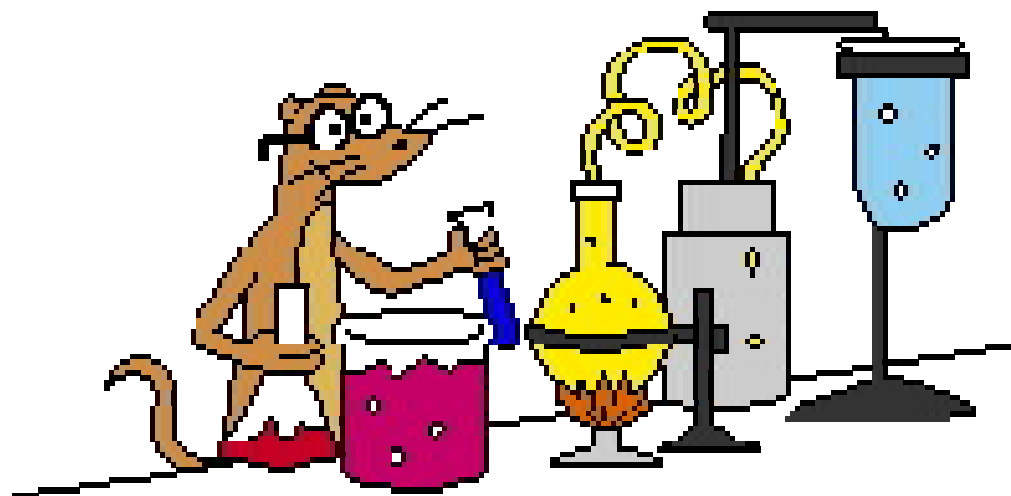




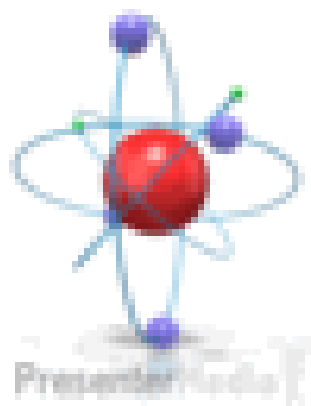
methods of determining mechanism and Isotopic effects



- ❑ In scientific experiments and chemical reactions, all we can do is try to account for the observations by proposing theories and mechanisms.
- ❑ Reaction mechanisms have been an integral part of the teaching of organic chemistry and in the planning of routes for organic syntheses for about 50 years.
- ❑ The first sentence of Hammett's influential book, *Physical Organic Chemistry*, states,
"A major part of the job of the chemist is the prediction and control of the course of chemical reactions"



chemical reaction, mechanism depicts the actual process by which the reaction has
n place. It indicates which bonds are broken, in what order, the steps involved and
tive rate of each step. The positions of all atoms, including those of the solvent
ecules, and the energy of the system, at every point in the process need to be specif
mechanism.



When a new reaction is discovered, more than one mechanism is proposed and the mechanism is the one which fits all the evidence sought.

It is seldom possible to provide complete information like structural, energetic, and spectrochemical about the pathway that is traversed by a reaction, thus, it is subject to change with the discovery of new facts.

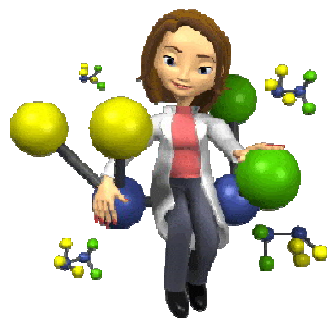
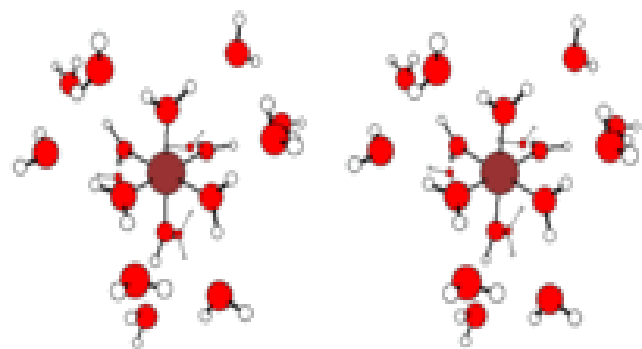
However, there are examples of reactions which by different mechanisms under different conditions and in each case the proposed mechanism completely explains all the data.

