

Methods of determining organic reaction mechanism

Reaction mechanism:

A reaction mechanism is the actual process by which a reaction takes place. It explains which bonds are broken, in what order, how many steps are involved, the relative rate of each step etc.

- The reaction mechanism describes the sequence of elementary reactions that must occur to go from reactants to products.
- Reaction intermediates are formed in one step and then consumed in a later step of the reaction mechanism.

Thermodynamic and kinetic requirements for a reaction

Thermodynamic requirements for a chemical reaction :

For a reaction to take place spontaneously, the free energy of the products must be lower than the free energy of the reactants. i.e. 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

To be ΔG negative, there should be decrease in enthalpy and increase in entropy of the system.

For many reactions entropy effects are small and it is the enthalpy that mainly determines whether the reaction can take place spontaneously. However, in certain types of reactions, entropy is important and can dominate enthalpy. Some of the examples are:

1. Generally, **gases have higher entropy than liquids and solids** because the molecules of gas have much more randomness. Liquids have higher entropy than that of solids but lower than that of gases. Hence, any reactions in which the reactants are solids and the products are liquids and gases are thermodynamically favored.
2. **When the number of products formed are more than that of reactants**, degree of freedom increase and hence entropy also increases making the reaction thermodynamically favored. On the other hand, reactions in which the **number of product molecules is less than the number of reactant molecules**, entropy decreases and in such cases there must be significantly decrease in enthalpy to be ΔG negative.

3. An **open chain molecule** has more entropy than a **similar cyclic molecule** because there are more conformations. Hence, ring opening reactions are thermodynamically favorable.

Kinetic requirements for a chemical reaction :

A negative ΔG is a necessary but not a sufficient condition for a reaction to occur spontaneously. For example, the reaction between H_2 and O_2 to give H_2O has a large negative ΔG , but mixtures of H_2 and O_2 can be kept at room temperature for many centuries without reacting to any significant extent.

So, for a reaction to occur, the chemical reactions require some activation energy. Activation energy is defined as the minimum amount of extra energy required by a reacting molecule to get converted into product. It can also be described as the minimum amount of energy needed to activate or energize molecules or atoms so that they can undergo a chemical reaction or transformation.

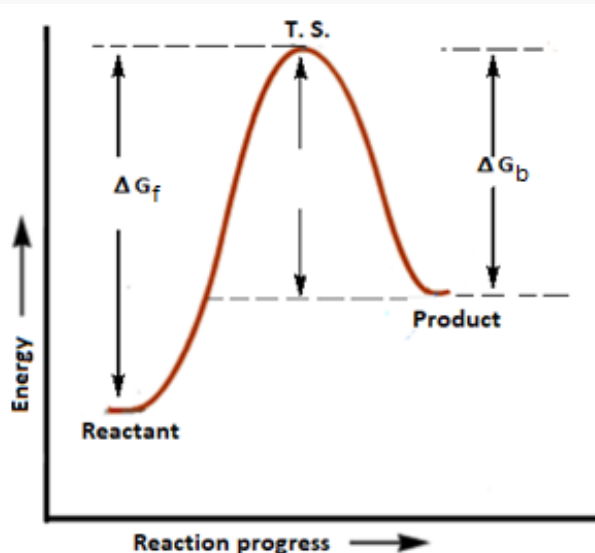


Fig. Free energy profile diagram for endothermic reaction.

In the above energy profile diagram, ΔG_f is the free energy of activation for forward reaction and ΔG_r is the free energy of activation for backward reaction.

Kinetically vs Thermodynamically controlled reaction

Let us consider a chemical reaction in which a reactant 'A' gives two different products 'B' and 'C' by different mechanisms.

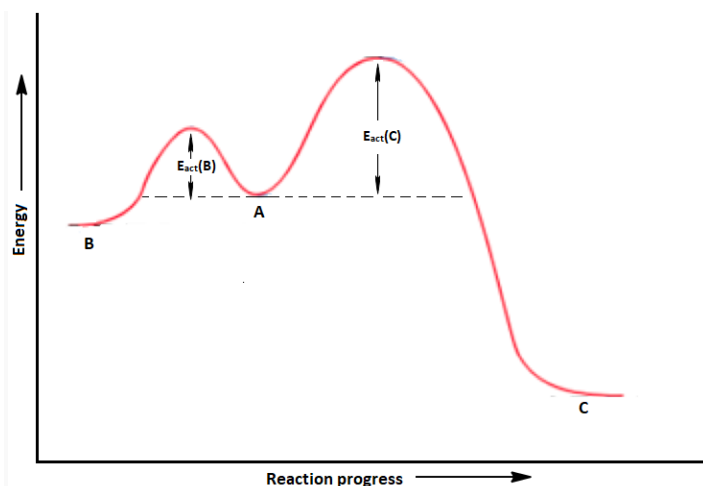


Fig. Energy profile diagram illustrating kinetic vs thermodynamic control of products.

