College of Education for Pure Science
Department of Chemistry

Summary of Reactive Intermediates

In chemistry, a reactive intermediate or an intermediate is a short-lived, high-energy, highly reactive molecule. When generated in a chemical reaction, it will quickly convert into a more stable molecule. Only in exceptional cases can these compounds be isolated and stored, e.g. low temperatures, matrix isolation. When their existence is indicated, reactive intermediates can help explain how a chemical reaction takes place.

Most chemical reactions take more than one elementary step to complete, and a reactive intermediate is a high-energy, yet stable, product that exists only in one of the intermediate steps. The series of steps together make a reaction mechanism. A reactive intermediate differs from a reactant or product or a simple reaction intermediate only in that it cannot usually be isolated but is sometimes observable only through fast spectroscopic methods. It is stable in the sense that an elementary reaction forms the reactive intermediate and the elementary reaction in the next step is needed to destroy it.

When a reactive intermediate is not observable, its existence must be inferred through experimentation. This usually involves changing reaction conditions such as temperature or concentration and applying the techniques of chemical kinetics, chemical thermodynamics, or spectroscopy. We will often refer to certain reactive intermediates based on carbon, viz., carbocations, radicals, carbanions and carbenes.

Common features

Reactive intermediates have several features in common:

- low concentration with respect to reaction substrate and final reaction product

- often generated on chemical decomposition of a chemical compound

- it is often possible to prove the existence of this species by spectroscopic means

- cage effects have to be taken into account

- often stabilization by conjugation or resonance

- often difficult to distinguish from a transition state

- prove existence by means of chemical trapping
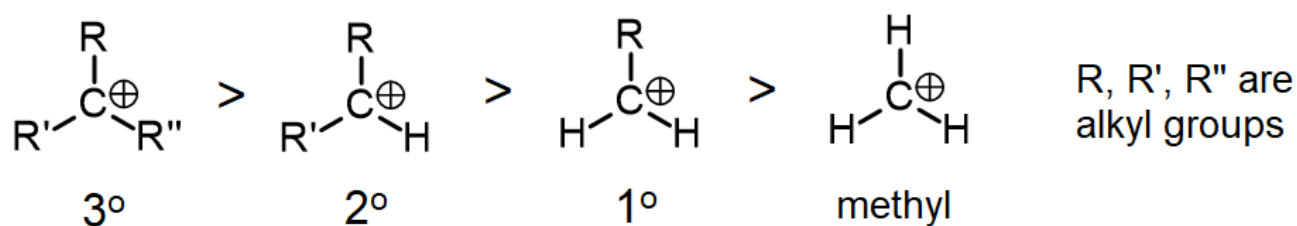
<u>Carbocations (R+)</u>

A carbocation is an ion with a positively-charged carbon <u>atom</u>. Among the simplest examples are methenium CH_3^+, methanium CH_5^+, and ethanium $C_2H_7^+$. Until the early 1970s, all carbocations were called carbonium ions.[1] In present-day chemistry, a carbocation is any positively charged carbon atom, classified in two main categories according to the valence of the charged carbon:

- +3 in carbenium ions (protonated carbenes),

- +5 or +6 in the carbonium ions (protonated alkanes, named by analogy to ammonium). These are much less common.

Structure and properties

The charged carbon atom in

a carbocation is a "sextet", i.e. it has only six electrons in its outer valence shell instead of the eight valence electrons that ensures maximum stability (octet rule). Therefore, carbocations are often reactive, seeking to fill the octet of valence electrons as well as regain a neutral charge. One could reasonably assume a carbocation to have sp3sp3 hybridization with an empty sp3sp3 orbital giving positive charge. However, the reactivity of a carbocation more closely resembles sp2sp2 hybridization with atrigonal planar molecular geometry. An example is the methyl cation, CH+3CH3+.

Order of stability of examples of tertiary (3°), secondary (2°), and primary (1°) alkylcarbenium ions, as well as the methyl cation (far right). The methyl group is so unstable it is only observed in the gas phase.

Carbocations are often the target of nucleophilic attack by nucleophiles such as water or halide ions.