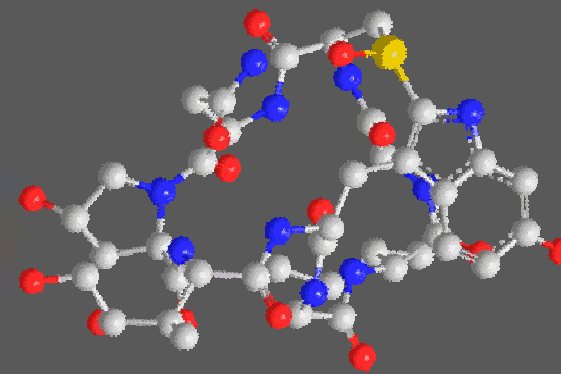
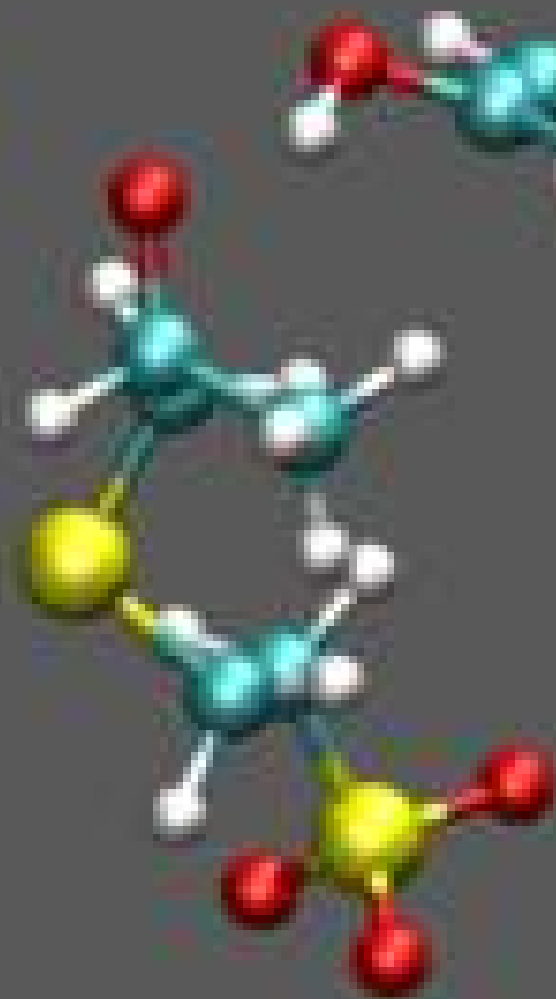
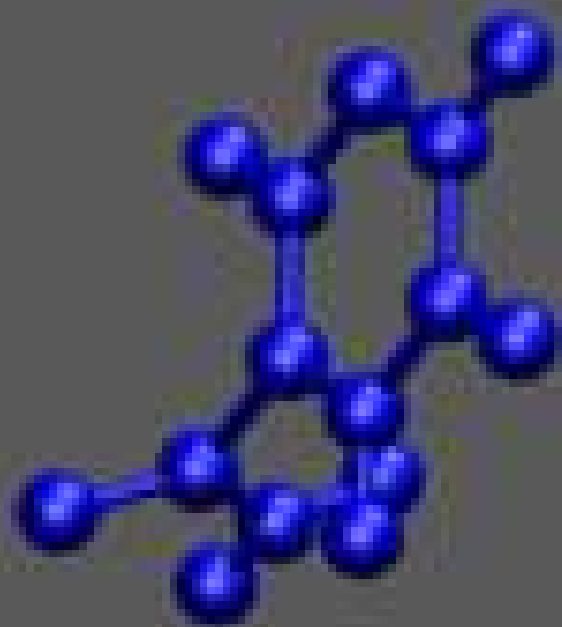
Organic reactions generally involve the cleavage of more than one covalent bonds and on the basis of cleavage of bonds organic reaction mechanisms can be categorized into two types, viz.,

Heterolytic bond cleavage mechanisms: If a bond breaks in such a way that electrons remain with one fragment, the mechanism is called heterolytic. Such reactions do not necessarily involve ionic intermediates, although they often do.

Homolytic bond cleavage mechanisms: If a bond breaks in such a way that each fragment gets one electron, free radicals are formed and such reactions are said to proceed by homolytic or free radical mechanisms.

Pericyclic Reaction mechanisms: In this type of reaction mechanism, the electrons move in a closed ring and there are no intermediates, ions or free radicals, and it is impossible to determine whether the electrons are paired or unpaired.



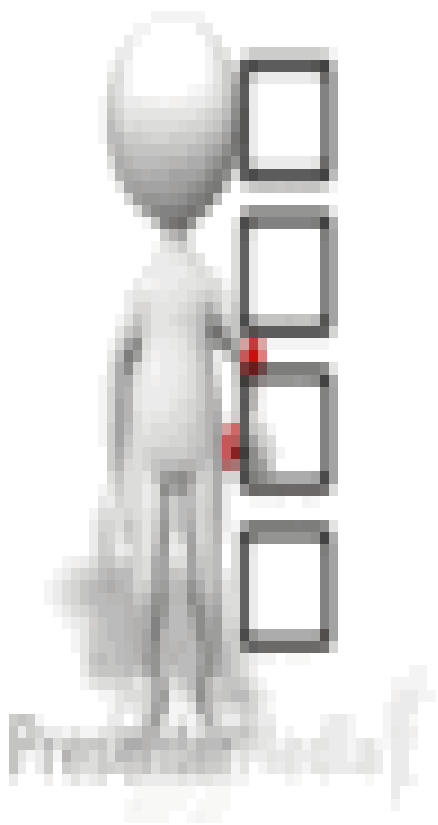




covalent bonding

A. METHODS OF DETERMINING MECHANISM





1. Determination of the products formed
2. Study of Intermediate formed
3. Study of catalyst
4. Stereochemical Evidence
5. Kinetic evidence
6. Isotope Labelling

are a number of commonly used methods for determining mechanisms. In most cases, one method is not sufficient, and the problem is generally approached from several directions.