In this figure, 'C' is thermodynamically more stable (due to lower energy) but 'B' is formed faster (due to lower energy of activation).

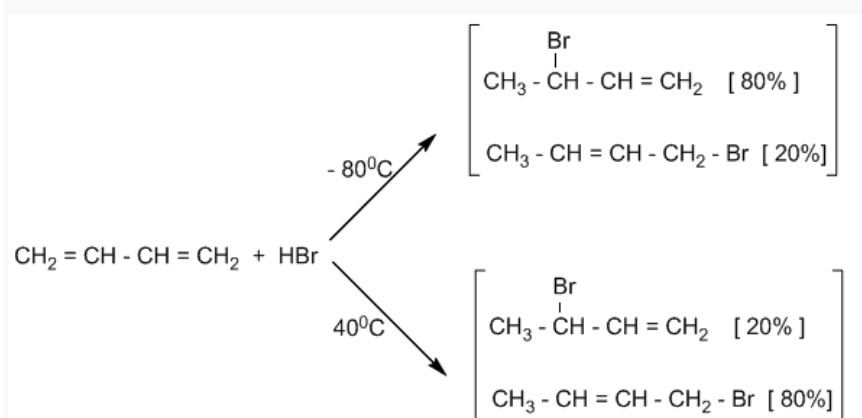
If the reaction is irreversible, energy of activation is lower for the formation of B, so B is formed faster. So, the product 'B' is said to be kinetically controlled.

However, if the reaction is permitted to approach equilibrium (i.e. if the reaction is reversible), the more stable product C predominates. Under these conditions, the product B that is first formed reverts to A. So, the product 'C' is said to be thermodynamically controlled.

Example of kinetic and thermodynamic control of the reaction :

The kinetic and thermodynamic control of the reaction can be understood by taking an example of addition of HBr to 1,3-butadiene.

Addition of HBr to 1,3-butadiene gives two types of products: 1,2-addition product and 1,4-addition product.



Mechanism :

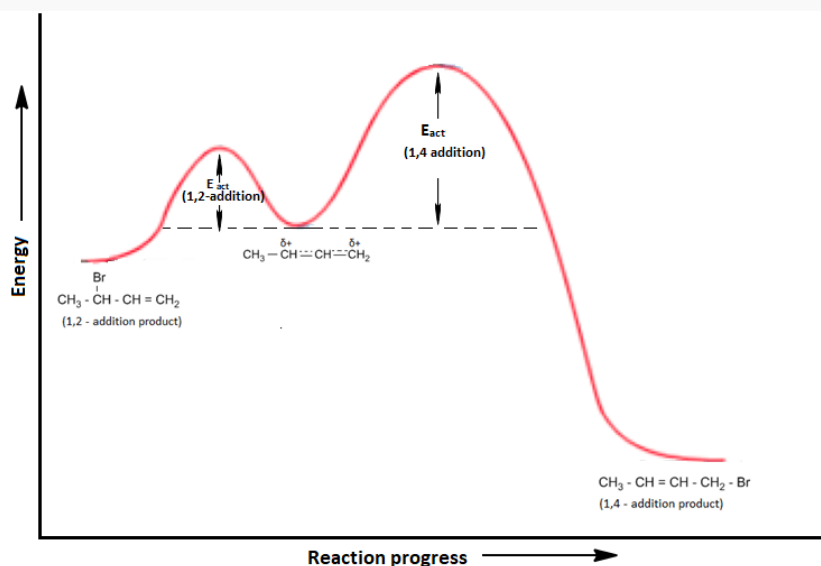
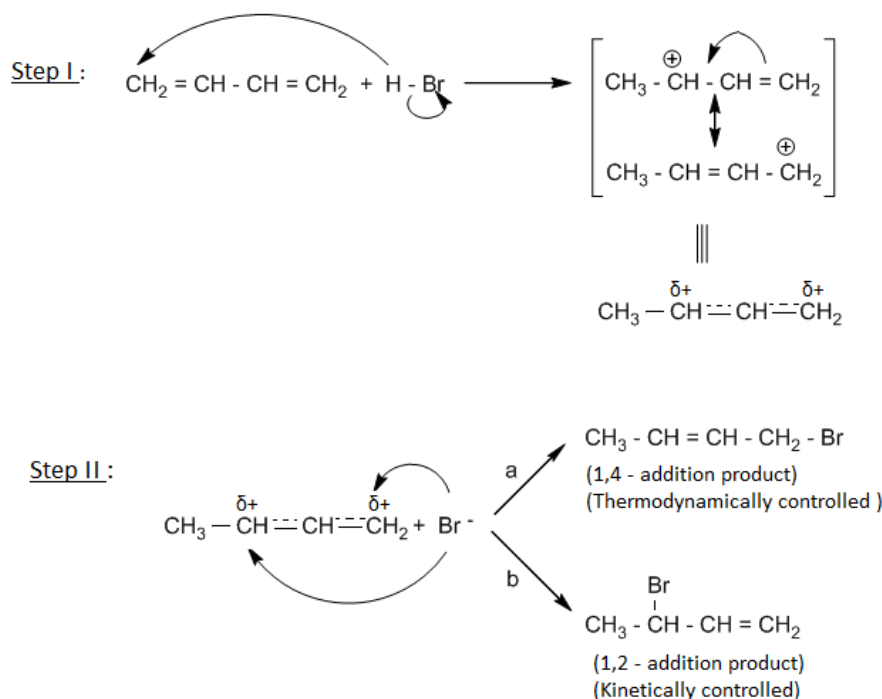


