# Classification and determination of reaction mechanism

**Key words:** reaction mechanism, intermediates, kinetic studies, trapping of intermediates, rate of reaction

## Introduction

**Reaction mechanism is** a step by step description of a sequence of elementary reactions through which the overall chemical change occurs.

Which bonds are broken, which are formed, in what sequence/order, how many steps are involved and relative rates of each such steps are the details one can obtain through the study of reaction mechanism.

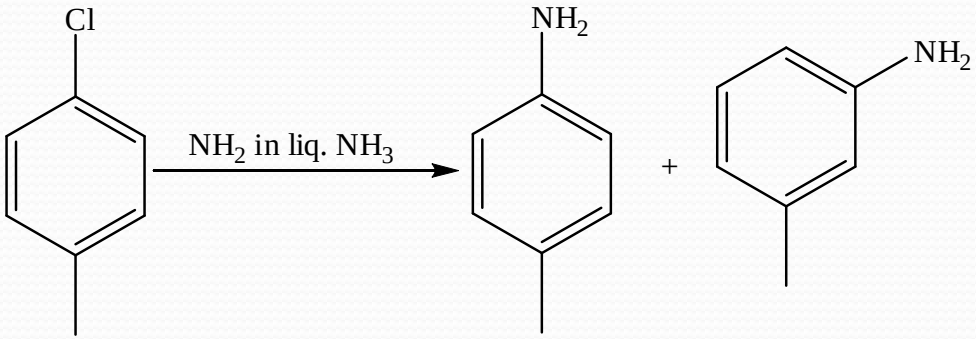
Course of reaction i.e. mechanism of reaction can be determined by various methods available.

- **Nature of products :**

Of all available ones, most useful information can be obtained by, study of products obtained, in course of a chemical reaction.

In organic reactions, more than one product can be obtained. So, in order to determine the mechanism of reaction, one should know the relative amount of products formed. This can be done by various methods available like chromatography, spectroscopy etc.

e.g. in reaction of p-chlorotoluene with amide in liquid ammonia, m-toluidine is also obtained, along with expected p-toluidine and is in fact major product.




Later can not be obtained by simple substitution of chloro by amino group. And if both products are obtained through same intermediates then, the former also, can not be obtained by direct substitution. And some different mechanism is taking place, in which, symmetrical intermediate is formed, which later proved to be benzyne intermediate.

## Kinetic studies :

Determining reaction mechanism from kinetic data is one of the most widely used techniques. This technique is based on the study of change in concentration of either the reactant or product.

The choice of method depends on its applicability to the reaction being studied. Some common methods include

Monitoring through periodic or continuous measurements (using spectroscopy, polarimetry), quenching and analyzing the reaction mixture at regular intervals by taking out aliquots etc.,

In a chemical reaction, a reacting species may be or usually different from what is been introduced into the reaction mixture. The relation between these two may be quite complex too.

In an aromatic nitration reaction, the effective attacking species is, $NO_2^+$, but changing concentration of $HNO_3$ is what one would typically measure.

Also, merely by observing the rates of chemical reaction, its mechanism can not be deduced.

In hydrolysis of alkyl halide in aqueous solution, rate is found to be, rate=k[alkyl halide].

From this equation, it can not be concluded that, water is not taking part in the rate determining step. But, its concentration is so large that it virtually remains unchanged.

Many organic reactions are carried out in solution and small changes in solvent can have profound effect on mechanism. This is particularly true for ion forming reactions, when used in polar solvents.

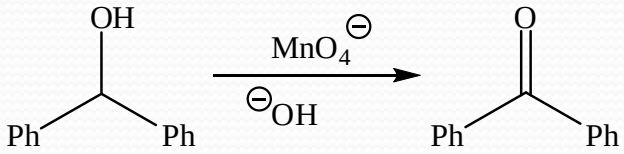
In contrast, reactions involving radicals are less influenced by solvents, but are influenced by the presence of radical sources or radical quenchers.

## ❑ Use of isotopes :

Whether, a particular bond is broken or not, in the rate determining step of a reaction under also provides useful information. Simple kinetic studies can not explicitly provide this information. But, can be obtained by **using isotopically labeled compounds.**

For example, whether C-H bond is being broken or not in the rate determining step can be confirmed by replacing the C-H bond of interest with a C-D bond and measuring the relative rates between modified and unmodified substrates .

Two bond dissociation energies will be different as the two atoms have different masses. This will influence the rate of reaction. E.g., The rate of oxidation of $Ph_2CHOH$ is 6.7 times faster than $Ph_2CDOH$.




