario: in a p-substituted arene (1a), one of the resonance structures (1b) resembles a quinoid with a positive charge on the substituent X. This arrangement causes the release of electrons, which in turn destabilizes the Y group. However, such destabilization is unlikely to occur when X is located at the m-site.



1*a* 1*b* 2*a* 2*b*

In addition, substituents like ethoxy and methoxy can exhibit different signs for the substituent constant because of the contrasting inductive and resonance effects. However, aryl and alkyl substituents like methyl contribute electrons to both the inductive and resonance effects. Lastly, if the sign of the reaction constant is negative, substituents with a negative substituent constant will increase the Ka values.

Although the substituent constants obtained from substituted benzoic acid were generally accurate in predicting $\log(Ka)/(Ka)0$ or $\log k/k0$ for many reactions, there were instances where the rates or dissociation constants predicted did not align with the substituent being strongly electron-withdrawing or strongly electron-donating in nature. For example, the $\log(Ka)/(Ka)0$ values of substituted phenols with p-CN and p-NO_2 were higher than expected, indicating that systems with these substituents acted as stronger acids. This was because the electron-withdrawal caused by mesomeric effects extended to the reaction site through conjugation, making the conjugated acid exceptionally stable. As the substituent developed a negative charge during this process, the modified substituent constant was labelled as σp^-. Similarly, if the electron-donating effect arising from mesomeric effects extended to the reaction site through conjugation, the conjugated acid became less stable. As the substituent developed a positive charge during this process, the modified substituent constant was labelled as σp^+.



SN_1 hydrolysis of substituted phenyldimethyl carbinyl chloride (σ^+)

Dissociation of substituted para-nitro phenol (σ^-)

The magnitude by which $\log(K_a)/(K_a)_0$ or $\log k/k_0$ deviate from σ value is added to produce a new scale of substituent constants. The same is true for the m-site accepting the fact that values of σ_m^+ will be same as the σ_m values.

Group	σ_p	σ_m	$\sigma p+$	$\sigma m+$	$\sigma p-$
COOH	0.44	0.35	0.42	0.32	0.73
COOR	0.44	0.35	0.48	0.37	0.48
CN	0.70	0.62	0.66	0.56	1.00
NO_2	0.81	0.71	0.79	0.73	1.27
Cl	0.24	0.37	0.11	0.40	–

Table 3. Substituent constants: para and meta substituted benzene rings.

Reaction Constants (ρ)

After knowing the values of substituent constants, the reaction constant (ρ) can be obtained for an extensive range of reactions. The 'prototype or base' reaction is the alkaline hydrolysis of ethyl benzoate in a water mixture at 25 °C. For instance, plotting experimental values of $\log(K_a)/(K_a)_0$ and $\log k/k_0$ for the acid dissociation of phenyl phosphonic acid and base hydrolysis of substituted ethyl benzoates vs substituent constants yielded the ρ values equal to 0.76 and 2.4, respectively.

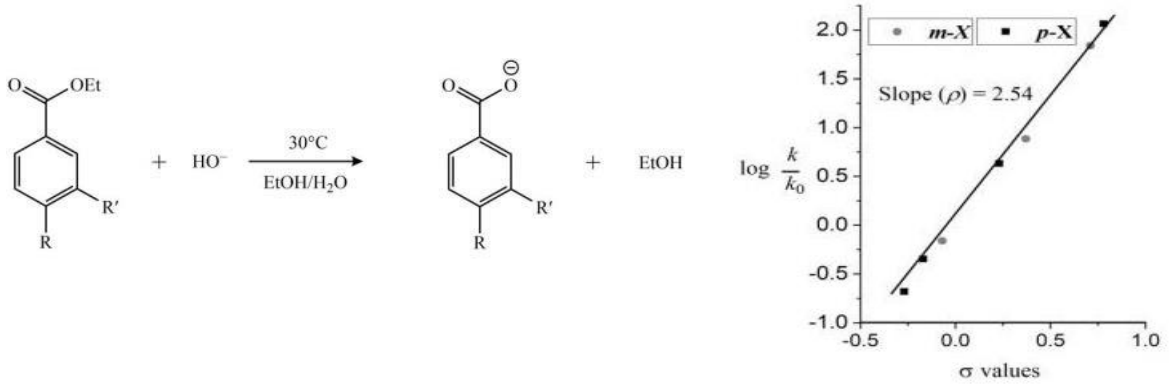


Figure log $k/k_{o\ vs}$ σ for alkaline hydrolysis of substituted ethyl benzoate.

Reaction constants or ρ values for many other reactions and equilibria have been obtained over years. P-values for some of the important reactions provided by Hammett himself are given below.

i) Hydrolysis of substituted cinnamic acid ester in water /ethanol (+1.267).

ii) Acid-catalysed esterification of substituted benzoic esters in C_2H_5OH (−0.085).

iii) Ionization of substituted phenols in H_2O (+2.008).

iv) Substituted benzyl chlorides' hydrolysis in H_2O-acetone at 69.8 °C (−1.875).
v) The acid-catalysed bromination of substituted acetophenones in CH_3COOH (acetic acid) or water or hydrochloric acid (+0.417).

Now, as far as the significance is concerned, the sensitivity constant (i.e. reaction constant ρ), defines the reaction's susceptibility to different substituents, relative to the ionization of benzoic acid; and is equal to the slope of the Hammett's equation or plot. The reaction's information and the mechanism involved can be found using the value of ρ as given below.
Case 1: if $\rho > 1$, the reaction has a greater sensitivity to substituents than the benzoic acid and a negative charge will accumulate (or a loss of positive charge) in the course of the reaction.
Case 2: if $0 < \rho < 1$, the reaction will be less sensitive to substituents than the benzoic acid and a negative will accumulate (or a loss of positive charge).
*Case 3:*if $\rho = 0$, the reaction will show no sensitivity to substituents, and no charge will be lost or built.
Case 4: if $\rho < 0$, a positive will accumulate (or a loss of negative charge) during the reaction.

The correlations given above can be used to explain the mechanism of an organic reaction. Since the ρ-value is connected to the charge in the course of the rate-limiting step, the mechanism involved can be developed using the data obtained. For instance, if an aromatic compound's reaction is believed to happen via one of two routes, the organic compound can simply be modified with substituents with dissimilar σ values and then the shortlisting can is done by taking kinetic measurements. After the measurements we mentioned, the Hammett plot can be raised to find the ρ value. Now, if the mechanisms we believe to be true encompass the charge formation, the ρ value will easily confirm our predictions. On the other hand, if the Hammett plot demonstrates that no charge is created during the reaction (i.e., slope or $\rho = 0$), the mechanism with the charge development can simply be neglected.

It is also worthy to note that the Hammett plots may not always be flawlessly linear. For example, a plot may have an unexpected or rapid change in the ρ value or slope. A case like this means that the mechanism responsible for the reaction has simply been changed due to the addition of different substituents. Some other kinds of deviations from linear variation may be attributed to a change in the site of the transition state. A situation like this means that certain substituents may cause the transition state to form later (or earlier) during the mechanism involved.

Table 4. The reaction constants (ρ-values) for a relative analysis for some typical organic chemical reaction types.

Reaction type	ρ-value
Ionization of acids	1.464
Alkaline hydrolysis of ethyl esters	2.494
Acids with diphenyldiazomethane	0.937
Acid dissociation of phenyl phosphonic acid	0.76

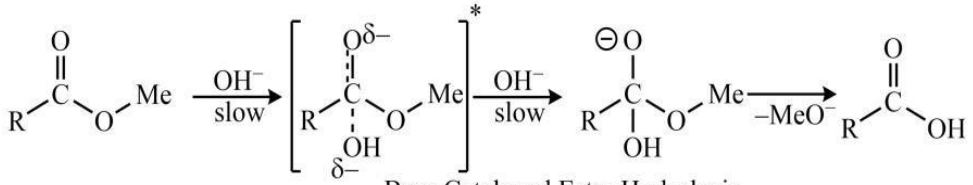
The Taft equation: The Taft equation, similar to the Hammett equation, is a linear free energy relationship (LFER) used in physical organic chemistry to study reaction mechanisms and establish the quantitative relationships between structure and activity in organic species. Robert W. Taft introduced this equation in 1952 as a modification of the Hammett equation. However, unlike the Hammett equation, which only considers the effects of inductive, field, and resonance on the reaction rate, the Taft equation also accounts for the steric effects of a substituent. The mathematical representation of the Taft equation is provided below.

$$\log k/\mathrm{ko} = \sigma^{*}\rho^{*} + \delta Es$$

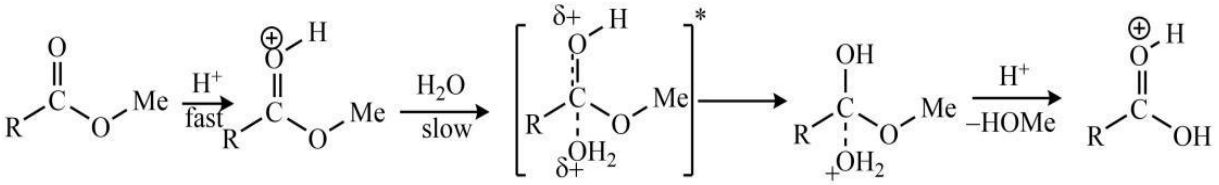
Where k and k_0 are the constants for the group X ≠ H and X = H, respectively; ρ* and σ* are the modified reaction constants, representing the sensitivity factor for the reaction to polar effects and the field and inductive effects of substituent X, respectively. The symbol δ represents the sensitivity factor for the reaction to steric effects, while Es denotes the steric substituent constant.

Polar Substituent Constants (σ^{*})

The polar substituent constants explain the way a substituent affects a reaction pathway via polar (field, inductive, and mesomeric effect) influences. Taft examined the hydrolysis of methyl esters to get σ* values. The idea of using rates of ester hydrolysis to study polar effects was initially proposed by Ingold in early 1930. Esters hydrolysis can proceed via either acid- or base-catalysed pathway, and both routes involve a tetrahedral intermediate species. During the base-catalysed pathway, the reactant transforms from a neutral entity to a negatively charged intermediate in the rate-limiting step; whereas in the acid-catalysed pathway, a positively charged reactant transforms to an intermediate species with a positive charge.



Base Catalyzed Ester Hydrolysis



Acid Catalyzed Ester Hydrolysis

Owing to the same nature of intermediates (tetrahedral), Taft suggested that any steric factors under identical conditions should be approximately the same for the two pathways; and so would not affect the rates' ratio. Nevertheless, since a charge difference is built up in the rate-limiting steps it was suggested that polar effects would only affect the rate of reaction for base-catalyzed transformation because a new charge was created. The mathematical formulation of polar substituent constant (σ*) can be written as given below.:

$$\sigma^{*} = 1 / 2.48\rho^{*}[(\log k/k_o)_B-(\log k/k_o)_A]+\delta Es$$

Where $(\log k/k_0)_B$ represents the ratio of the base-catalysed reaction rate compared to the reference transformation; whilst $(\log k/k_0)_A$ represents the ratio of the acid-catalysed reaction rate relative to the reference transformation. The symbol ρ^{*} shows the reaction constant which explains the sensitivity of the series of reactions. For the base reaction series, we use $\rho^{*} = 1$ and R = CH_3 is set as the reference transformation with $\sigma^{*} = 0$. The incorporation of 1/2.48 is to make the magnitude σ^{*} equal σ values given by Hammett.

Steric Substituent Constants (E_s)

Though the base- and acid-catalysed esters' hydrolysis yield transition states for the rate-limiting steps which have different densities of charge, their molecular structures differ by 2 H atoms only. Therefore, Taft thought that the steric effects should affect both pathways by equal extent. Owing to this fact, the magnitude of E_s (steric substituent constant) can be obtained from purely the acid-catalysed pathway since polar effects would be excluded this way. E_s was defined as:

$$E_s = 1/\delta \log k/k_o \rightarrow (6)$$

Where symbol δ represents the reaction constant which explains the reaction's susceptibility to steric factor. The values δ = 1 and E_s =0 was used for the definition reaction series. The equation (1) can be combined with equation (2) to write the complete form of the Taft equation. Comparing E_s values for CH_3, C_2H_5, isopropyl, and tert-butyl; it is obvious that it increases with growing steric bulk. Nevertheless, E_s values can deviate from expectation due to steric interactions. For instance, the phenyl's E_s is larger than tert-butyl; however, if we compare these groups using another measure, the tert-butyl will come out to be dominant.

Table 5. Constants used in the Taft equation.

Group	E_s	σ^*
–H	1.24	0.49
$–CH_3$	0	0
$–CH_2CH_3$	–0.07	–0.1
$–CH(CH_3)_2$	–0.47	–0.19
$–C(CH_3)_3$	–1.54	–0.3
$–CH_2Ph$	–0.38	0.22
–Ph	–2.55	0.6

Sensitivity Factors

A brief discussion on the nature and significance of all the sensitivity factors used in the Taft equation is given below.

1. Polar sensitivity factor (ρ^*): Just like Hammett's ρ-values, Taft's ρ^*-values describe the reaction's susceptibility to polar effects. If the steric effects of substituents do not influence the rate of reaction significantly, the Taft equation will reduce to Hammett equation as given below.

$$\log k/k_o = \sigma_* \rho* \rightarrow (7)$$

The ρ^* value can be found by plotting the log of the ratio of the experimental rates (k) to the reference reaction (k_0) vs the σ^* values of different substituents. The slope of such plot will be equal to ρ^*. Just like Hammett's ρvalue:

i) If $\rho^* > 1$, a negative charge will accumulate in the transition state during the reaction, and the reaction will be accelerated by electron-withdrawing substituents.

ii) If $1 > \rho^* > 0$, a negative charge will accumulate in the transition state during the reaction, and the reaction will show mild sensitivity to polar effects. *iii)* If $\rho^* = 0$, the reaction will simply not get influenced by polar effects.

iv) If $0 > \rho^* > -1$, a positive charge will accumulate in the transition state during the reaction, and the reaction will show mild sensitivity to polar effects.

v) If $-1 > \rho^*$, a positive charge will accumulate in the transition state during the reaction, and the reaction will be accelerated by electron-donating substituents.

2. Steric sensitivity factor (δ): Just like the polar sensitivity factor, δ or the steric sensitivity factor of reaction explains to what extent the rate of reaction is affected by steric effects. If the polar effects of substituents do not influence the rate of reaction significantly, the Taft equation will reduce to the equation as given below.

$$\log k/k_0 = \delta E_s \rightarrow (8)$$

By plotting the log of the ratio rates vs the E_s value of different substituents, we get a straight line with a slope equal to δ. Similarly to Hammett's ρ–value, the magnitude of δ gives the extent of steric effects:

i) If the δ-value is very high, the reaction will be extremely sensitive to steric effects, whereas a smaller δvalue implies that the reaction has little to no sensitivity to steric influence.

Also, owing to larger and negative E_s-values for bulkier substituents, we may conclude that the flowing point about the reaction profile.

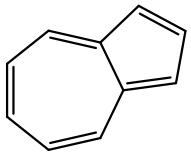
i) If $\delta > 1$, the raise in steric bulk cuts the rate of reaction and steric effects will be higher in the transition state. *ii)* If $\delta < 1$, the raise in steric bulk will raise the rate and steric effects will be reduced in the transition state.

3. Reactions influenced by polar and steric effects: If the steric, as well as polar effects, influence the rate of chemical reaction, the Taft equation can be employed to evaluate ρ^*- and δ-values via the use of standard least-squares fitting for getting a bivariant regression plane. The application of this technique was outlined by Taft in 1957 as a demonstration of accuracy.

UNIT-II: Aromatic and Aliphatic Electrophilic Substitution: Aromaticity: Aromaticity in benzenoid, non-benzenoid, heterocyclic compounds and annulenes. Aromatic electrophilic substitution: Orientation and reactivity of di- and polysubstituted phenol, nitrobenzene and halobenzene. Reactions involving nitrogen electrophiles: nitration, nitrosation and diazonium coupling; Sulphur electrophiles: sulphonation; Halogen electrophiles: chlorination and bromination; Carbon electrophiles: Friedel-Crafts alkylation, acylation and arylation reactions. Aliphatic electrophilic substitution Mechanisms: SE2 and SEi, SE1- Mechanism and evidences.

NON-BENZENOID AROMATIC COMPOUND

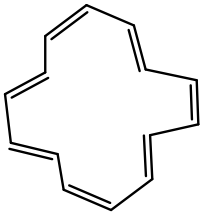
Azulene: It has 10 π electron and is non-benzenoid aromatic compound (4n+2 = 10- electron, n=2). It is an intense blue stable solid (melting point 99 degree celcius) and undergoes electrophilic substitution reaction like other aromatic compounds.



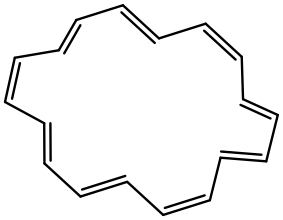
azulene (10π electron)

Annulenes: Annulenes are completely conjugated monocyclic hydrocarbons. They have a general formula CnHn. According to the IUPAC naming conventions. They have a named as [n]-annulene, where n is the number in the bracket indicates the ring sizes or the number of carbon atoms in their ring.

Mono cyclic conjugated polyenes containing 10 or more carbon atoms in the ring are called annulenes. They are named by prefixing the no. of C atoms placed in square brackets. [14] and [18] Annulenes, obey Huckel's (4n+2) rule and show aromatic character.



[14] Annulene

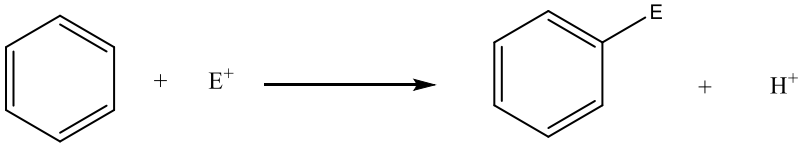


[18] Annulene

Annulene with large no (≥30) C atoms are non aromatic.

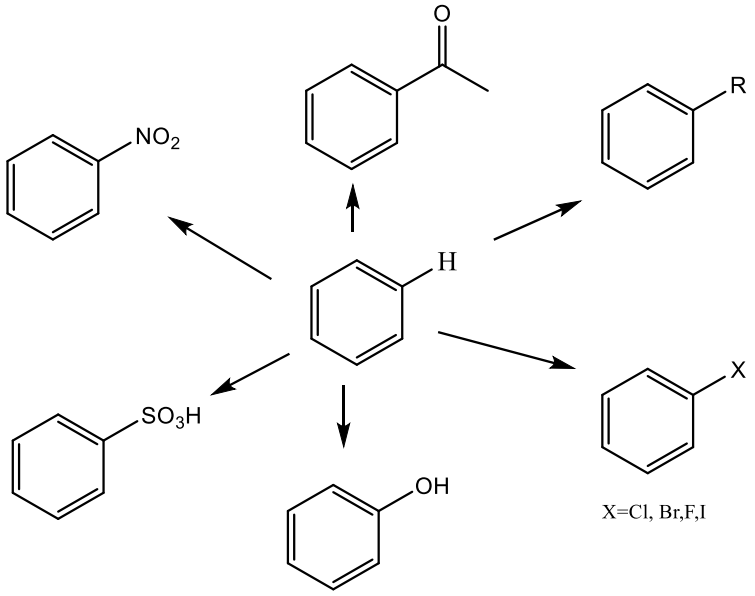
Electrophilic Aromatic Substitution

The most common reaction of aromatic compounds is **electrophilic aromatic substitution**, in which an electrophile (E+) reacts with an aromatic ring and substitutes for one of the hydrogens. The reaction is characteristic of all aromatic rings, not just benzene and substituted benzenes. In fact, the ability of a compound to undergo electrophilic substitution is a good test of aromaticity.



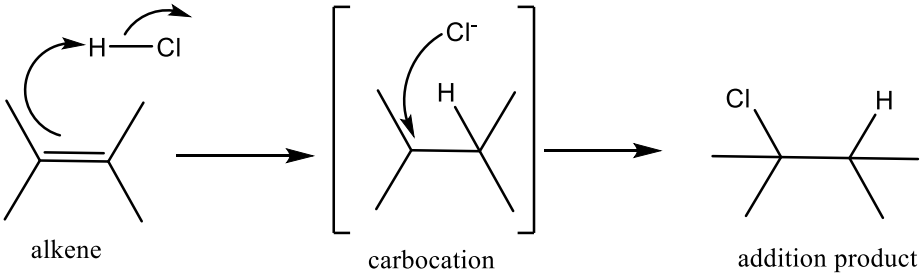
Many different substituents can be introduced onto an aromatic ring through electrophilic substitution. To list some possibilities, an aromatic ring can be substituted by a halogen (-Cl, -Br, -I), a nitro group (-NO_2), a sulfonic acid group (SO_3H), a hydroxyl group (-OH), an alkyl group (-

R), or an acyl group (-COR). Starting from only a few simple materials, it's possible to prepare many thousands of substituted aromatic compounds.

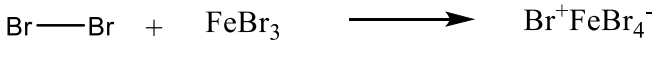


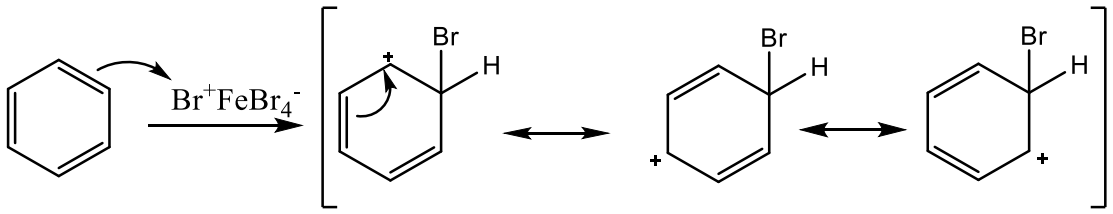
Electrophilic Aromatic Substitution Reactions: Bromination

Before seeing how electrophilic aromatic substitutions occur, let's briefly recall about electrophilic alkene additions. When a reagent such as HCl adds to an alkene, the electrophilic hydrogen approaches the P electrons of the double bond and forms a bond to one carbon, leaving a positive charge at the other carbon. This carbocation intermediate then reacts with the nucleophilic Cl_2 ion to yield the addition product.



An electrophilic aromatic substitution reaction begins in a similar way, but there are a number of differences. One difference is that aromatic rings are less reactive toward electrophiles than alkenes. For example, Br_2 in CH_2Cl_2 solution reacts instantly with most alkenes but does not react with benzene at room temperature. For bromination of benzene to take place, a catalyst such as $FeBr_3$ is needed. The catalyst makes the Br_2 molecule more electrophilic by polarizing it to give an $FeBr_4^-Br^+$ species that reacts as if it were Br^+ The polarized Br_2 molecule then reacts with the nucleophilic benzene ring to yield a nonaromatic carbocation intermediate that is doubly allylic and has three resonance forms.





Another difference between alkene addition and aromatic substitution occurs after the carbocation intermediate has formed. Instead of adding Br^- to give an addition product, the carbocation intermediate loses H^+ from the bromine-bearing carbon to give a substitution product. Note that this loss of H^+ is similar to what occurs in the second step of an E1 reaction. The net effect of reaction of Br_2 with benzene is the substitution of H^+ by Br^+ by the overall mechanism shown in **Figure-1**.

Mechanism

The mechanism for the electrophilic bromination of benzene. The reaction occurs in two steps and involves a resonance stabilized carbocation intermediate.

1) An electron pair from the benzene ring attacks the positively polarised bromine, forming a new C-Br bond and leaving a nonaromatic carbocation intermediate.

2) A base removes H^+ from the carbocation intermediate, and the neutral substitution product forms as two electrons from the C-H bond move to re-form the aromatic ring.

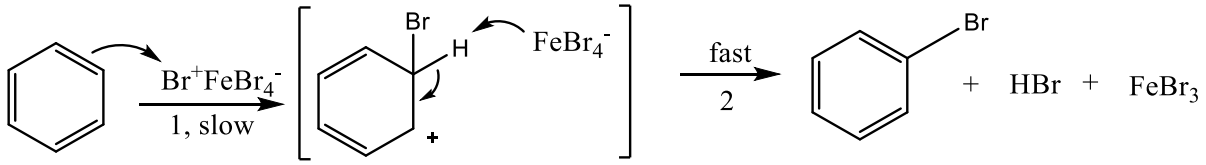
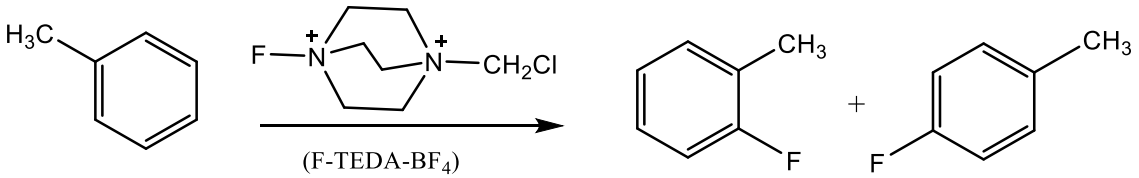


Figure-1 The mechanism for the electrophilic bromination of benzene.

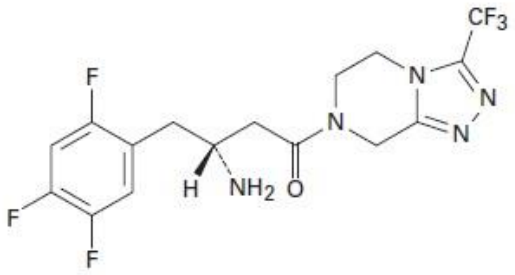
Other Aromatic Substitutions : There are many other kinds of electrophilic aromatic substitutions besides bromination, and all occur by the same general mechanism. Let's look at some of these other reactions briefly.

Aromatic Halogenation : Chlorine, bromine, and iodine can be introduced into aromatic rings by electrophilic substitution reactions, but fluorine is too reactive and only poor yields of Mon fluoroaromatic products are obtained by direct fluorination. Instead, other sources of —F^+‖ are used, in which a fluorine atom is bonded to a positively charged nitrogen. One of the most common such reagents goes by the acronym F-TEDA-BF_4 and is sold under the name Select fluor.

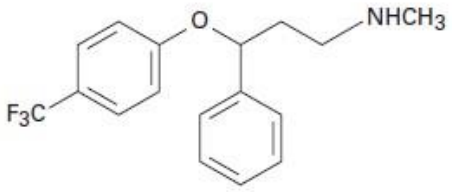


3:1 ratio ; 82% yield

Many fluorine-containing aromatic compounds are particularly valuable as pharmaceutical agents. Approximately 80 pharmaceuticals now on the market, including 18 of the top 100 sellers, contain fluorine. Sitagliptin (Januvia), used to treat type 2 diabetes, and fluoxetine (Prozac), an antidepressant, are examples.

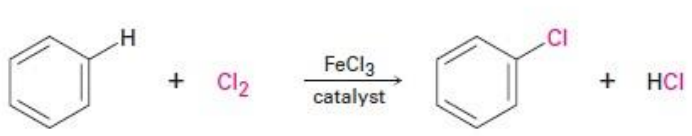


Sitagliptin
(Januvia)



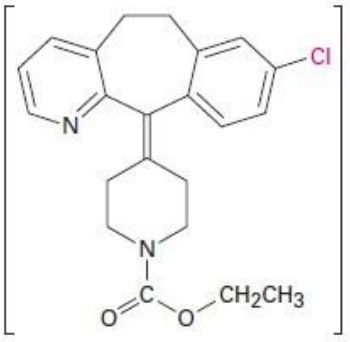
Fluoxetine
(Prozac)

Aromatic rings react with Cl_2 in the presence of $FeCl_3$ catalyst to yield chlorobenzenes, just as they react with Br_2 and $FeBr_3$. This kind of reaction is used in the synthesis of numerous pharmaceutical agents, including the antiallergy medication loratadine, marketed as Claritin.



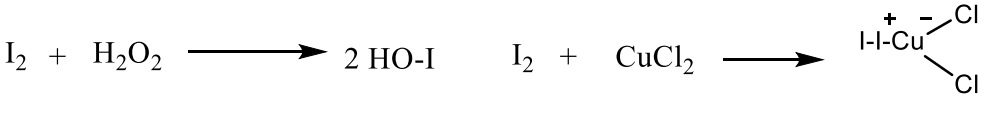
Benzene

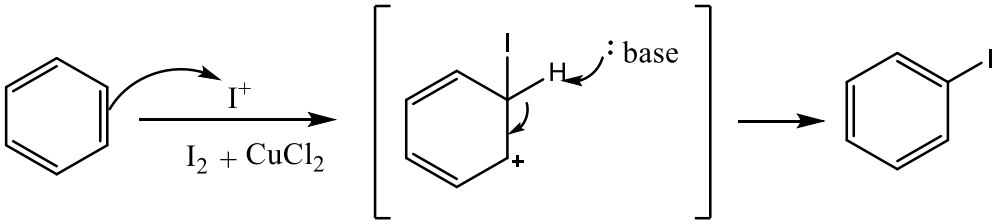
Chlorobenzene (86%)



Loratadine

Iodine itself is unreactive toward aromatic rings, so an oxidizing agent such as hydrogen peroxide or a copper salt such as $CuCl_2$ must be added to the reaction. These substances accelerate the iodination reaction by oxidizing I_2 to a more powerful electrophilic species that reacts as if it were I^+. The aromatic ring then reacts with I^+ in the typical way, yielding a substitution product.





Aromatic Nitration : Aromatic rings are nitrated by reaction with a mixture of concentrated nitric and sulfuric acids. The electrophile is the nitronium ion, NO_2+, which is formed from HNO_3 by protonation and loss of water. The nitronium ion reacts with benzene to yield a carbocation intermediate, and loss of H+ from this intermediate gives the neutral substitution product, nitrobenzene **(Figure-2)**.

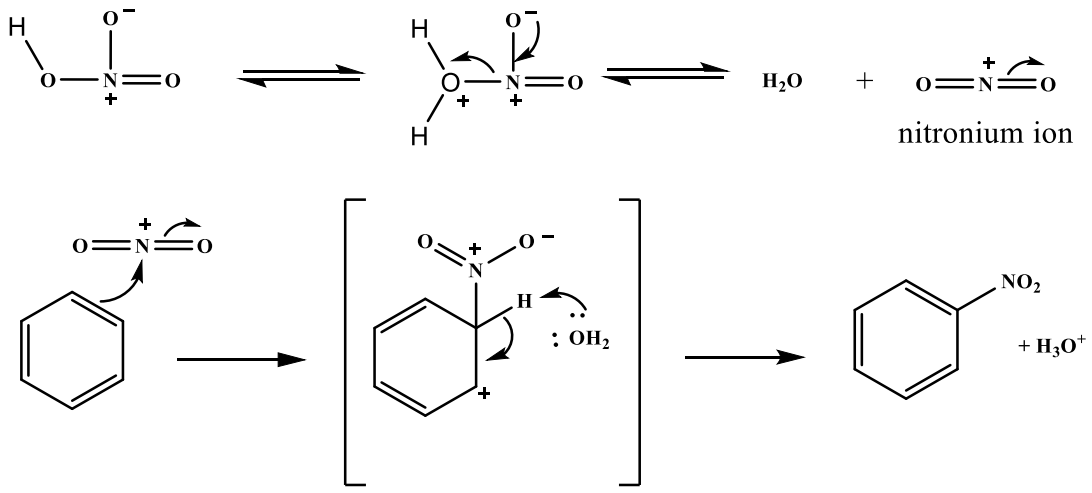
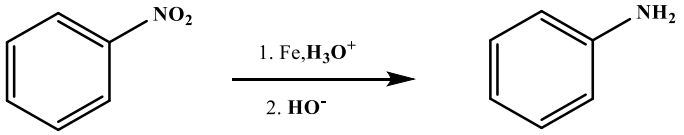


Figure-2 The mechanism for electrophilic nitration of an aromatic ring. An electrostatic potential map of the reactive electrophile NO_2 + shows that the nitrogen atom is most positive.

Electrophilic nitration of an aromatic ring does not occur in nature but is particularly important in the laboratory because the nitro-substituted product can be reduced by reagents such as iron, tin, or $SnCl_2$ to yield an *arylamine,* $ArNH_2$. Attachment of an amino group to an aromatic ring by the two-step nitration/reduction sequence is a key part of the industrial synthesis of many dyes and pharmaceutical agents.



Aromatic Sulfonation : Aromatic rings can be sulfonated by reaction with fuming sulfuric acid, a mixture of H_2SO_4 and SO_3. The reactive electrophile is either HSO_3+ or neutral SO_3, depending on reaction conditions, and substitution occurs by the same two-step mechanism seen previously for bromination and nitration **(Figure-3)**. Note, however, that the *sulfonation* reaction is readily reversible; it can occur either forward or backward, depending on the reaction conditions. Sulfonation is favoured in strong acid, but desulfonation is favoured in hot, dilute aqueous acid.

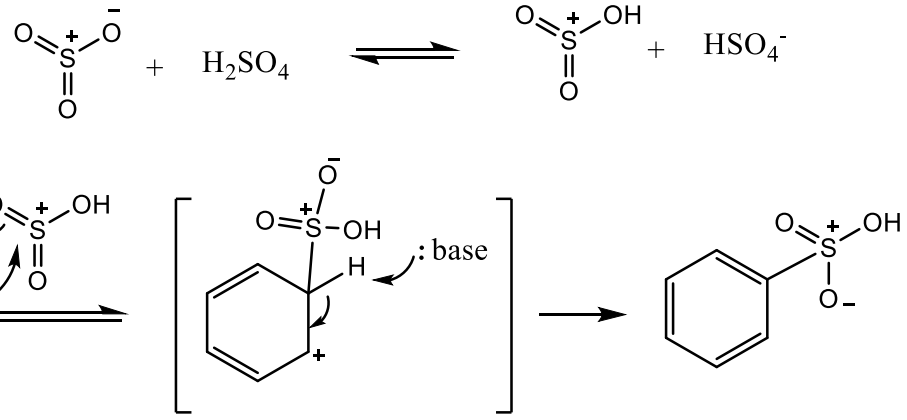
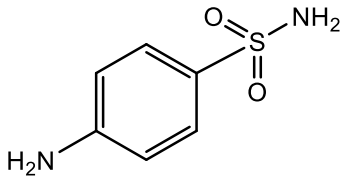


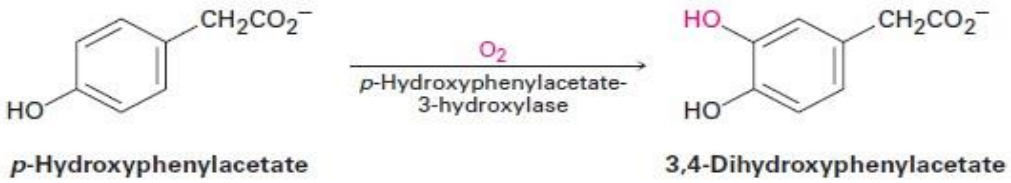
Figure-3 The mechanism for electrophilic sulfonation of an aromatic ring. An electrostatic potential map of the reactive electrophile $HOSO_2$+ shows that sulphur and hydrogen are the most positive atoms.

Aromatic sulfonation does not occur naturally but is widely used in the preparation of dyes and pharmaceutical agents. For example, the sulpha drugs, such as sulphanilamide, were among the

first clinically useful antibiotics. Although largely replaced today by more effective agents, sulpha drugs are still used in the treatment of meningitis and urinary tract infections. These drugs are prepared commercially by a process that involves aromatic sulfonation as its key step.



Aromatic Hydroxylation :Direct hydroxylation of an aromatic ring to yield a hydroxybenzene (a *phenol*) is difficult and rarely done in the laboratory but occurs much more frequently in biological pathways. An example is the hydroxylation of *p*-hydroxyphenylacetate to give 3,4-dihydroxyphenylacetate. The reaction is catalyzed by *p*hydroxyphenylacetate-3-hydroxylase and requires molecular oxygen plus the coenzyme reduced flavin adenine dinucleotide, abbreviated $FADH_2$.



Alkylation and Acylation of Aromatic Rings:
The Friedel–Crafts Reaction

Among the most useful electrophilic aromatic substitution reactions in the laboratory is **alkylation**—the introduction of an alkyl group onto the benzene ring. Called the **Friedel–Crafts reaction** after its discoverers, the reaction is carried out by treating an aromatic compound with an alkyl chloride, RCl, in the presence of $AlCl_3$ to generate a carbocation electrophile, R+. Aluminum chloride catalyzes the reaction by helping the alkyl halide to dissociate in much the same way that $FeBr_3$ catalyzes aromatic brominations by polarizing Br_2. Loss of H+ then completes the reaction **(Figure-4)**.

Mechanism

Mechanism for the Friedel-Caft alkylation reaction of benzene with 2-chloropropane to yield isopropyl benzene. The electrophile is a carbocation. Generally by $AlCl_3$ assisted dissociation of an alkyl halide.

1. An electrophile pair from the aromatic ring attacks the carbocation, forming a C-c bond and yielding a new carbocation intermediate.
2. Loss of a proton then gives the neutral alkylated substitution product.

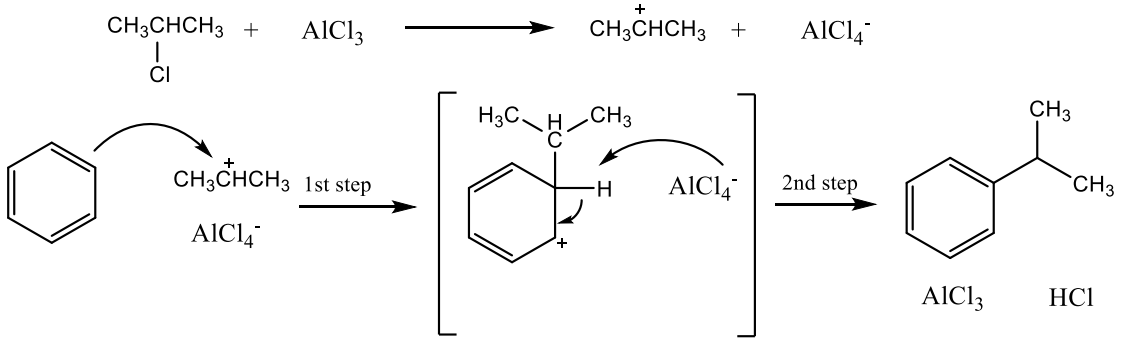
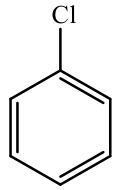
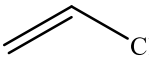


Figure-4 Mechanism for the Friedel–Crafts alkylation reaction of benzene

Despite its utility, the Friedel–Crafts alkylation has several limitations. For one thing, only *alkyl* halides can be used. Aromatic (aryl) halides and vinylic halides don't react because aryl and vinylic carbocations are too high in energy to form under Friedel– Crafts conditions.



an aryl halide



a vinylic halide

Another limitation is that Friedel–Crafts reactions don't succeed on aromatic rings that are substituted either by a strongly electron-withdrawing group such as carbonyl (C=O) or by a basic amino group that can be protonated. We'll see in the next section that the presence of a substituent group already on a ring can have a dramatic effect on that ring's reactivity toward further electrophilic substitution. Rings that contain any of the substituents listed in **Figure-5** do not undergo Friedel–Crafts alkylation.

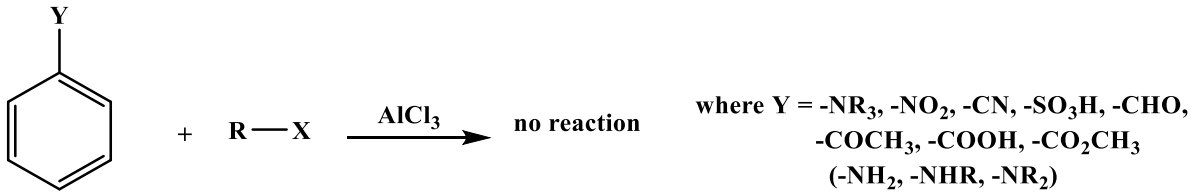
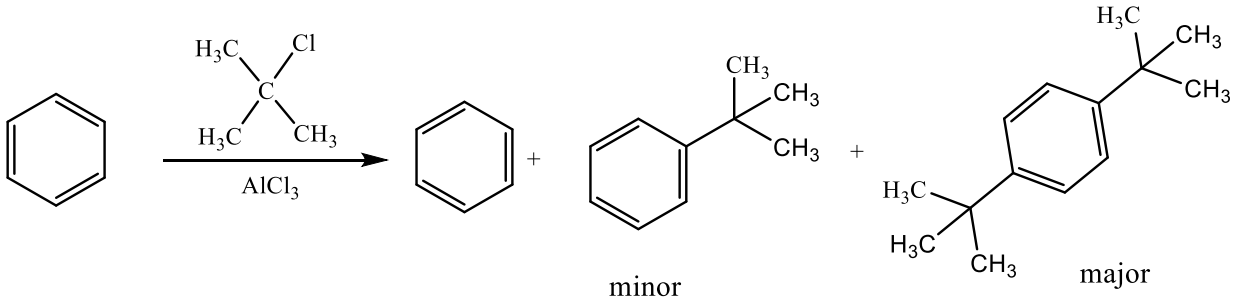


Figure-5 Limitations on the aromatic substrate in Friedel–Crafts reactions. No reaction occurs if the substrate has either an electron-withdrawing substituent or a basic amino group.

A third limitation to the Friedel–Crafts alkylation is that it's often difficult to stop the reaction after a single substitution. Once the first alkyl group is on the ring, a second substitution reaction is facilitated for reasons we'll discuss in the next section. Thus, we often observe *polyalkylation.* Reaction of benzene with 1 mol equivalent of 2chloro-2-methylpropane, for example, yields *p*-di-*tert*-butylbenzene as the major product, along with small amounts of *tert*butylbenzene and unreacted benzene. A high yield of monoalkylation product is obtained only when a large excess of benzene is used.

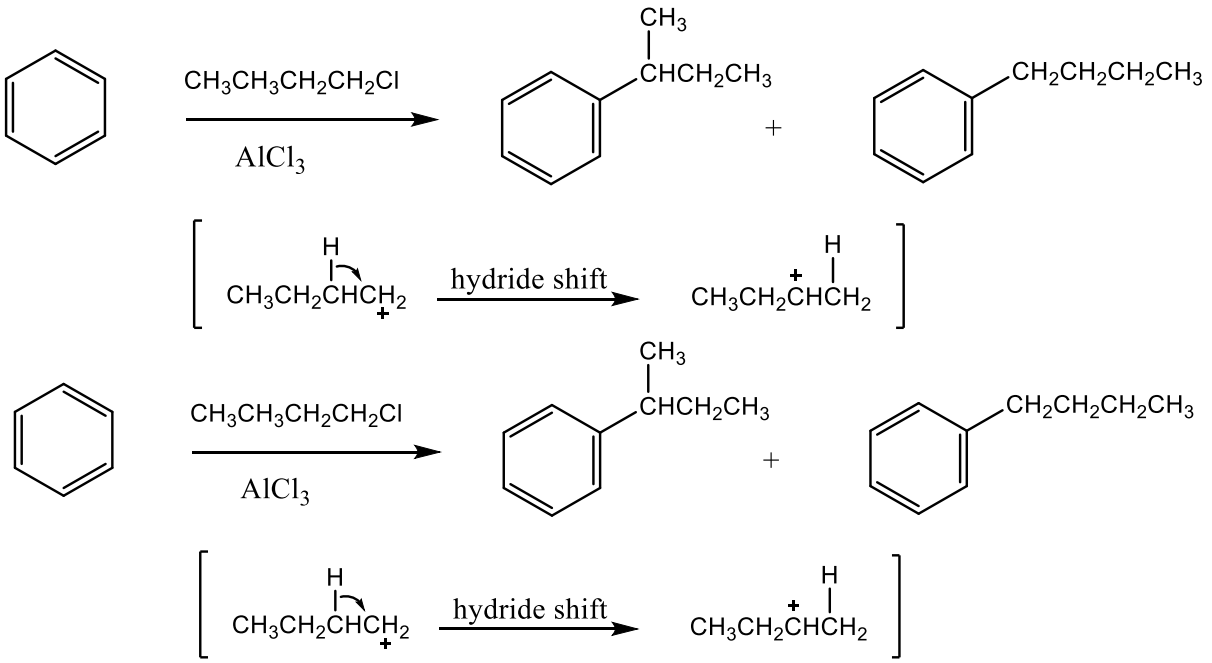


minor major

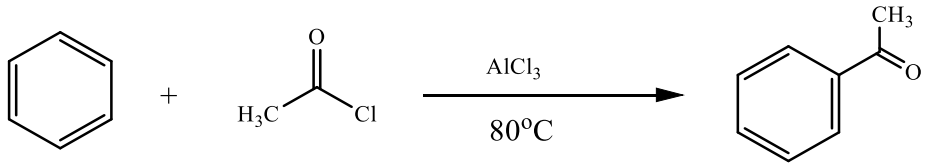
A final limitation to the Friedel–Crafts reaction is that a skeletal rearrangement of the alkyl carbocation electrophile sometimes occurs during reaction, particularly when a primary alkyl halide is used. Treatment of benzene with 1-chlorobutane at 0 °C, for instance, gives an approximately 2;1 ratio of rearranged (*sec*-butyl) to unrearranged (butyl) products.

The carbocation rearrangements that accompany Friedel–Crafts reactions are like those that accompany electrophilic additions to alkenes and occur either by hydride shift or alkyl shift. For example, the relatively unstable primary butyl carbocation produced by reaction of 1-chlorobutane with $AlCl_3$ rearranges to the more stable secondary butyl carbocation by the shift of a hydrogen atom and its electron pair (a hydride ion, H**:**-) from C2 to C1. Similarly, alkylation of benzene with 1-chloro-2,2dimethylpropane yields (1,1-dimethylpropyl)benzene. The initially

formed primary carbocation rearranges to a tertiary carbocation by shift of a methyl group and its electron pair from C2 to C1.



Just as an aromatic ring is alkylated by reaction with an alkyl chloride, it is **acylated** by reaction with a carboxylic acid chloride, RCOCl, in the presence of $AlCl_3$. That is, an **acyl group** (-COR; pronounced **a**-sil) is substituted onto the aromatic ring. For example, reaction of benzene with acetyl chloride yields the ketone acetophenone.



The mechanism of Friedel–Crafts acylation is similar to that of Friedel–Crafts alkylation, and the same limitations on the aromatic substrate noted previously in Figure-8 for alkylation also apply to acylation. The reactive electrophile is a resonance-stabilized acyl cation, generated by reaction between the acyl chloride and $AlCl_3$ **(Figure-6)**. As the resonance structures in the figure indicate, an acyl cation is stabilized by interaction of the vacant orbital on carbon with lone-pair electrons on the neighbouring oxygen. Because of this stabilization, no carbocation rearrangement occurs during acylation.

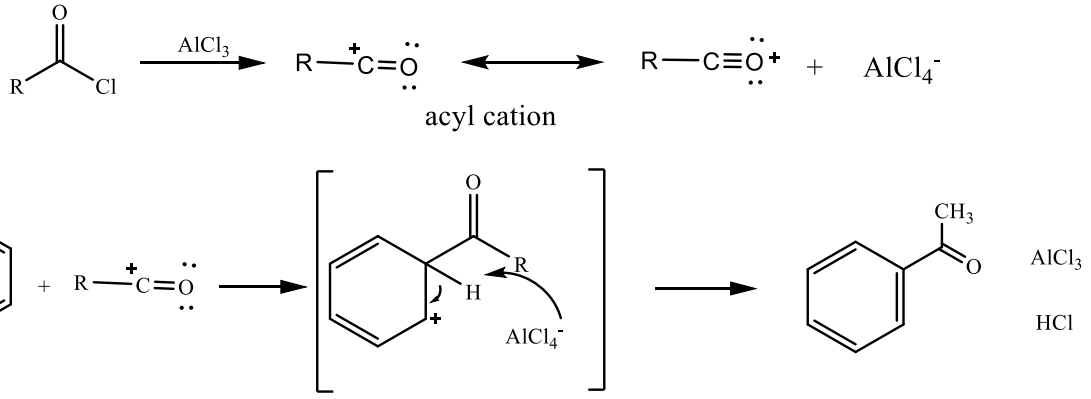


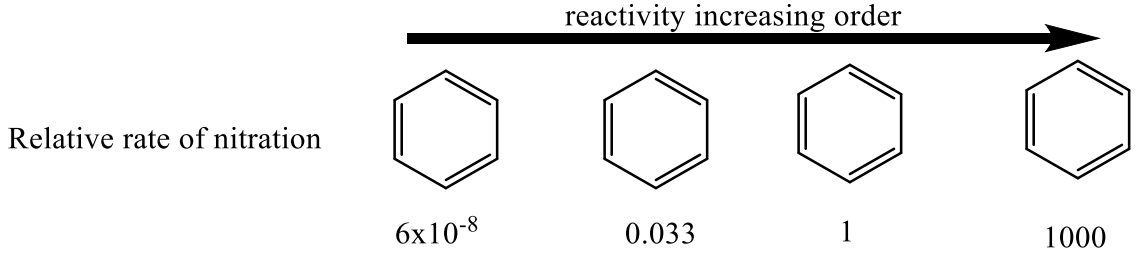
Figure -6 Mechanism of the Friedel–Crafts acylation reaction. The electrophile is a resonance-stabilized acyl cation, whose electrostatic potential map indicates that carbon is the most positive atom.

Unlike the multiple substitutions that often occur in Friedel–Crafts alkylation, acylation never occur more than once on a ring because the product acyl benzene is less reactive than the nonacylated starting material.

Substituent Effects in Electrophilic Substitutions

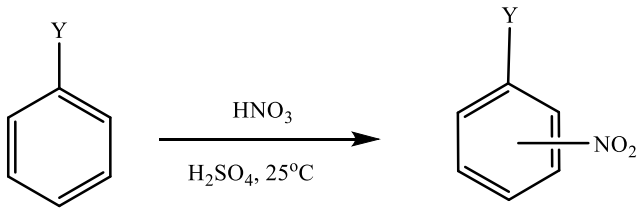
Only one product can form when an electrophilic substitution occurs on benzene, but what would happen if we were to carry out a reaction on an aromatic ring that already has a substituent? The initial presence of a substituent on the ring has two effects.

