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GENERATION OF INTERMEDIATES

Review Article

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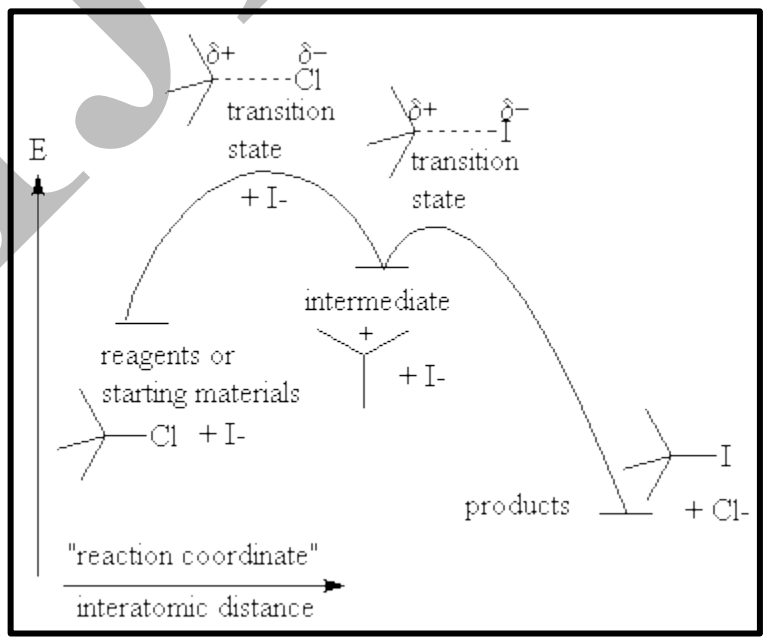
Abstract :
This study involved explanation about intermediate .Intermediate: In a chemical reaction or mechanism, any reacting species which is no longer starting material or reactant, and has not yet become product, and which is not a transition state.

Keywords : process , reactant , product , energy .

Introduction :

The easiest way to understand the difference between a transition state and an intermediate is to use what is commonly called a reaction (energy) diagram, like the one below. For a simple reaction like the S_N1 reaction of 2-chloro-2-methylpropane with iodide, we know that the rate-determining step is breaking the C-Cl bond, i.e. ionization to form a carbocation. Thus we could make a graph of the change in energy as a function of C ... Cl distance (at least for the first part of the reaction). The only energy values that are actually measurable are the energies of the transition state and the carbocation relative to the halide, but we assume the energy changes smoothly. The energy of the 2-chloro-2-methylpropane with its bond partially broken is actually higher than the energy of the carbocation and it is this highest energy state that is the *transition state*. Any stretching or shrinking of the C...Cl distance from that transition state is downhill in energy, and, just like a ball, it rolls to the bottom of that energy "hill". The transition state has essentially no lifetime - it is a fleeting arrangement that happens to have the highest energy.

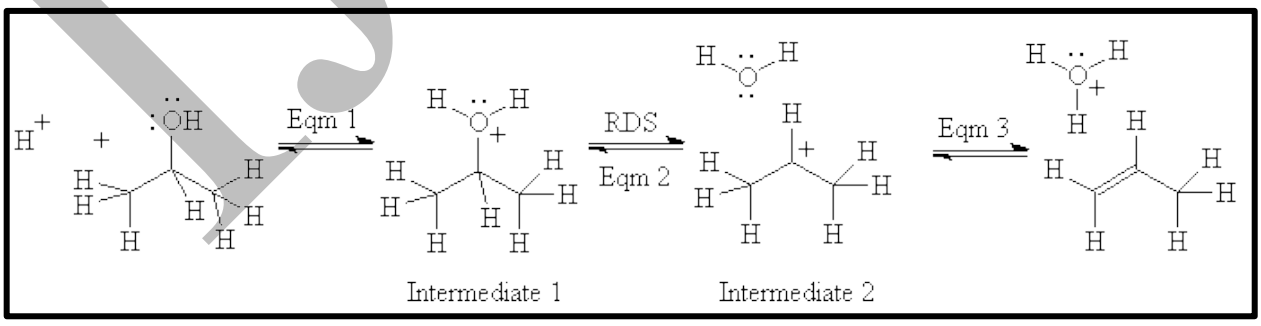


An intermediate differs from a transition state in that the intermediate has a discrete lifetime (be it a few nanoseconds or many days), whereas a transition state lasts for just one bond vibration cycle. Intermediates may be unstable molecules (in which case they are called reactive intermediates) or highly stable molecules.
The carbocation, once it is made, is stabilized by solvation, and can move closer or farther from the chloride without being destroyed, so it lasts for a little while before reacting with the iodide, i.e., it has a lifetime. The finite lifetime, created by the small energy "hills" around it, is what makes the carbocation an intermediate and not a transition state.