Fig. Energy profile diagram illustrating kinetic vs thermodynamic control of products.

From the above data, it can be concluded that at -80°C , 1,2-product is formed faster than 1,4-product due to less energy of activation for 1,2-product. 1,2-addition product is formed as a major product. Thus 1,2-addition product is kinetically controlled product.

But when the temperature is raised the equilibrium is attained and the reaction becomes reversible. At this condition, the 1,4-addition product is formed as a major product because it is more stable (less energy) than 1,2-addition product. The 1,2-product is formed faster but it ionizes and converts into more stable 1,4-addition product. Thus 1,4-addition product is thermodynamically controlled.

Difference between transition states and intermediates:

The transition state refers to an imaginary molecule having zero life time and cannot be isolated. In this state the system possesses maximum energy and is most unstable. It is impossible to observe them directly and information about their geometries must be obtained from inference.

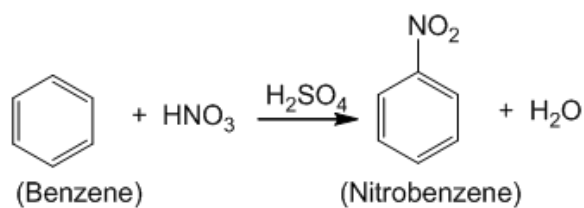
On the other hand, the relatively stable products formed from the reactants during reaction that further reacts to give the final product is called intermediate. The energy of intermediate is less than that of transition state and can be isolated and studied. Their geometries can be obtained by using many techniques such as IR, NMR spectroscopy, etc. We often use the knowledge of intermediates to determine the shape and geometry of transition states.

Methods of determining reaction mechanisms:

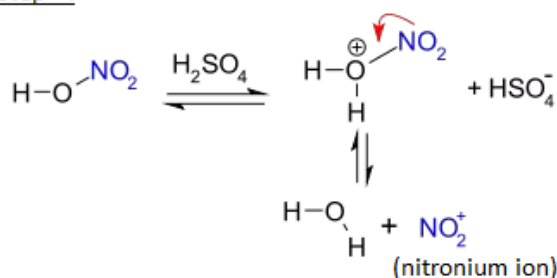
There are a number of commonly used methods for determining reaction mechanism. In most cases, one method is not sufficient. Reaction intermediates are the important class of chemical species, which are quite helpful in understanding the mechanism of a chemical reaction.

1. Detection of intermediates:

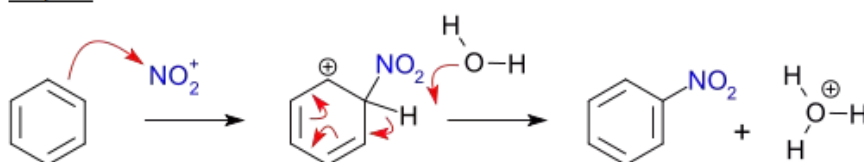
In many cases, intermediate cannot be isolated but can be detected. It can be detected by IR, NMR or other spectroscopic technique. The detection of Raman spectra of NO_2^+ (nitronium ion) indicates that nitronium ion is an intermediate in nitration of benzene. Hence, nitration of benzene is electrophilic substitution reaction and the following mechanism for the nitration of benzene was proposed:



Step - I

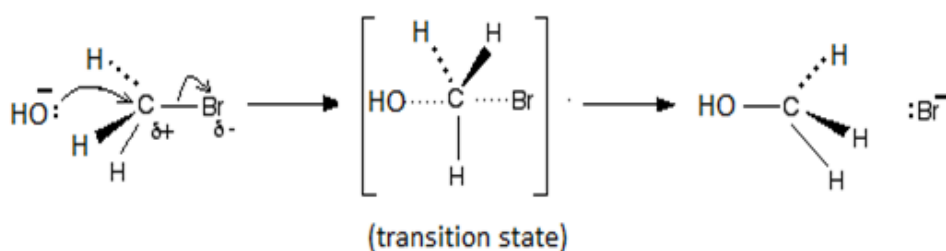
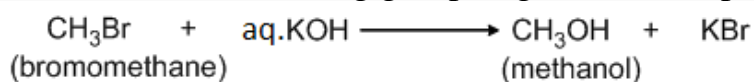


Step - II



2. Stereochemical evidence:

If the products of a reaction are capable of existing in more than one stereoisomeric forms, the form which is obtained may give information about the mechanism. For example, in $\text{S}_{\text{N}}2$ reaction the product obtained is always inverted. This is only possible if the attack of nucleophile and removal of leaving group takes place simultaneously. In such cases, nucleophile attacks from backside of leaving group to give inverted product.



3. Kinetic evidence:

The rate of a homogeneous reaction is the rate of disappearance of a reactant or appearance of a 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.

Example: In the determination of kinetics of the reaction between bromomethane and sodium iodide, the rate expression derived from the experimental data is obtained. The rate of the reaction depends on the concentration of both reactants therefore, both are involved in the rate-determining step.

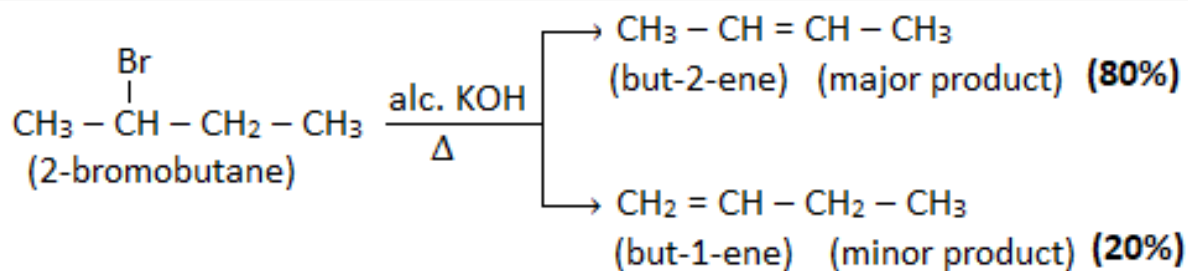


Kinetics investigations are the single most important group of techniques in mechanistic determinations. Various kinetics parameters like order of a reaction, rate law, rate constants, kinetic isotope effects, etc. summed up with other evidences provide great insights into the mechanisms to be proposed. 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.

4. Identification of products:

Identification of the products of a reaction also helps to define the reaction mechanism.

For example, elimination reaction of 2-bromobutane.



From the identification of but-2-ene as major product and but-1-ene as minor product, following mechanism can be proposed:

Q) Show that hydrolysis of ethyl acetate occurs acyl-oxygen bond fission but not ethyl-oxygen bond fission with the help of tracer technique.

6. Crossover Experiments:

The results of crossover experiments are often straightforward to analyze, making them one of the most useful and most frequently applied methods of mechanistic study. In organic chemistry, crossover experiments are most often used to distinguish between intramolecular and intermolecular reactions.

In crossover experiment the reaction is carried out with a mixture of two similar but non-identical reactants. After completion of the reaction, the products are analyzed. Since the migrating group must come free in a intermolecular rearrangement (that is two step reaction), one should obtain a product containing fragments of both the reactants in such a process. This product is known as crossover product. Thus formation of crossover product confirmed that the rearrangement is intermolecular. If no crossover product is formed then the rearrangement will be intramolecular.

Example: Claisen rearrangement involves conversion of an allyl phenyl ether into an allyl alcohol. No crossover products were obtained when two different ethers were heated together. This confirmed the rearrangement to be intramolecular. On the other hand, if the migrating group (allyl group) of reactant 1 migrates to the ortho position of the phenyl ring of reactant 2, the rearrangement is referred to as intermolecular.