Smith explains that one approach for determining mechanisms is the application of widely ranging principles, but another approach involves “bit-by-bit development of theoretical generalizations, aided by theories of approximate validity whenever they serve to rationalize a useful empirical conclusion or to suggest interesting lines for experimental investigation”

Step 1. Determination of the products formed

The mechanism of any reaction should tell us about all the products formed and the amount also. Even it should account for the formation of any side product, though it is formed in very small amount. The yield and purity of each product depends in part on competing reactions.

Now examples of different kinds of products formed in reactions are discussed below:

Example 1: A well-known example of the application of mechanistic understanding to help to control product yields is a reaction of commercial significance – the addition of HBr to alkenes which may occur via cationic or radical mechanisms. Very pure alk-1-enes, in the absence of peroxides, react to give the 2-bromo-products by Markovnikov addition. In the presence of peroxides or other radical initiators, anti-Markovnikov addition gives the 1-bromo-products.

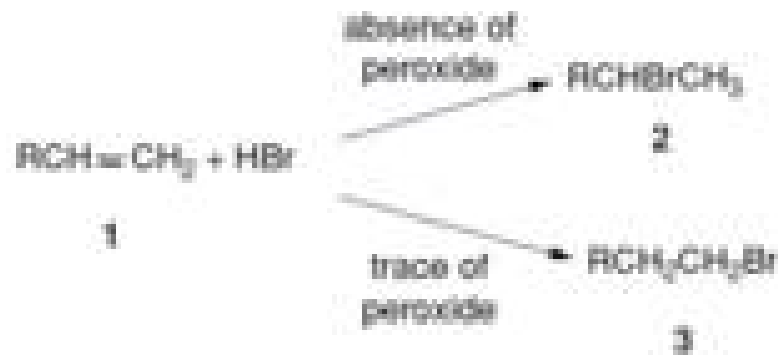


Fig. 1: Radical and ionic additions of HBr to an alk-1-ene

Example 2: Another example is the mechanism for the chlorination of methane which accounts for the formation of a large amount of ethane along with chloromethane, dichloromethane, trichloromethane and tetrachloromethane.

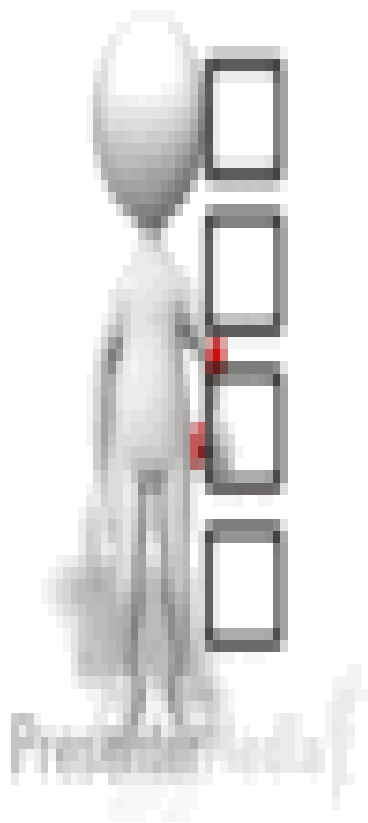


Fig. 2: Chlorination of methane

Example 3: In the Hofmann rearrangement amide gets converted to amine. The mechanism for the Hofmann rearrangement explains that the carbon is lost as CO₂.



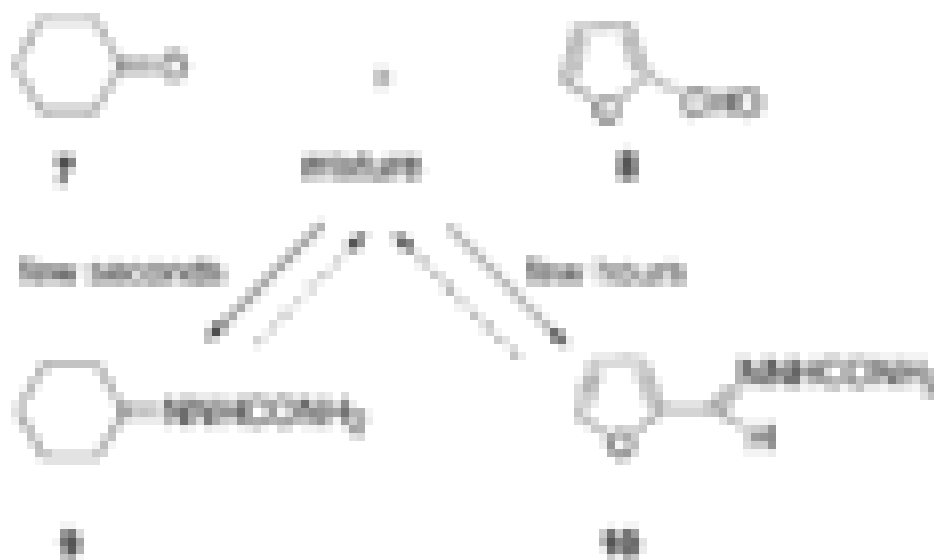
Fig. 3: Hofmann rearrangement



- In some cases, one may be limited to the study solely of reactants and the products.
- With the availability of a wide range of spectroscopic techniques (IR, MS, NMR, UV–vis), incorrect assignments of the structures of pure organic compounds are very rare nowadays.
- Uncertainties about structure can often be resolved by X-ray crystallography.
- Some other factors relating to product formation affecting the mechanism are discussed below.