In many reactions, lots of distances are changing simultaneously, for example, in the E2 reaction, 3 bonds are made and broken at once. Even in the ionization of 2-chloro-2-methylpropane, several things are happening in addition to the stretching of the C...Cl distance: the methyl groups are moving away from each other and the carbon is changing its hybridization from sp^3 to sp^2as it becomes positively charged. Thus, most of the reaction (energy) diagrams we make are rather vague about the x-axis, calling it "reaction coordinate" rather than labeling it with any particular distance. We are essentially making a plot of a molecular roller-coaster ride by omitting all the twists and turns and plotting only the ups and downs.

Writing Mechanisms with Intermediates
When you write a mechanism, you do not have to include the reaction (energy) diagram, just the steps showing all the intermediates. Here are the conventions for writing a particular mechanism:

1. Show all intermediates that you know about as separate sequential drawings (part E gives tips for figuring out what might come next).
2. Link all intermediates by straight arrows, double if you know the step is reversible and single if you know it is not. Each set of arrows followed by a new structure is a step.
3. Show one change in bonding for each step (e.g. for E1: ionization, removal of proton), unless you know that more than one bond is changed in a given step (e.g. E2).
4. If there are steps that you have little evidence about because they are after the rate determining step, use analogies to other known reactions to fill in the blanks (e.g. loss of a proton after an acid-catalyzed reaction)
5. If necessary, add an intermediate to the set you know about, again using analogies to other known reactions, to ensure that only one bond-making / bond-breaking occurs for each step.
6. If there are no known intermediates , Here is an annotated example using the dehydration of an alcohol:



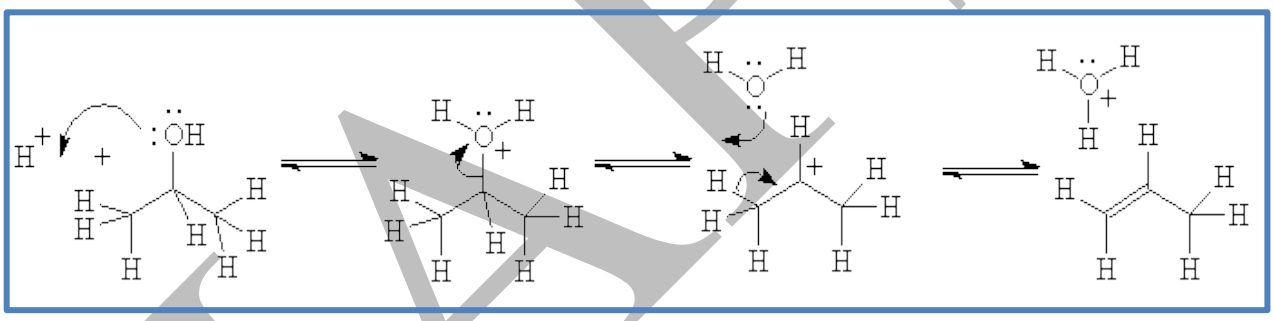
Equilibrium 1: reaction is acid-catalyzed; spectroscopy shows the conjugate acid of the alcohol, intermediate 1, is formed very fast - proton transfers are almost never rate-determining steps for other reactions.
Equilibrium 2: the rate determining step (acid and alcohol concentrations affect the rate). Evidence for a carbocation, intermediate 2? With all alcohols, some substitution is observed, more if the acid is something like HBr, whose conjugate base is nucleophilic; with some alcohols, rearrangement occurs.

Both of these observations are consistent with carbocation formation (and not with concerted, carbanion or radical reactions)
Equilibrium 3: This reaction cannot be readily observed under these reaction conditions since it is after the rate-determining step. However, we observe separately that alkenes dissolve in concentrated sulfuric acid, and thus must undergo an acid-base reaction themselves (protonation) to form soluble ions, which must be carbocations.