Substituents affect the *reactivity* of the aromatic ring. Some substituents activate the ring, making it more reactive than benzene, and some deactivate the ring, making it less reactive than benzene. In aromatic nitration, for instance, an -OH substituent makes the ring 1000 times more reactive than benzene, while an $-NO_2$ substituent makes the ring more than 10 million times less reactive.



Substituents affect the *orientation* of the reaction. The three possible disubstituted products—ortho, meta, and para—are usually not formed in equal amounts. Instead, the nature of the substituent initially present on the benzene ring determines the position of the second substitution. An -OH group directs substitution toward the ortho and para positions, for instance, while a carbonyl group such as -CHO directs substitution primarily toward the meta position. **Table-1** lists experimental results for the nitration of some substituted benzenes.

Table-1 Orientation of Nitration in Substituted Benzenes:



Meta-directing deactivators - Product (%)				Ortho and para-directing deactivators - Product (%)			
	Ortho	Meta	Para		Ortho	Meta	Para
$-^{+}N(CH_3)_3$	2	87	11	-F	13	1	86
-COOH	7	91	2	-Cl	35	1	64
-CN	17	81	2	-Br	43	1	56
$-CO_2CH_3$	28	66	6	-I	45	1	54
$-COCH_3$	26	72	2	Ortho and para-directing activators - Product (%)			
-CHO	19	72	9	-OH	50	0	50
				$-CH_3$	63	3	34
				$-NHCOCH_3$	19	2	79

Substituents can be classified into three groups, as shown in **Figure-7**: *ortho- and para-directing activators, ortho- and para-directing deactivators,*and *meta-directing deactivators.* There are no meta-directing activators. Notice how the directing effect of a group correlates with its reactivity. All metadirecting groups are strongly deactivating, and most ortho- and para-directing groups are activating. The halogens are unique in being ortho- and paradirecting but weakly deactivating.

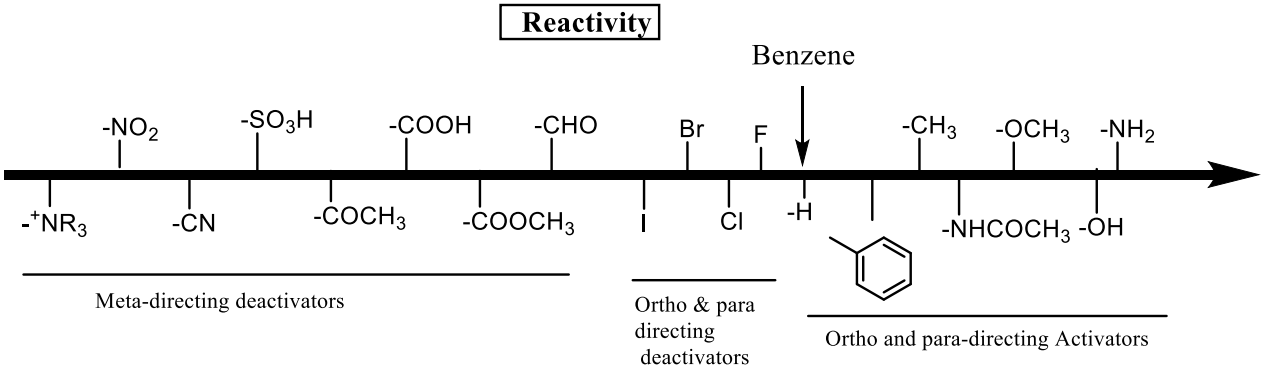
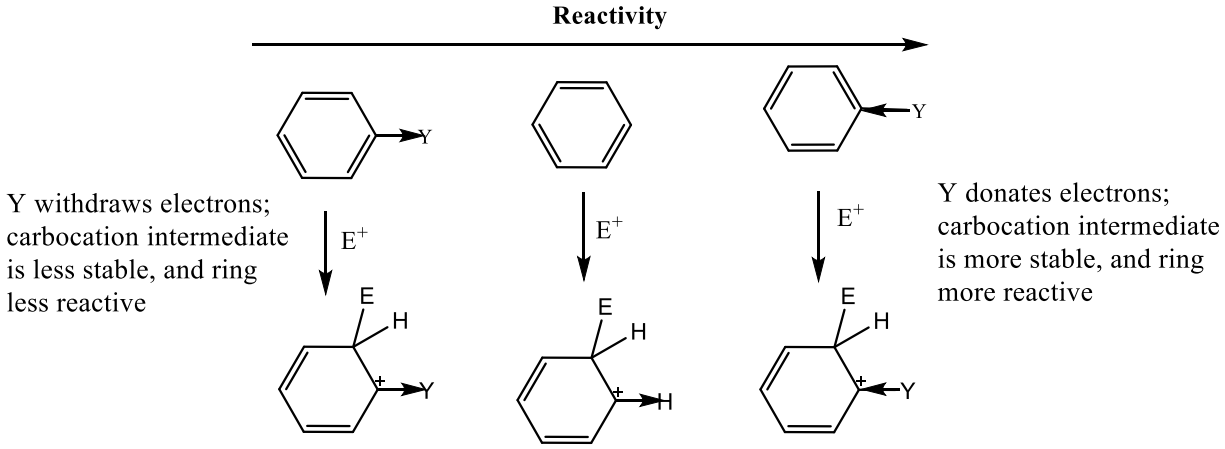


Figure-7 Classification of substituent effects in electrophilic aromatic substitution. All activating groups are ortho- and para-directing, and all deactivating groups other than halogen are meta-directing. The halogens are unique in being deactivating but ortho- and para-directing.

Activating and Deactivating Effects

What makes a group either activating or deactivating? The common characteristic of all activating groups is that they donate electrons to the ring, thereby making the ring more electron-rich, stabilizing the carbocation intermediate, and lowering the activation energy for its formation. Conversely, the common characteristic of all deactivating groups is that they withdraw electrons from the ring, thereby making the ring more electron-poor, destabilizing the carbocation intermediate, and raising the activation energy for its formation.



Compare the electrostatic potential maps of benzaldehyde (deactivated), chlorobenzene (weakly deactivated), and phenol (activated) with that of benzene. As shown in **Figure-8**, the ring is more positive (yellow-green) when an electronwithdrawing group such as -CHO or -Cl is present and more negative (red) when an electron-donating group such as -OH is present.

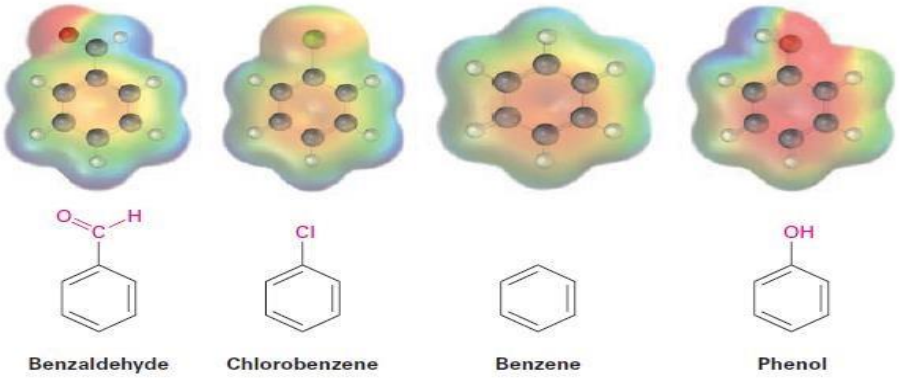
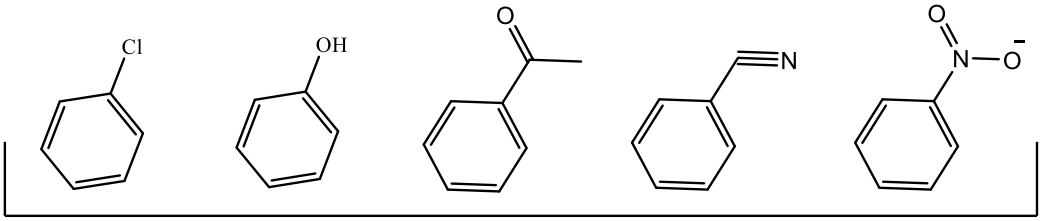
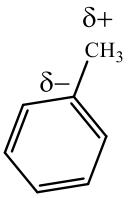


Figure-8 Electrostatic potential maps of benzene and several substituted benzenes show that an electron-withdrawing group (-CHO or -Cl) makes the ring more electron-poor,while an electron-donating group (-OH) makes the ring more electron-rich.

The withdrawal or donation of electrons by a substituent group is controlled by an interplay of *inductive effects* and *resonance effects.* As we saw, an **inductive effect** is the withdrawal or donation of electrons through a *s* bond due to electronegativity. Halogens, hydroxyl groups, carbonyl groups, cyano groups, and nitro groups inductively withdraw electrons through the *s* bond linking the substituent to a benzene ring. This effect is most pronounced in halobenzenes and phenols, in which the electronegative atom is directly attached to the ring, but is also significant in carbonyl compounds, nitriles, and nitro compounds, in which the electronegative atom is farther removed. Alkyl groups, on the other hand, inductively donate electrons. This is the same hyperconjugative donating effect that causes alkyl substituents to stabilize alkenes and carbocations.



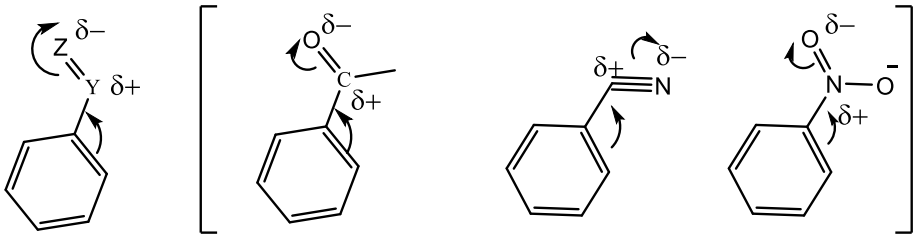
Inductive electron withdrawal



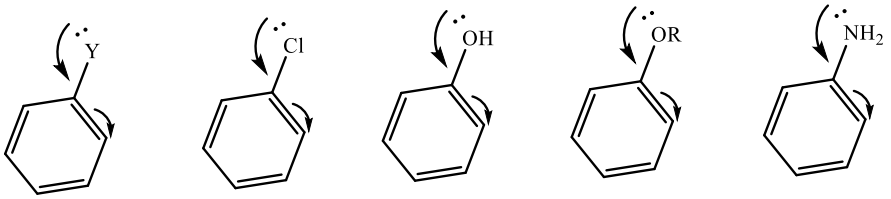
Inductive electron donation

A **resonance effect** is the withdrawal or donation of electrons through a *Π* bond due to the overlap of a *p* orbital on the substituent with a *p* orbital on the aromatic ring. Carbonyl, cyano, and nitro substituents, for example, withdraw electrons from the aromatic ring by resonance. The *Π* electrons flow from the ring to the substituent, leaving a positive charge in the ring. Note that substituents with an electronwithdrawing resonance effect have the general structure –Y=Z, where the Z atom is more electronegative than Y.

Conversely, halogen, hydroxyl, alkoxyl (-OR), and amino substituents donate electrons to the aromatic ring by resonance. Lone-pair electrons flow from the substituents to the ring, placing a negative charge on the ring. Substituents with an electron-donating resonance effect have the general structure -Y:,where the Y atom has a lone pair of electrons available for donation to the ring.



Resonance electron withdrawing groups



Resonance electron donsting groups

One further point: inductive effects and resonance effects don't necessarily act in the same direction. Halogen, hydroxyl, alkoxyl, and amino substituents, for instance, have electron-withdrawing inductive effects because of the electronegativity of the -X, -O, or -N atom bonded to the aromatic ring but have electron-donating resonance effects because of the lone-pair electrons on those -X, -O, or -N atoms. When the two effects act in opposite directions, the stronger one dominates. Thus, hydroxyl, alkoxyl, and amino substituents are activators because their stronger electron-donating resonance effect outweighs their weaker electron-withdrawing inductive effect. Halogens, however, are deactivators because their stronger electronwithdrawing inductive effect outweighs their weaker electron-donating resonance effect.

Ortho- and Para-Directing Activators: Alkyl Groups

Inductive and resonance effects account not only for reactivity but also for the orientation of electrophilic aromatic substitutions. Take alkyl groups, for instance, which have an electron-donating inductive effect and are ortho and para directors. The results of toluene nitration are shown in **Figure-9**.

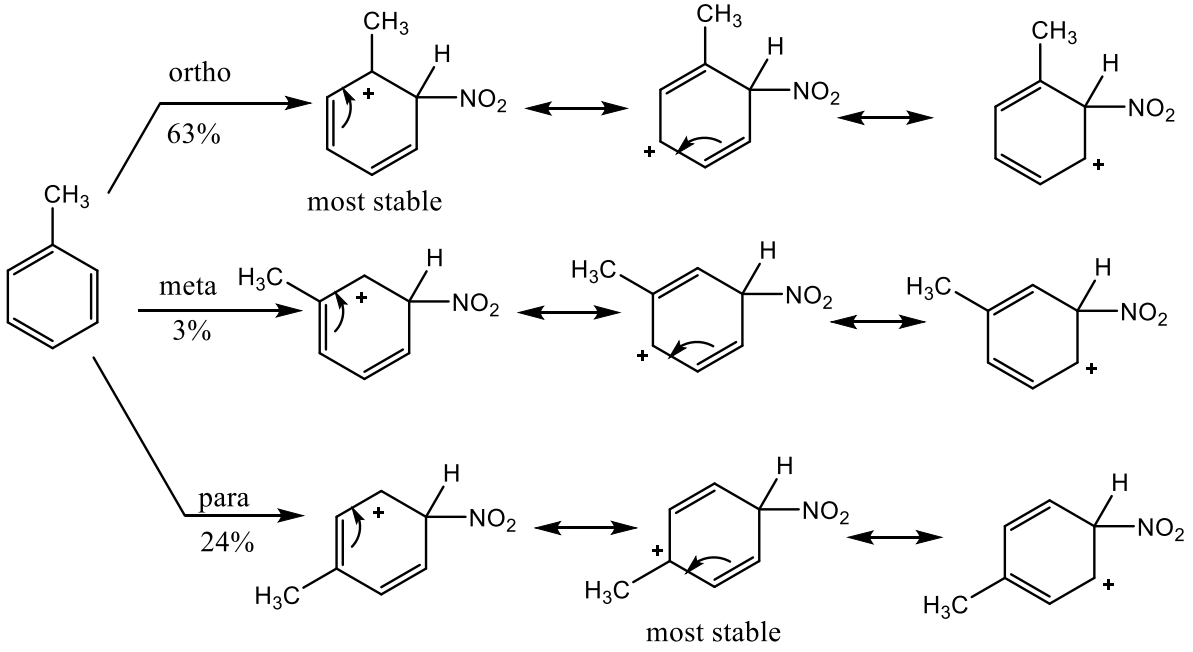


Figure-9 Carbocation intermediates in the nitration of toluene. Ortho and para intermediates are more stable than the meta intermediate because the positive charge is on a tertiary carbon rather than a secondary carbon.

Nitration of toluene might occur either ortho, meta, or para to the methyl group, giving the three carbocation intermediates shown in Figure-13. Although all three intermediates are resonance-stabilized, the ortho and para intermediates are more stabilized than the meta intermediate. For both the ortho and para reactions, but not for the meta reaction, a resonance form places the positive charge directly on the methyl-substituted carbon, where it is in a tertiary position and can be stabilized by the electron-donating inductive effect of the methyl group. The ortho and para intermediates are thus lower in energy than the meta intermediate and form faster.

Ortho- and Para-Directing Activators: OH and NH_2

Hydroxyl, alkoxyl, and amino groups are also ortho–para activators, but for a different reason than for alkyl groups. As described earlier in this section, hydroxyl, alkoxyl, and amino groups have a strong, electron-donating resonance effect that outweighs a weaker electron-withdrawing inductive effect. When phenol is nitrated, for instance, reaction can occur either ortho, meta, or para to the -OH group, giving the carbocation intermediates shown in **Figure-10**. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms, including one particularly favorable form that allows the positive charge to be stabilized by electron donation from the substituent oxygen atom. The intermediate from the meta reaction has no such stabilization.

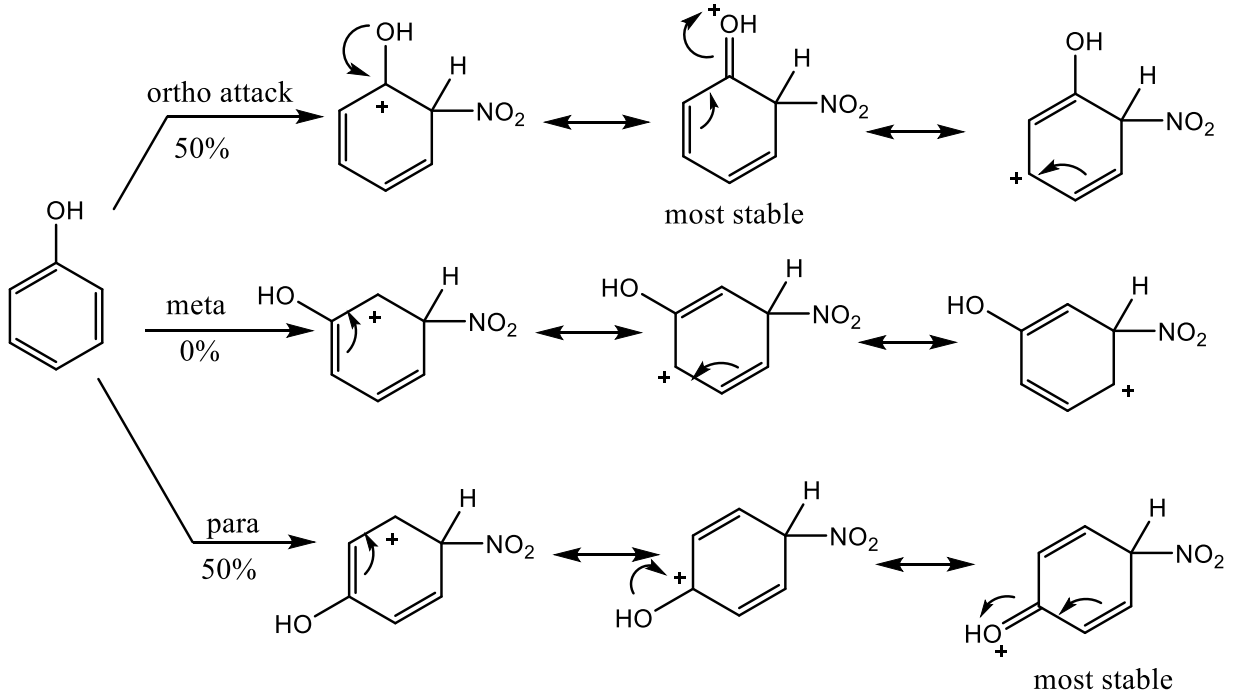


Figure-10 Carbocation intermediates in the nitration of phenol. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms, including one particularly favorable form that involves electron donation from the oxygen atom.

Ortho- and Para-Directing Deactivators: Halogens

Halogens are deactivating because their stronger electron-withdrawing inductive effect outweighs their weaker electron-donating resonance effect. Although weak, that electron-donating resonance effect is nevertheless felt only at the ortho and para positions and not at the meta position **(Figure-11)**.Thus, a halogen substituent can stabilize the positive charge of the carbocation intermediates from ortho and para reaction in the same way that hydroxyl and amino substituents can. The meta intermediate, however, has no such stabilization and is therefore formed more slowly.

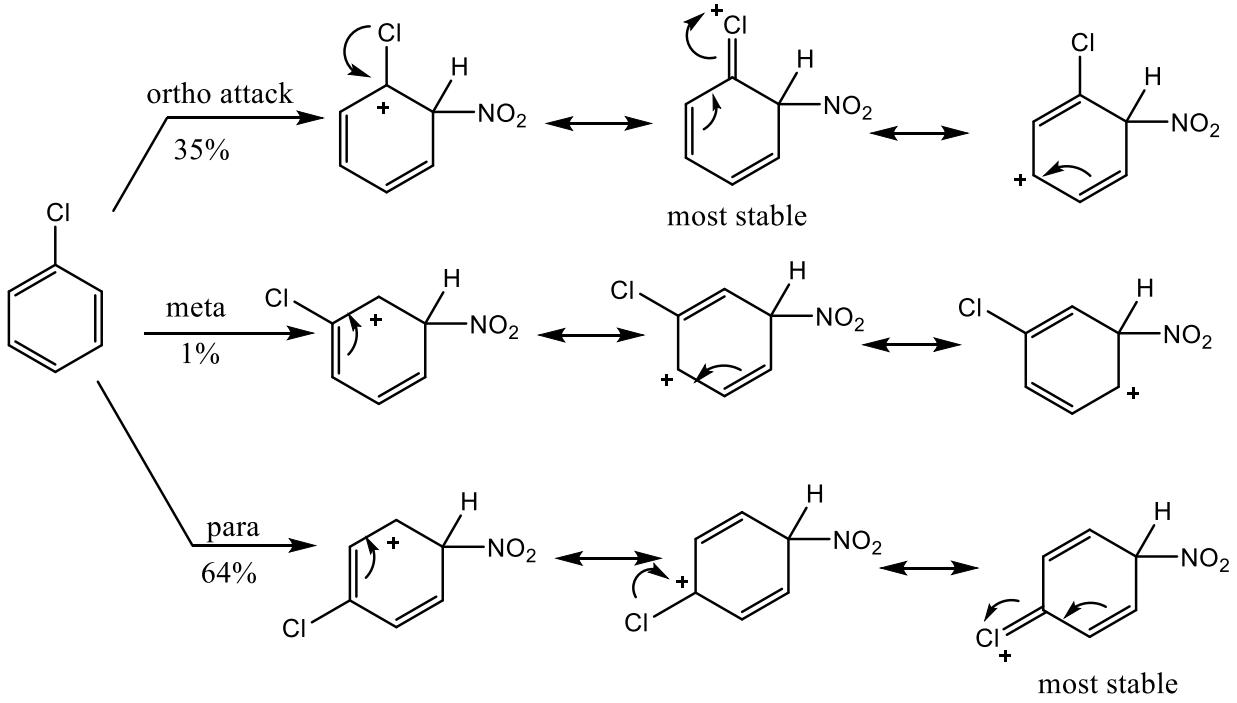


Figure-11 Carbocation intermediates in the nitration of chlorobenzene. The ortho and para intermediates are more stable than the meta intermediate because of electron donation of the halogen lone-pair electrons.

Note again that halogens, hydroxyl, alkoxyl, and amino groups all withdraw electrons inductively but donate electrons by resonance. Halogens have a stronger electronwithdrawing inductive effect but a weaker electrondonating resonance effect and are thus deactivators. Hydroxyl, alkoxyl, and amino groups have a weaker electronwithdrawing inductive effect but a stronger electron-donating resonance effect and are thus activators. All are ortho and para directors, however, because of the lone pair of electrons on the atom bonded to the aromatic ring.

Meta-Directing Deactivators

The influence of meta-directing substituents can be explained using the same kinds of arguments used for ortho and para directors. Look at the nitration of benzaldehyde, for instance **(Figure-12)**. Of the three possible carbocation intermediates, the meta intermediate has three favorable resonance forms, whereas the ortho and para intermediates have only two. In both ortho and para intermediates, the third resonance form is unfavorable because it places the positive charge directly on the carbon that bears the aldehyde group, where it is disfavored by a repulsive interaction with the positively polarized carbon atom of the C=O group. Hence, the meta intermediate is more favored and is formed faster than the ortho and para intermediates.

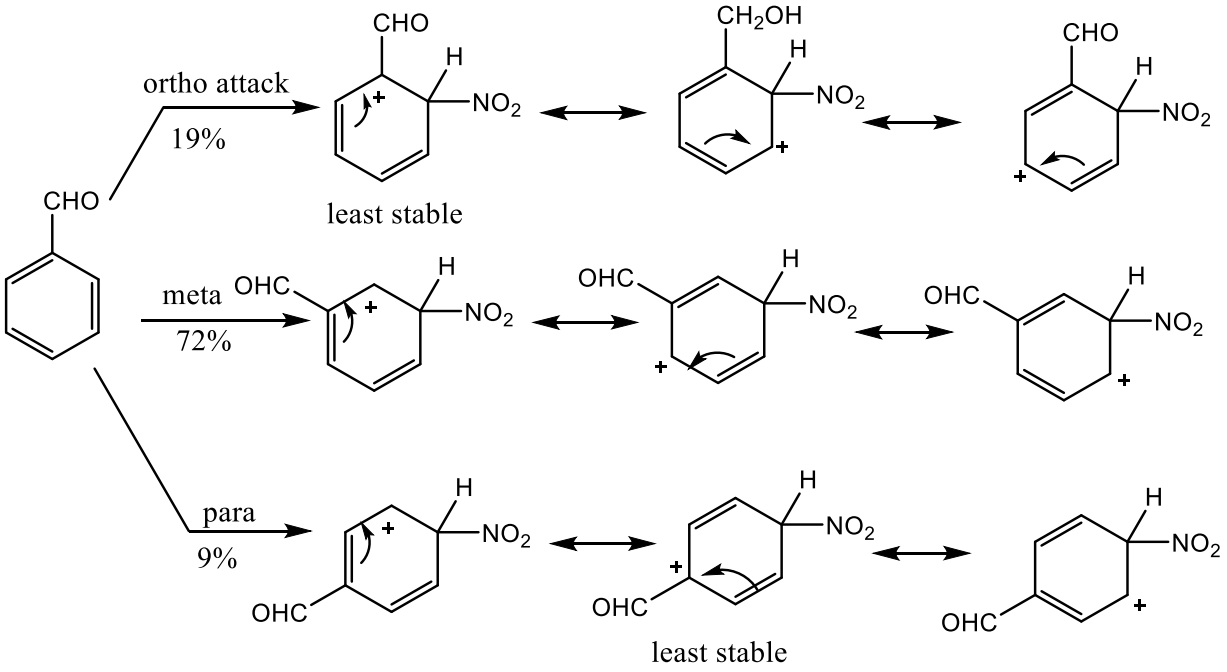


Figure-12 Carbocation intermediates in the nitration of benzaldehyde. The ortho and para intermediates are less stable than the meta intermediate. The meta intermediate is more favorable than ortho and para intermediates because it has three favorable resonance forms rather than two.

In general, any substituent that has a positively polarized atom (δ+) directly attached to the ring will make one of the resonance forms of the ortho and para intermediates unfavorable and will thus act as a meta director.

A Summary of Substituent Effects in Electrophilic Aromatic Substitution

A summary of the activating and directing effects of substituents in electrophilic aromatic substitution is shown in **Table-2**.

Table-2 Substituent Effects in Electrophilic Aromatic Substitution

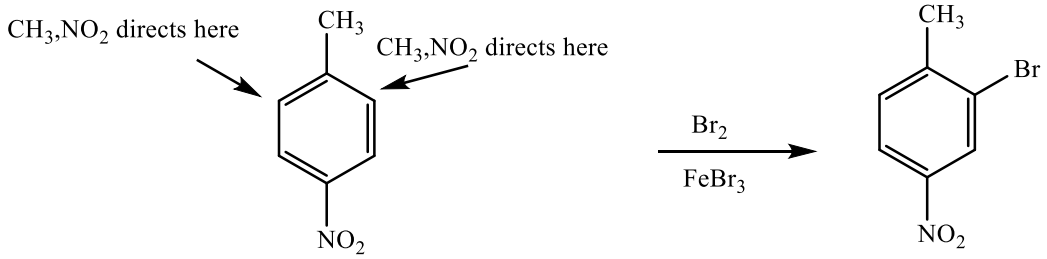
Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho,para	Weak donating	-
-OH,$-NH_2$	Activating	Ortho,para	Weak withdrawing	Strong donating
-F,-Cl,-Br, -I	Deactivating	Ortho,para	Strong withdrawing	Weak donating
$-NO_2$,-CN,-CHO,$-CO_2R$,-COR,$-CO_2H$	Deactivating	Meta	Strong withdrawing	Strong withdrawing

Trisubstituted Benzenes: Additivity of Effects

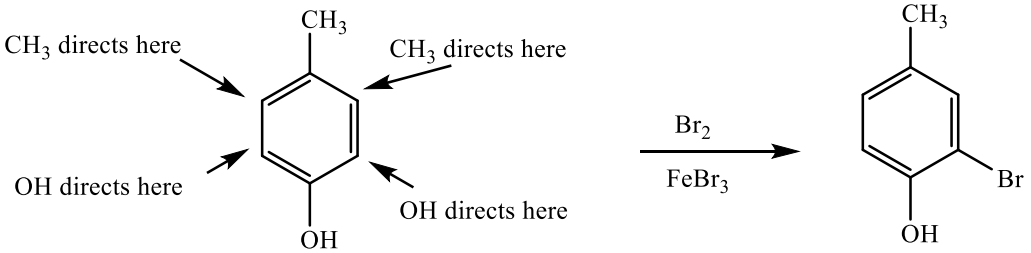
Electrophilic substitution of a disubstituted benzene ring is governed by the same resonance and inductive effects that influence monosubstituted rings.

The only difference is that it's necessary to consider the additive effects of two different groups. In practice, this isn't as difficult as it sounds; three rules are usually sufficient.

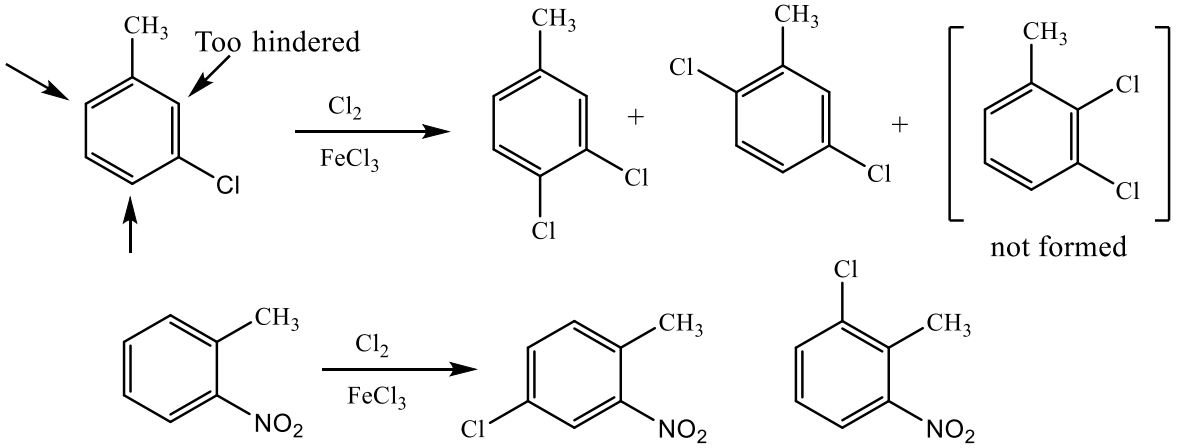
- If the directing effects of the two groups reinforce each other, the situation is straightforward. In *p*-nitrotoluene, for example, both the methyl and the nitro group direct further substitution to the same position (ortho to the methyl = meta to the nitro). A single product is thus formed on electrophilic substitution.



- If the directing effects of the two groups oppose each other, the more powerful activating group has the dominant influence, but mixtures of products are often formed. For example, bromination of *p*-methylphenol yields primarily 2bromo-4-methylphenol because -OH is a more powerful activator than -CH_3.



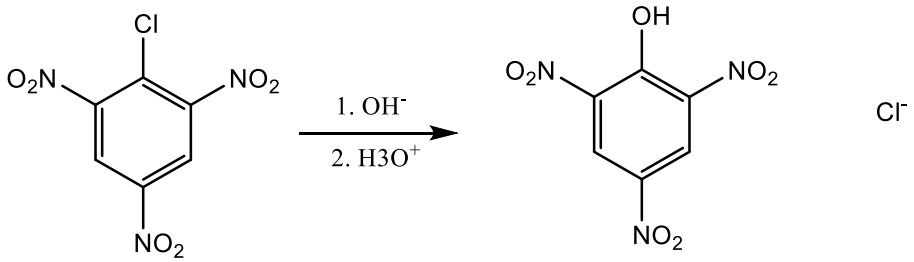
- Further substitution rarely occurs between the two groups in a metadisubstituted compound because this site is too hindered. Aromatic rings with three adjacent substituents must therefore be prepared by some other route, such as by substitution of an ortho-disubstituted compound.



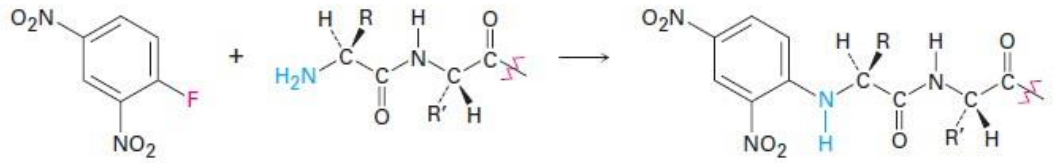
UNIT-III: **Aromatic and Aliphatic Nucleophilic Substitution:** Aromatic nucleophilic substitution: Mechanisms - SNAr, SN1 and Benzyne mechanisms - Evidences - Reactivity, Effect of structure, leaving group and attacking nucleophile. Reactions: Oxygen and Sulphur-nucleophiles, Bucherer and Rosenmund reactions, von Richter, Sommelet- Hauser and Smiles rearrangements. SN1, ion pair, SN2 mechanisms and evidences. Aliphatic nucleophilic substitutions at an allylic carbon, aliphatic trigonal carbon and vinyl carbon.SN1, SN2, SNi, and SE1 mechanism and evidences, Swain- Scott, Grunwald-Winstein relationship - Ambident nucleophiles.

Nucleophilic Aromatic Substitution

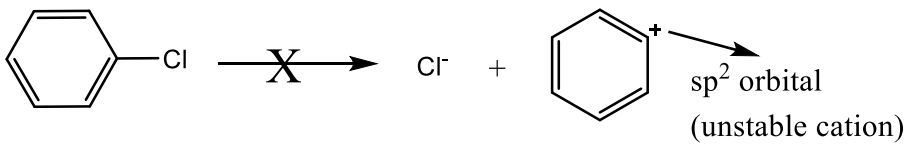
Although aromatic substitution reactions usually occur by an *electrophilic* mechanism, aryl halides that have electron-withdrawing substituents can also undergo a *nucleophilic* substitution reaction. For example, 2,4,6-trinitrochlorobenzene reacts with aqueous NaOH at room temperature to give 2,4,6-trinitrophenol. Here, the nucleophile OH- substitutes for Cl-.



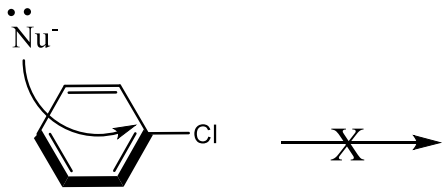
Nucleophilic aromatic substitution is much less common than electrophilic substitution but nevertheless does have certain uses. One such use is the reaction of proteins with 2,4-dinitrofluorobenzene, known as *Sanger's reagent,* to attach a ―label‖ to the terminal NH_2 group of the amino acid at one end of the protein chain.



Although the reaction appears superficially similar to the S_N1 and S_N2 nucleophilic substitutions of alkyl halides, it must be different because aryl halides are inert to both S_N1 and S_N2 conditions. S_N1 reactions don't occur with aryl halides because dissociation of the halide is energetically unfavorable, due to the instability of the potential aryl cation product. S_N2 reactions don't occur with aryl halides because the halo-substituted carbon of the aromatic ring is sterically shielded from a backside approach. For a nucleophile to react with an aryl halide, it would have to approach directly through the aromatic ring and invert the stereochemistry of the aromatic ring carbon—a geometric impossibility.



Dissociation reaction does not occur because the aryl cation is unstable; therefore, no S_N1 reaction.



Backside displacement is sterically blocked; therefore, no S_N2 reaction

Nucleophilic substitutions on an aromatic ring proceed by the mechanism shown in **Figure-13**. The nucleophile first adds to the electrondeficient aryl halide, forming a resonance-stabilized, negatively charged intermediate called a *Meisenheimer complex* after its discoverer. Halide ion is then eliminated.

Mechanism

Mechanism of nucleophilic aromatic substitution. The reaction occurs in two steps and involves a resonance stabilised carbanion intermediate.

Step 1: nucleophilic addition of hydroxide ion to the electron poor aromatic ring takes place, yielding a stabilised carbanion intermediate.

Step 2: the carbanion intermediate undergoes elimination of chloride ion in a second step to give the substitution product.

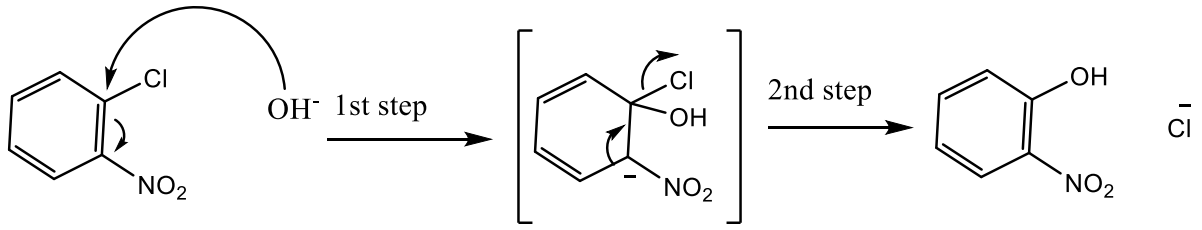


Figure-13 Mechanism of nucleophilic aromatic substitution.

Nucleophilic aromatic substitution occurs only if the aromatic ring has an electronwithdrawing substituent in a position ortho or para to the leaving group to stabilize the anion intermediate through resonance **(Fig ure-14)**. A meta substituent offers no such resonance stabilization. Thus, *p*-chloronitrobenzene and *o*-chloronitrobenzene react with hydroxide ion at 130 °C to yield substitution products, but *m*-chloronitrobenzene is inert to OH-.

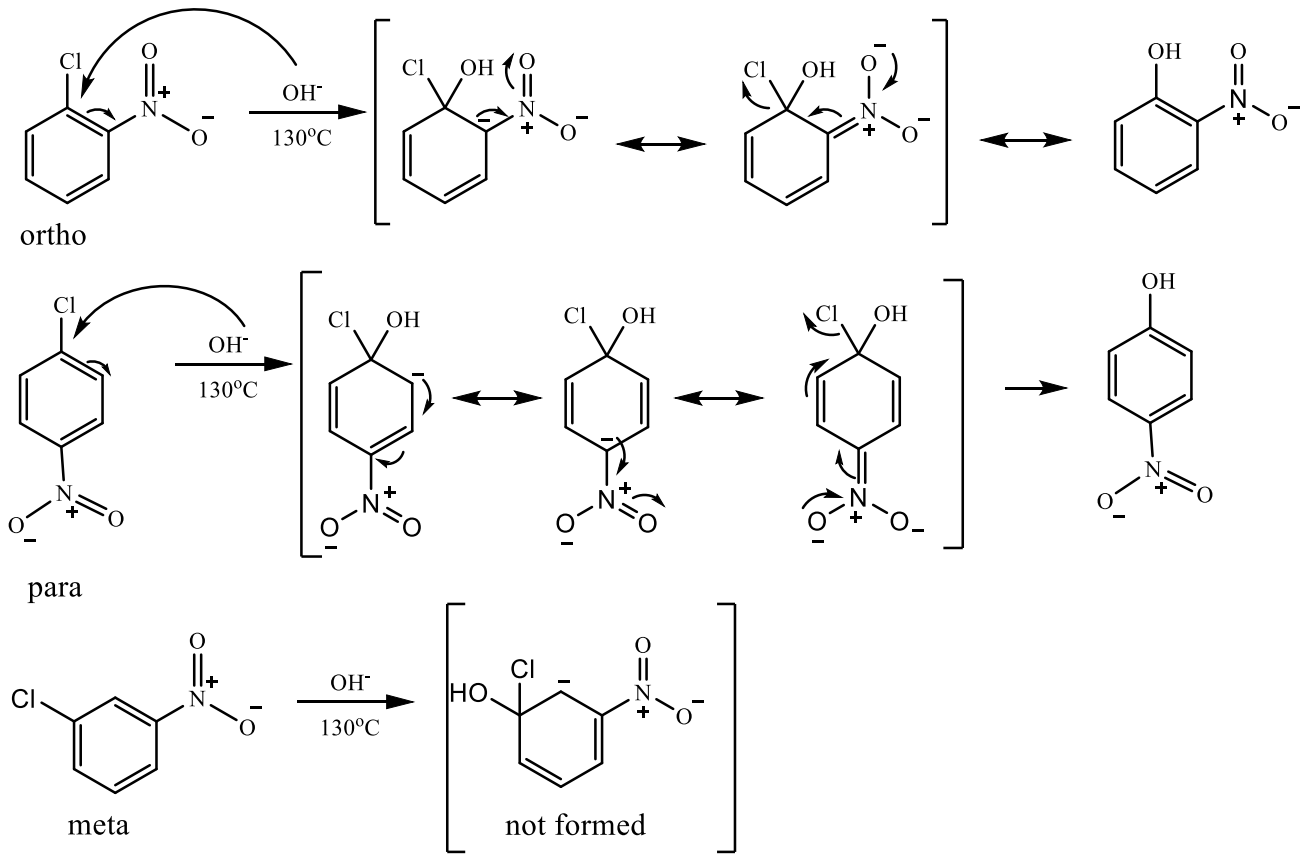


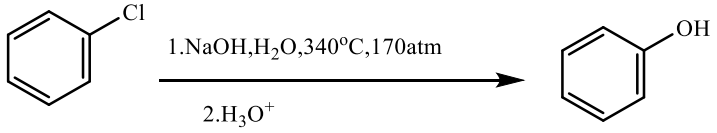
Figure-14 Nucleophilic aromatic substitution on nitrochlorobenzenes. Only in the ortho and para intermediates is the negative charge stabilized by a resonance interaction with the nitro group, so only the ortho and para isomers undergo reaction.

Note the differences between electrophilic and nucleophilic aromatic substitutions.

Electrophilic substitutions are favored by electron-*donating* substituents, which stabilize a carbocation intermediate, while nucleophilic substitutions are favored by electron-*withdrawing* substituents, which stabilize a carbanion intermediate. Thus, the electron-withdrawing groups that *deactivate* rings for electrophilic substitution (nitro, carbonyl, cyano, and so forth) *activate* them for nucleophilic substitution. What's more, these groups are meta directors in electrophilic substitution but are ortho–para directors in nucleophilic substitution. And finally, electrophilic substitutions replace hydrogen on the ring, while nucleophilic substitutions replace a leaving group, usually halide ion.

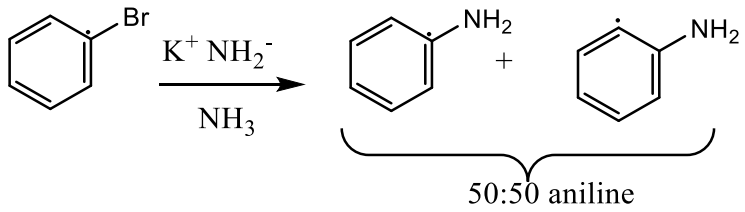
Benzyne

Halobenzenes without electron-withdrawing substituents don't react with nucleophiles under most conditions. At high temperature and pressure, however, even chlorobenzene can be forced to react. Phenol could be prepared on an industrial scale by treatment of chlorobenzene with dilute aqueous NaOH at 340 °C under 170 atm pressure.

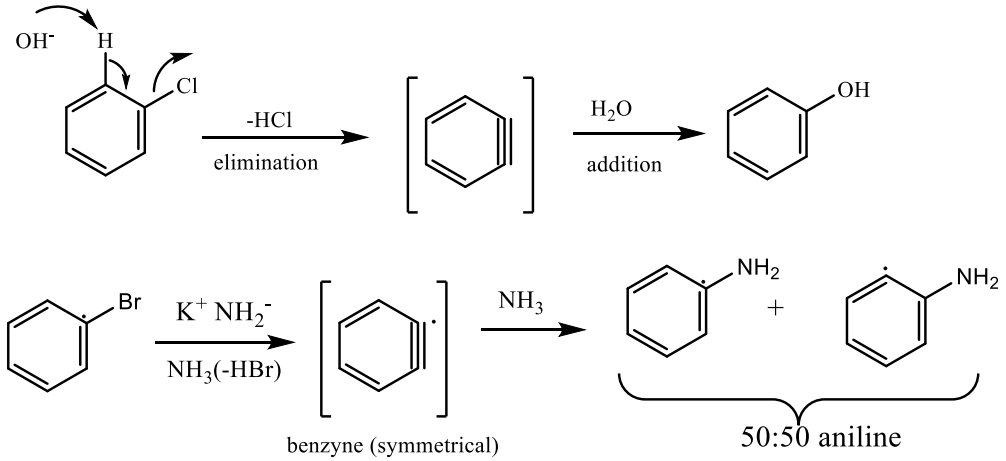


A similar substitution reaction occurs with other strong bases. Treatment of bromobenzene with potassium amide (KNH_2) in liquid NH_3 solvent, for instance, gives aniline. Curiously, though,

when using bromobenzene labeled with radioactive ^{14}C at the C1 position, the substitution product has equal amounts of the label at both C1 and C2, implying the presence of a symmetrical reaction intermediate in which C1 and C2 are equivalent.



Further mechanistic evidence comes from trapping experiments. When Bromobenzene is treated with KNH_2 in the presence of a conjugated diene, such as furan, a Diels–Alder reaction occurs, implying that the symmetrical intermediate is a **benzyne**, formed by elimination of HBr from bromobenzene. Benzyne is too reactive to be isolated as a pure compound but, in the presence of water, addition occurs to give phenol. In the presence of a diene, Diels–Alder cycloaddition takes place.



The electronic structure of benzyne, shown in **Figure-15**, is that of a highly distorted alkyne. Although a typical alkyne triple bond uses *sp*-hybridized carbon atoms, the benzyne triple bond uses sp^2-hybridized carbons. Furthermore, a typical alkyne triple bond has two mutually perpendicular *p* bonds formed by *p*–*p* overlap, but the benzyne triple bond has one *p* bond formed by *p*–*p* overlap and one *p* bond formed by sp^2–sp^2 overlap. The latter *p* bond is in the plane of the ring and is very weak.

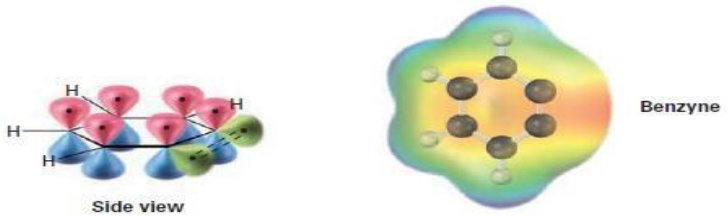


Figure-15 An orbital picture and electrostatic potential map of benzyne. The benzyne carbons are sp^2-hybridized, and the "third" bond results from weak overlap of two adjacent sp^2 orbitals.

Synthesis of Polysubstituted Benzenes

One of the surest ways to learn organic chemistry is to work synthesis problems. The ability to plan a successful multistep synthesis of a complex molecule requires a working knowledge of the uses and limitations of a great many organic reactions. Not only must you know *which* reactions to use, you must also know *when* to use them because the order in which reactions are carried out

is often critical to the success of the overall scheme. The ability to plan a sequence of reactions in the right order is particularly important in the synthesis of substituted aromatic rings, where the introduction of a new substituent is strongly affected by the directing effects of other substituents. Planning syntheses of substituted aromatic compounds is therefore a good way to gain confidence in using the many reactions.

Aliphatic Electrophilic Substitution

Bimolecular Mechanisms − SE_2 and SE_i

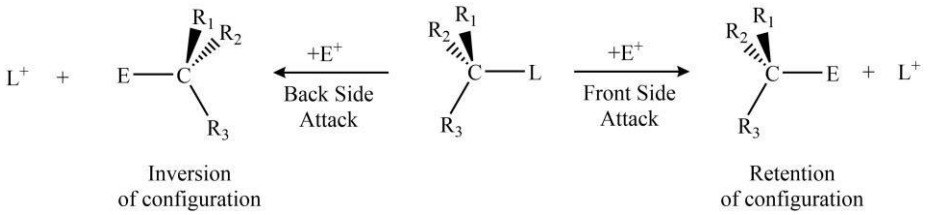
The electrophilic substitution in the aliphatic compounds is just similar to the aliphatic nucleophilic substitution, except for the fact that here an electrophile displaces a functional group rather than an electrophile. In this section, we will discuss the two major types of electrophilic substitutions; SE_2 (substitution electrophilic bimolecular) and SE_i (substitution electrophilic internal) mechanisms.

SE_2 (Substitution Electrophilic Bimolecular) Mechanism

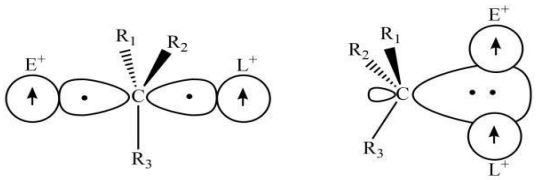
The bimolecular electrophilic substitution (SE_2) reactions may simply be defined as the chemical changes where a stronger electrophile displaces a weaker one in an aliphatic substrate.

This mechanism is quite analogous with the SN_2 route excepting the mode of attack. In the SN_2 mechanism, a stronger nucleophile replaces a weaker one via the backside attack due to its inter-cloud repulsion with the leaving group; however, in the SE_2 route, the attacking electrophile may come from the front, as well as from the backside because it is only using is vacant orbital towards substates causing little to no repulsion. So, the SE_2 mechanism can be divided into SE_2-front and SE_2-back based upon the front and back attacks, respectively.

Illustrative reaction: The general reaction showing both types of electrophilic attacks (with their corresponding products), is shown below.