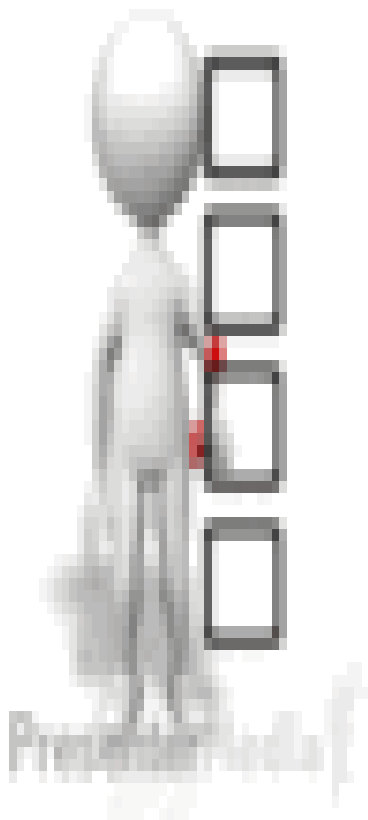
product stabilities, and kinetic and thermodynamic control of product formation

Initial products of a reaction are formed under kinetic control. However, subsequent products formed are governed by thermodynamic control. When a mixture of 0.01 m of cyclohexanone, furfural and semicarbazide reacted in aqueous ethanol at 25°C, the product isolated after a few seconds was cyclohexanone semicarbazone (initial kinetic product); but, after a few hours, the product was the semicarbazone (subsequent thermodynamic control).



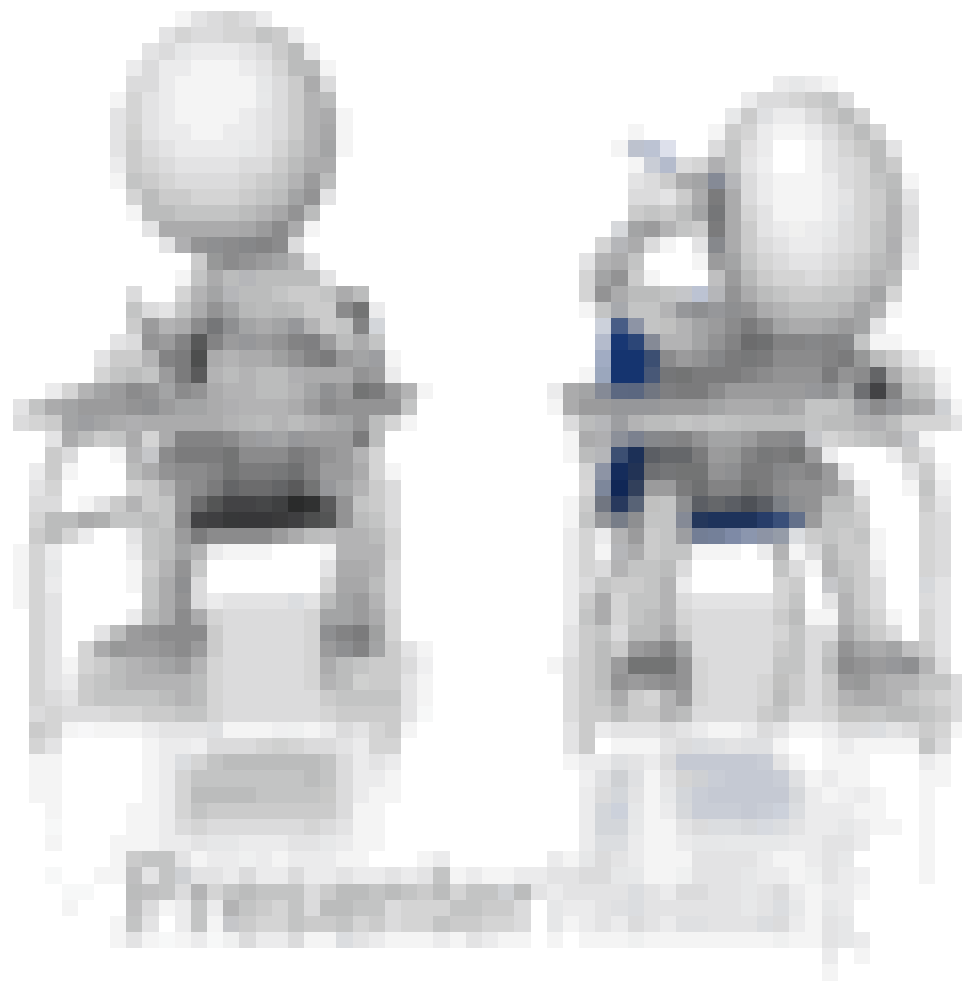
: Kinetic and thermodynamic products from equimolar amounts of cyclohexanone, furfural and semicarbazide