Note that this whole reaction is reversible, and in fact, alkenes can be hydrated to form alcohols. How would you change the conditions to produce alcohol as the major product from this equilibrium?

Understanding and Predicting Mechanisms:
To help us understand how and why these steps occur, we add one important detail to the outline of a mechanism above: *we show how the electrons are used*. For the bonds to break and form, electrons must change their affiliation: unshared become shared, shared with one atom become shared with another.
We illustrate this dynamic process with a curved arrow for each electron pair which

1. starts in the middle of the original location of the electron pair,
2. ends at the middle of the final location of the electron pair, as shown below, and
3. uses the electrons at a negative or d- site for binding to positive or d+ site.

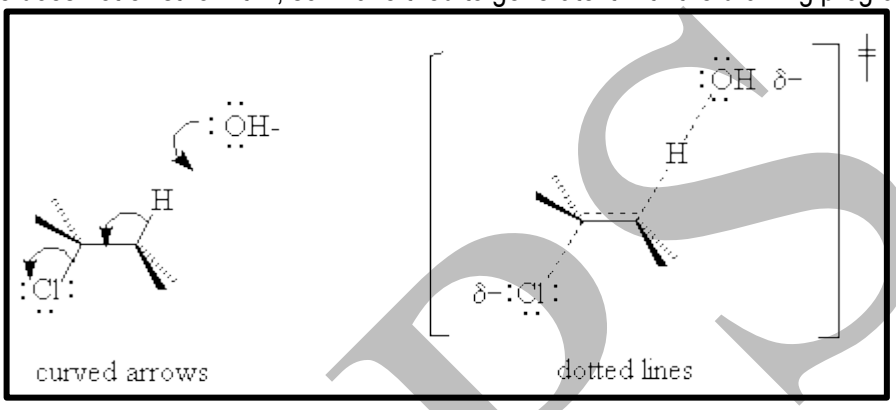


To avoid confusion, arrows may never be used to show the motion of molecules or ions.

Note that this convention for drawing mechanisms is a shorthand. What is "really" happening is that atoms are rehybridizing and otherwise reorganizing orbitals to adjust to new bonding patterns. The arrows show what electron reorganization has to occur to convert the structure with the arrows into the *next* one in the sequence of steps in the mechanism, i.e. the structure after the arrow. Our shorthand does not automatically show stereochemistry - we have to arrange the molecule so that we convey that information too.
These arrows are powerful tools to help clarify our thinking about mechanism. They give us a formalism to show how bonds are broken and made during a reaction which allows us to predict reactions that *might* occur in new compounds with new reagents. They are very useful for keeping track of what does happen - if you use the arrows, they will help you remember the mechanism without memorizing a sequence of structures. Some instructors require that they be included in the mechanism that you write. Learn to use them and it will make your life easier.
The curved arrow notation is also very good at showing the effect of resonance stabilization on a reaction - the arrow notation is also used to illustrate the relationship between contributors to a resonance hybrid. If your drawings include contributors to a resonance hybrid, enclose all the sketches of the same molecule in square brackets (the standard connection is a double-headed arrow, but you can omit that) to let people know that the sequence of structures is a set of drawings of one molecule. See the tips by Liina Ladon for further help.

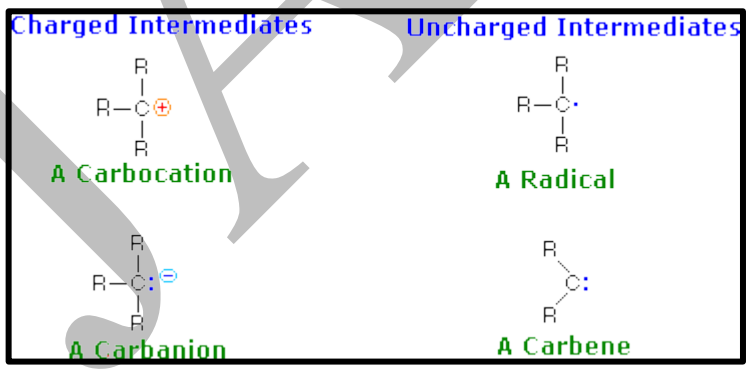
Mechanisms without Intermediates:

If experiments indicate that no intermediates exist, that the reagents are converted to products in one step, the reaction is said to be "concerted". Such reactions are even called "no mechanism" reactions. Many of them are stereospecific (e.g. E2 and S_N2), and we know from the rate law what ingredients go into the transition state, so we do know a lot about how they happen. We do in fact know the mechanism - it is just short. To tell people what we know, we try to make a sketch of the transition state. There are two ways to do this: with curved arrows or with dotted lines (the dotted lines are a simplified version of a molecular orbital picture). The E2 reaction is shown below in both notations. Be sure your transition state is in parentheses to indicate its instability and labeled as such. The character traditionally used for transition state does not exist for html, so I have tried to generate it with the drawing program.