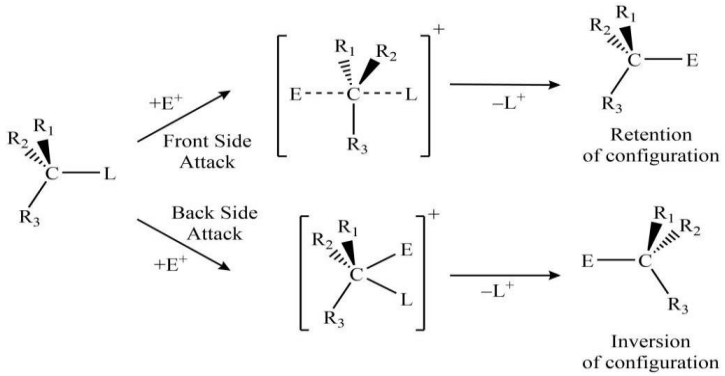


Mechanism involved: The proposed mechanism for the reaction given above says that the two electrons of the carbon-electrophile bond reside in the central orbital. Ingold proposed that the electronic distribution responsible for different stereochemistry of products is a function of bond-extension's magnitude and the extent of bond ionicity of the transition state.



It is obvious that the transition state needs to have high ionicity and good bond extension potential for SE_2back reactions so that the carbon's orbital is sufficiently spread on both ends, resulting in the inverted configuration in the case of a chiral substrate. On the other hand, if there is a very little bond extension and low ionicity in the transition state, the electron-pair of the original bond pretty much retains its position and gives rise to the retention of the configuration, and we get SE_2-front case.

Where E^+ is the attacking electrophile whereas L+ is the leaving group. Furthermore, it is also worthy to note that organometallic compounds have exceptional susceptibility towards electrophilic substitution.



Salient features: the main features of the mechanism involved in electrophilic substitution bimolecular or SE2 type raction are given below.

i) SE reaction follow second order kinetics with the rate law $k[RX][E]$

Where k is the rate constant. The symbol $[RX]$ and $[E]$ represent the molar concentration of the substrate and attacking electrophile, respectively.

ii) If the substrate is chiral, then the SE_2 mechanism can lead to the inversion, as well as, retention of the configuration; depending upon the mode of attack (front or back).

iii) The rate of the substitution becomes independent of the concentration of the attacking electrophile if its concentration is extremely high in comparison to the substrate.

iv) Stereochemical studies can be employed to differentiate between SE_2-front and SE_2-back.

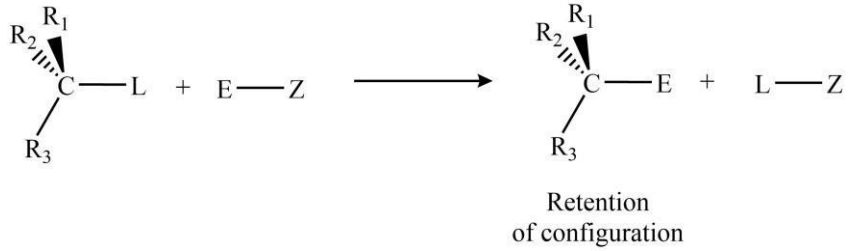
v) The SE_2 reactions are favoured by the more polar C−L bond.

SE_i (Substitution Electrophilic Internal) Mechanism

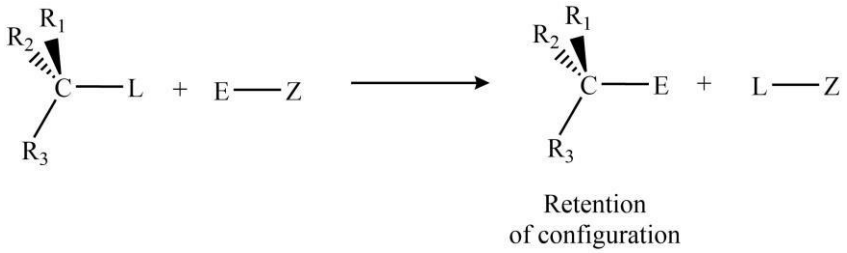
The internal electrophilic substitution (SE_i) reactions may simply be defined as the chemical changes where a stronger electrophile displaces a weaker one in an aliphatic substrate by assisting its departure.

This mechanism is also very analogous with the SN_2 route excepting the mode of attack. In the SN_2 mechanism, a stronger nucleophile replaces a weaker one via the backside attack due to its inter-cloud repulsion with the leaving group; however, in the SE_i route, the attacking electrophile comes from the front and assists the departure of leaving group by forming a bond with it.

Illustrative reaction: The general reaction showing this type of electrophilic attack (with the corresponding product) is shown below.



Mechanism involved: The proposed mechanism for the reaction given above says that the two electrons of the carbon-electrophile bond reside in the central orbital. It is observed that if there is a very little bond extension and low ionicity in the transition state, the electron pair of the original bond pretty much retains its position and gives rise to the retention of the configuration, and we get Sei



Salient Features: The main features of the mechanism involved in electrophilic substitution internal or SE_i type reactions are given below.

i) SE_i reactions follow second-order kinetics with the rate law

$Rate = k[RX][EZ]$

Where k is the rate constant. The symbol $[RX]$ and $[EZ]$ represent the molar concentration of the substrate and attacking electrophile, respectively.

ii) Like SE_2-front, SE_i reactions result in the retention of the configuration.

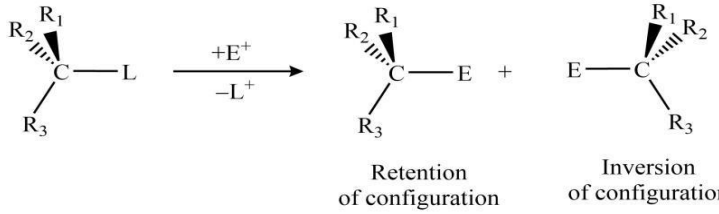
iii) iii) The SE_2 reactions are favored by the more polar C−L bond.

The SE_1 Mechanism

The unimolecular electrophilic substitution (SE_1) reactions may simply be defined as the chemical change in which a stronger electrophile displaces a weaker one in an aliphatic substrate via the formation of a carbanion.

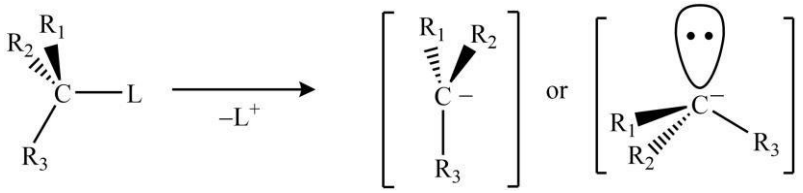
This mechanism is quite analogous with the SN_1 route excepting the nature of intermediate. In the SN_1 mechanism, a stronger nucleophile replaces a weaker one via the formation of a carbocation intermediate; however, in the SE_1 route, before the attacking electrophile attack, the intermediate formed after the dissociation of electrofuge is a carbanion.

Illustrative reaction: The general reaction showing this type of electrophilic attack (with its corresponding product) is shown below.

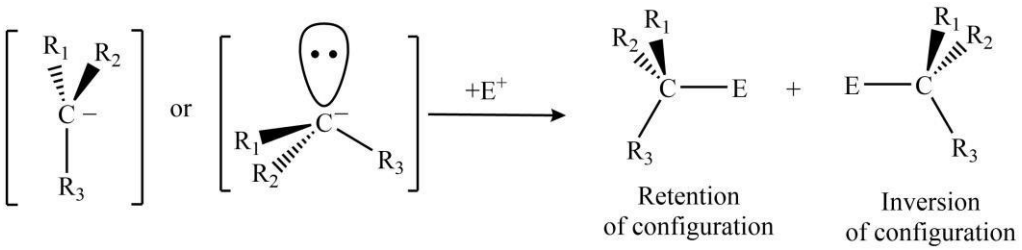


Mechanism involved: The proposed mechanism for the reaction given above involves a three-step route which must be discussed before we give the salient features of the same.

i) Heterolysis in substrate: This is the slowest, and therefore, is the rate-determining step that gives rise to a carbanion.



ii) Electrophilic attack: This is a very fast step and involves the combination of attacking electrophile with the carbanion produced in the previous step.



The stereochemistry of SE_1 reactions is quite complicated to rationalize because of the configuration of intermediatory carbanions obtained via the first step of heterolysis. Generally, we consider carbanions planar (sp^2 hybridization) or pyramidal (sp^3 hybridization), or an in-between configuration. As far as the energy is concerned, pyramidal geometry is more advantageous because lone pair will stay in sp^3 hybridized orbital. Furthermore, a pyramidal carbanion can retain its structure in the course of substitution to result in the retention of the final configuration. However, it does not always go this way because a pyramidal carbanion has been shown to results in racemization due to 'pyramidal inversion'; amines and R_3C^- carbanions are typical examples.

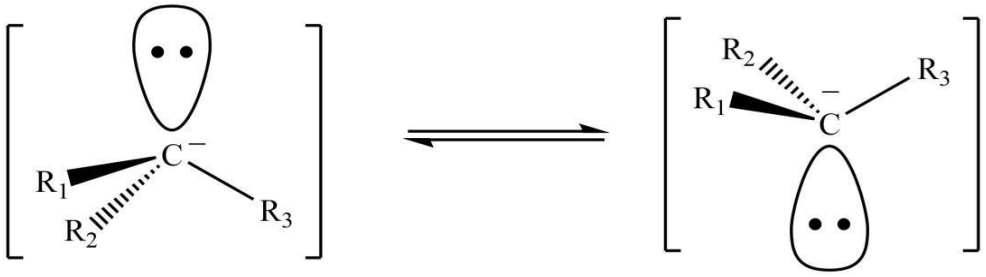


Figure 1. The pyramidal inversion of carbanion

On the other hand, if the carbanion is of trigonal planar geometry, the electrophile can attack from both sides to give rise to racemized yield. So, we can conclude that racemization is the characteristic feature of the SE route. However, it is quite tedious to determine how the racemization actually occurred; via pyramidal inversion or planar carbanions.

Salient Features: The main features of the mechanism involved in electrophilic substitution bimolecular or SE type reactions are given below.

i) SE2 reactions follow first order kinetics with rate law
$Rate = k[RX]$

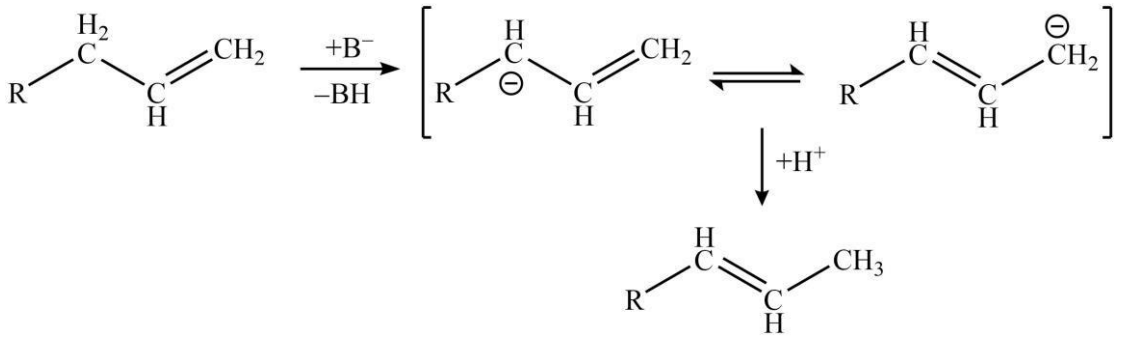
Where k is the rate constant. The symbol $[RX]$ represents the molar concentration of the substrate.

ii) If the substrate is chiral, then this always leads to the racemization of the final product.
iii) Unlike SN1-type, SE1 reaction can also occur at bridgehead carbon because the intermediate (carbanion in this case) need not to be planar.
iv) The rate of the substitution increases as the steric bulk around the carbon center decreases.
v) The SE2 reactions are favored by the more polar C−L bond.

Electrophilic Substitution Accompanied by Double Bond Shifts If the substrate in electrophilic substitution is allylic in nature, the final product may undergo rearrangement, which is quite similar to the allylic rearrangements in nucleophilic substitutions. There are two main routes for this behavior to occur; one is analogous to the SE_1 pathway (leaving group is detached first) giving a resonance-stabilized allylic carbanion which attacks the electrophile E, the second one involves the initial attack on E by the π-bond to yield a carbocation which then which loses X forming new alkene unit.

Base-catalyzed Double Bond Migration

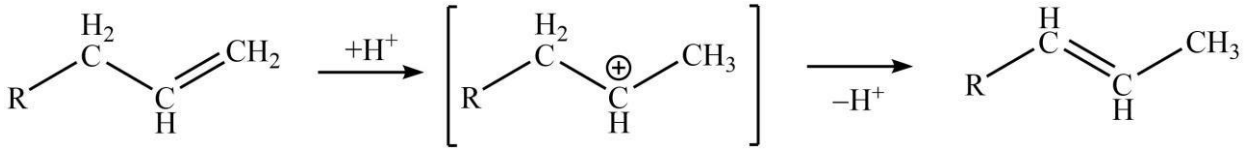
The first pathway is the base-catalyzed double bond migration, where an equilibrium mixture of isomers is obtained with stable configuration as the major product. The reaction occurs in two steps, in which the step is the abstraction of a proton by the base to yield a resonance stabilized carbanion, which in turn, is attacked by electrophile (proton in this case) to give rise to a more stable species. The typical reaction portraying mechanism is given below.



It is also worthy to note that terminal and non-conjugated alkenes can easily be converted into internal and conjugated olefins using this route, proving its significance in synthetic organic chemistry.

Acid-catalyzed Double Bond Migration

The second pathway is the acid-catalyzed double bond migration, where an equilibrium mixture of isomers is obtained with a stable configuration as the major product. The reaction initiates with the attack of E on the π-bond to yield a carbocation which then loses L forming a new alkene unit. The typical reaction portraying mechanism is given below.



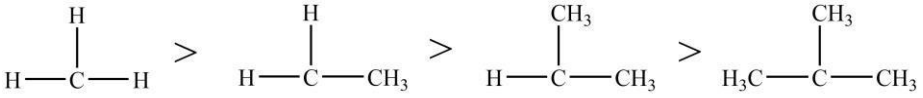
Just like base-catalyzed double bond migration, this route can also be used to convert terminal and nonconjugated alkenes into internal and conjugated olefins.

Effect of Substrates, Leaving Group and the Solvent Polarity on the reactivity

The reactivity of aliphatic electrophilic substitution reactions is affected by many factors that can be better understood via experimental data and theoretical treatment combined. In this section, we will discuss some major factors that greatly influence the electrophilic substitution's rate in aliphatic compounds like substrate structure, leaving group and reaction medium.

Effect of substrate structure

The electron-donating groups of the substrate decrease the rate of SE_1 reactions whereas electronwithdrawing groups show an opposite trend. This declining rate in the SE_1 pathway with electron-donating groups is quite normal for a reaction-type where the proton's dissociation is the rate-determining step (like in the case of acidic character). Jensen and Davis proved that the reactivity of alkyl groups is similar in SE_2-back as that for the SN_2 pathway, which can be attributed to the backside attack and steric hindrance, simultaneously.



Reactivity of alkyl groups for SE_2-back pathway

Furthermore, it has also been observed that the rate of front-mode electrophilic substitution in aliphatic compounds increases as the branching in the substrate increases increased, which can be attributed to the electron-releasing effect of the alkyl groups that makes the electron-deficient transition state more stable. However, it is also worthy to note that β-branching will reduce the substitution rate in SE_2-front because of the steric hindrance.

Effect of Leaving Group

The ease of electrofuge's detachment in both types (SE_1 and SE_2) increases with the increasing polarity of the C−X bond. Nevertheless, if the leaving group is metallic in nature and metal has a valence greater than one, then any group attached to the metal center will affect its electrofugal ability. For instance, consider the case of $Me_3C-Hg-W$ (organomercurials) where the rate of reaction has decreased. The reason lies in the fact that although Hg and W have less electronegativity than carbon (which is why the C−Hg bond is polar), the C−Hg bond becomes less polar due to the higher electronegativity W than Hg. In other words, carbon will have a lower negative charge in the C−Hg bond when W is attached to Hg because tungsten will support Hg to hold the shared pair more firmly. Therefore, −HgMe will be a better leaving group than −HgCl.

Hg–*t*-Bu > Hg–*i*Pr > HgEt > HgMe

Leaving-group order

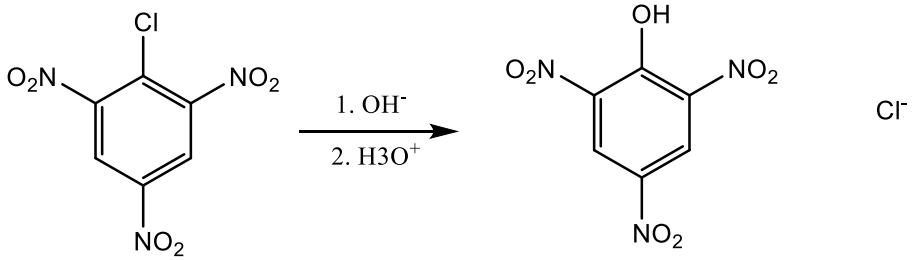
Furthermore, it is also worthy to note that carbon-based leaving groups support the SE_1 mechanism, whereas SE_2 or SE_i mechanisms are favored by metal-based leaving groups.

Effect of Solvent Polarity

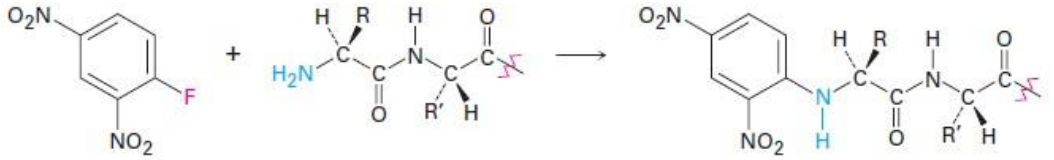
Just like the case of aliphatic nucleophilic substitution reactions, the raise in solvent polarity boosts the chances of the SE_1 pathway by supporting the ionization because of the better solvation of carbanions. However, if SE_2 and SE_1 reactions are competing with each other in parallel propagation, then less polar solvents favor the SE_2 pathway and polar solvents favor the SE_1 mechanism. Finally, If the nucleophilic character of the solvent is very small, the electrophile with properly placed assisting functionality might support the reaction; and therefore, motivating the reaction towards the SE_i pathway; otherwise, solvent polarity has little to no effect upon SN_i reactions.

Nucleophilic aromatic substitution

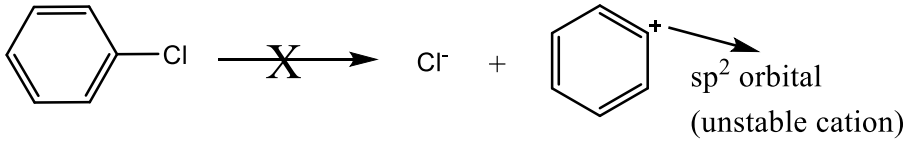
Although aromatic substitution reactions usually occur by an *electrophilic* mechanism, aryl halides that have electron-withdrawing substituents can also undergo a *nucleophilic* substitution reaction. For example, 2,4,6-trinitrochlorobenzene reacts with aqueous NaOH at room temperature to give 2,4,6-trinitrophenol. Here, the nucleophile OH- substitutes for Cl-.



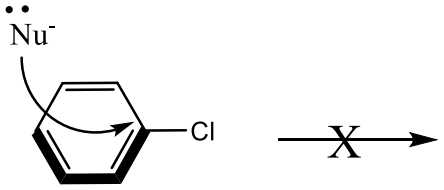
Nucleophilic aromatic substitution is much less common than electrophilic substitution but nevertheless does have certain uses. One such use is the reaction of proteins with 2,4-dinitrofluorobenzene, known as *Sanger's reagent,* to attach a ―label‖ to the terminal NH_2 group of the amino acid at one end of the protein chain.



Although the reaction appears superficially similar to the S_N1 and S_N2 nucleophilic substitutions of alkyl halides, it must be different because aryl halides are inert to both S_N1 and S_N2 conditions. S_N1 reactions don't occur with aryl halides because dissociation of the halide is energetically unfavorable, due to the instability of the potential aryl cation product. S_N2 reactions don't occur with aryl halides because the halo-substituted carbon of the aromatic ring is sterically shielded from a backside approach. For a nucleophile to react with an aryl halide, it would have to approach directly through aromatic ring and invert the stereochemistry of the aromatic ring carbon—a geometric impossibility.



Dissociation reaction does not occur because the aryl cation is unstable; therefore, no S_N1 reaction.



Backside displacement is sterically blocked; therefore, no S_N2 reaction

Nucleophilic substitutions on an aromatic ring proceed by the mechanism shown in **Figure 13**. The nucleophile first adds to the electrondeficient aryl halide, forming a resonance-stabilized, negatively charged intermediate called a *Meisenheimer complex* after its discoverer. Halide ion is then eliminated.

Mechanism

Mechanism of nucleophilic aromatic substitution. The reaction occurs in two steps and involves a resonance stabilised carbanion intermediate.

Step 1: nucleophilic addition of hydroxide ion to the electron poor aromatic ring takes place, yielding a stabilised carbanion intermediate.

Step 2: the carbanion intermediate undergoes elimination of chloride ion in a second step to give the substitution product.

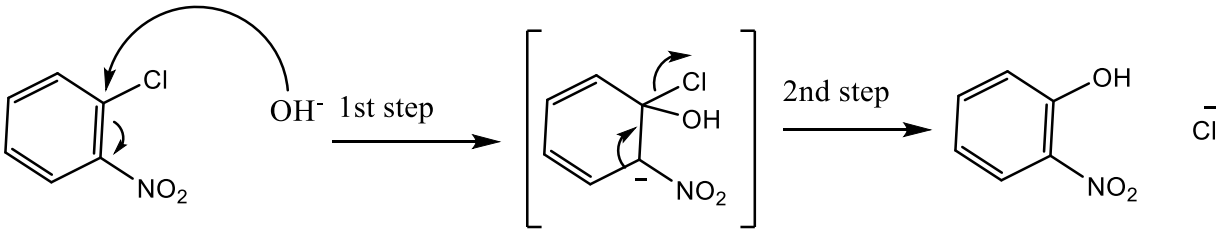


Figure-13 Mechanism of nucleophilic aromatic substitution.

Nucleophilic aromatic substitution occurs only if the aromatic ring has an electronwithdrawing substituent in a position ortho or para to the leaving group to stabilize the anion intermediate through resonance **(Fig**

ure-14). A meta substituent offers no such resonance stabilization. Thus, *p*-chloronitrobenzene and *o*-chloronitrobenzene react with hydroxide ion at 130 °C to yield substitution products, but *m*-chloronitrobenzene is inert to OH-.

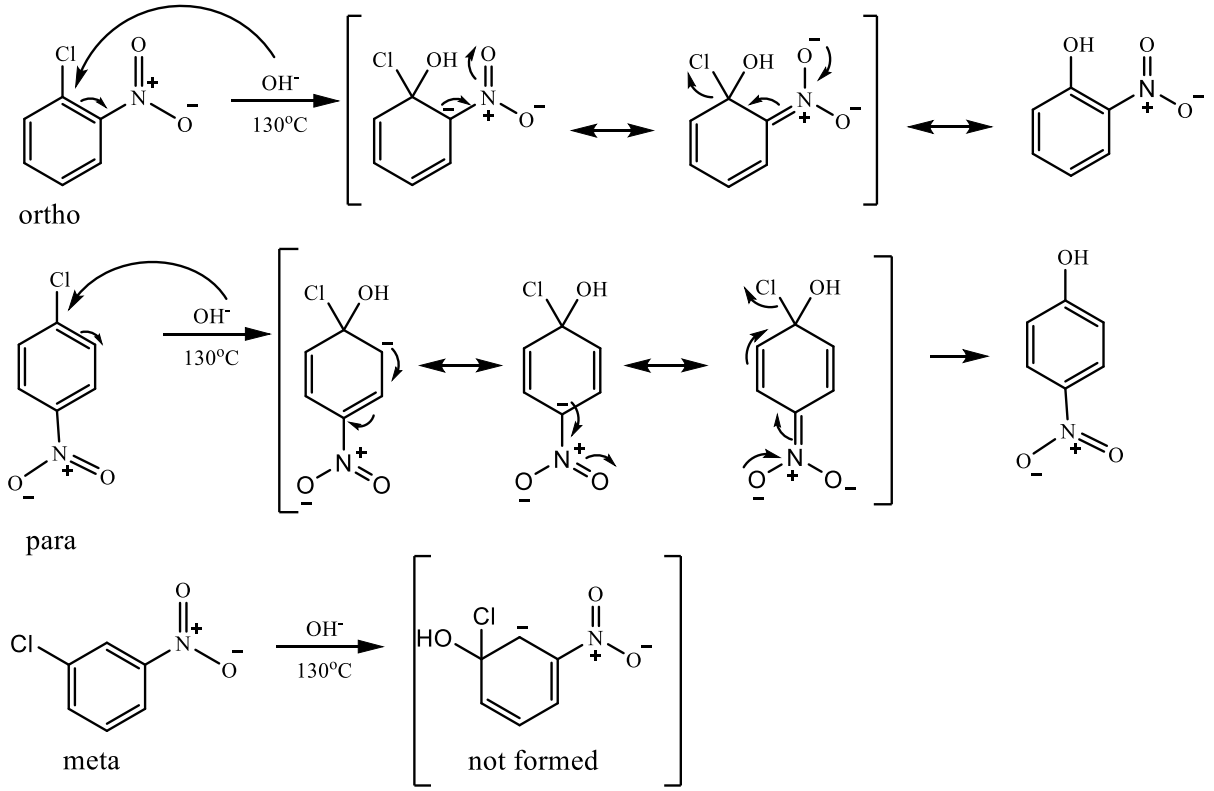


Figure-14 Nucleophilic aromatic substitution on nitrochlorobenzenes. Only in the ortho and para intermediates is the negative charge stabilized by a resonance interaction with the nitro group, so only the ortho and para isomers undergo reaction.

Note the differences between electrophilic and nucleophilic aromatic substitutions.

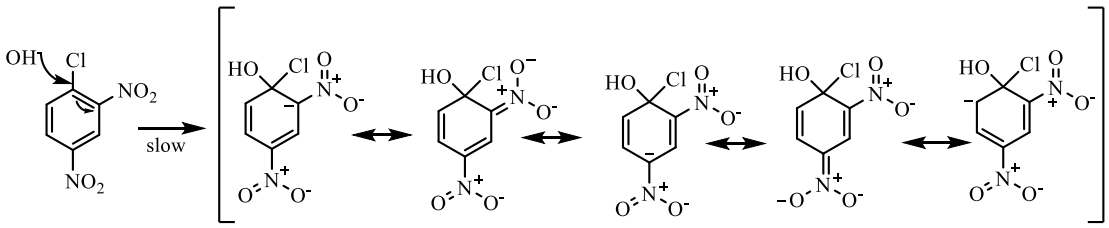
Electrophilic substitutions are favored by electron-*donating* substituents, which stabilize a carbocation intermediate, while nucleophilic substitutions are favored by electron-*withdrawing* substituents, which stabilize a carbanion intermediate. Thus, the electron-withdrawing groups that *deactivate* rings for electrophilic substitution (nitro, carbonyl, cyano, and so forth) *activate* them for nucleophilic substitution. What's more, these groups are meta directors in electrophilic substitution but are ortho–para directors in nucleophilic substitution. And finally, electrophilic substitutions replace hydrogen on the ring, while nucleophilic substitutions replace a leaving group, usually halide ion.

Nucleophilic Aromatic Substitution

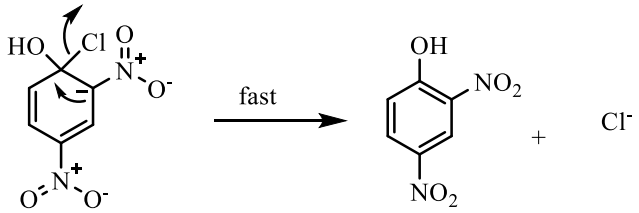
A **nucleophilic aromatic substitution** is a substitution reaction in organic chemistry in which the nucleophile displaces a good leaving group, such as a halide, on an aromatic ring. Electron-withdrawing substituents activate the ring for nucleophilic substitution. There are different nucleophilic substitution mechanisms encountered with aromatic systems:

S_NAr reaction mechanism: (addition–elimination)

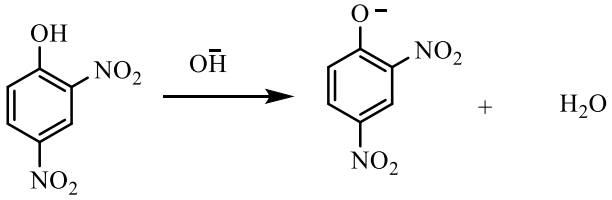
Step 1: Attack by hydroxide gives a resonance-stabilized complex.



Step 2: Loss of chloride gives the product.



Step 3: Excess base deprotonates the product.

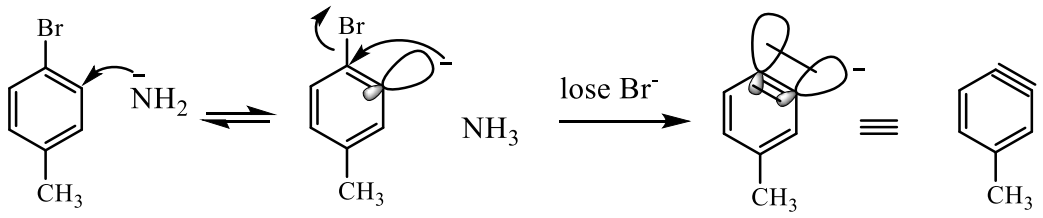


Since the nitro group is an activator toward nucleophilic substitution, and an ortho/para director, it allows the benzene carbon to which it is bonded to have a negative charge. In the Meisenheimer complex, the nonbonded electrons of the carbanion become bonded to the aromatic pi system which allows the ipso carbon to temporarily bond with the hydroxyl group (-OH).

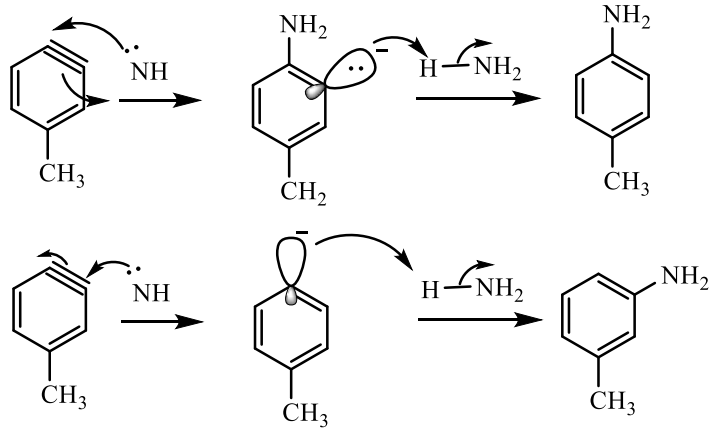
In order to return to a lower energy state, either the hydroxyl group leaves, or the chloride leaves. In solution both processes happen. A small percentage of the intermediate loses the chloride to become the product (2,4-dinitrophenol), while the rest return to the reactant. Since 2,4-dinitrophenol is in a lower energy state it will not return to form the reactant, so after some time has passed, the reaction reaches chemical equilibrium. The formation of the resonance-stabilized Meisenheimer complex is slow because it is in a higher energy state than the aromatic reactant. The loss of the chloride is fast, because the ring becomes aromatic again.

Benzyne Reaction: (Elimination-Addition) Reactant is halobenzene with no electron-withdrawing groups on the ring. A very strong base like $NaNH_2$ is used.

Step 1:Sodium amide abstract a proton.



Step 2: The benzyne intermediate forms when the bromide is expelled and the electrons on the sp2 orbital adjacent to it overlap with the empty sp2 orbital of the carbon that lost the bromide.



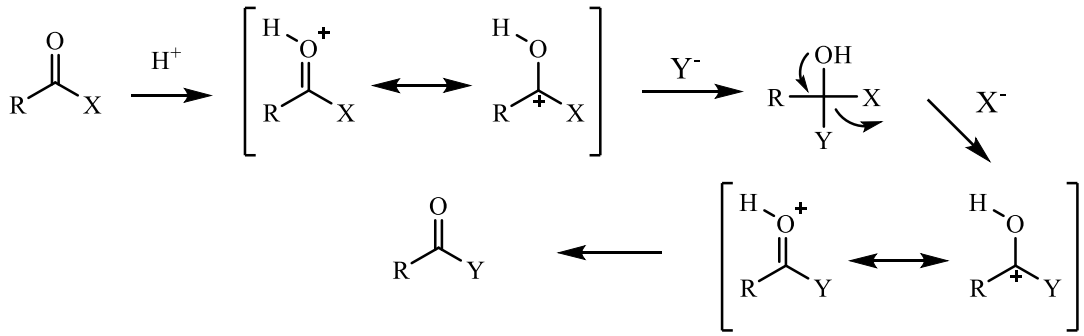
Benzynes are very reactive species due to the high strain of the triple bond.

Nucleophilic substitution reaction at an aliphatic trigonal carbon: tetrahedral mechanism

Nucleophilic Substitution at an Allylic Carbon: Allylic Rearrangements

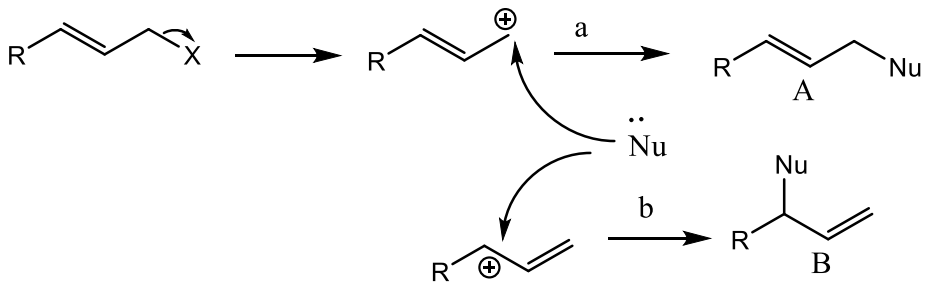
For aliphatic trigonal carbons, nucleophilic substitution is very important, especially when the carbon is doubly bonded to oxygen, sulfur, or nitrogen. As predicted, acid catalyzes this reaction because protonation reduces the electron density near the carbon undergoing substitution, which facilitates the attack of nucleophiles.

The tetrahedral process, also known as addition-elimination, occurs with much less ease than with carbonyl groups because the negative charge of the intermediate must be carried by carbon, which is less electronegative than oxygen, sulfur, or nitrogen:



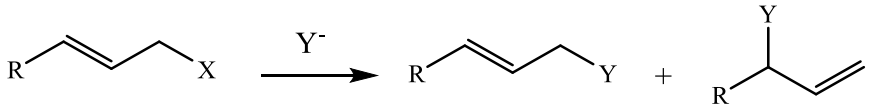
Nucleophilic Substitution at an Allylic Carbon: Allylic Rearrangements

Allylic substrates undergo nucleophilic substitution reactions quickly, but we treat them separately because they are frequently accompanied by a type of rearrangement known as allylic rearrangement. When allylic substrates are treated with nucleophiles under SN1 conditions, two products are often obtained: the regular product and a rearrangement product.

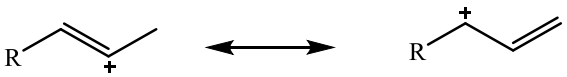


Allylic substrates undergo nucleophilic substitution reactions, rapidly and are usually accompanied by a rearrangement known as an allylic rearrangement or an allylic shift when allylic substrates are treated with nucleophiles under SN1 condition, two products are usually formed the

1. Normal product
2. Rearranged product

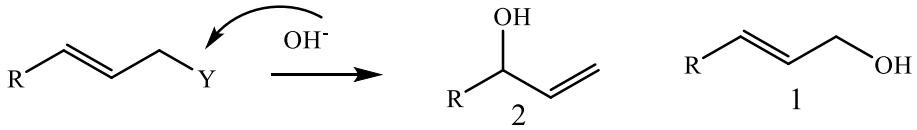


The formation of two products can be easily explained because the allyl cation is resonance hybrid of two structure.



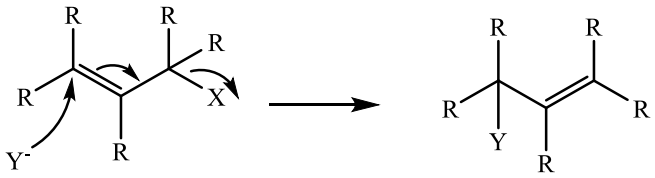
Thus, c- 1 and c-2, each carry a partial positive charge, and both are attacked by Y– (nucleophile) in the formation of two product. This mechanism is called SN1 mechanism.

Ex: when allylic substrate are treated with nucleophile under SN1 condition.

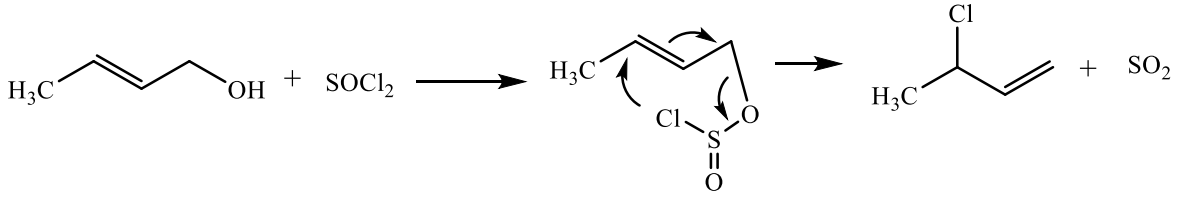


100 %of the (1) is formed at equilibrium because it is more stable due to conjucation of its double bond with the ring . It equilibrium is not reached, then (2) is the major product.

Nucleophilic substitution at an allylic may also take place S_N^2 mechanism without allylic rearrangement However, allylic rearrangement can also take place under S_N^2 condition. through the following mechanism in which the nucleophile attack the (γ)- carbon instead of the usual position. This mechanism is called S_N^2 mechanism and is an allylic rearrangement.



If a compound has in allylic position a leaving group capable of giving SNi reaction, then it is possible for nucleophile to attack the(γ)position. This is called SNi mechanism.



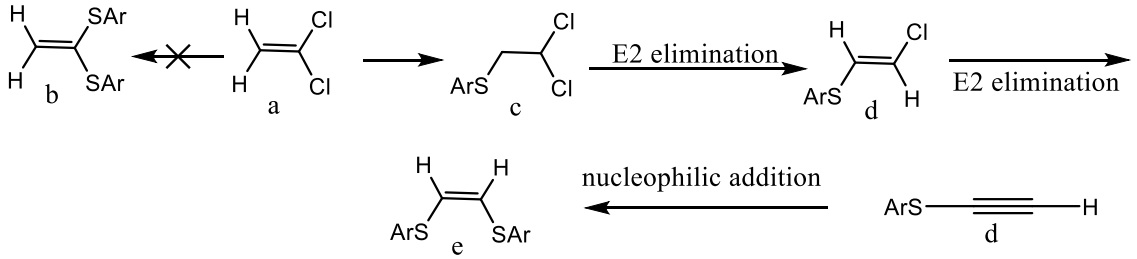
Similarly, 3- butene-2-ol (MeCHOHCH = CH_2) gives 100 %. MeCH = $CHCH_2Cl$.

An allylic rearrangement in which the nucleophile is the same as the leaving group in an isomerization.

Nucleophilic substitution at vinylic carbons

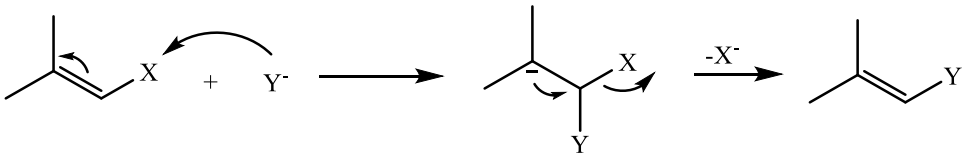
Although nucleophilic substitution at a vinylic carbon is challenging, there are several occurrences. The tetrahedral process and the closely related addition–elimination mechanism are the most prevalent mechanisms. At a saturated substrate, both processes are impossible.

The addition–elimination mechanism for the reaction between 1,1-dichloroethene (a) and ArS catalyzed by OEt has been shown. The result was the "rearranged" chemical (e), not the 1,1-dithiophenoxy compound (b). The isolation of (c)and (d) revealed that an addition-elimination process had occurred. ArSH adds to the double bond (nucleophilic addition) in the first step, yielding the saturated (c). The alkene (d) is produced in the second stage by an E2 elimination process. The result of a second elimination and addition is (e).



Nucleophilic substitution at a vinylic carbon is difficult, but many example are known. It may take place through addition - elimination mechanism, the closely related tetrahedral mechanism, elimination - addition mechanism or sol mechanism.

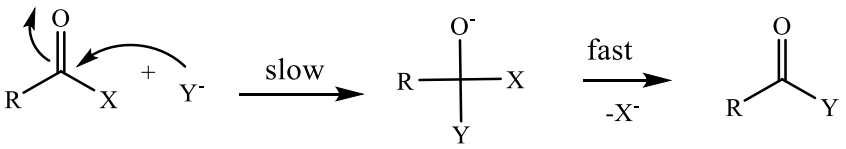
The tetrahedral mechanism is called addition - elimination take place. Vinylic carbon than with compound containing c = x (X= O, S, or N). Remember the greater electronegativity of a atom bearing a negative charge, the more is the stabilization of the anion.



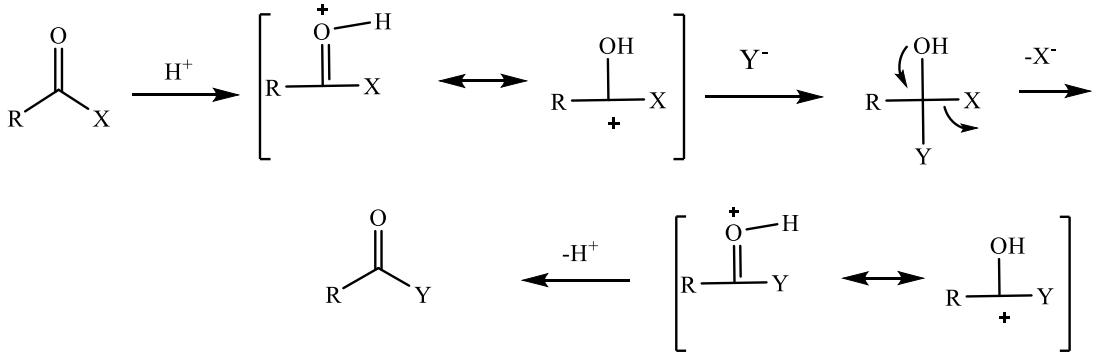
This type of isomerization may proceed by S_N1, S_N2 or S_Ni.

Aliphatic Trigonal carbon

Compounds containing a trigonal (Sp^2) carbon attached to an oxygen, Sulphur or a nitrogen undergo nucleophilic substitution through tetrahedral mechanism often called as addition - elimination. The reaction follows second order kinetics but the mechanism is not the same as Simple SN2 mechanism. In the tetrahedral mechanism first the nucleophile attacks to give a tetrahedral intermediate and then the leaving group (X) departs.



As expected, this reaction is catallysed by acids because protonation decreases the election density at the carbon undergoing substitution which facilities the or attack of nucleophile.



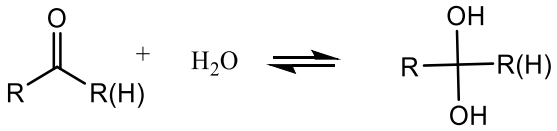
Aromatic And Aliphatic Nucleophilic Substitution :Oxygen and Sulphur Nucleophiles

Oxygen Nucleophiles : Oxygen nucleophiles fall into three major categories:

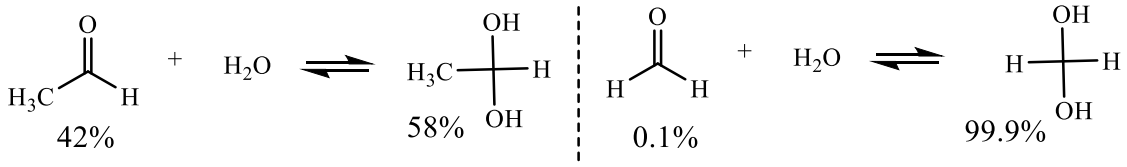
i) Water and Alcohol
ii) Hydroxide and Alkoxide ions
iii) Carboxylate ions.

The members of each category have about the same base strength, but each category has a different base strength.

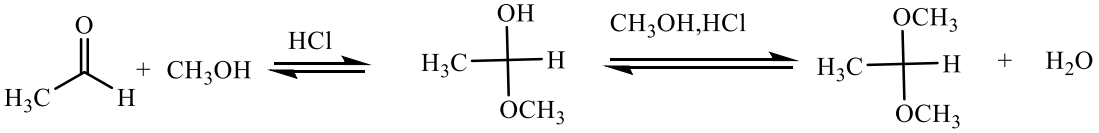
Water (H_2O): Water adds to an aldehyde or a ketone to form a hydrate. A hydrate is a molecule with two OH groups on the same carbon. Hydrates are also called gem-diols. Hydrates of aldehydes or ketones are generally too unstable to be isolated because the tetrahedral carbon is attached to two oxygen atoms.



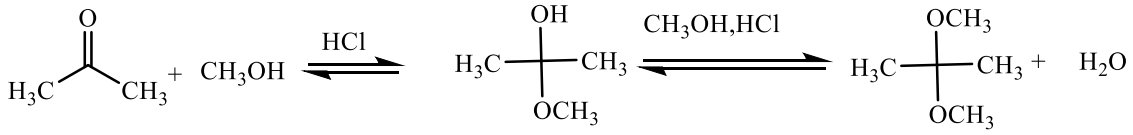
Water is a poor nucleophile and therefore adds relatively slowly to a carbonyl group. The rate of the reaction can be increased by an acid catalyst. The catalyst affects the rate at which an aldehyde or a ketone is converted to a hydrate; it has no effect on the amount of aldehyde or ketone converted to hydrate.



Alcohols ($^-$OH): The product formed when one equivalent of an alcohol adds to an aldehyde is called a hemiacetal. The product formed when a second equivalent of alcohol is added is called an acetal. Like water, an alcohol is a poor nucleophile, so an acid catalyst is required for the reaction to take place at a reasonable rate.

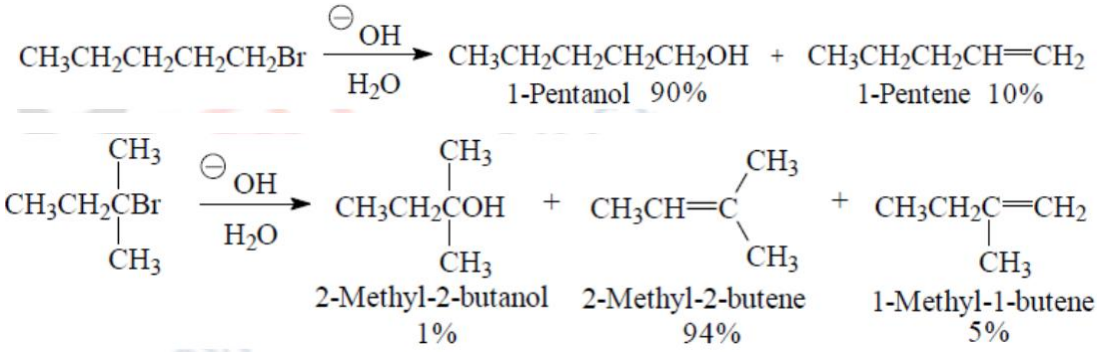


When the carbonyl compound is a ketone instead of an aldehyde, the addition products are are called a hemiketal and a ketal, respectively. When one equivalent of alcohol has added to an aldehyde or a ketone, the compound is halfway to the final acetal or ketal, which contains groups from two equivalents of alcohol.



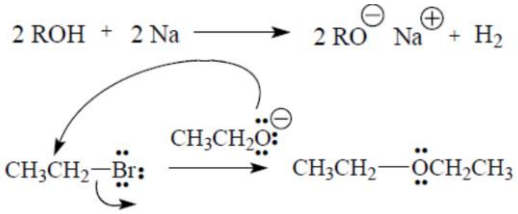
Hydroxide Ions (OH^-): The OH– is a better nucleophile than H_2O, so adding OH– to the reaction mixture increases the rate of reaction while alcohols are somewhat better nucleophiles than water. An elimination reaction is an especially significant competing reaction for reactions involving hydroxide ion with alkyl halides. With these reactions, the proportion of competing elimination reaction rises with the increase of steric crowding on the substrate.

For example, compare the percentages of the product mixture in the reaction of the following alkyl bromide isomers with hydroxide ion.

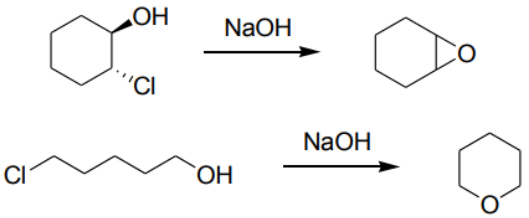


Alkoxide Ions (ROH^-): The solvolysis of 1° alkyl halides and most 2° alkyl halides with alcohols does not generally work well. However, the use of alkoxide ion, a stronger nucleophile, on these substrates does make the reaction go. This reaction is an irreversible preparation for ethers and is called the Williamson ether synthesis.