This clearly indicates that C-H bond is involved in the rate determining step.

It is known as **Primary kinetic isotope effect**

The change in reaction rate that occurs upon isotope substitution is known as kinetic isotope effect.

An isotopic substitution will have a pronounced effect on the reaction rate when the isotopic substitution (i.e. D for H) is part of a chemical bond that is broken, formed or modified in the rate determining step. The magnitude of the effect is dependent on whether the bond with the isotopic substitution is being broken or formed (primary KIE) or if the hybridization of the atom to which isotope is attached is changing (secondary KIE).

In summary, primary kinetic isotope effect is a change in rate due to isotopic substitution at a site of bond breaking or bond making in the rate determining step of a mechanism.

Kinetic isotope effect can also be observed with other pair of isotopes such as H & T; $^{12}C$ & $^{13}C$ or $^{14}C$; $^{16}O$ & $^{18}O$; $^{35}Cl$ & $^{37}Cl$ etc.,

Kinetic isotope effects are expressed as the ratio of the reaction rates in the presence of the reactants when containing one isotope as compared to the other.

It is observed experimentally and its values are intermediate between unity i.e. no isotope effect and maximum as large as ~7 (at $25^0C$) in case of H & D.

For other elements, these values are low because relative mass difference is small.

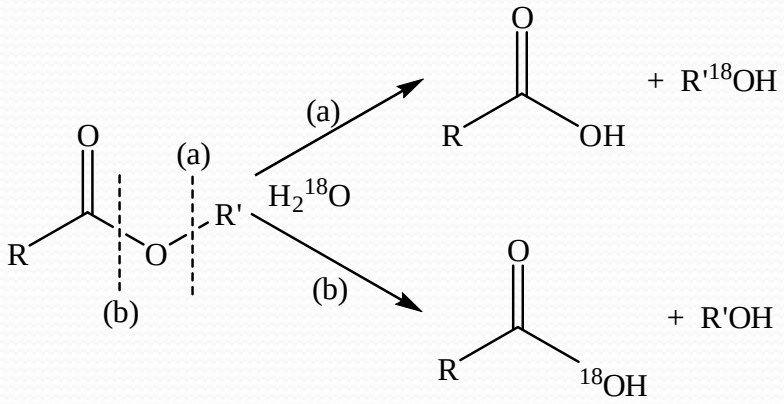
Secondary kinetic isotope effect, on the other hand, is the change in rate due to isotopic substitution at site(s) than that of bond breaking or bond making in the rate determining step of a mechanism.

# Primary Kinetic Isotope Effect: Typical Values

| Nuclide | $k_{light} / k_{heavy}$ (at 25°C) |
|---|---|
| C-H/C-D | 6 - 8 |
| C-H/C-T | 15 - 16 |
| $^{12}C/^{13}C$ | 1.04 |
| $^{12}C/^{14}C$ | 1.07 |
| $^{14}N/^{15}N$ | 1.03 |
| $^{16}O/^{18}O$ | 1.02 |
| $^{32}S/^{34}S$ | 1.01 |
| $^{35}Cl/^{37}Cl$ | 1.01 |

Isotope can also be used in studying mechanistic problems that are non-kinetic and useful information can be obtained by isotopic labeling.

e.g. Aqueous hydrolysis of esters to yield acid and alcohol can, in principle, proceed through alkyl or acyl oxygen fission.
If the reaction is carried out in labeled water containing $^{18}O$, *path-a* will give alcohol with $^{18}O$ and *path-b* will give acid with $^{18}O$ (shown below)

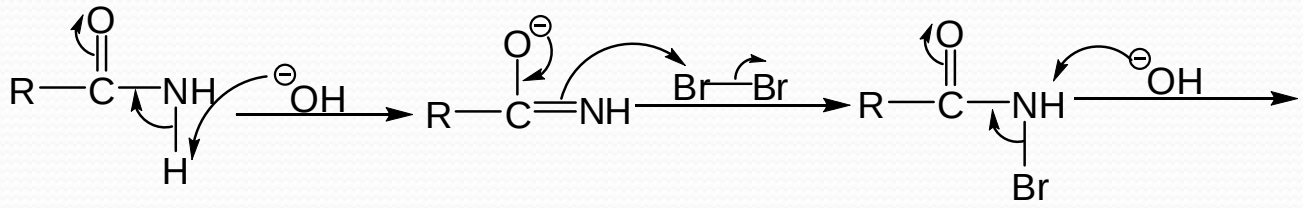



Most simple esters are found to yield $^{18}O$ enriched acid, indicating path (b) i.e., acyl oxygen fission.