Carbocations typically undergo rearrangement reactions from less stable structures to equally stable or more stable ones with rate constants in excess of 10^9/sec. This fact complicates synthetic pathways to many compounds. For example, when 3-pentanol is heated with aqueous HCl,

the initially formed 3-pentyl carbocation rearranges to a statistical mixture of the 3-pentyl and 2-pentyl. These cations react with chloride ion to produce about 1/3 3-chloropentane and 2/3 2-chloropentane.

A carbocation may be stabilized by <u>resonance</u> by a carbon-carbon double bond next to the ionized carbon. Such cations as <u>*allyl*</u> cation $CH_2=CH–CH_2^+$ and <u>*benzyl*</u> cation $C_6H_5–CH_2^+$ are more stable than most other carbocations. Molecules that can form allyl or benzyl carbocations are especially reactive. These carbocations where the C+ is adjacent to another carbon atom that has a double or triple bond have extra stability because of the overlap of the empty p orbital of the carbocation with the p orbitals of the π bond. This overlap of the orbitals allows the charge to be shared between multiple atoms – delocalization of the charge – and, therefore, stabilizes the carbocation.

Carbocations are the key intermediates in several reactions and particularly in nucleophilic substitution reactions.

Structure of Carbocations : Generally, in the carbocations the positively charged carbon atom is bonded to three other atoms and has no nonbonding electrons. It is sp^2 hybridized with a planar structure and bond angles of about 120°. There is a vacant unhybridized p orbital which in the case of CH_3^+ lies perpendicular to the plane of C—H bonds.

Stability of Carbocations: There is an increase in carbocation stability with additional alkyl substitution. Thus one finds that addition of HX to three typical olefins decreases in the order $(CH_3)_2C=CH_2>CH_3—CH = CH_2 > CH_2 = CH_2$. This is due to the relative stabilities of the carbocations formed in the rate determining step which in turn follows from the fact that the stability is increased by the electron releasing

methyl group (+I), three such groups being more effective than two, and two more effective than one.
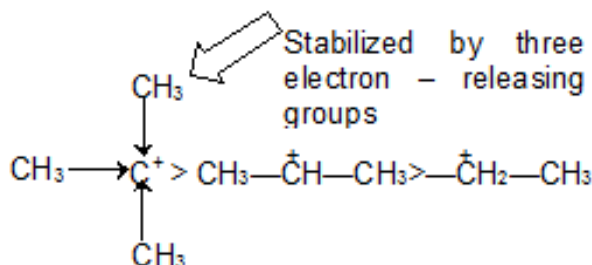
Stability of carbocations $3° > 2° > 1° > CH_3^+$

Electron release : Disperses charge, stabilizes ion.

Further, any structural feature which tends to reduce the electron deficiency at the tricoordinate carbon stabilizes the carbocation. Thus when the positive carbon is in conjugation with a double bond, the stability is more. This is so, because due to resonance the positive charge is spread over two atoms instead of being concentrated on only one. This explains the stability associated with the allylic cation. The benzylic cations are stable, since one can draw canonical forms as for allylic cations.
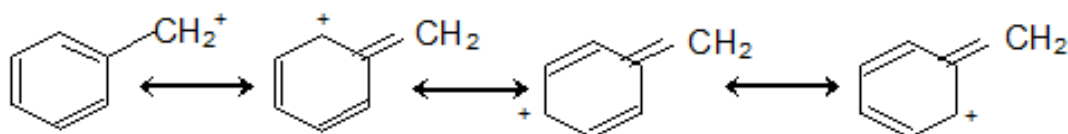
The benzyl cation stability is affected by the presence of substituents on the ring. Electron donating p-methoxy and p-amino groups stabilize the carbocation by 14 and 26 kcal/mole, respectively. The electron withdrawing groups like p-nitro destabilize by 20 kcal/mol.

A hetero atom with an unshared pair of electrons when present adjacent to the cationic centre strongly stabilizes the carbocation. The methoxymethyl cation has been obtained as a stable solid

$CH_3O^+CH_2SbF_6^-$. Cyclopropylmethyl cations are even more stable than the benzyl cations. This special stability is a result of conjugation between the bent orbitals of the cyclopropyl ring and the vacant p orbital of the cationic carbon. That the carbocations are planar is shown by the fact that these are difficult or impossible to form at bridgeheads, where they cannot be planar.