The Williamson ether synthesis works because an alcohol reacts with Na-metal or some stronger base to form an alkoxide ion which then reacts with an alkyl halide leading to ether via S_N2 reaction mechanism as follows:

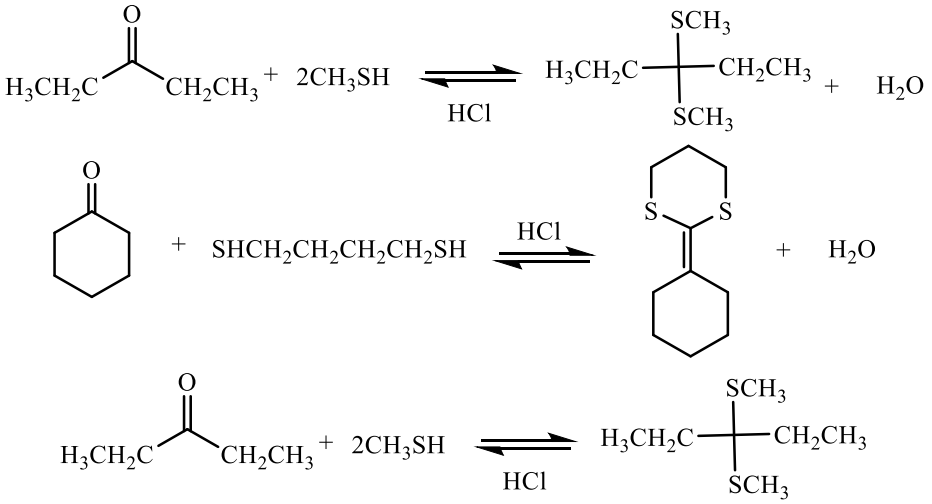


For example: This method produces cyclic as well as acyclic ethers also

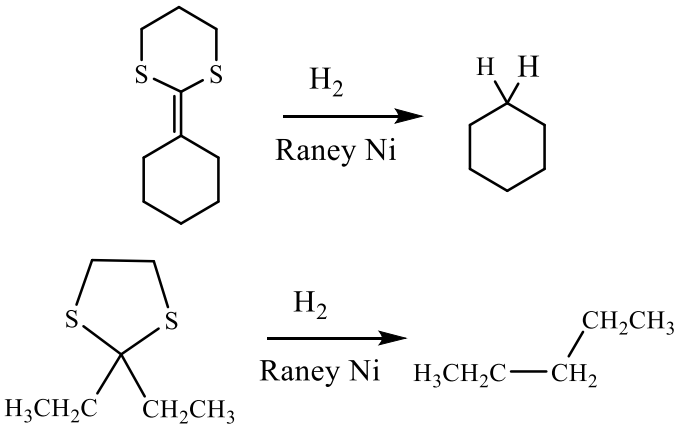


Carboxylate Ions (COO^-): Carboxylate ions are relatively poor nucleophiles. Their alkylation with an alkyl halide, though not widely used, is a method for the formation of esters via SN2 reaction mechanism. Nucleophilicity of carboxylate ions can be enhanced by using a polar-aprotic solvent.

Sulphur Nucleophiles: Compounds incorporating a C–S–H functional group are named thiols or mercaptans. Aldehydes and ketones react with thiols to form thioacetals and thioketals. The mechanism for the addition of a thiol is the same as that for the addition of an alcohol. thiols are sulphur analogues of alcohols.



Thioacetal (or thioketal) formation is a synthetically useful reaction because a thioacetal (or thioketal) is desulfurized when it reacts with H2 and Raney nickel. Desulfurization replaces the C − S bonds with C − H bonds.



Bucherer reaction :

The Bucherer reaction in organic chemistry is the reversible conversion of a naphthol to a naphthylamine in the presence of ammonia and sodium bisulfite. The reaction is widely used in the synthesis of dye precursors aminona phthalene sulfonic acids.

$$C_{10}H_7\text{-}2\text{-}OH + NH_3 \rightleftharpoons C_{10}H_7\text{-}2\text{-}NH_2 + H_2O$$

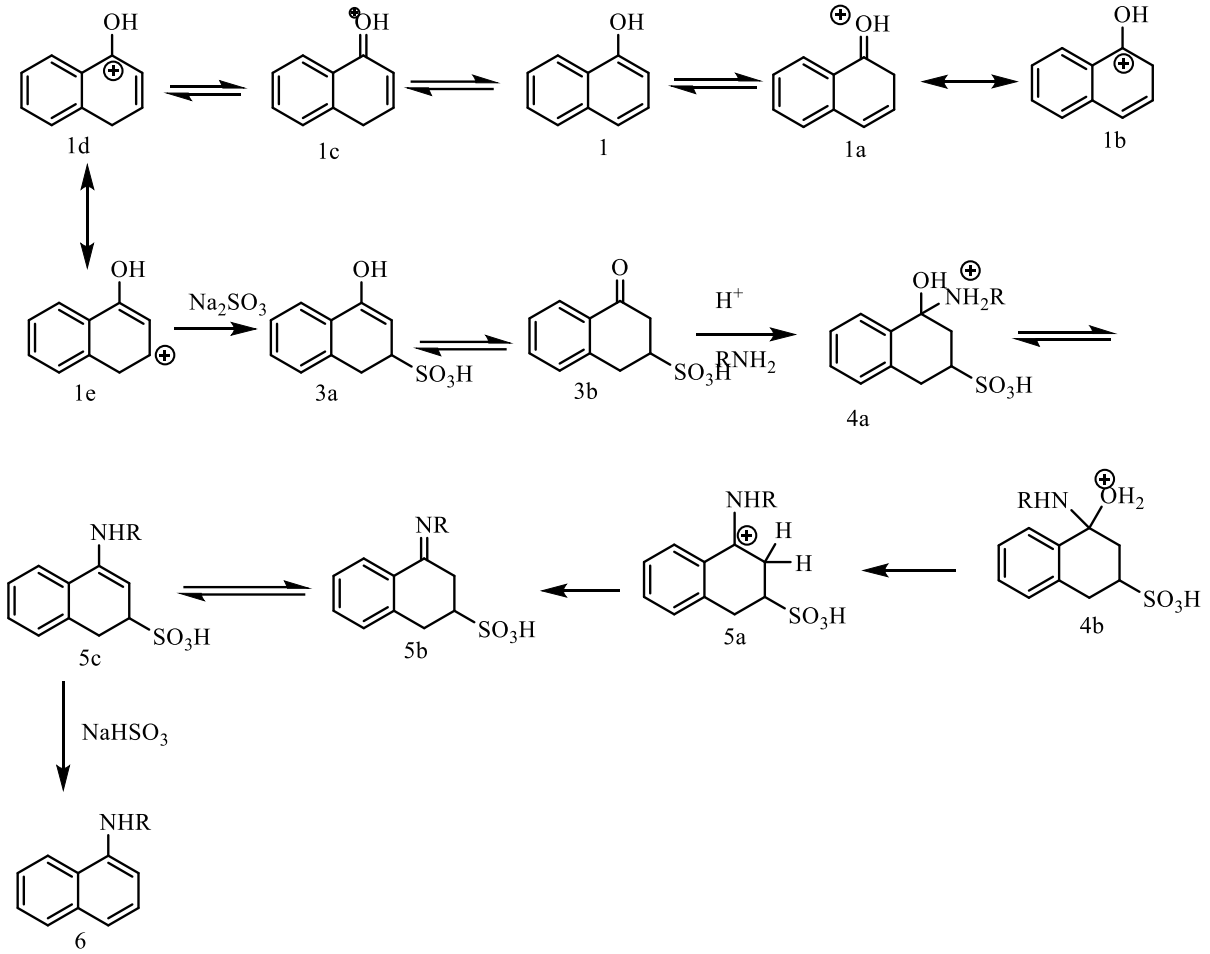
The French chemist Robert Lepetit was the first to discover the reaction in 1898. The German chemist Hans Theodor Bucherer (1869–1949) discovered (independent from Lepetit) its reversibility and its potential especially in industrial chemistry. Bucherer published his results in 1904 and his name is connected to this reaction. The organic reaction also goes by the name Bucherer-Lepetit reaction or (wrongly) the Bucherer-Le Petit reaction.

The reaction is used to convert 1,7-dihydroxynaphthalene into 7-amino-1-naphthol and 1-aminonaphthalene-4-sulfonic acid into 1-hydroxynaphthalene-4-sulfonic acid. It is also useful for transamination reactions of 2-aminonaphthalenes

Mechanism:

In the first step of the reaction mechanism a proton adds to a carbon atom with high electron density therefore by preference to C2 or C4 of naphthol (**1**). This leads to resonance stabilized adducts **1a**-**1e**. De-aromatization of the first ring of the naphthalene system occurs at the expense of 25 kcal/mol. In the next step a bisulfite anion adds to C3 through **1e**. This results in the formation of **3a** which tautomerizes to the more stable **3b** to the sulfonic acid of tetralone.

A nucleophilic addition follows of the amine with formation of **4a** and its tautomer **4b** loses water to form the resonance stabilized cation **5a**. This compound is deprotonated to the imine **5b** or the enamine **5c** but an equilibrium exists between both species. The enamine eliminates sodium bisulfite with formation of naphthylamine **6**.



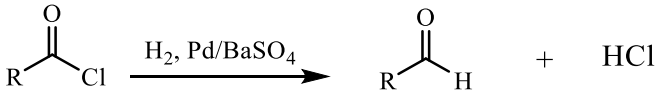
Rosenmund reduction

Rosenmund reduction is a reaction where acid chlorides are converted into aldehydes by employing hydrogen gas over palladium poisoned by barium sulphate. In rosenmund reduction hydrogen gas(H_2) is passed through palladium(Pd) on barium sulfate(BaSO4).

Tertiary amine(R3N) is required to control the activity of the catalyst as well as to neutralize the HCl produced during the reaction (and prevent over reduction). Barium sulfate has less surface area; it restricts the activity of palladium. Thus, it reduces the ability of palladium to react in order to prevent over- reduction of acid chloride.

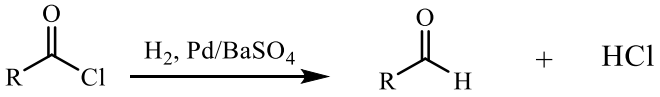
Therefore, $BaSO_4$ or $CaCO_3$ act as a support by facilitating easy escape of the product to prevent over-reduction. With the addition of poison, the activity is further diminished for the more reactive acyl chlorides. To avoid excessive hydrogenation, a toxin like thioquinanthrene or thiourea is utilised. If the deactivation does not occur, it could result in additional aldehyde reduction and the production of primary alcohol. If this primary alcohol is created, it will subsequently interact with the residual acyl chloride to generate ester.

An example of this catalytic hydrogenation of acyl chlorides forming aldehydes is shown below.

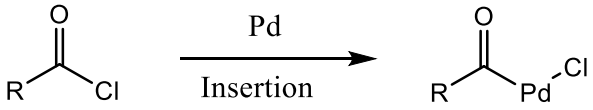


Due to the high reactivity of hydrogen gas, it readily initiates a substitution in the acyl chloride, forming HCl and the required aldehyde.

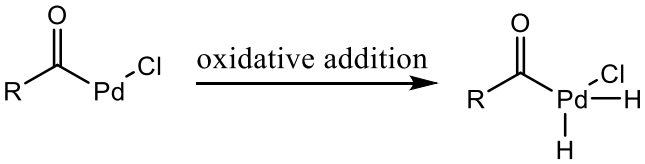
Mechanism of Rosenmund Reduction: Hydrogen gas (in the presence of the Rosenmund Catalyst) is passed through acyl chloride, resulting in the formation of an aldehyde and hydrochloric acid.



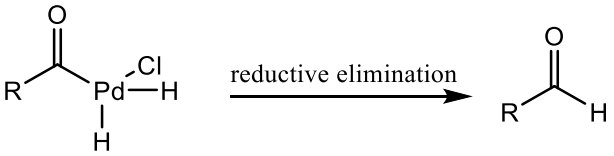
Step 1: Insertion: palladium gets inserted between C-Cl bond.



Step 2: Oxidative addition



Step 3: Reductive elimination: palladium and hydrochloric acid gets eliminated to give aldehyde as the final product.



Uses of Rosenmund reduction

1. Rosenmund reduction is used in the synthesis of saturated fatty aldehydes.
2. It is also useful in manufacturing alkyl halides and aryl halides.

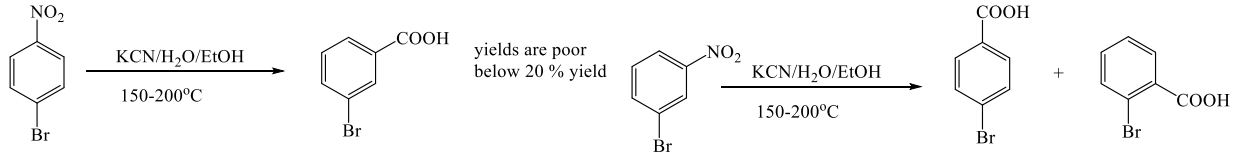
Limitations of Rosenmund reduction

This reduction method cannot be used in the preparation of formaldehyde. This is because formyl chloride formed upon reduction, is highly unstable at room temperature.

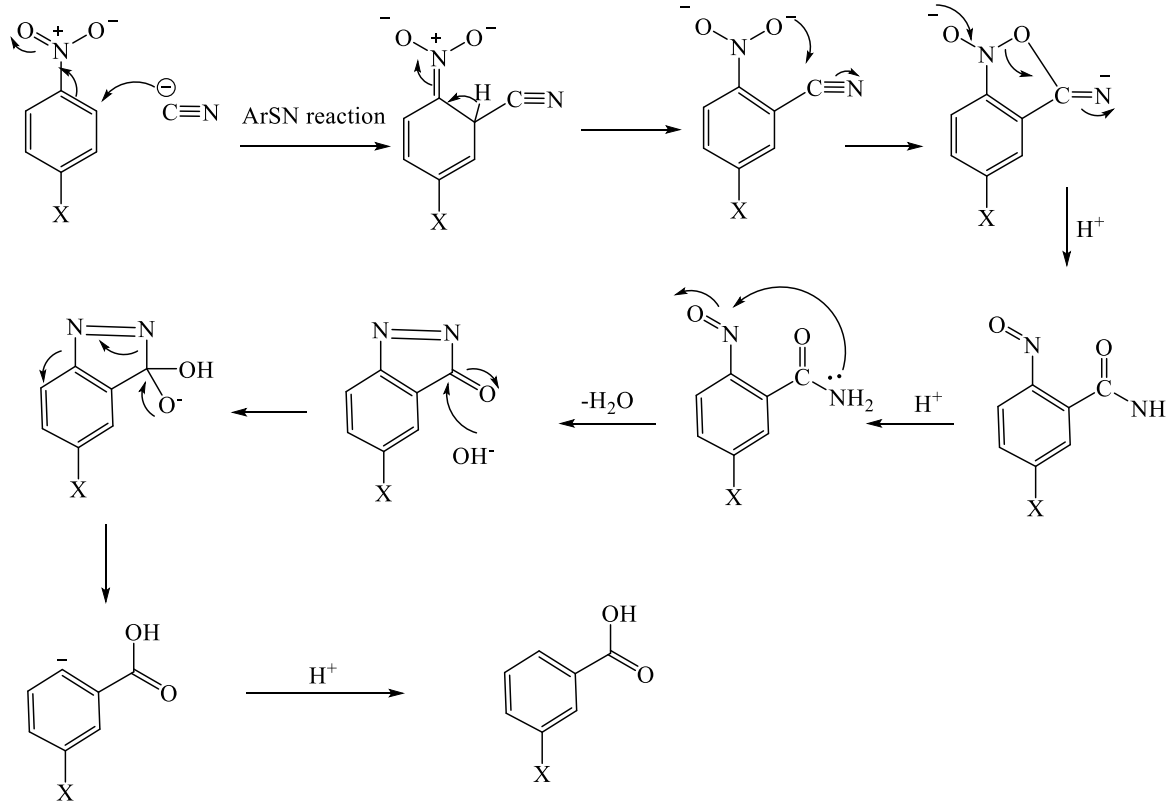
Von Richter rearrangements

This rearrangement is given by aromatic nitro compounds in the presence of aqueous alcoholic potassium cyanide or sodium cyanide. Cine aromatic nucleophilic substitution take place.

Nitro group is replaced by carboxylic acid, the position of acid group is always ortho. When electron withdrawing group are present in ortho and/ or para position with respect to the nitro groups



Mechanism:

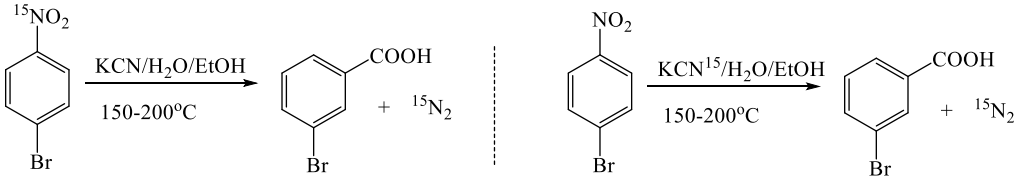


Evidence of the mechanism:

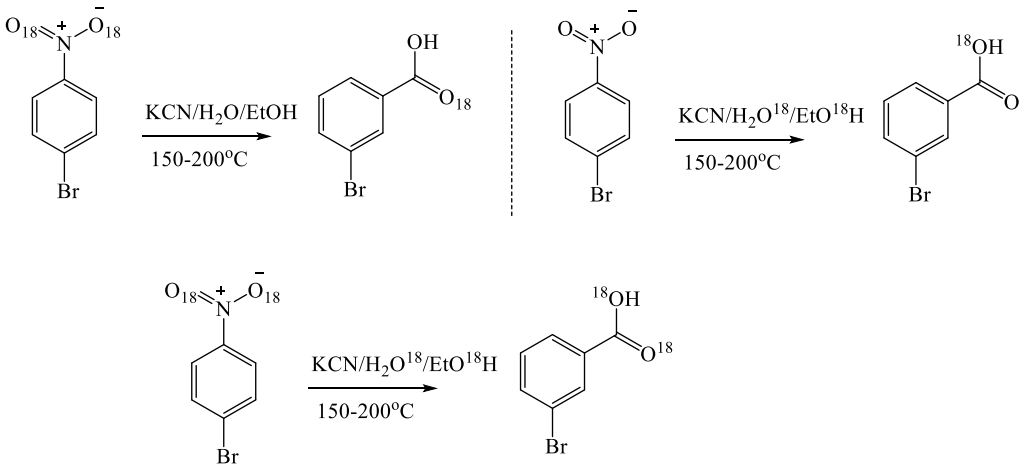
i. Both carboxylic acid and nitrogen are formed in equal amounts.

ii. Formation of N≡N conforms the intermediate I and II.

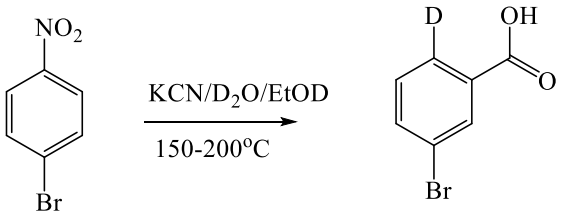
iii. By isotopic labelling of nitrogen, it has been shown that are atom of the molecular nitrogen comes from the -NO2 group and other from CN^-



iv. In carboxylic group one atom of the oxygen comes from the nitro group and another oxygen atom comes from the product.

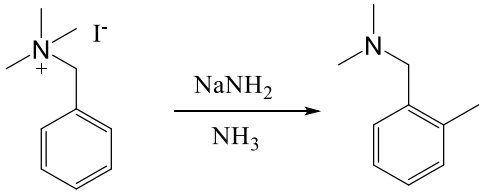


v. When the reaction is carried out in the presence of D_2O/EtOD, the carboxylic acid formed contains D at the position of NO_2.



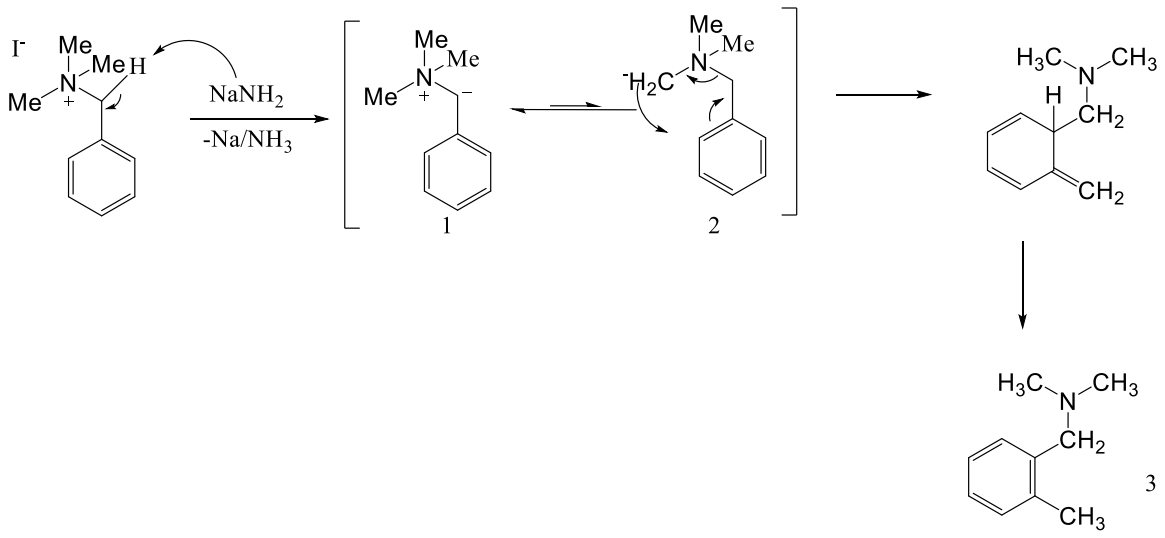
Sommelet–Hauser rearrangement

The Sommelet–Hauser rearrangement (named after M. Sommelet and Charles R. Hauser) is a rearrangement reaction of certain benzyl quaternary ammonium salts. The reaction product a N,N-dialkylbenzylamine with a new alkyl group in the aromatic ortho position.



Mechanism:

The benzylic methylene proton is acidic and deprotonation takes place to produce the benzylic ylide (1). This ylide is in equilibrium with a second ylide that is formed by deprotonation of one of the ammonium methyl groups (2). Though the second ylide is present in much smaller amounts, it undergoes a 2,3-sigmatropic rearrangement because it is more reactive than the first one and subsequent aromatization to form the final product.



Features：1. when there are two possible sites of deprotonation, usually the more stable ylide is formed (derived from the more stable carbanion)

2. when it is not possible to form the ylide by deprotonation because the initial benzylic carbanion is significantly stabilized (e.g., R1=EWG group such as CN, NO_2, Cl, Br), the rearrangement may not occur.

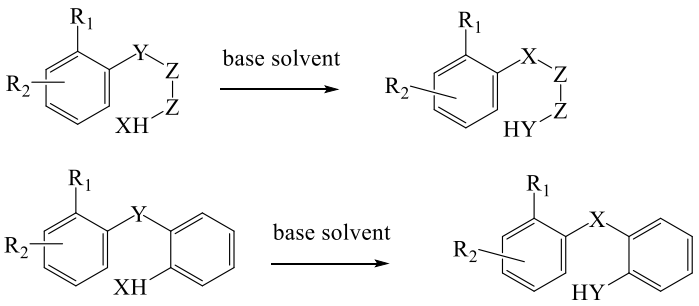
3. when the alkyl groups attached to the nitrogen contain a hydrogen atom at their β-position, the Hofmann elimination may compete; cyclic quaternary ammonium salts react by ring-expansion.

4. One major competing reaction is the Stevens rearrangement; in systems where both the Stevens- and S.-H. rearrangements are possible, the choice of reaction conditions allow control over which of these competing processes dominate.

Smiles rearrangement:

Smiles rearrangement is an organic reaction known for synthesizing the isomeric compound 2-hydroxy-2′-mercapto-bis-(1-naphthyl) ether. It is an intramolecular nucleophilic aromatic substitution rearrangement. R. Henriques reported the actual method in 1894. Still, later on, O. Hinsberg carried out similar experiments with the corresponding sulfones, but it was S. Smiles who established the structure of the products.

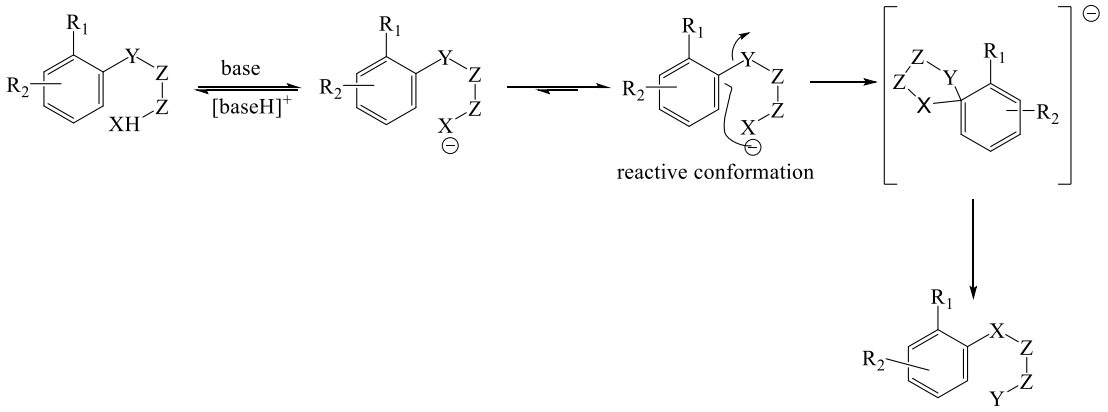
Electron-withdrawing groups at the ortho- or para-positions of the aromatic ring are necessary for activation of the ring for Smiles rearrangement. In cases where more than one is activating, the groups will help to increase the rate of rearrangement (when R_2 =EWG). Instead of substituted benzene rings, the aromatic ring can also be heteroaromatic, such as pyridine or pyrimidine.



where XH= $NHCOR,CONH_2,OH,SH,NH_2,SO_2H,CH_3$(smile -truce rearrangement); Z = sp2 or sp3 hybridized substituted or unsubstituted carbon, C=O, sp3 nitrogen; Y = $S,O,SO_2,CO_2,SO_3,I^+,P^+$, R_1= EWG = NO_2,SO_2R,Cl,R_2=alkyl,halogen, NO_2,acyl,base NaOH,KOH,RONa,RLi, K_2CO_3/DMSO

Mechanism of Smiles Rearrangement:

The base will deprotonate Y (NHCOR $CONH_2$, SO_2NH_2, OH, NH_2, SH, SO_2H, or CH_3), generating the nucleophile, as the initial stage of the chemical process. The substrate then assumes a reactive conformation in which the Z-Z bond is perpendicular to the plane of the migrating ring. In an ipso manner, the nucleophile attacks the ring to create a transition state with five members, which allows for the formation of the product.



Applications of Smiles Rearrangement:

- The total synthesis of the lichen diphenyl ether epiphorellic acid 1 has been don by using Smiles Rearrangement
- Novel non-nucleoside inhibitors of HIV-1 reverse transcriptase, dipyrido[2,3-b]diazepinone

In general, in a group across the periodic table, the more basic the ion (the higher the pKa of the conjugate acid) the more reactive it is as a nucleophile. Within a series of nucleophiles with the same attacking element (e.g. oxygen), the order of nucleophilicity will follow basicity. Sulfur is in general a better nucleophile than oxygen. Many schemes attempting to quantify relative nucleophilic strength have been devised. The following empirical data have been obtained by measuring reaction rates for many reactions involving many nucleophiles and electrophiles. Nucleophiles displaying the so-called alpha effect are usually omitted in this type of treatment.

Swain–Scott equation

The first such attempt is found in the Swain–Scott equation derived in 1953:

$$\log\frac{k}{ko} = sn$$

where k=rate constant for nucleophile

k_0=rate constant for standard

n=nucleophilic constant

s=substrate constant depends on sensitivity of substrate to nucleophile attack

This free-energy relationship relates the pseudo first order reaction rate constant (in water at 25 °C), k, of a reaction, normalized to the reaction rate, k_0, of a standard reaction with water as the nucleophile, to a nucleophilic constant n for a given nucleophile and a substrate constant s that depends on the sensitivity of a substrate to nucleophilic attack (defined as 1 for methyl bromide). This treatment results in the following values for typical nucleophilic anions: acetate 2.7, chloride 3.0, azide 4.0, hydroxide 4.2, aniline 4.5, iodide 5.0, and thiosulfate 6.4. Typical substrate constants are 0.66 for ethyl tosylate, 0.77 for β-propiolactone, 1.00 for 2,3-epoxypropanol, 0.87 for benzyl chloride, and 1.43 for benzoyl chloride. The equation predicts that, in a nucleophilic displacement on benzyl chloride, the azide anion reacts 3000 times faster than water

Consider methyl bromide as the standard reference reaction,

CH_3-Br →CH_3-OH +Br^-

Here OH is the incoming nucleophile and Br is the leaving group.
Therefore, the equation also be written as

$$\log \frac{k\ new\ nucleophile}{kH2O} = sn$$

Here water is taken as standard; s is 1.0 for methyl bromide.

The values of n calculated as per above equation coincide with the values given by Edward and Pearson.

Nucleophile	n	Nucleophile	n	Nucleophile	n
$S_2O_3^{2-}$	6.4	SH^-	5.1	CN^-	5.1
I^-	5	$PhNH_2$	4.5	OH^-	4.2
N_3^-	4.0	Py	3.6	Br^-	3.5
PhO^-	3.5	AcO^-	2.7	Cl^-	2.7
F^-	2.0	NO_3	1.0	H_2O	0.0

When n value increases, nucleophilicity increases.

Thus we can say that absolute value of nucleophilicity does not exhibit even in gas phase.

But when the leaving group and nucleophile both are hard or soft the relative rates are larger.

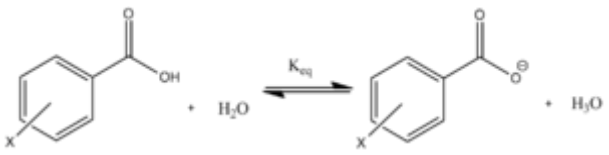
When one is hard and the other is soft the rate is reduced.

Grunwald-Winstein equation

The Grunwald-Winstein equation describes the action of the solvent as a nucleophile on various substrates in physical organic chemistry. It is a linear free energy equation that describes relative rate constants and the ionizing power of distinct solvent systems. Developed in 1948 by Ernest Grunwald & Saul Weinstein, the equation could be written

$$\log \frac{Kx, sol}{Kx, 80\%EtOH} = mY$$

where the solvolysis rate constants for a given molecule in various solvent systems and in the chosen reference solvent, 80% aqueous ethanol, are represented by the variables kx, sol and kx, 80% EtOH, respectively. The sensitivity of the solvolysis rates with regards to Y, the solvent's ionizing power, is measured by the parameter m..



Dissociation of substituted benzoic acids.

The substitution on the benzene ring and the reaction's ionizing rate constant are related, according to the Hammett equation (Equation 1). Hammett defined a set of substituent parameters σX using the ionization of benzoic acid as the standard reaction. From there, he generated the ρ values, which indicate the ionizing capacities of various substrates. A Hammett plot can be used to visualize this relationship.

$$\log\frac{kX}{kH} = \rho\sigma X\text{------}1$$

However, the rate constant might also alter if the reaction's solvent is altered without also altering the substrate's structure. In accordance with this notion, Grunwald and Winstein created the Grunwald–Winstein equation by charting the relative rate constant vs. the solvent system change. Considered an extension of the Hammett equation, this equation follows the similar trend but accounts for the change in the solvent system. Reference compound

SN1 substitution reaction mechanism

The reference reaction selected was the tert-Butyl chloride substitution reaction. The nucleophilic solvent, or SO, is what determines the rate in the first step, also known as the ionizing phase. By volume, the reference solvent is made up of 80% ethanol & 20% water. They are both capable of attacking the carbocation with a nucleophilic assault.

Since the SN1 reaction uses a stable carbocation intermediate, a more nucleophilic solvent will be able to stabilize the carbocation more effectively, potentially increasing the reaction's rate constant. Since the SN1 and SN2 reactions do not have a distinct boundary, t-BuCl was selected as the reaction that passes through the SN1 mechanism the most in order to produce a better linear connection.

Y values

$$log\frac{Kt-BuCl,sol}{Kt-BuCl,80\%\ EtOH} = Y\text{ ------}2$$

Solvent, % by vol	Y	Solvent, % by vol	Y	Solvent, % by vol	Y
EtOH-H_2O		25	2.908	30	2.753
100	-2.033	20	3.051	20	3.025
98	-1.681	15	3.189	10	3.279
95	-1.287	10	3.312	AcOH-HCOOH	
90	-0.747	5	3.397	100	-1.639
80	0	H_2O	3.493	90	-0.929
70	0.595	MeOH-H_2O		75	-0.175
60	1.124	100	-1.09	50	0.757
50	1.655	90	-0.301	25	1.466
45	1.924	80	0.381	10	1.862
40	2.196	70	0.961		
37.5	2.338	60	1.492		
35	2.473	50	1.972		
30	2.721	40	2.391		
Solvent, % by vol	Y	Solvent, % by vol	Y	Solvent, % by vol	Y
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37.5	2.338	60	1.492		
35	2.473	50	1.972		

The rate constant of the t-BuCl reaction in 80% aqueous ethanol is represented by the symbol kt-BuCl, 80% EtOH in equation 2, which is used as the reference. The rate constant of an identical reaction in a different solvent system, such as acetic acid-formic acid, methanol-water, or ethanol-water, is represented by the variable kt-BuCl, sol. Y, which thus represents the ionizing potential of various nucleophile solvents.

m values

The equation parameter *m*, called the sensitivity factor of solvolysis, describes the compound's ability to form the carbocation intermediate in given solvent system. It is the slope of the plot of $\log(k_{sol}/k_{80\%EtOH})$ vs Y values. Since the reference reaction has little solvent nucleophilic assistance, the reactions with *m* equal to 1 or larger than 1 have almost full ionized intermediates. If the compounds are not so sensitive to the ionizing ability of solvent, then the *m* values are smaller than 1. That is:

$m \geq 1$, the reactions proceed through S_N1 mechanism.

$m < 1$, the reactions proceed through a mechanism between S_N1 and S_N2.

Disadvantages

The Grunwald–Winstein equation cannot fit all data for different kinds of solvent mixtures. The combinations are limited to certain systems and only to nucleophilic solvents.

For many reactions and nucleophilic solvent systems, the relationships are not fully linear. This derives from the growing S_N^2 reaction character within the mechanism.

UNIT-IV: Stereochemistry-I:

Introduction to molecular symmetry and chirality – axis, plane, center, alternating axis of symmetry. Optical isomerism due to asymmetric and dissymmetric molecules with C, N, S based chiral centers. Optical purity, prochirality, enantiotopic and diastereotopic atoms, groups, faces, axial and planar chirality, chirality due to helical shape, methods of determining theconfiguration. Racemic modifications: Racemization by thermal, anion, cation, reversible formation, epimerization, mutarotation. D, L system, Cram's and Prelog's rules: R, Snotations, proR, proS, side phase and re phase Cahn-Ingold-Prelog rules, absolute and relative configurations. Configurations of allenes, spiranes, biphenyls, cyclooctene, helicene, binaphthyls, ansa and cyclophanic compounds, exo-cyclic alkylidene-cycloalkanes. Topicity and prostereoisomerism, chiral shift reagents and chiral solvating reagents. Criteria for optical purity: Resolution of racemic modifications, asymmetric transformations, asymmetric synthesis, destruction. Stereoselective and stereospecific synthesis.

Elements of symmetry

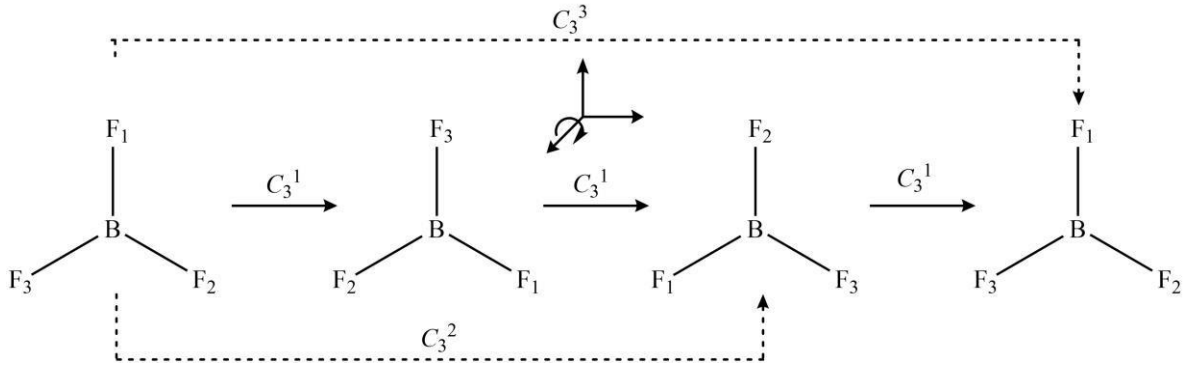
A simple definition of elements of symmetry is any point, line, or plane inside or through the molecular geometry that produces indistinguishable pictures when certain operations are performed on it, such as rotation, inversion, or reflection. Most people refer to these processes as symmetry operations. Below is a general description of several symmetry elements.

Axis of Rotation (C_n)

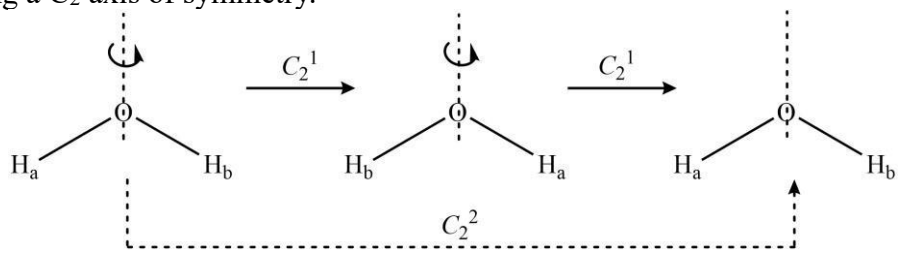
The symmetry axis, also known as the axis of rotation, is the line that passes through the geometry of a molecule at which a specific angle of rotation produces images that are indistinguishable from one another. The axis of rotation is generally symbolized by C_n where n can have the value from 1, 2, 3, 4… and so on. The expression for n is

$n = 360^o/\theta$

Where θ is the minimum angle required to generate indistinguishable images. For instance, in the case of a regular trigone or BF_3 molecule, the geometry must be rotated through 120° minimum about the line perpendicular to the molecular plane to get indistinguishable images. Therefore, we can say that it is a C_3 (three-fold) axis of symmetry.



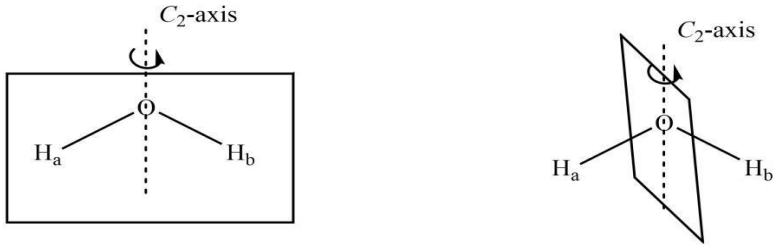
Where C_3^1, C_3^2 and C_3^3 are the symmetry operations via 120°, 240°, and 360°, respectively. Similarly, for the H_2O molecule, the minimum angle required to generate indistinguishable images is 180°, giving a C_2 axis of symmetry.



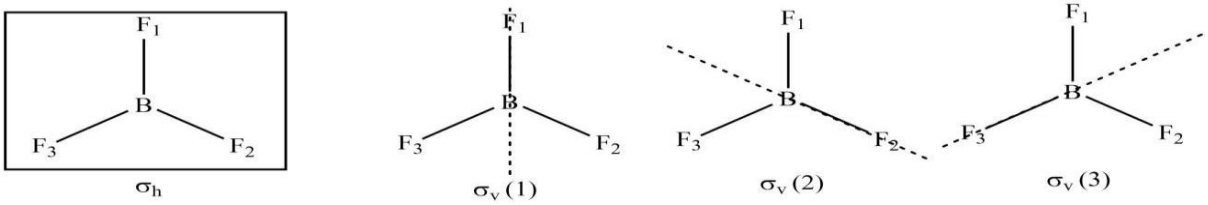
Plane of Symmetry (σ)

The plane of symmetry or simply the symmetry plane may be defined as the plane bisecting the molecular geometry in such a way that one half is the mirror image of the other.

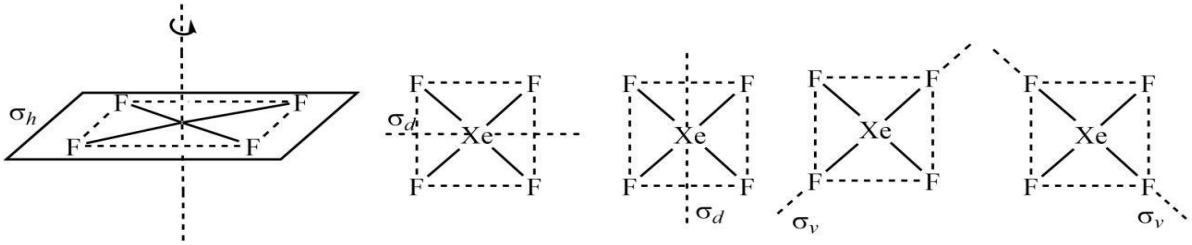
The axis of rotation is generally symbolized by σ_h *or* σ_v where the subscript *h* or *v* is to denote wheater the plane is parallel or perpendicular to the principal axis (symmetry axis of the highest order). There is also a third kind of plane of symmetry called the dihedral plane (σ_d): In other words, we can say that a dihedral plane bisects two σ_v planes. On a final note, a plane of symmetry can also be designated by the Cartesian orientation encompassing it, e.g., (*yz*-plane) or (*xz*-plane). For instance, there are two σ_v planes in water molecules as shown below.



Similarly, there are a total of three vertical (sv) planes and one horizontal (sh) plane in the case of BF molecules as shown below.



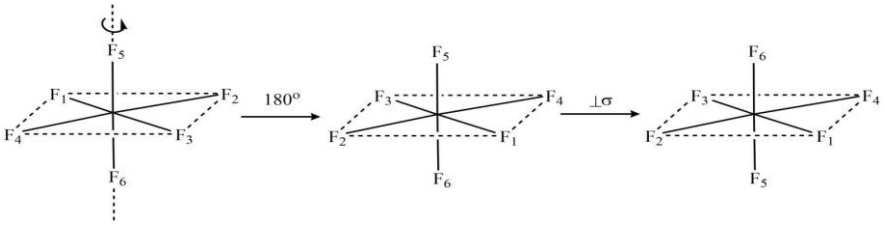
Similarly, there are a total of two vertical (σv) planes and one horizontal (σ_h) and two dihedral planes in the case of XeF_4 molecules as shown below.



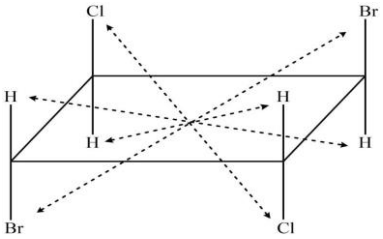
Centre of Symmetry (i)

The molecular geometry is said to possess the center of symmetry if a rotation through 180° followed by the perpendicular reflection generates an indistinguishable image.

The center of symmetry or simply the 'inversion center is denoted by the symbol '*i*', which is a point inside the geometry at such a position that if an object is inverted about this point, the position vector of any point in an object ⟨say *x*, *y*, *z*⟩ is also inverted (–x, –y, –z⟩. For instance, consider the case of the SF_6 molecule.



Similarly, the complete staggered form of CHClBr-CHClBr also possesses the centre of symmetry as it produces indistinguishable images after inverting through the centre. Furthermore, the centre of symmetry in any molecule geometry can also found by drawing lines of equal length in the opposite direction from the centre, provide that similar points are observed.



Similarly, other examples of molecules with the center of symmetry are acetylene, a staggered form of ethane and ethylene.

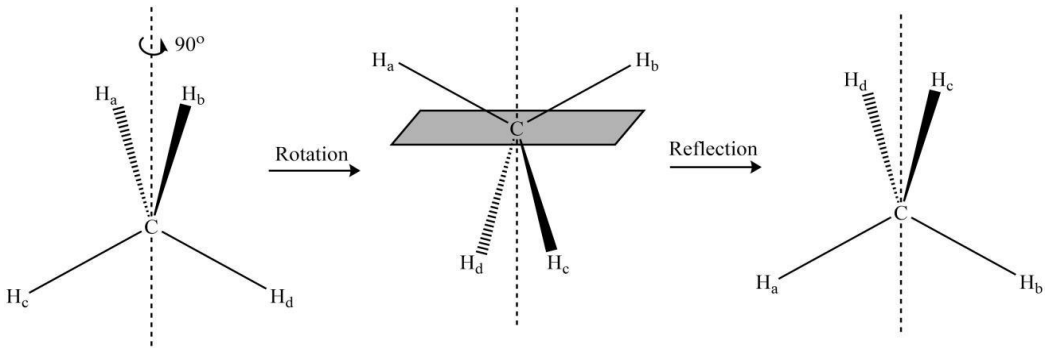
Alternating Axis of Symmetry (S_n)

The alternating axis of symmetry or improper axis of rotation may simply be defined as the line passing through a molecular geometry about which a rotation followed by a perpendicular reflection generates indistinguishable images.

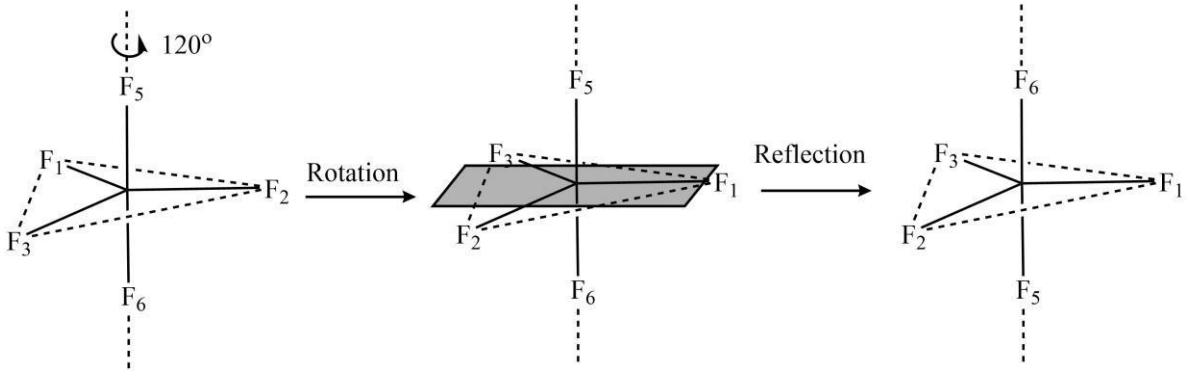
The improper axis of rotation is generally symbolized by S_n where n can have the value from 1, 2, 3, 4… and so on. The expression for n is

$$n = 360^o/\theta$$

Where θ is the minimum angle required before perpendicular reflection to generate indistinguishable images. For instance, in the case of a regular trigone or CH_4 molecule, the geometry must be rotated through 90° before the reflection in a perpendicular plane is carried out to get indistinguishable images. Therefore, we can say that it is an four fold) alternating axis of symmetry.



Similarly, for the BF_3 molecule, indistinguishable images can also be obtained by rotating the molecule through 120° about a line perpendicular to the molecular plane followed by the reflection.



Therefore, we can say that it is an S_3(three fold) alternating axis of symmetry.

Chirality and Optical Activity

Optical activity is the ability of a chiral substance to rotate the plane of plane-polarized light and is measured using an instrument called a polarimeter.

Polarimetry is one of the important instrumental methods employed in analysis. This measures the rotation of the polarized light as it passes through an optically active compound. This technique involves the measurement of change in the direction of vibration of polarized light when interact with an optically active compound. A substance is said to be optically active if it rotates the plane of the polarized light.

In normal light, the electric field oscillates in all directions. When normal light passes through a polarizing filter, only light oscillating in one single plane can go through, and the resulting light that oscillates in one single direction is called plane-polarized light.

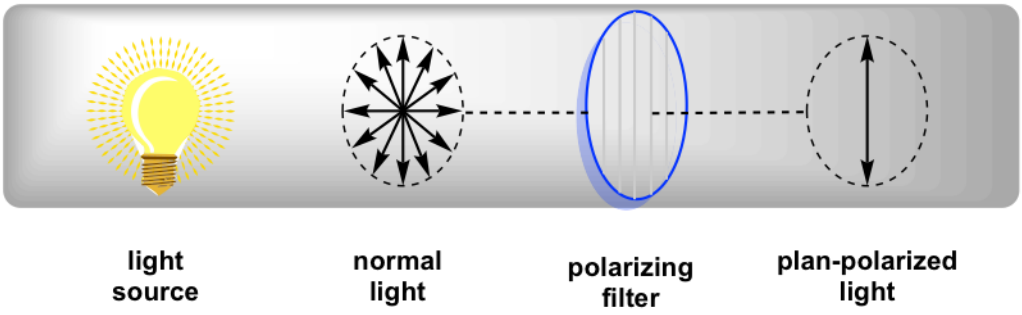
When plane-polarized light interacts with chiral molecules, the plane of polarization will be rotated by the chiral substances. It was first discovered by Jean-Baptiste Biot in 1815 that some naturally occurring organic substances, like camphor, are able to rotate the plane of polarization of plane-polarized light. He also noted that some compounds rotated the plane clockwise and others counterclockwise. Further studies indicate that the rotation is caused by the chirality of the substances.

The property of a compound being able to rotate the plane of polarization of plane-polarized light is called the **optical activity**, and a compound with such activity is labelled as **optical active**. A stereoisomer that is optical active is also called an **optical isomer**.

Chiral compound is optical active. Achiral compound is optical inactive.

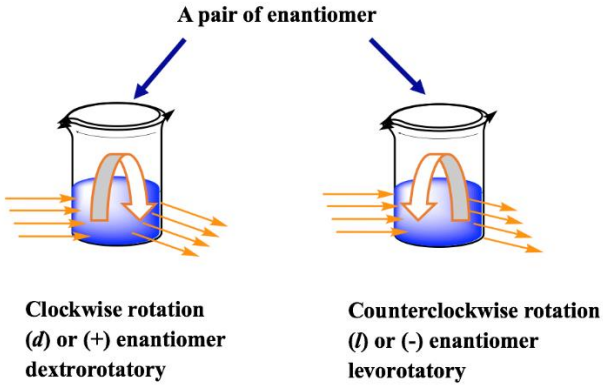
The sample containing a chiral compound rotates the plane of polarization of plane-polarized light, and the direction and angles of the rotation depend on the nature and concentration of the chiral substances. The rotation angles can be measured using a polarimeter (later in this section).