Reactive Intermediates

The products of bond breaking, shown above, are not stable in the usual sense, and cannot be isolated for prolonged study. Such species are referred to as reactive intermediates, and are believed to be transient intermediates in many reactions. The general structures and names of four such intermediates are given below.

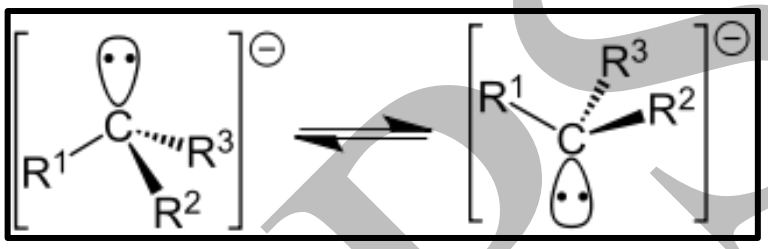


A pair of widely used terms, related to the Lewis acid-base notation, should also be introduced here.

Electrophile: An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.
Nucleophile: An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile (or Lewis acid).

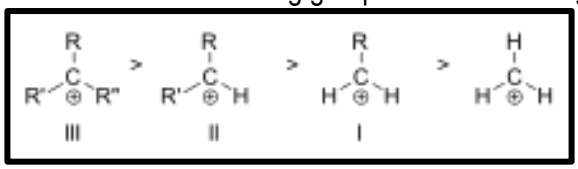
Using these definitions, it is clear that carbocations (called carbonium ions in the older literature) are electrophiles and carbanions are nucleophiles. Carbenes have only a valence shell sextet of electrons and are therefore electron deficient. In this sense they are electrophiles, but the non-bonding electron pair also gives carbenes nucleophilic character. As a rule, the electrophilic character dominates carbene reactivity. Carbon radicals have only seven valence electrons, and may be considered electron deficient; however, they do not in general bond to nucleophilic electron pairs, so their chemistry exhibits unique

differences from that of conventional electrophiles. Radical intermediates are often called free radicals. The importance of electrophile / nucleophile terminology comes from the fact that many organic reactions involve at some stage the bonding of a nucleophile to an electrophile, a process that generally leads to a stable intermediate or product. Reactions of this kind are sometimes called ionic reactions, since ionic reactants or products are often involved. The shapes ideally assumed by these intermediates becomes important when considering the stereochemistry of reactions in which they play a role. A simple tetravalent compound like methane, CH_4, has a tetrahedral configuration. Carbocations have only three bonds to the charge bearing carbon, so it adopts a planar trigonal configuration. Carbanions are pyramidal in shape (tetrahedral if the electron pair is viewed as a substituent), but these species invert rapidly at room temperature, passing through a higher energy planar form in which the electron pair occupies a p-orbital. Radicals are intermediate in configuration, the energy difference between pyramidal and planar forms being very small. Since three points determine a plane, the shape of carbenes must be planar; however, the valence electron distribution varies.

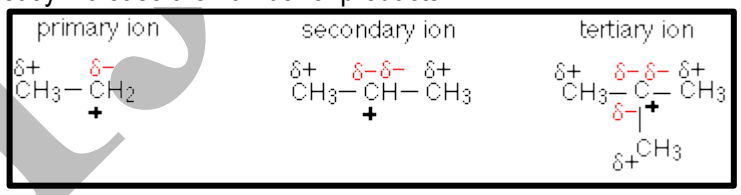


Carbocation Rearrangement and Stability:

Carbocations are most stable next to electron donating groups. Alkanes are slightly electron donating.



This explains why S_N1 and E1 reactions need a secondary or tertiary α -carbon.
The carbocation-like transition state of the tertiary α -carbon is more stable than that of the secondary α -carbon, and so on. Increased stability of the rate-limiting transition state increases the rate of the reaction.
Some secondary α -carbocations take stability into their own hands and rearrange to form tertiary carbocations. Such rearrangements greatly increase the number of products.