The stability order of carbocation is explained by hyperconjugation. In vinyl cations

$(CH_2 = C^+H)$, resonance stability lacks completely and these therefore are very much less stable.

Carbanions

A (sp³)   B (sp²)
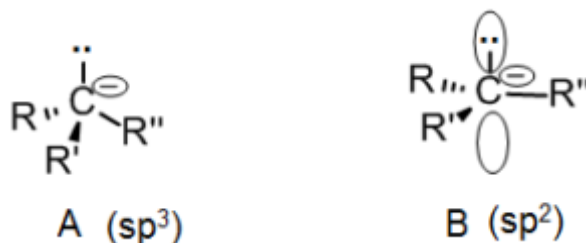
A carbanion is aneight electron intermediate with an sp^3 structure as shown in A. Despite its full octet, it is very reactive due to the fact that carbon is not very electronegative. Although it is sp^3, it can participate in resonance because it can easily re-hybridize to an sp^2 structure (see B), which allows overlap.

Carbanions are electron-rich and nucleophilic, so in fact they are destabilized by alkyl groups. This means that the order for stability is the

opposite of that for carbocations, namely methyl > primary > secondary > tertiary.

Structure of Carbanions: A carbanion possesses an unshared pair of electron and thus represents a base. The best likely description is that the central carbon atom is sp^3 hybridized with the unshared pair occupying one apex of the tetrahedron. Carbanions would thus have pyramidal structures similar to those of amines. It is believed that carbanions undergo a rapid interconversion between two pyramidal forms.

There is evidence for the sp^3 nature of the central carbon and for its tetrahedral structure. At bridgehead a carbon does not undergo reactions in which it must be converted to a carbocation. However, the reactions which involve carbanions at such centres take place with ease, and stable bridgehead carbanions are known. In case this structure is correct and if all three R groups on a carbanions are different, the carbanion should be chiral. All reactions therefore, which involve the formation of chiral carbanion should give retention of configuration. However, this never happens and has been explained due to an umbrella effect as in amines. Thus the unshared pair and the central carbon rapidly oscillate from one side of the plane to the other.

Stability and Generation of Carbanions: The Grignard reagent is the best known member of a broad class of substances, called organometallic compounds where carbon is bonded to a metal lithium, potassium sodium, zinc, mercury, lead, thallium – almost any metal known. Whatever the metal it is less electronegative than carbon, and the carbon metal bond like the one in the Grignard reagent highly polar. Although the organic group is not a full-fledged carbanion – an anion in which carbon carries negative charge, it however, has carbanion character. Or organometallic compounds can serve as a source from which carbon is

readily transferred with its electrons. On treatment with a metal, in RX the direction of the original dipole moment is reversed (reverse polarization).

Acetylene is ionized on treatment with amide ion in liquid ammonia to form a sodium acetylide; this has a little covalent character and may be regarded as a true carbanion. This property is used in making substituted alkynes. The stability order of carbanions points to their high electron density. Alkyl groups and other electron – donating groups in fact destabilize a carbanion. The order of stability is the opposite of that for carbocations and free radicals, which are electron deficient and are stabilized by alkyl groups. Based on this stability order it is easy to understand that carbanions that occur as intermediates in organic reactions are almost always bonded to stabilizing groups. An imporant method of preparation thus involves a loss of proton from a haloform to afford a stabilized carbanion. Another factor which leads to stability is resonance e.g., a carbonyl group stabilizes an adjacent carbanion via resonance e.g., a carbonyl group stabilizes an adjacent carbanion via overlap of its pi bond with the nonbonding electrons of the carbanion. Carbanions derived from carbonyl compounds are often called enolate anions. Among the other functional groups which exert a strong stabilizing effect on carbanions are nitro and cyano groups. The second row elements, particularly phosphorus and sulphur stabilize the adjacent carbanions. A very important nucleophilic carbon species constitute the phosphorus and sulphur ylide. The preparation of ylide is a two stage process, each state of which belongs to a familiar reaction type: nucleophilic attack on an alkyl halide, and abstraction of a proton by a base.
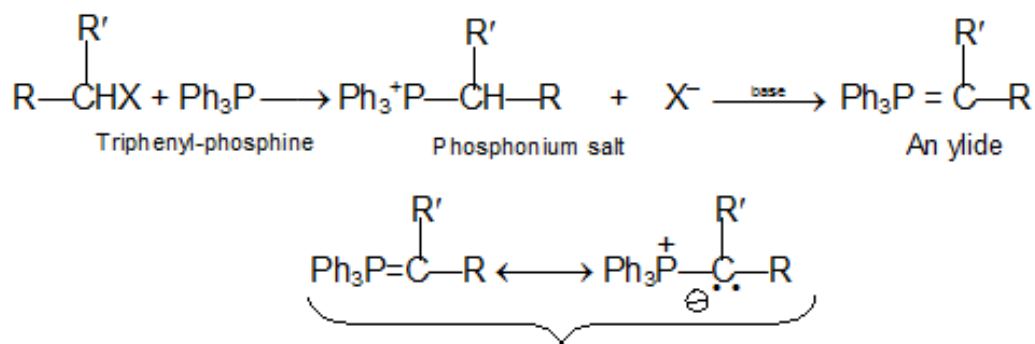
The phosphorus ylide have hybrid structure, and it is the negative charge on carbon i.e, the carbanion character of ylide which is responsible for their characteristic reactions. The sulphur atoms stabilize carbanions. When a double or triple bond is located a to the carbanionic carbon the ion is stabilized by resonance as in the case of benzylic type carbanions .