b. Stereochemical considerations in products formation

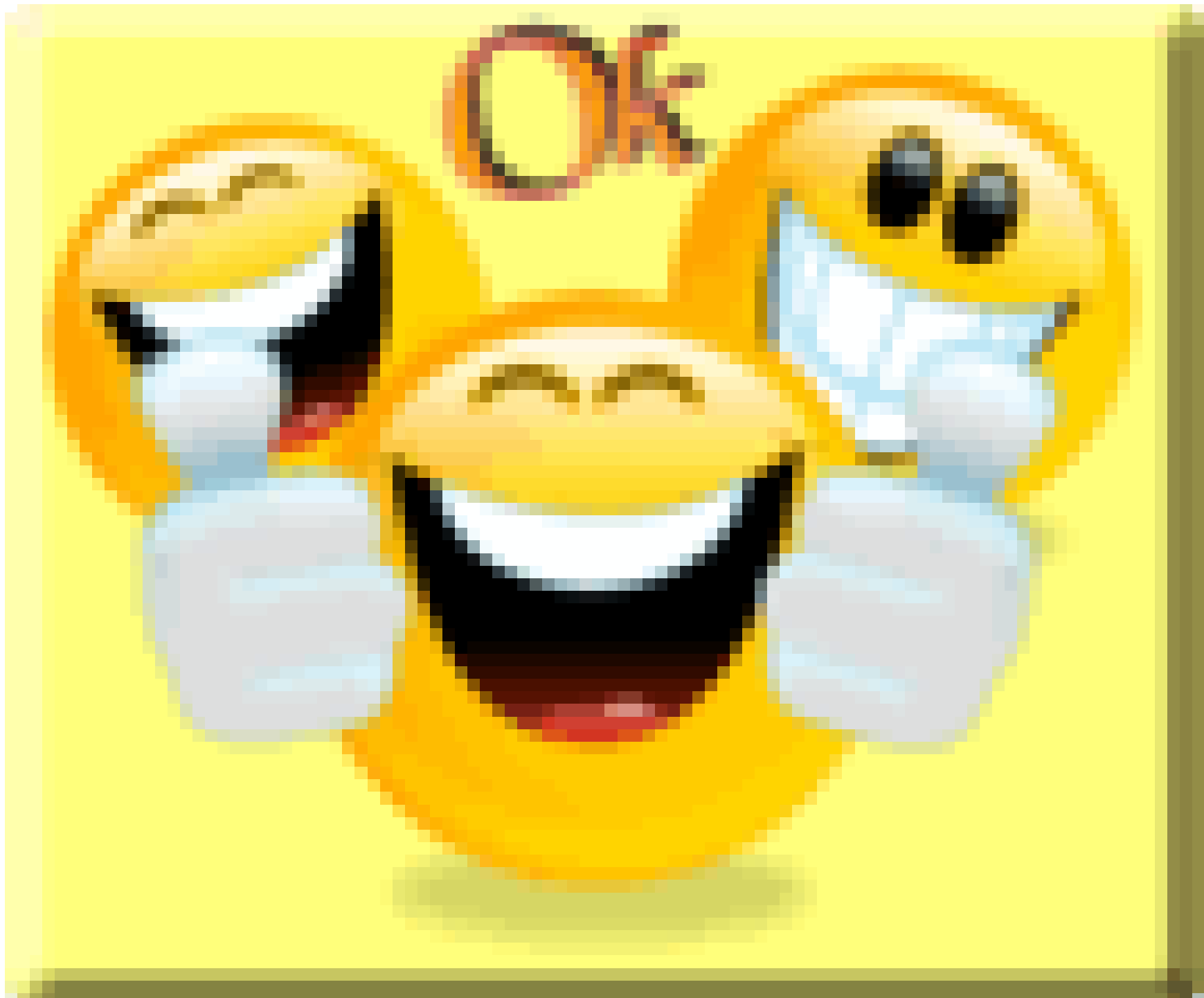


- ❑ The stereochemistry of product must be accounted while studying the mechanistic details of a reaction, which played a major role in developing our current understanding of organic reaction mechanisms (e.g. Walden inversion and SN2 mechanism, neighbouring group participation and reactions controlled by orbital symmetry).
- ❑ Nowadays, the stereochemical course of many reactions is known although the mechanistic explanation may still be under debate.
- ❑ While planning of organic syntheses, knowledge of the expected product stereochemistry is an integral part.
- ❑ The most useful reactions for controlling product stereochemistry are usually kinetically controlled, and much current research involves investigations of suitable reagents or catalysts (including enzymes/biocatalysts).
- ❑ Under more vigorous reaction conditions, thermodynamic control may take over. If there is no change in bonding to the stereocentre, there can be no configurational change.