For a pair of enantiomers with the same concentration, under the same conditions, they rotate the plane of polarization with the **same angles** but in the ***opposite* direction**. One is clockwise, and the other is counterclockwise.



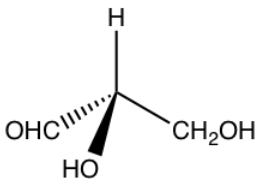
Generation of Plane-Polarized Light

The two enantiomers are mirror images of each other. They are very alike and share many properties in common, such as the same b.p., m.p., density, color, and solubility. In fact, the pair of enantiomers have the same physical properties, *except* the way they interact with plane-polarized light.

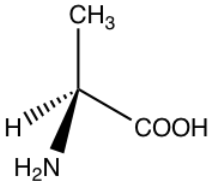


Clockwise rotation/enantiomer dextrorotatory vs. counterclockwise rotation/enantiomer levorotary

The enantiomer rotates the plane of polarization clockwise and is said to be **dextrorotatory** (*Latin*, means to the right), and it is labelled with the prefix (d) or (+). The enantiomer rotates the plane of polarization counterclockwise and is said to be **levorotatory** (*Latin*, means to the left), and it is labelled with the prefix (***l***) or (–). The ***d/l*** (or +/-) indicate the direction in which an optical active compound rotates the plane of polarization of plane-polarized light, which has to be determined by an experiment to measure the optical rotation. The d/l (or +/–) **symbol has nothing to do with R/S**. R/S indicates the arrangement of the groups around the chirality center, which can be determined by knowing the exact spatial arrangement of the groups. That means a compound with an ***R*** configuration can be either ***d*** or ***l***, and a compound with an ***S*** configuration can also be either ***d*** or ***l***. For the examples below, both compounds are ***S***-isomers, but one is ***d (+)*** and the other is ***l (-)***.



(S)-(+)-glyceraldehyde

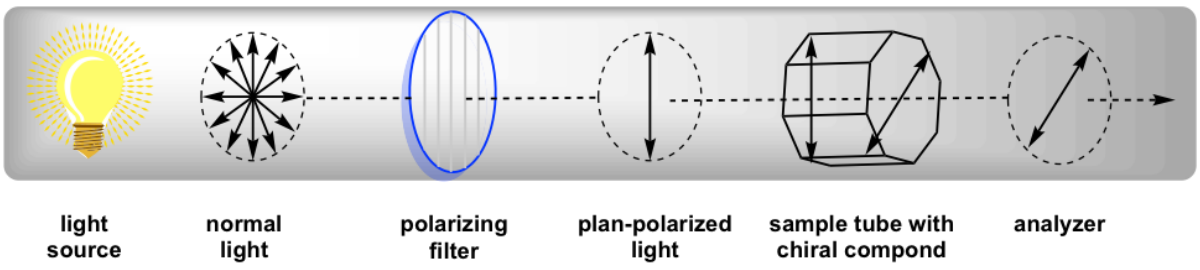


(S)-(-)-alanine

The only thing we can be sure of is that for a pair of enantiomers, if one enantiomer has been determined as ***d***, then the other enantiomer must be ***l***, and vice versa.

Measurement of Optical Rotation

The polarimeter is an instrument that measures the direction and angles of rotation of plane-polarized light. The plane-polarized light passes through the sample tube containing the solution of a sample, and the angle of rotations will be received and recorded by the analyzer, as summarized in Figure.



Measurement of Optical Rotation with Polarimeter

Since the measurement results vary with the wavelength of the light being used, the specific light from a sodium atomic spectrum with the wavelength of 589 nm, which is called the sodium D-line, is used for most polarimeters. The rotation degree measured by the polarimeter is called the **observed rotation** (α), and the observed rotation depends on the length of the sample tube, a concentration of the sample and temperature.

To compare the optical rotation between different compounds under consistent conditions, the **specific rotation** $[\alpha]_D^{20°C}$ ($[\alpha]_D^T$) is used. **Specific rotation** is the rotation caused by a solution with a concentration of 1.0 g/mL in a sample tube of 1.0 dm length. The temperature is usually at 20°C. Based on this definition, the specific rotation can be calculated from the observed rotation by applying the formula:

$$[\alpha]_D^T = \frac{\alpha}{l \times c}$$

T: usually at 20 °C

α: observed rotation in degree;

l : length of the sample cell (**dm**);

c: concentration (**g/mL**)

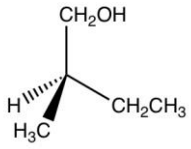
Specific rotation equation

Please note: In this formula, the unit of concentration (g/mL) and length of the sample tube (dm) are not the units we are familiar with. Also, the unit of the specific rotation is in degree (°), don't need to worry about the units cancellation in this formula.

Examples: Calculate the specific rotation. The observed rotation of 10.0g of (R)-2-methyl-1-butnaol in 50mL of solution in a 20-cm polarimeter tube is +2.3° at 20 °C, what is the specific rotation of the compound? Solution:

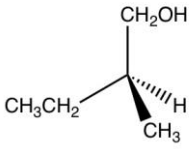
$$[\alpha]_D^{20°C} = \frac{\alpha}{l \times c} = \frac{+2.3}{2dm \times \frac{10.0g}{50\,mL}} = 5.75$$

Specific rotation is the characteristic property of an optical active compound. The literature specific rotation values of the authentic compound can be used to confirm the identity of an unknown compound. For the example here, if it has been measured that the specific rotation of (***R***)-2-methyl-1-butnaol is +5.75°, then we can tell that the other enantiomer (***S***)-2-methyl-1-butnaol must have the specific rotation of -5.75°, ***without*** further measurement necessary.



(R)-2-methyl-1-butnaol

$[\alpha]_D^{20°C}$= +5.75°



(S)-2-methyl-1-butnaol

$[\alpha]_D^{20°C}$= –5.75°

Optical Activity of Different Samples

When a sample under measurement only contains one enantiomer, this sample is called **enantiomerically pure**, which means only one enantiomer is present in the sample.

The sample may also consist of a mixture of a pair of enantiomers. For such a mixture sample, the observed rotation value of the mixture, together with the information of the specific rotation of one of the enantiomers allows us to calculate the percentage (%) of each enantiomer in the mixture. To do such a calculation, the concept of enantiomer excess (ee) will be needed. The enantiomeric excess (**ee**) tells how much of an excess of one enantiomer is in the mixture, and it can be calculated as:

$$ee = \frac{observed\ rotation}{specific\ rotation\ of\ pure\ enantiomer}$$

Important Terminology

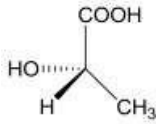
- **Dissymmetric molecules** - Molecules that do not possess a plane of symmetry, centreof symmetry and improper axis of rotation are called Dissymmetric molecules.
- **Asymmetric molecules** - Molecules that do not contain any element of symmetry arecalled Asymmetric molecules.
- **Enantiomers** – Enantiomers are stereoisomers that form non-superimposable mirrorimages of each other.
- **Diastereomers** – Diastereomers are sterioisomers that do not form mirror images ofeach other.
- **Epimer** – These are diastereomers that differ in the configuration of a single chiralcentre.
- **Anomer -** Anomers are diastereoisomers of cyclic forms of sugars or similar moleculesdiffering in the configuration at the newly formed chiral centre.
- **Chiral centre** – A tetrahedral carbon containing four different groups is said to be achiral centre. It is also called a stereogenic centre.
- **Achirality** – If a molecule is superimposable on its mirror image, it is said to be achiral.
- **Chirality** – If a molecule is not superimposable on its mirror image, it is said to bepossess chirality.

Representation of organic molecules

Since stereochemistry refers to molecules in three dimensions, appropriate modes of representations of three dimensional molecules on two-dimensional paper is essential. The wedge formula is most commonly used. Of the projection formula, Fischer, Newmann and Sawhorse projections are the most important.

I.Wedge formula

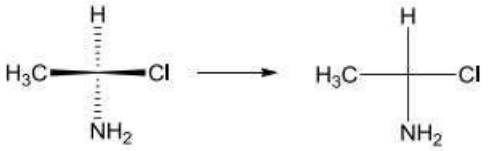
In the wedge formula, there are two line bonds, one solid wedge bond and one broken wedge bond for a tetrahedral stereogenic centre. The two line bonds are on the plane of the paper, thesolid wedge is pointing towards the observer out of the plane and the broken wedge is pointingaway from the observer out of the plane.



II.Fischer Projection formula

In the Fischer projection formula, the horizontal bonds are coming out of the plane of the paper

and the vertical bonds are going away from the plane of the paper.



Rules for Fischer projection

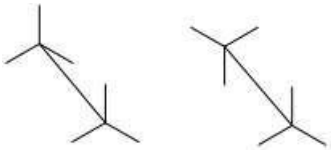
a. 90° in plane or out of plane rotation is not allowed.
b. 180° in plane rotation is allowed.
c. 180° out of rotation is not allowed.
d. Exchange in groups of 2 is not allowed.
e. Exchange in groups of 3 is allowed.

III. Newmann projection formula

This is applicable for two carbon systems. The front carbon is written as a dot. The second carbon is represented as a circle behind the dot. The substituents on the dot are usually written in the form of a Y or inverted Y. The back carbon substituents are written in a similar fashion.

IV. Sawhorse Projection formula

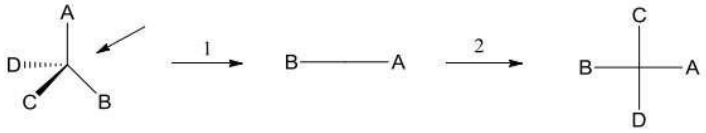
This is also applicable to two carbon systems. The C-C bond is elongated to represent a sawhorse in an angular fashion. The substituents on each carbon can be represented in the formof a Y or inverted Y.



Interconversion between Fischer and Wedge Formulae

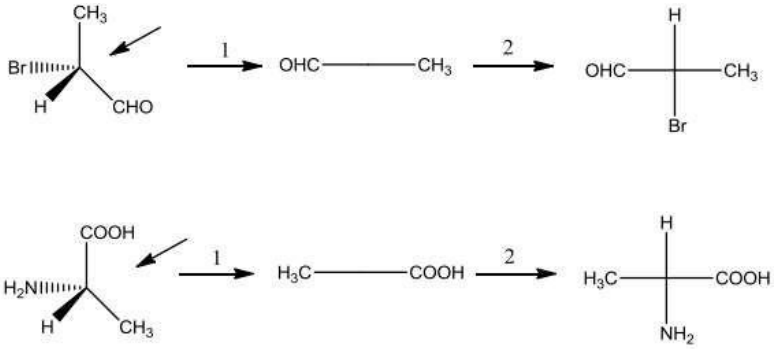
A. Compounds with one stereocenter

i)Conversion of wedge structure into Fischer projection

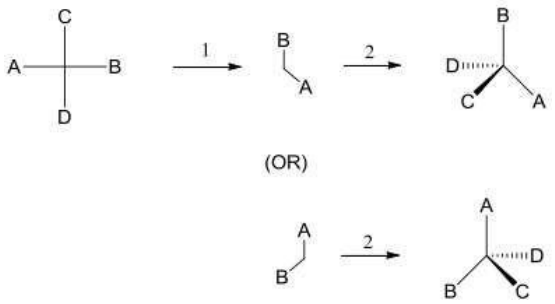


Step 1: View the molecule from in between the two bonds on the plane of the paper. The observer is standing perpendicular to the plane of the paper.

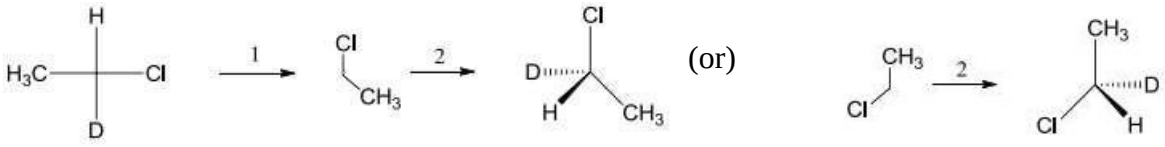
Step 2: The group A is to the right of the observer. The group B is to the left of the observer. Hence these two groups should be drawn on the horizontal plane of the Fischer projection withA to the right and B to the left.
Step 3: The group C in the solid wedge is above the observer and group D in the broken wedgeis below the observer. Hence these two groups should be drawn on the vertical plane of the Fischer projection with C to the top and D to the bottom.
The same rules will apply no matter how the wedge formula is drawn. The observer should always be placed in between the bonds on the plane of the paper and stand perpendicular to theplane.



i. Conversion of Fischer projection into wedge structure.

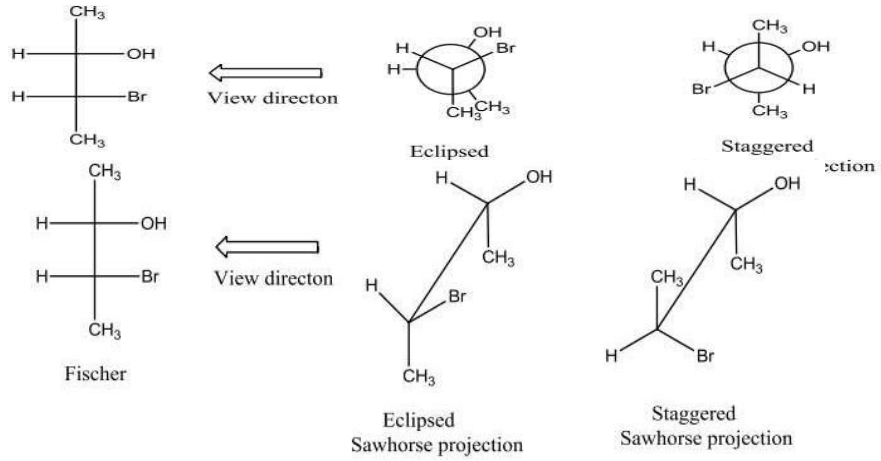


Step 1: The horizontal groups should be placed on the two bonds on the plane of the paper in either of the two ways shown above.
Step 2: The top group C should be written on the solid wedge and the bottom group D shouldbe written on the broken wedge. Both forms will give the same representation.

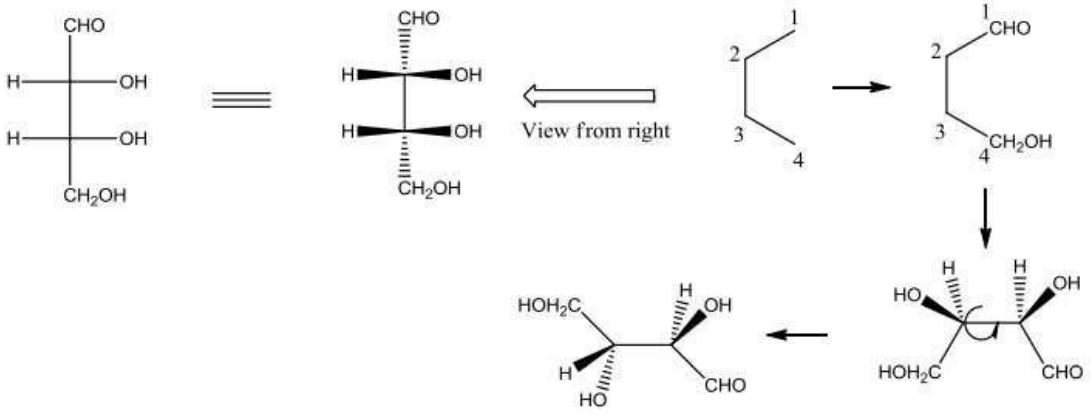


B. Compounds with two stereocenters:

i. Interconversion of Fischer into Sawhorse and Newman projections.

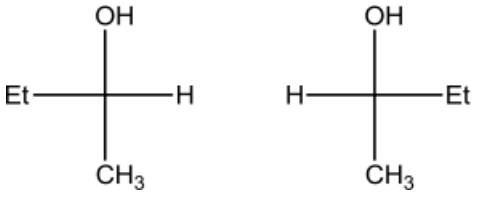


ii. Conversion of Fischer projection into Dashed-wedge line or Zig-zag projection

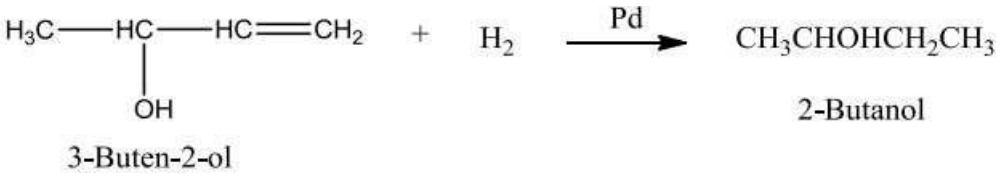


Absolute Configuration

The spatial arrangement of substituents at a stereogenic center is its absolute configuration. Neither the sign nor the magnitude of rotation by itself can tell us the absolute configuration ofa substance. Thus, one of the following structures is (+)-2-butanol and the other is (-)-2-butanol,but without additional information we can't tell which is which.



Although no absolute configuration was known for any substance before 1951, organicchemists had experimentally determined the configurations of thousands of compounds relative to one another (their relative configurations) through chemical interconversion. To illustrate, consider (+)-3-buten-2-ol. Hydrogenation of this compound yields (+)-2-butanol.



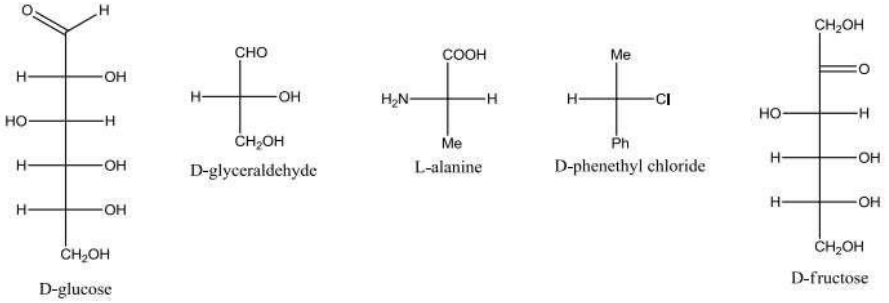
3-Buten-2-ol

2-Butanol

Since hydrogenation of the double bond does not involve any of the bonds to the stereogenic center, the spatial arrangement of substituents in (+)-3-buten-2-ol must be the same as that of the substituents in (+)-2-butanol. The fact that these two compounds have the same sign of rotation when they have the same relative configuration is established by the hydrogenation experiment; it could not have been predicted in advance of the experiment.

i. D and L Notation.

There are several systems of configurational nomenclature. The oldest one is the D and L system and is applicable to molecules of the type R-CHXR' where R-C-R' is the main chain
e.g. carbohydrates and amino acids. The number one carbon of the main chain is at the top in a Fischer projection. Then, if X is to the right of the stereocentre, the molecule is called D, if to the left, it is called L.

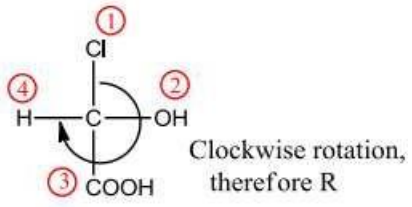


ii. R and S Notation (Cahn-Ingold-Prelog's rules)

This system is based on the actual three dimensional formula of the compound to be named. In order to name a compound Xabcd (X-asymmetric atom), the groups a, b, c and d are first arranged in a priority sequence according to the sequence rules. If in this sequence, the order of priority is a > b > c > d, then the molecule is viewed with d on the vertical line.
If a → b → c traces a clockwise or right handed turn, the configuration is R (rectus). If it tracesan anti- clockwise turn, the configuration is S (sinister).

Sequence Rules

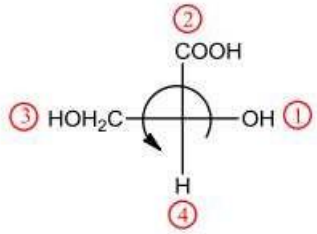
1. The groups are arranged in order of decreasing atomic number of the atoms directly attached to the asymmetric atom. The group with lowest priority should be in the vertical plane (back). If not, the order of priority is determined and the resulting configuration is inverted.



Since H is in the horizontal
plane (front), the configuration is S

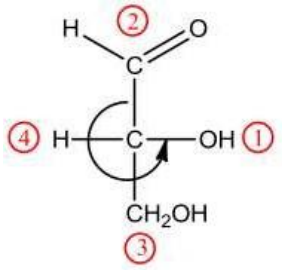
2. If two atoms attached to the asymmetric atom are the same, their respective states of substitution are considered. The atoms substituted with other atoms of higher atomic number takes priority or if two atoms are equivalent in that respect, then with more substituents of high atomic number

comes first. If the second atoms afford no choice, then the third is selected.



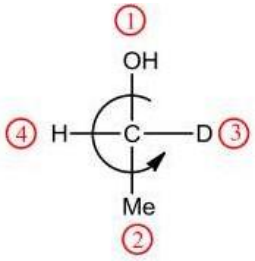
Anticlockwise rotation, therefore S

3. For multiple bonds like double bonded N, O, etc, substitute N or O twice, for triple bonded N, substitute N thrice, etc. Phenyl group corresponds to C bonded to three othercarbon atoms. Two N or O atoms attached to C takes priority over =N or =O.



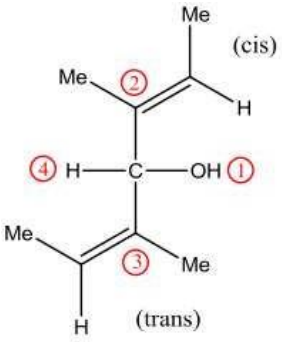
R

4. In a case such as XabHD, the isotope of higher mass number precedes that of lower mass number



R

5. In a case such as Xaa'bc, where a and a' are stereoisomeric, the cis takes precedence over the trans group and R takes precedence over S group.

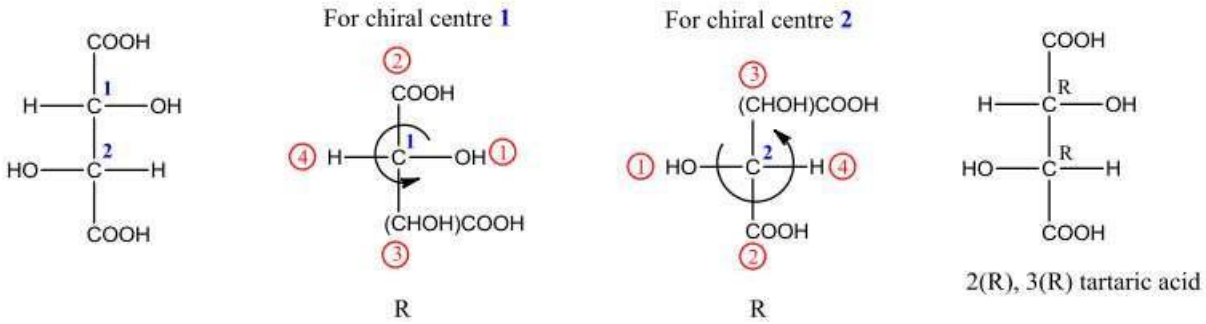


R

6. By applying these rules to some common substituents, one obtains the followingsequence (group of highest priority first)

-I	-OH	$-CH_2OH$	$-CH_2-CH=CH_2$
-Br	$-NO_2$	$-C_6H_5$	$-CH_2(CH_2)NCH_3$
-Cl	-NO	$-C\equiv CH$	$-CH_2CH_3$
$-SO_2R$	$-NHCH_3$	$-C(CH_3)$	$-CH_3$
-SOR	$-NH_2$	$-CH=CH_2$	-D
-SH	-COOH	$-CH(CH_3)_2$	-H
-F	$-CONH_2$	$-CH_2C_6H_5$	
$-OC_6H_5$	-COR	$-H_2C-C\equiv CH$	
$-OCH_3$	-CHO		

7. This system can be used for compounds with more than one asymmetric atom also.

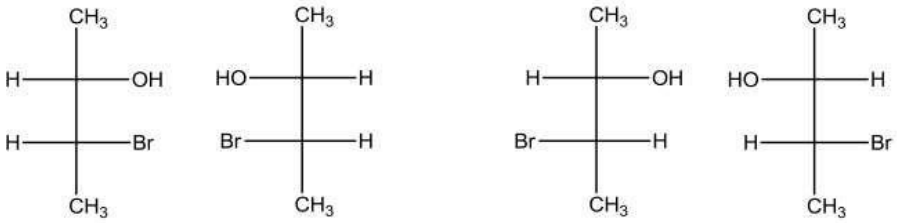


Relative Configuration

Relative configuration is the position of atoms or groups in space relative to something else inthe molecule. Prior to 1951 only relative configuration of compounds were known. For example, if (+) glyceraldehyde is converted to glyceric acid using a reaction that is known to put the COOH group where the CHO was, then the two compounds have the same relative configuration at their stereocenters even though one may not know their absolute configuration. Relative configuration at a stereocenter is also the relation with that of any other stereocenter in the same molecule.

A. Erythro and Threo Nomenclature

A molecule with two adjacent stereocenters, when there are two groups which are common toeach carbon while the third is different i.e., C_{abx}-C_{aby} gives rise to erythro and threo diastereomers. Since erythrose and threose are diastereomers, other diastereomeric pairs of molecules which have two adjacent stereocenters are designated as erythro or threodependingon whether similar groups are on the same side (erthyro) or on opposite sides (threo) of the Fischer projection respectively. Thus 3-bromo-2-butanol with two stereocenters has (2^2) four stereoisomers.

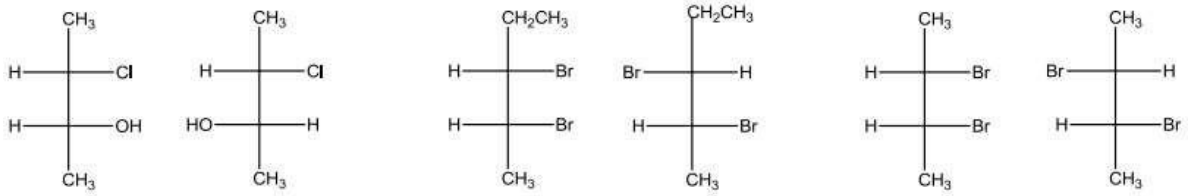


Erythro enantiomers Threo enantiomers

Erythro and threo is the short hand method employed by organic chemists to name appropriate compounds. R and S is used to refer to a particular enantiomer of the erythro and threo pair. The terms erythro and threo are applied only to those molecules which do not have symmetricends. When, however, the ends are symmetric as in 2, 3-dibromobutane and tartaric acid, the terms meso and dl are preferred since the use of these terms show if the diastereomer has an enantiomer or not.

Optical activity in the absence of chiral carbon

Stereoisomerism in organic compounds is usually based on chiral centres acting as stereogenic

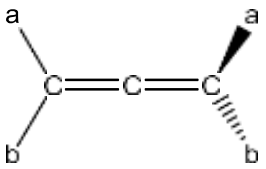


Erythro Threo Erythro Threo Meso dl

units. Two other elements of chirality (axes and planes) also behave as stereogenic units. Hence, compounds such as allenes, hemispiranes, spiranes and biphenyls exhibit optical activity even in the absence of a chiral carbon. These two elements of chirality are called stereoaxis and stereoplanes.

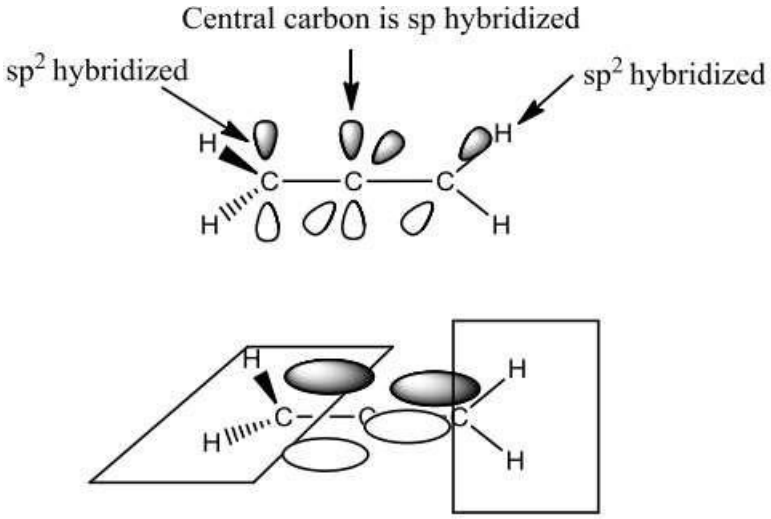
i. Allenes and Spiranes

An allene is said to be chiral if the two substituents at each end are different from each other (a≠ b).



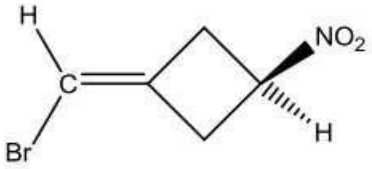
In an allene, the central carbon is sp hybridized and linear and the two other carbon atoms are

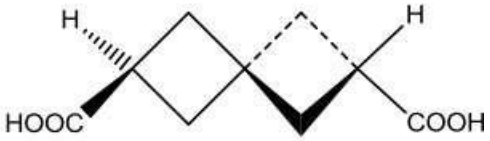
sp2 hybridized and trigonal. In allene, the C=C=C is a potential chiral axis. The two double bonds lie in perpendicular planes. Hence unsymmetrical substituents give chirality to the molecule.



The two methylene groups are perpendicular.

The replacement of one double bond in allene with a ring gives a hemispirane. These types of molecules are also chiral provided the groups at each end are not identical. The replacement ofboth double bonds by ring systems gives a spirane. Similar rules of optical activity apply here.



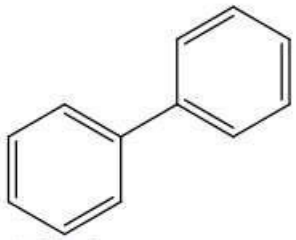


ii. Optical activity in Biphenyls

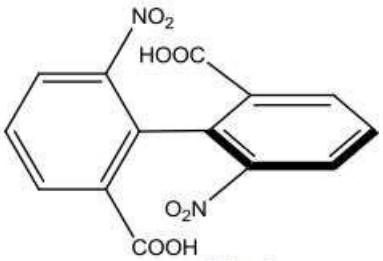
Atropisomers are stereoisomers resulting from hindered rotation about single bonds. Biphenylsis a class of compounds that exhibit atropisomerism. In the crystal state, both benzene rings ofbiphenyl lie in the same plane. In solution, the two rings are twisted with respect to each otherby an angle of 45^{o} due to steric interactions between the 2, 2' and 6, 6' pairs of hydrogens. These interaction effects are further enhanced by ortho substituents larger than hydrogen.

- The rotation about the bond linking the two phenyl rings does not occur due to sterichindrance between the bulky ortho groups.
- The two rings lie in different planes which are perpendicular to each other.
- Chiral biphenyls must contain two different ortho substituents on each ring.

- In order to display optical activity, the substituents in the ortho position must be large enough to prevent the two rings from becoming coplanar.



Achiral

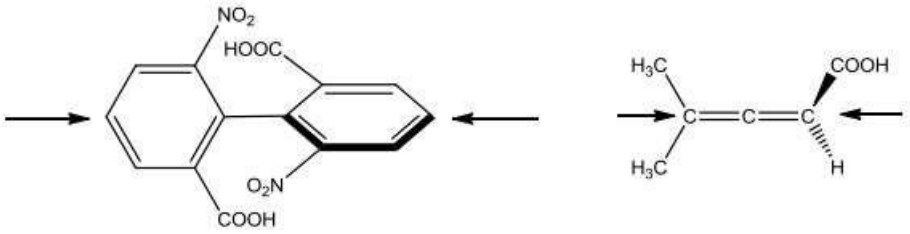


Chiral

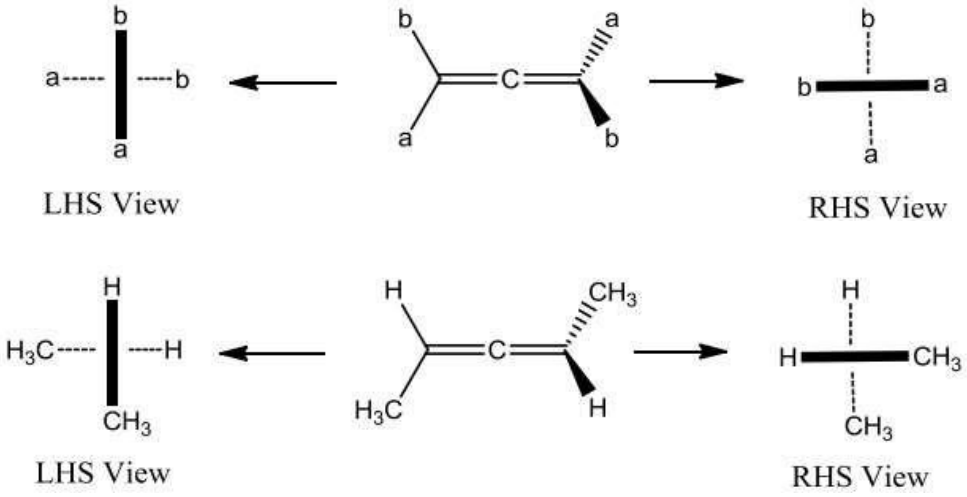
iii. Absolute Configuration for allenes, spiranes and biphenyls

1. The CIP rules are used to assign priority to the end groups but with one addition: Thatthe front groups take precedence over the rear groups. Thus the two front and two groups are ranked according to the priority rules.

2. The chiral axis is viewed end on and the observer is standing parallel to the plane of thepaper.

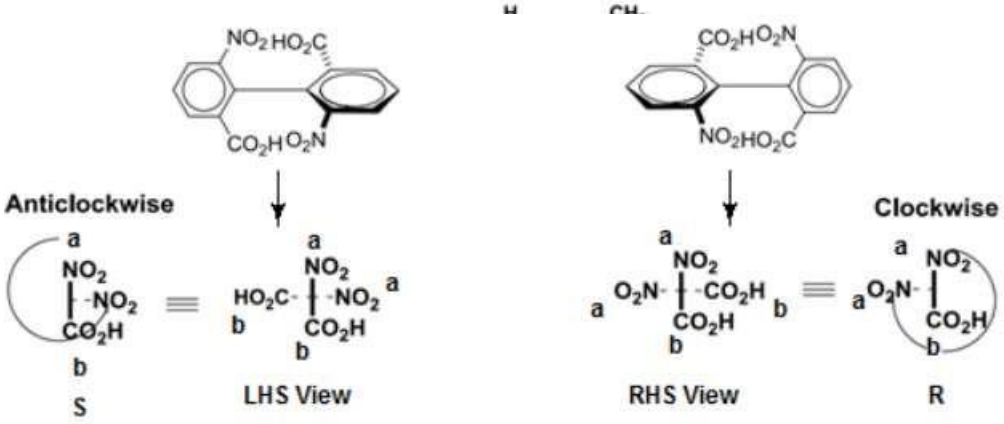


3. The model below shows the side views and representation of the allene along the chiralaxis.



4. Assigning priority to substituents - assign priority to the substituents on each of the terminal carbons of the allene system (you may use a (higher priority) and b (lower priority).

5. The same rule applies for biphenyls also.



6. **Racemic modifications or racemic mixture or racemates**

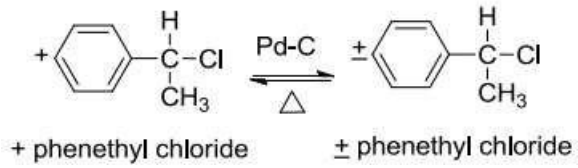
A racemic mixture consists of equal amounts of dextrorotatory and laevorotatory molecules such that the average optical rotation is zero.

Racemization:

Racemization is the process of producing a racemic modification starting with one of the pure enantiomers. Since the two enantiomers have the same free energy, the equilibrium mixture will correspond to a 50-50 composition.

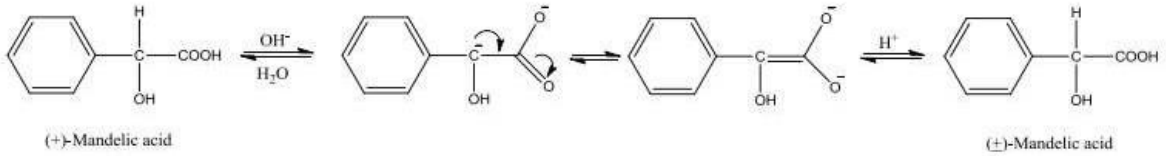
There are several chemical methods for reaching the racemization equilibrium.

Thermal racemization – One method of racemization of an optically active material is by breaking, temporarily one of the four bonds in an asymmetric carbon. If in the subsequent reformation of the bond, the group separated exchanges places with one of the remaining groups, the dissymmetric molecule is converted to its enantiomer. Homolytic cleavage takes place.

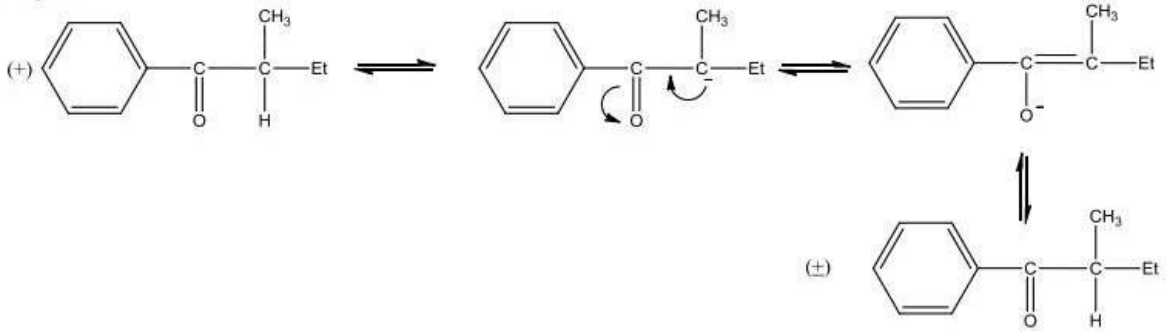


By Anion formation – This is an example of heterolytic cleavage. Racemization occurs through anion formation. If a group is removed from a tetrahedral and chiral carbon leaving behind a carbanion, it undergoes rapid inversion so that when the group recombines, it can doso either from the right or the left. Hence the product is racemic. The group that leaves withoutits electrons is usually a proton.

E.g. 1



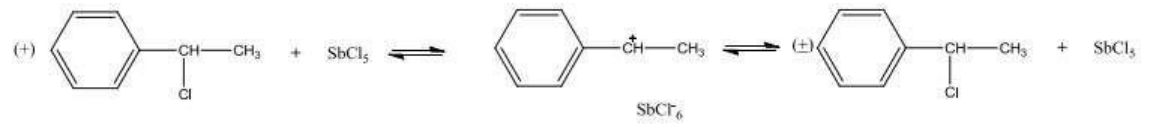
E.g. 2



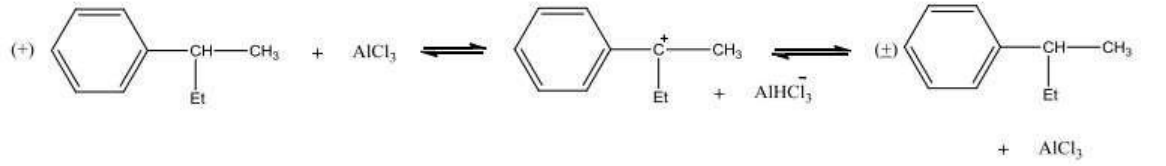
The anion in each case is stabilized by resonance. The base used to abstract the acidic proton is usually NaOH or NaOEt. If enolisable hydrogen is not present, racemization does not take place.

By cation formation – This is also an example of heterolytic cleavage. Racemization is done by removing the group R with its pair of electrons and leaving a carbonium ion or carbocation. It is brought about by a Lewis acid. The carbocation formed must be stable. The reagents used are Lewis acids like $SbCl_5$, $AlCl_3$, $ZnCl_2$, etc.

E.g. 1

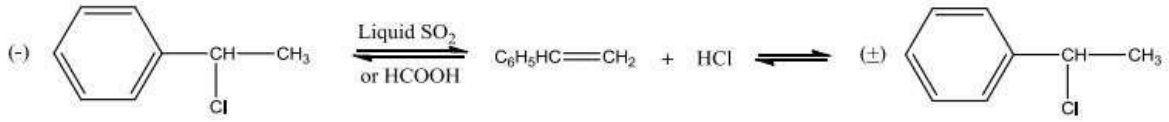


E.g. 2

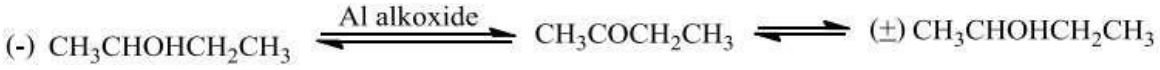


By reversible formation of stable inactive intermediate – The carbocations and carbanions involved in the racemization have very short half-life. In this method, symmetric intermediates which are stable entities are formed.

E.g. 1



E.g. 2



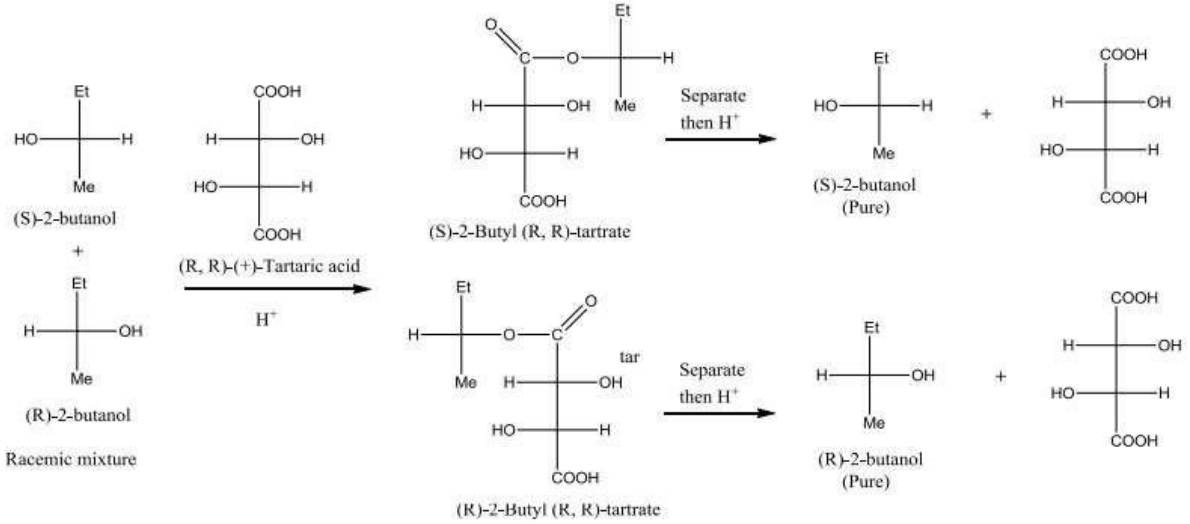
Resolution of Racemic Modifications

Resolution is the separation of a racemic mixture into its enantiomeric constituents. An optically active compound can be obtained from a racemic mixture by using two methods.

1. Via resolution of individual enantiomers from a racemic mixture and
2. By carrying out an asymmetric synthesis using a chiral reagent or a catalyst

i) Resolution through the formation of diastereomers

A racemic mixture of an alcohol e.g. 2-butanol reacts with pure (+)-tartaric acid to give diastereomeric esters. These esters are separated by chromatography easily since they are now diastereomeric. The resolving agent is then cleaved from the separated enantiomers of 2- butanol by hydrolysis to give (R)-2-butanol and (S)-2-butanol in their pure form.

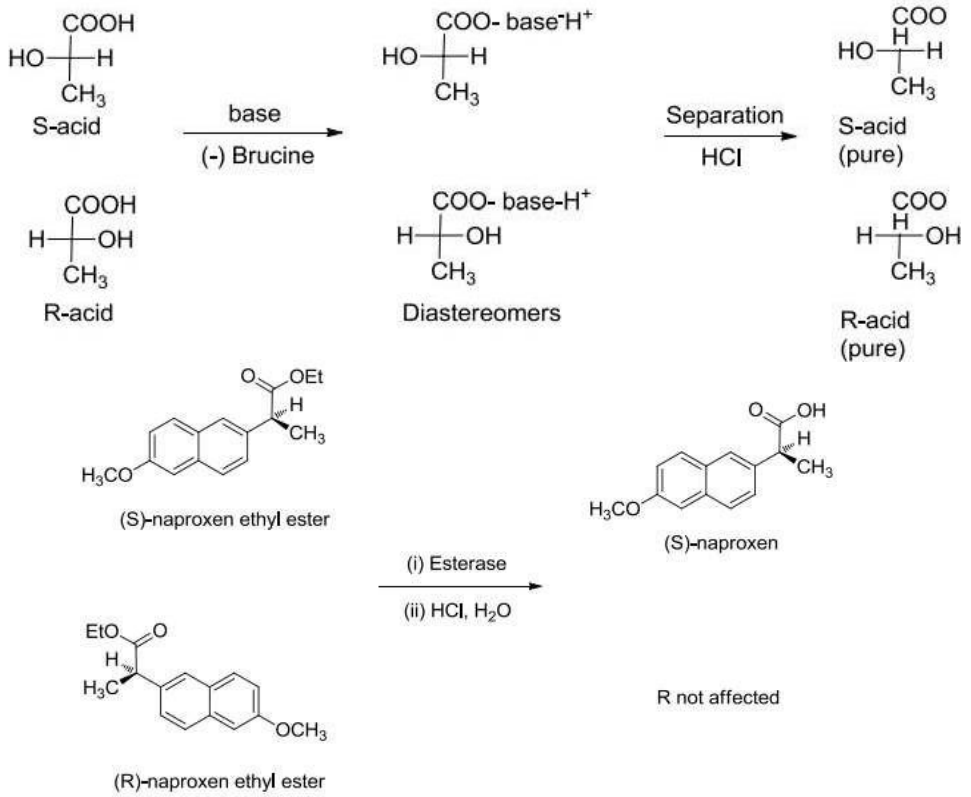


The most important criterion is the proper choice of the resolving agent. Thus, a racemic mixtureof organic acids can often be separated into its pure enantiomers by using the naturally occurring alkaloid brucine (a base).

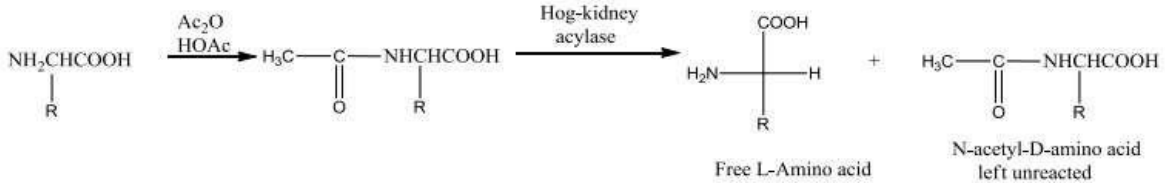
ii) Resolution with the use of enzymes

Amino acids can be resolved with the help of enzymes.

E.g. - The enzyme esterase hydrolyzes only the S enantiomer of naproxen ethyl ester leavingthe R enantiomer unaffected. Thus the racemic mixture can be separated.

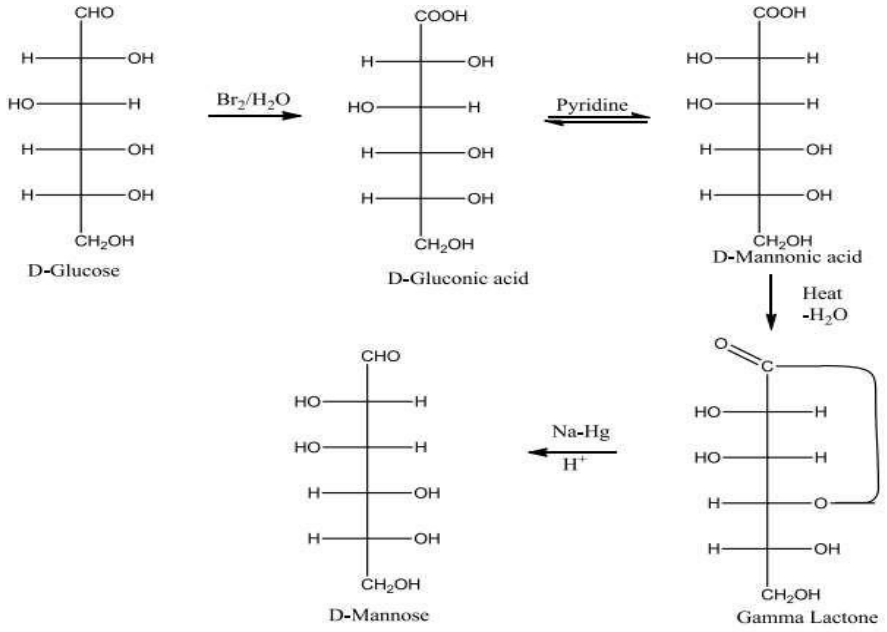


E.g.: A (±) amino acid is acylated and the acylated racemic mixture is treated with an enzymeacylase 1 (hog kidney acylase). This enzyme is capable of hydrolyzing amide links of L-aminoacids only (stereospecificity). Thus at the end, a free L-enantiomer with the acylated D- enantiomer is obtained. The mixture can now be easily separated by various methods.



Epimerization

Epimers are diastereomers that differ in the configuration of a single chiral centre. They are related by the inversion of configuration at a single chiral center. Epimerization is the process of conversion of one form of epimer into another. E.g. conversion of D-glucose to D-mannose. Glucose is an epimer of both mannose and galactose because they differ by the configuration of a single chiral center. Mannose and galactose have different configurations at both C2 and C4 and are not epimers.



Asymmetric Transformations

When a racemic mixture is converted into a pure enantiomer or a mixture in which one enantiomer predominates, it is called asymmetric transformation. It holds true fordiastereomers as well. This is sometimes called deracemisation. There are two types of asymmetric transformation – first order and second order.