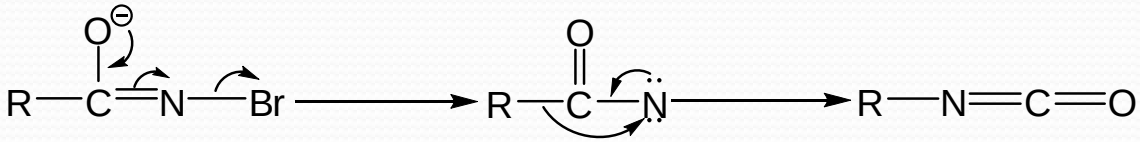
## Study of intermediates :

Among all these methods, most concrete evidence is obtained by, actual isolation of intermediate involved in the reaction.

In Hofmann rearrangement, thus, if carefully isolated, all intermediates can be obtained. These are N-bromoamide, its anion and an isocynate. This clearly gives insight of the mechanism of reaction.


N-bromoamide

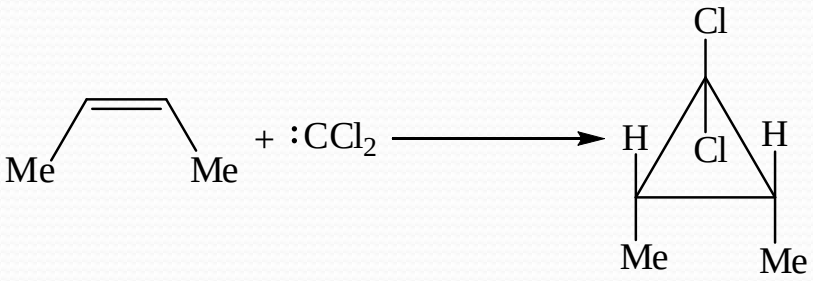



Isocynate

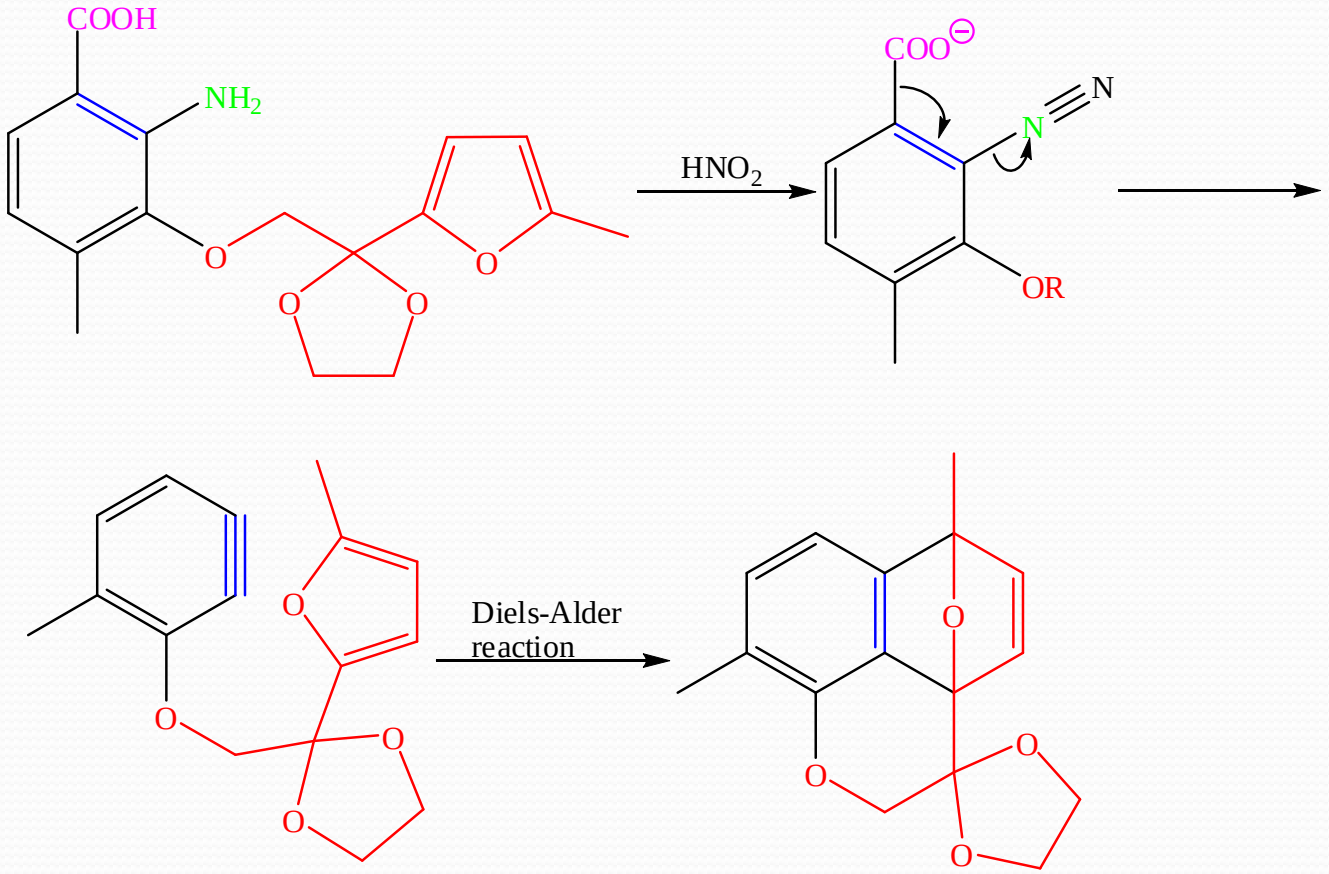
The isolated intermediate should be distinguishable from the final product or other side products. The species isolated should also be a true intermediate or should be in equilibrium with a true intermediate (toward establishing the mechanism convincingly)