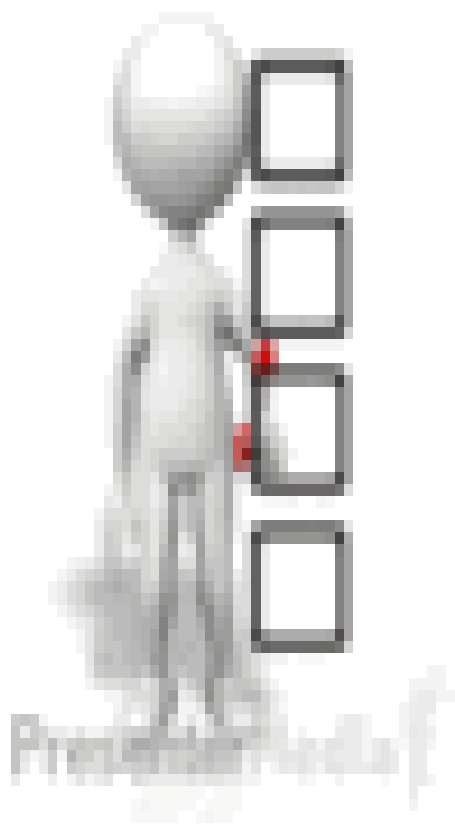








Step 2. Study of Intermediates formed



- Intermediates are postulated in many mechanisms.
- Their presence or absence of is an essential information for proposing a fairly correct mechanism for a reaction.
- The simplest variations are reaction time and temperature can yield different intermediates in a reaction.
- The evidence is provided by product analysis.
- Many reactions are proposed to proceed via the formation of intermediates such as carbocations, carbanions, free radicals, carbenes, nitrenes.
- The intermediate and its structure is determined and studied by several ways

a. Isolation of an Intermediate

Intermediates can be isolated sometimes from a reaction mixture by stopping the reaction after a short time or use of very mild conditions.

For example, in the Neber rearrangement the intermediate an azirene has been isolated.



Fig. 5: Neber Rearrangement



Fig. 6: Structure of azirenes

When a compound is subjected to the reaction conditions, if the isolated intermediate gives the same product and at a rate not significantly slower than the starting compound, this constitutes strong evidence that the reaction involves that intermediate. However, this is not conclusive, since the compound may arise by an alternate path and by coincidence give the same product.

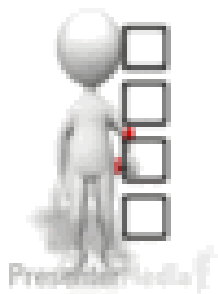
b. Detection of an intermediate

- ❑ If the intermediate cannot be isolated, then it can be detected by various spectroscopic techniques such as IR, ReactIR, NMR, or other spectra.
- ❑ For example during nitration of benzene, the formation of nitronium ion has been detected by Raman spectra of NO_2^+ . ESR (Electron Spin Resonance) and CIDNP (Chemically Induced Dynamic Nuclear Polarization) are often used for the detection of free radical and triplet intermediates.
- ❑ Free radicals (as well as radical ions) can also be detected by isomerisation, with the use of spectroscopy.
- ❑ In this method, a double bond compound is added to the reaction mixture, and its isomerization is traced.
- ❑ One possible result is cis–trans conversion. For example, cis-stilbene is isomerized to the trans isomer via a radical.
- ❑ Since the trans isomer is more stable than the cis, the reaction does not go the other way, and the detection of the isomerized product is evidence by the presence of the radical.



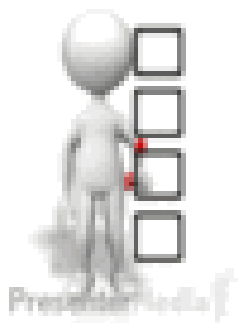
Fig. 7: A radical intermediate

c. Trapping of an intermediate



- Sometimes the mechanistic details of a reaction can be better understood by trapping the intermediate formed.
- For example, when a benzyne is an intermediate, the addition of a diene and the detection of the Diels–Alder adduct indicates the presence of benzyne as an intermediate.

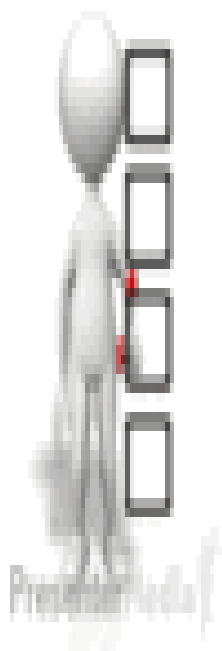
d. Addition of a suspected intermediate



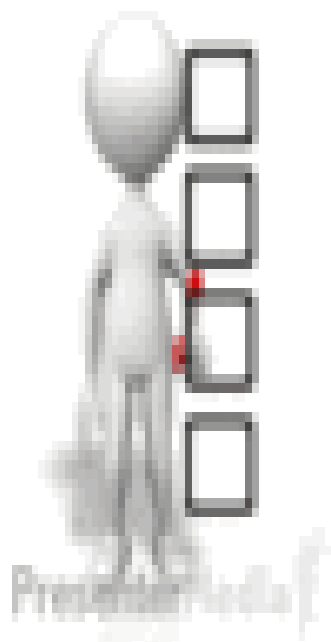
- If a certain intermediate can be obtained by other means, then under the same reaction conditions it should give the same products.
- This provides us with a negative evidence, since if the desired product is not formed then the intermediate is wrongly interpreted.
- However, if the desired product is formed, then the intermediate is (in most cases) the correct one in proposing a suitable mechanism for a reaction.

Step 3. Study of catalyst

- ❑ Catalysts perform their actions by providing an alternate pathway for the reaction.
- ❑ The knowledge of catalyst also provides sufficient information about the mechanism of a reaction.
- ❑ The proposed reaction mechanism for any reaction which uses catalysts should be compatible with it apart from being compatible with products and intermediates.