When a racemic mixture A is reacted with an optically active reagent B, it forms two isomers.If for eg. 2 is more than 1, then the equilibrium will shift towards the right and more and moreof 1

$$(+)\,A \;+\; (+)\,B \longrightarrow (+)\,A\,(+)\,B \;+\; (-)\,A\,(+)\,B$$

$$(+)\,A\,(+)\,B \rightleftharpoons (-)\,A\,(+)\,B$$

1 2

will be transformed to 2. This is asymmetric transformation. The change in optical rotationwill take place naturally.

First and Second Order asymmetric transformations

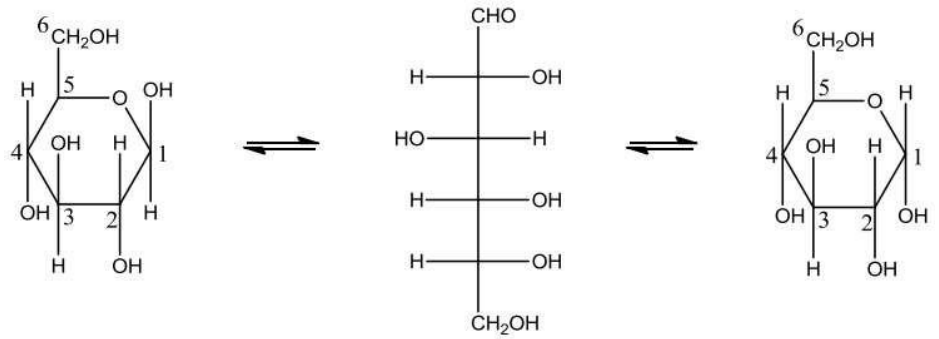
This occurs when a compound containing a chiral centre undergoes a spontaneous configurational change in solution. If there is a second chiral element present, then one of the enantiomers predominates in equilibrium. Mutarotation is an example of first order asymmetrictransformation.

If in an asymmetric transformation, one of the species crosses the phase boundary and precipitates out of the solution, it is called **second order asymmetric transformation**. For example, a concentrated solution of glucose in ethanol precipitates out in the α form, while a concentrated solution of glucose in pyridine precipitates out the β form.

Mutarotation

Two crystalline forms of D-Glucose have been isolated. α-D-glucose crystallized from a concentrated aqueous solution at 30°C. It has a melting point of 146°C and a specific rotation of +112°. β-D-glucose crystallized from hot, glacial acetic acid solution. It melts at 148-150°Cand has a specific rotation of +19.2°. When either of these forms of D-glucose is dissolved in water and allowed to stand, a gradual change in specific rotation occurs. The specific rotation of the alpha form falls and that of the beta form rises until a constant value of +52.7° is reached.**This change in optical rotation of a solution of a chiral substance until a constant value isreached is called mutarotation**.

Glucose forms a stable cyclic hemiacetal between the CHO group and the OH group on the fifth carbon. In this process, the first carbon becomes asymmetric, giving two isomers which differ only in the configuration of the new asymmetric carbon. They are called anomers and the new asymmetric carbon is called anomeric carbon. **Anomers are diastereoisomers of cyclic forms of sugars or similar molecules differing in the configuration at the anomericcarbon (C-1 atom of an aldose or the C-2 atom of a 2-ketose).**



Enantiomeric excess or Criteria for Optical Purity

Optical activity can be measured in a mixture of enantiomers if these are present in unequal amounts. For example, if a solution of (+) and (-) isomers consist of 75% (+) isomer and 25%(-) isomer, the racemic mixture present is 25%, and the (+) enantiomer exists in excess. This iscalled enantiomeric excess. The 25% (-) enantiomer cancels the rotation of a corresponding amount of the (+) enantiomer. This mixture is called 50% optically pure. Optical purity can befound from the following relationship.

$$\%\ Optical\ Purity = \left(\frac{[\alpha]_{observed}}{[\alpha]}.100\right) = Enantiomeric\ excess$$

Where $[\alpha]_{observed} = specific\ rotation\ of\ mixture$

$[\alpha] = specific\ rotation\ of\ pure\ enantiomer$

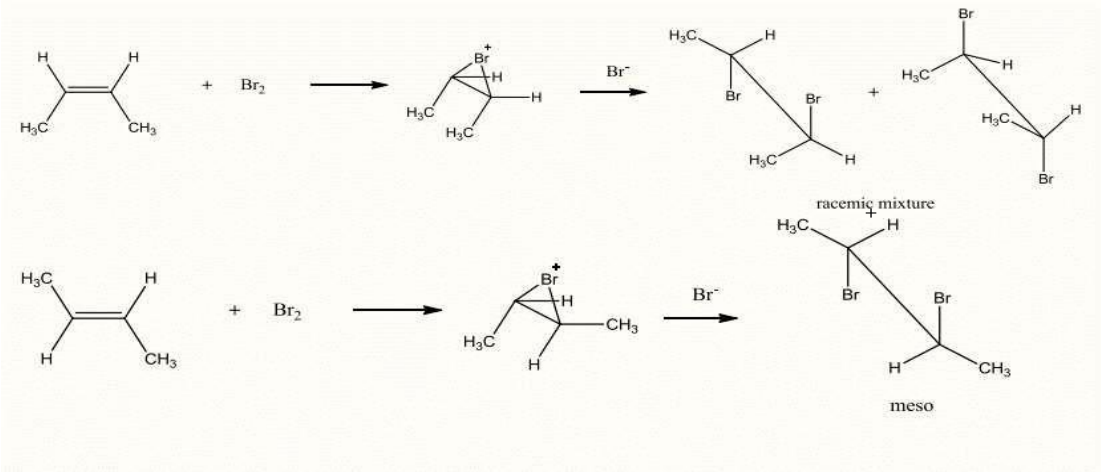
Stereospecific Synthesis:

A reaction is stereospecific provided the reactant can exist as stereoisomers and each stereoisomeric reactant gives a different stereoisomeric product which may be a ± pair.

i. Bromination of cis and trans-2-butene

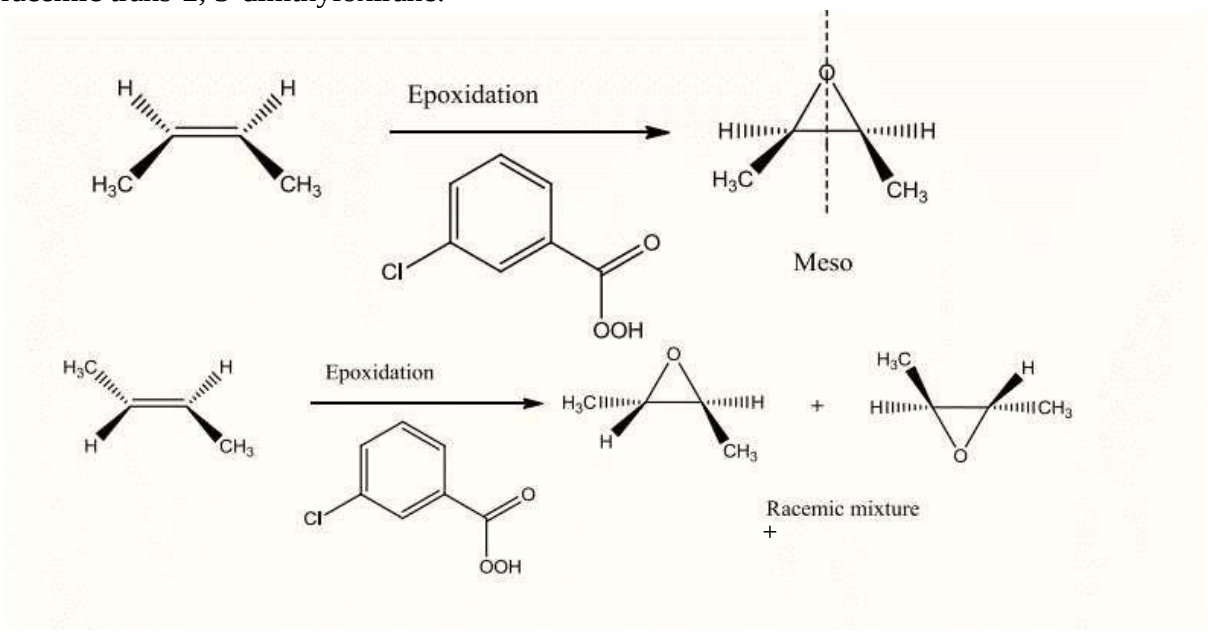
Addition of bromine to cis-2-butene gives a racemic mixture of 2, 3 – dibromobutane while addition to trans-2-butene gives the *meso* stereoisomer. Cis-2-butene add bromine from the topface to give the intermediate bromonium ion which is achiral. The bromide ion then attacks the bromonium ion at either carbon from bottom (S_N2) type of displacement at equal rates to yieldthe two enantiomers in equal amounts i.e. the racemic form.

Trans-2-butene reacts with bromine from the top face to give a chiral bromonium ion. When the bromonium ion is opened by S_N2 type displacement at either carbon, the same achiral *meso* compound is formed.



ii. Epoxidation of cis and trans-2-butene:

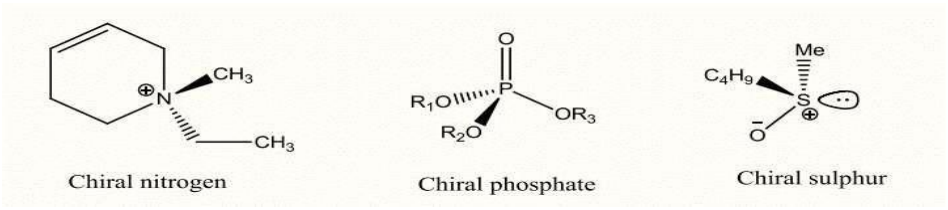
The reaction of alkenes with peroxy acid takes place in a stereospecific way, cis-2-butene for example yields only cis-2, 3-dimethoxyoxirane (meso) and trans-2-butene yields only the racemic trans-2, 3-dimthyloxirane.



Stereochemistry of compounds containing nitrogen, phosphorous andsulphur

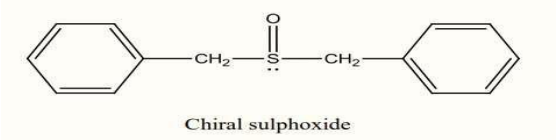
Single-bonded nitrogen is pyramidal in shape, with the non-bonding electron pair pointing to the unoccupied corner of a tetrahedral region. If the nitrogen in these compounds is bonded to three different groups, its configuration is considered to be chiral. Amines are approximately tetrahedral with the lone pair being assigned the lowest priority group. Pyramidal nitrogen is normally not configurationally stable. It rapidly inverts its configuration by passing through a planar, sp2 hybridized transition state, leading to a mixture of interconverting R and S configurations.

Phosphines, phosphine oxides, sulphoxides and amine oxides display chirality provided the ligands are non-equivalent. The phosphorus centre of phosphate ion and organic phosphate esters is tetrahedral, and is a stereocenter. Consider a chiral phosphine in which the electron lone pair and the phenyl group are in the plane of the paper while pentafluorphenyl is projectedin front of the plane and the methyl group is projected away. Absolute configuration can be assigned by viewing from below or from the side.



Chiral nitrogen Chiral phosphate Chiral sulphur

Sulphur exhibits pyramidal bonding in sulphoxides, sulphonium salts, etc many of which havebeen resolved.



Chiral sulphoxide

Absolute Configuration (R and S designations) for compounds containing nitrogen, phosphorous and sulphur.

UNIT-V: Stereochemistry-II:

Conformation and reactivity of acyclic systems, intramolecular rearrangements, neighbouring group participation, chemical consequence of conformational equilibrium - Curtin-Hammett Principle. Stability of five and six-membered rings: mono-, di- and polysubstituted cyclohexanes, conformation and reactivity in cyclohexane systems. Fused and bridged rings: bicyclic, poly cyclic systems, decalins and Brett's rule. Optical rotation and optical rotatory dispersion, conformational asymmetry, ORD curves, octant rule, configuration and conformation, Cotton effect, axial haloketone rule and determination of configuration.

Conformation Analysis

S. No.	Conformation	Configuration
1.	It refers to different arrangement of atoms or groups relative to each other and raiseddue to free rotation round a sigma bond.	It refers to different arrangement of atomsor groups in space about a central atom.
2.	The energy difference between two conformers is lower.	The energy difference between two configuration forms is large.
3.	Conformers are not isomers and they cannot be separated from each other.	These are optical isomers and can be separated from each other.
4.	These are easily inter converted to one another.	These are not easily converted to one another.

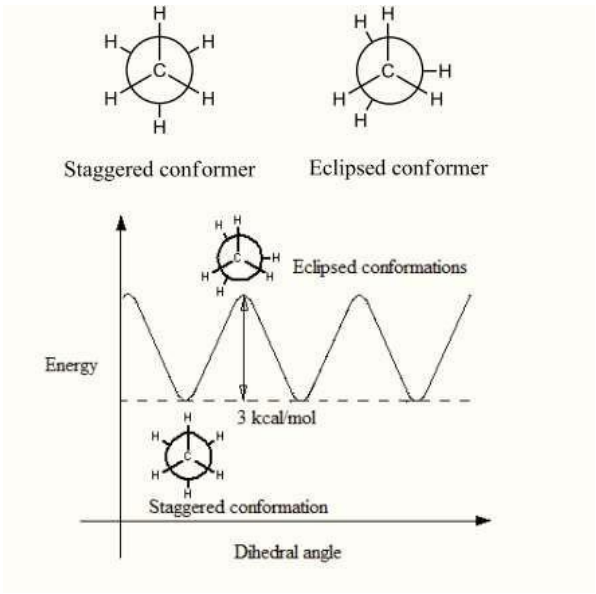
Conformational Analysis

The different spatial arrangements that a molecule can adopt due to rotation about σ bonds arecalled conformations and hence conformational isomers or conformers. The study of the energy changes that occur during these rotations is called conformational analysis. Conformers are stereoisomers that are separated by relatively low energy barriers (< 60 kJ/mol). A molecule canhave an infinite number of conformations, but only one configuration.

1. Conformational Analysis in Acyclic systems

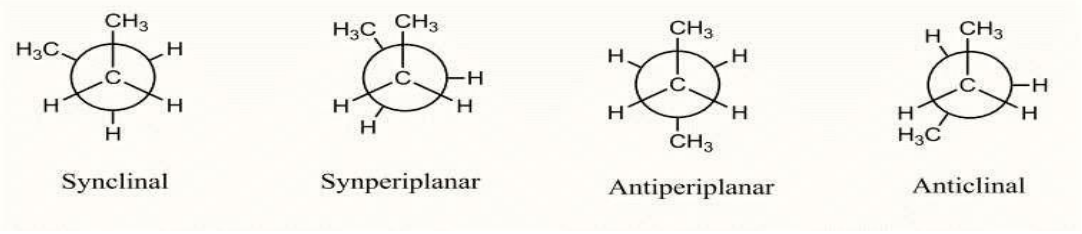
Conformational analysis of ethane

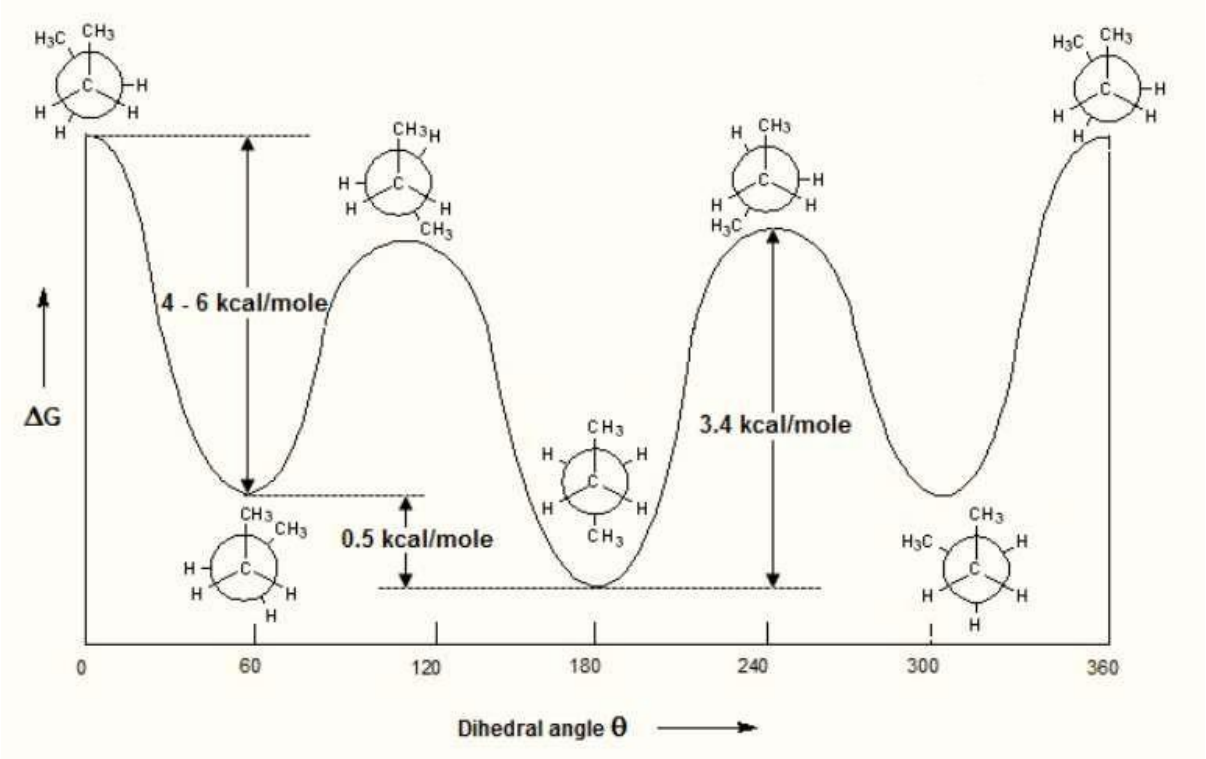
- There are two conformations of ethane – eclipsed and staggered conformations.
- The staggered conformations of ethane are the low energy forms while the eclipsed conformations represent transition states.
- The energy difference between the two conformers which represent the barrier of interconversion between two staggered conformers is about 3 kcal/mol.
- The activation energy for rotation about the C-C bond in ethane is small.



i) Conformational analysis of 1, 2-disubstituted ethane derivatives Butane

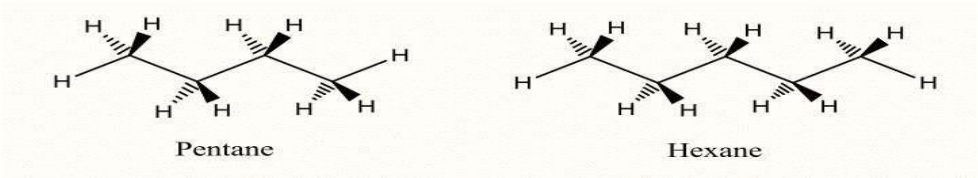
- For a compound of the type A-CH_2-CH_2-B, there are four extremes - A fully eclipsed conformation (**syn-periplanar**), partly eclipsed conformation (**anticlinal**), a fully staggered conformation (**anti-periplanar**) and another staggered conformation (**gauche or syn-clinal**).
- In ethane, all the staggered conformations are equivalent, but in butane, there are two different staggered conformations.
- The fully staggered form is the most stable because the methyl groups are far apart.
- Two groups are said to be gauche when the dihedral angle between them is 60^o.
- In the anti-conformation, the groups are maximum distance apart and the dihedral angle between them is 180^o.
- The methyl groups in the gauche conformation are close enough to each so that the vander Waal's forces between them are repulsive.
- The eclipsed conformation represents the energy maxima in the potential energy diagram.
- Eclipsed conformations not only have torsional strain, but also additional van derWaal's repulsions from the eclipsing methyl groups and hydrogen atoms.



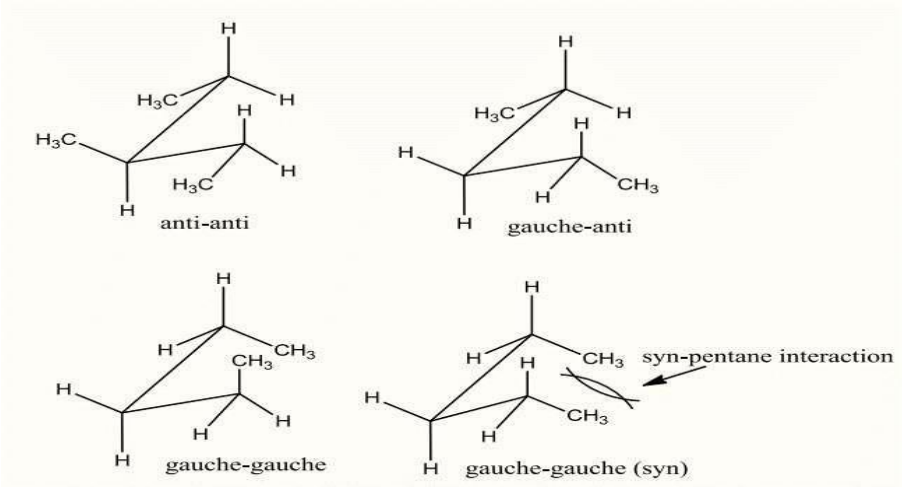


ii) Conformations of unsymmetrically substituted ethane n-pentane

- Pentane and higher alkanes have conformational preferences similar to ethane and butane.
- Each dihedral angle tries to adopt a staggered conformation and each internal C-C bond attempts to take on an anti-conformation to minimize the potential energy of themolecule.
- The most stable conformation of any unbranched alkane follows these rules to take onzigzag shapes:
-

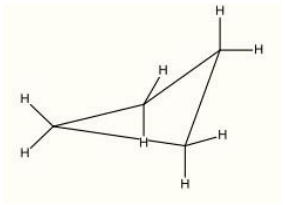


- In n-pentane, conformations about the C2-C3 and C3-C4 bonds.
- The most stable conformation is anti at both bonds, whereas less stable conformationscontain gauche interactions.
- One gauche-gauche conformer is particularly unfavorable because methyl groups arealigned with parallel bonds in close proximity. This conformation is called syn.
- This type of steric hindrance across five atoms is called a syn-pentane interaction.
- Syn-pentane interactions have an energetic cost of about 3.6 kcal/mol relative to theanti-anti conformation and are therefore disfavored.

- 

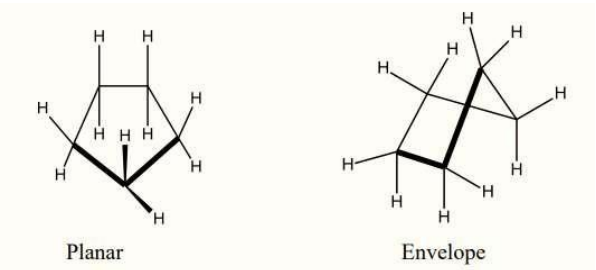
2. Conformational analysis of cyclic systems

i) Conformational analysis of cyclobutane

- In cyclobutane, the internuclear angle is 90º and the C-C bonds are not. There are fourstrained bonds and there are eight eclipsed hydrogen atoms.
- Cyclobutane exists in a non- planar conformation.
- One methylene group is bent at an angle of 25º from the plane of the other three ring carbons. In this conformation, some increase in bond angle strain is compensated by the reduction in the eclipsed hydrogen interactions.
- 

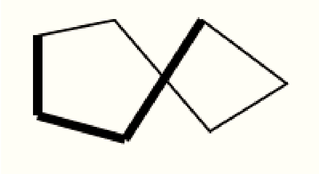
ii) Conformational analysis of cyclopentane

- In planar cyclopentane, all the hydrogens are completely eclipsed and there would betorsional strain.
- The molecule undergoes distortion to form a non-planar conformation.
- The structure has an envelope shape and the out of plane methylene group isapproximately staggered with respect to its neighbours.



iii) Conformational analysis of cycloheptane

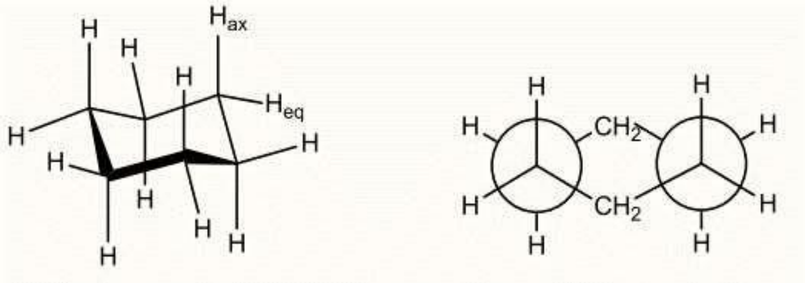
- It exists in non-planar conformation.
- The instability is due to torsional strain and van der Waal's repulsions betweenhydrogens across rings.
- The conformation is called the twist chair.



iv) Conformational analysis of cyclohexane

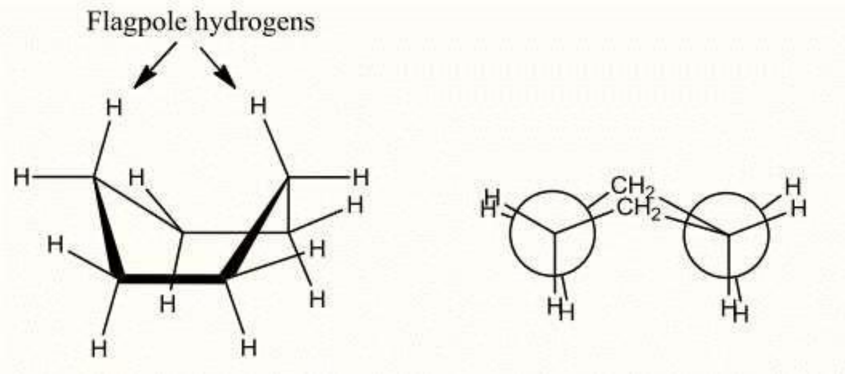
- **Chair Conformation**

  Cyclohexane exists predominantly in a non-planar puckered conformation called the CHAIR conformation. All the bonds are staggered. However, there is gauche interactions between neighbouring methylene groups leading to steric strain. Bond angle is 111^o. Dihedral angle is 56^o.



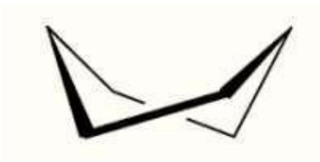
- **Boat conformation**

  There is complete eclipsing of the hydrogens. The inside hydrogens on C1 and C4 interferesterically in transannular interaction. The Newmann projection has two butane type unitseclipsed. Dihedral angle is 54^o. The two hydrogens are called flagpole hydrogens.

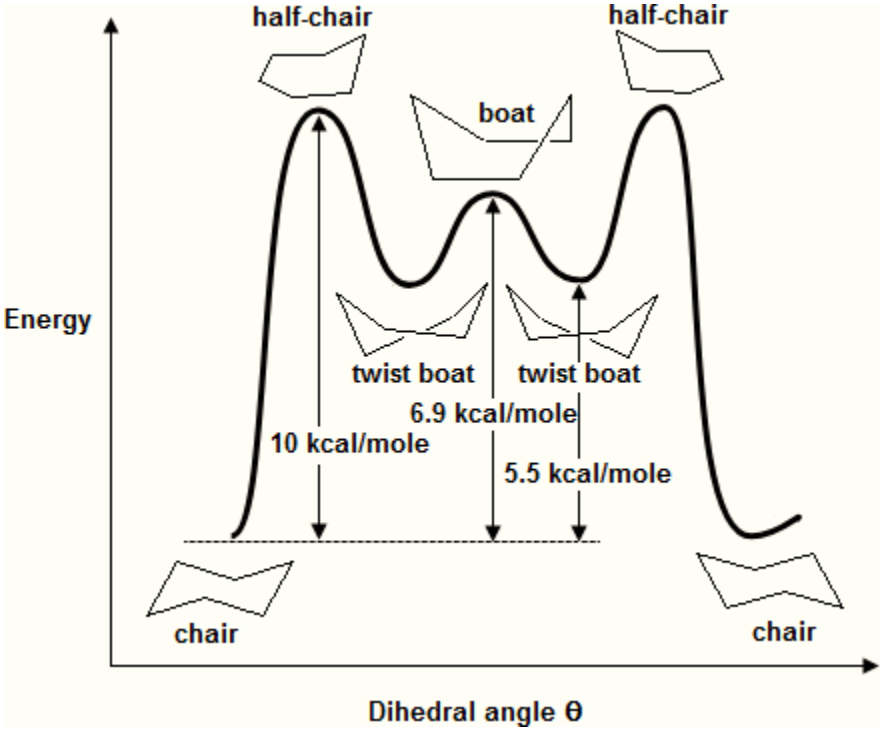


- **Twist Boat Conformation**

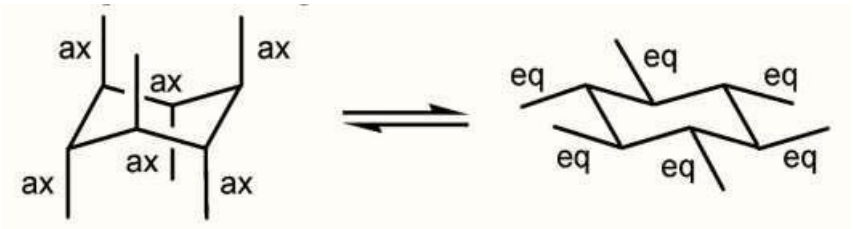
  The boat conformation is slightly stabilized by moving apart the C1 and C4 hydrogens.This is called the TWIST BOAT. The molecule is chiral.



- Energy diagram



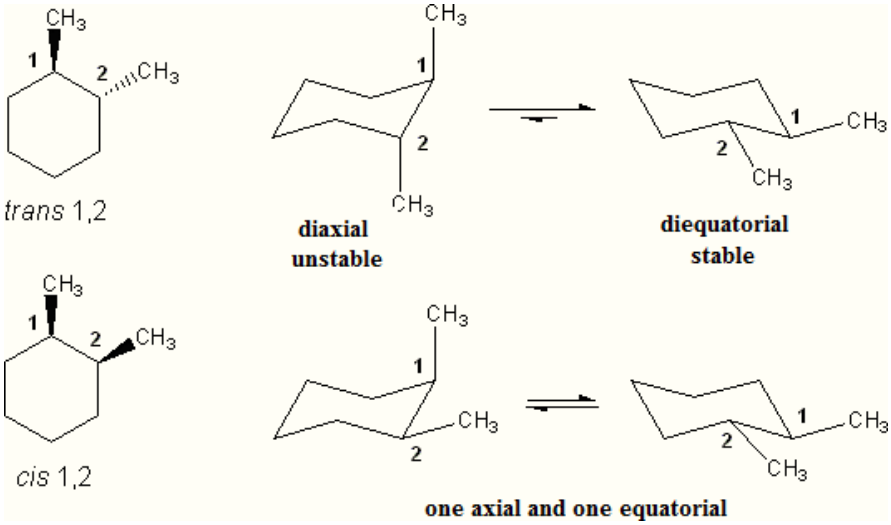
- The transition state conformation is called half chair.
- Ring flipping is fast and occurs ~100,000 times per second
- During inversion, the chair is converted into twist boat first which lies 5.5kcal abovethe chair.
- The full boat lies above the barrier separating two twist forms and is also a transitionstate.
- The twist boat passes through a second half chair to give the other cyclohexane.
- Equatorial and Axial bonds in the chair form of cyclohexane
- The 12 C-H bonds in the chair form of cyclohexane are of two types.
- Six of these are parallel to the three fold axis of symmetry of the chair.
- These are represented by vertical lines in the plane of the paper and are designated asaxial.
- The remaining six bonds are inclined at an angle of 109º.28' to the three fold axis andare called equatorial.
- Of the six axial bonds, three are above and three below.
- Similarly, three equatorial bonds point above and three below.



3. Conformation and Reactivity in disubstituted cyclohexanes

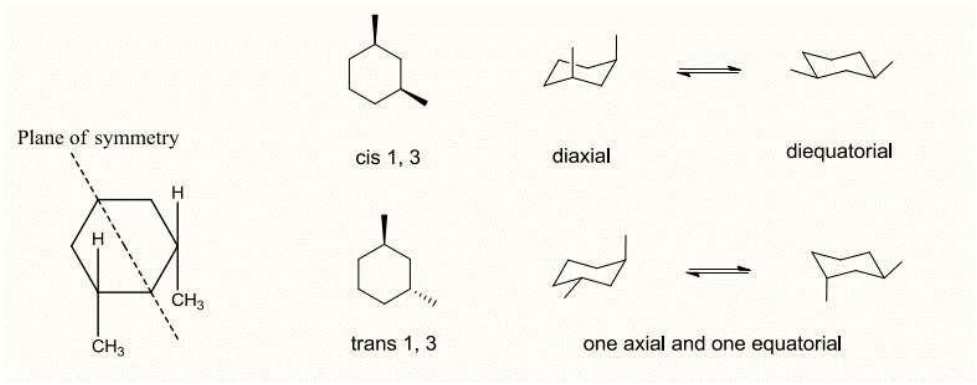
i) 1, 2-disubstituted cyclohexanes

- 1, 2-Dimethyl cyclohexane has 2 stereocentres, hence there are four isomers.
- The trans isomer exists as enantiomers where the equatorial conformer is the moststable.
- In 1, 2 substituents, the trans form has substituents in the two axial or equatorialposition.
- The cis form has substituents in one axial and one equatorial position.



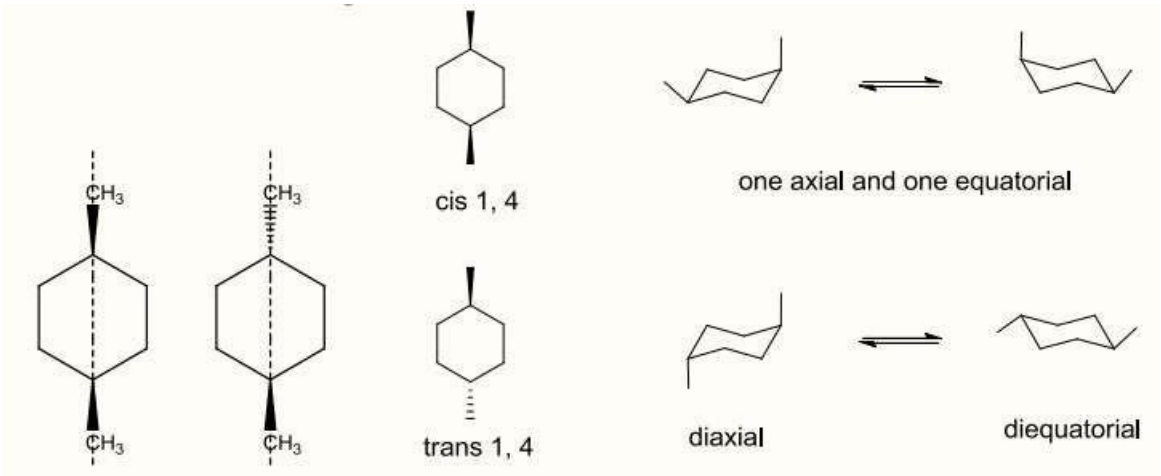
ii) 1, 3 – di-substituted cyclohexane

- 1, 3 – dimethyl cyclohexane has two stereocenters. Hence 4 isomers are expected ($2^n = 2^2 = 4$)
- However, only 3 isomers exist since the cis form has a plane of symmetry and existsas a meso compound.
- The trans isomer does not have a plane of symmetry and exists as a pair of enantiomers.
- In trans, one group is axial and the other equatorial. In cis, the two groups are eitherequatorial or axial.



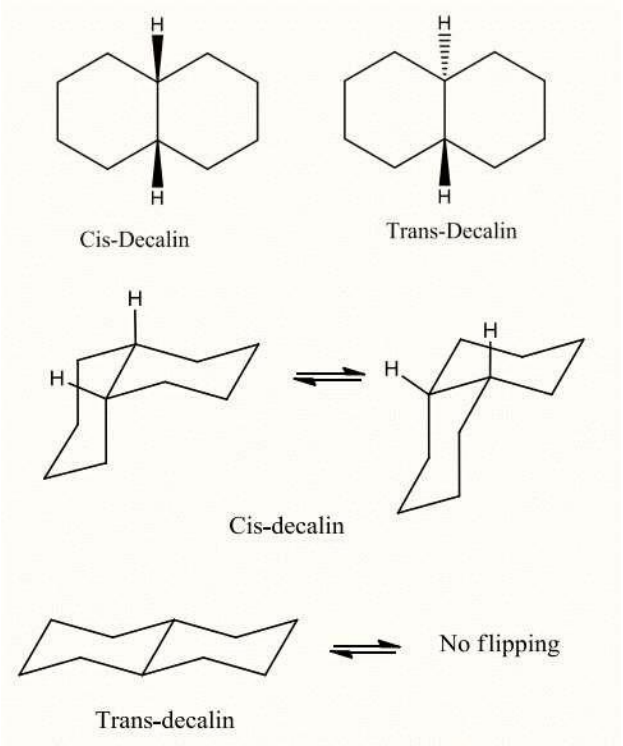
iii) 1, 4-disubstituted cyclohexane

- The cis isomer exists in two identical conformations (axial-equatorial and equatorial-axial) while the trans exists in two non-equivalent conformations (axial-axial and equatorial- equatorial).
- It has a plane of symmetry so both conformers are achiral.
- The cis and trans forms represent diastereomers.
-



4. Cis and Trans Decalins

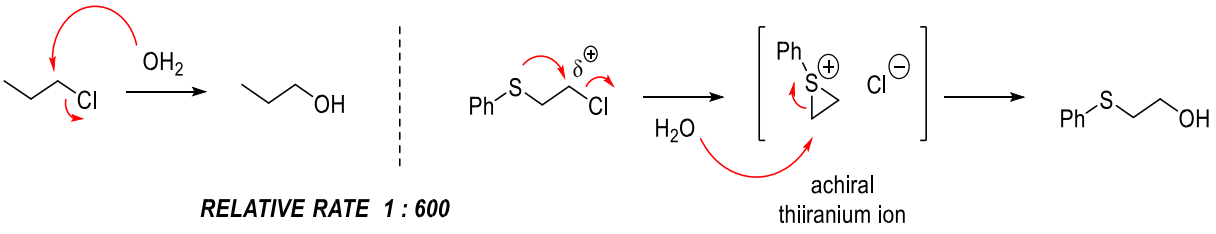
The compound bicycle [4.4.0] decane, known as decalin, exists in two diastereomeric forms. The cis and trans forms are diastereomers since they cannot be interconverted into each other by bond rotations. Decalin may be considered as a fusion of a four carbon chain connected to the chair form of cyclohexane. Trans decalin is fused with this 4-carbon chain in equatorial position while the cis decalin has equatorial-axial position.



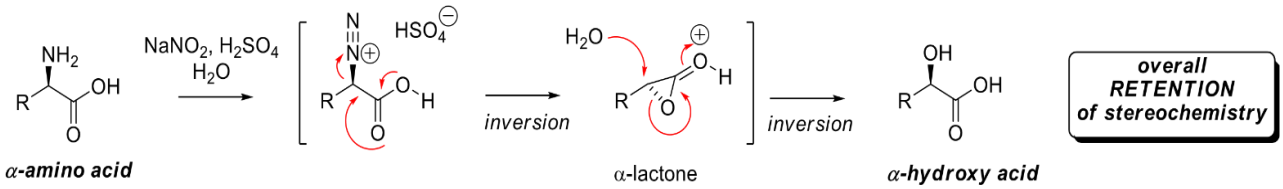
Cis decalin exists as an equilibrium between two enantiomeric all chair conformations which are interconvertible. Any substituent attached to the cis decalin system is free to adopt the equatorial conformation. Trans decalin has a unique and rigid conformation. Inversion is not possible. A substituent is forced to remain in a particular conformation which depends on its configuration.

Neighbouring group participation (NGP)

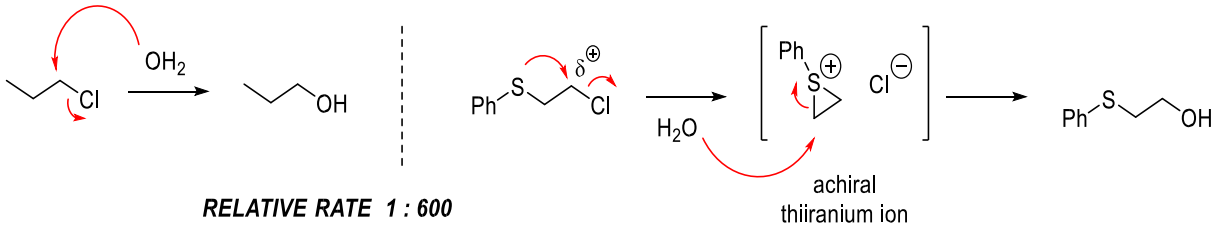
Groups remote from a reaction centre can participate in substitution reactions – Neighbouring Group Participation (NGP) (or anchimeric assistance): lone pairs of electrons, typically on N, O, S or Hal atoms interact with electron deficient/cationic centres – NGP is characterised by:



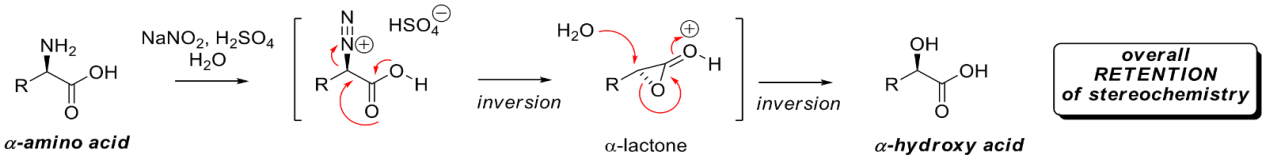
retention of stereochemistry (via double inversion):



Groups remote from a reaction centre can participate in substitution reactions – Neighboring Group Participation (NGP) (or anchimeric assistance): lone pairs of electrons, typically on N, O, S or Hal atoms interact with electron deficient/cationic centres – NGP is characterised by:
rate acceleration

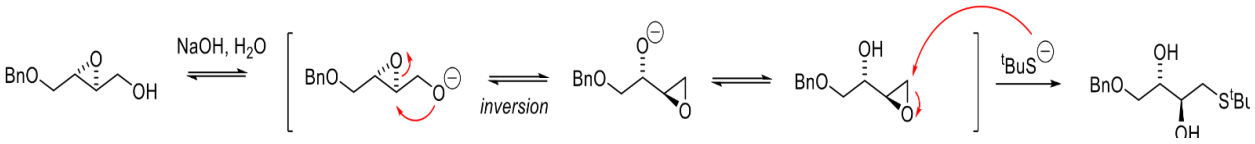


retention of stereochemistry (via double inversion):

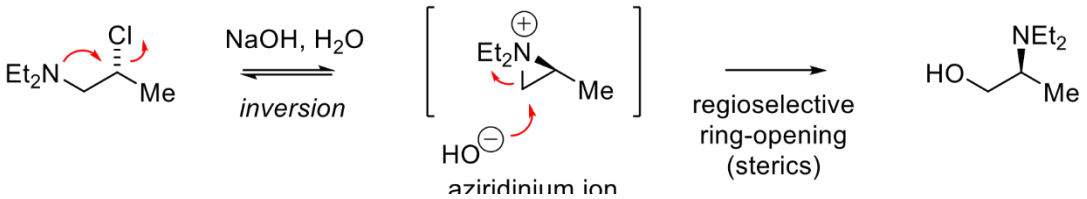


Rearrangements occur when the participating group ends up bonded to a different atom.

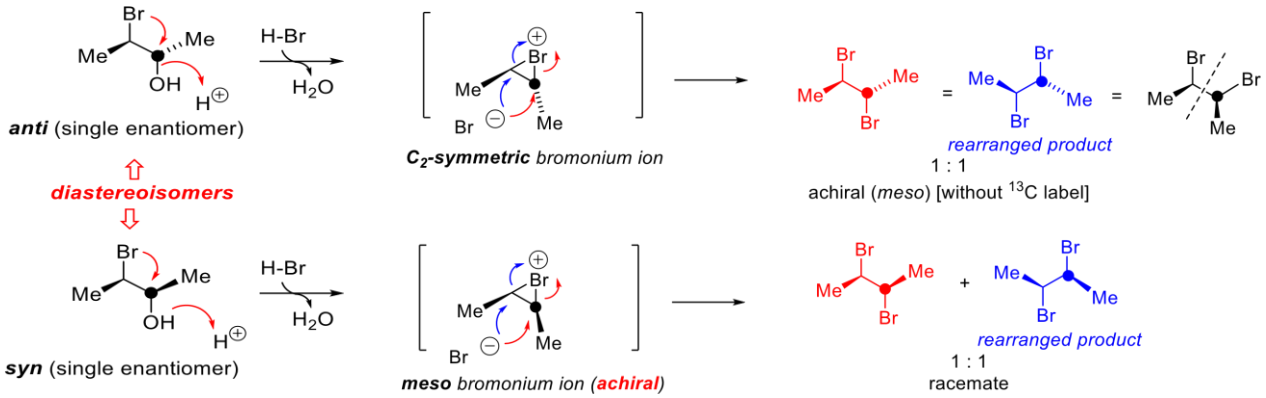
NGP with rearrangement: Payne rearrangements:



aza-Payne rearrangements

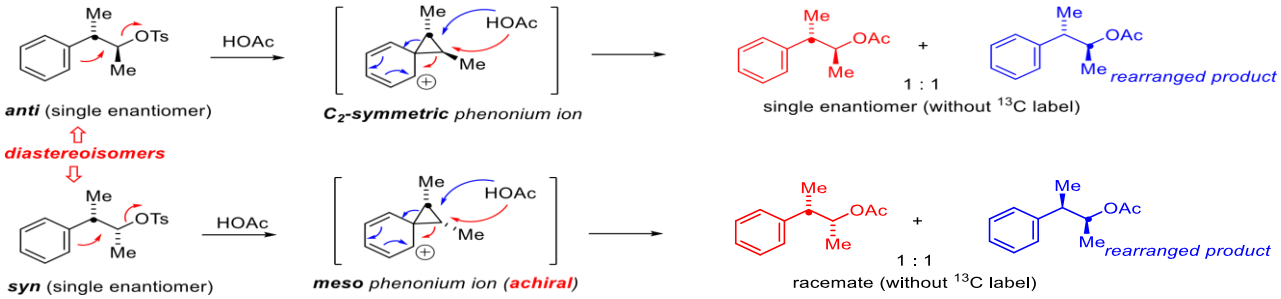


Bromonium ion rearrangements:

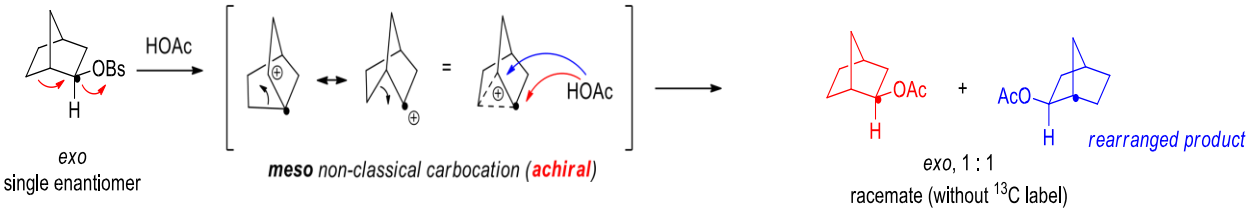


NGP with rearrangement – involvement of p& s bonds

NGP by aryl groups (& alkenes) results in related rearrangements via phenonium/arenium ions:



NGP by alkyl groups can also proceed via non-classical cations: Crystal structure of this carbocation finally obtained in 2013

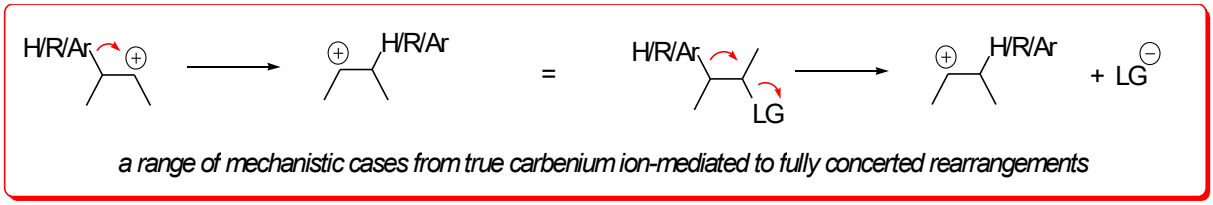


The rearranged products of the above "NGP" processes can also be regarded as having undergone rearrangements/shifts/migration.

NGP with 1,2-Rearrangements/Shifts/Migrations:

1,2-Rearrangements/shifts/migrations take place when an electron deficient/cationic centre is formed adjacent to a group capable of migration using a lone or bonding pair of electrons.