Some intermediates are very **labile** to be isolated by regular techniques. Such species can be detected by physical techniques (spectroscopic methods such as ESR, NMR, IR), or by trapping with other species so as to divert it from forming the final product.

Presence of one such species, carbene can be confirmed by its reaction with cis-2-butene. It gives stable cyclopropane derivative.



Another example for the existence of of intermediate such as benzyne can be proven by trapping through a Diels-Alder reaction as shown below.



Application of Raman spectroscopic methods have helped in the detection of $NO_2^+$ species in nitration of benzene.

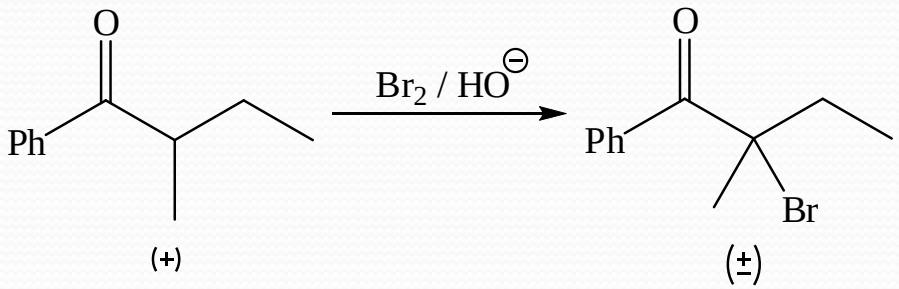
To be convincing, evidence for an intermediate should include:

- detection of intermediate in the reaction mixture, perhaps by trapping reaction
- demonstration that intermediate gives product when added to the reaction mixture i.e. it can be prepared as reasonably stable compound
- kinetic evidence that the rate of formation and rate of disappearance are adequate

## ❑Stereochemical criteria :

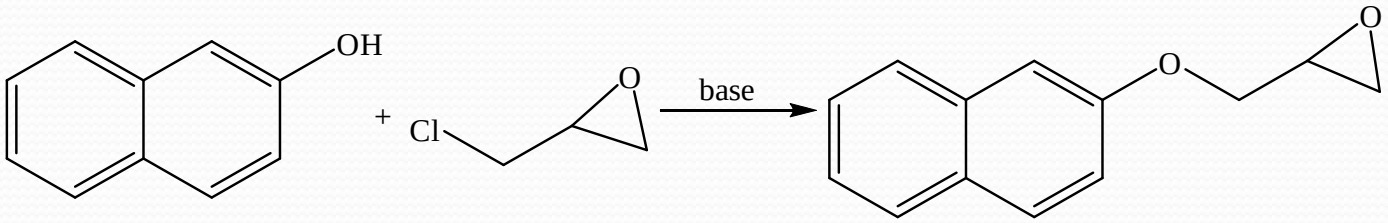
Study of stereochemistry of product can also provide some useful insight on the course of reaction.