Properties of Carbenions: Carbanions are nucleophilic and basic and in this behaviour these are similar to amines, since the carbanion has a negative charge on its carbon, to make it a powerful base and a stronger nucleophile than an amine. Consequently a carbanion is enough basic to remove a proton from ammonia.
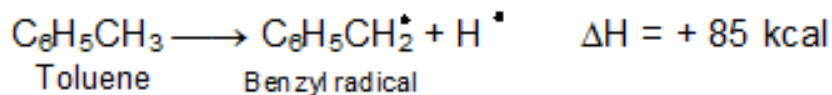
Free Radicals
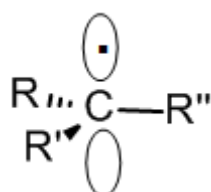
Structure and Geometry of Free Radicals: A free radical is a species which has one or more unpaired electrons. In the species where all electrons are paired the total magnetic moment is zero. In radicals, however, since there are one or more unpaired electrons, there is a net magnetic moment and the radicals as a result are paramagnetic. Free

radicals are usually detected by electron spin resonance, which is also termed electron paramagnetic resonance. Simple alkyl radicals have a planar (trigonal) structure, i.e., these have sp^2 bonding with the odd electron in a p orbital. The pyramidal structure is another possibility when the bonding may be sp^3 and the odd electron is in an sp^3 orbital. The planar structure is in keeping with loss of activity when a free radical is generated at a chiral center. Thus, a planar radical will be attacked at either face after its formation with equal probability to give enantiomers. Unlike carbocations, the free radicals can be generated at bridgehead shows that pyramidal geometry for radicals is also possible and that free radicals need to be planar.

p-orbital   sp³ hybridized orbital

Trigonal structure   Pyramidal structure
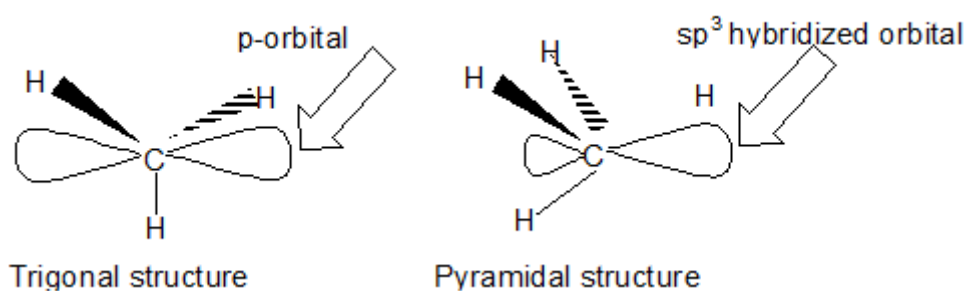
Stability of Free Radicals: As in the case of carbocation, the stability of free radicals is tertiary > secondary > primary and is explained on the basis of hyperconjugation. The stabilizing effects in allylic radicals and benzyl radicals is due to vinyl and phenyl groups in terms of resonance structures. Bond dissociation energies shown that 19 kcal / mol less energy is needed to form the benzyl radical from toluene than the formation of methyl radical from methane. The triphenyl methyl type radicals are no doubt stabilized by resonance, however, the major cause of their stability is the steric hindrance to dimerization.