Participation of bonding electrons of aryl, alkyl and hydride groups are of particular importance:
– 1,2-Aryl-, alkyl- & hydride shifts towards carbenium ions/electron deficient carbon:

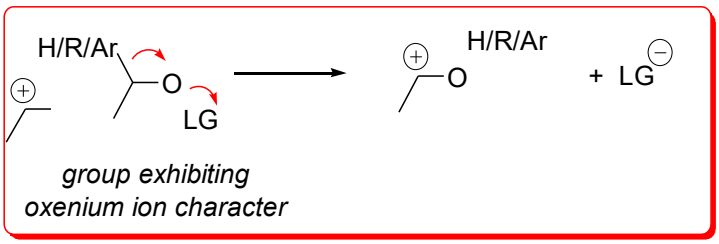


1,2-Aryl-, alkyl- & **hydride shifts** towards **electron deficient oxygen:**

H/R/ArH/R/Ar

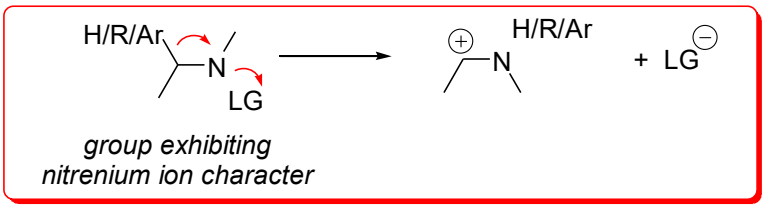
=

oxenium ion too high in energy to exist



1,2-Aryl-, alkyl- & **hydride shifts** towards **electron deficient nitrogen**

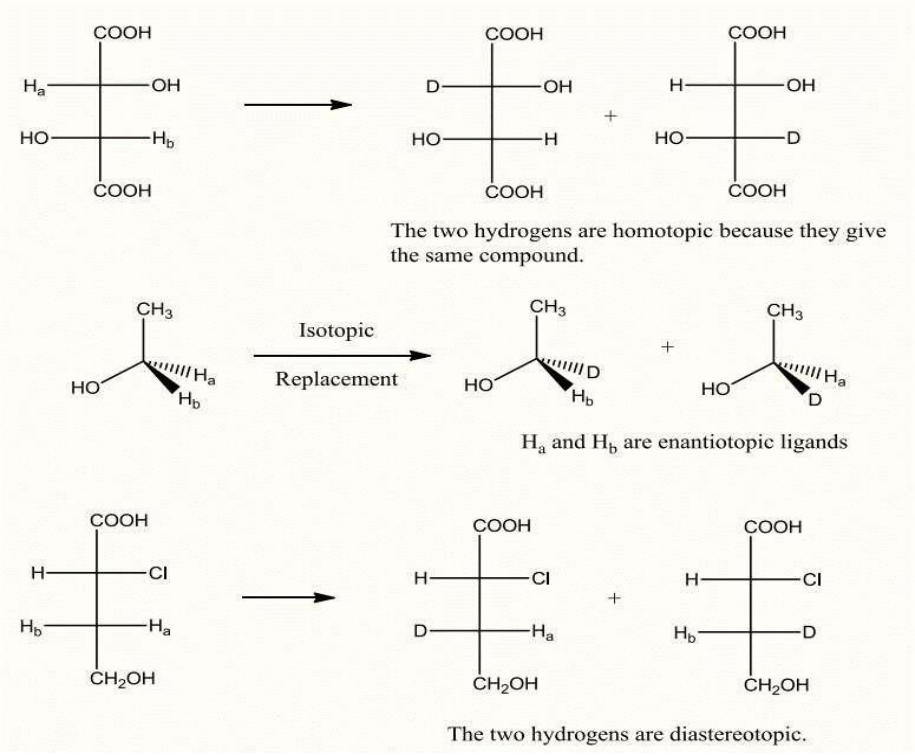
H/R/ArH/R/Ar



nitrenium ion too high in energy to exist

Topicity of Ligands and Faces

Topicity is the spatial relationship between constitutionally and configurationally identical atoms or groups of atoms in a molecule. The groups are homotopic to mean that they occupy equivalent places in the molecule as in propane. The groups may also be heterotopic which are further subdivided into enantiotopic and diastereotopic groups. Such alteration or replacement of one or other of the ligands leads to stereoisomeric compounds. The idea of topism is also applied to spaces on either face of a trigonal atom which may become occupied by an incomingatom or group and are again classified as homotopic, enantio or diastereotopic based on the environment generated by the ligands.

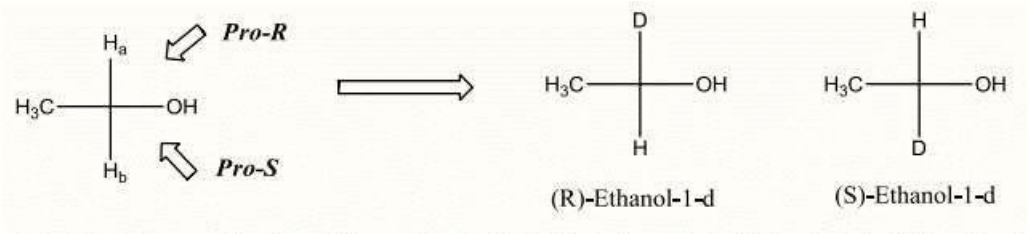


i. Nomenclature of Heterotopic ligands and faces

A. Pro-R and Pro-S nomenclature

To name the enantiotopic ligands at a prochiral centre, e.g. Ha and Hb in ethanol, the ligand to be labelled is arbitrarily assigned a higher priority over the other.

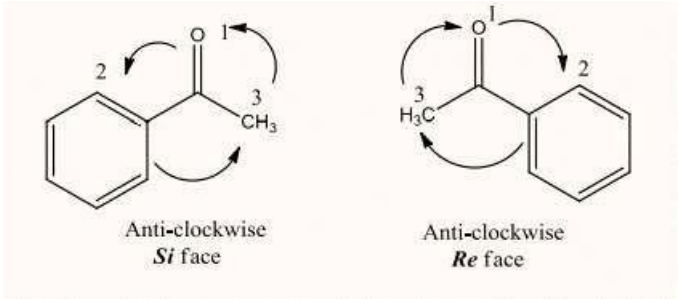
If Ha is preferred over Hb in the sequence rule, the sequence is OH > CH_3 > Ha > Hb, then the configurational symbol at the prochiral centre will be R, thus Ha is designated ***pro-R***. Thenby default, Hb becomes ***pro-S***.

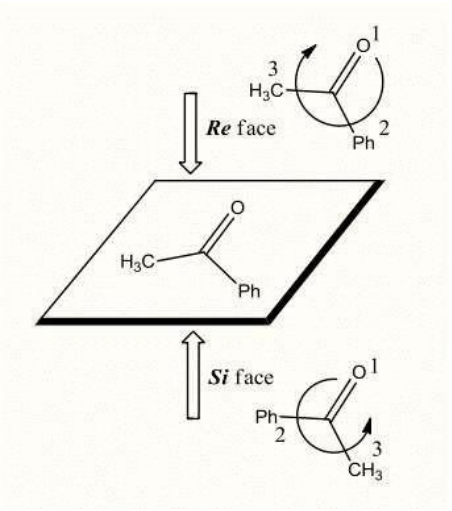


B. Heterotopic faces of carbonyl compounds (*Re, Si* nomenclature)

The groups and faces in a molecule which are enantiotopic or diastereotopic are collectively termed as heterotopic. In the case of carbonyl compounds when the groups R and R' are different, the two faces of the trigonal centre are different and the carbonyl carbon is called prostereogenic carbonyl carbon.

The faces of the carbonyl group are differentiated by the Re-Si nomenclature. The groups around the carbonyl group are given priorities as per Cahn-Ingold-Prelog's rules. If going fromthe group of highest priority to the group of lowest priority, the path is clockwise, the face is ***Re*** and if it is anti-clockwise, the face is ***Si***.



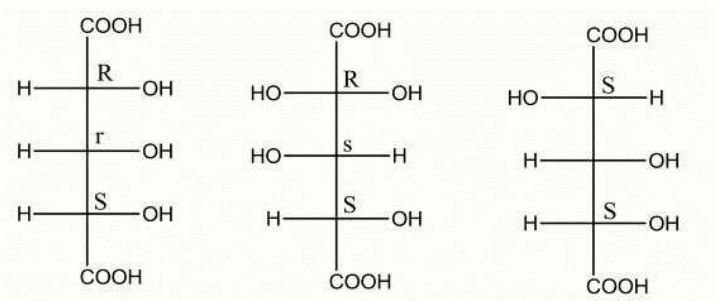


Summary of topic relationship

Topicity	**Substitution-addition criterion**	**Symmetry criterion**	**Difference**
Homotopic	Identical product	Ligands related through *Cn* and faces by *C2* axis	No difference by any method.
Enantiotopic	Enantiomeric products	Ligands and faces relatedthrough *σ*, *i* or *Sn*	Distinguishable in principle in chiral media (NMR) by chiralreagents, and enzymes.
Diastereotopic	Diastereomeric products	Ligands and faces not related by any symmetry elements	Distinguishable in principle by allmethods

C. Pseudo asymmetry

In compounds in which two or more chiral ligands of the central atom are constitutionallyidentical but have the opposite configuration the central atom is formally chiral because it has four different ligands. However, since such a compound also has a plane of symmetry it is, in fact, achiral as a whole. The central atom is termed a pseudo asymmetric center. The configuration of such atom is determined according to normal precedence rules assuming that R takes priority over S.

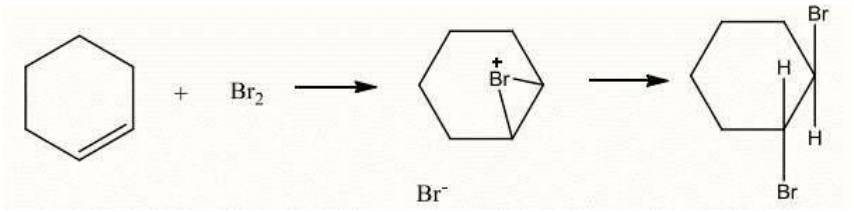


Stereoselective reaction

A reaction in which there is a choice of pathway, but the product stereoisomer is formed due to its reaction pathway being more favourable than the others available is called a stereoselective reaction. When this selectivity results in the formation of an excess of one enantiomer over the other from an achiral or racemic substrate, it is sometimes called asymmetric induction.

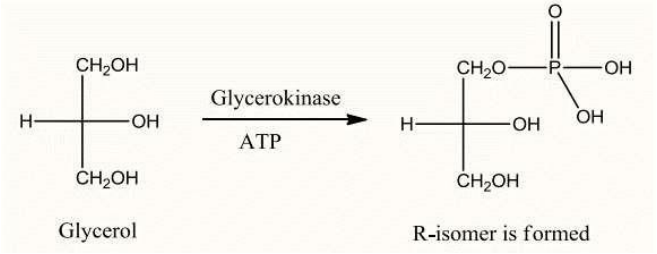
i. Bromination of cyclohexane

Cyclohexane can only exist in one stereoisomeric form with cis geometry of the double bond. When cyclohexene is brominated, the product is one stereoisomeric product trans 1,2-dibromocyclohexane is formed. No cis isomer is formed.



ii. Stereoselectivity of enzymes

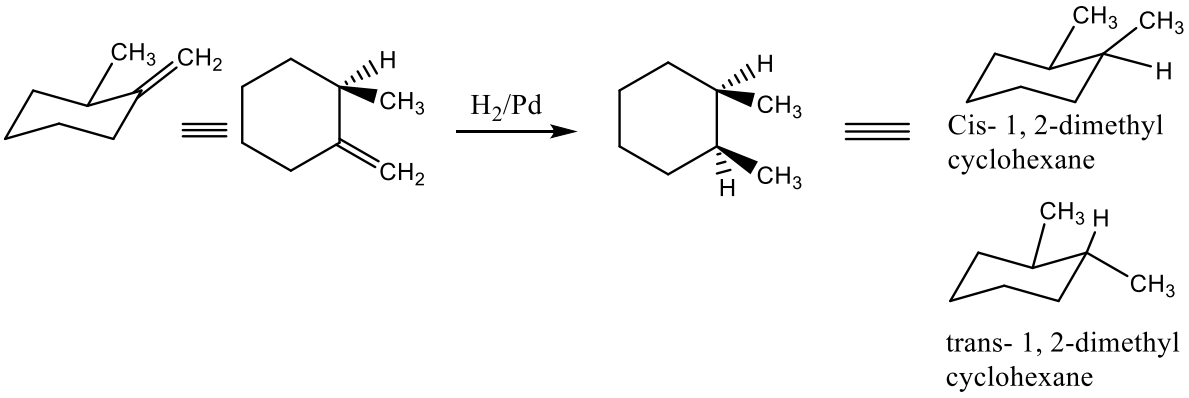
The enzymes when in contact with prochiral molecules react only with one of the enantiotopic ligands or faces, a property called stereoselectivity. E.g. glycerol undergoes phosphorylation exclusively at the pro-R hydroxymethylene group with ATP in the presence of enzyme- glycerol kinase.



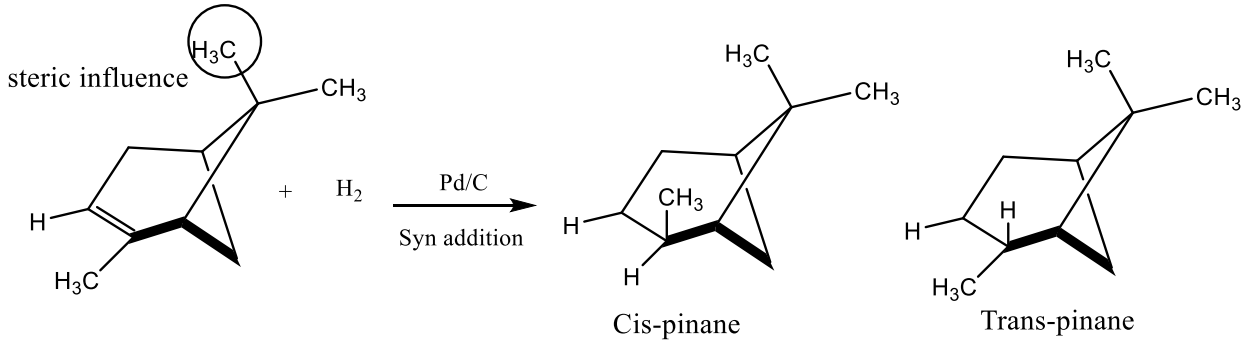
iii. Hydrogenation (syn addition) of a chiral alkene

A reaction which introduces a second stereocenter into a starting reactant which already has one may not give equal quantities of two possible diastereomers.

E.g. 1: The catalytic hydrogenation of 2-methyl (methylene) cyclohexane gives cis and trans-1, 2-dimethyl cyclohexane, but in unequal amounts. The major product is the cis and the minorproduct is the trans. The less hindered face of the double bond approaches the catalyst surface,and this is the face to which hydrogen is added – syn addition.



E.g. 2: The catalytic hydrogenation of α-pinene is also a stereoselective syn addition of hydrogen. It depends on the mode of alkene approach to the catalyst surface. The two hydrogens are added on the less hindered side of α-pinene. Cis-pinane is formed exclusively.



iv. Asymmetric synthesis

If an enantiomer or diastereomer is to be synthesized, then either the reactant or the reagent orthe solvent must be the pure enantiomeric form. The chiral agent must play an active part in the reaction and has to be integral to the transition state so that two diastereoisomeric transitionstates are formed. Hence, one stereoisomer is produced more rapidly than the other. Thus, asymmetric synthesis involves competing reactions with diastereoisomeric transition states which takes place at different rates.

There are several categories of asymmetric synthesis

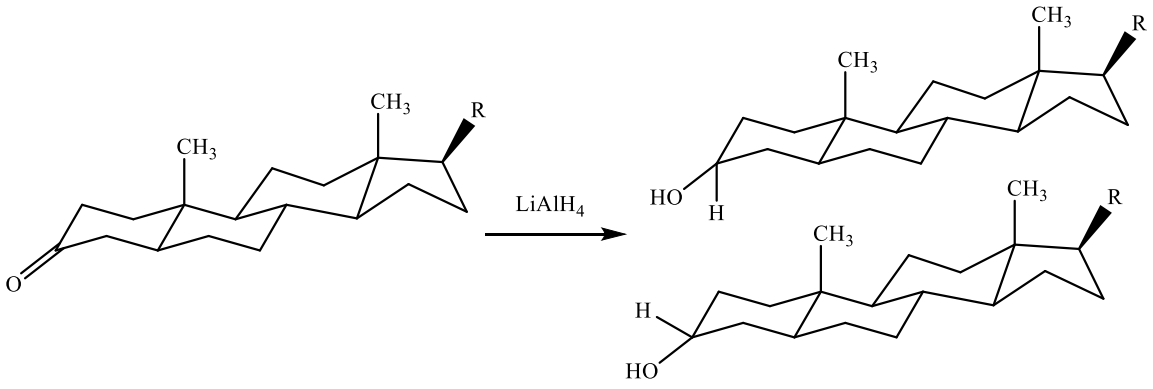
- The use of chiral substrates
- Diastereoselectivity in Aldol reactions
- The use of chiral auxiliaries
- Use of chiral reagents and chiral catalysts

a. The use of chiral substrates

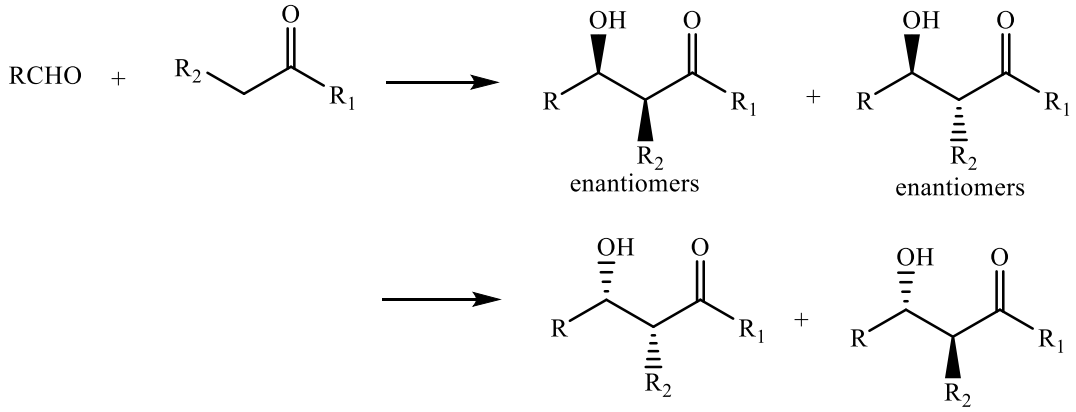
Stereoselective reduction of cholestan-3-one (Diastereoselectivity)

Cholestan-3-one on reduction with lithium aluminium hydride gives exclusively the equatorial alcohol by attack of the reagent from the less hindered face of the molecule. The alcohol I is the only product since it is more stable than II since II has sterically hindered beta face due toangular methyl groups.

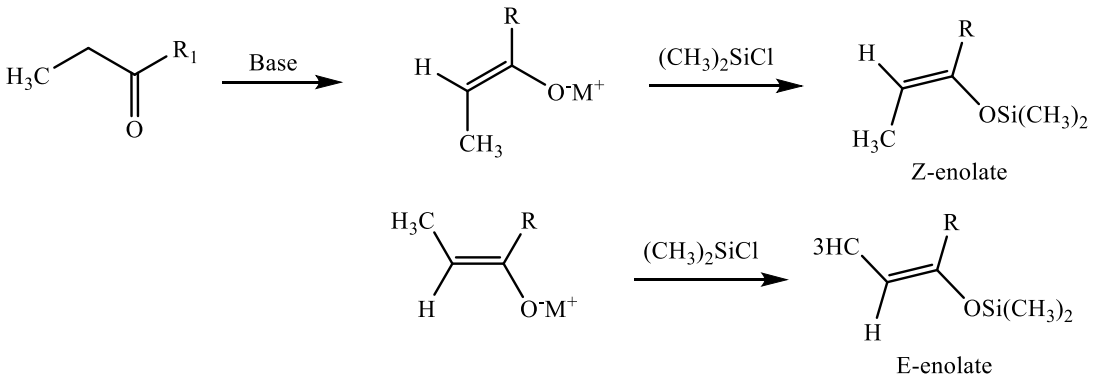
b. Diastereoselectivity in Aldol reactions (Directed Aldol reaction).



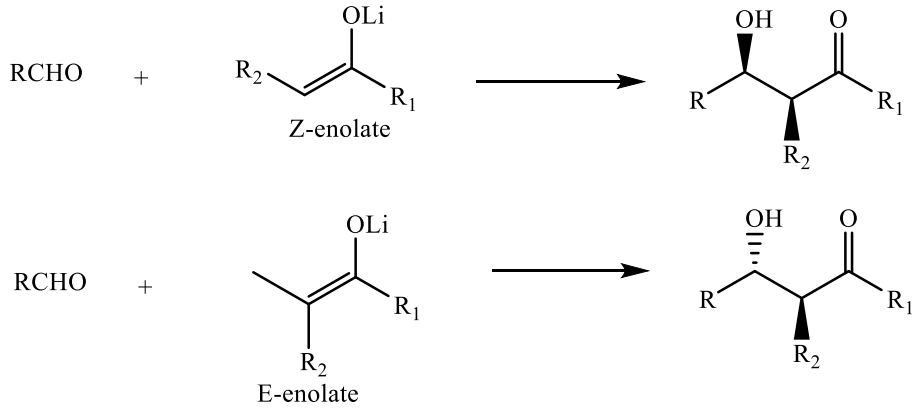
An aldol reaction creates two stereocenters from achiral starting materials. Thus syn and anti diastereomers are produced, each a pair of enantiomers.



Diastereoselectivity in aldol reaction is achieved by employing the enolate of desired stereochemistry.



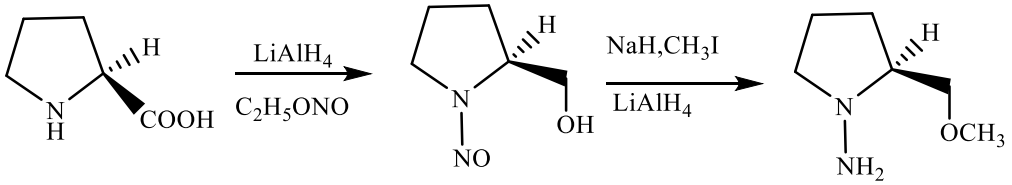
These are separated and purified and converted into pure Z or E enolate with fluoride ions. Z-enolates give mainly syn aldols while the E-enolates give anti aldols.



c. Use of chiral auxiliaries

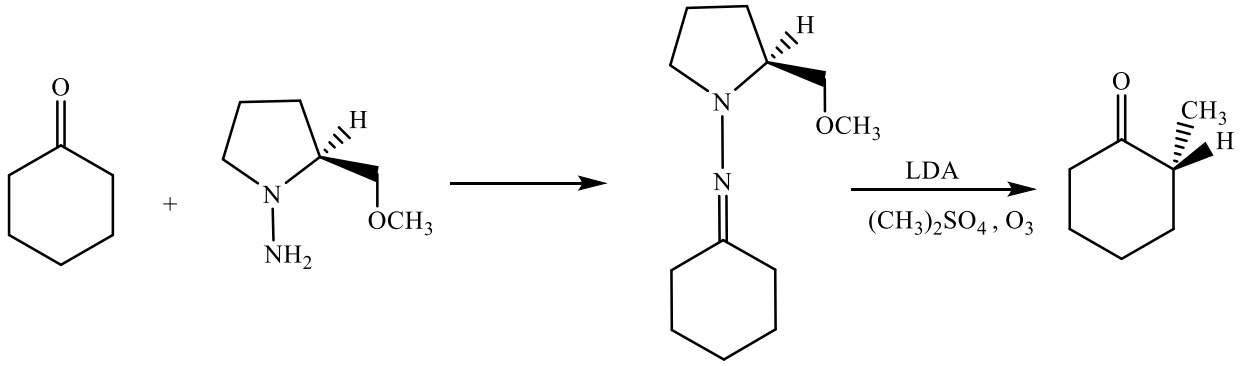
During asymmetric synthesis, a chiral auxiliary is attached chemically to the achiral substrate to give a chiral intermediate. This is followed by the reactions of asymmetric synthesis. Attheend, the chiral auxiliary is removed.

Enantioselective alkylation of aldehydes and ketones via chiral hydrazones



SAMP and its enantiomer RAMP are prepared from S- and R- prolines respectively. They beara chelating methoxy group and are used as chiral auxiliaries in enantioselective alkylation of aldehydes and ketones.

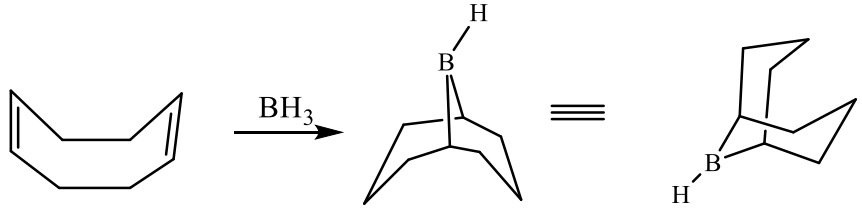
Conversion of cyclohexanone into 2-methyl cyclohexanone.



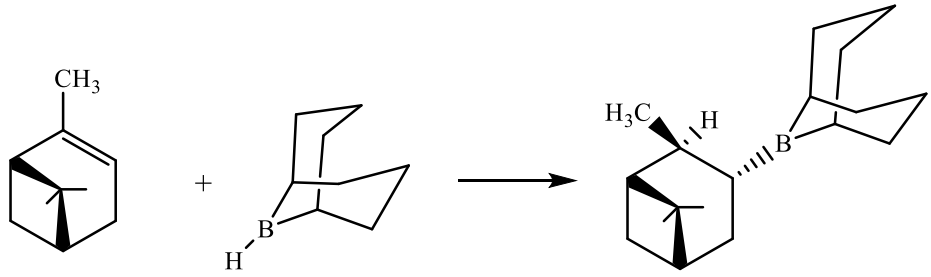
d. Use of chiral reagents and catalysts

Asymmetric reduction using chiral trialkylboranes (enantioselective reduction of aldehydes and ketones)

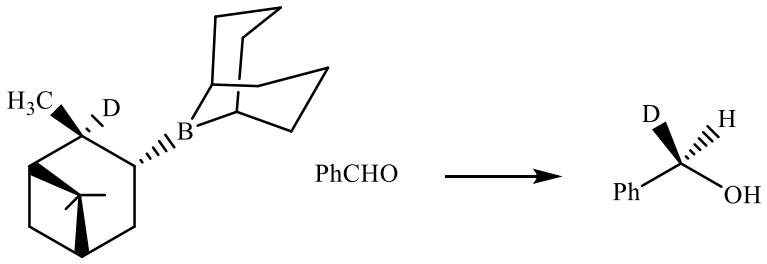
Useful reagents: **9-BBN (9-borabicyclo (3.3.1) nonane).**



Alpine borane



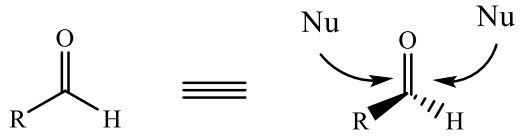
Hydroboration of α-pinene with 9-BBN gives alpine borane, which is used as a chiral reagent.It reduces a variety of carbonyl compounds. Monodeuteriated and chiral primary alcohols canbe made by using this reagent.



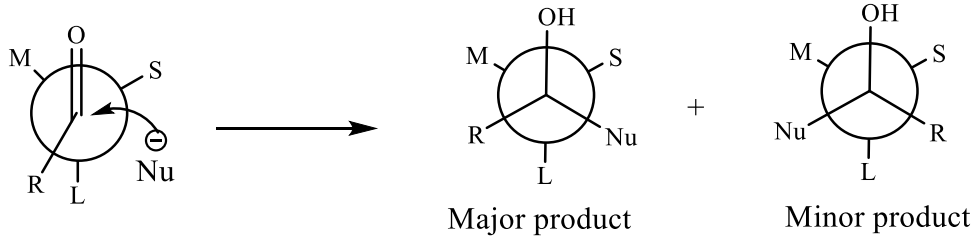
Cram's Rule, Felkin-Ahn Modification and Prelog's Rule

In carbonyl compounds, the carbonyl carbon and the three other atoms attached to it would bein one plane. A nucleophile attacking the carbonyl carbon could attack from either side of thisplane with equal ease.

E.g. benzaldehyde. The phenyl group is also flat. Nucleophilic attack on benzaldehyde could take place from either side with equal ease. Since a new asymmetric center is now created by this reaction, both enantiomers could be formed with equal ease, resulting in a racemic mixture.



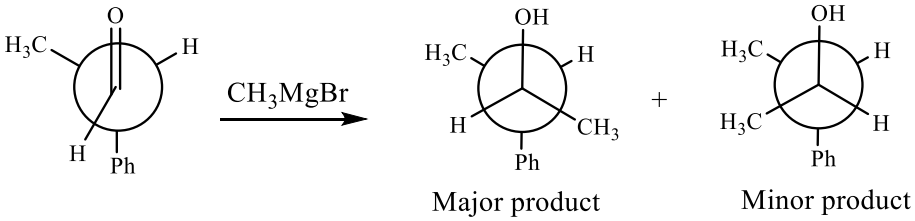
In complex organic molecules, the nucleophile would experience more steric hindrance from one side, leading to unequal synthesis of the two enantiomers. Hence, reaction would take placein the conformation having the least steric strain.



A. Cram's Rule

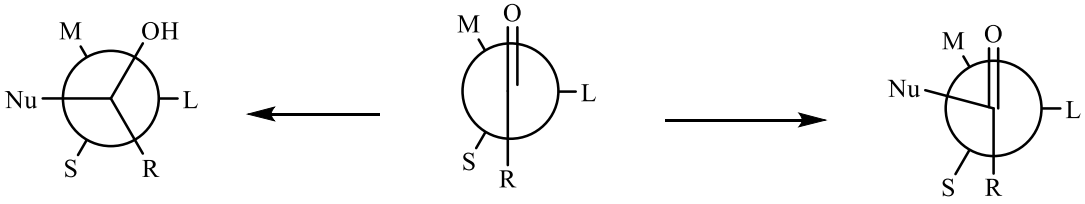
- The existing asymmetric center would have a Small, Medium and Large group, denotedS, M and L respectively.
- In the reactive conformation, the carbonyl group would orient itself in such a way thatit will rest between the Small group and the Medium group.
- The attacking nucleophile would prefer to attack from the side of the small group,resulting in the predominant formation of one diastereomer in the product.

B. Felkin-Ahn modification



Major product Minor product

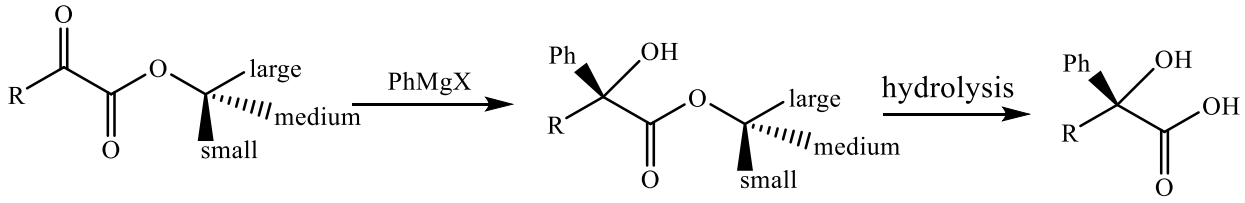
- The Felkin-Ahn model differs from Cram's rule in the conformation adopted by thecarbonyl compound.
- The C-L bond is positioned perpendicular to the carbonyl group.
- This arrangement removed unfavourable eclipsing interactions between L and R.
- The nucleophile approaches the carbonyl carbon in a plane perpendicular to that of the –CO- fragment from the side opposite the C-L bond and at an obtuse angle with C=O.



major product preferred not preferred

C. Prelog's Rule

An extension of Cram's idea of reactive conformation is the Prelog's Rule. The rule has been applied for asymmetric synthesis of α-hydroxyl acids and for assigning the configuration of secondary and tertiary alcohols.

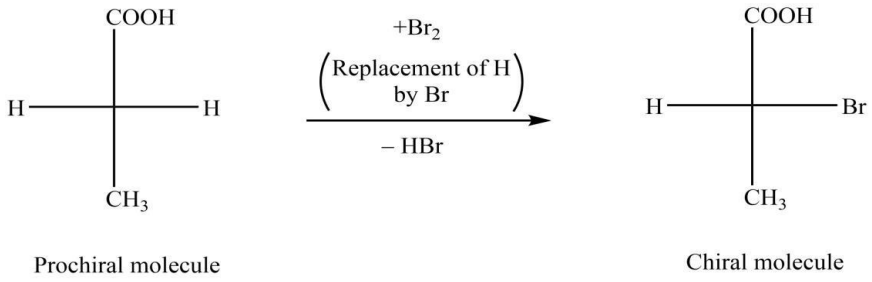


The Grignard reagent approaches the electrophilic carbon from the side of the small group (S) rather than from the side of the medium group (M). Thus, the major product is formed by attackfrom this side. This on hydrolysis gives the acid.

Prochirality

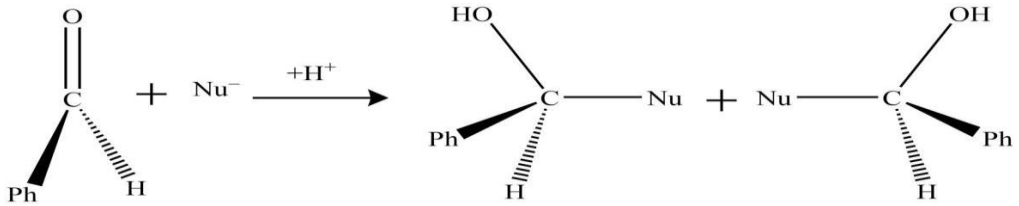
The prochirality in stereochemistry may simply be defined as the property of a molecule by which can be converted from achiral to a chiral entity in a single step, and such molecules are called as prochiral molecules.

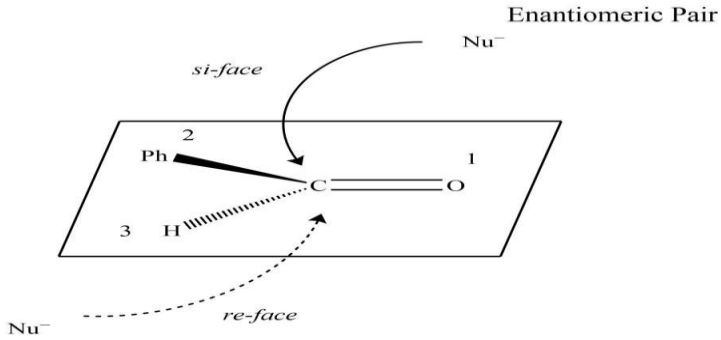
This can be understood by taking the example of propanoic acid where two identical substituents are attached to an sp^3-hybridized carbon atom, and the pro-R and pro-S descriptors are used to differentiate between the two.



In other words, if we promote the pro-R substituent to a higher priority than the other identical substituent, we will get an R chirality center at the sp^3-hybridized carbon, and vice-versa is also true.

An sp^2-hybridized carbon atom with trigonal planar coordination can also be converted to a chiral center if a group is attached to the '*re*' or '*si*' face of the organic molecule under consideration. For instance, imagine the case of benzaldehyde where the attack from the front and rear sides results in an enantiomeric pair.





The face will be labelled 're' if the substituents priority decreases in clockwise order at the trigonal atom when looking at that face will be labelled 'si' if the substituents priority decreases in anticlockwise order at the trigonal atom when looking at the face. Also, the designation of the resulting optically active carbon as S or R is a function of the priority of the incoming substituents.

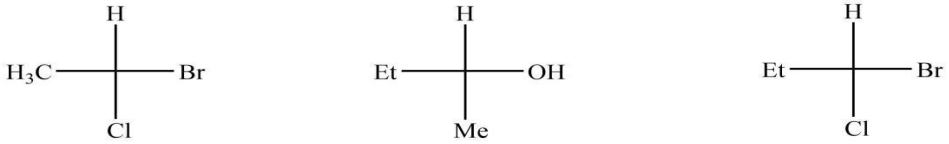
Furthermore, if an achiral species can be converted to a chiral one in two steps, it will be called a prochiral.
converted to a chiral one in two steps, it will be called a prochiral.

Types of Chirality

Depending upon the geometrical profile of molecular species, chiral compounds or chirality can primarily be divided into four categories as given below.

1. **Chirality arising from a center (chiral center):** This type of chirality arises when all the four groups around tetrahedrally coordinated carbon atom become different. In other words, an

organic molecule can no longer be superimposed on its mirror image if it has a center with all different groups.

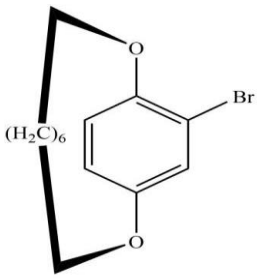


Examples of organic molecules with this type of chirality are CH_3-CHClBr, but-2-ol and 1-bromo-1-chloropropane.

2. Chiral arising rom an axis (chiral axis): this type of chirality arises when a tetrahedrally coordinated prochiral molecule becomes chiral by extending the centre along an axis . in other words, a prochiral moleculecan no longer be superimposed on its mirror image if its centre has been extended to a line with same groups at different ends.

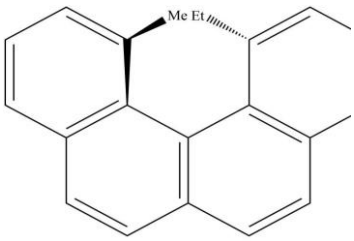
Examples of organic molecules with this type of chirality are (R) penta-2,3-diene and 2,2'-dimethyl-1,1'-biphenyl (a biphenyl derivative).

3. **Chirality arising from a plane (chiral plane):** This type of chirality arises when relacing a group in a plane makes the molecule chiral. In other words, an organic molecule can no longer be superimposed on its mirror image if the replacement of a particular group induces chirality.



Example of organic molecule wilth this type of chirality are ansa compounds like 13-bromo-1,10-dioxa[8]paracyclophane.

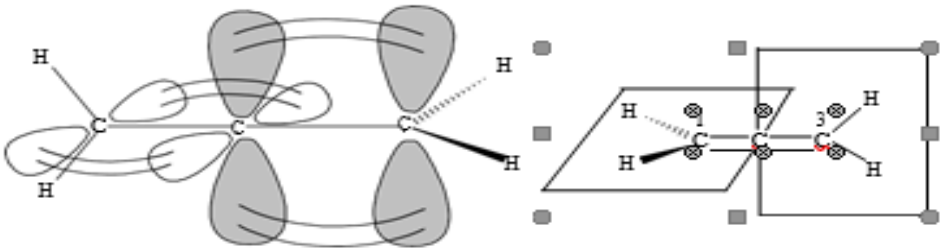
4. Chirality arising from a spiral (helical chirality): this type of chirality arises when the molecules has a helical structure. In other words, an organic molecule can no longer be superimposed on its mirror image if its geometry resembles a helix.



Example of organic molecule with this type of chirality are helical compounds like 1-ethyl-12-methylbenzo[c]phenanthrene.

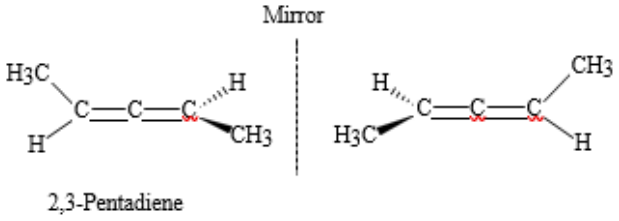
Optical Isomerism in allenes

Allenes are compounds, having the structure deC=C=Cab. In an allene, middle carbon atom of the cumulative double bond is sp hybridized and so it is linear, and the two outer carbon atoms are sp^2 hybridized and trigonal. The central, sp hybrid carbon atom must therefore use different p orbitals to form the pi bonds with the two outer carbon atoms. The two unhybridized p orbitals on a sp hybrid carbon atom are perpendicular so the two pi bondsmust also be perpendicular as follows.



In allene (1,2-propadiene) planes defined by H(C1) H and H (C3) H are mutually perpendicular. Allene is achiral, it has two planes of symmetry.

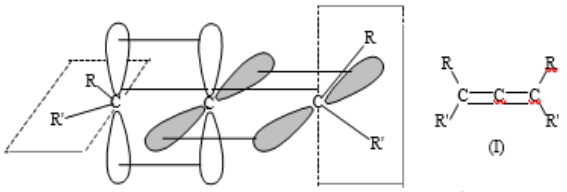
In the spatial arrangement of the cumulative double bonds of allene, the four substituents of the allene grouping are situated at the apexes of an imaginary tetrahedron. In order to produce molecular dissymmetry it is not necessary for all of the substituents to be different. It is sufficient to have each terminal substituents should be different.
Therefore, allene of the type ABC = C = CAB (A ≠ B) as in 2,3-pentadiene is chiral, (not superimposable on its mirror image) and exist as enantiomers despite the absence of a asymmetric center. Thus, in allenes there is restricted rotation giving rise to perpendicular dissymmetric planes.



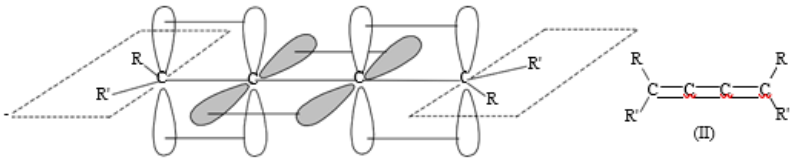
2,3-Pentadiene

Chiral allene 2,3-pentadiene have a C_2 axis. The interchange of groups at eitherend reverses the chirality results in an enantiomer

Hence allene itself is achiral and when different substituents are present at each end, the substituted allene becomes chiral. Thus the cumulated bonding systems (compounds with twoor more successive double bonds) with an even number of double bonds do not have a plane of symmetry or a centre of symmetry and therefore, must show optical isomerism and can be resolvable into enantiomers.



A cumulene (even number of double bonds) shows enantiomerism if R ≠ R'



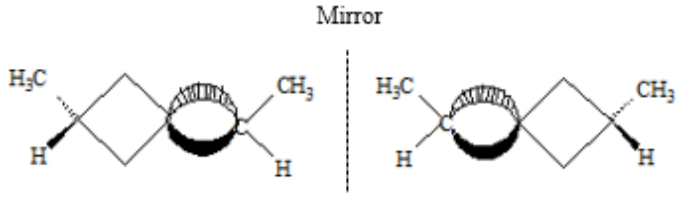
A cumulene (odd number of double bonds) shows geometrical isomerism

Interestingly the compounds with odd number of cumulated double bonds display Z-E (geometrical) isomerism and do not show enantiomerism. When the allene chain of compound I, is extended by one more double bond (introduction of another sp-hybridized carbon atom) then gets a system II, in which the substituted groups at the two ends of the cumulated chain now lie in the same plane and geometrical isomerism is shown.

Optical isomerism of Spiranes

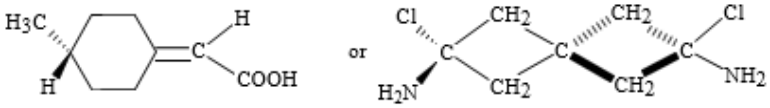
The name *"spirane"* is derived from the Latin *spira* meaning twist or whorl, implies that spiranes are not planar; it is because of their nonplanarity that gives rise to their chirality.

When one or both of the double bonds in allenes are replaced by one and two rings, the resulting systems are respectively known as alkylidene, cycloalkanes and spiranes as shown below.



1-Ethylidene-3-methyl cyclobutane

Alkylidenecycloalkanes (a distinct class) are also chiral (like allenes), if the pair of geminal substituents are non equivalent due to the presence of stereoaxis these can have C_2 axes as the sole symmetry element.



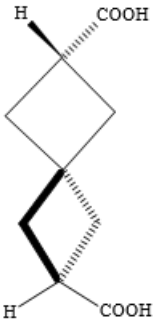
1-Methyl cyclo hexylidene-4-acetic acid (Alkylidene cycloalkane)

Spiranes

The replacements of one double bond in an allene by a ring gives alkylidene cycloalkanes (sometimes referred to an hemispiranes) does not alter the basic geometry of the system of allenes and suitably substituted compounds, therefore, exist in optically active forms Related compounds in which sp^2-carbon are replaced by nitrogen, e.g., compound has also been obtained as Enantiomers.

Among the chiral spiranes one may find three types

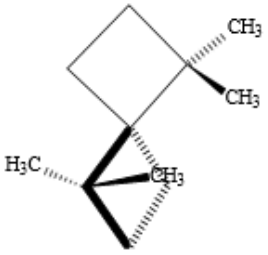
1) **A**, which definitely displays axial chirality similar to that of allenes and alkylidenecycloalkanes:



Spirane Type **A**

(S)-Spiro[3,3]heptane-2,6-dicarboxylic acid

2) **B**, which displays central rather than axial chirality
3) **C**, which contains chiral center according to Cahn-Ingold-Prelog Priority rules (CIP)



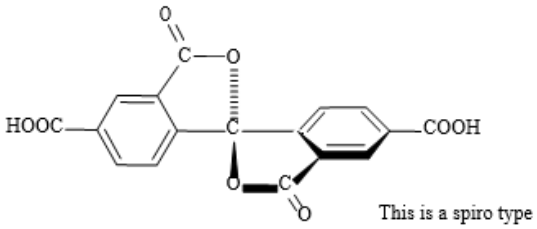
Spirane Type **C**

(R)-1,1,5,5-tetramethylspiro [3,3]heptane

Spiro[2,2]pentane

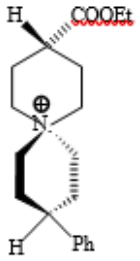
The most strained saturated spirane, spiro[2,2]pentane, was first synthesized in 1896 by Gustavson

Chirality of spiranes was demonstrated by Mills and Nodder (1920) by resolution of the following **spirodicarboxylic acid.**



This is a spiro type

A spiro type A was resolved 5 years later by Mills and Warren.

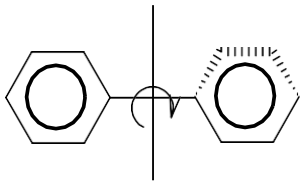


This is a Spiro type **A**

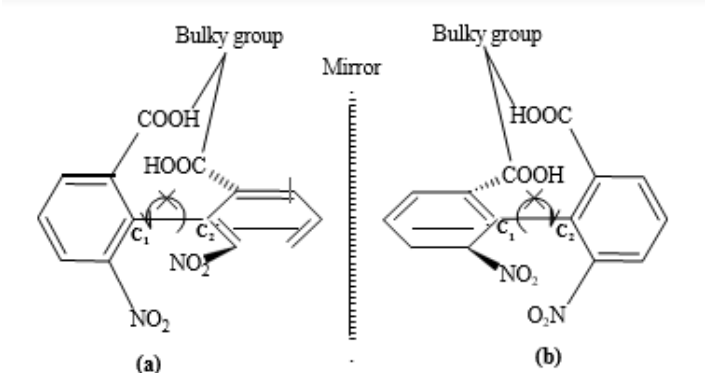
Please notice that the spiro center in this compound is a quaternary nitrogen rather than a carbon atom.

Optical isomerism in biphenyls (Atropisomerism)

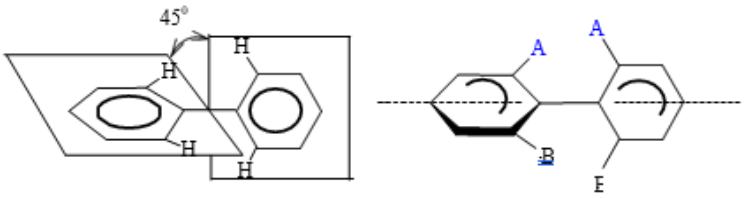
Biphenyl is optically inactive the reason is molecules show plane of symmetry and there isfree rotation along C-C bond of two phenyl groups.
At ortho-ortho positions, if there is a bulky group then the free rotation is restricted along C_1-C_2.



This type of enantiomerism was first discovered by Christie and Kenner (1922) in the case of 6,6'-dinitro-2,2'-diphenic acid, which they were able to resolve: Hence the isomer (a) isnot super imposable on (b). Hence (a) and (b) are enantiomers.



In solution two rings of biphenyl are twisted (450) due to repulsion of O-hydrogens this repulsion enhances with larger O-substituents which arrests the rotation. Chirality in biphenylsis generated due to two different bulky ortho-substituents in each rings (A□B)due torestricted rotation. The two enetiomers (atropisomers) can exist provided the rings display dissymmetric planes.

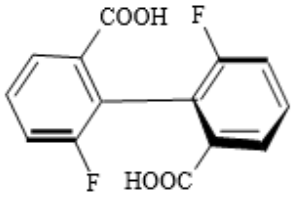


Suitably substituted biphenyl (diphenyl) compounds are also devoid of individual chiralcarbon atom, but the molecules are chiral due to restricted rotation around the single bond between the two benzene nuclei and hence they must exist as two non–superimposible mirror images of each other. *Such type of stereoisomerism which is due to restricted rotation about single bond, is known as atropisomerism* and the stereoisomers are known as atropisomers. atropoisomerism

a = not tropus = turn

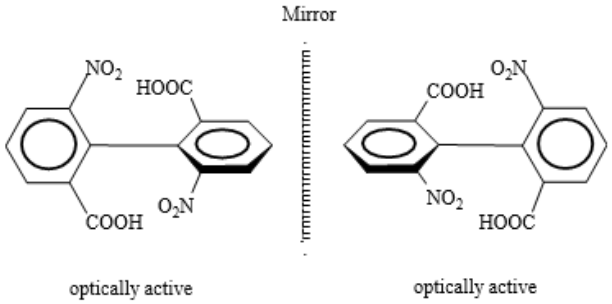
The followings makes the biphenyls are optically active.

a) The restricted rotation about the bond linking the two phenyl rings due to steric hindrance between the bulky ortho substituents makes the biphenyl compounds dissymmetric.
b) The two rings lie in different planes which may or may not be exactly perpendicular to each other.



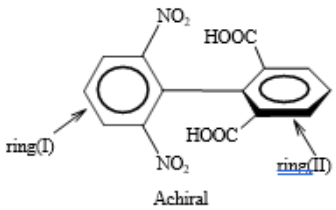
O,O'- diflurorodiphenic acid.

c) Isolable stereoisomers resulting from restricted rotation about single bonds are called atropisomers, while rotamers are stereoisomers obtained by rotation about a single bond. The, 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid can be resolved into its enantiomers and each enantiomer is stable. The nitro and carboxylic groups are so bulky that the two rings lie in different planes which are perpendicular to each other. Hence, the molecule does not have symmetry and will be optically active.