Optically active stereoisomer of a ketone (shown below), on base catalyzed bromination, gives an optically inactive racemic product. This indicates the involvement of a planar transition state or intermediate, which can be attacked by the incoming nucleophile from both sides to give equal amount of both stereoisomers.



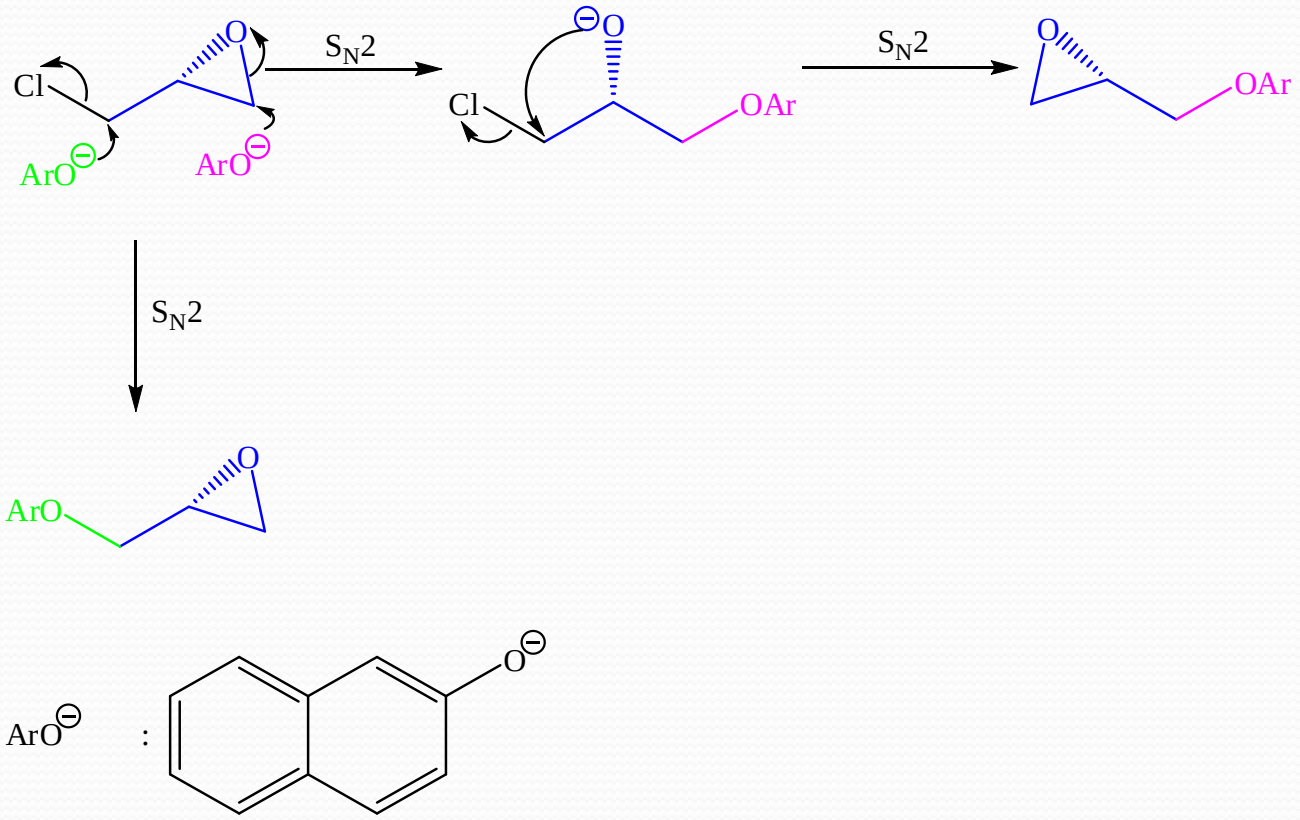

This implies that reaction must be taking place in two steps.

Another useful reaction is nucleophilic substitution of epichlorohydrin by naphthyloxide anion.




Investigation of product formed in the reaction, when enantiomerically pure epichlorohydrin is used, suggests that, reaction can not be taking place by simple $S_N2$ pathway. As it would give the product with opposite stereochemistry, than is obtained in the reaction.

Formation of the product other than expected can be accounted by taking into consideration, the other way of nucleophilic substitution.




In fact the reaction goes through this mechanism where naphthyloxide anion attacks other side of epoxide ring, resulting in ring opening and then followed by ring closure other way round.