$$C_6H_5CH_3 \longrightarrow C_6H_5CH_2^{\cdot\cdot} + H^{\cdot} \qquad \Delta H = + 85 \text{ kcal}$$

Toluene   Benzyl radical

Ease of formation of free radicals } Benzyl > allyl > 3° > 2° > 1° > $CH_3^{\cdot}$ > vinyl

A radicals is a seven electron intermediate that adopts a flat, sp^2 structure despite the fact that it has four electron groups; the lone electron resides in a half-filled p-orbital. This sp^2 structure allows radicals to delocalize the single electron through resonance. We will study radical reactions in detail in the second semester.

Being short of the octet, radicals are electrophilic, and therefore they are stabilized by alkyl groups. Thus the order for stability is the same as for carbocations, namely tertiary > secondary > primary > methyl .

Carbenes
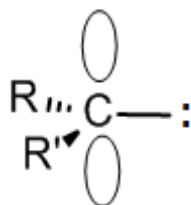
Carbenes are the least obvious of the four common intermediates; in most cases they have a six-electron sp^2 structure that has a lone pair but no overall charge. Although they are short of a full octet, they also have a

reactive lone pair, so (depending on structure) carbenes can be either electrophilic or nucleophilic.

Carbenes are neutral intermediates having bivalent carbon, in which a carbon atom is covalently bonded to two other groups and has two valency electrons distributed between two non bonding orbitals. When the two electrons are spin paired the carbene is a singlet, if the spins of the electrons are parallel it is a triplet.

Structure of Carbenes : A singlet carbene is thought to possess a bent sp2 hybrid structure in which the paired electrons occupy the vacant sp2 orbital. A triplet carbene can be either bent sp2 hybrid with an electron in each unoccupied orbital, or a linear sp hybrid with an electron in each of the unoccupied p-orbital. It has however, been shown that several carbenes are in a non-linear triplet ground state. However, the dihalogenocarbenes and carbenes with oxygen, nitrogen and sulphur atoms attached to the bivalent carbon, exist probably as singlets. The singlet and triplet state of a carbene display different chemical behaviour. Thus addition of singlet carbenes to olefinic double bond to form cyclopropane derivatives is much more stereoselective than addition of triplet carbenes.

Generation of Carbenes: Carbenes are obtained by thermal or photochemical decomposition of diazoalkanes. These can also be obtained by a-elimination of a hydrogen halide from a haloform with base, or of a halogen from a gem dihalide with a metal.

Reactions of Carbenes: These add to carbon double bonds and also to aromatic systems and in the later case the initial product rearranges to give ring enlargement products (a car-benoids –oranometallic or complexed intermediates which, while not free carbenes afford products expected from carbenes are usually called carbenoids).

When a carbene is generated in a three membered ring allenes are formed by rearrangement. However, a similar formation at a cyclopropylmethyl carbon gives ring expansion. Carbenes are also involved in Reimer —Tiemann reaction.
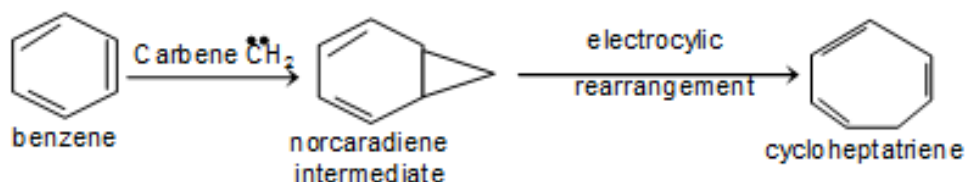
Arenium Ions

A considerable amount of experimental evidence indicates that electrophiles attack the p system of benzene to form a delocalized non-aromatic carbocation known as arenium ion or sometimes a s complex CMR spectroscopic evidence is available in favour of s complex.

Benzynes

It is a reactive intermediate in some nucleophilic aromatic substitutions. It is a benzene with two hydrogen atoms removed. It is usually drawn with a highly strained triple bond in the six membered ring. Benzyne intermediate has been observed spectroscopically and trapped.