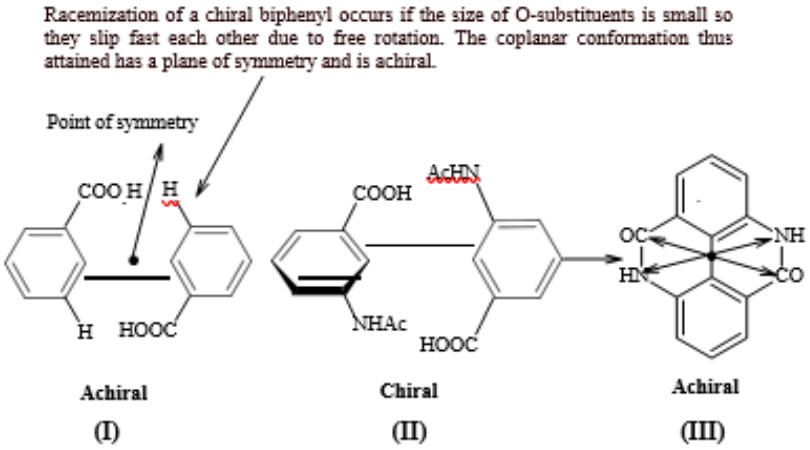
The minimal conditions for optical activity in biphenyls are

a) None of the rings should be symmetrically substituted, so that the molecule cannot have a plane of symmetry. Thus, the biphenyl is chiral (A ≠ B in either pair, COOH ≠ NO_2 of the ortho substituents. The compound 2,6-dinitro 2',6'-dicarboxylic biphenyl is, however, achiral. In this case e.g., ring is symmetrically substituted (A = B = NO_2) as well ring II (A=B= COOH). A plane drawn perpendicular to ring contains all the atoms and groups of ring in it, hence it is a plane of symmetry and since it bisects the plane of ring B into two equal halves, thus the biphenyl is achiral. In both the rings all the atom are in a single plane. So each plane cuts the other plane into equal halves. Hence plane of symmetry exists so that the molecule becomes optically inactive.

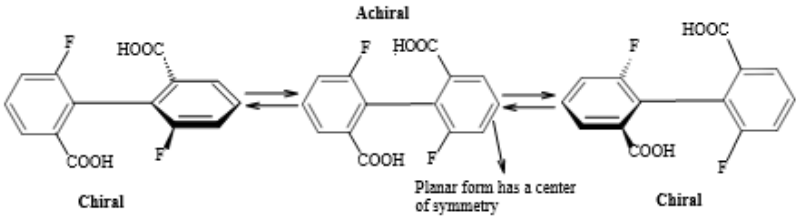


b) In order to display optical activity the substituents in the ortho position must be large enough to prevent the two rings from becoming coplanar (the rotational energy barrier must be high enough so that interconversions of enantiomeric conformers does not occur). Thus all attempts to resolve diphenic acid I into its enantiomers have failed. The process of slipping small hydrogen past the carboxylic acid group is very facile so that racemization of enantiomers occurs very rapidly through the planar form at room temperature. In the planar form the center of symmetry is clearly seen. Interestingly the diamide dicarboxylic biphenyl

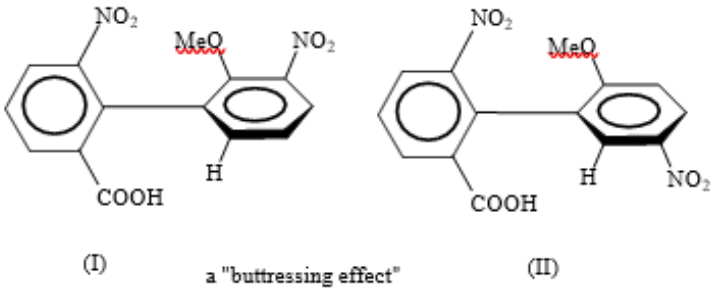
II is optically active and is resolvable since there is no free rotation along the C-C bond of biphenyl due to the large substituents. The optical activity is lost on hydrolysis and lactumisation since the resulting dilactum III is forced to be planar and a point of symmetry isobserved in it.



When the bulky nitro groups are replaced by the smaller fluorine atoms the resulting compound, 6,6'-difluorobiphenyl-2,2'-dicarboxylic acid can still display optical activity (Figure 48). However, the compound racemizes readily, i.e., the Enantiomers are readily interconverted. The process involves squeezing fluorine past the adjacent carboxyl groups via the planar conformation. Once they reach the planar conformation the Chirality is lost and racemization results. This transition state is congested and requires the bending of bonds. Theprocess takes energy and is measurably slow.

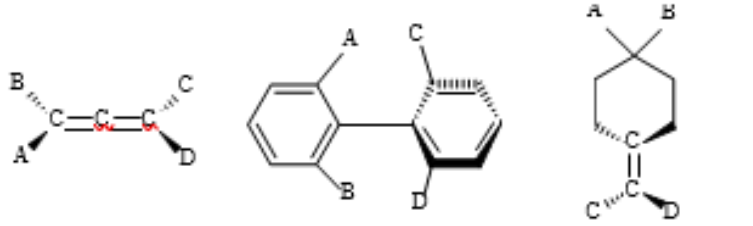


c) In the second case the benzene ring that is unsubstituted in the ortho-positions must have a substituent in a meta-position.
d) In addition to the bulk of the ortho substituents, the substituents in the meta-position tendto enhance racemization barriers by what is called as "buttersing effect", i.e., by preventing the outward bending of an ortho substituent, which otherwise occur in the transition state (coplanar conformation) for racemization. This bending would allow the ortho substituents to slip past each other more readily. Thus the rate of racemization of the 3-nitroderivative (structure I,) is much lower compared with the 5'-nitroderivative (Structure II,)



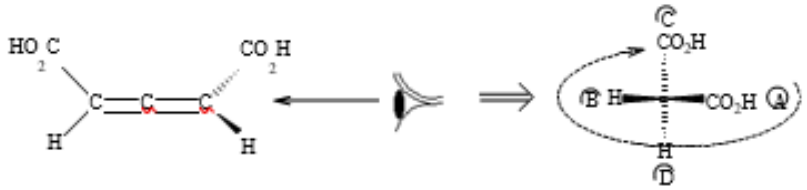
The (R) and (S) nomenclature system of Allenes & Biphenyls

The Cahn-Ingold-Prelog system has also been extended to chiral compounds that do not contain stereogenic centers, but have a chiral axis. Compounds having a chiral axis include unsymmetrical allenes, biaryls, alkylidene cyclohexane derivatives that exhibit atropisomerism,. A series of rules have been proposed to address the few cases where the rules can be ambiguous, as in cyclophanes and other system. Thus the (R) and (S) nomenclature system can also be used for structures with an axis or plane of Chirality. The dissymmetry is factorized into stereogenic units with the following order of priority: centers, axis, and planes are as follows.

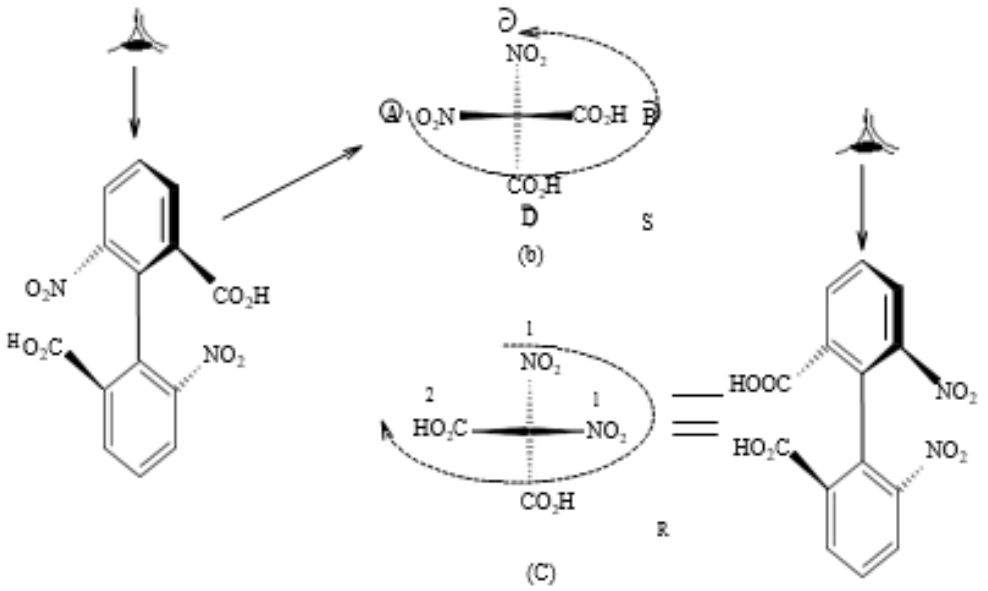


In an allenic compound, *Glutamic acid* (a)

1. Viewing the structures along the C=C=C axis from the right of the drawing (as indicated by the eye symbol) would produce the image **(b)**.
2. Using the rule that near groups precede the far groups in priority.
3. We first assign highest priority (A) to the COOH group and second priority (B) to the hydrogen on the near carbon atom.
4. The COOH group on the far carbon atom is third priority (C), and the hydrogen on that carbon atom is lowest in priority (D).
5. Now we determine the configuration as we would do for a chiral carbon having the same substituents with priorities A,B,C and D bonded to it. Thus, the structure ‘a’ has R configuration.



1. Viewing the three-dimensional representation from the perspective indicated by the top eyesymbol would produce the image.
2. Again assigning the two near groups higher priority than the two far ones, the structure isfound to be (S).



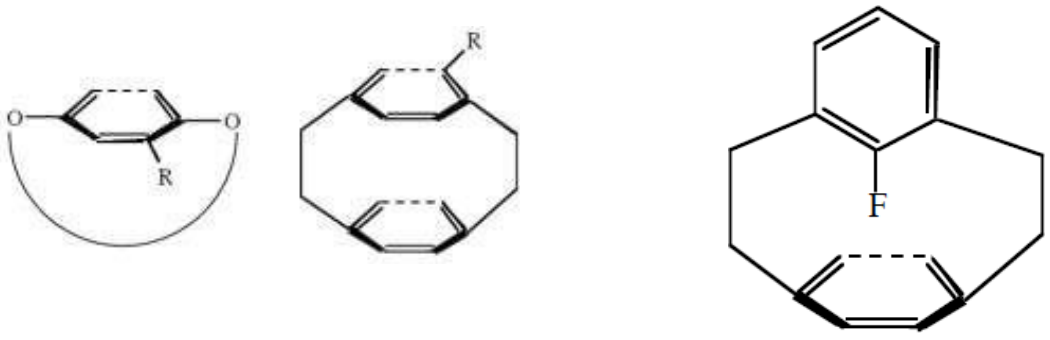
Determination of (R) or (S) designation for an atropisomer

Cyclophanes

Cyclophanes are compounds having two *p*-phenylene groups held face to face by $–[CH_2]_n–$ bridges. They are also called Para cyclophanes. They consist of a Para substituted aromatic ring whose substituents are bound together forming an aliphatic bridge above the plane of the ring. If the bridge is small enough, or if the aromatic ring carries an additional third substituent, the rotation of the aromatic ring through the aliphatic ring may be restricted. In this case, the par cyclophane is optically active because the enantiomers cannot rapidly interconvert. Due to their handle-like aliphatic ring above the plane of the aromatic ring, cyclophanes are also called ansa compounds (from the Latin *ansa*, handle).

Restricted rotation in the compounds below also give rise to dissymmetric planes of symmetry, and chiral isomers can be resolved.

The cyclophane below shows much more restricted rotation when the R is a fluorine atom than when the R is a hydrogen atom. Ring flipping in the hydrogen compound occurs 10^{11} times faster than in the fluorine compound. This also shows that F is larger than H.

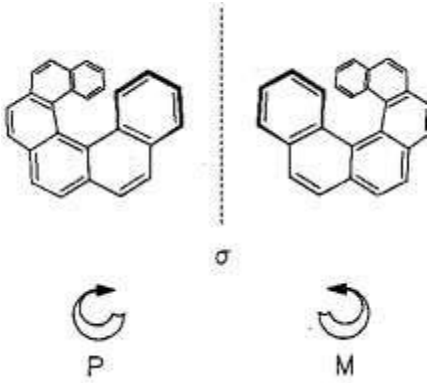


Helicenes

Helicenes are ortho-condensed polycyclic aromatic compounds in which benzene rings or other aromatics are angularly annulated to give helically-shaped molecules, Helicines are chiral and can be resolved into enantiomers that show optical activity. The chirality in the molecule occurs because the rings are distorted to avoid bumping into each other. Thecomputerized structure on

the right shows the shape of the molecule.

hexahelicine
optically active



Bredt's Rule stated that bridged ring systems (like camphane (A) and pinane (B) (Fig-1) cannot have a double bond at the bridgehead position (the points marked by bold dots in structures 'A' and 'B'). This rule came from observations on dehydration of alcohols in these ring systems. When you look at these molecules carefully, you could see that the bridged rings are made out of a larger ring (shown by thick lines in the Figure s) bearing a bridge at specified points. Most of the rings studied by Bredt had six-membered ring as the largest ring. The constraint dictated by Bredt's Rule has now been attributed to the fact that the small and common rings can accommodate only a cis-double bond. A bridgehead olefin demands a trans- geometry at the olefin. Hence the rule was applicable to almost all naturally occurring bridged ring systems known at that time.

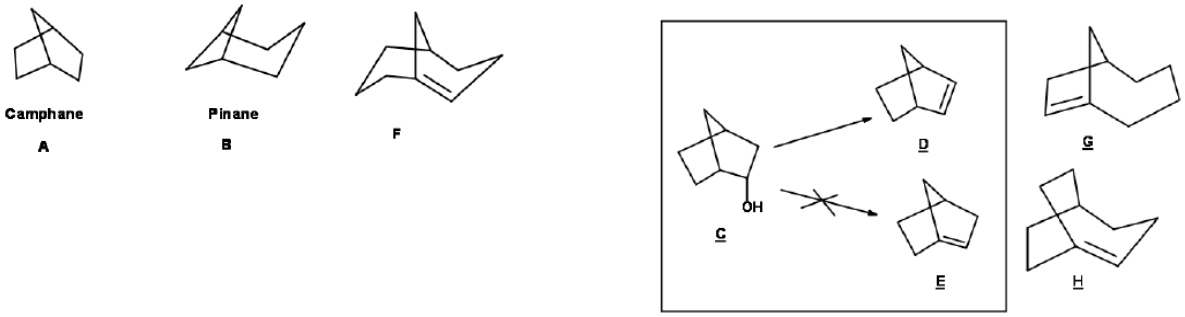


Fig-.1

The scope of this rule has been investigated in detail. Medium sized rings are large enough to accommodate a trans- double bond. Hence the bicyclic rings F and G, bearing a cyclooctane ring as the outer ring, were synthesized and were indeed found to be stable. On the other hand, the isomeric cycloheptene ring system [1.2.1.1]H was unstable. Faweet (1950) suggested that the S value, which is a summation of the numbers found in the nomenclature (m + n + o = S), would determine the stability of the ring system. Bicyclic ring systems with a bridgehead double bond having S value less than 9 would be highly strained. As the S value increases, the strain decreases.

Bretd's Rule cautions us on the type of rings that could bear a double bond. When a synthetic intermediate or a transition state in a mechanism demands such an intermediate, one should exercise caution on the position of the olefin. For example, Prelog (1948, 1949) attempted an aldol condensation on the ring systems shown (Fig 2). When n = 5, both products bicyclo[6,4,0]alkene (S = 10) (C), and

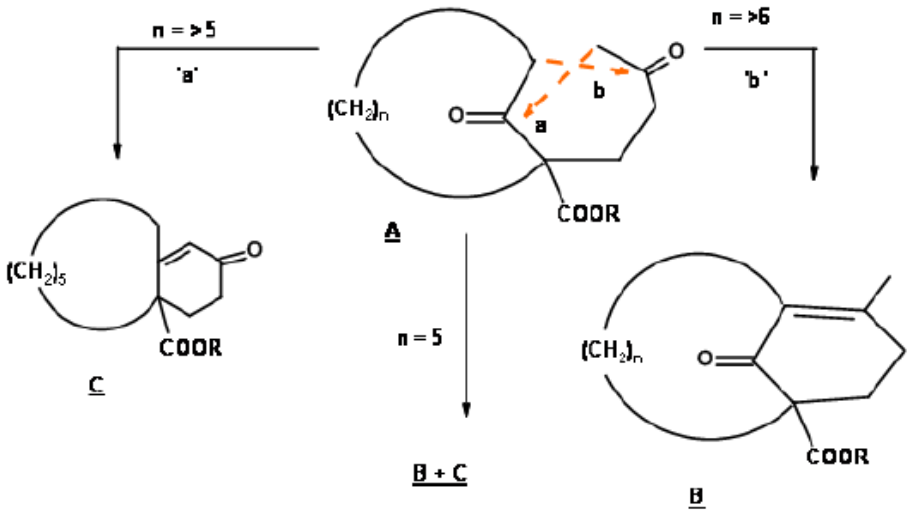


Fig-2

bicyclo[5,3,1]alkene (S=9) (B) were formed. On the other hand, when n=>6, the main product was a bicyclo[6,3,1]alkene system (B) (S=10). When n = <5 product B was not observed. Note that these models were based on reversible aldol condensation reactions (equilibrium reactions) and therefore correspond to the thermodynamic stability of the product. Under forced conditions however, the rule may not hold, as seen in the following example (Fig -3).

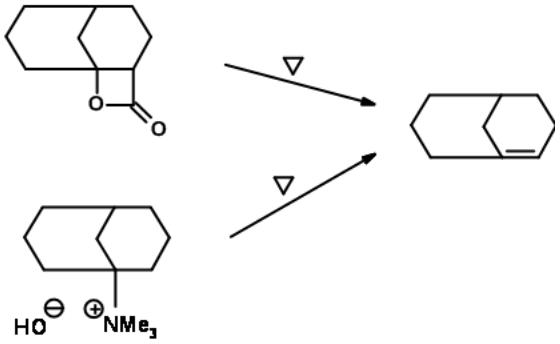
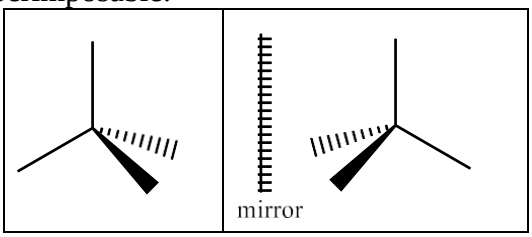


Fig-3

Optical spectroscopy: it is of two types

1. Absorption and Emission Spectroscopy
2. ORD & CD Spectroscopy

ORD & CD: Fundamental theory of ORD and CD depends on the chirality. Chirality: Mirror images but not superimposable.

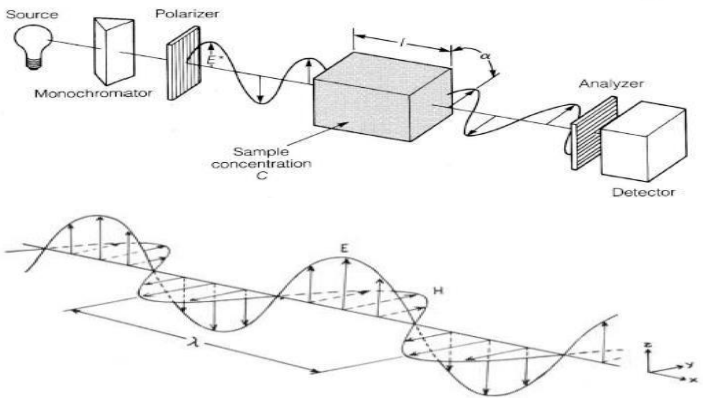


Chiral molecules exist as pair of isomers, they lacks plane of symmetry, and they are optically active.

Enantiomers: Same chemical formula/stereoisomers. Mirror images not super imposable

to each other. They have identical physical properties *e.g*., density, mp, bp, vp etc. only one difference (exception) they reacts to light differently. Even, NMR spectroscopy cannot distinguish enantiomers.

Polarized light: Ordinary light consists of many components which vary in wavelength and amplitude. Light which oscillates in a single plane is called plane-polarized or linearly polarized light. Electric vector is randomly oriented/distributed around the z-axis in x-y plane.



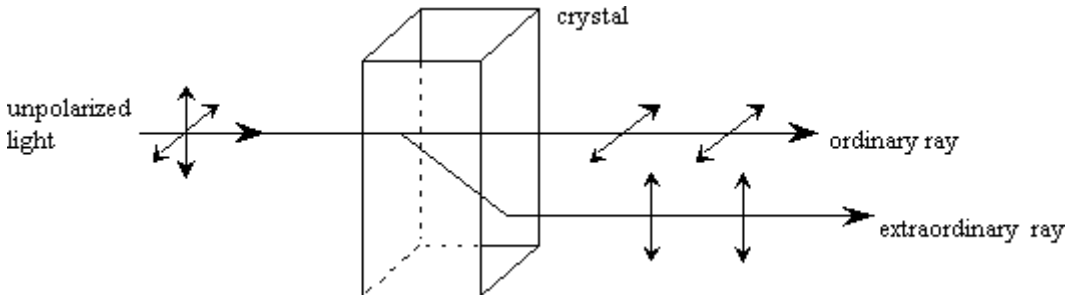
Types of polarized light

- Plane polarized light consists of two circularly polarized components of equal intensity.
- Two circularly polarized components are like left- and right-handed springs/helices.
- As observed by looking at the source, right-handed circularly polarized light rotates clockwise.

Optical activity: interactions between enantiomers & polarized light and its consequences. It has two phenomena:

1. Birefringence
2. Dichroism

Birefringence: its and optical properties that involves direction dependences of refractive index, double refraction (Birefringence).

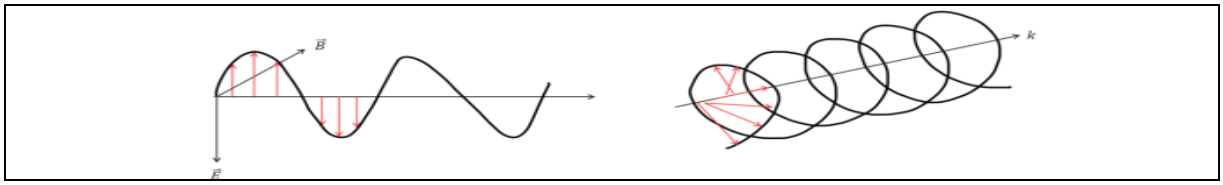


Since Birefringence refers to the direction-dependent index of Refraction. Hence Asymmetric crystals and plastics under mechanical stress can give birefringence. It is of two types – Linear and Circular

Linear Birefringence: it's an optical property that involves unequal refraction/speed of linear polarized light in two orthogonal planes.

Circular Birefringence: It is an optical property that involves unequal refraction/speed of left circularly polarized light (LCPL) and right circularly polarized light (RCPL). Shorter wavelength rotates more (clockwise – dextrorotary & anti clock wise – laevorotatory). Since

the speed of light in a medium is manifested in the refractive index of the medium, the essential property of an optically active substance is that it has different refractive indexes for the left and the right circularly polarized light, nL and nR, respectively. Linearly (left) and circularly (right) polarized light are shown below.

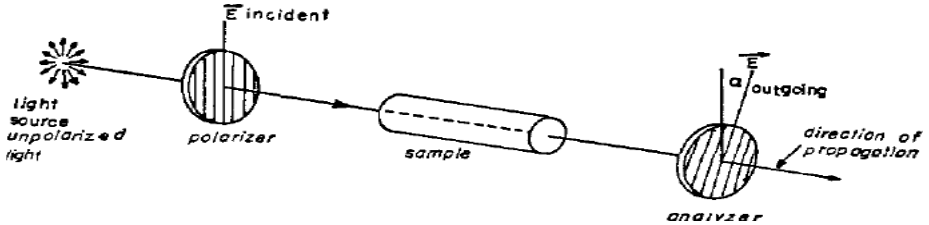


ORD Spectroscopy: It is observed by dependence of optical rotation on wavelength. Optical Rotatory Dispersion method measures the ability of optically active compound to rotate plane polarized light, as a function of the wavelength. ORD based on index of refraction.

- If the refractive indices of the sample for the left and right handed polarized light are different, when the components are recombined, the plane-polarized radiation will be rotated through an angle α
  - nl, nr are the indices of the refraction for left-handed and right handed polarized light
  - α is in radians per unit length [α = nl-nr/λ].
  - ORD curve is a plot of molar rotation [α] or M vs λ
  - Clockwise rotation is plotted positively; counter clockwise rotation is plotted negatively
  - ORD is based solely on the index of refraction
  - plain curve is the ORD for a chiral compound that lacks a chromophore
  - Chiral compounds containing a chromophore can give anomalous, or Cotton effect, curves

Specific rotation (α)**:** The specific rotation of a chemical compound is defined as the observed angle of optical rotation, when plane-polarized light is passed through a sample with a path length of 1 dm and a sample concentration of 1g/ml.

Specific rotation (α) = 100 x $\alpha_O/l.c$
Where, α_O is observed rotation, l is path length (dm) and c is concentration (g/100 ml).



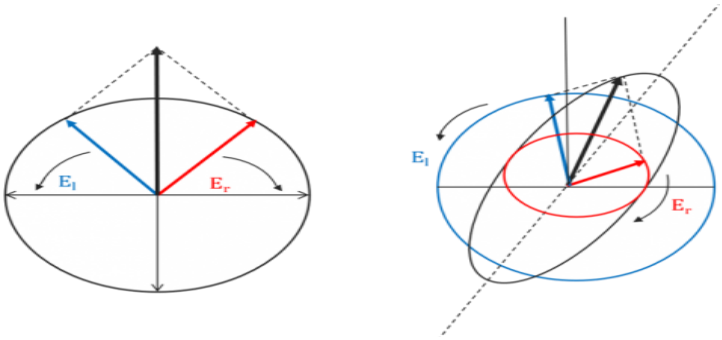
Dichroism: Dichroism – direction depended light absorption. It is of two types – Linear Dichroism and Circular Dichroism.

Linear Dichroism: A differential absorption in parallel and perpendicular directions. Linear Dichroism (LD) is a spectroscopic technique that can be used with systems that are either intrinsically oriented, or can be oriented during an experiment by external forces. It gives information about conformation and orientation of structures within molecules.

To measure *LD*, the sample is oriented then the difference in absorption of light linearly polarized parallel and perpendicular to the orientation axis is measured

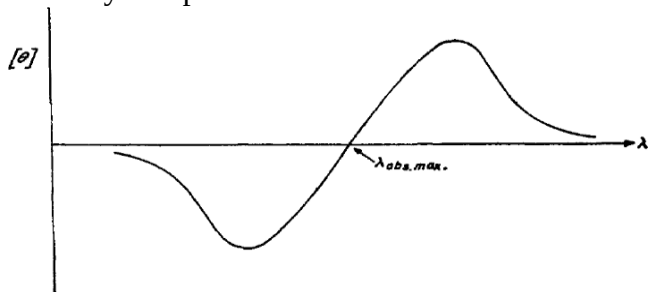
$$LD = A_{||} - A_{\perp}$$

Circular Dichroism (CD): Some materials possess special properties of absorption of the left circularly polarized light to different extent that the right circularly polarized light. This phenomenon is called circular dichroism. CD is the differential absorption of LCPL and RCPL. Elliptically polarized light shown below.



The difference between the absorption of left and right handed circularly-polarised light and is measured as a function of wavelength. CD is measured as a quantity called mean residue ellipticity, whose units are *degrees-cm^2/dmol*. So emerging light is elliptically polarized. CD Spectrum is difference of $\Delta\varepsilon = \varepsilon L - \varepsilon R$

Plot of molar ellipticity (θ) as a function of wavelength. CD – exhibited because of dextrorotatory & laevorotatory compounds.



- Measurement of how an optically active compound *absorbs* right- and left- handed circularly polarized light
- All optically active compounds exhibit CD in the region of the absorption band
- For CD, the resulting transmitted radiation is not plane-polarized but elliptically polarized
- Optically active absorbing chromophores present different extinction coefficients for R and L circularly polarized waves
- The technique is good at estimating alpha helical content, and at studying dynamic changes is secondary structure

Applications:

- α – helix of properties has its distinct spectral signatures. Nucleic acid double helix (α helix & β sheet). Comparison of the UV absorbance (left) and the circular dichroism (right) of poly-L-lysine in different secondary structure conformations as a function of pH.
- Proteins – CD spectra sensitive to secondary structure change – α- β- polyproline, irregular
- Aromatic amino acids – CD spectra sensitive to tertiary structure change Phenylamine Tryptophan, tyrosine etc.
- Proteins 2^o structure determination, proteins folding unfolding & nucleic acid/peptide/hormones

structural behavior.

- pH, heat or solvent induced structural changes
- ligand or ion induced structural changes

CD- differential absorption of light and right circularly polarized light

Region	Application
Near UV CD >250 nm	Tertiary structure of protein
UV CD	secondary structure of protein
UV/Vis CD	Charge transfer transitions
Near IR CD	Geometric & electronic structure by probing metal d-d transitions
Vibrational CD	Structural studies of proteins and DNA

CD & ORD comparison.

In the absence of magnetic field – only chiral molecule show CD and ORD In the presence of magnetic field- all molecules show CD & ORD.

ORD – differential speed of LCDL and RLPL $C_L \neq C_R$ CD – differential absorption of LCDL & RLPL $\varepsilon_L \neq \varepsilon_R$

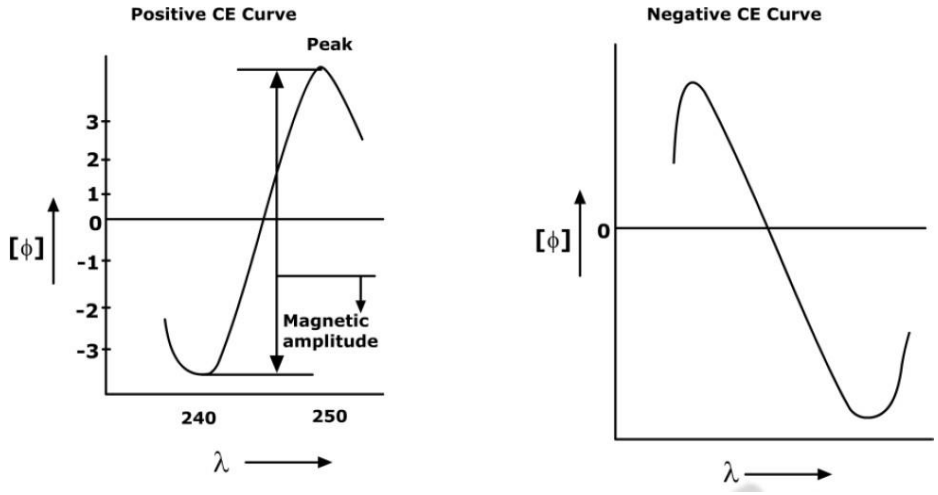
ORD	CD
• ORD is the refractive indices of the sample for the left and right handed polarized light are different, when the components are recombined, the plane polarized radiation will be rotated through angle α (differential speed of LCDL and RLPL $C_L \neq C_R$)	• CD is a differential absorption of left and right handed circularly polarized light (differential absorption of LCDL & RLPL $\varepsilon_L \neq \varepsilon_R$)
• ORD spectra are dispersive	• CD spectra are absorptive
• In ORD the circular polarized light is used is not converted to elliptical light	• In CD the circular polarized light is used and its converted to elliptical light
• ORD grades are obtained by plotting specific rotation vs wavelength	• CD graphs are obtained by plotting molar ellipticity vs wavelength

Cotton Effect: The characteristics change in ORD &/or CD in the vicinity of an absorb band. The combination of both (circular birefringence and circular dichroism) effect in the region in which optically active absorption bands are observed gives rise to a phenomenon called cotton effect.

Cotton effect curves: It has the following points:

- These curves will show the high peak ns through which depends on the absorbing groups.
- These curves will obtain for the compounds which are having asymmetric carbon & chromophore which absorbs near UV region.
- A chromophore with +ve cotton effect cause a right rotation at low frequency.

- A chromophore with negative cotton effect cause left rotation at low frequency.
- It is of two types: Single cotton effect curves and multiple cotton effect curves.



Advantage of ORD & CD:

- Simple and quick experiments
- No extensive preparation
- Relatively low concentration/amounts of sample required for experiment
- Any size of macromolecules can be observed
- Better resolution, better sensitivity and Easier to assign.

The octant rule is one of the first and arguably the most effective of the several chirality sector rules that connect the cotton effect to organic stereochemistry. It establishes an absolute configuration or stereochemistry from the sign and intensity of the cotton effect and is unquestionably the most well-known and often-utilized rule.

octant rule

An octant rule is an empirical generation that links the arrangement of the chiral centres near the carbonyl chromophore to the sign of the Cotton effect of the chromophore as observed at about 300 nm in saturated cyclic ketones.

The study of the properties of chiral ketones began around 1954 at Wayne State University in the laboratory of Djerassi, which coincided with the understanding of conformational effects. Djerassi, Moscowitz, Woodward, Moffitt, and Klyne developed the formulation based on extensive optical rotatory dispersion data for n-π*. The octant rule mainly governs the cotton effect, which is observed in the case of chiral ketones.

Octant rule for ketones

Many studies have been carried out on steroidal ketones. The position of carbonyl groups with different substituents in the steroidal backbones shows the cotton effect, which helps in the determination of the conformation or configuration of numerous substituent groups. The main

reason for choosing the steroid backbone was to minimize the conformational ambiguities and to allow the easy determination of the configuration and conformational effects of the different substituent groups. Besides, the carbonyl chromophore was chosen because of two factors:

1. The excitation of the carbonyl chromophore due to n π* is in the readily accessible region having a UV absorption wavelength of 300 nm, and the next absorption band of higher energy (λmax 190 nm) is so far away that it removes the problem of overlapping and confusing the nature of the transition under study.
2. The problems obtained experimentally during the measurement of the rotation from the absorption band are avoided due to the weakness of the n-π* transition.

In its most basic form, the rule states that a set of coordinates is drawn across a carbonyl group, with the origin in the middle of the carbonyl bond and the z-axis collinear with the bond. The xz and yz planes (two C2v symmetry planes), which are the nodal planes of the molecular orbital, split the carbonyl chromophore. The coordinate system divides the area surrounding the carbonyl group into eight regions (octants or sectors), four front sectors, and four sectors as shown in the figure below:

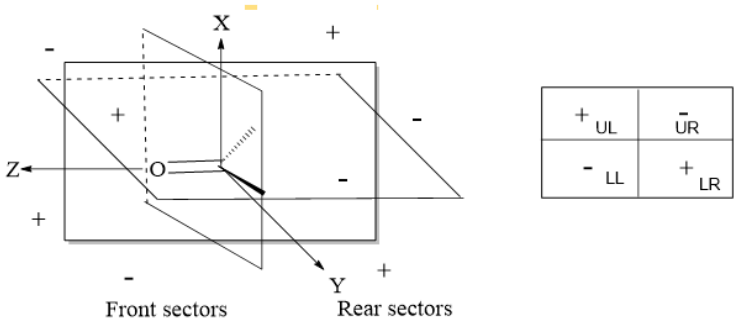


Fig: Octant rule for saturated ketones showing sign of the sectors in the left side and the view of the rear sectors in the right side

The main point of this rule is that the atom lying in the vicinity of the carbonyl group, at any point, let's say P(x,y,z), bears a contribution and determines the sign of the cotton effect (n-π*) depending on its location. For example, the atom that is present in the lower right rear sector with coordinates -x, +y, -z, shows a positive cotton effect as it lies in the positive sector in the left-handed coordinate system.

Octant rule for cyclohexanone The Octant rule for cyclohexanone is one of the most studied types. The cyclohexanone molecule, with its well-known geometry and fixed conformations, was the first compound in which the octant rule was followed. The cyclohexanone molecule is oriented in the three-dimensional coordinate system, or three orthogonal planes A, B, and C. These planes basically split the carbonyl group into eight sectors in the same way as described above and are shown in the figure below:

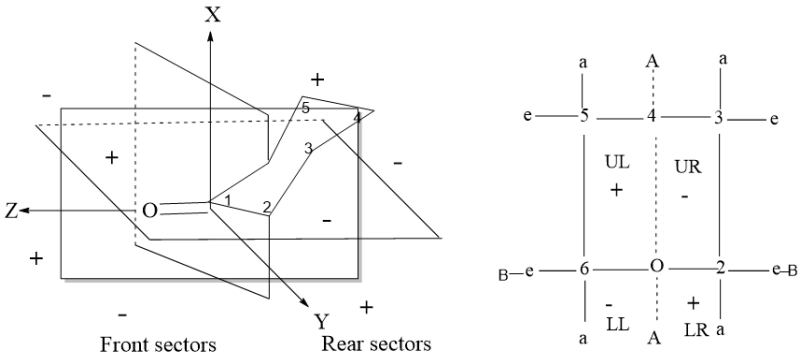


Fig: Octant rule for cyclohexanone ring (chair form) in the left side and the view of the rear sectors in the right side

A= xy
B= zy
C= xz

In the figure, the carbonyl group is the origin of the three-dimensional coordinate system and the Z-axis is collinear with the carbonyl group. Xy, zy planes, and xz are denoted as ‘A’, ‘B’, and ‘C’ planes respectively.

Plane A passes through the carbonyl group and carbon number 4 bisecting the cyclohexanone and the second horizontal Plane B passes through carbon numbers 2 and 6 and also contains the carbonyl group, they are denoted as lower right and lower left. Plane C passes through the carbon-oxygen bond at the right angle at the midpoint of the carbonyl group and separates the rear octants from the front octants and in most of the ketones, the substituents lie in rear octant regions behind the carbonyl group.

The two planes (A and B) split the space around the carbonyl group into four quadrants and the four rear quadrants are denoted as upper left (UL), upper right (UR), lower left (LL), and lower right (LR)
shown in the above figure and these sectors are denoted with (+) and (-) sign

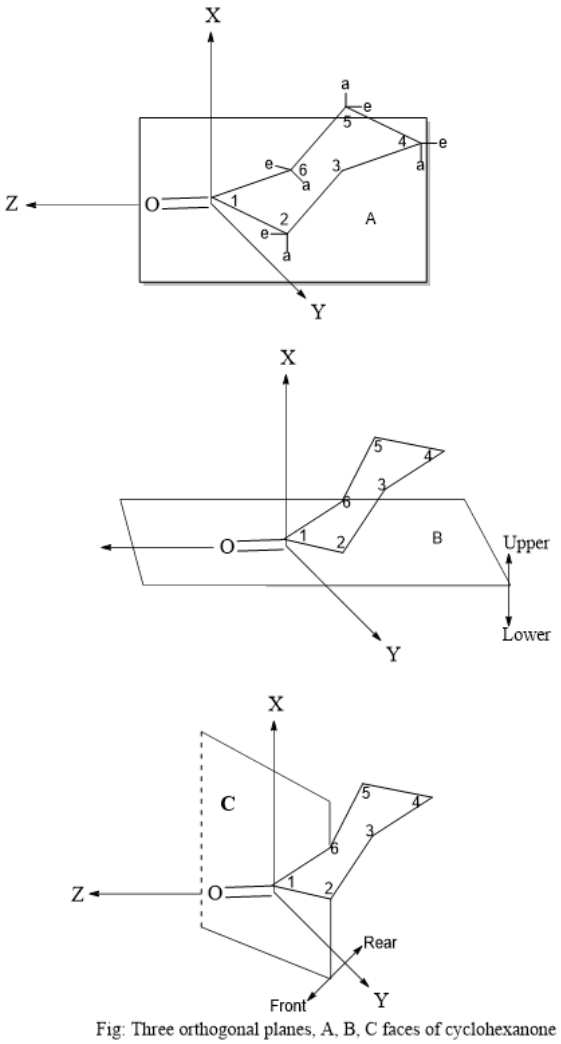


Fig: Three orthogonal planes, A, B, C faces of cyclohexanone

Octant rule in stereochemistry

The octant rule demonstrates the different signs of the cotton effect depending on the substituents lying in different octants and is considered as:

- The substituents present near the nodal planes show no contributions to the cotton effect like in the case of cyclohexanone, the groups present at C(2), C(3), C(5), and C(6) can make such contributions. Furthermore, the equatorial substituents at C(2) and C(6) do not have any effect (or little) because they lie in the B plane (yz plane) and the substituents at C(4) also lie in the A plane and thus, have no effect.
- The substituents that lie at the rear lower right octant give a positive contribution to the cotton effect and the sign is also positive for the upper left octant at the rear side. Similarly, the substitution in the rear upper right and rear lower left makes a negative contribution
- The substituents present at the lower right and upper left axially give a positive cotton effect, and those present at the lower left and upper right axially show a negative contribution to the cotton effect.
- It is occasionally feasible to provide a semiquantitative evaluation of contributions that occur in many rings because they are additive.
- As previously expected, contributions from carbon atoms, Sulphur, and halogen atoms are the same but because of their substantially greater atomic refraction, the halogens (except fluorine) dominate the cotton effect, totally outweighing contributions from the alkyl groups. It is

noteworthy that out of all the halogens, fluorine has the lowest atomic refraction; in fact, it is less than that of hydrogen.

- Groups that include both oxygen and nitrogen may behave in an octant or antioctant (inverse) manner. For instance, the -N(CH3)3+ group demonstrates anti-octant activity.

(Cosignate (Octant) is the effect caused by a specific substituent if the sign occurred from the product of the coordinates coincides with its contribution in circular dichroism intensity and Dissignate (antioctant) is the effect that shows a contrast in the relationship in the sign of the contribution to the circular dichroism and the sign from the cartesian coordinates).

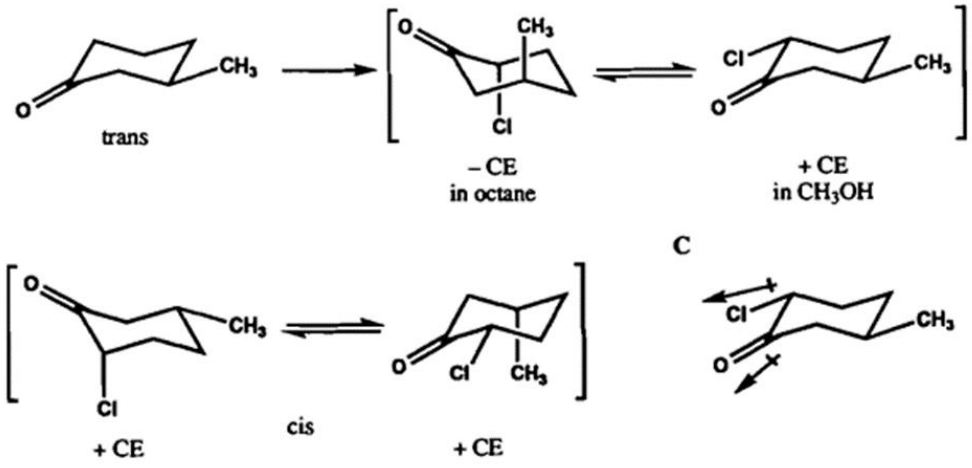
Axial haloketone rule

The axial haloketone rule is the special case of the octant rule and it determines the sign of the cotton effect based on the conformation of α-halogens in α-halocycloketones. The equatorial α-halogens do not show much effect in the cotton effect but the axial α-halogens change the sign of the cotton effect according to the axial haloketone rule.

When the carbonyl carbon is positioned at the head of a chair or boat form of cyclohexanone, the molecule is seen along the axis of the carbonyl bond for the purpose of this rule. The cotton effect is expected to be positive if the halogen is on to the observer's right, and negative if it is to their left.

Basically, the sign of the cotton effect depends on the conformation, configuration, and constitution of the haloketone in the area of the carbonyl group.

The negative cotton effect is shown mostly by trans stereochemistry in non-polar solvent but in polar solvent, the positive effect is shown. The main reason behind this could be that the shifting of conformation has taken place in the case of more polar solvents due to low repulsion between the equatorial carbonyl and chlorine atoms. This rule can be illustrated as:



The application of the octant rule with some examples is listed below:

- Determination of absolute configuration of ketones:

Octant diagram plays a crucial role in the determination of the configuration of ketones which can be easily justified with the example of 3-methylcyclohexanone, which is a chiral and optically active compound.

• Since equatorial 3-methylcyclohexanone is more stable predominating the equatorial conformation and its optical rotation can be determined from a polarimeter which results in a laevorotatory compound. So, in this compound based on the octant rule, the methyl group lies in the upper left octant in equatorial 3-methylcyclohexanone which gives a positive effect.

Similarly, the methyl group in the axial 3-methylcyclohexanone lies in the upper right octant demonstrating a negative effect but overall, 3-methylcyclohexanone demonstrates a positive effect, which means the methyl group is in the equatorial position.

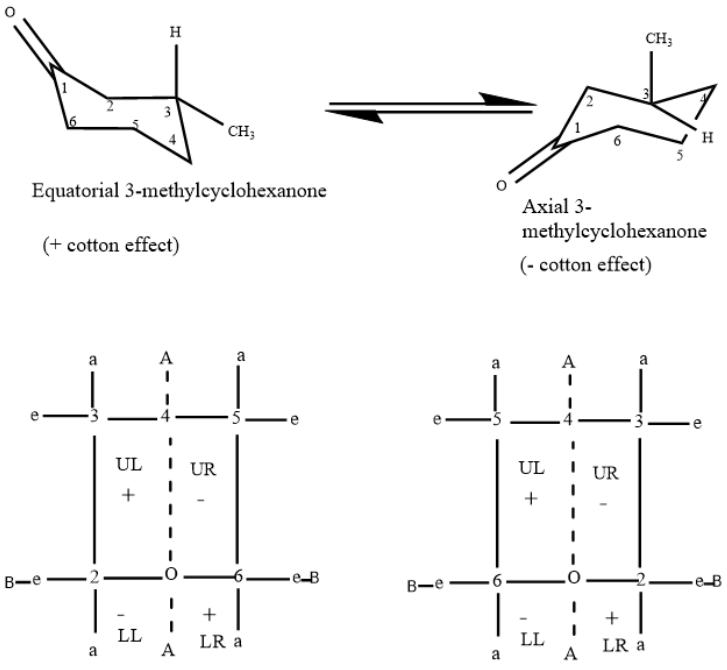


Fig: Octant diagram of 3-methylcyclohexanone showing the sign of the sectors in the coordinate system

- **Determination of optical properties of chromophores**
  A chiral chromophore that exhibits circular dichroism at ultra-violet absorption bands is optically active and shows the cotton effect. An intrinsically achiral chromophore requires extrachromophoric disruption to display circular dichroism: in contrast, an intrinsically chiral chromophore's circular dichroism originates from the chromophore's dissymmetry. Generally, the former's cotton effect has a magnitude that is one or two orders of magnitude more than the latter.

  For example, the carbonyl chromophore can be a very sensitive chiroptical probe since its optical activity is from chiral perturbers located inside the molecule. According to the Octant rule, this means that it provides a window for the detection of extra chromophore stereochemistry.

- **Conformational and stereochemistry analysis of saturated ketones**
  Some examples of conformational and stereochemistry analysis of saturated ketones are shown in the table below:

Table: Chair conformers of 2-oxo-p-menthanol along with octant diagram and sign of cotton effect (https://doi.org/10.1016/S0167-9244(08)70178-1)

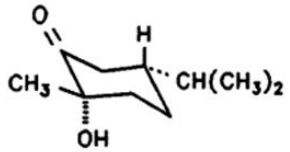
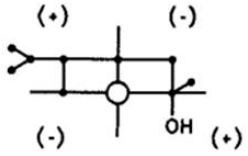
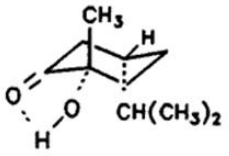
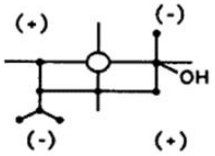
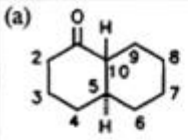
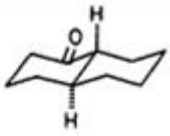
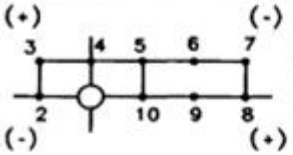
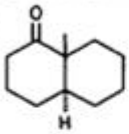
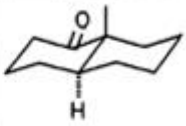
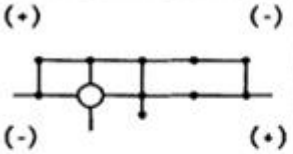
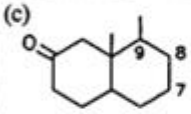
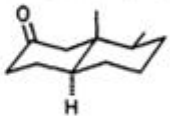
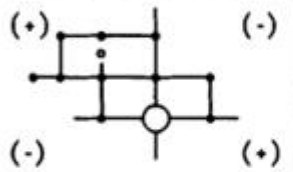
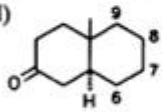
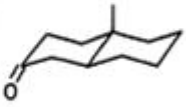
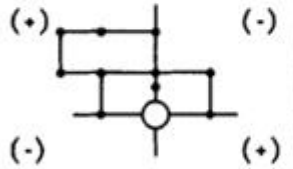
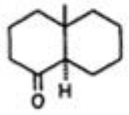
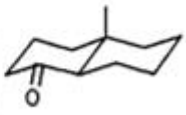
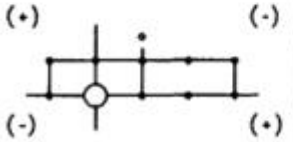
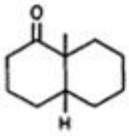
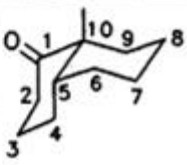
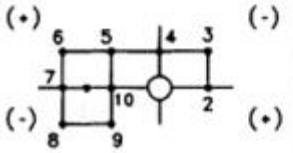
Conformation	Octant Diagram	Predicted CE	Observed CD
		(+)	$\Delta\epsilon$ + 1.76 (CH_3OH)
		(-)	$\Delta\epsilon$ = -1.36 (isopentane-methylcyclo-hexane 5:1)

Table: Conformation of Decalones with octant diagrams and predicted cotton effects.(https://doi.org/10.1016/S0167-9244(08)70178-1)

Decalone[a]	Conformation	Octant Projection Diagram[b]	CE	
			Pred.	Obs.
(a) 			—	-1.0
(b) 			+	+0.7
(c) 			+	+1.3
(d) 			+	+1.2
(e) 			—	-0.8
(f) 			—	+1.3

- Determination of absolute stereochemistry of αβ-unsaturated ketones.
- Synthesis of the (1s,5s)-dimethyladamantan-2-one form the optically active compound, adamantane shows no contribution in cotton effect by octant and quadrant rules.

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