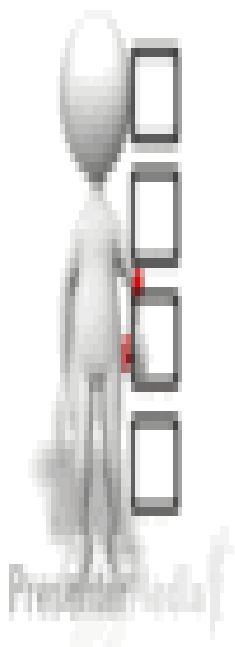
Step 4. Stereochemical evidence



- ❑ A lot of information about the mechanism is revealed if the products of a reaction can exist in different stereoisomeric forms.
- ❑ The preferred isomer can lead a chemist to give a more trustworthy mechanism.
- ❑ For example, Walden discovered that (+) malic acid gives (-)- chlorosuccinic acid when treated with PCl_5 and the (+) enantiomer when treated with SOCl_2 , showing that the mechanisms of these apparently similar conversions could not be the same.
- ❑ Much useful information has also been obtained about various important types of organic reactions like nucleophilic substitution, elimination, rearrangement, and addition reactions from this type of experiment.

Step 5. Kinetic evidence

- ❑ The rate of a homogeneous reaction is the rate of disappearance of a reactant or appearance of product.
- ❑ A study of which reactants influence the rate often gives a good deal of information about the mechanism of a reaction.
- ❑ The rate law of a reaction is an experimentally determined fact.
- ❑ The molecularity which is the number of molecules that come together to form the activated complex, also gives a good deal of information about the mechanism.
- ❑ Kinetics investigations are the single most important group of techniques in mechanistic determinations.
- ❑ Various kinetics parameters like order of a reaction, rate law, rate constants, kinetic isotope effects, etc. summed up with other evidences provide great insights into the mechanisms that are proposed.
- ❑ In practice, some methods are much more widely used than others, and UV-vis spectrophotometric techniques are amongst these.
- ❑ A major recent development is the increasing exploitation of time-resolved IR spectrophotometry for kinetics which has a major advantage over UV methods – in addition to kinetic data, it also provides readily interpretable IR spectroscopic information which allows some degree of structural characterisation of reactive intermediates.



Step 6 Isotope Labelling

Commercial availability of a wide range of isotopically enriched organic compounds provides many opportunities to investigate reaction mechanisms using isotopic labelling. The techniques involved for determination of labelled compounds during the course of reaction by NMR and MS.



Fig. 8: ^{14}C Isotopic labelling rules out a mechanism involving the replacement of CO_2 by CN

Do the CN group in the product come from the CN in the BrCN ? The use of ^{14}C supplied the answer, since R^{14}CO_2 is a radioactive RCN . This surprising result saved a lot of labour, since it ruled out a mechanism involving the replacement of CO_2 by CN .

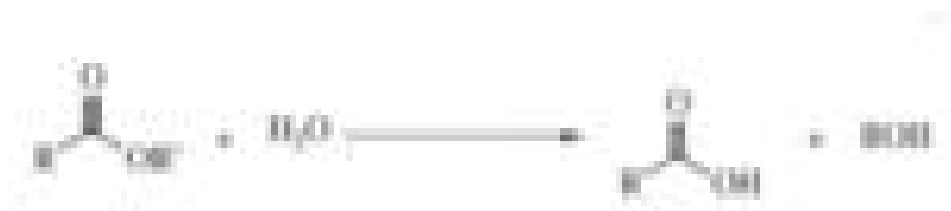
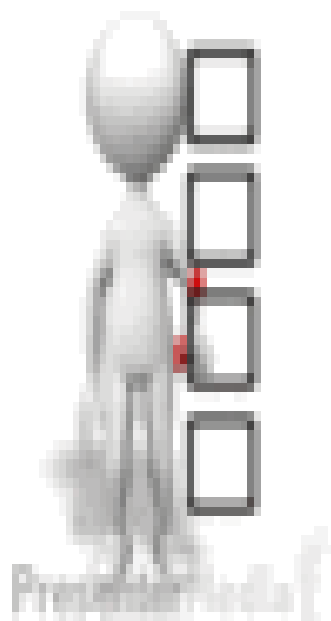


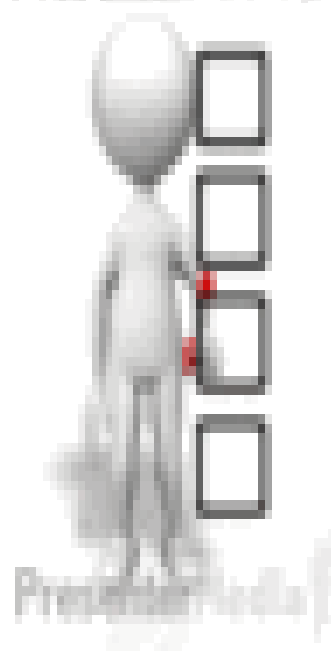
Fig. 9: Mechanism explained by using H_2^{18}O

Another example is the hydrolysis of esters, which bond of the ester is broken, the acyl-O or the alkyl-O bond? Explained by using H_2^{18}O . If the acyl-O bond breaks, the labelled oxygen will appear in the acid; otherwise it will be in the alcohol. The benefits of initial product studies, followed by a more detailed examination using isotopic labelling, are well illustrated by the amination of halobenzenes.