Reaction Intermediates :

A – Radical :

- Typically electrons come in pairs. However there are unpaired electrons known as radical electrons. These are usually just called radicals.
- Radical stability : Radicals prefer a greater degree of alkyl substitution. Even more so, radicals prefer to be in the allylic position.

B- Carbocation :

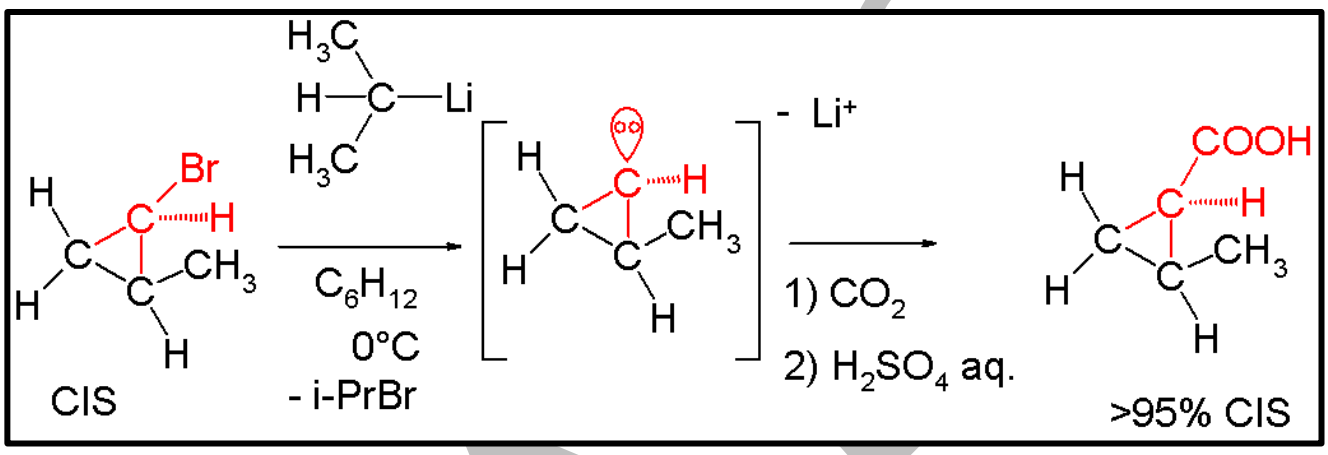
- Carbocations serve as electrophiles in reactions. They will attract electrons easily as the carbon is deficient in electrons.
- Carbocation stability : Carbocations prefer a greater degree of alkyl substitution. Even more so, carbocations prefer to be in the allylic position.

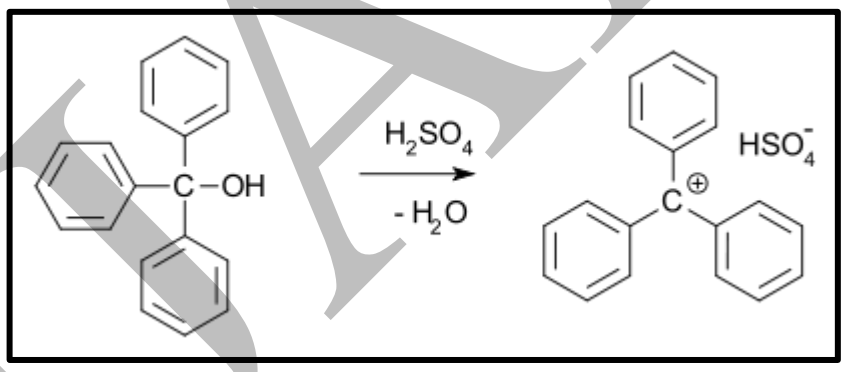
C-Carbanion :

- Carbanions serve as nucleophiles in reactions. They will donate electrons easily as the carbon has excess electrons.
- Carbanion stability : Carbanions prefer a lesser degree of alkyl substitution. Even more so,

carbanions prefer to be in the allylic position.