Isotopic Effects



- ❑ Isotope effect can be observed when one atom of a reactant molecule is replaced with another isotope of that atom. For example the replacement of hydrogen in a reactant molecule by deuterium which often causes a change in the rate of the reaction. This change in rate is known as the deuterium isotope effect. The deuterium isotope effect is expressed as k_H/k_D .
- ❑ During a chemical reaction if H-C, H-O, or H-N bond is not broken in the rate determining step, there will be no change by the substitution of deuterium for hydrogen. However, if H-C, H-O, or H-N bond is broken in the rate-determining step, the rate gets lowered by the substitution with deuterium.
- ❑ Deuterium isotope effects (k_H/k_D) usually range from 1 (no isotope effect at all) to ~7 or 8, although in a few cases, larger or smaller values have been reported.
- ❑ If the value of $k_H/k_D < 1$ then it is called inverse isotope effect.
- ❑ The ground-state vibrational energy (or the zero-point vibrational energy) of a bond depends on the mass of the atoms.
- ❑ The zero-point vibrational energy is less when the reduced mass is high.
- ❑ If zero point energy is lowered, then more energy is required to break a bond. The D-C, D-O, and D-N bonds, have lower vibrational energies in the ground state than the corresponding H-C, H-O, and H-N bonds in which hydrogen is replaced with deuterium.



The dissociation of a deuterium bond thus requires more energy than that for a corresponding hydrogen bond. The energy required to break a bond is significant for the determination of mechanism.

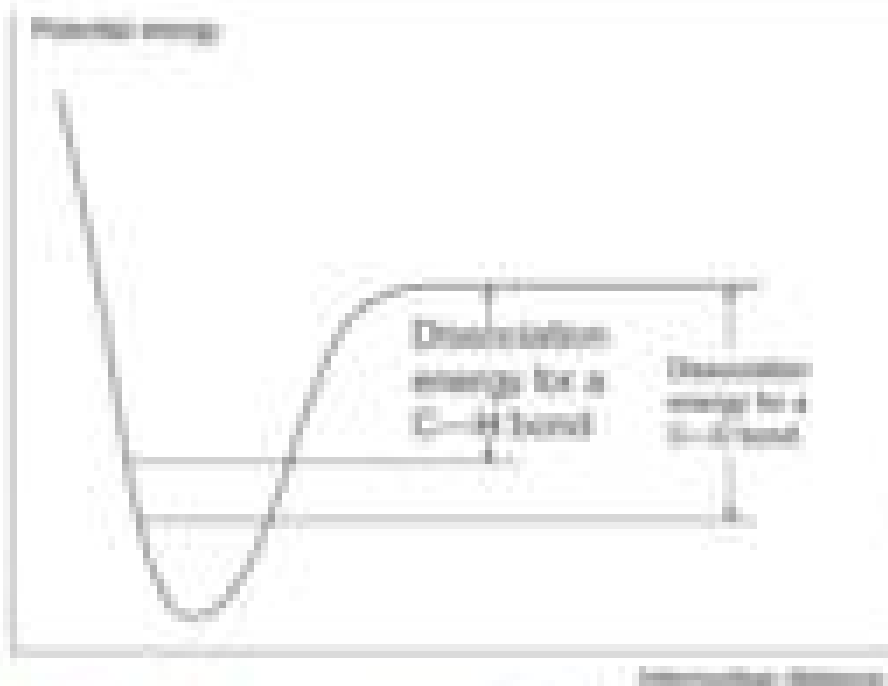



Fig. 19: Dissociation energy for C-D and C-H bonds, C-D bond has lower zero point than C-H bond

For example, the bromination of acetone involves tautomerization of the acetone and it is the determining step. The rate is independent of bromine concentration.



The rate-determining step of the tautomerization involves cleavage of a C-H bond. Thus there should be a substantial isotope effect if acetone is brominated.

The k_2/k_1 was found to be -7.6 .

- 
- ❑ A larger isotope effect can be observed on substitution of hydrogen by tritium.
 - ❑ Isotope effects have also been observed with other elements, but they are much smaller.
 - ❑ Deuterium isotope effects have been found even where it is certain that the C-H bond does not all in the reaction.
 - ❑ Such effects are called secondary isotope effects, the term primary isotope effect being reserved for the type discussed previously. Secondary isotope effects can be divided into α and β effects.
 - ❑ In a β secondary isotope effect, substitution of deuterium for hydrogen β to the position of bond cleavage slows the reaction.
 - ❑ The other type of secondary isotope effect results from a replacement of hydrogen by deuterium on a carbon containing the leaving group.
 - ❑ The γ secondary isotope effects have also been reported.
 - ❑ The solvent isotope effect is another known isotope effect.
 - ❑ A change in reaction rates is observed when the solvent is changed from H₂O to D₂O or from H₂SO₄ to D₂SO₄.
 - ❑ These changes may occur due to any of three factors or a combination of all of them.

ary

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