Example:

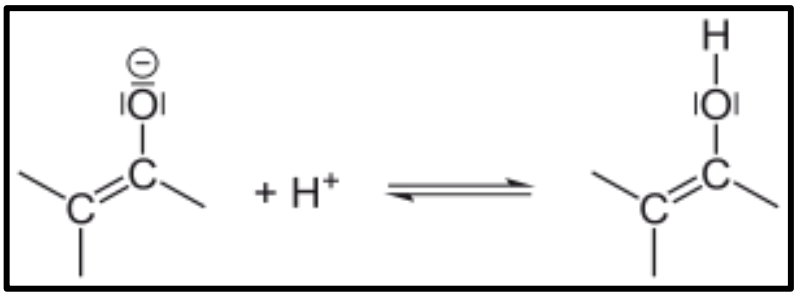


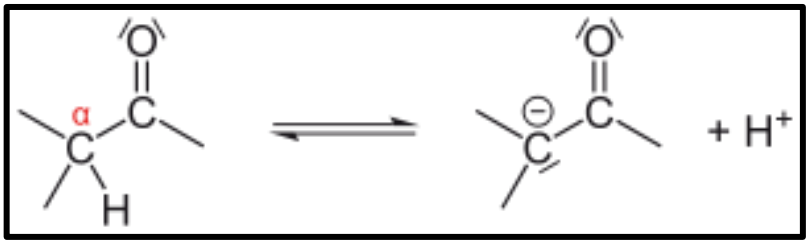


Enolates:

When *keto-enol tautomerism* occurs the keto or enol is deprotonated and an anion, which is called the enolate, is formed as intermediate. Enolates can exist in quantitative amounts in strictly Brønsted acid free conditions, since they are generally very basic. In enolates the anionic charge is delocalized over the oxygen and the carbon . Enolates are somewhat stabilized by this delocalization of the charge over three atoms.

Keto-enol-tautomerism





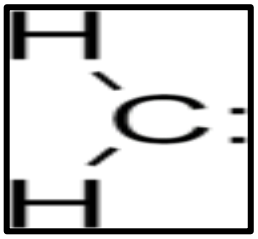
Carbene :

In chemistry, a carbene is a molecule containing a neutral carbon atom with a valence of two and two unshared valence electrons. The general formula is R-(C:)-R' or R=C:.

The term "carbene" may also refer to the specific compound H_2C:, also called methylene, the parent hydride from which all other carbene compounds are formally derived.

Carbenes are classified as either singlets or triplets depending upon their electronic structure. Most carbenes are very short lived, although persistent carbenes are known.

One well studied carbene is dichlorocarbene Cl_2C: , which can be generated *in situ* from chloroform and a strong base.



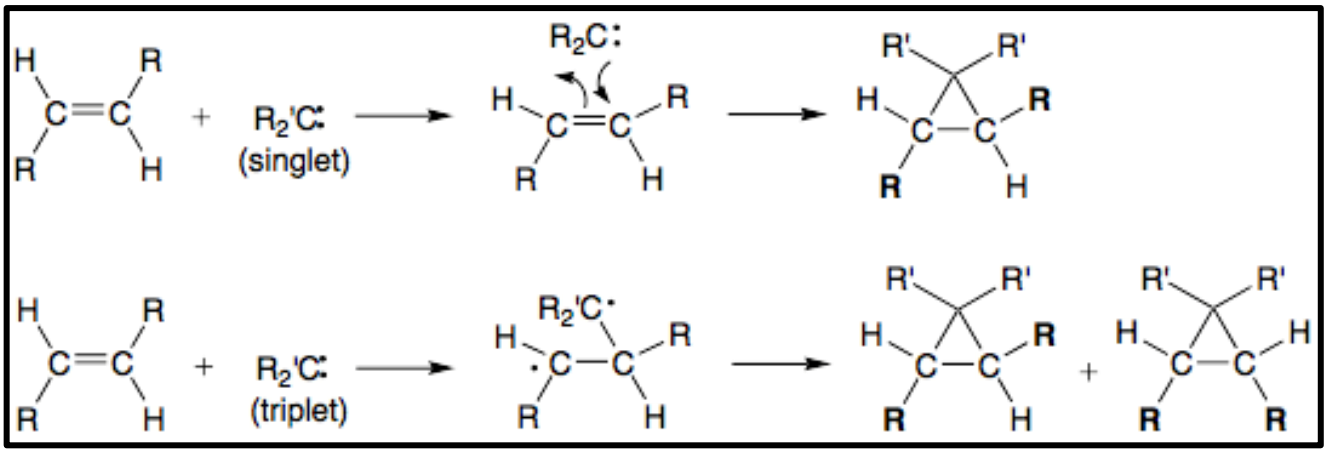
Reactivity of Carbene:

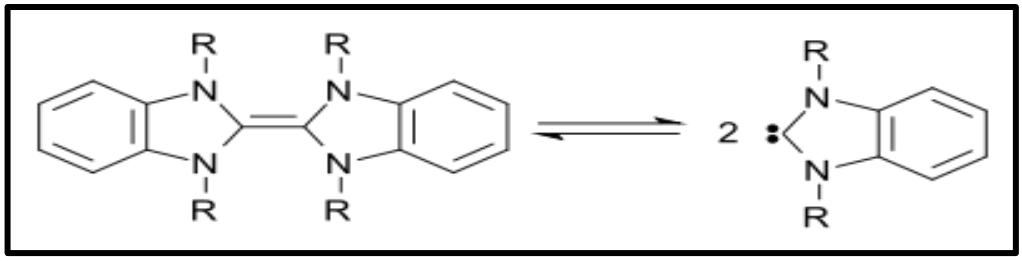
Singlet and triplet carbenes exhibit divergent reactivity. Singlet carbenes generally participate in cheletropic reactions as either electrophiles or nucleophiles. Singlet carbenes with unfilled p-orbital should be electrophilic. Triplet carbenes can be considered to be di radicals, and participate in stepwise radical additions. Triplet carbenes have to go through an intermediate with two unpaired electrons whereas singlet carbene can react in a single concerted step.

Due to these two modes of reactivity, reactions of singlet methylene are stereospecific whereas those of triplet methylene are stereo selective. This difference can be used to probe the nature of a carbene. For example, the reaction of methylene generated from photolysis of diazomethane with *cis*-2-butene or with *trans*-2-butene each give a single diastereomer of the 1,2-dimethylcyclopropane product: *cis* from *cis* and *trans* from *trans*, which proves that the methylene is a singlet.[5] If the methylene were a triplet, one would not expect the product to depend upon the starting alkene geometry, but rather a nearly identical mixture in each case.

Reactivity of a particular carbene depends on the substituent groups. Their reactivity can be affected by metals. Some of the reactions carbenes can do are insertions into C-H bonds, skeletal rearrangements, and additions to

double bonds. Carbenes can be classified as nucleophilic, electrophilic, or ambiphilic. For example, if a substituent is able to donate a pair of electrons, most likely carbene will not be electrophilic. Alkyl carbenes insert much more selectively than methylene, which does not differentiate between primary, secondary, and tertiary C-H bonds.





Generation of Carbene :

- A method that is broadly applicable to organic synthesis is induced elimination of halides from gem-dihalides employing organolithium reagents. It remains uncertain if under these conditions free carbenes are formed or metal-carbene complex. Nevertheless, these metallocarbenes (or carbenoids) give the expected organic products.

  $R_2CBr_2 + BuLi \rightarrow R_2CLi(Br) + BuBr$

  $R_2CLi(Br) \rightarrow R_2C + LiBr$

  - For cyclopropanations, zinc is employed in the Simmons–Smith reaction. In a specialized but instructive case, alpha-halomercury compounds can be isolated and separately thermolyzed. For example, the "Seyferth reagent" releases CCl_2 upon heating.

  $C_6H_5HgCCl_3 \rightarrow CCl_2 + C_6H_5HgCl$

    - Most commonly, carbenes are generated from diazoalkanes, via photolytic, thermal, or transition metal-catalyzed routes. Catalysts typically feature rhodium and copper. TheBamford-Stevens reaction gives carbenes in aprotic solvents and carbenium ions in protic solvents.
    - Base-induced elimination HX from haloforms (CHX_3) with under phase-transfer conditions.
    - Photolysis of diazirines and epoxides can also be employed. Diazirines are cyclic forms of diazoalkanes. The strain of the small ring makes photoexcitation easy. Photolysis of epoxides gives carbonyl compounds as side products. With asymmetric epoxides, two different carbonyl compounds can potentially form. The nature of substituents usually favors formation of one over the other. One of the C-O bonds will have a greater double bond character and thus will be stronger and less likely to break. Resonance structures can be drawn to determine which

part will contribute more to the formation of carbonyl. When one substituent is alkyl and another aryl, the aryl-substituted carbon is usually released as a carbene fragment.

- Carbenes are intermediates in the Wolff rearrangement

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